Predicting Outcomes of Indeterminate Bone Lesions on ^{18}F-DCFPyL PSMA PET/CT Scans in the Setting of High-Risk Primary or Recurrent Prostate Cancer

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Indeterminate bone lesions (IBLs) on prostate-specific membrane antigen (PSMA) PET/CT are common. This study aimed to define variables that predict whether such lesions are likely malignant or benign using features on PSMA PET/CT. **Methods:** ^{18}F-DCFPyL PET/CT imaging was performed on 243 consecutive patients with high-risk primary or biochemically recurrent prostate cancer. IBLs identified on PSMA PET/CT could not definitively be interpreted as benign or malignant. Medical records of patients with IBLs were reviewed to determine the ultimate status of each lesion. IBLs were deemed malignant or benign on the basis of evidence of progression or stability at follow-up, respectively, or by biopsy results; IBLs were deemed equivocal when insufficient or unclear evidence existed. Post hoc patient, lesion, and scan variables accounting for clustered data were evaluated using Wilcoxon rank-sum and χ^2 tests to determine features that favored benign or malignant interpretation. **Results:** Overall, 98 IBLs within 267 bone lesions (36.7%) were identified in 48 of 243 patients (19.8%). Thirty-seven of 98 IBLs were deemed benign, and 42 were deemed malignant, of which 8 had histologic verification; 19 remained equivocal. Location and SUV_{max} categorical variables were predictive of IBL interpretation ($P = 0.0201$ and $P = 0.0230$, respectively). For IBLs with new interpretations, 34 of 37 (91.9%) considered benign showed an SUV_{max} of less than 5 or exhibited focal uptake without coexisting bone metastases; 37 of 42 (88.1%) deemed malignant demonstrated an SUV_{max} of at least 5 or were present with coexisting bone metastases. Logistic regression predicted IBLs with a high SUV_{max} (univariable: odds ratio [OR], 9.29 [$P = 0.0016$]; multivariable: OR, 13.87 [$P = 0.0089$]) or present with other bone metastases (univariable: OR, 9.87 [$P = 0.0112$]; multivariable: OR, 11.35 [$P = 0.003$]) to be malignant. **Conclusion:** IBLs on PSMA PET/CT are concerning; however, characterizing their location, SUV, and additional scan findings can aid interpretation. IBLs displaying an SUV_{max} of at least 5 or present with other bone metastases favor malignancy. IBLs without accompanying bone metastases that exhibit an SUV_{max} of less than 5 and are observed only in atypical locations favor benign processes. These guidelines may assist in the interpretation of IBLs on PSMA PET/CT.

Key Words: prostate cancer; PET/CT; PSMA; bone metastases; indeterminate bone lesions

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Prostate-specific membrane antigen (PSMA) PET/CT is a highly sensitive and specific diagnostic tool enabling early detection of primary and metastatic prostate cancer (PCa) (*1*). PSMA overexpression is observed in nearly 95% of all cases of primary PCa, and PSMA expression on histology correlates with tumor aggressiveness (*2*). The recent Food and Drug Administration approval of ^{18}F-DCFPyL has increased the use of PSMA PET/CT in staging and in suspected early metastatic involvement of patients with high-risk PCa and biochemically recurrent (BCR) PCa (*3*). However, ^{18}F-DCFPyL and other PSMA PET tracers commonly demonstrate nonspecific and indeterminate PSMA uptake in soft tissue or bones with unclear or no anatomic correlation on CT (*4–6*). To interpret lesions with PSMA uptake, several PSMA PET/CT reporting systems, including the European Association of Nuclear Medicine standardized reporting criteria (E-PSMA), the PSMA Reporting and Data System (PSMA-RADS), and the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE), were developed with structured categories for lesions that are benign, likely benign, indeterminate or equivocal, likely malignant, and malignant (*7–9*). Lesion classification is based on location, size, SUV_{max}, relative uptake compared with expected physiologic uptake, number of lesions with PSMA uptake, and scan-based regional distribution (*7*); however, lesions classified as indeterminate require follow-up for definitive assessment. Since metastatic PCa commonly involves bones, PSMA uptake in indeterminate bone lesions (IBLs) that are benign processes, such as fibrous dysplasia, Paget disease, and hemangiomas, can easily be mistaken for bone metastases and lead to inappropriate changes in patient management (*10–14*). On the other hand, IBLs interpreted as benign when they are true metastases may delay necessary treatment. Recent PSMA PET/CT imaging studies using ^{18}F-PSMA-1007 (*5,15,16*), ^{68}Ga-PSMA-11 (*6,16–18*), and ^{18}F-DCFPyL (*4*) tracers have investigated indeterminate PSMA-avid uptake in soft-tissue and bone lesions. Although these studies associate certain imaging features with IBLs that are usually benign—specifically, a single IBL located in the rib with subtle PSMA uptake and no

additional metastases—there lacks consensus regarding features that predict which IBLs are likely malignant. In this study, we defined features of ^{18}F-DCFPyL PET/CT that predict IBLs as benign or malignant.

MATERIALS AND METHODS

Patient Population

Between July 2017 and October 2021, ^{18}F-DCFPyL PET/CT imaging was performed on 243 consecutive patients with histologically confirmed high-risk PCa or BCR PCa without prior evidence of metastatic disease. All patients gave written informed consent before participating in a prospective clinical trial (NCT03181867). In a post hoc subanalysis, patients included in this study had at least 1 IBL in the presence or absence of other soft-tissue or bone lesions suggestive of metastatic PCa on ^{18}F-DCFPyL PET/CT. Patients without an IBL were excluded.

^{18}F-DCFPyL PET/CT Imaging

^{18}F-DCFPyL was synthesized under good manufacturing practices as previously described (*19*). Patients received an intravenous injection of ^{18}F-DCFPyL (mean, 262.7 ± 37.9 MBq [7.10 ± 1.02 mCi]; range, 167.6–317.8 MBq [4.53–8.59 mCi]) and underwent whole-body PET/CT after a 2-h uptake period (3 min/bed position) using a 3-dimensional time-of-flight Discovery MI DR scanner (GE Healthcare) with a 20-cm coronal and a 70-cm axial field of view. Image reconstruction applied an attenuation-corrected 3-dimensional iterative maximum-likelihood expectation-maximization algorithm using 29 subsets, 3 iterations, time-of-flight, a point spread function regularization parameter of 6.0, and a gaussian postprocessing filter with a 4.1-cm kernel. A low-dose unenhanced CT scan (120 kV, 60 mAs) was acquired with each PET scan for attenuation correction and anatomic coregistration.

Assessment of PSMA-Avid IBLs

^{18}F-DCFPyL PET/CT images were prospectively interpreted by 2 expert nuclear medicine physicians (both with 5 y of experience reading PSMA PET/CT images). Scans of patients with at least 1 PSMA-avid IBL, defined as focal radiotracer uptake in bone without correlative sclerotic or lytic features on CT, or not clearly benign—equivalent to the definition of the PSMA-RADS-3B category (*9*)—were further analyzed. Two different readers retrospectively reviewed each IBL using medical records until January 2022, including other pre-PSMA and post-PSMA follow-up imaging, therapeutic interventions, and laboratory or biopsy-based pathology, to provide an updated interpretation as benign, malignant, or equivocal based on the following criteria.

Benign findings were, first, no evidence of progression (i.e., a stable lesion without morphologic changes) between pre-PSMA and PSMA imaging for patients without follow-up or between pre-PSMA and post-PSMA imaging for patients with follow-up; second, PCa-negative biopsy findings for the lesion; or third, stable lesion uptake before therapeutic intervention at follow-up ^{18}F-DCFPyL PET/CT.

Malignant findings were, first, evidence of progression (i.e., new lesions, sclerotic changes, or lytic changes) between pre-PSMA and PSMA imaging for patients without follow-up or between pre-PSMA and post-PSMA imaging for patients with follow-up; second, PCa-positive biopsy findings for the lesion; or third, evidence of lesion regression after therapeutic intervention based on a significantly reduced SUV_{max} at follow-up ^{18}F-DCFPyL PET/CT imaging.

TABLE 1
Clinical Characteristics of Patients with IBLs

Characteristic	Data
Patients with IBL	48
Age (y)	
Median	66
Range	53–79
PSA (ng/mL)	
Median	4.00
Range	0.44–203.8
Disease phase	
BCR PCa	35
High-risk PCa	13
TNM stage	
Not available	5
T1	10
T2	13
T3	15
T2 N1	1
T3 N1	3
T4 N1	1
Gleason grade group	
1	2
2	14
3	10
4	7
5	15

Data are number of events unless otherwise indicated.

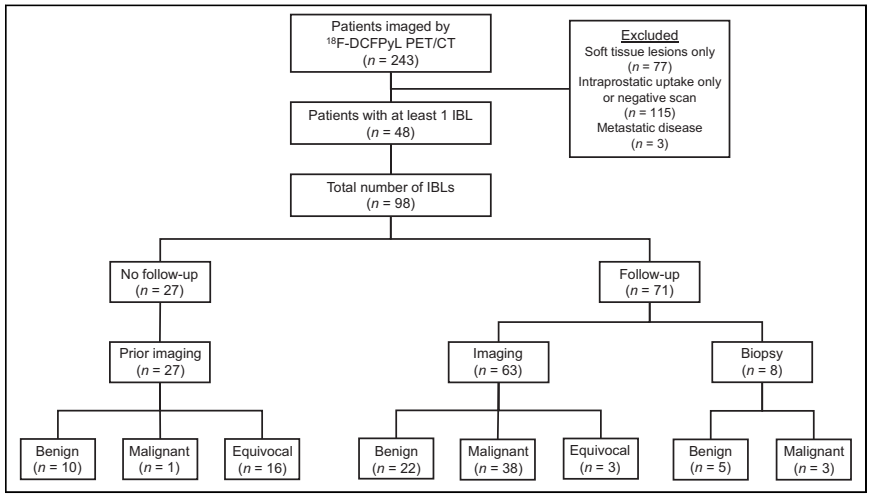

FIGURE 1. Flowchart of patient selection criteria and lesion-level follow-up for patients with at least 1 IBL. Interpretations (benign, malignant, or equivocal) are shown for IBLs with no follow-up (prior imaging) and follow-up (imaging or biopsy).

TABLE 2
Histopathologic Assessment of IBL Biopsy Specimens

Location of biopsied IBL	SUV_{max}	CT morphology	Histopathologic result	
			Finding	Features
Fifth rib	4.1	Sclerotic	Benign	Fibrous replacement of bone marrow
Third rib	3.6	Sclerotic	Benign	Trabecular bone with trilineage hematopoiesis
Sixth rib	2.9	Sclerotic	Benign	Fragments of bone marrow fibrosis
Ischium bone	17.4	Mixed sclerotic/lytic	Malignant	Metastatic prostate adenocarcinoma involving bone and bone marrow
Iliac bone	1.3	Negative	Malignant	Metastatic moderately differentiated prostate adenocarcinoma
Clavicle bone	3.1	Negative	Benign	Bone marrow with trilineage hematopoiesis
Seventh rib	2.8	Sclerotic	Benign	Bone with hematopoietic bone marrow
Fifth rib	15.2	Mixed sclerotic/lytic	Malignant	Metastatic poorly differentiated prostate adenocarcinoma

Equivocal findings were insufficient evidence for either a benign or a malignant interpretation due to a short follow-up duration or unclear imaging features.

Statistical Analysis

The association of IBL characteristics with an updated interpretation was evaluated using the Wilcoxon rank-sum test for clustered data (*20*) in continuous variables and the χ^2 test for clustered data (*21*) in categorical variables to account for multiple lesions sampled per patient. The characteristics evaluated included SUV_{max}, anatomic location; CT features (including no CT abnormality in bone sclerotic, lytic, and mixed sclerotic and lytic bone morphologies; and the presence or absence of other suggestive findings on PSMA imaging (including lymph node or bone uptake). Tests were repeated considering distribution of benign versus malignant lesion assignments as well as benign versus malignant versus equivocal categorizations. Logistic regression analysis, using weighted generalized estimation equations with working independence correlation structure to account for the correlation of multiple lesions per patient, was performed to evaluate the association of IBL characteristics with a malignant interpretation. Lesions with an equivocal clinical or pathologic interpretation were excluded from logistic regression analysis. Weights were calculated as $100 \times (1/N_p)$, where N_p is the number of lesions sampled per patient. P values of less than 0.05 were considered significant for all statistical analyses. Receiver-operating-characteristic curve and Youden index ([sensitivity + specificity − 1]) analyses were evaluated for the SUV_{max} of IBLs to be interpreted as benign or malignant. The SUV_{max} threshold with the highest sensitivity and lowest false positive rate was selected to differentiate lesions likely to be malignant.

RESULTS

Incidence and Interpretation of IBLs

Overall, 98 IBLs within 267 total bone lesions (36.7%) were identified in 48 of 243 patients (19.8%). Patient characteristics are shown in Table 1, and patient selection criteria with lesion-level follow-up and IBL interpretation based on review are shown in Figure 1. Median patient follow-up was 7.5 mo (range, 0.0–54.0 mo); median lesion follow-up was 4.8 mo (range, 1.1–54.0 mo) in patients with post-PSMA follow-up and 9.1 mo (range, 0.0–54.0 mo) in patients with prior imaging only. Detailed patient follow-up information was used to interpret each IBL as benign, malignant, or equivocal (Supplemental Fig. 1; Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

The 98 IBLs had a median SUV_{max} of 3.6 (interquartile range, 2.3–9.8) and were identified in the pelvis (28.6%), spine (21.4%), ribs (39.8%), or other atypical locations including the scapula, clavicle, skull, sternum, and extremities (10.2%). Only 8 of 98 (8.2%) IBLs had biopsy confirmation—3 were malignant (metastatic prostate adenocarcinoma) and 5 were benign (Table 2). At the lesion level, 42 of 98 (42.9%) IBLs were considered malignant, 37 (37.7%) were benign, and 19 (19.4%) remained equivocal. Most IBLs were assessed as equivocal (18/19, 94.7%) because of short follow-up (<7 mo). At the

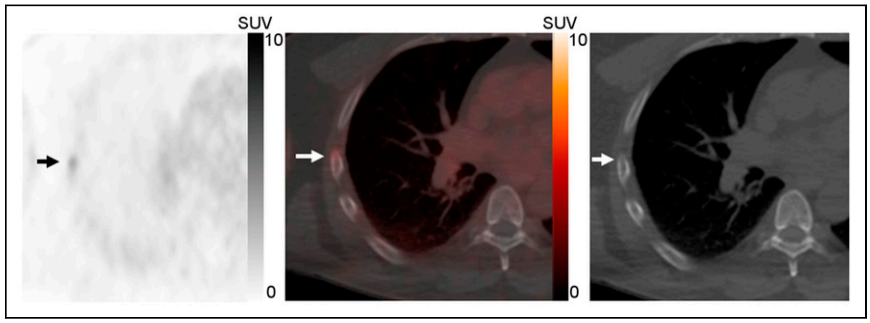

FIGURE 2. A 63-y-old patient with BCR PCa and PSA of 0.46 ng/mL. Axial ^{18}F-DCFPyL PET (left), ^{18}F-DCFPyL PET/CT (middle), and CT (right) images show a single area of subtle PSMA-avid uptake with SUV_{max} of 2.4 in the right fifth rib and no CT correlate (arrows). This IBL was determined to be benign based on negative 17-mo follow-up bone scintigraphy findings.

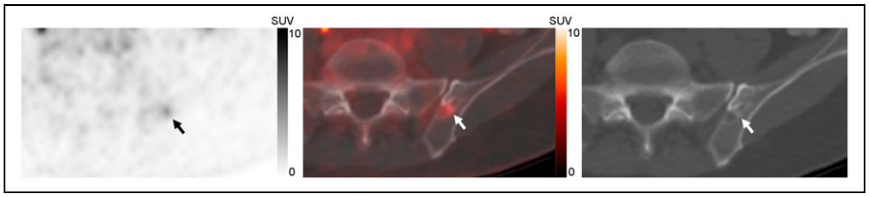

FIGURE 3. A 60-y-old patient with BCR PCa and PSA of 3.9 ng/mL. Axial ^{18}F-DCFPyL PET (left), ^{18}F-DCFPyL PET/CT (middle), and CT (right) images show a single area of subtle PSMA-avid uptake with SUV_{max} of 3.9 in left iliac bone and mixed sclerotic and lytic CT features (arrows). This IBL was stable for 4 mo and negative on 4 other staging modalities; thus, the IBL was interpreted as benign.

patient-level, 11 of 48 (22.9%) had a malignant IBL, 24 (50.0%) had a benign IBL, and 13 (27.1%) had equivocal findings; 1 patient with multiple IBLs had mixed determinations. Examples are given of patients with IBLs on ^{18}F-DCFPyL PET/CT which demonstrate benign (Figs. 2 and 3) or malignant (Fig. 4; Supplemental Fig. 2) characteristics based on their location, SUV_{max}, and CT morphology. PSMA PET/CT features in the pelvis (Fig. 3) and spine (Fig. 4) can show similarity but have different interpretations; thus, additional follow-up may assist with assessment.

Imaging Features of IBLs That Predict for Malignancy or Benignancy

Two lesion-based categorical variables were predictors for malignancy or benignancy: lesion location ($P = 0.0201$)—categorized as spine, pelvis, ribs, and other regions (e.g., skull, sternum, and scapula)—and lesion SUV_{max} ($P = 0.0230$)—categorized as less than 5 versus 5 or more (Table 3). No other ^{18}F-DCFPyL PET/CT–based continuous and categorical variables were predictive (Supplemental Table 2). Logistic regression analysis for benign versus malignant findings ($n = 79$) revealed that a high SUV_{max} (univariable: odds radio [OR], 9.29 [95% CI, 3.19–24.75; $P = 0.0016$]; multivariable: OR, 13.87 [95% CI, 1.91–100.9; $P = 0.0089$]) and the presence of additional bone metastases on the PSMA PET/CT scan (univariable: OR, 9.87 [95% CI, 2.00–48.82; $P = 0.0112$]; multivariable: OR, 11.35 [95% CI, 3.05–42.25; $P = 0.0030$]) were associated with malignancy (Table 4). Selection of an SUV_{max} threshold of at least 5 was based on receiver-operating-characteristic curve and Youden index analyses that maximized the sensitivity (71.4%, 30/42) for predicting IBLs as malignant with the fewest false positives (2.7%, 1/37) (Supplemental Fig. 3). Although this SUV_{max} threshold missed 12 of 42 (28.6%) IBLs with an SUV_{max} of less than 5 that were deemed malignant, 7 of these 12 IBLs were identified in the presence of other bone metastases. Therefore, a model incorporating all 3 ^{18}F-DCFPyL PET/CT imaging variables that predicted for malignancy or benignancy ($n = 79$) was developed to assess the likelihood that an IBL would be benign or malignant based on a single PSMA PET/CT scan (Fig. 5). Overall, 89.9% of the model's predictions agreed with our assessment, but 10.1% disagreed, including 5 false negatives and 3 false positives (Table 5). Although our model suggests that a single IBL located in the pelvis or spine with an SUV_{max} of less than 5 is probably benign, these are common sites for PCa bone metastases and represented a greater number of false negatives, such as the example in Figure 4. Ultimately, the relationship of these predictive variables may improve IBL interpretation on PSMA PET/CT scans (Fig. 6).

DISCUSSION

PSMA PET/CT can impact management decisions in patients with high-risk primary and BCR PCa, and multiple studies have demonstrated that up to 68% of predetermined interventions can change after PSMA PET/CT (*22,23*). Although the PSMA-RADS, PROMISE, and E-PSMA structured PSMA PET/CT reporting systems have improved lesion classification and interpretation based on particular imaging features, several lesions with PSMA uptake categorized as indeterminate or equivocal have been shown to be false positives (*11–13*) whereas some have been shown to be true positives at follow-up (*4,18*). A particular issue with PSMA PET/CT is the incidence of indeterminate lesions with mild focal uptake in bone and unclear or negative anatomic features; currently, these lesions require biopsy or follow-up imaging for definitive assessment. Interpreting such lesions as metastatic without sufficient evidence can have far-reaching implications for patients and lead to unnecessary interventions that alter a patient's quality of life. Understanding specific features that increase the certainty of interpreting IBLs as probably benign or probably malignant is, therefore, of great clinical importance.

Our study demonstrated that 3 PSMA PET/CT–based features predict IBL interpretation: the presence or absence of other bone metastases on the scan, IBL SUV_{max}, and IBL location. Prior studies investigating IBLs using a variety of PSMA PET tracers have mentioned that these particular features may predict interpretation or are important. Specifically, a follow-up ^{18}F-PSMA-1007 PET/CT study by Arnfield et al. monitoring 159 IBLs for more than 12 mo in 77 patients suggested that IBLs were likely benign when

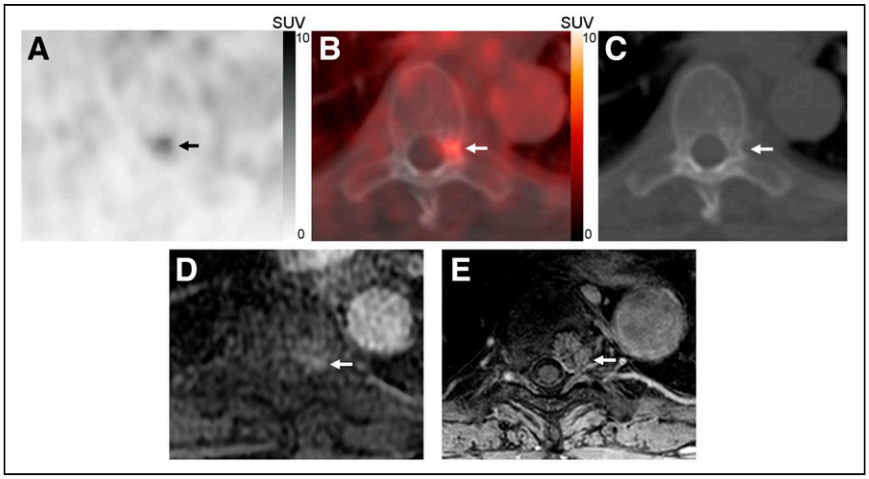

FIGURE 4. A 73-y-old patient with BCR PCa and PSA of 4.9 ng/mL. Axial ^{18}F-DCFPyL PET (A), ^{18}F-DCFPyL PET/CT (B), CT (C), pre-PSMA MRI (D), and follow-up MRI (E) images show a single area of subtle PSMA-avid uptake with SUV_{max} of 3.3 in left T8 lamina and subtle sclerotic CT features (arrows). This IBL became more prominent and enhanced over a 3-y period between retrospective MRI (D) and follow-up MRI (E) and was determined to be malignant.

TABLE 3
^{18}F-DCFPyL PSMA PET/CT-Based Variables That Predict IBL Interpretation (n = 98)

Predictive variable	Incidence (n = 98)	IBL interpretation			P*
		M (n = 42)	B (n = 37)	E (n = 19)	
Location					0.0201
Spine	28 (28.6%)	16	12	0	
Pelvis	21 (21.4%)	12	7	2	
Rib	39 (39.8%)	8	14	17	
Other	10 (10.2%)	6	4	0	
SUV_{max}					0.0230
<5	64 (65.3%)	12	36	16	
≥5	34 (34.7%)	30	1	3	

*For 3-way assessment (M vs. B vs. E) statistical significance is evaluated using χ^2 test for clustered data.
M = malignant; B = benign; E = equivocal.

showing an SUV_{max} of less than 7.2 in the absence of other definite bone metastases (*15*). In contrast, a multicenter ^{18}F-PSMA-1007 PET/CT study analyzing 351 IBLs with an SUV_{max} of less than 10 determined that SUV_{max} did not predict interpretation (*5*). Moreover, a follow-up ^{68}Ga-PSMA-11 PET/CT study by Chen et al. reported that 61 of 62 patients with primary PCa and a single rib IBL with a mean SUV_{max} of 3.0 were benign; however, 1 lesion showing an SUV_{max} of 2.2 later proved to be a metastasis (*18*). Lastly, a ^{18}F-DCFPyL PET/CT longitudinal follow-up study found that 3 of 14 IBLs showed changes indicative of malignancy (*4*). These prior studies collectively demonstrate that a single IBL in an atypical location in the absence of metastases is meaningful for predicting IBLs as benign but that SUV_{max} is not reliable. In addition, our findings agree with previous studies that no patient variables (including age, primary PCa, Gleason grade group, TNM stage, and serum prostate-specific antigen [PSA]) predict IBL interpretation.

There are some similarities between these prior studies and our findings regarding which IBLs favor benign outcomes; however, we expand on the current understanding of imaging features that predict IBLs for malignancy. First, we suggest that IBLs are likely malignant in the presence of other bone metastases, independent of SUV_{max} and location, but not necessarily with accompanying soft-tissue metastases. In our cohort, 7 of 48 patients with an IBL had no more than 3 other bone metastases, of which 3 of 7 also had lymph node involvement and 4 of 7 had no PSMA-avid lymph nodes. On the basis of our predictive model, 3 of the 4 patients with no PSMA-avid lymph nodes could be classified as oligometastatic and might have had the option to undergo local PCa interventions. Second, IBLs with an SUV_{max} of at least 5 after 2 h of ^{18}F-DCFPyL uptake increased the likelihood of malignancy. Of the 34 IBLs showing an SUV_{max} of at least 5, 30 of 34 (88.2%) were deemed malignant, and only 1 of 34 (2.9%) was a false positive lesion deemed benign whereas 3 of 34 (8.8%) were equivocal because of insufficient evidence. However, IBLs with an increased SUV_{max} can result from inflammatory events such as trauma or hemangiomas (*13*), as well as from benign bone remodeling processes such as fibrous dysplasia (*10*) or Paget disease (*24*). Although the SUV_{max} threshold of at least 5 after 2 h of uptake was feasible to classify 88.2% of IBLs as malignant for our cohort, this SUV_{max} threshold requires validation in separate cohorts receiving ^{18}F-DCFPyL PET/CT. Third, IBLs in typical locations were more

TABLE 4
Logistic Regression Analysis Showing OR at 95% CI for Clinically Relevant ^{18}F-DCFPyL PET/CT-Based Features That Predict IBLs as Benign vs. Malignant (n = 79)

^{18}F-DCFPyL PET/CT feature	Univariable analysis		Multivariable analysis	
	OR	P	OR	P
IBL located in pelvis	1.68 (0.48–5.96)	0.516	—	—
IBL located in spine	1.42 (0.55–3.65)	0.613	—	—
IBL located in ribs	0.38 (0.14–1.03)	0.170	—	—
IBL SUV_{max}	9.29 (3.49–24.75)	0.0016	13.87 (1.91–100.9)	0.0089
Other bone metastases	9.87 (2.00–48.82)	0.0112	11.35 (3.05–42.25)	0.0030
Other lymph node metastases	2.26 (0.62–8.26)	0.315	—	—

Data in parentheses are 95% CI. Features significantly associated with malignant interpretation were included in multivariable analysis.

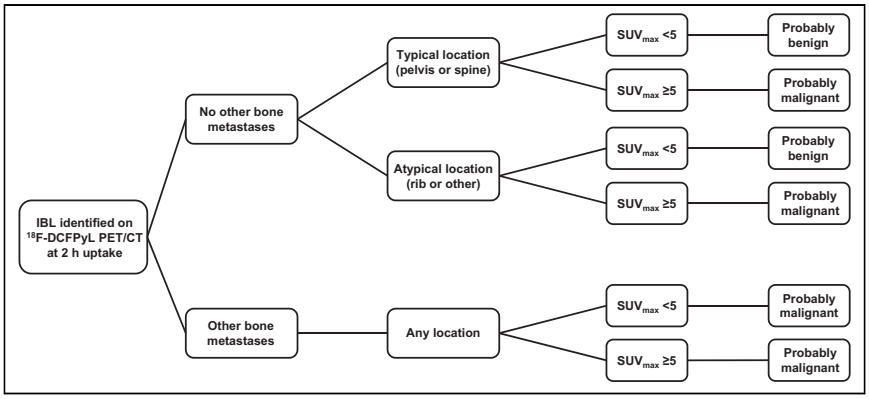

FIGURE 5. Model assessing the likelihood that an IBL is benign or malignant based on ^{18}F-DCFPyL PET/CT imaging variables that predicted for benignancy or malignancy (n = 79).

commonly malignant based on follow-up review, but the association of lesion location with SUV_{max} and other PSMA scan bone findings, particularly whether lesions are solitary, multifocal, or present with other bone metastases, can improve assessment as displayed in Figures 5 and 6.

Although these predictors can guide interpretation, follow-up imaging may be necessary when insufficient evidence is available or conflicting imaging features are present on other studies. In this scenario, equivocal interpretation avoids misdiagnosis, and follow-up imaging can assist with assessment. Of the 19 of 98 (19.4%) IBLs that remained equivocal in our study, 16 had no available post-PSMA follow-up records, 2 had short follow-up (<3 mo), and 1 had sufficient follow-up (12 mo) but CT changes were not clear enough for a definitive interpretation. Overall, most IBLs that were determined to be equivocal (14/19, 74%) showed an SUV_{max} of less than 5 and were located in the ribs without other bone metastases.

IBLs showing subtle PSMA uptake only outside the pelvis or spine in the absence of definite bone metastases are likely benign; however, malignancy is always possible. For example, in the ^{68}Ga-PSMA-11 PET/CT study mentioned earlier, 1 of 62 (1.6%) single rib IBLs with an SUV_{max} of 2.2 in the absence of other metastases demonstrated evidence of malignancy on follow-up imaging (*18*). In our study, only 1 of 42 (2.3%) IBLs was a single atypical lesion in the scapula that had a subtle SUV_{max} of 1.0 and no coexisting metastases but that nonetheless showed sclerotic progression consistent with malignancy. Considering common PSMA pitfalls, the SUV_{max} threshold of at least 5 minimized false positives in our study. However, among PET imaging protocols that use different uptake times or different PSMA tracers, there may be significant variation in SUV_{max} measurements, such as a higher lesion uptake on delayed scans (*19*) or a higher SUV_{max} for ^{18}F-PSMA-1007 versus ^{68}Ga-PSMA-11 (*17*). For instance, a recent ^{18}F-PSMA-1007 PET–guided biopsy study after 1.5 h of uptake demonstrated that 10 of 11 IBLs with a mean SUV_{max} of 12.5 (range, 5.1–26.0) were benign, indicating that several lesions were not clinically concerning despite exceeding a prior proposed SUV_{max} threshold of 7.2–11.1 after 2 h of uptake (*15,25*). Thus, standardized imaging protocols for each class of PSMA tracer are necessary before SUV_{max} can reliably serve as a predictor of risk of malignancy. Ultimately, pairing detailed patient history with these predictive imaging features may increase the predictive value of IBL categorization among different PSMA agents and scanning conditions.

Our study had 3 main limitations. First, the follow-up time for our patients was short (mean, 7.5 mo; range, 0.0–54.0 mo); thus, nearly 20% of the IBLs remained equivocal because of insufficient evidence. Second, only a minority of IBLs were biopsied (8%, 8/98) since biopsy was not always safe to obtain or accepted by patients; however, all biopsy results supported our predictive model. Despite careful analysis of imaging and clinical findings, the lack of pathology confirmation may misrepresent the true nature of some IBLs deemed benign or malignant. Third, our results are limited to one type of PSMA-targeted PET tracer, ^{18}F-DCFPyL, after 2 h of uptake, and quantitative SUV_{max} PET findings may not apply to other tracers scanned under different conditions. However, other variables such as location and additional bone findings may still be relevant with other tracers.

TABLE 5
Model Predicting the Likelihood That IBLs Identified on ^{18}F-DCFPyL PET/CT at 2 Hour of Uptake Are Benign or Malignant (n = 79)

Other PSMA-avid bone findings	IBL location	IBL SUV_{max}	Likelihood of interpretation	Interpretation accuracy
No bone metastases	Typical	<5	81.0% benign	True positive (n = 17); false negative (n = 4)
No bone metastases	Typical	≥5	94.7% malignant	True positive (n = 18); false positive (n = 1)
No bone metastases	Atypical	<5	94.4% benign	True negative (n = 17); false negative (n = 1)
No bone metastases	Atypical	≥5	100% malignant	True positive (n = 8)
Bone metastases	Any	<5	77.8% malignant	True positive (n = 7); false positive (n = 2)
Bone metastases	Any	≥5	100% malignant	True positive (n = 4)

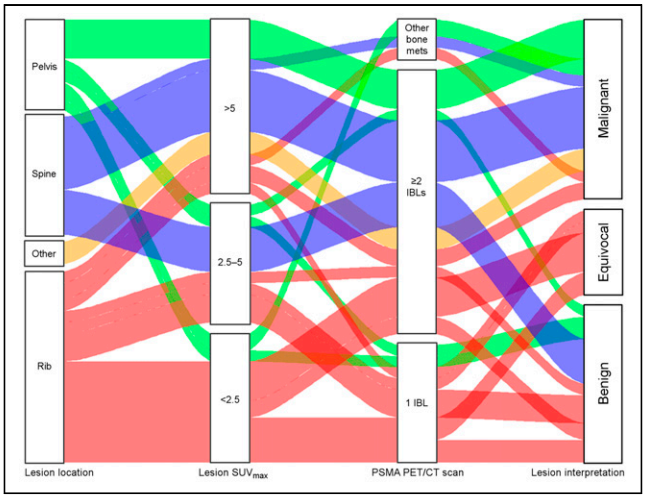

FIGURE 6. Sankey diagram showing the relationship of multiple predictive ^{18}F-DCFPyL features (n = 98). Specifically, lesion location, lesion SUV_{max}, and type of bone findings on a PSMA PET/CT scan are more likely associated with a particular lesion interpretation (right). Pathways with 1 lesion have been removed for clarity.

CONCLUSION

IBLs on PSMA PET/CT are concerning in patients with high-risk primary and BCR PCa; however, IBL location, SUV, and additional scan findings can aid interpretation. IBLs in any location with an SUV_{max} of at least 5 or with coexisting bone metastases irrespective of location and SUV_{max} have an increased risk for malignancy. Conversely, IBLs with an SUV_{max} of less than 5 that are present only in atypical locations such as the ribs without accompanying bone metastases are likely benign. These predictors may assist in decreasing the number of bone lesions on PSMA PET/CT that are truly indeterminate.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Can imaging-based features on PSMA PET/CT predict the likelihood that an IBL is benign or malignant?

PERTINENT FINDINGS: Categorizing IBL location and SUV_{max} can predict for malignancy versus benignancy in ^{18}F-DCFPyL PET/CT scans. An IBL with coexisting bone metastases or an IBL with an SUV_{max} of at least 5 after 2 h of uptake, independent of location, is suggestive of malignancy. An IBL in an atypical location such as the rib with an SUV_{max} of less than 5 after 2 h of uptake and without accompanying bone metastases is usually benign.

IMPLICATIONS FOR PATIENT CARE: Considering the location and SUV_{max} of IBLs and other findings on PSMA PET/CT scans can reduce the number of patients with an IBL by reassigning such lesions to either the benign or malignant category.

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