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Bone metastases

Predictive model for survival in patients having repeat radiation treatment for painful bone metastases

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ABSTRACT

Purpose: To establish a survival prediction model in the setting of a randomized trial of re-irradiation for painful bone metastases.
Methods: Data were randomly divided into training and testing sets with an approximately 3:2 ratio. Baseline factors of gender, primary cancer site, KPS, worst-pain score and age were included with backward variable selection to derive a model using the training set. A partial score was assigned by dividing the value of each statistically significant regression coefficient by the smallest statistically significant regression coefficient. The survival prediction score (SPS) was obtained by adding together partial scores for the variables that were statistically significant. Three risk groups were modelled.
Results: The training set included 460 patients and the testing set 351 patients. Only KPS and primary cancer site reached the 5%-significance level. Summing up the partial scores assigned to KPS (90–100, 0; 70–80, 1; 50–60, 2) and primary cancer site (breast, 0; prostate, 1.3; other, 2.6; lung, 3) totalled the SPS. The 1/3 and 2/3 percentiles of the SPS were 2 and 3.6. For the testing set, the median survival of the 3 groups was not reached, 11.3 (95% C.I. 8.5 – not reached) and 5.2 months (95% C.I. 3.7–6.5). The 3, 6 and 12 month survival rates for the worst group were 64.4% (95% C.I. 55.3–72.1%), 43.0% (95% C.I. 34.0–51.8%) and 19.7% (95% C.I. 12.4–28.1%) respectively, similar to that in the training set.
Conclusion: This survival prediction model will assist in choosing dose fractionation. We recommend a single 8 Gy in the worst group identified.
 Radiotherapy and Oncology 118 (2016) 547–551

We conducted a randomized controlled trial comparing the effectiveness of a single versus multiple fractions of repeat radiation for painful bone metastases. Treatment with a single 8 Gy seems to be non-inferior and less toxic than multiple fractions; however because of the attrition rate and incomplete data, the findings were not robust. We concluded that tradeoffs between efficacy and toxicity might exist [1,2].

The predicted patient survival may help in decision making and also in discussion with the patient and family members. In patients with short survival, a single treatment may be ideal. Patients with bone metastases have a widely varying survival. A reliable estimation of survival is needed for appropriate treatment strategies [3]. Our goal was to use routinely available clinical characteristics to build a prognostic model and divide patients into different risk groups to predict survival in patients with painful bone metastases requiring reirradiation.

Methods

We employed the database of NCIC Clinical Trials Group Symptom Control.20 trial (SC-20) randomizing patients with painful bone metastases requiring repeat radiation to a single or multiple fractions. The eligible patients were 18 years or older with a pro-

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ven diagnosis of cancer with radiologically confirmed bone metastases that had previously received radiation. Patients with clinical or radiological evidence of spinal cord compression, a pathological fracture, or an impending fracture that needed to be fixed surgically were excluded from the study. Other exclusion criteria included a Karnofsky performance status (KPS) of less than 50, recent radionuclide or half body irradiation within 30 days before enrolment into the trial [1].

Statistical analysis

SC-20 accrued 850 patients with 425 on each treatment arm. We previously reported after a median follow-up of 12.2 months in both treatment groups, 227 (53%) of 425 patients assigned to 8 Gy had died compared with 220 (52%) of 425 patients assigned to 20 Gy (median survival was 9.3 months vs. 9.7 months; HR 0.96, 95% C.I. 0.8–1.2; $p = 0.66$) [1]. Because there was no difference in the overall survival between the 2 arms, we therefore pooled these two groups to perform all analyses.

Baseline factors included in this analysis were gender, primary cancer site, KPS, worst-pain score at baseline and age at enrolment. The primary outcome was overall survival, defined as time from date of randomization to the date of death or censored at the date of last follow up.

To develop and validate the model, we randomly divided the data into training and testing sets in a 3:2 ratio roughly, i.e., 3/5 of the data was used for model building and 2/5 of the data for testing. Patients were stratified by the following variables: treatment arm (single fraction vs. multiple fractions), age (<65 vs. $\geqslant$65 years), KPS (50–60 vs. 70–80 vs. 90–100); primary cancer site (prostate vs. lung vs. breast vs. other), and worst-pain score at baseline (2–4 vs. 5–6 vs. 7–10) Using the training set, the multi-variable survival model was built using a Cox regression model, using a backward 5% significance level for variable selection To obtain a prognostic score for the factors, a partial score was assigned to each of them. The partial score was derived by dividing the value of each statistically significant regression coefficient by the smallest statistically significant regression coefficient. The survival prediction score (SPS) for a given patient was obtained by adding together his/her partial score for the variables that were statistically significant [4]. Three risk groups with approximately equal number of patients in each group were modelled. We ensured there was an excess of 10–20 events per variable, which is a recommended minimum ratio to avoid the problem of overfitting a model in a multivariate analysis [5].

We used the following methods to evaluate discrimination (i.e. the ability of a predictive model to discern patients having good outcomes from those with poor outcomes).

First, a simple index of separation, PSEP, between prognostic groups, as proposed by Altman and Royston, was used [6]. PSEP is the difference between Pworst (predicted probability of dying for a patient in the group with the worst prognosis) and the Pbest (predicted probability of dying for a patient in the group with the best prognosis). PSEP was calculated for both the training and testing sets at 3, 6 and 12 months from randomization.

Second, an index of predictive discrimination, called C for "concordance" as proposed by Harrell et al., was employed [5]. The C index is the probability that for a randomly chosen pair of patients, the predicted and observed outcomes are concordant (i.e. the patient having the better outcome is the one having the better-predicted outcome). A value of 0.5 indicates no predictive discrimination and a value of 1.0 indicates perfect separation of patients with different outcomes.

The survival distribution for different risk groups was estimated using the Kaplan–Meier method and compared using the log-rank test [7].

Results

From the SC.20 dataset of 850 patients, 39 patients with missing data were excluded. The training set was made up of 460 patients and the testing set 351 patients. The training and testing sets were comparable among the baseline factors (Table 1). Only KPS and primary cancer site reached the 5% significance level for prediction of survival (Table 2). The partial scores assigned were KPS (90–100, 0; 70–80, 1; 50–60, 2) and primary cancer site (breast, 0; prostate, 1.3; other, 2.6; lung, 3). Hence, the SPS ranged from 0 to 5 (Table 3).

Training set

Based on the estimates of the effect of two candidate prognostic factors included in the model, we derived the SPS for each patient, and then used the 1/3, 2/3 percentiles of the SPS to divide patients into the low, medium and high risk groups. The 1/3 and 2/3 percentiles of the SPS were 2 and 3.6. Using the SPS, 158 (34%) of 460 patients were classified in group A when the SPS was 2 or less, 122 (27%) were in group B when the SPS was greater than 2–3.6, and 180 (39%) were in group C when the SPS was greater than 3.6. As shown in Fig. 1, this grouping led to good separation of the survival curves with a significant difference among the 3 groups ($p < 0.0001$). The median overall survival was not reached, 9.2 (95% C.I. 7.3–10.5), and 4.5 months (95% C.I. 3.8–5.1) for groups A, B and C respectively. The 3, 6 and 12 month survival rates were 93.4% (95% C.I. 88.0–96.4%), 82.3% (95% C.I. 75.1–87.6%) and 64.6%

Table 1
Baseline factors by training and testing cohorts.

Patient characteristics	Training set # (%)	Testing set # (%)	Total # (%)
Total	460 (100)	351 (100)	811 (100)
Median age (years)	65.4	64.8	65.0
Gender			
Female	196 (43)	138 (39)	334 (41)
Male	264 (57)	213 (61)	477 (59)
Primary cancer site			
Prostate	115 (25)	101 (29)	216 (27)
Breast	123 (27)	88 (25)	211 (26)
Lung	113 (25)	73 (21)	186 (23)
Other	109 (24)	89 (25)	198 (24)
Karnofsky performance status			
50–60	104 (23)	75 (22)	179 (22)
70–80	247 (54)	200 (57)	447 (55)
90–100	109 (23)	76 (22)	185 (23)
Worst pain score at baseline			
2–4	62 (13)	37 (10)	99 (12)
5–6	116 (25)	84 (24)	200 (24)
7–10	282 (61)	230 (65)	512 (63)
Site of painful bone lesion			
Pelvis/hips	163 (35)	126 (36)	289 (36)
Lumbosacral spine	76 (17)	72 (21)	148 (18)
Superficial bones	55 (12)	44 (13)	99 (12)
Upper limbs	48 (10)	33 (9)	81 (10)
Lower limbs	28 (6)	14 (4)	42 (5)
Thoracic spine	45 (10)	36 (10)	81 (10)
Thoracolumbar spine	30 (7)	19 (5)	49 (6)
Other	15 (4)	7 (2)	23 (3)
Response to initial radiation			
Further pain relief desired	45 (10)	35 (10)	80 (10)
No response	72 (16)	66 (19)	138 (17)
Pain returned	342 (74)	248 (71)	590 (73)
Unknown	1 (0)	2 (1)	3 (0)
Treatment arm			
Single fraction	230 (50)	175 (50)	405 (50)
Multiple fractions	230 (50)	176 (50)	406 (50)