Improving Providers' Survival Estimates and Selection of Prognosis- and Guidelines-Appropriate Radiotherapy Regimens for Patients with Symptomatic Bone Metastases:

Development and Evaluation of the BMETS Model and Decision Support Platform

by
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ABSTRACT

In the management of symptomatic bone metastases, selection of appropriate palliative radiotherapy (RT) regimens should be based on patient-specific characteristics including estimated survival time. Yet, provider predictions of patient survival are notoriously inaccurate. Moreover, available evidence- and consensus-based guidelines do not provide clear criteria for selecting between the range of palliative RT regimens available.

In an effort to improve selection of prognosis- and guidelines-appropriate palliative bone treatments, we developed the Bone Metastases Ensemble Trees for Survival (BMETS) model. Built using an institutional database of 397 patients seen in consultation for symptomatic bone metastases, this machine-learning model estimates survival time following RT consultation using 27 prognostic covariates. Cross validations procedures revealed excellent discrimination for survival, and the BMETS outperformed validated, simpler statistical models, justifying its use in this population.

To better characterize a component of decisional uncertainty faced by providers, we next sought to identify the prevalence of “complicated” symptomatic bone metastases across a breadth of possible operational definitions. Our efforts identified up to 96 possible definitions of “complicated” bone metastases, present in up to 67.1% of patients in our database. Given that such “complicated” lesions may have been excluded from clinical trials in this setting, these data highlight the difficulty faced by providers when attempting to select appropriate RT regimens using inadequately defined selection criteria.

Informed by these insights, we developed the BMETS Decision Support Platform (BMETS-DSP). This provider-facing, web-based tool was created to (1) collect relevant

patient-specific data, (2) display an individualized predicted survival curve as per the BMETS model, and (3) provide case-specific, evidence-based recommendations for treatment of symptomatic bone metastases. We then conducted a pilot assessment of the clinical utility of the BMETS-DSP. In this preliminary assessment, the BMETS-DSP significantly improved physician accuracy in estimating survival and increased prognostic confidence, likelihood of sharing prognosis, and use of prognosis-appropriate RT regimens in the care of case patients.

Collectively, this research provides early justification for the use of a machine-learning survival model and resultant decisions support platform to guide individualized selection of palliative RT regimens for symptomatic bone metastases. These data support a multi-institutional, randomized trial of the BMETS-DSP.

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LIST OF ABBREVIATIONS

ACR= American College of Radiology
ASCO= American Society of Clinical Oncology
ASTRO= American Society for Radiation Oncology
AUC= area under receiver-operator characteristic curve
BMETS= Bone Metastases Ensemble Trees for Survival
BMETS-DSP= Bone Metastases Ensemble Trees for Survival Decision Support Platform
C-3= Chow's 3-variable Number of Risk Factors model
CC/NFS= central canal and/or neuroforaminal stenosis
CCS= central canal stenosis
CE= cord edema
CEA= carcinoembryonic antigen
CEC=cauda equine compression
CI= confidence interval
CNS= central nervous system
DSP= decision support platform
EBRT= external beam radiotherapy
ECOG PS= Eastern Cooperative Oncology Group Performance Status
ESAS: Edmonton Symptom Assessment Scale
KPS= Karnofsky Performance Status
MESCC= malignant epidural spinal cord compression
N/A= not applicable
NCCN= National Comprehensive Cancer Network (NCCN)
NOS=not otherwise specified
NFS= neuroforaminal stenosis
NRF= Number of Risk Factors method
NSCLC= non-small cell lung cancer
PNS=peripheral nervous system
QOPI= Quality Oncology Practice Initiative
R^2= multiple correlation coefficient
RT=radiotherapy
SBRT=stereotactic body radiotherapy
SCC=spinal cord compression
tAUC= time dependent area under receiver-operator characteristic curve
VAS-gh= Visual Analogue Scale of general health
VRS-vl= Verbal Rating Scale of overall valuation of life
W-2= Westhoff's 2-variable model
WBC= white blood cells

Chapter 1: Introduction

Bone metastases are common among patients with advanced cancer and can substantially worsen quality of life through associated morbidities[1]. Radiotherapy (RT) serves as a particularly useful means for managing bone metastasis, with evidence supporting its efficacy for (1) reduction of pain and analgesia requirements[2,3], (2) treatment of or prophylaxis for morbidities from local progression such as fracture[4,5] and neuraxis compromise[6–8], and (3) potential provision of long-term disease control in select patients with expected prolonged survival[9,10]. Correspondingly, dose and technique may vary according to the intent of treatment, from single- and multiple-fraction conventional external beam radiotherapy (EBRT) to highly conformal stereotactic body radiotherapy (SBRT) regimens.

Because intent of therapy is often linked to prognosis, RT providers report strong consideration of life expectancy when selecting appropriate RT regimens in this setting[11]. Meta-analyses suggest that pain control for uncomplicated bone metastases is equivalent for single- versus multiple-fraction EBRT regimens, with pain response generally lasting from 3 to 7 months[3]. As such, guidelines and consensus statements generally support the use of single-fraction EBRT for patients with shorter life expectancies who are unlikely to benefit from more prolonged local control[12–14]. Conversely, retreatment rates were significantly higher for single- versus multiple-fraction regimens (20% versus 8%, respectively, $p<0.001$), and individual studies suggest higher rates of fracture and spinal cord compression with single-fraction EBRT[3]. Thus, dose escalation strategies using multiple-fraction EBRT[15] and SBRT techniques may be considered for patients with prolonged life expectancy, particularly for lesions such as spinal metastases at risk for morbidity at local progression.

However, studies repeatedly indicated that physicians' unaided estimates of survival time are notably inaccurate for patients with advanced cancer, ranging from 20-60% across studies[16]. In one systematic review, physicians overestimated survival in this population in 9 out of 12 included studies[17]. Such over-optimism of survival predictions is associated with selection of more aggressive—and likely low value—therapies near the end of life[18]. Specifically regarding palliative RT, practice patterns show persistent use of prolonged palliative RT regimens for symptomatic bone metastases irrespective of survival. A study of the National Cancer Database reported that from 2010 to 2014, 85% of patients with bone metastases from prostate cancer received palliative RT delivered in 10 or more fractions, with no difference in survival detected as compared to patients treated in 1-5 fractions[19]. Indeed, our own institutional data suggests that single-fraction RT was only delivered in 8% of patients during their final course of palliative bone radiotherapy[20].

In order to address these issues, a number of prognostic models have been developed to guide in clinical decision-making for patients treated with metastatic cancer[21–26]. Most of these models rely on traditional statistical approaches such as Cox proportional hazards` using a limited number of prognostic covariates. Yet despite the breadth of options, few providers report common use of these models in standard clinical practice, potentially due to the barriers including complexity of use, time, and inability to incorporate the tool into clinical workflow[11].

In the era of Big Data, increasing access to large-volume clinical databases and advanced statistical methodology offer the promise of new approaches to improve survival model predictions in medicine. Standardized use of electronic medical records (EMR) provides new access to enormous reservoirs of data, [27] and large-scale transitions to EMR across health systems create a novel environment for efficiently data sharing between institutions[28]. In parallel, statistical advances including growing use of

machine learning algorithms offer a means for effectively processing these complex data sources, in which limitations of traditional statistical approaches may render them inadequate[29].

However, simply improving prognostic estimates using these novel technologies may not be sufficient to alter providers' recommendations for treatment selection. For management of bone metastases, available evidence- and consensus-based guidelines imply that selection of regimens should be made on the basis of specific patient characteristics including prognosis but do not generally provide concrete criteria upon which to make treatment choices. Even when prognosis is addressed, there remains conflicting information regarding which patient characteristics are best matched to specific palliative regimens. As such, multiple aspects of the decision-making process may need to be addressed to improve selection of palliative regimens most appropriate for individual patient characteristics.

An appealing means for potentially improving individualized selection of palliative RT regimens is through the application of decision support aids. Often drawing from general psychology, social psychology, and decision theory, these tools seek to target specific aspects of the decision-making process[30] and are consistently associated with selection of more conservative treatment options[31]. While there are no such aids specifically developed to address management of symptomatic bone metastases with palliative RT, there is a growing body of evidence for the use of similar aids in other clinical scenarios in advanced cancer[32].

The overarching goal of this dissertation is to combine an optimized statistical approach for survival estimation with a theory-grounded decision support framework to aid the selection of prognosis-appropriate and evidence-based palliative RT regimens for managing symptomatic bone metastases. In Chapter 2, we use information from a large institutional database containing granular patient-level data to build the Bone Metastases

Ensemble Trees for Survival (BMETS), a machine learning approach that provides patient-specific survival estimations on the basis of 27 prognostic covariates. Our hypothesis is that use of the BMETS will improve survival predictions as compared to those produced by traditional statistical methods. If so, these data will justify the use of similar machine learning models for prediction in the setting of evolving complex, large datasets in Radiation Oncology.

Chapter 3 will address concerns regarding definitions used to delineate what types of bone metastases may be eligible to receive shorter-fraction palliative RT. Specifically, we will provide the first detailed review of rates of “complicated” bone metastases encountered after applying a breadth of possible operational definitions for this term. Given that “complicated” bone metastases have been excluded from trials establishing non-inferiority of single- versus multiple fraction regimens, these data seek to characterize the uncertainties faced by providers in the decision-making process when choosing appropriate RT treatment regimens in the absence of concrete selection criteria.

Chapters 4 and 5 will detail the development and evaluation of the BMETS Decision Support Platform (BMETS-DSP), built to guide clinical decision-making in this setting. In Chapter 4, we will use an established theoretical framework build a decision aid that (1) collects relevant patient-specific data, (2) displays an individualized predicted survival curve as per the BMET survival model, and (3) provides case-specific, evidence-based recommendations for radiotherapy (RT) and other interventions to aid in the decision-making process for patients with symptomatic bone metastases. In Chapter 5, we will use a simulated clinical environment with case presentations to perform a pre-post analysis of the BMETS-DSP and its ability to improve both providers’ survival predictions as well as their selection of palliative RT regimens that are appropriately matched to patient characteristics. We hypothesize that the BMETS-DSP will improve

the decision-making process in the management of symptomatic bone metastases by affecting both of these outcomes.

As opposed to simply testing the impact of the BMETS model and BMETS-DSP on improving providers' prognostic accuracy, our methodology is specifically selected to ensure that use of the tool significantly impacts clinically important outcomes as well (i.e., change in treatment choice). These results will provide the justification for a larger-scale assessment of the BMETS-DSP in a multi-institutional validation study and will form the foundation for development of similar tools for use in improving outcomes in treatment of advanced cancer.

CHAPTER 2: Optimized Survival Estimation to Guide Bone Metastases Management: Developing an Improved Statistical Approach

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ABSTRACT

Background: In managing bone metastases, estimation of life expectancy is central for individualizing patient care when selecting appropriate radiotherapy (RT) treatment options. Yet providers' estimates of patient survival are often inaccurate, leading to the development of numerous survival models using traditional statistical methods for use in patients with metastatic disease. Interestingly, simpler survival models tend to perform as well as more complex models in this setting. To determine if a machine learning approach may further improve survival predictions, we developed the Bone Metastases Ensemble Trees for Survival (BMETS) model to predict survival for patients with bone metastases using up to 27 predictor variables. To establish its relative clinical utility, we then compared our method to two simpler, validated Cox regression models.

Materials/Methods: For 397 patients evaluated in RT consultation for bone metastases from 1/2007 to 1/2013, data for 27 readily available clinical variables was collected. Primary outcome was time from consultation to death. We then performed Cox regressions per Chow's 3-item Number of Risk Factors model (C-3) and Westhoff's 2-item tool (W-2). Model performance was then assessed using 200 repeats of pooled 5-fold cross-validation and measured by time-dependent area under the curve (tAUC) for the BMETS, C-3, and W-2 models.

Results: Patient mean age was 62 years (SD 13). Median survival across the group was 6.3 months. Variable importance was greatest for performance status, blood cell counts, recent chemotherapy type, and receipt of concurrent palliative RT to non-bone sites. The cross-validation technique revealed excellent discrimination of the BMETS model across time points following consultation, with tAUC at 3 months, 6 months, and 12 months measured at 0.83, 0.81, and 0.81 for the BMETS model, respectively. The BMETS

outperformed simpler models across all time points, with respective values of tAUC of 0.78, 0.76, and 0.74 for the C-3 model and 0.80, 0.78, and 0.77 for the W-2 model.

Conclusion: For patients with bone metastases, the BMETS model substantially improved survival predictions versus relatively simpler traditional models. As such, we have developed a web platform to facilitate ease of data entry and display predicted patient survival probabilities from our BMETS to guide in selection of appropriate RT regimens.

INTRODUCTION

In the management of symptomatic bone metastases, selection of treatments including palliative radiotherapy (RT) depends on accurate estimation of life expectancy. However, providers are notoriously inaccurate at estimating survival—particularly at the end-of-life[33]—which can result in the delivery of high-cost care and reduced quality of life[18].

In order to address this concern, a number of prognostic models have been developed to guide in clinical decision-making for patients treated with palliative RT. Table 1 summarizes prediction models for patients treated with palliative RT across treatment site and primary cancer type. Numerous other models offer predictions for specific subpopulations such as those with spinal metastases[34–37]. Review of these models show that most depend on Cox proportional hazards methodology, with final models using up to 7 prognostic covariates.

Yet despite the breadth of options, one survey of 113 radiation oncologists found that only 31% rated such tools as moderately or very important to their estimation of life expectancy[11]. Potential reasons for underuse include the complex and time-consuming nature of available models.

In response to such limitations, two of the models summarized in Table 1 compared the predictive capacity of full versus reduced lists of predictor variables. Chow, et. al., compared survival predictions from 6- versus 3-covariate Cox proportional hazard models[38]. Their 3-variable number of risk factors (NRF) model comprised of non-breast cancer, presence of metastases other than bone, and KPS $\leq$60 yielded a C-statistic of 0.65, as compared to the C-statistic of 0.67 for the full 6-variable model. Similarly, Westhoff, et al.[25], compared discriminative capacities of an 6-versus 2-variable Cox proportional hazard model. Their 2-variable model comprised of only primary tumor site and KPS yielded a C-statistic of 0.71, which was comparable to the C-statistic of

0.72 for the full 6-variable model. In both cases, authors concluded that the reduced models resulted in similar predictive capacity and should be used instead of the full models due to ease of clinical application.

While these data offer compelling evidence that simpler models may be preferred when rendered from traditional statistical methods, newer machine learning approaches may offer a means to further optimize survival predictions using a larger number of covariates. Yet, no such machine-learning model is currently available for clinical use in this setting. As such, we built the **B**one **M**etastases **E**nsemble **T**rees for **S**urvival (BMETS) model to provide survival estimates for patients with bone metastases using up to 27 prognostic variables. To establish its clinical utility relative to simpler, traditional statistical methods, we then compared survival estimations from our approach to predictions from two validated Cox regression models.

METHODS

Data Source and study population

Patients seen in consultation for bone metastases between 3/1/2007 and 7/31/2013 at the Johns Hopkins Department of Radiation Oncology were identified through query of our departmental treatment database on the basis of ICD9 codes for bone site or treatments using $\leq$15 fractions and age $\geq$18 years.

Study population

The query yielded 424 patients seen in consultation for bone metastases. We limited analysis to patients with pathologically- or radiologically-confirmed metastatic cancer with dissemination to the bone, resulting in pain or other neurological sequelae. Due to infrequent use of stereotactic body radiotherapy (SBRT) during the study period, patients seen in consultation for this approach were excluded. In total, 20 patients were excluded

of the basis of these criteria. To minimize the statistical implications of multiple treatments within the same patient, only data from the first palliative treatment consultation within the study period was included.

Patient and disease characteristics

Electronic medical records (EMR) were retrospectively assessed for 27 patient, disease, and treatment factors felt to be prognostic for survival in this patient population. In addition to covariates evaluated in models from Table 1, new covariates of interest were identified from the literature: white blood cell (WBC) and lymphocyte counts within 1 month of consultation[39,40], steroid use[41,42], opiate pain medication use (as a proxy for magnitude of pain)[43], type of chemotherapy most recently (including newer targeted oral agents[44–46]), and presence of central spinal canal and/or neuroforaminal stenosis (CC/NFS) at the site of palliative RT[47]. Moreover, to capture granular data of metastatic burden, detailed information on other sites of metastatic disease was included.

Table 2 lists the 27 covariates, values coded for categorical variables, and pertinent definitions used. Notably, symptomatic bone lesions considered for primary RT (preferred to as the RT target site) were categorized as spine, hip/pelvis, extremity, chest wall, and skull. If the bone lesion involved more than one site category, the site affected by the majority of the lesion was recorded. When evaluated other sites of metastatic involvement, radiologic confirmation of a definite lesion at a given metastatic sites was considered to be positive, whereas indeterminate lesions or sites without directed radiologic evaluation were considered to be negative for metastatic involvement.

A documented performance status was available in the EMR for 72% of patients, including Karnofsky Performance Status (KPS) in 60% and Eastern Cooperative Performance Status (ECOG PS) in an additional 12% of patients. To minimize missing

values for performance status, a single author (SA) reviewed all EMR notes within 1 month of consultation to estimate a KPS based on documentation reflecting the patient's functional level at the time. For those with a recent EMR-recorded KPS, a clinically significant difference of >15 points between EMR-recorded and author-estimated KPS was identified in 3% of patients. Given rarity of discordance, the estimated KPS was used for all patients in our analysis. A total of 7 patients did not have recorded KPS, ECOG PS, or sufficient information to permit for author estimation and were thus excluded from this analysis.

The primary outcome was survival time between the date of palliative RT consultation and the date of death or last follow-up. Date of death was identified in the EMR and/or via the Social Security Death Index.

Statistical Analysis

1. BMETS methodology

We utilized established random survival forests methodology[48] to model survival time following consultation for palliative RT using the 27 candidate prognostic covariates. To do so, we employed bootstrap aggregation (bagging) by first taking 1,000 bootstrap samples from the original dataset. A binary survival tree was grown in each bootstrap sample[48]. To estimate the survival curve for a new individual based on the model, we first "dropped" the observation down each survival tree and obtained a Kaplan-Meier curve for each tree, based on the observations in the terminal node in which the dropped observation landed. The algorithm then averaged these Kaplan-Meier curves across trees for the final prediction. Specific methodology for the RSF model and subsequent survival time predictions is described in Appendix 1. We named the final model the **B**one **M**etastases **E**nsemble **T**rees for **S**urvival (BMETS).

Notably, multiple symptomatic bone sites considered for RT treatment during the same consultation visit in the same patient were all included in the model. To account for this, each different target site and the number of concurrent bone sites treated were coded as covariates.

To offer insight into the covariates that were most important for predicting survival, we used the minimal depth statistic. It is assumed that a highly prognostic variable will more frequently split the tree closer to the root node across the random survival forest. As such, the distance between the root node and the node first used to split each covariate was calculated for each tree and then averaged across trees to estimate the variable minimal depth. With the root node positioned at 0, increasing minimal depth values thus signify decreasing prognostic importance for a variable[48].

2. BMETS model validation

Estimation of the model's expected performance on external data was achieved using 200 repeats of pooled 5-fold cross-validation. Model discrimination was measured using time-dependent area under the curve (tAUC). Utilizing methodology for time-to-event data from Heagerty and Zheng[49], we let $\hat{S}(t|X_i)$ denote the estimated probability that individual *i* survives past time *t.* Then tAUC(t) is the probability that $\hat{S}(t|X_i) < \hat{S}(t|X_j)$ for any two individuals *i* and *j* picked at random from the population with $T_i \leq t$ and $T_j > t$, where the true time-to-death of the two individuals is T_i and T_j respectively. Thus, this is a measure of discrimination, asking the question, "Does the model predict a higher survival probability for individuals who live past a certain time when compared to those who do not?" A model with tAUC of 0.5 would predict survival no better than chance, whereas a tAUC of 1 would suggest perfect model discrimination. tAUC was measured for survival times from 0 to 12 months post consultation.

3. Comparative clinical utility of RSF versus existing models

To assess the relative utility of the BMETS model to simpler, traditional statistical models, we selected the 2-variable (W-2) model by Westhoff, et. al.[25], and the 3-variable NRF model (C-3) by Chow, et. al.[38], for comparison. For both, the Cox proportional hazards models described were re-fitted using a complete dataset from our source population. Model discrimination between RSF, W-2, and C-3 models was compared across time points using tAUC estimates, utilizing the cross-validation methodology noted above.

All statistical analysis was performed using the R statistical computing language, Version 3.5.1.

RESULTS

A total of 397 patients met the inclusion criteria and were evaluated in this analysis. Patient, disease, and treatment characteristics are summarized in Table 2. Median age was 62.3 years (standard deviation 13.4), with median KPS of 80 (range 40-100). The most common primary cancer site was lung (32% of cases), and the most frequent sites of palliative RT were spine and hip/pelvis (55% and 20% of cases, respectively). A large majority of patients (88%) had known metastatic disease outside of the current palliative RT site, most commonly within other bone (69% of cases). Over the study period, 370 deaths were observed, and median survival from the time of consultation was 6.3 months. Figure 1 shows the Kaplan-Meier curve for the overall group.

As per above, we built the BMETS model from 1000 bootstrap samples using the 27 candidate prognostic covariates. KPS, WBC count, the type of chemotherapy last

used, concurrent delivery of palliative RT to non-bone sites, and primary cancer site showed the lowest minimal depth across survival trees, suggesting that these covariates offer the greatest prognostic information (Figure 2). Among these covariates, KPS and primary cancer site were included in both C-3 and W-2 final models, whereas WBC count, the type of chemotherapy last used, concurrent delivery of palliative RT to non-bone sites were not assessed by any of the previous published models from Table 1.

Given the complexity and number of survival trees produced by the BMETS algorithm, model output cannot be easily visualized in tree form for clinical use. For illustrative purposes, Figure 3 shows an example single survival tree from one bootstrap sample limited to just the five variables with lowest minimum depth. In order to facilitate clinical application of the BMETS model, we have developed a web platform that collects patient information for the 27 prognostic covariates and displays the predicted survival probabilities across time points based on these data. This can be accessed at http://oncospace.radonc.jhmi.edu/Overview/Topics/PalliationPrediction.aspx. Figure 4 demonstrates the BMET model output for a sample patient.

Model validation

Cross-validation techniques revealed excellent discrimination for the BMETS model across time points (Figure 5). Specifically, tAUC at 1 month, 3 months, 6 months, and 12 months post-consultation was 0.87, 0.83, 0.81, and 0.81 for the BMETS model, respectively.

Relative utility as compared to simpler, traditional models

Table 3 shows Cox proportional hazards analyses for the C-3 and W-2 models re-fit using the data from our source population. The hazard ratios and confidences intervals for the reduced C-3 and W-2 models were not published. However, our hazard

ratios were of similar magnitude and directionality relative to the specified control groups when compared to values published for the full 6-variables models from each author group[25,38].

Comparing discriminative capacity between models, tAUC remained $\geq$0.74 for survival times up to 12 months post consultation for all three models (Figure 4). However, tAUC was highest for the BMET model across all time points. For comparisons, the tAUC at 1 month, 3 months, 6 months, and 12 months post-consultation was 0.79, 0.78, 0.76, and 0.74 for the C-3 model, respectively, and 0.82, 0.80, 0.78, and 0.77 for the W-2 model, respectively. Whereas the W-2 model begins to converge toward the BMETS model after the 6-month time point, tAUC for the C-3 model continues to decline over time.

DISCUSSION

In this study, we successfully developed the BMETS machine-learning model for predicting survival in patients seen in consultation for symptomatic bone metastases. To our knowledge, the BMETS model is the first of its kind to use granular patient data and a random survival forests methodology to create patient-specific predicted survival curves for clinical use. Further, we demonstrated that the BMETS model out-performed survival predictions made by simpler, traditional models in this setting, providing justification for its use. To offset its added complexity, we have created a web-based platform to facilitate ease of data entry, display, and interpretation of BMETS predictions.

As compared to use of the Cox regression models generally employed for survival prediction in this setting, the BMETS methodology offers a host of potential advantages. First, the random survival forest algorithm does not require a priori understanding of the relationships between variables. Thus, it may be better able to handle complex interactions and non-linear effects than Cox models, where these

components must be pre-specified[50]. Unlike traditional statistical methods, the random survival forests approach is robust to inclusion of non-prognostic and collinear covariates—perhaps even when the number of covariates exceeds the number of subjects[51]. Further, this algorithm handles missing data in a native fashion, by imputing missing values based on similar individuals within the same branch of the tree. Both of these factors permitted for our inclusion of a larger number of covariates than past models, perhaps explaining why the BMETS outperformed simpler approaches.

Moreover, all of the studies reported in Table 1 presented survival estimates according to prognostic groups categorized on the basis of covariate values. While this was likely performed to facilitate ease of clinical use, such groupings are associated with loss of important clinical information conveyed by the shape and slope of the underlying survival curves. Moreover, these categories do not provide information on the relative position of an individual patient within the ranges of survival provided, nor do they allow providers to estimate survival at specific time points that may be used as thresholds for selecting clinical interventions[16]. Conversely, visualization of even a 5-covariate random survival forests model produces output that is too complex for standard clinical use, as demonstrate in Figure 3. Our web-based platform circumvents both of these issues by permitting for display of a patient-specific survival curve that provides useful prognostic details while maintaining simplicity of interpretation.

A significant limitation to this analysis is the retrospective nature of our data collection. Namely, this design limited our ability to include patient-reported outcomes (PRO), which previous studies have identified as potentially useful for prognostication in advanced cancer[52]. In part, PRO were omitted in line with our goal of designing a model that could be applied using only information collected in standard clinical practice. It is noted that in addition to the best reduced model comprised of KPS and primary tumor site, Westhoff, et. al., also analyzed 2 other reduced models containing primary tumor

site plus either patient-reported visual analogue scale of general health (VAS-gh) or verbal rating scale of overall valuation of life (VRS-vl) outcomes. Both of these models had worse predictive accuracy than the best reduced model, and the authors concluded that these PRO were less prognostic than provider-reported KPS[25]. At least two other studies for patients with metastatic cancer also found that inclusion of PRO did not substantially improve prediction over models comprised of clinical and physician-reported factors[53,54]. Nonetheless, the value of PRO in a RSF model has not been described, and our future work may include prospective collection of PRO in the model.

Moreover, although our model is well calibrated, its performance in clinical practice must be tested. Because random survival forests may be especially susceptible to loss of validity when applied to non-source populations, next steps must certainly include testing in external environments[55]. However, proof of external validity for a survival model does not necessarily provide evidence of its clinical utility. For example, if our model improves survival estimates but these improved predictions fail to result in measurable changes in the decision-making process, we have failed to move science forward. As such, even before attempting to establish external validity of the BMETS model, we will first attempt to establish clinical utility by assessing the model for its capacity to measurably affect the decision-making process in the management of symptomatic bone metastases. Chapters 4 and 5 describe these efforts.

Table 1: Summary of previously published survival prediction models for patients treated with palliative radiotherapy across treatment site and primary cancer type*

Model	Setting and patient population	Model type	Candidate covariates	Results	Test of model performance / external validation
Chow 2002[21], 2009[22]	Prospective, 395 patients seen in consultation for palliative radiotherapy to any treatment site at a single institution	Cox proportional hazards model	Included in final model: Non-breast primary cancer site, presence of metastases other than bone, KPS≤60, and ESAS scores for fatigue≥4, appetite≥8, and shortness of breath≥1 Not included in final model: Age, weight loss, time from cancer diagnosis to consultation, analgesia type, and ESAS scores for pain, nausea, depression, anxiety, drowsiness, and sense of well-being	Total number of risk factors (1 point each)= NRF score Survival estimate at 3, 6 and 12 months*: NRF score≤3: 80%, 64% 41% NRF score 4: 51%, 25%, 10% NRF score≥5: 20%< 13%, 3%	C-statistic for NRF model= 0.67** R^2 = 0.31 _____ Temporal validation set with same source population: C-statistic for NRF model= 0.65 R^2= 0.27[22]
Chow 2009[23]	Same source population as above	Recursive partitioning analysis	Included in final model: KPS and site of metastases Not included in final model: Primary caner site, age, weight loss, time from cancer diagnosis to consultation, analgesia type, and ESAS scores for appetite, drowsiness, pain, nausea, depression, anxiety, fatigue, shortness of breath, and sense of well-being	3 prognostic groups on basis of KPS and site of metastases Survival estimate at 3, 6 and 12 months: KPS >60: 79%, 62%, 37% KPS ≤60 and bone metastases only: 65%, 36%, 32% KPS ≤60 and non-bone metastases: 39%, 43%, 29%	C-statistic = 0.64 R^2 = 0.23 External validation set: C-statistic= 0.61 R^2= 0.15

Model	Setting and patient population	Model type	Candidate covariates	Results	Test of model performance / external validation
Katagiri 2014[37]	Prospective, 808 patients treated for symptomatic bone metastases at a single institution	Cox proportional hazards model	Included in final model: Rapidly growing primary tumor type, presence of visceral or cerebral metastases, abnormal laboratory data+, ECOG PS≥3, previous receipt of chemotherapy, and presence of multiple skeletal metastases Not included in final model: Gender, age, neurological deficits, disease remaining at primary site, RT treatment site, presence of pathologic fracture	Total number of risk factors (1 point each)=risk category score 12-month survival estimate: Score ≤3: >80% Score 4–6: 30–80% Score 7–10: ≤10%	Not reported _____ External validation set with 12-month survival estimates: Score ≤3: 58% Score 4–6: 32% Score 7–10: 9%[56]
Krishnan 2014[24]	Retrospective, 862 patients who received palliative radiotherapy to any treatment site at a single institution	Cox proportional hazards model	Included in final model: Non-breast or prostate primary cancer site, age>60 years, presence of liver metastases, ECOG PS≥2, hospitalization in past 3 months, and ≥2 previous palliative radiotherapy courses Not included in final model: KPS, location of metastasis, time from diagnosis of primary disease to metastatic disease, time from metastasis diagnosis to radiotherapy consultation, presence of non-bone metastases, and other metastases to bone, lung, liver, CNS, and other sites	Total number of risk factors (1 point each)= NRF score Median survival in months: NRF score 0-1: 19.9 NRF score: 2-4: 5.0 NRF score: 5-6: 1.7	C-statistic= 0.59 _____ External validation with C-statistic=0.78 R^2=0.17[57]
Westhoff 2014[25]	Prospective, 1157 patients treated for symptomatic bone metastases at multiple institutions	Cox proportional hazards model	Included in final model: Sex, primary tumor site, presence of visceral metastases, baseline KPS, VAS-gh, and VRS-vl Not included in final model: Age and pain scale	Survival estimate at 3-18 months presented in table by category of primary tumor site and KPS	C-statistic= 0.72 (95% CI 0.70-0.74) _____ External validation set with C-statistic= 0.71[25]

Model	Setting and patient population	Model type	Candidate covariates	Results	Test of model performance / external validation
Zhang 2016[26]	Retrospective, 125 patients treated for bone metastases at a single institution	Cox proportional hazards model	Included in final model: Male sex, KPS<80, esophageal or colorectal primary cancer site, <3 years between tumor diagnosis and diagnosis of bone metastases, T-staging≥3, and poorly differentiated tumor Not included in final model: Age, postoperative status, CEA, N-stage, M-stage, anatomic group stage, and previous metastases to lung, liver, or brain	Each risk factor is scored from 0 to -2; total score divided into 3 prognostic groups Median survival estimates in months: Group 1: 4.9 Group 2: 10.5 Group 3: 29.7	Not reported _____ No validation set

*Due to calculation error in 2002 publication, these data reflect values reported as per the authors' 2009 publication
[+]Laboratory values included C-reactive protein, LDH, serum albumin, platelet count, serum calcium level, and total bilirubin
CEA= carcinoembryonic antigen, CI= confidence interval, ECOG PS= Eastern Cooperative Oncology Group Performance Status, ESAS= Edmonton Symptom Assessment Scale, KPS= Karnofsky Performance Status, NRF= Number of Risk Factors method, R^2= Multiple correlation coefficient for comparison of actual survival with predicted survival, VAS-gh= Visual Analogue Scale of general health, VRS-vl= Verbal Rating Scale of overall valuation of life

Table 2: Patient, disease, and treatment characteristics for 397 patients included in the BMETS model

Patient-specific factors		Disease-specific factors		Treatment-specific factors	
Name		**Name**		**Name**	
1. Age in years—mean (SD)	62 (12)	9. Primary cancer site—%		17. RT target site‡—%	
2. Sex—%		Breast	19%	Spine	53%
Female	48%	Prostate	12%	Hip/pelvis	13%
Male	52%	Lung	32%	Extremity	18%
3. Race—%		Leukemia, lymphoma, myeloma	5%	Chest wall	13%
White	72%	Other	32%	Skull	4%
Black	23%	10. Number of concurrent palliative RT to other non-contiguous bone sites§—%		18. CC/NFS¶—(%)	
Asian	2%			Yes	38%
Other	3%			No	62%
4. KPS in unites of 10—median (range)	80 (40-100)	0	81%	19. Time from initial diagnosis in months—mean (SD)	40 (55)
5. WBC count within prior 1 month in cells per microliter—mean (SD)	8,8,78 (5,725)	1	15%	Other metastases to# (% Yes):	
		2+	4%	20. Brain	12%
6. Lymphocyte count within prior 1 month in cells per microliter—mean (SD)	1,519 (2,565)	11. Concurrent palliative RT to non-contiguous sites other than bone§—%		21. Lung	40%
		None	92%	22. Liver	20%
		Brain	5%	23. Adrenal gland	8%
		Lung	2%	24. Lymph nodes**	42%
		Other or > 1 type	1%	25. Soft tissue	5%
7. Inpatient status+—%		12. Current steroid use—%		26. Other bone	69%
Yes	25%	Yes	25%	27. Other sites	7%
No	75%	No	75%		
8. Any weight loss in prior 6 months—%		13. Current opiate analgesic use—%			
Yes	67%	Yes	29%		
No	33%	No	71%		
		14. Chemotherapy delivered within the previous 1 month—%			
		Yes	55%		
		No	45%		
		15. Type of chemotherapy last delivered‖—%			
		None	31%		
		Intravenous	39%		
		Non-hormonal oral	11%		
		Hormonal	19%		
		16. Prior surgery at RT target site—%			
		Yes	12%		
		No	88%		

+Admission to offsite inpatient rehabilitation or nursing home facilities were excluded
‡ If RT target lesion encompassed multiple sites, site containing majority of target lesion was selected
§ Does not include RT target sites requiring multiple contiguous fields due to large target size
‖ If multiple types of chemotherapy were delivered concurrent, a single response was selected in the following order: IV > non-hormonal oral > hormonal
¶ Defined as radiologic evidence of spinal cord, spinal canal, nerve root, or neuroforaminal impingement from direct involvement of the target lesion
#Includes all radiologically-confirmed definite areas of metastatic disease outside of the current palliative RT field. Indeterminate lesions or sites without radiologic evaluation were as "no."
** Includes locoregional nodal metastases for the primary site
BMETS= Bone Metastases Ensemble Trees for Survival, CC/NFS= central canal and/or neuro-foraminal stenosis, KPS= Karnofsky Performance Status, RT=radiotherapy, WBC= white blood cells

Table 3: Multivariate Cox proportional hazards analyses for covariates from two validated Cox proportional hazards models, re-fitted using our source population data*

Model and covariates**	Hazard ratio	95% Confidence interval
Chow's 3-variable NRF (C-3) model[38]		
Primary cancer site		
Breast	1.00	-
Non-breast	1.75	1.34−2.29
KPS		
>60	1.00	-
≤60	3.70	2.88−4.75
Site of metastases		
Bone only	1.00	-
Other	2.25	1.79−2.82
Westhoff's 2-variable (W-2) model[25]		
Primary cancer site		
Breast	1.00	-
Prostate	1.17	0.78−1.75
Lung	2.57	1.89−3.49
Other	2.05	1.53−2.77
KPS		
90-100	1.00	-
70-80	1.81	1.37−2.40
20-60	6.17	4.41−8.58

*A complete dataset with no missing values for the above covariates was used to refit the models.
**Covariate values are specified as per the source model's definitions.

KPS= Karnofsky Performance Status, NRF= Number of Risk Factors

Figure 1: Kaplan-Meier survival estimate for the overall group, N=397.

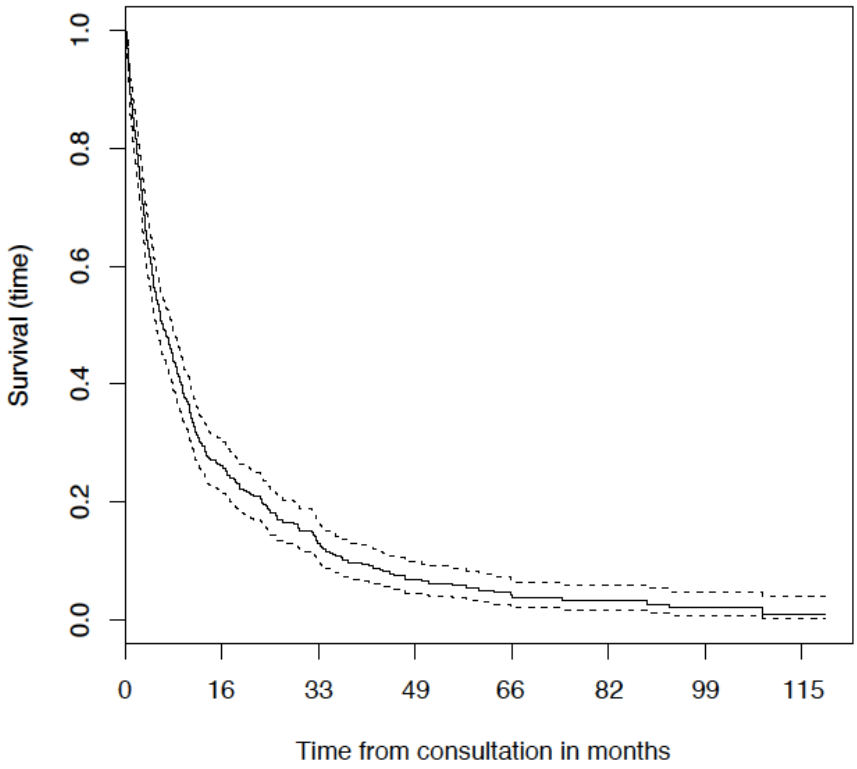


Figure 2. Minimal depth for each covariate within the BMETS model.
This value represents the distance between the root node (at position 0) and the node first used to split each covariate, averaged across trees. A lower minimum depth indicates higher prognostic importance for a given variable.
BMETS= Bone Metastases Ensemble Trees for Survival, KPS= Karnofsky Performance Status, CC/NFS= central canal and/or neuroforaminal stenosis, RT= radiotherapy, WBC= white blood cells

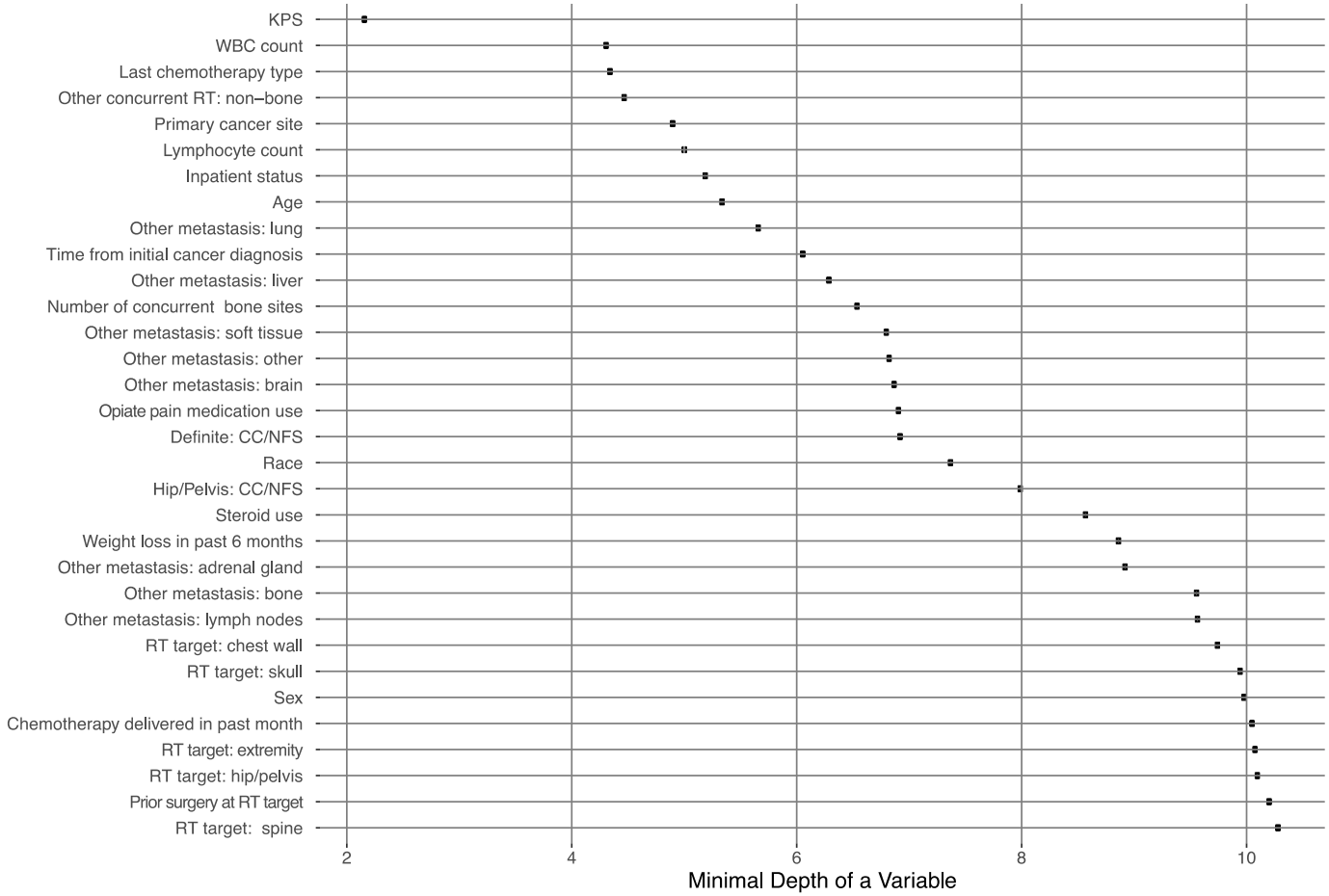


Figure 3. An example single survival tree grown from our full data set, limited to 5 prognostic covariates.
Numbers 1-29 represent model nodes. Estimated percent survival following consultation for palliative radiotherapy is displayed in months for each terminal node.
KPS= Karnofsky Performance Status, WBC= white blood cells

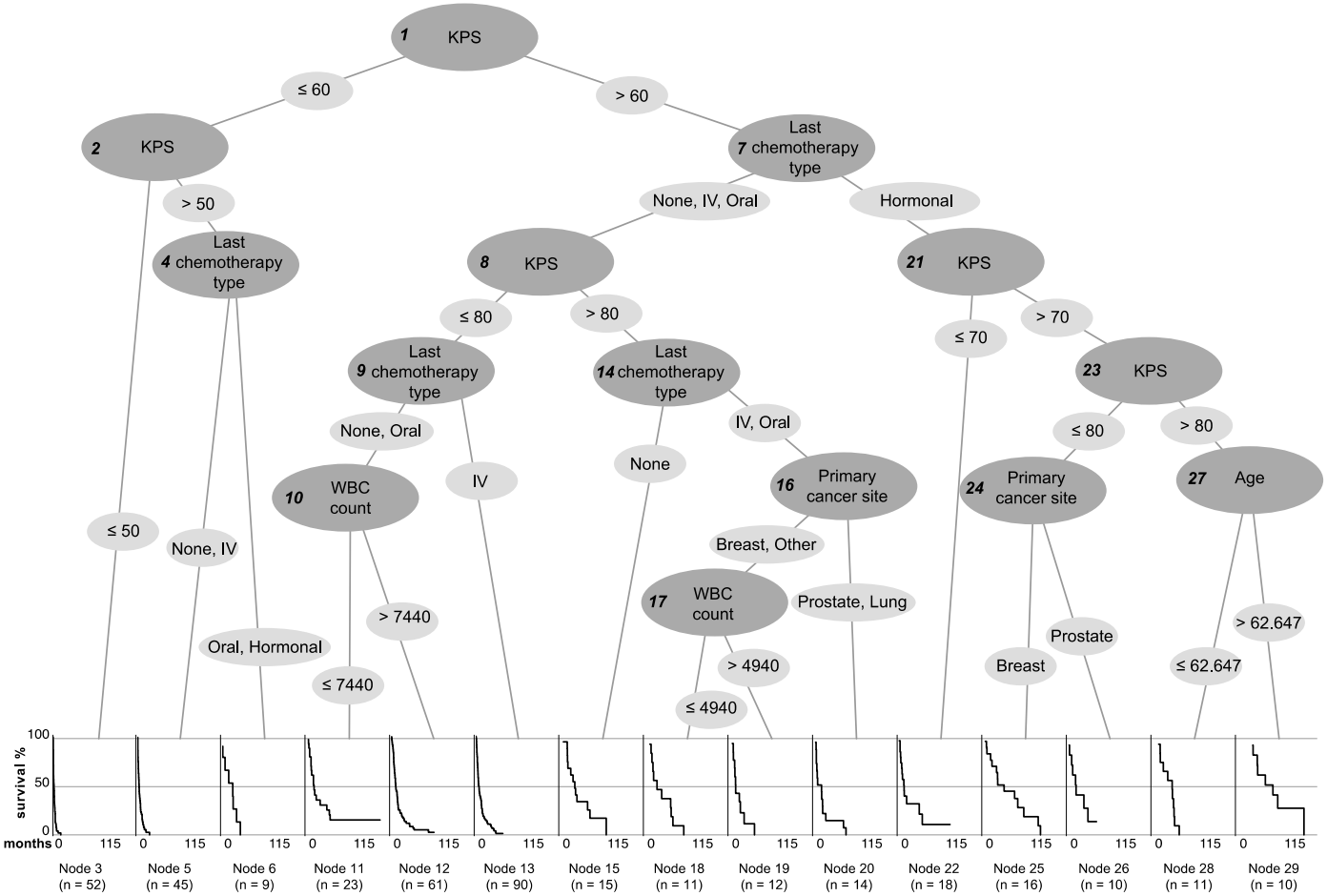
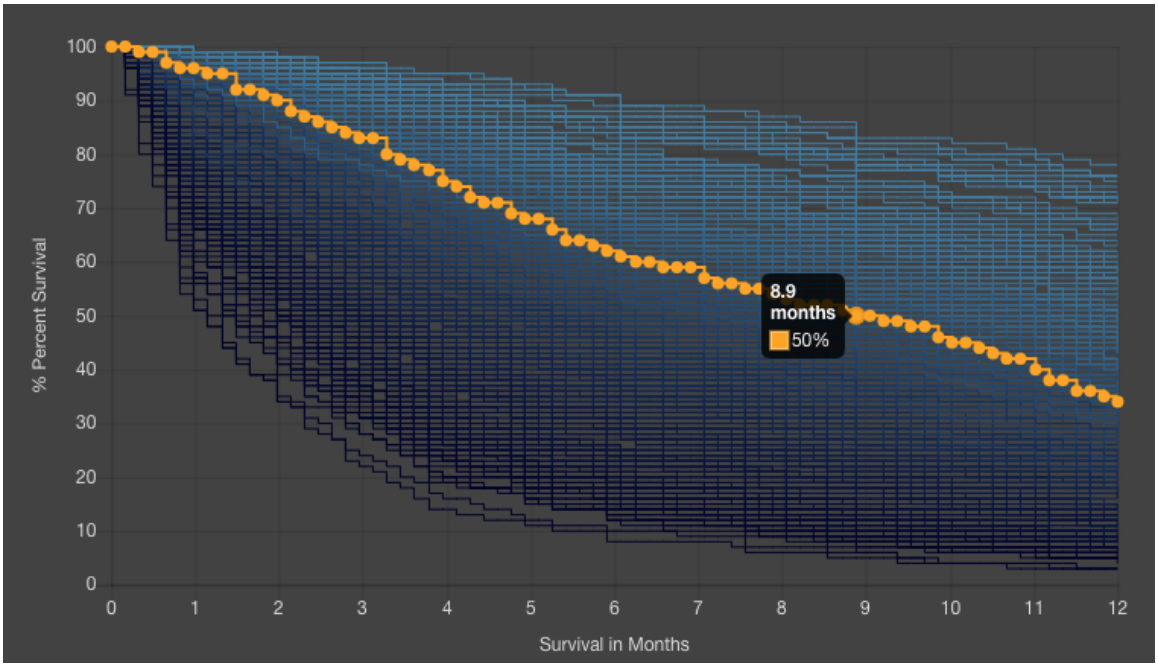


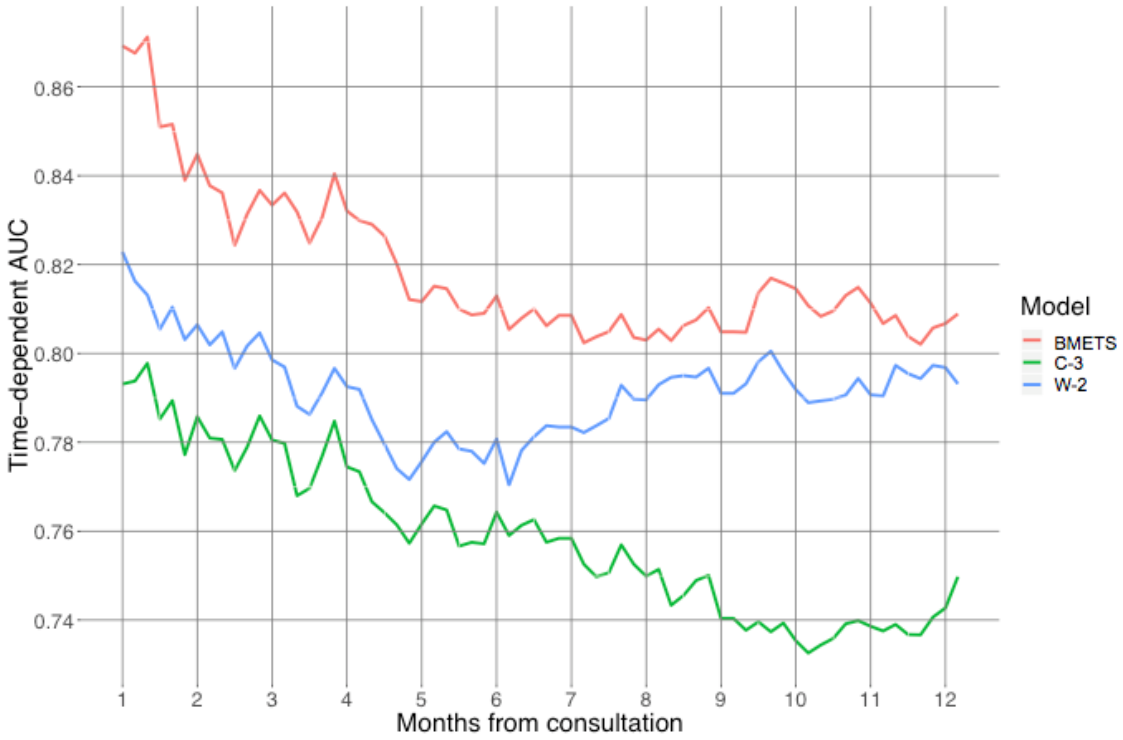
Figure 4. Example output for the web platform developed to collect covariate information and display the estimated survival probabilities from time of consultation to death as predicted by the BMETS model.

Case: 71-year-old Black/African American woman with metastatic thyroid cancer is seen in outpatient consultation for symptomatic metastatic disease at the lumbar spine. She was initially diagnosed with cancer 5 years and 3 months ago. Her most recent systemic therapy was oral therapy (sorafenib), which has been administered within the past 1 month. She denies a history of prior surgery to the current symptomatic site. She reports weight loss in the past 6 months. KPS is 70. She is currently taking opiate pain medication but not steroids. White blood cell count is 9,160 and lymphocyte count is 2,390. Available imaging shows no definite impingement of the spinal canal or of the neuroforamina. Metastatic involvement is also identified at other bone sites. There are no plans to undergo concurrent palliative radiotherapy to any other non-contiguous metastatic sites.



The interactive orange curve displays the predicted survival for the case patient following consultation for palliative radiotherapy. The blue curves demonstrate the predicted survival for all other patients with symptomatic bone metastases in the database, displayed for comparison purposes only.

Figure 5. Comparison of time-dependent area under the curve (tAUC) between prognostic models across survival time points following palliative radiotherapy.
The BMETS model outperforms simpler, traditional model by Chow, et. al.[22], and Westhoff, et. al.[25], at all time points evaluated.
BMETS= Bone Metastases Ensemble Trees for Survival model, C-3= Chow's 3-variable Number of Risk Factors model, and W-2= Westhoff's 2-variable model



CHAPTER 3: Frequency of Complicated Symptomatic Bone Metastasis Over a Breadth of Operational Definitions

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ABSTRACT

Background: Numerous randomized trials have demonstrated non-inferior pain control from single- versus multiple-fraction palliative radiotherapy (RT) in the management of “uncomplicated” symptomatic bone metastases. Yet there is no clear definition of what constitutes a “complicated” lesion for which single-fraction RT may not be appropriate. Moreover, there are no published studies detailing the prevalence of “complicating” features in patients treated for such symptomatic lesions. Thus, we identify a range of operational definitions of “complicated” symptomatic bone metastases supported by the available literature and review our institutional data to characterize the frequency of potential “complicating” features at a high-volume, tertiary care center.

Methods: Patients seen in consultation for symptomatic bone metastases between 3/1/2007 and 7/31/2013 at the Johns Hopkins Department of Radiation Oncology were identified via the electronic medical record. Retrospective chart review including physician review of radiologic imaging was performed to collect patient and disease characteristics. Descriptive statistics were used to characterize the frequency of the following potential “complicating” features: prior RT, prior surgery, neuraxis compromise, pathologic fracture, and soft tissue component at the symptomatic site. A range of operational definitions for “complicated” bone metastases was evaluated based on all possible combinations of these “complicating” features. Uni- and multivariable logistic regression evaluated the odds of “complicated” bone metastases as a function of site of primary cancer and of the symptomatic target lesion.

Results: A total of 696 symptomatic bone metastases in 404 patients were evaluated. Percent of target sites with prior RT was 4.6%, prior surgery was 8.9%, pathologic fracture was 22.7% (of which 80% were vertebral body compression fractures), neuraxis compromise was 50% among spine and medial pelvis sites, and soft tissue component

was 42.2%. Based on the available literature, a total of 96 possible definitions of “complicated” bone metastases were identified. The presence of such “complicated” lesions ranged from 2.3% to 67.1%, depending on the operational definition used. Odds of a “complicated” lesion were significantly higher for spine sites.

Conclusions: In this retrospective study, we found “complicated” symptomatic bone metastases may be present in up to two-thirds of patients at our institution. Our review of the literature also demonstrates no clear standard definition of “complicated” bone metastases, potentially explaining underutilization of single-fraction palliative RT in this setting. These data will be used to inform development of a decision support platform to guide in selection of appropriate palliative RT regimens in this population.

INTRODUCTION

In a seminal systematic review of randomized trials comparing single- versus multiple fraction radiotherapy (RT) in the management of "uncomplicated" symptomatic bone metastases, Chow, et. al., found no significant difference in pain control across studies comparing single- versus multiple fraction RT[58]. These data have resulted in consensus recommendations from the American Society of Radiation Oncology (ASTRO)[12], the American College of Radiology (ACR)[59–61], and the National Comprehensive Cancer Network (NCCN)[62–67] supporting non-inferiority of 8 Gy in one fraction versus multiple-fraction regimens in a range of clinical scenarios.

Yet, the definition of "uncomplicated" bone metastases for which 8 Gy in one fraction is most appropriate remains ill-defined. Recently, Cheon, et al., sought to clarify this definition by reviewing inclusion and exclusion criteria for 25 trials included in the above-noted systematic review[68]. The authors concluded that a conservative definition of "uncomplicated metastases" supported across studies is the "presence of painful bone metastases unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression[1]."

Table 1 summarizes clinical features that would result in exclusion from the trials reviewed by Cheon, et. al., plus four additional randomized trials published subsequent to their analysis [69,70] and included in ASTRO's most recent systematic review[12]. Studies reporting the same patient population are listed in the same row and one study reported as abstract alone was excluded[71], resulting in 23 unique sets of exclusion criteria. Although 18 out of 23 trials excluded patients on the basis of existing or impending pathologic fracture, the studies notably lack details regarding clinical or radiologic features that constitute fracture. Similarly, 15 of the 23 trials excluded cases due to neuraxis compromise, but there is little description of what comprises spinal cord or peripheral nerve compression across trials.

Moreover, consensus recommendations for fractionation vary on the basis of features not contained with the conservative definition of “complicated” proposed by Cheon, et. al. Table 2 provides a summary of key differences across guidelines in the setting of prior RT, prior surgery, existing or impending pathologic fracture, presence of soft tissue component, location of the treatment site, and presence of neuraxis compromise. Moreover, there is little data describing the prevalence of these potentially “complicating” features despite their propensity to dictate treatment decisions.

In order to augment understanding of potential “complicating” factors for which single-fraction palliative RT may not apply, we review the frequency of these features at our institution across a breadth of operational definitions supported by the available literature.

METHODS

Data Source and study population

Patients seen in consultation for bone metastases between 3/1/2007 and 7/31/2013 at the Johns Hopkins Department of Radiation Oncology were identified through query of our departmental database on the basis of ICD9 codes for bone site or treatments using $\leq$15 fractions and age $\geq$18 years.

Study population

The query yielded 424 patients seen in consultation for bone metastases. We limited analysis to patients with pathologically- or radiologically-confirmed metastatic cancer with dissemination to the bone, resulting in pain or other neurological sequelae. Due to infrequent use of stereotactic body radiotherapy (SBRT) during the study period, patients

seen in consultation for this approach were excluded. In total, <5% of the initial population was excluded.

Patient and disease characteristics

A review of the electronic medical record was performed for each patient to collect basic demographic information. Site of bone metastasis was categorized as spine, hip/pelvis, extremity, chest wall, and skull. If the bone lesion involved more than one site category, the site affected by the majority of the lesion was recorded.

In order to characterize potential "complicating" features at symptomatic sites of disease, the following factors were identified on the basis of their inclusion in randomized studies or consensus statements reviewed in Table 1 or Table 2, respectively.

1. **Prior RT**. Treatment with prior definitive or palliative radiotherapy to the current site of symptomatic metastasis was recorded.
2. **Prior surgery**. Surgical intervention at the current site of symptomatic metastasis at any time prior to consultation were recorded, including open surgical procedures, vertebroplasty, and kyphoplasty.
3. **Pathologic fracture**. Presence of pathologic fracture as determined as per documentation of fracture by attending physicians in Radiology, Orthopedic Surgery, or Neurosurgery. Given lack of use of standardized means for characterizing impending fractures during the study period, only existing fractures were considered. For spine sites, fracture was defined as documentation of loss of vertebral body height, compression fracture, or vertebral body collapse.
4. **Neuraxis compromise**. Given a range of definitions employed to characterize spinal cord and peripheral nerve compression, we documented radiologic evidence of central canal stenosis, neuroforaminal stenosis, and/or spinal cord edema. Presence of

corresponding symptoms was not required. Radiologic evidence was determined by personal review of CT and MRI images performed within 1 month of consultation by SA whenever available. When not available, documentation per Radiology reports or per clinical notes was used. At a minimum, CT used for radiation planning was reviewed if performed. Neuraxis compromise was considered in spine and in medial pelvic sites in proximity to the central canal or neuroforamen.

5. Soft tissue component. The presence of an extraosseous, soft tissue component directly extending from the site of bone metastasis was noted. As with neuraxis compromise, this was confirmed via direct review of available CT and MRI images by SA whenever available, with minimum review of the planning CT if performed. In the absence of these studies, radiology reports or clinical notes were used.

For patients seen in consultation for more than one symptomatic site of bone disease, each non-contiguous site was evaluated separately. Non-contiguous sites were defined as sites for which radiotherapy would be delivered using two separate and non-abutting radiation fields. Contiguous sites treated with abutting fields due to large treatment area were considered as one site (i.e., T5-T12 and L1-L4 would be considered 1 site, whereas C1-3 and T5-T12 would be considered 2 sites.) Multiple courses of concurrent and non-concurrent palliative RT within the same patient but occurring within the study period were included in the analysis.

Outcomes analysis

The presence or absence of a “complicating” feature was evaluated as a binary outcome. When the presence of the “complicating” feature was indeterminate or could not be confirmed by imaging or documentation in the medical record, the feature was coded as absent. For target sites with prior surgery, no additional radiologically-

assessed “complicating” features were coded due to inability to accurately review imaging in the setting of artifact and postoperative changes. Thus, only prior RT status was documented in patients with prior surgery.

The frequency of each potential “complicating” feature was first considered individually. To demonstrate the breath of operational definitions that could constitute a “complicated” lesion as per the randomized trials and consensus guidelines in Table 1 and 2, the frequencies of “complicated” bone metastases were then estimated using definitions derived from all possible combinations of the above-noted “complicating” features. When assessed as combinations of features, presence of at least one “complicating” feature included in the definition was sufficient for coding as a “complicated” bone metastasis. For the variables of prior RT, prior surgery, and soft tissue component, one definition (described above) was utilized. For pathologic fracture, two definitions were considered: any fracture versus non-spine fractures only. For neuraxis compromise, three definitions were considered: all neuraxis compromise, central canal stenosis only, or spinal cord edema only. No study included consideration of neuroforaminal stenosis alone, so this component was not assessed individually. Only one definition of pathologic fracture and neuraxis compromise was included at a time when considering combinations of features.

Statistical analysis

Descriptive statistics were performed for patient and disease characteristics. Associations between potential “complicating” features and the corresponding target site of symptomatic bone metastasis were analyzed using Fisher’s exact tests. Odds ratios for presence of “complicated” bone metastases using the most inclusive definitions as a function of primary cancer site and target symptomatic metastasis site were assessed using uni- and multivariable logistic regression. Given the hypothesis that both primary

cancer site and target symptomatic metastasis site may be independently associated with the presence of “complicated” bone metastases, we made an a priori decision to include both variables in the multivariable assessment regardless of univariable results.

In the case of multiple palliative treatments within the same patient to different target sites, each target site was considered independently in these analyses.

All statistical tests utilized a two-sided $\alpha = 0.05$ for significance testing. Statistics were performed using Stata Version 14.0 (College Station, Texas).

This study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine.

RESULTS

A total of 696 non-contiguous sites of symptomatic bone disease were evaluated for 404 patients. Patients were treated at an average of 1.7 sites (standard deviation 1.1) during the study period. Among included patients, primary cancer site was 32% lung, 18.3% breast, 11.6% prostate, 5.0% leukemia/lymphoma, and 33.2% other. Among separate lesions considered, site of symptomatic sites were 50.1% spine, 21.1% hip/pelvis, 17.2% extremity, 8.3% chest wall, and 3.2% skull. Table 3 shows disease features and treatment characteristics by site of the target symptomatic bone metastasis.

Frequency of individual “complicating” features

Table 3 also displays the frequency of various “complicating” features arranged by target site. Fisher’s exact tests showed significant differences in prevalence of these features by target site for all factors except for presence of prior RT.

1. **Prior RT**. Prior radiotherapy to the target site was noted in 32 (4.6%) of target sites. Of all prior RT cases, 46.9% were spine, 12.5% were extremity, 25% were hip/pelvis, 9.4% were chest wall, and 6.3% were skull sites.

2. **Prior surgery**. Prior surgery to the target site was noted in 62 (8.9%) of target sites. Of all postoperative cases, 62.9% were spine, 21.0% extremity, 14.5% were hip/pelvis, 0% were chest wall, and 1.6% were skull sites.

3. **Pathologic fracture**. Definite pathologic fracture was identified in 144 (22.7%) of target lesions. Of all fractures, 79.9% were spine, 6.3% extremity, 9.7% were hip/pelvis, 4.2% chest wall, and 0% were skull sites.

4. **Neuraxis compromise.** Among sites of the spine and medial pelvis considered for this “complicating” feature, 180 (49.2%) were noted to have definite neuraxis compromise. Figure 1 delineates details of neuraxis compromise. When neuraxis compromise was present, 26.1% of cases were central canal stenosis (without spinal cord edema) only, 2.8% were central canal stenosis with spinal cord edema, 24.8% were neuroforaminal stenosis only, 41.1% were both central canal stenosis (without spinal cord edema) and neuroforaminal stenosis, and 6.1% were central canal stenosis with spinal cord edema and neuroforaminal stenosis.

5. **Soft tissue component**. A definite soft tissue component was identified in 268 (42.2%) of target lesions. Of all fractures, 50.4% were spine, 12.3% extremity, 20.5% were hip/pelvis, 11.9% chest wall, and 4.9% were skull sites.

Frequency of "complicated" bone metastases across a range of definitions

For illustrative purposes only, Appendix 2 shows the percent of cases with at least one "complicating" feature present across the 96 possible definitions created from various combinations of the 8 variables listed. Depending on the definition used, the percent of "complicated" bone metastases ranged from 2.3% to 67.1%.

Figure 2 shows the percent of cases with at least one "complicating" feature present across the most commonly used definitions of "complicated" symptomatic bone metastasis seemingly used in the randomized studies and census statements. Variable definitions of fracture and neuraxis compromise were included owing to the uncertainty on how these features were specified. The most inclusive definition yielded 67.1% "complicated" lesions, whereas a stricter definition requiring spinal cord edema and excluding vertebral body compression fractures and soft tissue components resulted in classification of 19.3% "complicated" lesions.

Odds of "complicated" metastasis by disease features

Table 4 shows the uni- and multivariable logistic regression for odds of having a "complicated" symptomatic bone metastasis using the most inclusive definition, as a function of primary cancer site and target symptomatic bone site. As compared to breast cancer metastases, leukemia/lymphoma and "other" cancer (but not prostate or lung cancer) yielded higher odds of "complicated" bone metastases on univariable analysis. As compared to spine target sites, extremity, hip/pelvis, and chest wall (but not skull) sites had significantly lower odds of "complicated" bone metastases on univariable analysis. All of these associations persisted on multivariable analysis.

DISCUSSION

In this retrospective study, we found “complicated” symptomatic bone metastases were identified in up to 67% of patients at our institution. However, when applying the breadth of operational definitions for “complicated” lesions that can be deduced from review of randomized trials and consensus statements, the percent of “complicated” lesions varies widely. To our knowledge, this is the first attempt to characterize frequency of “complicated” bone metastasis using granular patient-level data, detailed radiologic review, and a range of definitions for the outcome of interest. Given that such “complicated” lesions may be ineligible for management with single-fraction palliative RT, our results lend insight into the clinical applicability of consensus statements when selecting appropriate palliative regimens in our patient population.

Our data shows that one of the most frequently encountered “complicating” feature was neuraxis compromise. Further, we found that odds of having a “complicated” lesion were highest at spine sites. These findings are congruent with data reporting spine as the most common site of bone metastasis[72], with an associated high risk of developing skeletal-related events and resultant decrement to quality of life[73]. Notably, neuraxis compromise was among the most complex features to operationalize. In randomized trials, exclusion criteria related to the nervous system ranged from simple notation of “spinal cord compression” to the use of qualifiers such as “suspected compression”, radiologically-confirmed compression, effacement of the cord[74,75], or presence of clinical symptoms consistent with compression. Some trials also excluded cases due to effacement of or clinical or radiologic evidence of cauda equina or peripheral nerve compression (See Table 1). In the absence of standardized clinical or radiologic criteria to define neuraxis compromise, we erred on the side of recording radiologic presence of central canal stenosis, neuroforaminal stenosis, and/or spinal cord edema. Peripheral nerve compromise was included in the definition of *all neuraxis*

compromise but not considered independently when analyzing combination definitions since no trial excluded cases on the basis of peripheral nerve compromise alone.

Our definitions of neuraxis compromise are associated with significant strengths and limitations. Strengths include its utilization of relatively objective measures and coverage of most of the exclusion criteria from the randomized trials evaluated. Use of a radiologic measure is aligned with current management frameworks used for spinal tumors, which generally utilize assessments such as the MRI-based Bilksy Criteria to dictate care[76]. Yet unlike the Bilksy scoring method, our measure can be determined using CT- or MRI-based imaging, affording greater generalizability. Limitations of our definition include lack of detail regarding symptoms of neuraxis compromise. Unfortunately, use of these data was limited by the retrospective nature of our study. However, it is our assumption that morbidity associated with symptomatic lesions and its impact on treatment selection will be captured through estimates such as Karnofsky Performance Status, as detailed in Chapter 2. Another limitation is that the frequency of "complicated" metastasis varies widely depending on which of our criteria is applied when defining neuraxis compromise. While a flexible definition enhances applicability over a wider range of cases, it does not permit for a precise classification of which types of neuraxis lesions are best considered "complicated."

Another frequent "complicating" feature was fracture, which was again ill-defined on the basis of available studies and guidelines. Specifically problematic was whether vertebral body compression fractures should be included in the definition of a "complicating" fracture, given high rates of pathologic fracture of the spine among patients with metastatic disease[77]. Whereas some of the randomized studies analyzed expressly specified exclusion of non-spine fractures only, at least one excluded cervical through thoracic vertebral body collapse, and most did not specify site of fracture at all. Although there are available radiologic-based guidelines such at the SINS criteria for

measuring percent vertebral body collapse to guide management in this setting[78], the relevance of such ratings to questions regarding single- versus multiple-fraction radiotherapy is unknown. As with the definitions used for neuraxis compromise, the decision to consider both *all fractures* and *non-spine fractures* when estimating "complicated" metastases enhances flexibility but limits precision and results in a wider range of estimated "complicated" lesions. An additional limitation is our inability to include "impending" fracture in the absence of a standardized definition for this variable in our field.

Although not common in the study population, prior RT or surgery at the target symptomatic metastasis were included in all key definitions specified in Figure 2. Consistent with our decision to prioritize previous treatment, nearly all of the randomized trials analyzed cited prior RT as an exclusion criterion. Conversely, prior surgery was inconsistently specified as cause for exclusion. However, it is inextricably linked with existing or impending fracture for most bone sites, and it is a key feature for dictating fractionation schemes in both ACR and NCCN guidelines[59–62]. As such, we included it when selecting features most commonly used to define "complicated" metastases.

Perhaps most contentious was our decision to include the presence of a soft tissue component as a potential "complicating" feature. As found by Cheon, et.al., in their initial analysis[68], we also determined that none of the 29 trials considered in Table 1 excluded cases on the basis of a soft tissue component. However, a soft tissue component may contribute to bony instability or fracture, and when present near the neuraxis, it may lead to nervous system compromise. Moreover, presence of a soft tissue component is used to guide fractionation decision as per the NCCN consensus guidelines for non-small lung cancer[65] and mesothelioma[63], justifying our consideration of this feature.

An additional limitation to our analysis involves the fact that cases came from a high-volume Radiation Oncology clinic within a tertiary care hospital setting. It is feasible that “uncomplicated” cases are more likely to be referred out of our facility. As such, external generalizability regarding the frequency of “complicated” metastases noted may be restricted. However, our study question requires review of granular, patient-level data, which impairs the ability to use information from multi-institutional or national databases.

Because “complicated” bone metastases may have been excluded from randomized trials comparing single- versus multiple-fraction palliative RT, lack of a consensus definition and high frequency of possible “complicating” features may contribute to low utilization of single-fraction RT observed in current clinical practice. Despite efforts by campaigns such as Choosing Wisely to encourage use of foreshortened regimens of palliative RT[79], practice patterns suggest persistent use of prolonged palliative RT regimens irrespective of survival, as delineated in Chapter 1. In the absence of a concrete definition of “complicated” bone metastases, the data presented offers providers a range of definitions that may be used at their discretion to guide in selection of appropriate fractionation based on patient-specific clinical features. Moreover, we use these definitions to aid in the development of individualized recommendations for the decision support platform described in Chapter 3.

Table 1: Summary of features used as exclusion criteria by randomized studies of singe- versus multiple-fraction radiotherapy for symptomatic bone metastases*

Study N=23**	Prior therapy		Fracture				Nervous system compromise	
	RT	Surgery	Long bone	Vertebra	NOS	Impending	CNS	PNS
Altundag[80]	✓	✓			✓		✓ (Symptoms of SCC)	
Amouzegar Hashemi[81]					✓	✓	SCC	
Badzio[82]	✓				✓			
BPTWP[83]	✓		✓					
Cole[84]					✓	✓	✓ (SCC syndrome)	✓ (PN compression syndrome)
El-Shenshawy[85]	✓				✓ (Except vertebral compression fracture)		✓ (Suspicion of SCC)	
Foro[86]					✓	✓	✓ (Medulla compression)	
Foro Arnalot[87]	✓				✓	✓ (If Mirel's criteria ≥9)	✓ (Clinical or radiologic evidence of SCC)	
Gaze[88]	✓	✓		✓ (If collapse above L2)	✓	✓	✓ (SCC)	
Gutierrez Bayard[70]	✓				✓ (If lesion requires fixation)		✓ (SCC)	

Study	Prior therapy		Fracture				Nervous system compromise	
	RT	Surgery	Long bone	Vertebra	NOS	Impending	CNS	PNS
Hamouda[89]	✓				✓			
Hartsell[74], Howell[75]					✓	✓	✓ (Clinical or radiologic evidence of SCC or effacement)	✓ (Clinical or radiologic evidence of CEC or effacement)
Kaasa[90], Sande[91]	✓				✓ (If lesion requires fixation)		✓ (SCC)	
Kagei[92]					✓ (Except if vertebral compress-ion fracture)			
Koswig[93]	✓							
Majumder[69]	✓				✓	✓	✓ (SCC)	
Nielsen[94]	✓				✓ (Except if vertebral compress-ion fracture)		✓ (Suspicion of SCC)	
Ozsaran[95]	✓	✓						

Study	Prior therapy		Fracture				Nervous system compromise	
	RT	Surgery	Long bone	Vertebra	NOS	Impending	CNS	PNS
Price[96]	✓		✓					
Roos[97]	✓		✓				✓ (Clinical or radiologic evidence of SCC)	✓ (Clinical or radiologic evidence of CEC)
Safwat[98]	✓						✓ (Clinical or radiologic evidence of SCC)	✓ (Clinical or radiologic evidence of CEC)
Sarkar[99]	✓				✓			
Steenland[100], Van der Linden[101], Meeuse[102]	✓				✓ (If lesion requires fixation)		✓ (SCC)	
Total studies with exclusion criterion, N (%)	**18 (78%)**	**3 (13%)**	**3 (13%)**	**1 (4%)**	**17 (30%)**	**4 (17%)**	**15 (65%)**	**4 (17%)**

* Adapted from Cheon, et. al.[68], with 4 additional studies considered as per systematic review update[12]
** 29 studies considered, with published trials containing the same study population and exclusion criteria grouped in 1 row, resulting in 23 unique sets of exclusion criteria considered
✓ indicates presence of exclusion criteria, with qualifying details in parenthesis if present
CEC=cauda equine compression, CNS= central nervous system, NOS=not otherwise specified, PNS=peripheral nervous system, RT= radiotherapy, SCC=spinal cord compression

Table 2: Summary of key variations in consensus recommendations on the basis of possible "complicating" features of symptomatic bone metastasis

Clinical Feature	ASTRO[12]	ACR[59–61]	NCCN[62–64,103]
Prior radiotherapy	Consider 1-5 fractions EBRT	Consider 1-6 fractions EBRT	Consider SBRT for spine sites
Prior surgery	-	Consider multiple fraction radiotherapy	Consider SBRT for spine sites if oligometastatic or radioresistant
Pathologic or impending fracture	-	Consider multiple fraction radiotherapy	-
Soft tissue component	-	-	Consider multiple fraction radiotherapy for NSCLC metastases with soft tissue component
Uncomplicated spine and other critical sites	Single-fraction radiotherapy most appropriate when limited life expectancy	Consider multiple fraction radiotherapy unless limited life expectancy	Consider multiple fraction radiotherapy for estimated survival >6 months
Spinal cord or cauda equina compression	-	Consider multiple fraction radiotherapy unless limited life expectancy	Consider SBRT for spine sites if oligometastatic or radioresistant

ASTRO= American Society for Radiation Oncology, ACR= American College of Radiology, NCCN= National Comprehensive Cancer Network (NCCN), EBRT= external beam radiotherapy (conventional), SBRT=stereotactic body radiotherapy, NSCLC= non-small cell lung cancer

Table 3: Characteristics of the target symptomatic bone metastasis by treatment site

	Spine, N=349	Extremity, N=120	Hip/ pelvis, N=147	Chest wall, N=58	Skull, N=22	
	n (%)	n (%)	n (%)	n (%)	n (%)	p-value*
Primary cancer site						
Breast	67 (12.1%)	21 (17.5%)	33 (22.5%)	8 (13.8%)	5 (22.7%)	-
Prostate	57 (16.3%)	11 (9.2%)	20 (13.6%)	5 (8.6%)	4 (18.2%)	
Leukemia/ lymphoma	23 (6.6%)	5 (4.2%)	2 (1.4%)	0	5 (22.7%)	
Lung	101 (29.0%)	37 (30.8%)	43 (29.3%)	31 (53.5%)	3 (13.6%)	
Other	101 (28.9%)	46 (38.3%)	49 (33.3%)	14 (24.1%)	5 (22.7%)	
Other palliative RT						
≥1 concurrent site	118 (33.8%)	48 (40.0%)	53 (36.1%)	26 (44.8%)	4 (18.2%)	0.161
≥1 course in study period	208 (59.6%)	80 (66.7%)	108 (73.5%)	45 (77.6%)	15 (68.2)	0.009
Presence of "complicating" features at the target site						
Prior RT	15 (4.3%)	4 (3.3%)	8 (5.4%)	3 (5.2%)	2 (9.1%)	0.640
Prior surgery	39 (11.2%)	13 (10.8%)	9 (6.1%)	0	1 (4.6%)	0.015
Pathologic fracture	115 (37.1%)	9 (8.4%)	14 (10.1%)	6 (10.3%)	0	<0.001
Neuraxis compro-mise**	171 (55.6%)	-	9 (15.5)	-	-	<0.001
Soft tissue component	135 (43.5%)	33 (30.8%)	55 (39.6%)	32 (55.2%)	13 (61.9%)	0.008

* p-value as per Fisher's exact test. No statistical testing was performed on the site of bone metastasis x primary cancer site comparison due to prohibitive number of cells.
** Only sites of spine and medial pelvis considered, N=366
RT= radiotherapy

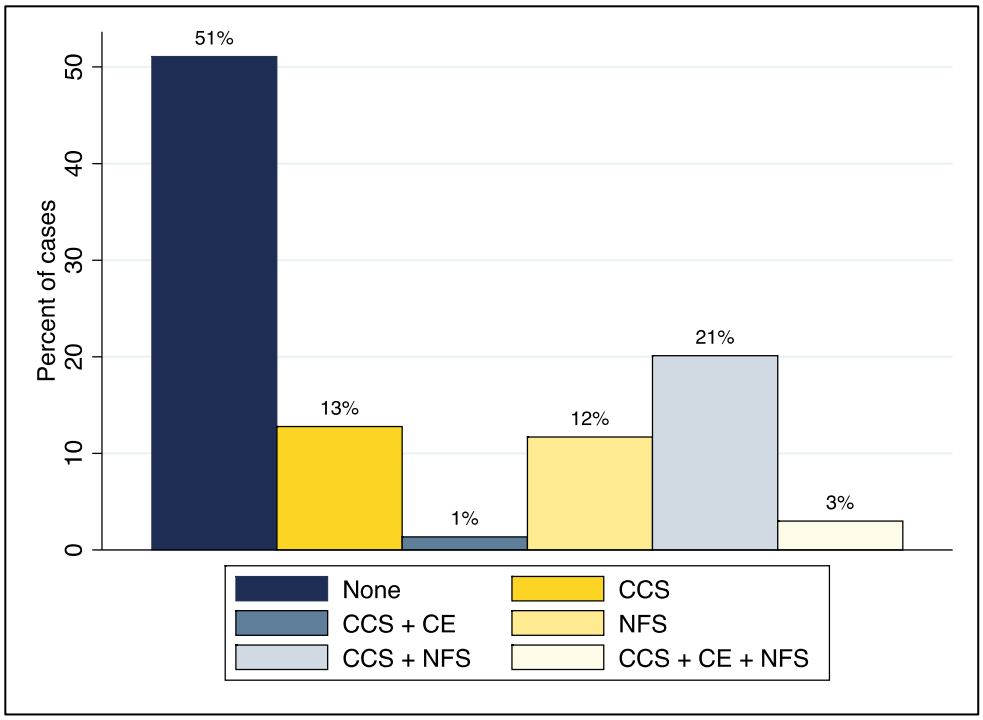

Figure 1: Percent of all target spine and medial pelvis bone metastases with neuraxis compromise, N=366. CCS= central canal stenosis, CE= cord edema, NFS= neuroforaminal stenosis.

Presence of "complicating" features							
Prior RT	Prior surgery	All fracture	Non-spine fracture only	All neuraxis com-promise	CCS only	CE only	Soft tissue com-ponent
✓	✓	✓		✓			✓
✓	✓	✓			✓		✓
✓	✓	✓				✓	✓
✓	✓		✓	✓			✓
✓	✓	✓		✓			
✓	✓		✓	✓			
✓	✓		✓		✓		
✓	✓		✓			✓	

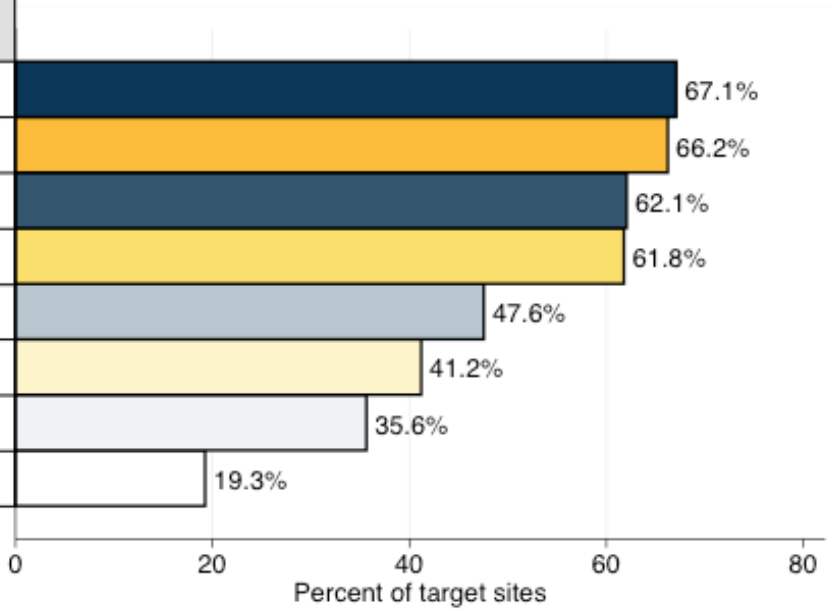

Figure 2: Percent of all target symptomatic bone metastases cases with at least one "complicating" feature across most common definitions of "complicated" symptomatic bone metastasis.
✓ Indicates that the selected variable was used as part of the operational definition for "complicated" bone metastasis
RT= radiotherapy, CCS= central canal stenosis, CE= cord edema

Table 4: Uni- and multivariable logistic regressions for odds of "complicated" symptomatic bone metastasis using most inclusive definition* as a function of primary cancer site and target symptomatic bone site

	Univariable			Multivariable		
	Odds ratio	**95% confidence interval**	**p-value**	**Odds ratio**	**95% confidence interval**	**p-value**
Primary cancer site						
Breast	-	-	-	-	-	-
Prostate	1.14	0.67-1.96	0.608	1.01	0.58-1.77	0.965
Leukemia/ lymphoma	3.58	1.39-9.19	0.008	3.09	1.14-8.38	0.026
Lung	1.47	0.94-2.29	0.089	1.60	1.00-2.58	0.051
Other	2.1	1.33-3.32	0.001	2.48	1.52-4.05	<0.001
Target symptomatic bone site						
Spine	-	-	-	-	-	-
Extremity	0.20	0.12-0.31	<0.001	0.18	0.11-0.28	<0.001
Hip/pelvis	0.28	0.19-0.43	<0.001	0.28	0.18-0.43	<0.001
Chest wall	0.36	0.20-0.65	0.001	0.34	0.19-0.64	0.001
Skull	0.51	0.20-1.30	0.157	0.48	0.18-1.23	0.135

* Definition includes the presence of at least one of the following features: prior RT, prior surgery, any facture, any neuraxis compromise, and/or soft tissue component

CHAPTER 4: Improving Providers' Survival Estimates and Selection of Prognosis- and Guidelines-Appropriate Treatment for Patients with Symptomatic Bone Metastases: Development of the BMETS Decision Support Platform

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ABSTRACT

Background: In the management of symptomatic bone metastases, current consensus-based guidelines do not provide clear methodology for selecting palliative radiotherapy (RT) regimens based on specific patient and disease features. Decision support aids may offer an effective means for translating the complex data needed to render individualized treatment decisions. However, there are currently no decision support tools available for use in this setting. Thus, in order to promote selection of evidence-based, individualized palliative RT regimens for patients with bone metastases, we created the BMETS decision support platform (BMETS-DSP). In this chapter, we describe methodology used to develop the BMETS-DSP.

Methods: The theoretical basis used to inform development of the decision aid was the Ottawa Decision Support Framework. First, we used stakeholder input and review of the literature to assess determinants underlying the provider decision. Based on these determinants and iterative stakeholder feedback, we then developed a web-based, provider-facing decision support platform. Consistent with the underlying theoretical framework, our design also included plans for assessing decision quality and decision outcomes. The International Patient Decision Aids Standards (IPDAS) certification checklist was used to evaluate quality of the BMETS-DSP.

Results: Stakeholder input and review of 54 evidence- or consensus-based publications identified the following determinants of the provider decision: estimated patient survival, characteristics of the target symptomatic lesion and the primary cancer type, consideration of alternative intervention strategies, access to patient-specific recommendations, and patient preferences. Based on these determinants, we developed a decision support platform that 1) collects relevant patient-specific data, (2) displays an individualized predicted survival curve and (3) provides case-specific, evidence-based recommendations for radiotherapy (RT), open

surgery, systemic therapy, and hospice referral to aid in the decision-making process. The finalized tool met quality and certification requirements as delineated by the IPDAS checklist.

Conclusions: We describe the successful development of a patient-facing decision support platform to aid in the provision of palliative RT in better alignment with prognosis and other relevant patient features. Assessment of the BMETS-DSP in Chapter 5 will provide insight into the efficacy of the tool in altering aspects of the decision-making process.

INTRODUCTION

As noted in Chapter 1, in the management of symptomatic bone metastases, there is currently no validated means for selecting individualized palliative radiotherapy (RT) regimens that match patient features and preference. While consensus guidelines support use of a range of RT regimens for palliative radiotherapy to symptomatic bone metastases, the source cooperative groups and professional organizations do not provide clear recommendations on how to select between regimens. Moreover, all groups imply the central role of patient prognosis, performance status, and patient preference in the treatment decision, but they provide no dedicated instructions on how to assess or incorporate these factors into the decision-making process[12,59–67].

Decision support aids may provide an effective means for translating complex data regarding individual patients' risks and benefits in order to guide treatment decisions[104]. While a number of decision aids have been proposed or developed in the management of cancer, there are no decision support tools to guide in management of symptomatic bone metastases[105]. Unlike available educational material and consensus guidelines available in this clinical setting, an optimal decision support tool would provide individualized estimates of patient survival time, magnitude of the relative efficacy and risks of available treatment regimens, and assessment of patient preference.

In order to promote selection of palliative RT regimens in better alignment with predicted patient prognosis and best evidence in the management of symptomatic bone metastases, we sought to develop the provider-facing BMETS decision support platform (BMETS-DSP) for use in this patient population. We aimed to design a tool that (1) collects patient-specific demographic, disease, and treatment data, (2) displays an individualized survival curve based on the BMETS model described in Chapter 2, and (3) provides case-specific, evidence-based recommendations for radiotherapy (RT), open

surgery, systemic therapy, and hospice referral to aid in the decision-making process. In this chapter, we describe the underlying conceptual framework, platform components, and steps in the development of the BMETS-DSP.

METHODS

The conceptual framework utilized for the BMETS-DSP is the Ottawa Decision Support Framework to Address Decisional Conflict (ODSF)[30]. Drawing its theoretical basis from general psychology, social psychology, and decision theory, the ODSF is based on concepts of decisional conflict, social support, and expectancy value[106]. This framework was selected due to its appropriateness for the clinical dilemma faced in selection of palliative RT regimens. Such choices are typified by *decisional conflict*, which is the state of uncertainty that arises when making a choice that may involve risk, loss, and regret[106,107]. The authors of the ODSF developed the framework to address health decisions involving such decisional conflict, specifically those that (a) arise from new circumstances or health transitions, (b) require particular consideration due to uncertainty regarding the nature of risks and benefits, and (c) require more effort in the decision-making phase than the implementation phase (i.e., decisions in which there are not clearly delineated or automatic responses[106]. It has been used in over 30 other patient- and provider-facing decision support aids, including several that address cancer-specific questions[108]. Figure 1 shows the three interrelated components of the ODSF[30]:

Functionally, the ODSF is organized into four steps, noted below[106]. The methodological approach performed or planned for the development of the BMETS-DSP is described for each step.

1. **Assessing determinants of the provider decision**.

To identify key determinants of the decision in the selection of appropriate RT regimens, key stakeholders were recruited, including attending and resident physicians in Radiation Oncology, Palliative Care/Medical Oncology, and Orthopedic Surgery. SA interviewed these stakeholders regarding key determinants of the decision-making process and what evidence- or consensus-based resources they rely upon for clinical decision-making when choosing RT regimens for symptomatic bone metastases. A review of the stakeholder-cited resources was then performed. A list of decision-making themes was then synthesized from stakeholder responses and their cited key resources. Lastly, the decision themes identified were again reviewed with these stakeholders for final feedback.

2. **Providing decision support**, **with the goal of preparing the provider and/or patient for the decision-making process and structuring the interaction**.

Based upon the decision-making themes identified, a provider-facing decision support platform was created. As per the ODSF, the goal of the BMETS-DSP was to address modifiable determinants of the decision, particularly those that contribute to decisional conflict and uncertainty[106]. From review of the literature in Chapter 1 and in alignment with the goals of the BMETS model from Chapter 2, we assumed that survival prediction would be a central theme and planned to use the BMETS model for this purpose in the decision support tool. In order to uphold delivery of standard-of-care and evidence-based medicine, we elected to provide educational material of the highest category of evidence available, with clear citations to enable review of the source data by users if desired.

To facilitate data collection needed for the BMETS model, enable it to interface with the electronic medical record, and permit for ease of future distribution, the BMETS-DSP

was created as a web-based platform. All regulatory standards for management of patient protected health information were maintained in the development of the platform.

3. **Evaluating decision quality and facets of the decision-making process**. Informed by the finalized components of the BMETS-DSP, the platform was developed with the expressed intent to create measurable changes to modifiable determinants of the decision-making process. To assess the platform's impact on these determinants, a pilot assessment of the BMETS-DSP was planned. Chapter 5 describes this process.

4. **Evaluating the decision outcome.** In addition to impacting the decision-making process itself, the BMETS-DSP was developed with the goal of potentially changing practice patterns in the realm of palliative bone RT. Thus, the pilot assessment was designed to also capture the impact of the BMETS-DSP on clinical outcomes relevant to the management of symptomatic bone metastases. This is also detailed in Chapter 5.

Following development of a preliminary version of the BMETS-DSP, stakeholder input was once again sought and incorporated regarding formatting, ease of use, and elements included.

Assessing Quality of the BMETS-DSP

To improve and standardize the quality of decision support aids, the International Patient Decision Aids Standards (IPDAS) collaboration developed a checklist of quality criteria for decision-making tools[109]. Based on this list, Joseph-Williams, et. al., created a set of minimum standards based on the most critical components of the checklist in an effort to potentially permit for certification of such tools[110]. A decision support tool meeting all

"qualifying" requirements can be considered for certification, and one meeting all "certification" requirements would be eligible to be certified. As such, the BMETS-DSP was intentionally developed to meet these criteria. To comment on the quality of the BMETS-DSP, we report its adherence to the minimum standards criteria.

RESULTS

Assessing Determinants of the Decision

Stakeholders queried regarding determinants of the decision-making process included attending physicians in Radiation Oncology (N=2), Palliative Care/Medical Oncology (N=1), and Orthopedic Surgery (N=1), as well as resident physicians in Radiation Oncology (N=2). Key resources included the American Society for Radiation Oncology (ASTRO) Guideline on Palliative Radiation Therapy for Bone Metastases[12], the American Society for Clinical Oncology (ASCO) Quality Oncology Practice Initiative (QOPI)[111], the ASCO Patient-Clinician Communication Guideline[112], the Choosing Wisely Campaign[113], the American College of Radiology (ACR) Appropriateness Criteria[114], and National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology[115]. In total, these resources yield 54 separate publications, which were individually assessed. When prior versions were available, only the most recently updated version was considered.

In review of stakeholder responses and the above resources, the following key themes were identified as determinants of the decision-making process:

1. Estimated patient survival time

As per the methodology in Chapter 2, 27 potential predictor covariates were identified from the literature and used to build the BMETS model. Stakeholder feedback

universally cited uncertainty with survival estimates as the primary sources of decisional conflict when selecting appropriate palliative RT regimens. Consideration of prognosis and/or performance status during treatment selection was identified in 9 of the 54 stakeholder-cited resources[12,59–62,67,103,112,113,116–118].

2. Characteristics of the target symptomatic bone metastasis

As described in Chapter 3, the presence of possible "complicating" features including prior surgery, prior RT, fracture, neuraxis compromise, and soft tissue component are associated with either exclusion from randomized trials of different palliative RT regimens or differential recommendations from consensus groups. Stakeholders also cited this factor as a key cause of decisional conflict when choosing among palliative RT regimens. Five stakeholder-cited resources recommended potential alteration of fractionation on the basis of the treatment site, particularly for spine and other critical sites including weight-bearing long bones[12,59–62].

3. Characteristics of primary cancer type

Guidelines' recommendations may vary by histology, particularly for tumor types deemed to be radioresistant or radiosensitive. In particular, review of the stakeholder-cited resources found histology-specific recommendations for palliative RT fractionation in 15 publications, including for cervical cancer[119], kidney cancer[120], mesothelioma[63], B-cell lymphoma[64], non-small cell lung cancer[65], small cell lung cancer[121], prostate cancer[66], soft tissue sarcomas[122], gastrointestinal stromal tumors[122], and thymic carcinoma[67], as well as "radioresistant" tumor types in general[12,59–62].

4. Consideration of alternate non-RT interventions

Stakeholder-cited resources noted that some subsets of patients may benefit from other interventions including surgery, systemic therapy, and hospice referral, either in place or in addition to RT[12,59–62]. Although not specifically mentioned by stakeholders, information regarding alternative options is felt to be a key component per the ODSF[106].

5. Access to patient-specific recommendations

Stakeholders also reported the need for individualized recommendations that matched a specific patient's demographic, disease, and treatment characteristics. This is aligned with the ODSF's providing "tailored information" to improve the decision-making process[106].

6. Patient preferences

Stakeholders reported consideration of patients' attitudes toward factors including cost, time, fraction of remaining life spent in treatment, and travel when selecting palliative RT regimens. Notably, decision-making on the basis of patient preference was not specifically referenced in the stakeholder-cited resources. This determinant is out of the scope of the current decision support tool but will be addressed in future phases of BMETS-DSP development (see Chapter 6).

Development of the Decision Support Platform

The web-based, provider-facing BMETS-DSP was designed to be utilized before or during consultation with a patient with symptomatic bone metastases. It is self-administered and self-paced. The BMETS-DSP is comprised of 3 components, each developed to address the determinants of the decision process listed above (1-5).

1. **Data entry**

Given the primacy placed on individualized recommendations based on a patient's prognosis and demographic and disease features, a web-based data collection platform was created. In addition to the 27 covariates required for the BMETS survival model, additional features felt to be critical to the decision are also entered: specific histology information (as per the stakeholder-cited resources—cervical cancer, kidney cancer, mesothelioma, B-cell lymphoma, non-small cell lung cancer, small cell lung cancer,

prostate cancer, soft tissue sarcomas[122], gastrointestinal stromal tumors[122], thymic carcinoma, and colorectal carcinoma), prior RT at the target site, features of neuraxis compromise, presence of soft tissue component, and weight-bearing bone status.

For internal users, the BMETS-DSP can be accessed through our department clinical web page, where it interfaces with the electronic medical record. As such, up to 50% of the BMETS model covariates can be pre-populated, and responses entered using the department clinical web page are saved into a prospective BMETS database. For external users, the BMETS-DSP will not save any data entered in order to maintain protection of health information. Data entry time is estimated at less than 1 minute for experienced users and less than 2 minutes for novice users.

2. Predicted survival time following consultation

Values of covariates entered that inform the BMETS survival model are used to create a survival curve. As described in Chapter 2, the survival curve is interactive, displaying probability of survival at various times from consultation. For comparison purposes only, the predicted survival curves for all patients included in the BMETS model are displayed behind the patient's survival curve to provide a relative measure of survival as compared to other patients with symptomatic bone metastases.

3. Individualized treatment recommendations

In order to provide individualized treatment options across a breadth of interventions, best evidence and consensus statements appropriate for patient characteristics (demographic, disease, and treatment) and median survival time (as estimated by the BMETS survival model) were provided. Recommendations were arranged according to the following potential interventions: (a) discussion of prognosis, (b) open surgery, (c) RT, (d) systemic therapy, and (e) hospice referral. Although "discussion of prognosis" was not cited as a determinant of the decision-making process, it was included due to its

status as an element of best practice[112] and as a means for future measurement of the impact of the DSP. Because the focus of the clinical question surrounds selection of appropriate RT regimens, the most detailed evidence-based information was provided for the RT intervention. Conversely, the inclusion of recommendations for open surgery, systemic therapy, and hospice referral was done in order to provide an appropriate range of alternatives to RT. We did not intend for the BMETS-DSP to permit for detailed decision-making within the context of these other interventions.

Output was individualized on the basis of values for specific variables from the data entry phase (i.e., histology, features of neuraxis compromise, etc.). Table 1 shows the evidence- or consensus-based output and source populated when the value of a given variable is selected on the data entry page. The default recommendation for each intervention is also listed, with factors that trigger a change to the alternate recommendation listed in blue. For the RT intervention, recommendations were categorized into three groups: consideration of shorter fraction, multiple-fraction, or a range of fractionation options. The “shorter fraction” option was specifically selected for predicted survival less than 3 months, whereas the “multiple fraction” regimen was selected for patients with prior surgery or non-spine fracture on the basis of available literature. Uncertainty regarding the definition of what constitutes a “complicated” lesion was emphasized when applicable, as per Chapter 3.

Figure 2 shows the sample output based on data entry for a case patient. Alternatively, pending peer review and publication, a demo can be accessed at: https://nomogram-demo.alcorn.dayflower.io/ Although the data entry cannot be altered in this demo, the survival curve is interactive.

Quality of the BMETS-DSP

Table 2 shows performance of the BMETS-DSP as per the minimum standard of quality required by the IPDAS collaborative group. With the exception of components that are not applicable for the population or aim of the BMETS-DSP, all qualifying and certification criteria are met.

DISCUSSION

Following the Ottawa Decision Support Framework, we developed a provider-facing decision support platform aimed at promoting selection of palliative RT regimens in better alignment with predicted patient prognosis and best evidence in the management of symptomatic bone metastases. To our knowledge, the BMETS-DSP is the first of its kind in oncology to incorporate an individualized patient survival prediction as well as evidence-based treatment recommendations specifically matched to patient features.

Several design elements of the BMETS-DSP reflect our dedicated attempts to optimize its clinical utility by circumventing a number of barriers to implementation cited in the literature. The web-based design was selected to provide answers in real-time, addressing issues faced when there is time lag or multiple steps required to access recommendations[123]. Since web-based access alone is insufficient to ensure its use[124], the BMETS-DSP was created to interface with our departmental clinical web page. Because providers used this clinical web page for a number of critical functions in a typical clinic day, its position on this web page means that the BMETS-DSP is poised for use as part of standard clinical workflow[123]. Up to half of the covariates from the BMETS

survival model can be populated directly from the electronic medical record into the data collection page, further avoiding problematic workflow obstruction[125].

Another strength of our tool is that it was developed with the expressed intention to improve clinically relevant and measurable outcomes. While assessments of decision aids often evaluate the impact of the tool on measures of the decision-making process, few tools comment on efficacy in the clinical setting or measure decision outcomes[32]. As noted by authors of the ODSF, it is critical to distinguish measurement of decision quality from decision outcomes; whereas the decision-making process may be optimized to improve participants' satisfaction, this feature may be independent from the actual clinical outcome[106].

One limitation of our design is that in its current incarnation, there is no direct input from patients regarding their preferences in the decision-making process. Indeed, whereas many decision support tools are patient-facing[108], we elected to start with a provider-facing component. Primarily this was a functional decision, since assessing the clinical efficacy of the BMETS-DSP would first require stakeholder buy-in from the perspective of the physician given the potentially sensitive subject matter. There was concern that providers might feel ill at ease with presenting survival estimates to patients if the tool was not first validated from the provider perspective. Second, given the sensitive nature of survival predictions, a patient-facing tool could pose ethical concerns if used by patients without provider input[126]. However, we did attempt to include a shared decision-making element in our design by encouraging discussion of prognosis among recommended interventions.

Moreover, evidence from the ODSF suggests that intervention at the level of the provider may be particularly important for aligning decisional conflict scores between patients and providers. In one pre-post assessment of the ODSF performed with 120

physicians and 903 patients, there was less dissimilarity in both patient and providers' decision conflict scores after ODSF implementation, with much of the variance in the outcome explained by physician scores[127]. While next steps in development of the decision tool will likely involve a patient-facing component, these data support our decision to emphasize a provider-facing aspect as well.

An additional limitation of the tool is that concrete and specific recommendations cannot be rendered for a sizable portion of patients. As demonstrated by our efforts in Chapter 3, available evidence- and consensus-based recommendations addressing this clinical question are complex, ill-defined, and do not provide instructions for selecting between available regimens. Consequently, our recommendations for radiotherapy fell within 3 relatively broad, overlapping categories: consideration of shorter fraction, multiple fraction, or a range of fractionation options. Whether these categories offer enough direction to alter practice patterns is the subject of the BMETS-DSP assessment discussed in Chapter 5.

Some may also criticize the decision to use 3 months as the cut point for recommending shorter fraction radiotherapy. This time point was selected because durability of single-fraction palliative RT from randomized trials is generally measured at 4-7 months. As such, the group of patients with survival time <3 months are unlikely to benefit from additional durability afforded by multiple-fraction RT. Moreover, 3 months is the median survival time of patients included in two recent trials of shorter fraction palliative radiation in the setting of symptomatic spinal cord compression[7,8]. Given that these studies showed adequacy of shorter treatment in the setting of complicated lesions posing substantial risk of morbidity, we felt that this served as reasonable justification for use of 3 months as a cutoff across a breadth of disease features. Although it is not codified in consensus guidelines, it is noted that other authors in the field have cited the 3-month time point as a threshold for using shorter fractionation

regimens as well[24,128,129].

As per the ODSF, development of an optimized decision support tool requires dedicated testing of its efficacy prior to broader implementation. In Chapter 5, we will assess the impact of the BMETS-DSP on providers' estimates of patient survival, their confidence in and willingness to share these prognoses with patients, and whether the tool improves delivery of palliative RT in better alignment with patient-specific factors including survival time.

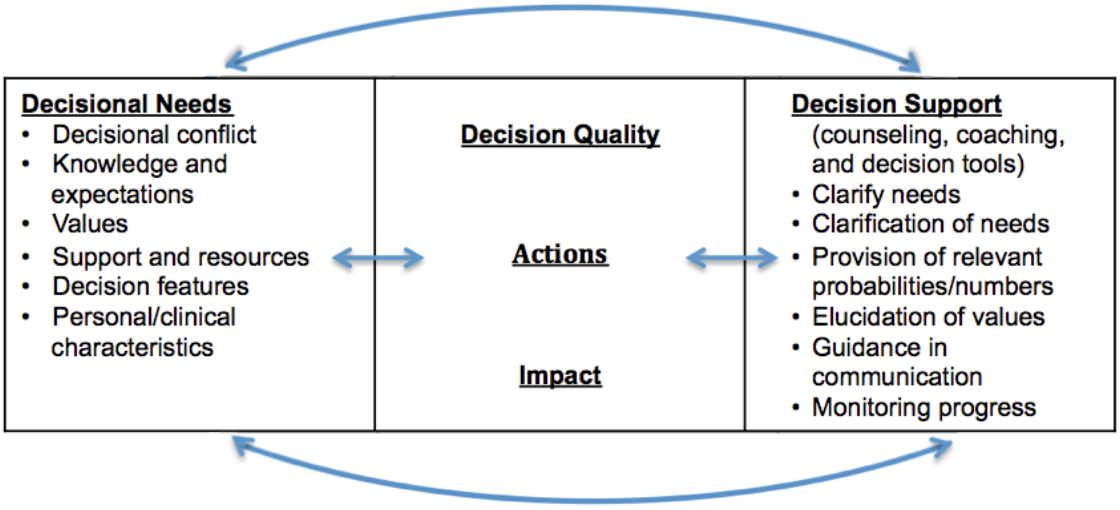


Figure 1: Three interrelated components of the Ottawa Decision Support Framework.
Adapted from O'Connor, et. al.[30]

Table 1: Evidence- or consensus-based output populated into the BMETS Decision Support Platform (BMETS-DSP) for each patient-specific value listed across interventions of (a) discussion of prognosis, (b) open surgery, (c) radiotherapy, (d) cancer-directed systemic therapy, and (e) hospice referral

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
(a) Discussion of prognosis			**Default: Recommend ed in all**
(all)	Prognosis should be discussed early in the course of terminal illness, ideally within 1 month of diagnosis with the terminal illness.	ASCO Patient-Clinician[112]	-
(b) Open surgery			**Default: No definite contraindica -tion**
Spine	Open surgery is recommended, except in the presence of the following contraindications to surgery: • **Hematologic tumors** (i.e., leukemia, lymphoma, myeloma) • Life expectancy **<3 months** • Paraplegia for >24 hours Vertebral augmentation (i.e., kyphoplasty, vertebroplasty) can also be used (not evaluated in the current assessment, since it is not an open surgical procedure).	NCCN CNS[62]	**Possible contraindica -tion**
Extremity-Femur	Open surgery is contraindicated for life expectancy **< 2 weeks**.	Institutional [+]	**Possible contraindica -tion**
Extremity-Other	Open surgery is contraindicated for life expectancy **< 1.5 months**.	Institutional [+]	**Possible contraindica -tion**

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
Hip/Pelvis-Hip	Open surgery is contraindicated for life expectancy **< 2 weeks**.	Institutional+	**Possible contraindica-tion**
Hip/Pelvis-Pelvis	Open surgery is contraindicated for life expectancy **< 2 months**.	Institutional+	**Possible contraindica-tion**
Chest wall	Open surgery is contraindicated for life expectancy **< 2 months**.	Institutional+	**Possible contraindica-tion**
Skull	Open surgery is contraindicated for life expectancy **< 2 months**.	Institutional+	**Possible contraindica-tion**
(c) Radiotherapy			**Default: Consider a range of radiotherapy regimens**
(all)	Palliative radiotherapy for bone metastases can be considered in patients with life expectancy greater than days to weeks.	NCCN Palliative Care[130]	-
Uncomplicated+-(all)	High-quality data demonstrate that 30 Gy/10 fractions, 20 Gy/5 fractions, and 8 Gy/1 fraction provide equivalent pain control for uncomplicated** _____ sites. 8 Gy x 1 optimizes convenience but is associated with a higher retreatment rate. Evidence of higher risk of fracture with 8 Gy/1 fraction is equivocal. Treatment in >10 fractions may be appropriate in select cases [*survival ≥ 3months*]. ** "Uncomplicated" metastases are painful lesions unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Presence of these features generally led to exclusion from trials comparing single versus multiple fraction radiotherapy.	ASTRO[12]; ACR Non-Spine[59]; Cheon[68]	-

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
Uncomplicated+-skull or femur	High-quality data demonstrate that 30 Gy/10 fractions, 20 Gy/5 fractions, and 8 Gy/1 fraction provide equivalent pain control for uncomplicated** _____ sites. Although more convenient for patients, 8 Gy/1 fraction is associated with higher retreatment rates. Evidence of higher risk of fracture with 8 Gy/1 fraction is equivocal. Given that the _____ may be considered critical site, 8 Gy/1 fraction to uncomplicated _____ sites may be most appropriate for patients with limited life expectancy. Treatment in >10 fractions may be appropriate in select cases [*survival ≥3 months*] ** "Uncomplicated" metastases are painful lesions unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Presence of these features generally led to exclusion from trials comparing single versus multiple fraction radiotherapy.	ASTRO[12]; ACR Non-Spine[59]; Cheon[68]	-
Uncomplicated+-spine	High-quality data demonstrate that 30 Gy/10 fractions, 20 Gy/5 fractions, and 8 Gy/1 fraction provide equivalent pain control for uncomplicated** _____ sites. Although more convenient for patients, 8 Gy/1 fraction is associated with higher retreatment rates. Evidence of higher risk of fracture with 8 Gy/1 fraction is equivocal. Given that the _____ may be considered critical site, 8 Gy/1 fraction to uncomplicated _____ sites may be most appropriate for patients with life expectancy ≤ 6 months. Treatment in >10 fractions may be appropriate in select cases [*survival ≥3 months].* ** "Uncomplicated" metastases are painful lesions unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Presence of these features generally led to exclusion from trials comparing single versus multiple fraction radiotherapy.	ASTRO[12]; ACR[60]; NCCN CNS[62]; Cheon[68]	-

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
Fracture-spine	There is no consensus statement regarding optimal fractionation for spine sites with fracture. It is unclear if spine sites with fracture were included in trials of single versus multiple fraction radiotherapy**. Thus, there may be insufficient evidence to support routine use of 8 Gy/1 fraction in this setting. **Trials comparing single versus multiple fraction radiotherapy were inconsistent in definitions of fracture, with some excluding and some including vertebral body collapse or fracture under this definition.	ASTRO[12]; Cheon[68]	-
Fracture-extremity, hip/pelvis, chest wall, skull	There is no consensus statement regarding optimal fractionation for _____ with fracture. Such complicated** hip/pelvis sites were likely excluded from trials comparing single versus multiple fraction radiotherapy. Thus, there may be insufficient evidence to support routine use of 8 Gy/1 fraction in this setting. ** “Uncomplicated” metastases are painful lesions unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Presence of these features generally led to exclusion from trials comparing single versus multiple fraction radiotherapy.	ASTRO[12]; Cheon[68]	-
Postoperative-spine	There is little evidence to guide in treatment selection in the postoperative setting. Such postoperative patients were generally excluded from trials comparing single versus multiple fraction radiotherapy. Thus, there may be insufficient evidence to support routine use of 8 Gy/1 fraction in this setting. Per ACR guidelines for postoperative spine sites, 30 Gy/10 fractions (preferred for good prognosis, which is not defined in the guidelines), 20 Gy/5 fractions, and use of >10 fractions are usually appropriate. 8 Gy/1 fraction may be appropriate in select cases.	Cheon[68]; ACR Spine[60]; ACR MESCC[61]	-

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
Postoperative-non-spine	There is little evidence to guide in treatment selection in the postoperative setting. Such postoperative patients were generally excluded from trials comparing single versus multiple fraction radiotherapy. Thus, there may be insufficient evidence to support routine use of 8 Gy/1 fraction in this setting. Per ACR guidelines for postoperative ____sites, 30 Gy/10 fractions is usually appropriate (particularly for good prognosis, which is not defined in the guidelines), whereas 20 Gy/5 fractions and 8 Gy/1 fraction may be appropriate in select cases.	Cheon[68]; ACR Non-spine[59]	-
SBRT [inserted addition to the above for all cases]			
SBRT- no modifier	Regarding SBRT, guidelines cite insufficient evidence to support the routine use of stereotactic radiotherapy in this setting, outside of oligometastatic disease, clinical trial, or registry research.	ASTRO[12]; ACR Non-spine[59]	-
Other RT modifying factors [inserted in addition to above when applicable]			
Life expectancy <3 months	-		**Consider shorter fractionation radiotherapy**
Postoperative and/or non-spine fracture	-	ACR Non-Spine, ACR Spine[59,60]	**Consider multiple fraction radiotherapy**

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
Soft tissue component	**"Uncomplicated" metastases are painful lesions unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Presence of these features generally led to exclusion from trials comparing single versus multiple fraction radiotherapy. Soft tissue component was not used as an exclusion criterion in any these trials and is thus not considered a definite "complicating" factor.	Cheon[68]	-
Neuraxis compromise‡ - survival ≥6 months	It is unclear if _____ features were included in trials of single versus multiple fraction radiotherapy**. Thus, there may be insufficient evidence to support routine use of 8 Gy/1 fraction in this setting. **Trials comparing single versus multiple fraction radiotherapy generally excluded patients with existing "spinal cord or cauda equina compression." However, the definitions of "spinal cord or cauda equina compression" were generally not provided, and a minority of trials required radiologic confirmation of these findings.	Cheon[68]	-
Neuraxis compromise‡ - survival <6 months	It is unclear if _____ features were included in trials of single versus multiple fraction radiotherapy**. Thus, there may be insufficient evidence to support routine use of 8 Gy/1 fraction in this setting. However, extrapolating early evidence from randomized trials for spinal cord compression in patients with life expectancy <3-6 months, 20 Gy/5 fractions may be non-inferior to 30 Gy/10 fractions, and 8 Gy/1 fraction may possibly be non-inferior to 20 Gy/10 fractions (data in abstract form only). **Trials comparing single versus multiple fraction radiotherapy generally excluded patients with existing "spinal cord or cauda equina compression." However, the definitions of "spinal cord or cauda equina compression" were generally not provided, and a minority of trials required radiologic confirmation of these findings.	SCORE-2[7]; SCORAD III[8]	-
SBRT-spine with fracture	There is no consensus statement regarding stereotactic radiotherapy in this setting of spine sites with fracture in the non-operative setting.	NCCN CNS	-

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
SBRT-spine, postoperative	Per ACR and NCCN guidelines, postoperative spine stereotactic radiotherapy may be appropriate in select cases, such as oligometastatic disease. However, other guidelines cite insufficient evidence to support the routine use of stereotactic radiotherapy in this setting, outside of clinical trial or registry research.	ACR Spine[60]; NCCN CNS[62]; ASTRO[12]	-
Spine, KPS<60	Stereotactic radiotherapy is generally contraindicated for KPS<60.	Spinal SBRT Guidelines[131]	-
SBRT- renal cell, melanoma, sarcoma, hepatocellular, colorectal, non-small cell lung	Per NCCN guidelines, stereotactic radiotherapy can be considered if cancer is oligometastatic and/or radioresistant (including renal cell, melanoma, sarcoma, hepatocellular, and some colorectal and non-small cell lung cancer cases).	NCCN CNS[62]	-
SBRT-cervical cancer	Per NCCN guidelines, aggressive local therapy can be considered for oligometastasis to bone, nodes, lung, or liver from cervical cancer.	NCCN Cervical[119]	-
SBRT-kidney cancer	Per NCCN guidelines, surgical resection or ablative techniques can be directed to sites of oligometastasis from kidney cancer.	NCCN Kidney[120]	-
SBRT-soft tissue sarcoma	Per NCCN guidelines, metastasis to a single organ with limited bulk that are amendable to local therapy: • Metastasectomy +/- neoadjuvant or postoperative radiotherapy • Stereotactic radiotherapy	NCCN Soft tissue sarcoma[122]	-
SBRT-thymic carcinoma	Per NCCN guidelines, stereotactic radiotherapy may be appropriate for limited focal metastases, and conventional radiotherapy may be preferred for larger metastases.	NCCN Thymoma and thymic carcinoma[67]	-
SBRT-thyroid cancer	Per NCCN guidelines, external beam radiotherapy or stereotactic radiotherapy cab be considered to iodine-resistant symptomatic metastatic sites.	NCCN Thyroid[132]	-

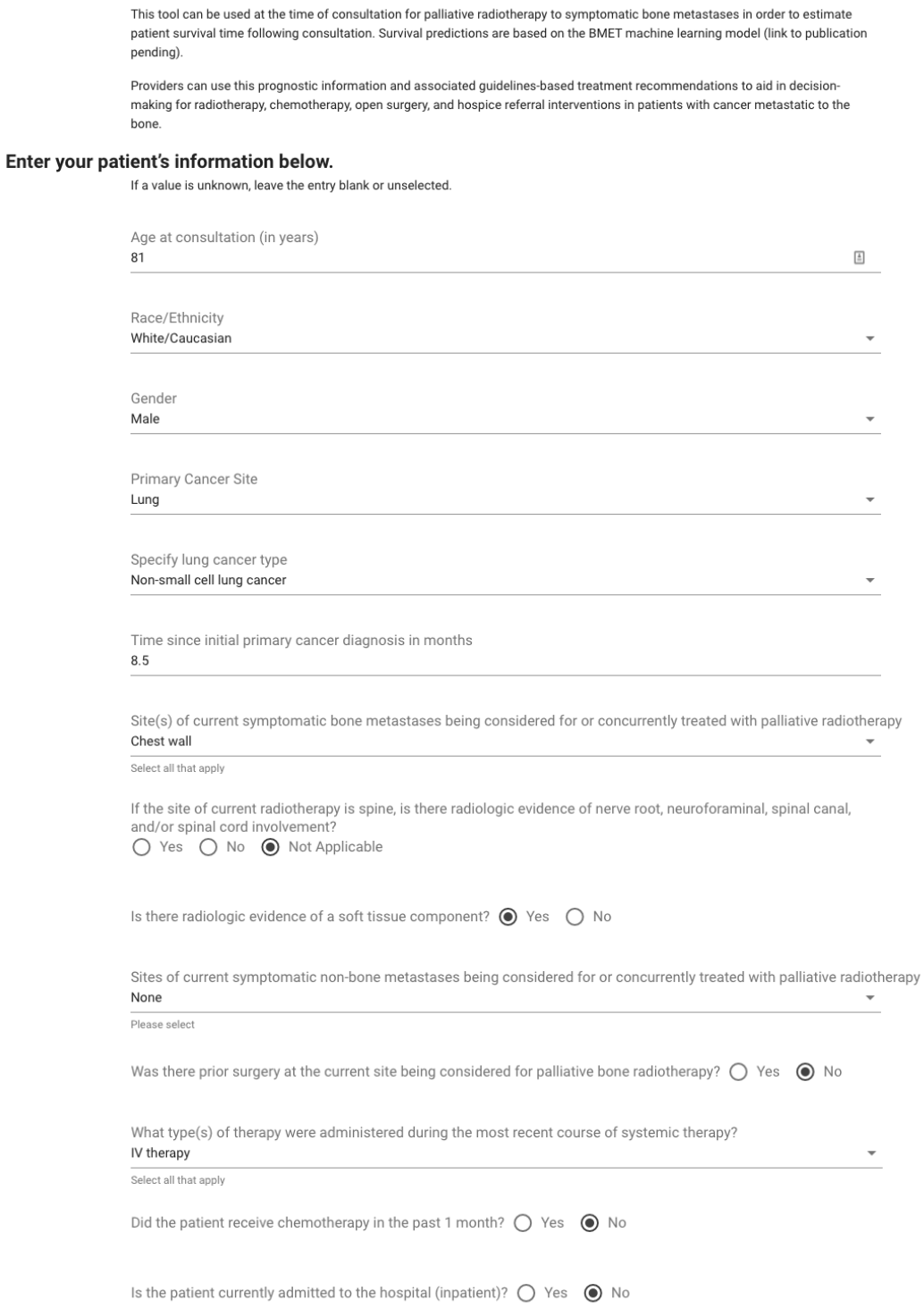
Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
B-cell lymphoma	Per NCCN guidelines, bone lesions from follicular, marginal zone, and mantle cell lymphoma can be treated in 4 Gy/1-2 fractions; doses up to 30 Gy may be appropriate in select circumstances; lesions from diffuse large B-cell lymphoma can be treated in 24-30 Gy	NCCN B-cell Lymphoma[64]	-
Non-small cell lung cancer-KPS<70	Per NCCN non-small cell lung cancer guidelines, 8 Gy/ 1 fraction or 20 Gy/5 fractions is recommended for any bone metastasis in patients with poor performance status (likely corresponds to KPS < 70).	NCCN Non-small cell lung cancer[65]	-
Non-small cell lung cancer-soft tissue component	Per NCCN non-small cell lung cancer guidelines, 20 Gy/5 fractions or 30 Gy/10 fractions are recommended for bone metastases with soft tissue mass.	NCCN Non-small cell lung cancer[65]	-
Non-small cell lung cancer- no soft tissue component	Per NCCN non-small cell lung cancer guidelines, 8 Gy/1 fraction, 20 Gy/5 fractions, or 30 Gy/10 fractions are recommended for bone metastases without soft tissue mass.	NCCN Non-small cell lung cancer[65]	-
Mesothelioma-chest wall	Per NCCN guidelines, pain from chest wall involvement should be treated in 20-40 Gy in $\geq$ 4 Gy fractions delivered in 1-2 weeks or in 30 Gy/10 fractions	NCCN Mesothelioma [63]	-
Mesothelioma-non-chest wall	Per NCCN guidelines, pain from non-chest wall bone metastases should be treated in 30 Gy/10 fractions	NCCN Mesothelioma [63]	-
Prostate cancer	Per NCCN guidelines, Strontium-89 or Samarium-153 can be administered for widespread bone metastases, with or without focal external beam radiotherapy.	NCCN Prostate[66]	-
Thymic carcinoma	Per NCCN guidelines, symptomatic lesions can be treated with 8 Gy/1 fraction, 20 Gy/5 fractions, 30 Gy/ 10 fractions, or definitive doses can be considered in the case of limited metastases.	NCCN Thymoma and thymic carcinoma[67]	-

Variable value	Evidenced- or consensus-based output	Source	Default or triggered recommend-ation*
Thyroid cancer	Per NCCN guidelines, metastases can be treated with radioactive iodine if not previously delivered. Suppression of TSH with levothyroxine can be started or continued.	NCCN Thyroid[132]	-
(d) Cancer-directed systemic therapy			**Default: No definite contraindica-tion**
(all)	Cancer-directed therapy should no be continued or initiated in patients with **either** of the following: • Solid tumors and low performance status (ECOG PS 3 or 4, corresponding to **KPS <50**). Exceptions include: those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy • Life expectancy **< 2 weeks**	Choosing Wisely[113]; ASCO QOPI[118]	**Possible contraindica-tion**
Hospice referral discussion			**Default: No definite contraindica-tion**
(all)	Hospice referral is recommended for patients with life expectancy **<6 months**.	Hospice Referral Eligibility[133]	**Possible contraindica-tion**

Lines marked in italics (e.g., *survival ≥3 months*) are only populated when italicized content is true.
Note: publications by Cheon, Jabbari, and Howell, as well as SCORE-2 and SCORAD III trials were not part of the 54 stakeholder-cited resources but were included due to citation by at least one of these resources
* Presence of blue text prompts recommendation header to change as indicated
⁺ No consensus-based data is available. As such, these recommendations are based on institutional practices only.
‡ Neuraxis compromise includes central canal or neuroforaminal stenosis, with or without cord edema or associated neurological symptoms
** Uncomplicated as defined per Cheon, et. al.[68]
ACR=American College of Radiology, ASCO=American Society of Clinical Oncology, ASTRO=American Society for Radiation Oncology, ECOG PS= Eastern Cooperative Oncology Group Performance Status, KPS= Karnofsky Performance Status, MESCC= malignant epidural spinal cord compression, NCCN=National Comprehensive Cancer Network, SBRT= stereotactic radiotherapy, QOPI= Quality Oncology Practice Initiative

Figure 2: A demonstration of the BMETS Decision Support Platform (BMETS-DSP) based on a sample patient

Example data entry and display for the BMET Decision Support Platform, to be published on Oncospace (Johns Hopkins Department of Radiation Oncology), pending peer review and publication.



Is the patient currently taking opioid pain medication? (•) Yes ( ) No

Is the patient currently taking steroid medication? ( ) Yes (•) No

Does the patient report weight loss in the past 6 months? ( ) Yes (•) No

What is the Karnofksy Performance Status (KPS) for the patient?
50

Select all radiologically-confirmed sites of metastases other than the current site(s) of palliative bone radiotherapy
Lung, Lymph node(s)

Select all that apply

Most recent lab values, within the prior 6 weeks:

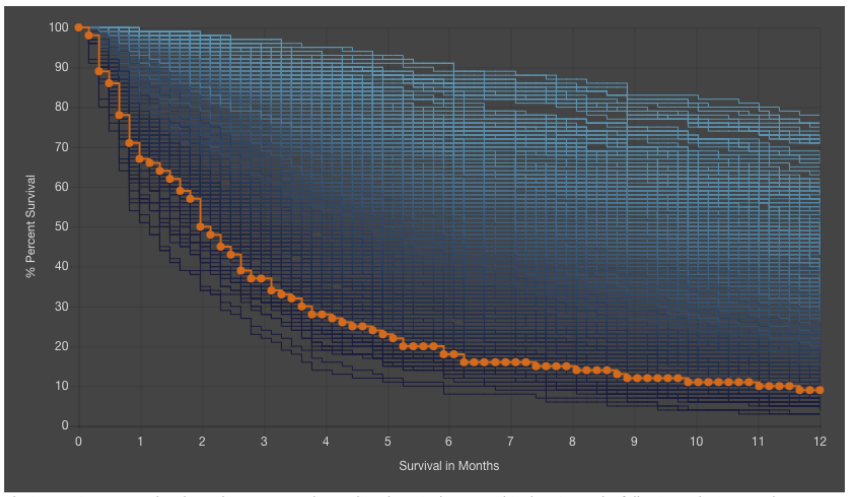
White blood cell count
7300

(cells/cubic mm)

Lymphocyte count
3200

(cells/cubic mm)

Predicted Survival Curve



The interactive orange plot above demonstrates the predicted survival curve within the 12 months following radiation oncology consultation for the specific patient based on the characteristics selected above. The blue curves demonstrate the predicted survival for all other patients with symptomatic bone metastases in the BMET database, arranged from lowest (dark blue) to highest (light blue) predicted survival. These blue curves are displayed for comparison purposes only.

NOTE: Both the plot displaying the patient's predicted survival and the consensus-based recommendations below reflect a **predicted** value from the BMET model. While the model is calibrated to be as accurate as possible across all patients, the predicted survival time may underestimate or overestimate an individual patient's actual survival time.

Treatment recommendations for a predicted median survival of 2.0 months.

	Source
Discussion of prognosis: Recommended	
Prognosis should be discussed early in the course of terminal illness, ideally within 1 month of diagnosis with the terminal illness.	ASCO Patient-Clinician Communication Consensus Guidelines 2017

Radiotherapy: Consider shorter fractionation radiotherapy

Palliative radiotherapy for bone metastases can be considered in patients with **life expectancy greater than days to weeks.**	NCCN Palliative Care Guidelines V2.2019
High-quality data demonstrate that 30 Gy/10 fractions, 20 Gy/5 fractions, and 8 Gy/1 fraction provide equivalent pain control for **uncomplicated** chest wall sites** . 8 Gy/1 fraction optimizes convenience but is associated with a higher retreatment rate.	ASTRO Bone Metastasis Guidelines 2017 , ACR Appropriateness Criteria None-spine Bone Metastases 2015
Per NCCN **non-small cell lung cancer** guidelines, 8 Gy/1 fraction or 20 Gy/5 fractions is recommended for **any bone metastasis** in patients with poor performance status (likely corresponds to **KPS < 70**).	NCCN Non-Small Cell Lung Cancer Guidelines V3.2019
Stereotactic radiotherapy would not usually be appropriate in this setting.	ACR Appropriateness Criteria None-spine Bone Metastases 2015
** "Uncomplicated" metastases are painful lesions unassociated with impending or existing pathologic fracture or existing spinal cord or cauda equina compression. Presence of these features generally led to exclusion from trials comparing single versus multiple fraction radiotherapy. **Soft tissue component** was not used as an exclusion criterion in any these trials and is thus not considered a definite "complicating" factor.	Definition of Uncomplicated Bone Metastasis 2015

Open surgery: No definite contraindication

Open surgery to **chest wall sites** is contraindicated for life expectancy <2 months.	Institutional practices

Cancer-directed systemic therapy: No definite contraindication

Cancer-directed therapy should no be continued or initiated in patients with **either** of the following: · Solid tumors and low performance status (ECOG 3 or 4, corresponding to KPS <50). Exceptions include: those with disease characteristics (e.g., mutations) that suggest a high likelihood of response to therapy	ASCO Choosing Wisely Consensus Recommendations 2013
· Life expectancy ≤ 2 weeks	ASCO Quality Oncology Practice Initiatives 2018

Hospice referral discussion: No definite contraindication

Hospice referral is recommended for patients with **life expectancy ≤6 months.**	Hospice Referral Eligibility 2016

Table 2: Performance of the BMETS Decision Support Platform (BMETS-DSP) at meeting features required for a minimum standard of quality as per the International Patient Decision Aids Standards*

	Section of BMETS-DSP addressing specific criteria
Qualifying criteria	
"Describes health condition or problem for which index decision is required"	Introduction section
"Explicitly states decision under consideration (index decision)"	Introduction section
"Describes the options available for the index decision"	Treatment Recommendations section
"Describes the positive features of each option"	Treatment Recommendations section
"Describes the negative features of each option"	Treatment Recommendations section
"Describes the features of options to help patients imagine the physical, social and/or psychological effects"	N/A; provider-facing tool
Certification criteria	
"Shows positive and negative features of options with equal detail"	Treatment Recommendations section
"Provides information about the funding source used for development"	Funding Source section
"Provides citations to the evidence selected"	Treatment Recommendations s
"Provides a production or publication date"	Publication Date section
"Provides information about update policy"	Update Date section (when applicable)
"Provides information about the level of uncertainty around outcome probabilities"	Treatment Recommendations section
"Describes what the test is designed to measure"	N/A
"Describes next steps taken if test detects a condition/problem"	N/A
"Describes next steps if no condition/problem detected"	N/A
"Describes consequences of detection that would not have caused problems if the screen was not done"	N/A
*Adapted from Durand, et. al.[134] N/A= not applicable	

CHAPTER 5: Evaluation of the Clinical Utility of the BMETS Decision Support Platform: A Case-Based Pilot Assessment

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ABSTRACT

Background: To improve selection of appropriate palliative radiotherapy regimens in patients with symptomatic bone metastases, we developed the BMETS Decision Support Platform (BMETS-DSP). This decision support aid displays a patient-specific predicted survival curve and provides case-specific, evidence-based recommendations for RT, open surgery, systemic therapy, and hospice referral for use in this patient population. In the present study, we conducted a pilot assessment of the clinical utility of the BMETS-DSP using a pre-post design in a simulated clinical environment.

Methods: Five trainee and 5 attending physicians in Radiation Oncology participated in the BMETS-DSP assessment. A total of 55 patient cases were randomly selected from the 397 patients used to build the BMETS model; each predicted survival curve displayed as part of the DSP was refitted leaving the case patient out. Relevant case data including BMETS covariates were summarized and presented to physicians at 2 times: without and then with use of the BMETS-DSP (separated by a 3- to 4-week washout). At each time, physicians were asked to estimate patient survival in the 12 months following radiotherapy consultation; their confidence in and likelihood of sharing this estimate with the patient (increasing 1-10 scales); recommendations for open surgery, systemic therapy, and hospice referral; and preferred radiotherapy regimen (0, 1, 5, 10, or >10 conventional fractions or stereotactic radiotherapy). Wilcoxon signed-rank test evaluated paired survival estimates and rating scales, and McNemar's test compared accuracy of survival estimates at clinically relevant binary time points.

Results: Assessment completion rate was 96%. Pre- vs. post-DSP, physicians' estimates of survival were mean 7.9 (SD 3.6) vs. 6.9 (SD 3.7) months, respectively, $p<0.001$. There was a significant reduction in overestimation of true minus estimated

survival time, with a mean difference of -2.1 (SD 4.1) vs. -1 month (SD 3.5), p<0.001. This improvement was observed across training level. Accuracy of survival prediction was significantly improved at clinically relevant binary time points of <3 (72 vs. 79%, p<0.001), ≤6 (64 vs. 71%, p=0.007), and ≥12 months (70 vs. 81%, p<0.001). Median ratings of confidence in and likelihood of sharing prognosis each increased from 6 to 8, both p<0.001. There was greater concordance in matching use of 1-fraction RT with true survival <3 months (70 vs. 76%, p=0.001) and <10 fraction RT with true survival <12 months (55 vs. 62%, p=0.006). There was also greater concordance in matching use of open surgery when not contraindicated by survival time (47% vs. 53%, p=0.022). There was no significant improvement in appropriate selection of hospice referral or systemic therapy.

Conclusions: In this pilot study, use of the BMETS-DSP significantly improved physician accuracy in estimating survival and increased prognostic confidence, likelihood of sharing prognosis, and use of prognosis-appropriate RT regimens in the care of symptomatic bone metastases. These preliminary data support future multi-institutional validation of the BMETS-DSP.

INTRODUCTION

In the management of symptomatic bone metastases, selection of appropriate palliative radiotherapy (RT) regimens would ideally be based on patient-specific characteristics including estimated survival. Yet as detailed in the previous chapters, provider estimates of patient survival are notoriously inaccurate and overoptimistic[135]. Moreover, available evidence-based and consensus guidelines do not provide clear criteria for selecting between the range of palliative RT regimens[12,114,115]. To address these issues, in Chapter 4, we described development of the provider-facing BMETS Decision Support Platform (BMETS-DSP), which (1) collects patient-specific characteristics critical to the treatment selection, (2) displays a patient-specific predicted survival curve based on the BMETS survival model described in Chapter 2, and (3) provides case-specific, evidence-based recommendations for RT, open surgery, systemic therapy, and hospice referral in the care of symptomatic bone metastases.

While a range of decision support aids have been described in the literature, fewer have undergone dedicated assessment of efficacy in the clinical setting[105]. In accordance with standards delineated by the International Patient Decision Aids Standards (IPDAS) Collaboration, a dedicated assessment of such tools is a required metric of decision aid quality[110]. However, features of an optimal decision aid assessment were not provided. An interesting approach to piloting a decision support tool was performed at our institution by Cheng, et. al.[136]. The authors sought to assess whether a model for predicting weight loss would improve providers' estimates of this outcome in the management of patients with head and neck cancer. To do so, four physicians were asked to review case patients and estimate risk of weight loss at two time points—first without and then with the use of the prediction model. Statistical

analysis appropriate for matched pairs were performed, and the assessment provided preliminary evidence of the efficacy of the model.

Given success of this assessment within our institution, we performed a similar pilot assessment of the BMETS-DSP, using a pre-post design in a simulated clinical environment using case presentation. The goal of this assessment was to provide early evidence of the clinical utility of the BMETS survival model and associated BMETS-DSP to provide justification for future evaluation in a multi-institutional randomized trial.

METHODS

Data source

All case patients included in the assessment were part of the initial BMETS database, described in Chapter 2. After stratifying by quartiles of actual survival time, 55 case patients were randomly selected from the BMETS database population.

Study population

To evaluate the clinical utility of the BMETS-DSP, an email query recruiting study participants was sent to physicians with clinical privileges and access to the electronic medical record at the Johns Hopkins Department of Radiation Oncology and Molecular Radiation Sciences. The first 5 trainee and 5 attending physicians to respond were selected to participate, and informed consent was obtained.

A total of 55 patient cases were randomly selected from the 397 patients used to build the BMETS model. Relevant case data was collected including the 27 BMETS survival model covariates described in Chapter 2 as well as additional covariates used to create individualized treatment recommendations in the BMETS-DSP: prior RT, specific histologic type, detailed description of neuraxis compromise at the target site, presence

of neurologic symptoms other than pain attributable to the target lesion, and the presence of soft tissue component at the target site. These data were summarized to create case histories. To estimate predicted survival for the BMETS-DSP assessment, the BMETS model was refitted to produce a survival curve for each case, leaving the case patient out. Individualized recommendations were rendered on the basis of the BMETS's median predicted survival time and other patient and disease characteristics for each case, as detailed in Chapter 4.

Case histories were presented to physicians at 2 times: without and then with use of the BMETS-DSP output. The two assessment times were separated by a washout period of no less than 3 and no greater than 4 weeks, as per Cheng et al[136]. Time between start and completion of each phase of the assessment once started was $\leq$1 week.

Outcome assessments

At each assessment time, physicians were asked to answer 7 identical questions regarding the case patients. They were instructed that there may be no single correct answer and to choose their response on the basis of their clinical knowledge and practice alone during time 1 and with the assistance of the BMETS-DSP at time 2.

1. **Estimated survival in the 12 months following the simulated consultation**. Answers were entered as continuous values between 0.0 to 12.0 months, with the instruction to select 12.0 for estimated survival time of $\geq$ 12 months.
2. **Confidence in their prognostic estimate**. Answers were collected on a Likert scale ranging from 1 to 10, where 1= not at all confident and 10= very confident.
3. **Likelihood of sharing the prognostic estimate with the case patient.** Answers were collected on a Likert scale ranging from 1 to 10, where 1= very unlikely and 10= very likely.

4. **Recommendations for open surgical intervention**. To capture recommendations for prognosis-appropriate surgical interventions, physicians were asked to assume that associated symptoms and/or radiologic features of the target site (including those potentially not listed in the case presentation) would meet criteria and feasibility for a surgical intervention if otherwise appropriate for the given clinical scenario. Responses accepted were: yes, no, or “not applicable” for patients who had already undergone surgery at the target site.
5. **Recommendations for RT**. To evaluate recommendations for RT, physicians were asked to assume that no further surgery (other than that mentioned in the case history, if applicable) was elected at the symptomatic site. Then they were told to assume that the symptomatic site could be encompassed in a reasonable RT treatment field and meet dosimetric objectives for any of the listed RT regimens if otherwise appropriate for the given clinical scenario. The six response options were: no radiotherapy; 1-, 5-, 10-, or >10- fraction conventional RT; and SBRT.
6. **Recommendations for cancer-directed systemic therapy**. To capture recommendations for appropriate systemic therapy interventions, physicians were asked to assume that a systemic agent appropriate for the metastatic cancer existed and could be administered if otherwise appropriate for the given clinical scenario. They were asked to make this decision independent of their answers regarding local therapy with surgery or RT. Responses accepted were: “yes” or “no.”
7. **Recommendations for hospice referral.** Responses accepted were: “yes” or “no.”

Regarding questions about recommendations for appropriate interventions, the term “appropriate” was define as the condition in which the patient would not be excluded from the intervention on the basis of patient or disease features described or implied in

the case presentation. This term was meant to capture decision uncertainties including prognosis. The complete assessment form is included in Appendix 3.

Survival estimates and intervention recommendations were also evaluated in relation to case patients' actual survival to clinically relevant binary time points of 3, 6, and 12 months. The 3-month time point was defined as <3 months vs. ≥ 3 months to mirror the cut point used for appropriateness of spine surgery[62]. As described in Chapter 4, this was also the cut point we used to determine whether "shorter fraction RT" would be recommended in the BMETS-DSP. The 6-month time point was defined as ≤ 6 months vs. > 6 months, corresponding to the cut point used for appropriate hospice referral[133]. This cut point also reflects the upper range of survival for which shorter fraction RT has been tested for patients with spinal cord compression[7]. Institutionally, this cutoff is sometimes used to determine appropriateness for stereotactic body RT (SBRT). The 12-month time point was defined as < 12 months vs. ≥ 12 months to reflect the phrasing used in the questionnaire for estimates of survival noted above.

Statistical analysis

Descriptive statistics were performed to characterize patient and disease features for case patients and to describe the participating physicians.

Physicians' estimates of survival were first assessed as a continuous variable, using Wilcoxon signed-rank test to evaluate paired survival estimates before and after use of the BMETS-DSP.

Physician performance in estimating survival time pre- and post-DSP was analyzed using accuracy, sensitivity, specificity, area under the receiver-operative characteristics

curve (AUC), and positive and negative predictive value (PPV and NPV, respectively), comparing physicians' estimates of survival versus actual survival at the clinically relevant binary time points of < 3 months, ≤ 6 months, and < 12 months. Accuracy was defined as number of correct predictions (sum of true positives and true negatives) divided by the total number of cases. To evaluate these performance measures, physicians' continuous survival estimates were converted to binary values of surviving versus not surviving at each binary time point. A true positive was defined as a correct prediction of surviving relative to actual survival at that time point, and a true negative was correct prediction of not surviving relative to actual survival. McNemar's test compared paired values of pre- and post-DSP accuracy.

Confidence in and likelihood of sharing prognostic estimates were evaluated using Wilcoxon signed-rank test for paired ratings of these measures, pre- and post-DSP.

Appropriate selection of treatment interventions was assessed by the match between the recommendation for a given intervention and appropriateness of that intervention, as defined by evidence- or consensus-based guidelines and/or clinically relevant binary time point. Percent of concordant matches at each assessment time was specified as the sum of ("correct" recommendation for the intervention in the case where it is appropriate) plus ("correct" recommendation for no intervention in the case where it is not appropriate), divided by the total number of cases. For each intervention, appropriateness was categorized as follows:

1. **Surgery**: Appropriateness was defined according to cut points of actual survival for which surgery at a given target site was contraindicated [i.e., open surgery is contraindicated when actual survival time is <3 months for spne[62]; <2 weeks for

extremity (femur) and hip/pelvis (hip); <1.5 months for extremity (non-femur); and <2 months for hip/pelvis (non-hip), chest wall, and skull].

2. **RT**. Appropriateness was defined according to both clinically relevant binary time points and presence of "complicating" features. For assessment by binary time points, an assumption was made that a "correct" choice would be the use of shorter fractionation/non-SBRT regimens for shorter actual survival time. For example, when evaluating ≤1-fraction RT and the binary time point of 3 months, percent concordant match would be the sum of (recommendation for ≤1-fraction RT given actual survival <3 months) plus (recommendation for multiple fraction RT given actual survival ≥ 3 months), divided by total cases. For assessment by complicating features, a "correct" recommendation was assumed to be the use of longer fractionation or SBRT regimens in the presence of a complicating feature.
3. **Systemic therapy**. Appropriateness was defined according to the cut points of both actual survival time and Karnofsky performance status (KPS) for which systemic therapy was contraindicated [i.e., systemic therapy is contraindicated when actual survival is ≤ 2 weeks **and** KPS <50[113,118]].
4. **Hospice referral**. Appropriateness was defined according to the cut point of actual survival ≤ 6 months used to establish hospice eligibility.

Concordant matches for each intervention were compared pre- and post-DSP using McNemar's test, using different definitions of "appropriateness" when indicated.

All statistical tests utilized a two-sided $\alpha = 0.05$ for significance testing. Confidence intervals were reported for logistic regressions as per Louis and Zeger[137]. Statistics were performed using Stata Version 14.0 (College Station, Texas).

This study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine.

RESULTS

Table 1 shows characteristics of the case patients included in the assessment of the BMETS-DSP. Distributions of key patient-, disease-, and treatment-specific factors were similar to those found in the larger BMETS database from Chapter 2.

All 10 physicians participated in both pre- and post-DSP assessments, and response completion rates were 96%. Half of the physicians were trainees and completed medical school an average of 3.5 years [standard deviation (SD 1.3)] prior. The remaining five participants were attending physicians who completed medical school an average of 16.5 years (SD 11.6) prior. All physicians were actively training in or board certified in the field of Radiation Oncology.

Estimates of survival time

Mean actual survival time across case patients was 5.9 months (SD 4.0). Pre- vs. post-DSP, physicians' estimates of survival were mean 7.9 (SD 3.6) versus 6.9 (SD 3.7) months, respectively, $p<0.001$. Use of the DSP resulted in a reduction in overestimation of actual minus estimated survival time, with a mean difference of -2.1 (SD 4.1) vs. -1 month (SD 3.5), $p<0.001$. This improvement was observed across training level.

Table 2 displays accuracy of physicians' survival estimates at clinically relevant time points, before and after use of the BMETS-DSP. Pre-DSP accuracy was lowest when considering exact matches into survival categories and highest for the binary time point

of 3-months. Use of the BMETS-DSP significantly improved accuracy across all time points considered. The largest absolute increase was noted for accuracy at the binary time point of 12 months, where post-DSP accuracy increased by over 10% from 70.1% to 80.5%.

Measures of physician performance for survival estimation without and with the use of the BMETS-DSP are listed in Table 3. Pre-DSP, sensitivity was lowest but specificity was highest for survival estimates at the binary time point of 3-months (0.15 and 1.00, respectively). Physician performance at distinguishing survivors was poor to satisfactory across time points without use of the DSP, ranging from 0.56 to 0.64. Positive predictive value was highest for survival estimates at the 12-month time point, whereas negative predictive value was highest at the 3-month time point (0.88 and 0.77, respectively).

Use of the BMETS-DSP improved nearly all measures of prediction performance across time points. Although it remained relatively low, sensitivity at the 3-month time point increased by more than 2-fold to 0.33. Specificity remained lowest at the 12-month time point but did not change appreciably with the use of the BMETS-DSP (from 0.53 to 0.52). AUC was improved to a satisfactory to good range for all time points, ranging from 0.66 to 0.71. Notably, positive predictive values were increased to $\geq$ 0.72 with use the BMETS-DSP. Negative predictive values increased across all time points but remained relatively low at 0.47 at the 12-month time point.

Ratings of confidence in and likelihood of sharing prognosis

Prior to use of the BMETS-DSP, median rating for confidence with survival estimate was 6 (range 1-10). Post-DSP, this rating increased to median score of 8 (range 2-10). Pre-DSP, median rating for likelihood of sharing the survival estimate with the case patient

was 6 (range 1-10). Post-DSP, this rating also increased to a median score of 8 (range 1-10). In both cases, this increase was statistically significant, $p<0.001$.

Recommendations for appropriate open surgical intervention

Seven cases were excluded for consideration due to previous open surgical intervention. After applying prognostic cutoffs specific for each treatment site, there was no clear contraindication to open surgery in 33 out of 48 cases (67.4%). Before use of the BMETS-DSP, open surgical intervention was recommended by physicians in 28.7% of cases. After use of the BMETS-DSP, surgical intervention was recommended in 38.6% of cases. Match between prognosis-appropriate surgery status and recommendation for surgery were 47.3% and 52.8%, respectively, without and then with use of the DSP. This increase in match agreement was statistically significant (McNemar's $X^2= 5.24$, $p=0.022$).

Recommendations for appropriate systemic therapy intervention

After applying prognostic and KPS cutoffs, there was no clear contraindication to systemic therapy in 51 out of 55 cases (92.3%). Before use of the BMETS-DSP, systemic therapy was recommended by physicians in 82.5% of cases. After use of the BMETS-DSP, systemic therapy was recommended in 80.8% of cases. Match between appropriate use of system therapy status and recommendation for systemic therapy were 83.1% and 82.9%, respectively, without and then with use of the DSP. This change in match agreement was not statistically significant (McNemar's $X^2= 0.01$, $p=0.915$).

Recommendations for appropriate hospice referral intervention

After applying prognostic cutoffs, there was no clear contraindication to hospice referral in 29 out of 55 cases (52.7%). Before use of the BMETS-DSP, hospice referral was

recommended by physicians in 55.8% of cases. After use of the BMETS-DSP, hospice referral was recommended in 53.1% of cases. Match between appropriate hospice referral status and recommendation for hospice referral were 66.5% and 70.9%, respectively, without and then with use of the DSP. This change in match agreement was not statistically significant (McNemar's X^2= 3.18, p=0.074).

Recommendations for appropriate RT intervention

Figure 1 shows the percent at which each fractionation scheme was recommended, pre- and post-DSP. Treatments above 10 fractions or with SBRT were more common at the pre- versus post-DSP assessment (12.6% versus 9.1%, respectively), whereas use of single-fraction (4.9% versus 6.8%, respectively) was more common in the post-DSP group, p<0.001. At both assessment times, regimens utilizing $\leq$ 5 fractions were selected in approximately half of cases.

Table 4 shows the percent of cases in which there was a concordant match between the "appropriate" choice of a shorter fraction regimen for a patient with a lower actual survival time, evaluated at different survival time and fractionation cut points. These data show that use of the BMETS-DSP increased concordant match of selection of $\leq$ 1 fraction palliative RT for patients with actual survival time < 3 months from 69.9% to 76.0% (McNemar's X^2=11.0, p<0.001) and for patients with actual survival time $\leq$ 6 months (McNemar's X^2=4.15, p=0.042). Additional, use of the BMETS-DSP increased concordant match of selection of $\leq$ 5 fractions palliative RT for patients with actual survival time <12 months (McNemar's X^2=7.71, p=0.006).

In Table 5 the percent of cases in which there was a concordant match between the "appropriate" choice of a longer fraction regimen for a patient with a potential

"complicating" feature is evaluated, using a range of fractionation cut points and types of "complicating" features. Unlike survival time, there were no significant differences in concordant match of fractionation according to presence of various "complicating" features.

DISCUSSION

In this pilot assessment of the BMETS-DSP, use of the decision support aid improved accuracy of physicians' survival estimates, increased confidence in and likelihood of sharing prognosis with the patient, and improved selection of prognosis- and guidelines-appropriate surgery and RT interventions. These data provide early evidence of the efficacy of the BMETS-DSP in guiding clinical decision-making, with the goal of optimizing individualized care for patients with symptomatic bone metastases.

In alignment with the underlying Ottawa Decision Support Framework (ODSF) used to develop our decision support tool[106], we sought to evaluate both facets of the decision-making process as well as decision outcomes in the assessment of the BMETS-DSP. We evaluated physicians' confidence in their prognostic estimates as a facet of the decision-making process, whereas we assessed their likelihood of sharing prognosis and their selection of interventions as measures of decision outcomes. The success of the BMETS-DSP in producing improvements in both of these capacities offers support of the quality of its design and its potential to reduce decisional conflict in this setting.

Results of the BMETS-DSP assessment confirm the trend that providers' survival estimates tend to be over-optimistic. In a systematic review regarding clinician estimates of survival for patients with cancer, 9 out of 12 included studies demonstrated an over-estimation in survival time[17]. Although the means by which survival estimates were

measured vary between studies and limit direct comparison, our physicians' survival overestimation ratio of 1.33 (7.9 months estimated/5.9 months actual survival) falls within the range of 1.08 to 5.3 reported in other publications. Use of the BMETS-DSP reduced this overestimation ratio to 1.17, which is among the lowest ratios reported[135]. This reduction in overestimation may be particularly important, since such over-optimism is linked to high-cost, low value care in this setting[18].

It is noted that past studies show survival estimates may be particularly inaccurate at the extremes of survival time. For example, the study by Vigano, et. al., found that physicians' sensitivity for prediction survival was lowest for patients with actual survival times $\leq$ 2 months[138]. Conversely, other publications have confirmed a "horizon effect"—that short-term forecasts for survival and other outcomes tend to be more accurate than longer-term predictions[17]. This effect was reflected in the results of a study of 39 patients with cancer, in which the AUC for providers' 3-month and 12-month survival predictions were 0.75 and 0.57, respectively[139]. Given that the magnitude of improvement in survival estimates with the BMETS-DSP was greatest for discriminating between survivals at the 3- and 12-month binary time points, our tool may be an especially valuable resource for use in this setting.

Regarding its effect on selection of appropriate palliative RT regimens, the primary impact of the BMETS-DSP appears to have occurred at the level of improved survival predictions. Whereas prognosis-appropriate RT decisions improved over several binary survival time points and fractionation schemes as per Table 4, there were no apparent changes in fractionation choice measured in relation to increasing "complicating" features of the target lesion. It is unclear if this is due to inadequate sample size for detecting changes or the inability of the authors to provide sufficiently concrete criteria for selecting between regimens on the basis of "complicating" features.

Interestingly, the BMETS-DSP improved prognosis-appropriate recommendations for surgical but not for systemic therapy or hospice referral interventions. Notably, when designing the BMETS-DSP, it was not our expressed goal to allow for detailed determination of the appropriateness of surgery or systemic therapy. Instead, the intended goal was to promote appropriate referral to Medical Oncology or Surgical Oncology colleagues should these interventions be deemed appropriate relative to expected prognosis. As such, the significance (or lack thereof) of the impact of the BMETS-DSP on these interventions should be interpreted with caution.

Recommendations for hospice referral were similar before and after use of the BMETS-DSP—and notably similar to the 56% referral rate measured by retrospective review of our own institutional data[20]. Given that physicians' accuracy for discriminating survival at the 6-month time point was improved to 70.9% at the post-DSP assessment, it is unclear why concordant match of appropriate hospice referral rates were not similarly increased. Additional efforts should be dedicated to understanding this residual non-adherence to hospice referral guidelines.

Most notably, this study is limited by its status as a pilot assessment, using a simulated clinical environment with limited sample size and non-randomized design. Small numbers preclude use of more advanced statistical approaches such as attempts to account for cluster effect at the level of the provider. It is noted that the primary goal of this assessment was to provide preliminary evidence of the feasibility and efficacy of the BMETS-DSP, to be used as justification for a randomized, multi-institutional study. While its results support this goal, caution must be used in drawing extensive conclusions outside of the study's intended context. Whereas numerous decision support tools have been assessed in pilot studies such as this, few have been evaluated in the clinical context[140], where early efficacy may not translate into measurable clinical effectiveness.

Given the complex, ill-defined, and conflicting nature of guidelines available for this patient population, testing the BMETS-DSP required that we make a number of assumptions regarding the "appropriateness" of the various interventions. For example, we assumed that shorter regimens of RT were most appropriate for patients with more limited estimated survival. As previously noted in Chapter 4, this decision was based on reasonable extrapolation from the literature and supported in the works of other authors[24,128,129]. Yet in reality, the trials of single- versus multiple-fraction palliative RT for uncomplicated symptomatic bone metastases were generally designed as non-inferiority studies[12,141]. Thus, while there is an implied benefit to the use of shorter treatment regimens in the setting of non-inferiority, these data do not conclude that use of longer regimens is contraindicated. Moreover, "appropriateness" is a highly subjective term that is likely to vary across institutions and medical systems, potentially limiting the generalizability of these results to external users.

An additional limitation of our assessment design is its reliance on review of case histories as opposed to in-person patient-physician interactions. As our review of the BMETS survival modal in Chapter 2 implies, a subjective provider-rated variable—KPS—is the strongest predictor of survival in this group. As such, it could be argued that the survival estimates and treatment choices garnered from our study may vary from what the physician might answer in a realistic clinical setting. However, the directionality of the impact of this potential bias is unclear. For example, one study showed that the length of time a physician has known a patient is linked to a reduction in prognostic accuracy—with each additional year of the patient-physician relationship resulting in a 12% increase in likelihood of prognostic error[142]. Moreover, while some studies indicate superiority of clinician predictions over use of prognostic tools such as performance status alone[143], other studies show similar predictions between methods[144]. Again,

prospective evaluation of the BMETS-DSP in the clinical environment will be required to confirm its true effectiveness.

In summary, this pilot assessment of the BMETS-DSP provides preliminary evidence of its impact on improving physicians' estimates of survival and selection of prognosis-appropriate palliative RT regimens in the management of symptomatic bone metastases. These data provide justification of the feasibility and efficacy of the tool, justifying more extensive assessment in a randomized, multi-institutional study. Moreover, results highlight the need for future studies that clarify optimal fractionation schemes in the setting of "complicated" metastases. Lastly, these results emphasize the need for interventions addressing inadequate hospice referral patterns, which appear to persist even in the setting of improved survival predictions.

Table 1: Patient, disease, and treatment characteristics for case patients included in the BMETS Decision Support Platform assessment.

Patient-specific factors		Disease-specific factors		Treatment-specific factors	
Name		Name		Name	
1. Age in years—mean (SD)	14.4%	9. RT target site‡—% Spine	52.7%	17. Primary cancer site—% Breast	16.4%
2. Sex—% female	45.5%	Hip/pelvis	12.7%	Prostate	14.6%
3. Race*—% White	70.9%	Extremity	18.2%	Lung	36.4%
Black	25.5%	Chest wall	12.7%	Leukemia, lymphoma, myeloma	1.8%
Other	3.6%	Skull	3.6%	Other	30.9%
4. KPS—median (range)	70 (30-100)	10. Concurrent palliative RT to other non-contiguous bone sites§—% Yes	20%	18. Neuraxis compromise¶—n (%) Yes	31.0%
5. WBC count within prior 1 month in cells per microliter—mean (SD)	11,014 (9,956)	11. Concurrent palliative RT to other non-contiguous sites other than bone§—% Yes	0%	20. Neurological symptoms other than pain — (%) Yes	14.5%
6. Lymphocyte count within prior 1 month in cells per microliter—mean (SD)	2119 (5853)	12. Current steroid use—% Yes	34%	19. Soft tissue component—(%) Yes	43.6%
7. Inpatient status+—% Yes	29.1%	13. Current opiate pain medication use— % Yes	77.8%	19. Time from initial diagnosis in months—mean (SD)	41.0 (49.6)
8. Any weight loss in prior 6 months—% Yes	76.1%	14. Chemotherapy delivered within the previous 1 month—% Yes	50%		
		15. Type of chemotherapy last delivered‖—% None	26.4%	Other metastases to# (% Yes):	
		Intravenous	35.9%	20. Brain	12.7%
		Non-hormonal oral	15.1%	21. Lung	40.0%
		Hormonal	22.6%	22. Liver	27.3%
		16. Prior surgery at RT target site—% Yes	12.7%	23. Adrenal gland	12.7%
				24. Lymph node**	45.5%
				25. Non-visceral soft tissue	2.8%
				26. Other bone	61.8%
				27. Other sites	5.5%

* Patient-reported

+Admission to offsite inpatient rehabilitation or nursing home facilities were excluded

‡ If the RT target lesion encompassed multiple sites, the site containing the majority of the target lesion was selected

§ Does not include RT target sites requiring multiple contiguous fields due to large target size

‖ If multiple types of chemotherapy were delivered concurrent, a single response was selected in the following order: IV > non-hormonal oral > hormonal

¶ Defined as radiologic evidence of spinal cord, spinal canal, nerve root, or neuroforaminal impingement from direct involvement of the target lesion

#Includes all radiologically-confirmed definite areas of metastatic disease outside of the current palliative RT field. Indeterminate lesions or sites without radiologic evaluation were as “no.”

** Includes locoregional nodal metastases for the primary site

KPS= Karnofsky Performance Status, RT=radiotherapy, WBC= white blood cells

Table 2: Physicians' accuracy for predicting survival at clinically relevant time points, before and after use of the BMETS-Decision Support Platform (BMETS-DSP)

	Pre-DSP	Post-DSP	McNemar's X^2	p-value
Survival category*	**34.8%**	**42.9%**	**9.5**	**0.002**
<3 vs. ≥ 3 months	**72.2%**	**80.3%**	**24.0**	**<0.001**
≤6 vs. >6 months	**64.2%**	**70.9%**	**7.32**	**0.007**
<12 vs. ≥ 12 months	**70.1%**	**80.5%**	**22.8**	**<0.001**
* Test of exact match using 4 survival categories: (1) <3, (2) ≥ 3 to ≤ 6 months, (3) > 6 months to < 12 months, and (4) ≥ 12 months				

Table 3: Sensitivity, specificity, area under the receiver operator characteristic curve, positive predictive value, and negative predictive value of physicians' survival estimates at clinically relevant time points, before and after use of the BMETS-Decision Support Platform (DSP)

	Sensitivity		Specificity		AUC		Positive Predictive Value		Negative Predictive Value	
	Pre-DSP	Post-DSP	Pre-DSP	Post-DSP	Pre-DSP	Post-DSP	Pre-DSP	Post-DSP	Pre-DSP	Post-DSP
<3 vs. ≥3 months	0.15	0.33	0.97	1.00	0.56	0.66	0.70	1.00	0.72	0.77
≤6 vs. >6 months	0.57	0.74	0.71	0.68	0.64	0.71	0.69	0.72	0.59	0.70
<12 vs. ≥12 months	0.75	0.87	0.53	0.52	0.64	0.70	0.88	0.89	0.32	0.47
AUC= area under receiver-operator characteristic curve										

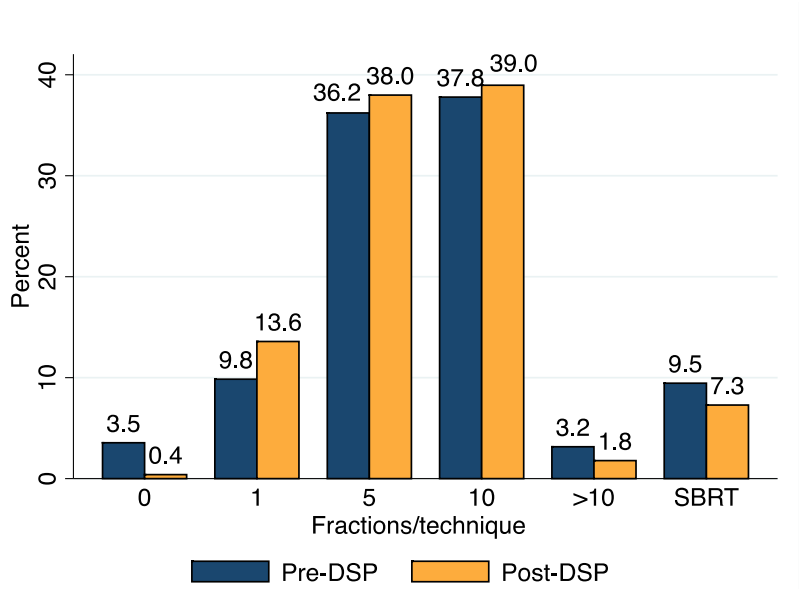

Figure 1: Percent of cases for which each fractionation scheme [1 to >10 or stereotactic body radiotherapy (SBRT)] was recommended, before and after use of the BMETS-Decision Support Platform (DSP)

Table 4: Percent concordant match between choice of lower fractionation regimen and lower actual survival time, before and after use of the BMETS-Decision Support Platform (DSP)

	< 3 months				< 6 months				< 12 months			
	Pre-DSP match	Post-DSP match	**McNemar's X^2**	**p-value**	Pre-DSP match	Post-DSP match	**McNemar's X^2**	**p-value**	Pre-DSP match	Post-DSP match	**McNemar's X^2**	**p-value**
≤ 1 fraction	**69.9%**	**76.0%**	**11.0**	**<0.001**	**54.3%**	**58.1%**	**4.15**	**0.042**	28.9%	32.3%	3.32	0.068
≤ 5 fractions	59.6%	60.0%	0.03	0.870	59.8%	63.0%	1.71	0.191	**55.3%**	**62.0%**	**7.71**	**0.006**
≤10 fractions	38.8%	37.2%	1.10	0.294	55.5%	55.2%	0.07	0.793	78.2%	79.7%	1.10	0.294

Table 5: Percent concordant match between choice of higher fractionation regimen and in the presence of "complicating" features, before and after use of the BMETS-Decision Support Platform (DSP)

	Prior surgery or fracture				Prior surgery, fracture or neuraxis compromise				Prior surgery, fracture, neuraxis compromise, or critical site			
	Pre-DSP match	Post-DSP match	**McNemar's X^2**	**p-value**	Pre-DSP match	Post-DSP match	**McNemar's X^2**	**p-value**	Pre-DSP match	Post-DSP match	**McNemar's X^2**	**p-value**
>1 fraction	44.7%	44.1%	0.10	0.748	59.0%	57.1%	0.93	0.335	69.1%	68.9%	0.01	0.915
> 5 fractions	52.2%	54.9%	1.3	0.253	57.7%	56.5%	0.24	0.624	62.8%	61.2%	0.24	0.624

Chapter 6. Conclusion

Our research provides preliminary evidence that the BMETS survival model and associated BMETS Decision Support Platform (BMETS-DSP) improve providers' prognostic estimates as well as selection of prognosis-appropriate and evidence-based palliative radiotherapy regimens in the management of patients with symptomatic bone metastases. Specifically, we have shown that the BMETS model and its underlying machine learning algorithm outperforms traditional statistical approaches in estimating survival time following consultation for symptomatic bone metastases. Moreover, we provided characterization of "complex" metastases and prevalence of these lesions across a range of operational definitions for this term. This lends insight into sources of decisional uncertainty encountered when applying clinical guidelines in the context of ill-defined selection criteria. We demonstrated the feasibility of creating a decision support platform based on the BMETS model that not only facilitates data entry and display but also attempts to provide individualized recommendations on the basis of patient-specific characteristics. Lastly, we used an innovative approach to testing the efficacy of the BMETS model and BMETS-DSP in which the success of the platform was measured in terms of both better survival predictions but also improved selection of patient-appropriate treatment regimens.

Next steps for the BMETS-DSP include a multi-institutional, randomized evaluation of the BMETS-DSP. Based on presentation of early data, we have formed a consortium of 4 international institutions that have agreed to participate in data-sharing and evaluation of the BMETS-DSP. Our end goal is to create a large, dynamically updating database from these shared sources from which the BMETS model can be frequently refitted. Our aim is to circumvent issues of external validity encountered with machine learning models by optimizing the size of the source repository for model

training. We will also work to incorporate patient preference into the decision support platform, as this is a key and untapped element of the decision-making process in this setting. Additionally, we will be working with patients and patient advocates to develop a patient-facing view of the BMETS model prediction in order to encourage discussion of prognosis between patients and providers. Given that more than half of patients with advanced cancer may not receive dedicated discussion of prognosis[145], this is an imperative next step in ensuring that patients have all the information that they need to make informed decisions and participate in advanced planning at the end of life.

Currently, there is a growing trend toward development of even more advanced machine learning models in our field. Notably, Banerjee, et al., have described a deep learning model analyzing free text clinical notes for 10,293 patients with metastatic cancer in order to predict survival outcomes. Authors report high model performance, with area under the curve (AUC) for prediction of survival <3 months of 0.89[146]. While such approaches are promising, it was our opinion that efforts should first be directed toward establishing the superiority of a machine-learning model as compared to more readily available and easier to use traditional models. As such, the success of the BMETS model provides justification for continued development of even more complex, deep learning models in this setting.

Lastly, the decisional dilemma underlying development of the BMETS-DSP is of course not unique to our clinical question. *Clinical Evidence* published a review of 2500 commonly-used medical treatments across fields and revealed that the relative costs and benefits of most medical treatments are rarely straight-forward: 13% of such treatments are rated as beneficial, 23% are likely beneficial, 8% are typified by the balance of costs and benefits, 6% are not likely to be beneficial, 4% may be harmful or ineffective, and 46% have unknown effectiveness[147]. An entire field of study is dedicated to describing difficulties with development of and adherence to consensus

guidelines, citing limitations including inadequate definitions and lack of concrete selection criteria[148–150] that parallel the experiences documented in our work. We are hopeful that our research may provide some valuable preliminary insights into the rationale and development of decision support tools to aid in the delivery of individualized care in ours and other contexts in medicine.

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APPENDIX 1

Supplemental Statistical Methods for the BMETS Survival Model

As per the primary Methods section, our objective was to use the collection of covariates $\{X_i\}$ for each patient *i* to model survival time, $S(t|X_i)$. As noted, our RSF model utilized bootstrap aggregation (bagging) by first taking *1000*bootstrap samples from the original data. We then grew a binary survival tree from each bootstrap sample via iterative binary splitting of the sample population into non-overlapping groups (nodes). Each split was created on the basis of a predictor covariate to maximize the log-rank statistic between the two nodes, creating clusters of patients with similar survival. The final predicted outcome was averaged across the B trees. In order to obtain a survival tree from each bootstrapped sample, all data from the sample was initially grouped together within a root node. For each covariate $X_j \in \{X1, \ldots, Xp\}$, where X_j is the collection of all values of covariate j (Xj = (X1j, X2j, …,XNj), and all possible cutpoints *s* of X_j , each individual *i* was placed in one of two groups, based on whether $X_{i,j} \leq s$ or $X_{i,j} > s$. The log-rank statistic for each of these groupings was calculated, and the covariate X_j and cut point *s* that maximized the log-rank statistic were used to split the data into two child nodes. This procedure was repeated for each node, growing the tree such that on average (across the forest), each final node contained 3 unique observations[48]. Within a given node, missing values for a covariate used for splitting were imputed by sampling with replacement from the empirical distribution of observed values within that node. After splitting into child nodes, the imputed values for the covariate of interest were reset to missing.

To estimate the survival curve for a new individual i, $\hat{S}(t|X_i)$, we first "dropped" the observation down each tree and observed the final node that it belongs to, based on its covariate values. For each tree built with *b*-th bootstrapped dataset ($b = 1, \ldots, B$), we denoted this final node η_b. Our estimated survival curve for individual i within the bth

tree, $\hat{S}_b\ (t|X_i)$, was the Kaplan-Meier estimate at time t based on observations in η_b. To make a prediction for a new observation, the algorithm collects the predicted values from each tree and averages these predictions together for the final prediction. Thus, our final prediction of survival time for an observation with covariates X_i using RSF is:

$$\hat{S}_{RSF}\ (t|X_i) = \frac{1}{B} \sum_{b=1}^{B} \hat{S}_b\ (t|X_i)$$

APPENDIX 2

Percent of target symptomatic bone metastases categorized as "complicated," calculated across all possible definitions for complicated bone metastases using the 8 variables listed.

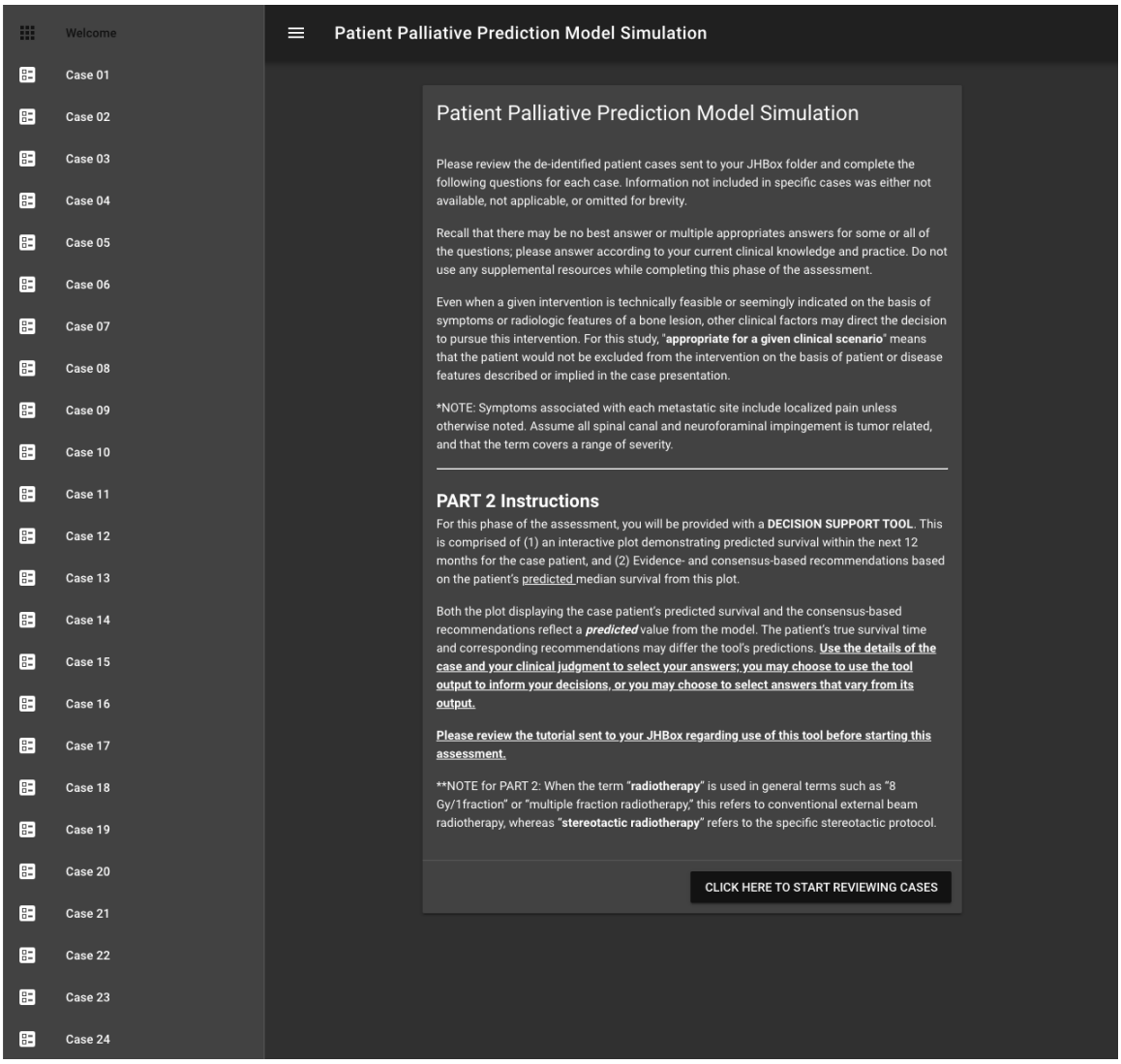
Prior RT	Prior surgery	All fracture	Non-spine fracture only	All neuraxis com-promise	CCS only	CE only	Soft tissue comp-onent	Percent of "complicated" cases
✓	✓	✓		✓			✓	67.1%
✓	✓	✓			✓		✓	66.2%
	✓	✓		✓			✓	65.7%
	✓	✓			✓		✓	64.8%
✓	✓	✓				✓	✓	62.1%
✓	✓	✓					✓	61.9%
✓	✓		✓	✓			✓	61.8%
✓	✓		✓		✓		✓	60.5%
	✓	✓				✓	✓	60.2%
	✓		✓	✓			✓	60.2%
	✓	✓					✓	60.1%
✓	✓			✓			✓	59.1%
	✓		✓		✓		✓	58.9%
✓		✓		✓			✓	58.6%
✓	✓				✓		✓	57.8%
✓		✓			✓		✓	57.8%
	✓			✓			✓	57.3%
		✓		✓			✓	56.8%
	✓				✓		✓	56.0%
		✓			✓		✓	55.9%
✓		✓				✓	✓	53.6%
✓		✓					✓	53.4%
✓			✓	✓			✓	53.3%
✓	✓		✓			✓	✓	53.0%
✓	✓		✓				✓	52.4%
✓			✓		✓		✓	52.0%
		✓				✓	✓	51.3%
			✓	✓			✓	51.3%
		✓					✓	51.1%
	✓		✓			✓	✓	50.9%
✓				✓			✓	50.6%
✓	✓					✓	✓	50.3%
	✓		✓				✓	50.3%
			✓		✓		✓	50.0%
✓	✓						✓	49.7%
✓					✓		✓	49.3%
				✓			✓	48.4%
	✓					✓	✓	48.0%
✓	✓	✓		✓				47.6%
	✓						✓	47.4%
					✓		✓	47.1%
	✓	✓		✓				45.3%
✓			✓			✓	✓	44.5%
✓			✓				✓	44.0%
✓	✓	✓			✓			43.2%
			✓			✓	✓	42.0%
✓						✓	✓	41.8%

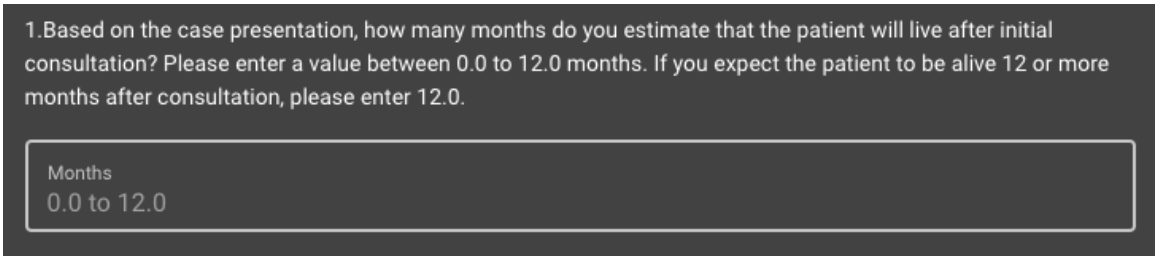
Prior RT	Prior surgery	All fracture	Non-spine fracture only	All neuraxis com-promise	CCS only	CE only	Soft tissue comp-onent	Percent of "complicated" cases
			✓				✓	41.4%
✓	✓		✓	✓				41.2%
✓							✓	41.2%
	✓	✓			✓			40.7%
✓		✓		✓				39.1%
						✓	✓	39.1%
	✓		✓	✓				38.8%
							✓	38.5%
✓	✓			✓				37.4%
		✓		✓				36.4%
✓	✓		✓		✓			35.6%
✓		✓			✓			34.8%
	✓			✓				34.8%
✓	✓	✓				✓		33.9%
✓	✓	✓						32.9%
✓			✓	✓				32.8%
	✓		✓		✓			32.8%
		✓			✓			31.8%
✓	✓				✓			31.6%
	✓	✓				✓		30.7%
			✓	✓				29.9%
	✓	✓						29.6%
✓				✓				28.9%
	✓				✓			28.6%
✓			✓		✓			27.2%
				✓				25.9%
✓		✓				✓		25.4%
✓		✓						24.4%
			✓		✓			23.9%
✓					✓			23.1%
		✓				✓		21.8%
		✓						20.7%
					✓			19.7%
✓	✓		✓			✓		19.3%
✓	✓		✓					17.1%
	✓		✓			✓		15.4%
✓	✓					✓		15.2%
✓	✓							13.1%
	✓		✓					13.1%
	✓					✓		11.2%
✓			✓			✓		10.8%
	✓							8.9%
✓			✓					8.6%
✓						✓		6.8%
			✓			✓		6.5%
✓								4.6%
			✓					4.2%
						✓		2.3%
								0.0%

✓ Indicates that the selected variable was used as part of the definition for "complicated" bone metastasis
CCS= central canal stenosis, CE= cord edema, RT=radiotherapy

APPENDIX 3

Data Collection Form for the BMETS Decision Support Platform Assessment





2.How confident are you regarding the prognosis you listed in question #1?

Scale: 1 (Not at all confident) to 10 (Very confident)
1 to 10

3.How likely are you to share the prognosis you listed in #1 with this patient, on a scale of 1 to 10.

Scale: 1 (Very unlikely) to 10 (Very likely)
1 to 10

4.First, would you advise **open surgical intervention** to the symptomatic bone lesion for this patient?

Assume that associated symptoms and/or radiologic features of the target site (including those not listed in the case presentation) would meet criteria and feasibility for a surgical intervention ***if otherwise appropriate for the given clinical scenario.***

- Yes
- No
- N/A - Patient already underwent surgery at the symptomatic site

5.Now assume that **no further surgery(other than that mentioned in the case history, if applicable)** is elected at the symptomatic site. Which **radiotherapy treatment option** do you think would be most appropriate for this patient?

Assume that the symptomatic site can be encompassed in a reasonable treatment field and meet dosimetric objectives for any of the listed radiotherapy regimens ***if otherwise appropriate for the given clinical scenario.***

- No radiotherapy
- Single fraction conventional radiotherapy
- 5 fraction conventional radiotherapy
- 10 fraction conventional radiotherapy
- > 10 fraction conventional radiotherapy
- Stereotactic radiotherapy

6.Would you refer the patient for hospice discussion?

6.Would you advise starting or continuing systemic cancer-directed therapy?

Assume that a systemic agent appropriate for the metastatic cancer exists and can be administered ***if otherwise appropriate for the given clinical scenario. Also please make this decision independent of your answers regarding any local therapies elected in #4 and #5.***

Yes

No

7.Would you refer the patient for hospice discussion?

Yes

No

CURRICULUM VITAE

Sara Rachel Alcorn, MD, MPH

DEMOGRAPHIC INFORMATION

Current Appointments

2015-present Assistant Faculty, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins

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Education and Training

Undergraduate

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Doctoral/graduate

2010 M.D., Harvard Medical School, Boston, MA
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Professional Experience

2010-2011 Intern, Transitional Year, Harvard Cambridge Health Alliance, Cambridge, MA
2011-2015 Resident, Radiation Oncology, Johns Hopkins Hospital, Baltimore, MD
2014-2015 Chief Resident, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins School of Medicine, Baltimore, MD
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RESEARCH ACTIVITIES

Peer Reviewed Original Science Publications

1. Alcorn S, Balboni M, Prigerson H, Reynolds A, Phelps A, Wright A, Block S, Peteet J, Kachnic L, Balboni T. “If God wanted me yesterday, I wouldn’t be here today”: Religious and spiritual themes in patients’ experiences of advanced cancer. Journal of Palliative Medicine. 2010;13(5): 581–8.
2. Phelps A, Lauderdale K, Alcorn S, Dillinger J, Balboni M, Van Wert M, Vanderweele T, Balboni TA. Addressing spirituality within the care of patients at the end of life: perspectives of patients with advanced cancer, oncologists, and oncology nurses. Journal of Clinical Oncology. 2012; 30(20): 2538–44.
3. Kumar R, Madanikia S, Starmer H, Yang W, Murano E, Alcorn S, McNutt, Le Y, Quon H. Radiation dose to the floor of mouth muscles predicts swallowing complications following chemoradiation in oropharyngeal squamous cell carcinoma. Oral Oncology. 2014; 50(1): 65–70.
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10. Parekh A, Fu W, Hu C, et al. Impact of race, ethnicity, and socioeconomic factors on receipt of radiation after breast conservation surgery: analysis of the national cancer database. Breast Cancer Res Treat. 2018;172(1):201-208.
11. Alcorn S, Nilsson K, Rao AD, et al. Practice Patterns of Stereotactic Radiotherapy in Pediatrics: Results From an International Pediatric Research Consortium. J Pediatr Hematol Oncol. 2018;40(7):522-526.
12. Rao AD, Nicholas SE, Kachniarz B, et al.., and Alcorn, SR. Association of a Simulated Institutional Gender Equity Initiative With Gender-Based Disparities in Medical School Faculty Salaries and Promotions. JAMA Netw open. 2018;1(8):e186054. doi:10.1001/jamanetworkopen.2018.6054.

13. Rao AD, Lee J, Fu W, ..Alcorn SR..et al. Precision of 2 Low-dose Abdomen/Pelvis Cone Beam Computed Tomography Protocols for Alignment to Bone and Soft Tissue in Pediatric Patients Receiving Image Guided Radiation Therapy. Pract Radiat Oncol. January 2019.

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18. Hazell S, Hu C, Alcorn S, Asiedu K, Pulido G, Frassica D, Meyer C, Levin A, Morris C, Terezakis S. Neoadjuvant chemoradiation compared to neoadjuvant radiation alone in the management of high-grade soft tissue extremity sarcomas. Cancer. In submission.

Invited Reviews

1. **Alcorn S,** Walker A (co-first authors), Gandhi N, Narang A, Wild A, Hales R, Song D, DeWeese T, Antonarakis E, Tran P. Molecularly targeted agents as radiosensitizers in cancer therapy--Focus on prostate cancer. International Journal of Molecular Sciences. 2013; 14(7): 14800–32.
2. Walker A, **Alcorn S (co-first authors),** Narang A, Nugent K, Wild A, Herman J, Tran P. Radiosensitizers in pancreatic cancer--Preclinical and clinical exploits with molecularly targeted agents. Current Problems in Cancer. 2014; 37(5): 301–12.

Inventions, Patents, Copyrights
None

Extramural Sponsorship (current, pending, previous)

Previous

7/2015-6/2018	KL2 Mentored Career Development Award 5KL2TR001077 NIH/Johns Hopkins School of Public Health $293,000 **PI: Alcorn** 90% salary support for 2 years, divided over 3 years

Research Program Building / Leadership

10/2011-7/2014	Optimizing Setup Accuracy with Image-Guided Radiotherapy Co-I: Hales and Alcorn
7/2014-7/2015	Evaluating Practice Patterns in Palliative Radiation PI: Alcorn
7/2014-2018	Low-dose Image Guidance Protocols in Pediatric CNS Radiotherapy Co-I: Terezakis, Alcorn
7/2015-present	Modeling Survival Using Dynamic Data in Palliative Bone Radiotherapy PI: Alcorn
6/2017-present	Shared decision-Making in Palliative Bone Radiotherapy PI: Alcorn
6/2017-present	Shortened Regimens for Postoperative Palliative Radiation PI: Alcorn
2/2017-present	Optimizing Bolus Use in Post-mastectomy Radiotherapy Co-I: Wright, Alcorn
5/2017-present	Shared Decision-Making in Elderly Breast Radiotherapy Co-I: Alcorn, Wright
1/2018-present	Evaluating Incidental Irradiation of Normal Tissues in Tangent Field Whole Breast Radiotherapy Co-I: Alcorn, Wright

EDUCATIONAL ACTIVITIES

Educational Publications

Editorials

1. Holdhoff M, Rosner G, **Alcorn S**, Grossman S. 'Elderly' patients with newly diagnosed glioblastoma deserve optimal care. Journal of Neurooncology. 2013; 113 (2): 343-344.

2. **Alcorn S**, Miller D, Hales R. Call to Action Regarding Under-Utilization of Combined-Modality Therapy in Limited-Stage Small-Cell Lung Cancer. JAMA Oncology. *JAMA Oncol.* 2018.

Case Reports

1. **Alcorn S**, Sorel M-A, Auerbach S, Shaffer K. Ehlers-Danlos Syndrome

Presenting as Severe Headache in a Young Adult. Radiology Case Reports. 2008; 3(2): 2–8.
2. **Alcorn S**, Gocke C, Woodard C, Tran P. Solitary Plasmacytoma of the Penile Urethra Treated With Primary Radiotherapy. Journal of Clinical Oncology. 2014; 32(28): e95-e97.

Books, Textbooks

1. **Alcorn S**, Agbahiwe H, Terezakis S. "Non-Hodgkin Lymphoma." In N Lee (Ed.), Target Volume Delineation and Field Setup: A Practical Guide for Conformal and Intensity-Modulated Radiation Therapy, Second Edition. New York, NY: Springer, 2015.
2. **Alcorn S,** Terezakis S. "Radiation Oncology." In J Kung, P Bishop, P Slanetz, and R Eisenberg (Ed.), Tips for the Residency Match: What Residency Directors Are Really Looking For. Hoboken, NJ: John Wiley and Sons, 2015.
3. Kumar R, **Alcorn S**, Redmond K, Sahgal A. "Stereotactic Radiation for Spinal Metastases." In A Fairchild (Ed.), Palliative Radiation Oncology. Hauppage, NY: Nova, 2015 (In press).
4. **Alcorn S** and Terezakis SA. Image-guided Pediatric Brain Radiotherapy in A. Mahajan and A. Paulino (Eds), Pediatric Brain Radiotherapy. In Press
5. **Alcorn S** and Terezakis SA. "Primary and Metastatic Soft Tissue Sarcomas: Altered fraction regimens with external beam radiation and brachytherapy." In altered Fractionation Regimens in Radiotherapy: Paradigm Change (First Edition). In Press
6. Sloan L and **Alcorn S. "**Acute and Late Skin Toxicity from Breast Radiation." In J Wright (Ed.), Toxicities of Radiation Treatment for Breast Cancer. New York: Springer, 2019

Other media

1. **Alcorn S**, Lieberman G. "Imaging Considerations for the Diagnosis and Management of Bronchioloalveolar Carcinoma." eRadiology Learning Lab, Brigham and Women's Hospital Department of Radiology. 2010. Available online at http://eradiology.bidmc.harvard.edu/LearningLab/respiratory/Alcorn.pdf.

Teaching

Classroom instruction

2014	Medical student surgical oncology series, lecturer. "Role of Radiation Oncology in the Management of Gastrointestinal Malignancies." Instruction for 50 medical students, 2 lectures, Johns Hopkins School of Medicine, Baltimore MD
2016-present	Radiation treatment for breast cancers, Instruction for 14 residents, 1 month intensive course per year, Johns Hopkins School of Medicine, Baltimore MD
2017	Update on NCCN guidelines for breast imaging. Instruction for breast cancer faculty and fellows, 1 lecture, Johns Hopkins School of Medicine,

Baltimore MD

Clinical instruction

2017-present Departmental oral boards examiner for breast cancer, Instruction for current and former residents, 1 week of instruction, Johns Hopkins School of Medicine, Baltimore MD

CME instruction

None

Workshops/seminars

None

Mentoring

Advisees

2014-2015 Powell Perng, medical student at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 3 pending publications and 1 oral presentation and 3 poster presentations at national academic meetings.

2014-2015 Sarah Saleemi, medical student at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 3 pending publications and 1 oral presentation and 3 poster presentations at national academic meetings.

2015-2016 Minh Hyunh-Le, medical student at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 manuscript and 1 oral presentation at a national academic meeting.

2016-2017 Linda Cao, medical student at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 pending manuscript.

2016-2017 Adam Ferro, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 oral presentations at national academic meeting

2016-present Jacob Fiksel, Biostatistics PhD candidate at Johns Hopkins Bloomberg School of Public Health, Baltimore, MD. Co-author of 1 oral presentation at a national academic meeting.

2016-present Sarah Hazell, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 manuscript

2016-present Arti Parekh, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 manuscript

2016-present Avani Rao, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 3 manuscripts

2017-present Sarah Nicholas, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 manuscript

2017-present Sarah Hazell, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 manuscript

2018-present Christen Elledge, Radiation Oncology resident at Johns Hopkins School of Medicine, Baltimore, MD. Co-author of 1 poster presentations at a national academic meeting

Thesis committees

None

Training grant participation
None

Educational Program Building/Leadership

2014-2015 Chief Resident, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins School of Medicine. In my capacity, I was responsible planning our resident educational lecture series, arranging for Grand Rounds speakers and Visiting Professor lectures, overseeing medical student rotations, creating resident rotation and call calendars, mentoring junior residents and medical students, and acting as a liaison between residents and other members of the department.

Educational Extramural Funding

None

CLINICAL ACTIVITIES

Certification

Medical, other state/government licensure

2010-2011 State of Massachusetts Medical License
2015 - present State of Maryland Medical License

Boards, other specialty certification

2017-present Board Certification in Radiation Oncology

Clinical (Service) Responsibilities

2016-present Attending Physician, Breast Oncology- Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins School of Medicine, attending 3.5 days/week

Clinical Program Building/Leadership

2015-present Facilitator, Palliative Radiotherapy Interdisciplinary Team, Johns Hopkins School of Medicine, Baltimore, MD

Clinical Extramural Funding

None

SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES

System Innovation and Quality Improvement efforts within JHM:

2013-present Improving palliative radiation delivery at Johns Hopkins. Primary Investigator: 75%. I lead a team of researchers in retrospectively evaluating our practice patterns of palliative bone irradiation at Johns Hopkins and presented these data in relation to national consensus guidelines during departmental and national academic meeting oral presentations. I created a decision support tool for clinical use that predicts survival for patients with symptomatic bone metastasis to guide

in clinical decision-making which I will be instituting within my department to improve adherence to national consensus practice recommendations.

ORGANIZATIONAL ACTIVITIES

Institutional Administrative Appointments

2013-2014 Member, Ethic Committee
2013-present Member, Housestaff Council

Editorial Activities

None

Editorial Board appointments
None

Invited Journal Reviewer
2016-present *Journal of Clinical Oncology*
2016-present *International Journal of Radiation Oncology*Biology*Physics*

Advisory Committees, Review Groups/Study Sections

2015-present Member, ASTRO Palliative Care Committee

Professional Societies

2012-present Member, Association of Residents in Radiation Oncology
2013-present Member, American Society of Clinical Oncology
2014-present Member, International Society of Paediatric Oncology, Young Investigator Steering Committee
2018-2019 Appointed member, American Society for Radiation Oncology, Committee on Health Equity, Diversity and Inclusion
2018-2019 Appointed member, American Society for Radiation Oncology, Research Grants Evaluation Subcommittee

Conference Organizer, Session Chair

None

Consultantships

None

RECOGNITION

Awards, Honors

2005 Howard Hughes Research Scholar, Cornell University, Ithaca, NY
2005 Magna cum laude honors for thesis entitled: Factors affecting mycorrhizal fungi growth in wetland ecosystems, Cornell University, Ithaca, NY
2010 Honors Award in Research for thesis entitled: Patients' experiences of religion and spiritualty in advanced cancer: a qualitative research study to guide spiritual care in the medical setting, Harvard Medical School,

Boston, MA

2011 Intern of the Year Award, Harvard Cambridge Health Alliance

2014 Travel Award, American Radium Society Annual Meeting

2014 Travel Award, American Society of Clinical Oncology Annual Meeting

2014 Workshop Scholarship, AACR/ASCO Workshop: Methods in Clinical Cancer Research

2014 Young Investigator Award, International Society of Paediatric Oncology Annual Congress, Toronto, Ontario, Canada

2014-2015 Chief Resident, Radiation Oncology, Johns Hopkins Department of Radiation Oncology and Molecular Radiation Sciences, Baltimore, MD

2015 Excellence in Patient Care Award, Miller-Coulson Academy, Johns Hopkins Hospital, Baltimore, MD

2018 Teaching Award, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Hospital, Baltimore, MD

2018 First Prize Presentation, Annual Research on Aging Showcase, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

2018 Best of ASTRO Award in Palliative Radiation Oncology, American Society for Radiation Oncology

Invited Talks, Panels

9/12/13 Speaker, Cancer Outcomes & Health Services Research Interest Group Meeting, Baltimore, MD

3/16/18 Panelist, The Ninth Biennial Johns Hopkins Breast Cancer Conference, Baltimore, MD

4/28/18 Panelist, 4th Annual Johns Hopkins Breast Cancer Survivorship Day, Baltimore, MD

5/11/18 Keynote Speaker, Johns Hopkins Breast Cancer Research Retreat, Baltimore, MD

3/22/19 speaker, Allegheny Health Network Updates in Breast Cancer, Pittsburg, PA

OTHER PROFESSIONAL ACCOMPLISHMENTS

National Scientific Meeting Presentations

2009 ASTRO Annual Meeting, Chicago, IL. Predictors of symptomatic failure after palliative radiation therapy for multiple myeloma. Presented by: Sara Alcorn MD

2012 ASTRO Annual Meeting, Boston, MA. Multisite Assessment of the Utility of Daily Cone Beam CT in Achieving Clinical CTV-PTV Setup Margin. Presented by: Sara Alcorn MD

2012 ASTRO Annual Meeting, Boston, MA. Assessing utility of daily cone beam CT in head and neck cancers: Effect of disease site. Presented by: Sara Alcorn MD

2012 ASTRO Annual Meeting, Boston, MA. Utility of daily cone beam CT in predicting setup within clinical CTV-PTV margins in lung radiotherapy. Presented by: Sara Alcorn MD

2012 ASTRO Annual Meeting, Boston, MA. Radiation dose to the floor of mouth muscles predicts swallowing complications after chemoradiation in oropharyngeal squamous cell carcinoma. Presented by: Rachit Kumar MD

2012 ASTRO Annual Meeting, Boston, MA. Analysis of cone beam CT shifts in image-guided radiation therapy for abdominopelvic soft-tissue sarcomas. Presented by: Andrew Sharabi MD

2013 American Society of Clinical Oncology Annual Meeting, Chicago, IL. Patterns of palliative radiation near the end of life: A single-institution retrospective analysis. Presented by: Sara Alcorn MD (Awarded a Travel Award)

2013 ASTRO Annual Meeting, Atlanta, GA. A Comparison of clinical outcomes of adult and pediatric medulloblastoma. Presented by: Sara Alcorn MD

2013 ASTRO Annual Meeting, Atlanta, GA. Utility of remarking regimens for improving setup accuracy in definitive lung radiotherapy. Presented by: Lauren Douglass, RT therapy

2013 ASTRO Annual Meeting, Atlanta, GA. Comparison of setup accuracy by immobilization type in image-guided lung radiotherapy. Presented by: Annette Souranis, RT therapy

2014 American Society of Clinical Oncology Annual Meeting, Chicago, IL. Pre- and post-radiation lymphopenia predicts survival in management of bone metastases. Presented by: Sara Alcorn MD

2014 American Society of Clinical Oncology Annual Meeting, Chicago, IL. Patterns of chemotherapy near the end of life for patients receiving palliative bone radiotherapy. Presented by: Powell Perng MD

2014 American Radium Society Annual Meeting, St. Thomas VI. Prospective and real-time of image-guided CNS radiotherapy across a multi-national pediatric consortium: Methodology and considerations. Presented by: Sara Alcorn MD (Awarded a Travel Award)

2014 ASTRO Annual Meeting, San Francisco CA. Comparison of setup accuracy with low-dose and standard-dose CBCT in pediatric and adult brain image-guided radiotherapy. Presented by: Minh Phuong Huynh-Le, MS III

2014 ASTRO Annual Meeting, San Francisco CA . A predictive model for survival following palliative radiation for bone metastases. Presented by: Sara Alcorn, MD

2014 ASTRO Annual Meeting, San Francisco CA. Predictors of setup accuracy in image-guided CNS radiotherapy: Prospective data from a multi-national pediatrics consortium. Presented by: Sara Alcorn, MD

2014 ASTRO Annual Meeting, San Francisco CA. Analysis of factors complicating treatment for bone metastases: Why are patients not receiving single fraction radiotherapy? Presented by: Sara Alcorn, MD

2014 ASTRO Annual Meeting, San Francisco CA. Nutritional parameters predict survival in chemoradiation for esophageal cancer. Presented by: Amanda Choflet, RN

2014 ASTRO Annual Meeting, San Francisco CA. Reduced lymphocytopenia following stereotactic body radiation therapy (SBRT) for spine metastases compared with conventional radiation therapy (CRT). Presented by: Omar Mian MD

2014 International Society of Pediatric Oncology (SIOP) Annual Congress, Toronto, Ontario Canada. Low-dose cone-beam CT protocol for image-guided CNS radiotherapy: Predictors of setup accuracy from a multi-national pediatric consortium. Oral presentation by: Sara Alcorn MD (Awarded the Young Investigator Award)

2015 ESTRO Annual Meeting, Barcelona Spain. Practice patterns of stereotactic radiotherapy in pediatrics: Results from an international pediatric research

consortium. Presented by: Sara Alcorn MD

2015 ASTRO Annual Meeting, San Antonio TX. Set-up Accuracy in Image-Guided CNS Radiation Therapy: Final Analysis from a Prospective Low-Dose Cone-beam CT Protocol from a Multi-national Pediatrics Consortium. Presented by: Sara Alcorn MD

2016 Association for Clinical and Translational Science Annual Translational Science Conference, Washington DC. Use of dynamic data modeling for optimizing survival predictions in palliative radiotherapy. Presented by: Sara Alcorn MD

2016 ASTRO Annual Meeting, Boston MA. Clinical outcomes of palliative radiotherapy for pediatric oncology patients. Presented by: Avani Rao, PGY-3

2016 ASTRO Annual Meeting, Boston MA. Practice Patterns of Palliative Radiation Therapy in Pediatric Oncology Patients Amongst an International Pediatric Research Consortium. Presented by: Avani Rao, PGY-3

2016 SIOP Annual Meeting, Dublin Ireland. Practice patterns of palliative radiation therapy in pediatric oncology patients in an international pediatric research consortium Presented by: Avani Rao, PGY-3

2016 SIOP Annual Meeting, Dublin Ireland. Clinical outcomes of palliative radiotherapy for pediatric oncology patients. Presented by: Avani Rao, PGY-3

2017 Association for Clinical and Translational Science Annual Translational Science Conference, Washington DC. Use of a computer-based decision tool to optimize shared decision-making between oncology patients and providers in palliative radiotherapy. Presented by: Sara Alcorn MD

2017 RSNA Annual Meeting, Chicago IL. Bolus Technique in Post-Mastectomy Radiotherapy: Practice Patterns and Acute Toxicity Outcomes. Oral presentation by: Adam Ferro, PGY-4

2018 ASTRO Annual Meeting, San Antonio TX. Precision of Two Low-Dose Abdomen/Pelvis CBCT Protocols for Alignment to Bone and Soft Tissue in Pediatric Patients Receiving Image-Guided Radiation Therapy. To be presented by: Avani Rao, PGY-5

2018 ASTRO Annual Meeting, San Antonio TX. Acute Toxicity Outcomes and Dosimetric Implications from Incidental Irradiation of Adjacent Tissues in Tangent Field Hypofractionated Breast Radiotherapy. To be presented by: Sara Alcorn, MD

2018 ASTRO Annual Meeting, San Antonio TX. Optimized Survival Evaluation to Guide Bone Metastases Management: Developing an Improved Statistical Approach. Oral presentation to be given by: Sara Alcorn, MD (Awarded Best of ASTRO Selection)

BRIEF BIOGRAPHICAL SKETCH

Dr. Sara Alcorn was born on October 5, 1983, in Mariposa, CA, and she grew up in the Central Valley of California. After graduating from Golden Valley High School, she studied ecology and sociology at Cornell University, where she graduated with Honors for her thesis regarding symbiotic fungi in wetland plants. She then attended Harvard Medical School, again graduating with Honors for her thesis on spiritual and religious themes cited by patients end-stage cancer. She also earned a Master of Public Health at the Harvard School of Public Health, where she studied family and community health as and research methods. After graduation in 2010, she completed internship at Harvard's Cambridge Health Alliance before starting residency in Radiation Oncology at the Johns Hopkins Hospital, where she served as Chief Resident during her fifth year. Since completing residency, Dr. Alcorn has served as an attending physician at the Johns Hopkins Hospital, with promotion to Assistant Professor in 2018.

Dr. Alcorn has focused her clinical and research efforts on the improvement of clinical outcomes and quality of life in the fields of breast and palliative radiotherapy. She established the foundations of her current research through earlier applications of big data analysis, including of assessments of setup accuracy to improve radiotherapy delivery, patterns of care in the management of metastatic cancer, and relationships between dose, treatment technique, and patient-reported adverse effects in breast radiotherapy. She was awarded a KL2 Career Development Award through the National Institutes of Health, which permitted her to complete the work described in this thesis. Her next steps include building decision support platforms that incorporate patient preference in an effort to promote shared decision-making. She is a member of the Committee on Health Equity, Diversity and Inclusion and the Research Grants Evaluation Subcommittee for the American Society for Radiation Oncology.