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Imaging and clinical characteristics predict near-term disablement from bone metastases: implications for rehabilitation

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Abstract

Objective—Bone metastases produce severe functional declines in some patients with cancer, but have little impact on others. Distinguishing which patients with bone metastases are at risk for near-term disablement may improve the appropriate and timeliness and referrals for rehabilitation services.

Design—Prospective cohort study

Setting—National Cancer Institute designated comprehensive cancer center imbedded in a tertiary medical center

Participants—Data were collected from the 78 members of a 311-patient cohort with Stage IIIB or IV Non-Small Cell (NSCLC) or Extensive Stage Small Cell Lung Cancer who developed new or progressive imaging-confirmed bone metastases during the 2-year course of the study.

Main Outcomes—Functional capabilities were assessed at 3–4 week intervals over the study's 2-year duration with the Activity Measure for Post-Acute Care Computer Adaptive Test (AM-PAC CAT).

Results—Seventy-eight (78) participants developed new or progressive bone metastases during the study. A majority was male and 83% had NSCLC. Metastases were most frequently located in the ribs (N=62), pelvis (N=49), or the thoracic (N=60) and lumbar spine (N=44). While, neither the number of bone metastases nor their specific location was associated with near-term changes in patient mobility, their association with pain or a focal neurological deficit was strongly associated with large declines in mobility. Similarly, patients whose imaging studies revealed new metastases and the expansion of established metastases were more likely to lose mobility.

Conclusions—The total burden, specific locations, and overall distribution of bone metastases did not predict disablement. Patients with lung cancer-associated bone metastases are at markedly

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increased risk for declining mobility when their metastases are expanding in size and increasing in number, or are associated with pain or with new neurological deficits.

Introduction

Although the need for a better understanding of the impact of advanced cancer on patients' functioning is well recognized,¹ much remains to be learned.² Bone metastases provide a case in point as they are known to engender severe disablement and increase health care utilization, yet some patients with extensive osseous metastases experience few, if any, adverse sequelae.³ Extensive efforts have been invested in the development of pathological fracture risk prediction rules,^{4–6} however similar efforts to develop an improved understanding of patient- and metastasis-level characteristics that predict the likelihood and magnitude of impending functional loss remain lacking.⁷ This is not a trivial issue as functional preservation is a key aim of cancer care delivered with palliative intent. Further, clinical decision making regarding the cost-to-benefit ratio of surgical, radiation, and antineoplastic treatments often hinges on the likelihood that a patient's performance status will remain stable or improve. Lung cancer (LC) offers an opportunity to better understand the factors that produce cancer-related disablement as it avidly metastasizes to bone and is known to produce physical impairment.^{8,9}

It has been widely accepted that bone metastases contribute significantly to patients' functional losses.³ Initial work by our group that studied a large cohort of patients with late stage LC, confirms this impression and provides an estimate of the magnitude of these losses in that patients with new or progressive bone metastases experienced abrupt functional declines that exceeded twice our assessment tool's minimal clinically important difference (MCID) in LC.¹⁰ However, the variance was also large and suggested that, even when symptomatic, some bone metastases have minimal impact on patients' ability to function while others are devastating.

The ability to distinguish the patients with bone metastases whose function is most likely to precipitously decline could inform management by aiding clinicians in assessing the appropriateness of different treatment options, e.g. surgery, radiopharmaceuticals, rehabilitation, etc. This study was designed to test our hypothesis that specific patient- and imaging-level characteristics predict near-term declines in the functionality of among patients with advanced stage LC and bone metastases. Because patients with advanced cancer inconsistently receive validated rehabilitation services,^{11–13} a related aim was to provide the medical, radiological, and surgical oncologists who manage patients with guidance as to whether and when to refer their patients for rehabilitation services.

Methods

Subjects and enrollment

The data utilized in this study were collected from the 78 members of a previously described 311 member late stage LC patient cohort¹⁰ who developed new or progressive imaging-confirmed bone metastases during the 2-year course of the study. All participants in the cohort had Stage IIIB or IV Non-Small Cell Lung Cancer (NSCLC) or Extensive Stage

Small Cell Lung Cancer (SCLC) at the time of enrollment. All cohort members' imaging studies and reports were reviewed as part of the study and all had their functional capabilities assessed by the Activity Measure for Post-Acute Care Computer Adaptive Test (AM-PAC CAT) at 3–4 week intervals. This study was approved by the Mayo Clinic Institutional Review Board.

Data collection

Data were collected from three sources: 1) verbally from patients (AM-PAC CAT and symptom numerical rating scale (NRS) scores), 2) Mayo Clinic electronic medical records (EMRs) and outside reports, and 3) neuroradiologic imaging review. AM-PAC CAT and NRS scores were telephonically collected over a 2-year interval by research assistants at enrollment and every 3–4 weeks thereafter until study completion, drop out, or death. Efforts to contact participants began 3 weeks after their last telephonic contact and continued until a patient either withdrew from the study or died.

Information abstracted from the EMR and outside records included type and stage of LC, Charlson Index,¹⁴ patient demographics and clinical characteristics, any treatment(s) administered for bone metastases, the clinical indication for obtaining the imaging that revealed new/progressive metastases, and whether the patient was symptomatic at the time of imaging. The reasons for imaging were classified as: 1) Pain, 2) Neurological deficit, 3) Routine screening, 4) Initial staging, 5) Non-pain symptom, and 6) Other. Treatments for bone metastases were characterized as: 1) Palliative radiation, 2) Interventional pain procedure, 3) Surgery, 4) initiation/change of chemotherapy, and 5) Other. For purposes of the analyses described below, imaging indication and treatments were treated as binary indicator variables and linked to the scan that precipitated either a change or the consideration of a change in management. All medical records were abstracted separately by three cancer rehabilitation physicians (AC, KT, & TP) with disagreements being resolved through an in-person consensus process involving all three physicians.

All imaging studies obtained within 8 weeks of an AM-PAC CAT data collection point were reviewed by experienced, board-certified, and fellowship trained musculoskeletal radiologists (NM and MR). Information recorded for each scan included: 1) Type of scan (CT Chest, CT Abdomen, CT Pelvis, Whole Body PET/CT, Whole Body Bone scan, MRI Pelvis, MRI C-spine, MRI T-spine, MRI L-spine); 2) Location of bone metastases (coded as binary); 3) Presence of bilateral or unilateral metastases for ribs, sacrum, pelvis, humeri, and femurs; and 4) Whether the scan led to a patient's initial diagnosis with bone metastases or revealed new and/or progressive metastases.

Patient reported outcomes (PROs)

AM PAC CAT—The AM-PAC is an item response theory-based functional assessment tool. Although the AM-PAC is comprised of three domains; Mobility, Daily Activities, and Applied Cognition,^{15,16} only the 132 item Mobility item bank^{17,18} was utilized in this study.^{12,13} Each item queries respondents regarding the amount of difficulty they experience performing a specific activity. Response options include “none,” “a little,” “a lot,” and

“unable.” The AM-PAC Mobility item bank demonstrates validity, reliability, and responsiveness when administered via CAT platform.^{10,15–17,19–22}

Symptom Numerical Rating Scale (NRS)—The eleven-point pain NRS has been extensively validated as a means to assess symptom intensity among patients with cancer.^{18,19} The scale ranges from 0 (none) to 10 (as bad as it can be).^{23,24,20,21,19,20} Participants were asked to rate their “worst pain,” fatigue, and dyspnea over the past seven days preceding each assessment point.

Statistical Analyses

Assessment intervals—The telephonic collection of AM-PAC CAT scores was not temporally linked to any aspect of participants’ clinical care, e.g., oncology clinic visits, imaging tests, chemotherapy/radiation treatment, etc. Since the primary outcome and unit of analysis was change in AM-PAC CAT score between two assessment points, we created score intervals that either included or were close to the date of the imaging studies. Given previous work suggesting that the impact of bone metastases on domains related to physical function may extend beyond the acute detection and treatment interval, we chose to include all AM-PAC CAT intervals that fell partially or entirely within 8 weeks of a scan

Descriptive statistics were calculated for the demographic and clinical characteristics of participants with bone metastases present at the start of the study, as well as for all those whose scans revealed new or progressive bone metastases and could be linked to an AM-PAC CAT interval. Mixed models were used to estimate the association of change in AM-PAC CAT score over an interval, the dependent variable in all models, with patients’ clinical and demographic characteristics, as well as radiographic bone metastasis characteristics. Since bone metastasis location was a principal focus of this study, we utilized variables that reflected different aspects of this broader construct, namely 1) binary variables for specific large bones including individual vertebrae; 2) binary variables for bone groupings into larger connected structures, e.g., cervical spine, pelvis, etc.; 3) a continuous “total burden” variable that was the summation of all involved bones; and 4) a continuous weighted “total burden” variable that was the weighted summation of all involved bones. The rationale for this aggregation was to afford busy clinicians a straightforward means of reducing potentially complex bone metastasis distributions into simple binary or continuous variables for use in decision making. Univariate models were constructed initially. All models were adjusted for AM-PAC CAT interval length in days, and AM-PAC CAT score at the beginning of the interval. For categorical variables that were significant in univariate models, the referent category was changed in serial models to allow comparison between all possible category pairs. Multivariate mixed models were constructed in a stepwise fashion with the ordering of variable inclusion determined by the Wald test p value of coefficients in the univariate models. The threshold for inclusion in the multivariate model was a coefficient Wald test p value ≤ 0.10 . Using a similar stepwise approach, logistic mixed models were constructed to determine which covariates were significantly associated with 2.5-, 5.0-, 7.5- and 10-point decreases in mobility scores during an interval. In these models, an $\alpha < 1.0$ was considered significant. Conventional diagnostics were performed for all models. Analyses were conducted in STATA version 13.0.

Results

Participants

Table 1 lists the demographic and clinical characteristics of the 78 members of the patient cohort with imaging studies that revealed new or progressive bone metastases. A majority was male, 63%, and had NSCLC, 83%. Participants' mean age was 63 (SD 10.3) years. Forty percent had a benign musculoskeletal disorder (e.g., chronic back pain, osteoarthritis), 26% chronic obstructive pulmonary disease, 21% coronary artery disease, and 9% a neurological disorder.

Imaging studies

The characteristics of the 113 imaging studies linked to AM-PAC CAT score intervals are outlined in Table 2. A majority consisted of CT scans with 68 (60%), 34 (30%), and 26 (23%) including the chest, abdomen, and pelvis, respectively. An additional 32 (28%) were whole body PET/CT scans extending from skull vertex to thighs. Routine imaging to assess progression was the most common reason for imaging. Metastases were most frequently noted in individual participants in the ribs (N=62, 55%), pelvis (N=49, 43%), thoracic spine (N=60, 53%), and lumbar spine (N=44, 39%). Long bones were involved less often, femur (N=20, 18%) and humerus (N=21, 19%). The largest number of scans, (N=43, 38%), led to patients' initial diagnoses with bone metastases. Roughly a quarter revealed expansion of established metastases (N=26, 23.0%), or both expansion of existing and development of new metastases (N=30, 27%). Image interpretation most commonly led to management with palliative radiation, (N=36, 32%), or the initiation/change of chemotherapy (N=28, 25%). Only 9 (8%) studies led to operative treatments. Still fewer studies, 4 (4%) triggered treatment by pain proceduralists. Table 3 lists the frequency with which isolated components, e.g., C1 vertebra, contained bone metastases at both the scan and interval level.

AM-PAC CAT score intervals

The mean duration of the 273 inter-AM-PAC CAT score intervals linked to imaging studies; the unit of analysis, was 35.5 days (SD 11.9, range 13 to 91 days). The mean beginning AM-PAC CAT score 62.6 (SD 8.2, range 14.6 to 94.0) and the mean intra-interval AM-PAC CAT score reduction (i.e., functional worsening) was -1.8 (SD 7.2, range -49.4 to 24.4). Mean NRS scores for pain, dyspnea, and fatigue, obtained concurrently with AM-PAC CAT scores and at the beginning of an interval averaged 3.9 (SD 3.3, range 0 to 10), 2.6 (SD 2.6, range 0 to 10), and 4.4 (SD 2.6, range 0 to 9), respectively.

Univariate models

Table 4 lists variables whose coefficients were significant in the adjusted univariate mixed models. Management with the need for an interventional pain procedure (-8.97, SE 2.55), and a neurological deficit being the indication for imaging (-6.37, SE 1.88) were significantly associated with large decrements in patients' mobility, both exceeding three times the AM-PAC's 1.5 point MCID in LC.¹⁰ Neither delivery of palliative radiation, nor the initiation/change of chemotherapy was significantly associated with changes in mobility. Each point in a patient's NRS "worst pain" score at the beginning of an interval was

associated with a roughly 0.5-point drop in their mobility score over the course of the subsequent interval. The decision to administer palliative radiation was associated with significantly reduced mobility (-3.07 , SE 0.91). Additionally, patients whose images revealed both the expansion of established bone metastases and the development of new metastatic sites, relative to patients whose scans revealed only new metastases or expanding metastases, or led to their initial diagnosis with bone metastases, were more likely to decline in mobility. No variable reflecting the location or regional/total burden of bone metastases was significantly associated with changes in mobility: 1) binary variables for specific large bones including individual vertebrae; 2) binary variables for bone groupings into larger connected structures, e.g., cervical spine, pelvis, etc.; 3) a continuous “total burden” variable that was the summation of all involved bones; and a continuous weighted “total burden” variable.

Multivariate models

The results of the final multivariate mixed model are presented in Table 5. As in the univariate models, the need for treatment with a pain procedure or imaging triggered by a neurological deficit was strongly associated with loss of mobility, with the magnitude and significance of the coefficients, -8.31 (SE 2.42) and -6.28 (SE), respectively, changing little relative to the univariate models. Similarly, the coefficient associated with the presence of new and expanding metastases remained fairly stable in the multivariate model at -3.35 (SE 1.07), $p=0.002$. NRS “worst pain” scores were also retained in the multivariate model.

Logistic models

Covariates associated with specific degrees of mobility loss during an interval; 2.5-, 5.0-, 7.5-, and 10.0 points, differed slightly from those identified in the linear multivariate mixed model and are presented in Table 6. Of note, no covariate was significant in all four logistic models. However, at least one covariate reflective of pain intensity, e.g., pain as the indication for imaging, a pain procedure as a component of bone metastasis management, was significant in each model. The presence of new and progressive metastases on imaging was significant in three of the four models; more than any other covariate. Imaging obtained to evaluate a neurological deficit was highly significant in the logistic models for 7.5- and 10-point reductions in mobility scores, essentially models to predict major degradations in function. These latter models had C statistics of or well exceeding 0.8, indicating excellent predictive capabilities.²⁵ The models were reasonable (5.0-point) or worse (2.5-point) at predicting smaller declines in mobility.

Discussion

In this study we described the temporal evolution of the anatomical distribution, burden, and progression, by imaging, of bone metastases detected among a cohort of patients with late stage LC and estimated associations of demographic, imaging and clinical characteristics with changes in patients’ mobility. To the best of our knowledge, this effort was unique in that a precise estimate of participants’ mobility prior to the detection of bone metastases was utilized to estimate changes in their functional status over time periods during which bone metastases were detected and treated.

This effort yielded several notable findings. First, neither the overall burden of bone metastases, nor the location of specific metastases, apart from involvement of the sacrum which appeared to have a protective effect relative to other locations, was associated with changes in patients' mobility. Second, the presence of pain or a focal neurological deficit was strongly associated with declines in mobility. Last, patients whose imaging revealed the expansion of established metastases, as well as new metastatic sites, were more likely to lose mobility. Collectively these findings suggest that general characteristics that reflect disease virulence and aggressiveness, e.g., propensity to invade neural tissue, produce painful metastases and progress rapidly and widely, may offer more useful guidance for decision making than the specific locations and cumulative burden of bone metastases. Reassuringly, our finding that the spine, ribs, and pelvis were most commonly involved accords with previous reports in the literature regarding the distribution of bone metastases.^{26,27}

Our finding must be tempered by clinical common sense. Specifically, the distribution and structural characteristics of bone metastases are clearly not immaterial to patients' functional wellbeing. Large lytic metastases that compromise bone cortex and are situated in the femoral neck or other load bearing structures are prone to fracture which will inevitably and precipitously undermine patients' functioning.⁶ However, our results suggest that, outside the relatively discrete context of impending or actual pathological fractures (which may have been rapidly ameliorated by treatment), the behavior of bone metastases, particularly their capacity to invade other tissues and cause pain, is most informative with regards to a patient's future mobility. Patients whose bone metastases both expand and spread to new sites are at significantly higher risk for disablement. Whether the expanding and spreading metastases directly mediate functional losses, or are simply epiphenomena reflective of worsening cancer is not trivial. If the non-bone related properties of a cancer are responsible, e.g. total body tumor burden, cachexia, etc., then antineoplastic treatments may be indicated or a transition to comfort cares. In contrast, if the bone metastases are responsible for patients' loss of mobility, then treatments directed at the metastases may be the best means of preserving their function.

What near-term practical utility may these bone metastasis-based models to predict patients' future functional capabilities offer? First, such models may help to identify patients in need of a multi-disciplinary approach to functional preservation that includes rehabilitation services and pain management, irrespective of concurrent surgical or radiation treatments. These models could also be used to determine the nature and intensity of needed services, as well as the acuity of need. Patients with bone metastases, related neurological deficits and severe pain (7/10) are at risk for drastic declines in their mobility, as reflected by the predicted 8- to 10-point drop in their AM-PAC CAT scores, Table 4. A 10-point drop in AM-PAC CAT score equates to transitioning from community to low level household-mobility, or even non-ambulatory status and institutionalization.²⁸ The social, familial and fiscal implications of such transitions can be profound. Such patients may require near-term inpatient rehabilitation or a careful reexamination of their care goals. Decision making regarding surgical and other invasive management approaches, which pose notable risk to patients with Stage IV cancer, may incorporate the functional prognoses offered by such these models when weighing pros and cons and estimating the functional outcomes, e.g., return to work, community-level mobility, of different treatment options.

This study is, to the best of our knowledge, the first to estimate functional losses associated with bone metastasis characteristics. As such it represents an important contribution to the literature. None-the-less, like any study, it has strengths and weaknesses which warrant consideration in interpreting our findings and planning future studies. A salient strength is that a patients' function was well documented before and after their diagnoses with new or progressive bone metastases through the use of a rigorously validated and highly discriminative measure of function. Further, in addition to the data collected for each scan by experienced musculoskeletal radiologists, we also collected extensive non-bone metastasis demographic, PRO, and clinical data relevant to participants' functional status, allowing us to estimate the contribution of these factors to functional decline.

Study limitations

Along with its strengths, the study has its limitations. We did not collect clinician-rated function or objective performance data such as a 6-minute walk or Timed Up and Go. However, studies in disabled and non-disabled populations have established that PROs are equally and, at times, more discriminative in distinguishing patients' functional capabilities than either clinician-rated or performance assessment tools.²⁹ Additionally, we did not collect information regarding the size of bone metastases or the extent to which they involved cortical bone. This was not feasible with all of the imaging modalities included in this study. Further, it would not have aligned with our goal of identifying information routinely available to practicing clinicians for improved decision making. The fact that some imaging studies, e.g., PET/CTs and bone scans, encompassed large anatomical regions, while others were more focused, e.g., cervical spine MRI, produced a data set that did not comprehensively capture all bone metastases at each radiographic assessment point. Since an absence of information typically biases to the null (the effect of non-differential errors in covariate measurements that reduces the apparent effect of a covariate on the dependent variable)³⁰, it is possible that we committed a β -type error by inappropriately accepting the absence of an association between patients' mobility and the location, distribution and overall burden of their bone metastases. However, we do not believe this to be the case since we found no suggestion of any signal. If a larger study was able to demonstrate an association, it would likely be small and of little relevance. Last, our study population was restricted to patients with lung cancer which is known to have a limited prognosis, to engender a heavier and more intense symptom burden than other cancers, and to produce extra-osseous effects that degrade function, e.g., cachexia and brain metastases.³¹ Therefore, our results cannot be directly generalized to patients with bone metastases related to other cancers.

Conclusion

The total burden, specific locations, and overall distribution of bone metastases did not predict disablement. Patients whose bone metastases are both expanding and spreading to new sites, and associated with pain and/or neurological deficits are at markedly increased risk for near-term declines in their mobility indicating a need to consider comprehensive management that may include rehabilitation and/or pain management services.

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Table 1

Demographic and clinical characteristics of participants with imaging that revealed bone metastases

Gender, % male	60.3% (N 47)
Age	63.2 (SD 10.3)
Primary caregiver	
Spouse	80.8% (N 63)
Child	10.3% (N 8)
Parent	2.6% (N 2)
Sibling	2.6% (N 2)
Other	3.9% (N 3)
Histology	
Stage IV NSCLC	83.3% (N 100)
Extensive Stage SCLC	16.7% (N 13)
Comorbidities	
Neurological disorder	6.4% (N 5)
CAD	20.5% (N 16)
COPD	25.6% (N 20)
Musculoskeletal disorder	39.7% (N 31)
Charlson index	8.8 (SD 2.2)

Table 2

Characteristics of the 113 scans linked to AM-PAC CAT score-based intervals.

Total	N=113	%
Imaging modality *		
CT chest	68	60.2
CT abdomen	34	30.1
GT pelvis	26	23.0
Bone scan	16	14.2
PET CT	32	28.3
MRI cervical spine	4	3.5
MRI thoracic spine	10	8.8
MRI lumbar spine	12	10.6
MRI pelvis	3	2.7
Indication †		
Pain	60	53.1
Neurological deficit	8	7.1
Scheduled assessment for progression of disease	69	61.1
Initial staging	5	4.4
Non-pain symptom	6	5.3
Location of metastases		
Skull	0	0.0
Scapula	25	22.1
Humerus	21	18.6
Clavicle	15	13.3
Sternum	27	23.9
Ribs	62	54.9
Pelvis	49	43.4
Periacetabular	34	30.1
Acetabular	9	8.0
Iliac	41	36.3
Obturator ring	32	28.3
Femur	20	17.7
Cervical vertebrae	9	8.0
Thoracic vertebrae	60	53.1
Lumbar vertebrae	44	38.9
Sacrum	29	25.7
Progression		
Initial Diagnosis	43	38.1
New site(s)	14	12.4
Expansion	26	23.0
New site(s) + expansion	30	26.5
Treatment		

Total	N=113	%
Palliative radiation	36	31.9
Pain procedure	4	3.5
Surgical management	9	8.0
Chemotherapy initiated or changed	28	24.8

* Some imaging procedures were performed in conjunction, therefore percentages do not add to 100.

† Multiple indications may have been listed in the medical record, therefore percentages do not add to 100

Table 3

Frequency with which discrete components of integrated osseous structures contained metastases at the scan- and interval-level; count, mean total involvement, and involvement, of any component (binary)

	Isolated component		Total		Any	
	Scan	Interval	Scan	Interval	Scan	Interval
C1	1	2				
C2	2	3				
C3	2	3				
C4	2	3	2.22	1.85	9	20
C5	2	3				
C6	4	8				
C7	7	15				
T1	21	55				
T2	31	05				
T3	20	55				
T4	24	69				
T5	21	59				
T6	28	73	5.23	5.68	60	147
T7	29	74				
T8	34	90				
T9	28	71				
T10	25	67				
T11	25	63				
T12	28	74				
L1	26	62				
L2	30	82				
L3	28	74	3.07	3.27	44	111
L4	23	66				
L5	28	79				
Obturator ring	32	83				
Periacetabular	34	90	2.42	2.43	48	124
Acetabulum	9	18				

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	Total			Any		
	Scan	Interval	Interval	Scan	Interval	Interval
Iliac	41	110				
Isolated component						

Table 4

Results of adjusted univariate mixed models to predict AM-PAC CAT score changes.

Variable	Coefficient	Robust Standard Error	P value	Lower limit	Upper limit
Management					
Pain procedure	-8.97	2.55	<0.001	-13.96	-3.97
Palliative radiation	-3.07	0.91	0.001	-4.85	-1.29
Indication for Imaging					
Neurological deficit	-6.37	1.88	0.001	-10.04	-2.69
Imaging interpretation					
Initial diagnosis [*]					
New site(s)	0.30	1.26	0.81	-2.16	2.77
Expansion	1.52	1.10	0.17	-0.63	3.67
Expansion + New site(s)	-3.84	1.11	0.001	-6.01	-1.67
Symptoms					
Worst pain [†]	-0.47	0.15	<0.001	-0.76	-0.19

^{*} Comparator is imaging that led to an initial diagnosis of bone metastases

[†] Worst pain rated at the beginning of an assessment interval

Table 5
Results of adjusted multivariate mixed model to predict AM-PAC CAT score changes.

Variable	Coefficient	Robust Standard Error	P value	95% Confidence Interval	
Management					
Pain procedure	-8.31	2.42	0.001	-13.05	-3.56
Indication for imaging					
Neurological deficit	-6.28	1.77	<0.001	-9.75	-2.81
Imaging interpretation					
Initial diagnosis [*]					
New site(s)	-0.09	1.2	0.940	-2.44	2.26
Expansion	1.38	1.06	0.190	-.69	3.46
Expansion + New site(s)	-3.35	1.07	0.002	-5.44	-1.26
Symptoms					
Worst pain [†]	-0.31	.14	0.027	-.58	-0.03

^{*} Comparator is imaging that led to an initial diagnosis of bone metastases

[†] Worst pain rated at the beginning of an assessment interval

Results of logistic mixed models to identify variables associated with 2.5-, 5.0-, 7.5-, and 10.0-point reductions in AM-PAC CAT scores With coefficients expressed as odds ratios

Table 6

	Pnt 2.5		Pnt 5.0		Pnt 7.5		Pnt 10.0 [‡]	
N	Coeff	p value	Coeff	p value	Coeff	p value	Coeff	p value
91			59		30		21	
Symptomatic *			2.01	0.19	10.14	0.036		
Pain indication			0.49	0.078	0.29	0.033		
Pain procedure					4.16	0.177	3.83	0.196
Neurological deficit					8.84	0.006	4.87	0.049
Sacral metastasis			0.4	0.025	0.43	0.171	0.32	0.146
Palliative radiation			1.81	0.152				
Progression and new Metastases [‡]	1.78	0.075			1.66	0.004	2.73	0.059
C statistic	0.66		0.70		0.87		0.80	

* Patient described as symptomatic in clinical documentation at the time of imaging

[‡] Comparator is all other progression patterns

[‡] Symptomatic dropped due to perfect prediction of failure, therefore predictive capacity in clinical application potentially superior