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FULL PAPER

Machine learning-based CT radiomics features for the prediction of pulmonary metastasis in osteosarcoma

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Objective: This study aims to build machine learning-based CT radiomic features to predict patients developing metastasis after osteosarcoma diagnosis.

Methods and materials: This retrospective study has included 81 patients with a histopathological diagnosis of osteosarcoma. The entire dataset was divided randomly into training (60%) and test sets (40%). A data augmentation technique for the minority class was performed in the training set, along with feature's selection and model's training. The radiomic features were extracted from CT's image of the local osteosarcoma. Three frequently used machine learning models tried to predict patients with lung metastases (MT) and those without lung metastases (non-MT). According to the higher area under the curve (AUC), the best classifier was chosen and applied in the testing set with

unseen data to provide an unbiased evaluation of the final model.

Results: The best classifier for predicting MT and non-MT groups used a Random Forest algorithm. The AUC and accuracy results of the test set were bulky (accuracy of 73% [95% coefficient interval (CI): 54%; 87%] and AUC of 0.79 [95% CI: 0.62; 0.96]). Features that fitted the model (radiomics signature) derived from Laplacian of Gaussian and wavelet filters.

Conclusions: Machine learning-based CT radiomics approach can provide a non-invasive method with a fair predictive accuracy of the risk of developing pulmonary metastasis in osteosarcoma patients.

Advances in knowledge: Models based on CT radiomic analysis help assess the risk of developing pulmonary metastases in patients with osteosarcoma, allowing further studies for those with a worse prognosis.

INTRODUCTION

Osteosarcoma (OS) is the most common primary malignant bone neoplasm, in children, adolescents, and young adults.¹ At presentation, 15–20% of patients show metastatic disease, mainly pulmonary (85–90%).² The survival rate of patients with the localized disease has improved with the introduction of multiple chemotherapeutic agents during treatment. However, the prognosis of patients with metastatic disease is still quite reserved.³ According to the EURAMOS-1 study, the largest OS trial performed to date, nearly four out of five patients with a non-metastatic disease and a wholly resected lesion are still alive five years later. Besides, the risk of relapse appears to reduce over time.⁴

CT of the chest is considered a non-invasive method and a reliable tool for diagnosing lung metastasis. However,

micrometastases, which are assumed to occur in 80 to 90% of OS patients, are not identified by the current diagnostic methods.⁵ Presently, there is a need to discover technologies that can better explain this disease's mechanisms, identify patients with a more reserved prognosis at the time of diagnosis, and allow therapeutic approaches to be initiated on a personalized basis.⁶

Imaging exams should no longer be the binomial visualization-interpretation, but instead, a database defined by complex numerical codes with hundreds and even thousands of specific characteristics of each disease. This concept has been analyzed and developed within the field of radiomics.⁷ The method is based on automated high-throughput extraction of quantitative imaging features and aims to capture the histological heterogeneity characterizing each

solid tumor individually.⁸ Initial studies through the extraction of radiomic attributes of soft tissue sarcomas have demonstrated that it is possible to assess overall survival⁹ and identify patients at risk of developing metastases.¹⁰ Machine learning is a subfield of artificial intelligence, being the most common approach for radiomics analyses with multiples applications in oncology, learning from available data to build decision-making models.¹¹

In osteosarcoma, CT is usually used to guide the primary lesion's biopsy, perform staging, and highly available at diagnostic centers. CT's extraction of radiomic features could probably identify patients at risk for developing lung metastases, which may reassess conventional therapeutic strategies. Therefore, this study aimed to analyze whether a machine learning model based on pre-treatment non-contrast-enhanced CT (NECT) radiomic features of the primary lesion could be predictive of metastases in patients with osteosarcoma.

METHODS AND MATERIALS

The ethical committee approved this retrospective study and waived the requirement for written informed consent.

STUDY PARTICIPANTS

All patients from January 2012 to June 2018 with the diagnosis of high-grade OS confirmed by histopathological examination were eligible for the study. Exclusion criteria were patients: without a pre-treatment NECT image of the primary bone lesion and the chest at presentation; without CT image of chest analyzed at follow-up sessions that took place every six months for two years; with follow-up less than 24 months after diagnosis; treated by protocols other than the one used at the institution; with poor imaging quality including artifacts and diagnosed with secondary or multifocal OS and skip metastasis.

The patients were classified according to the Musculoskeletal Tumor Society (MSTS) staging system after exclusion criteria. After a 2-year follow-up, the patients were further divided into two groups according to the presence (MT) or absence (Non-MT) of lung metastases. Patients from the MT group were those with multiple nodules at presentation or nonspecific nodules that increased in number or size during the 2-year follow-up on chest CT. Patients from the non-MT group have not demonstrated any suspicious nodules on chest CT exams during a 2-year follow-up.

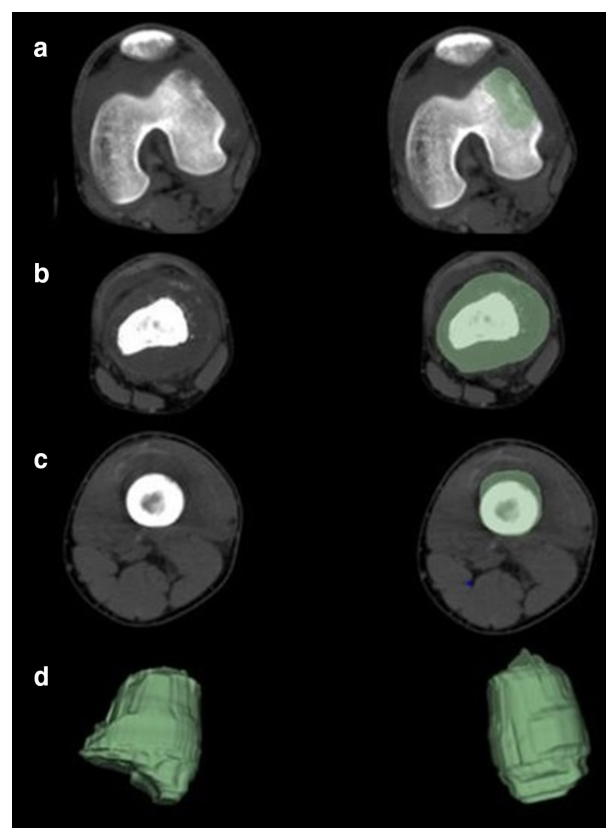
IMAGING PARAMETERS

The pre-treatment NECT images were acquired following the institutional protocol on a Philips brilliance scan, either 16 or 64 channels with a peak tube voltage of 120 Kvp, tube current between 200 and 300 mAs, rotation time of 0.5 s, and collimation of 16 × 0.6 mm. Axial images were reconstructed in a 512 × 512 matrix and with a slice thickness of 3.0 mm.

SEGMENTATION

The OS lesions were segmented by 3D-slicer software 4.10.2 version (<https://www.slicer.org/>) using a semi-automatic segmentation tool called "fill between slices." About five to six manual segmentation slices were made in the axial plane, from the most cranial to caudal tumor images, through a NECT. Next, the tool

Figure 1. Twenty-two years old, a young male with axial NECT image segmentation of a osteosarcoma of distal femur from the most cranial to caudal images (A,B,C) and the segment volume provided (D).



processed the data, and the result was provided as a segment volume (Figure 1). OS was recognized as any high abnormal attenuation, above 100 Hounsfield Units, or soft tissue (40–60 Hounsfield Units), both in intra- and extra-osseous compartments. When the sarcoma's intramedullary component reached the internal cortical layer, the cortical bone was included in the segmentation area. Tendons and neurovascular bundles with more than 50% circumferential involvement by the tumor tissue and periosteal reaction were also included. Articular effusions and areas of synovitis were not included. The segmentations were performed on 15 patients selected at random by three independent radiologists (A, B, and C) with 12, 3, and 1 year experience in orthopedic radiology to reduce operator-dependent bias. Dice Similarity Coefficients (DSC) were calculated using the Dice Computation module of 3D Slicer software to analyze the inter observer agreement. After five weeks, the same radiologists reanalyzed the selected patients' images to determine the intraobserver agreement.

Based on the 95% confidence interval, the intraclass correlation coefficient (ICC) was calculated for all radiomics features using SPSS statistical package v.20 (SPSS Inc, Chicago, IL) based on a mean-rating ($k = 3$), absolute-agreement, two-way mixed-effects model. All radiomics features susceptible to minor segmentation variances that received the reliability index test-retest with the ICC lower than 0.75 were excluded.

Preprocessing and radiomic features extraction

Radiomics features were extracted using Pyradiomics software v.2.2.0 (<https://www.radiomics.io/pyradiomics.html>) and further divided into four main classes: shape, intensity histogram or first-order features, texture or second-order features, and higher order features including wavelet and Laplacian Gaussian transforms filters.

Isotropic resampling was performed to receive a voxel size of $2 \times 2 \times 2$ mm, and first and second-orders features were calculated from a gray-level histogram composed of 64 bins. Higher order features were extracted from image reconstructions using wavelet filtering, yielding eight decompositions and Laplacian of Gaussian filters (sigma value of 3).

Radiomic features selection and machine learning model

The entire dataset was divided randomly into two samples: (i) training set containing 60% of the data used for features selection and to train the model and (ii) testing set containing 40% of hidden data to provide an unbiased final evaluation of the model.

A data augmentation technique for the minority class was performed due to the imbalance of data between MT and non-MT groups, along with feature's selection, training, and fine-tuning of the models were realized only in the training set to construct predictive models. The data augmentation technique was a synthetic minority oversampling technique (SMOTE). After SMOTE, both classes (non-MT and MT) in the training set had the same number of instances.

For features selection, using SPSS, only the stable features with the reliability index test-retest with the ICC higher than 0.75 were considered to feature selection in the training set. We also

removed features with a high correlation coefficient with the class (MT and non-MT) yet uncorrelated with each other using a *correlation-based-features selection* (CFS) algorithm using *Weka* (Waikato Environment for Knowledge Analysis) software, v.3.8.4 (<https://www.cs.waikato.ac.nz/ml/weka/>).

Random Forest, Naive Bayes, and Multilayer perceptron classifiers with 10-fold cross-validation in *Weka* software were used in the radiomic model. The classifier that demonstrated higher AUC was chosen as the final model and applied in the testing cohort, with unseen data, to provide an unbiased validation of the predictive model. (Figure 2).

STATISTICAL ANALYSIS

Statistical analysis were performed with SPSS software version 20. The differences in age, sex, and location of tumors between the two groups were assessed using an independent sample *t*-test, χ^2 test, or Mann-Whitney test, where appropriate. The significance level was set at 0.05.

Survival curves were compared between non-MT and MT groups and between patients with metastases at presentation and those who developed metastases during follow-up using the Kaplan-Meier method.

Several operating points from the analysis of the training set using 10-fold cross-validation from various thresholds constructed an empirical receiver operating characteristic (ROC) curve for each algorithm. The area under the ROC curve (AUC) was calculated to evaluate the performance of the radiomic model.

The best prediction algorithm in the training set was considered the one with a higher AUC, and it was applied in the test set. Patients were classified as having a high risk of lung metastases

Figure 2. Features selections steps used to build a radiomic signature and the best classifier algorithm to test the radiomics model.

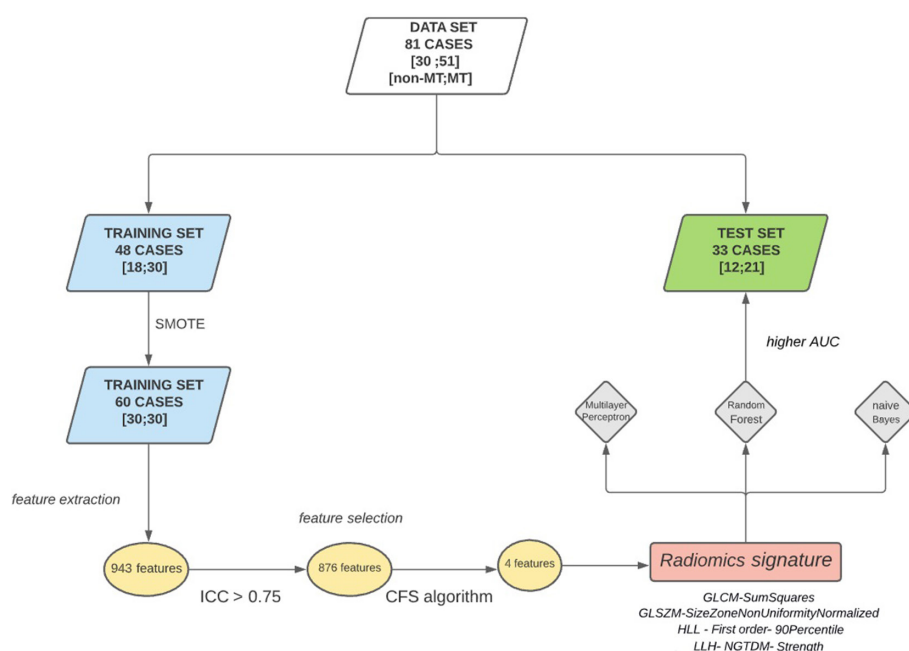
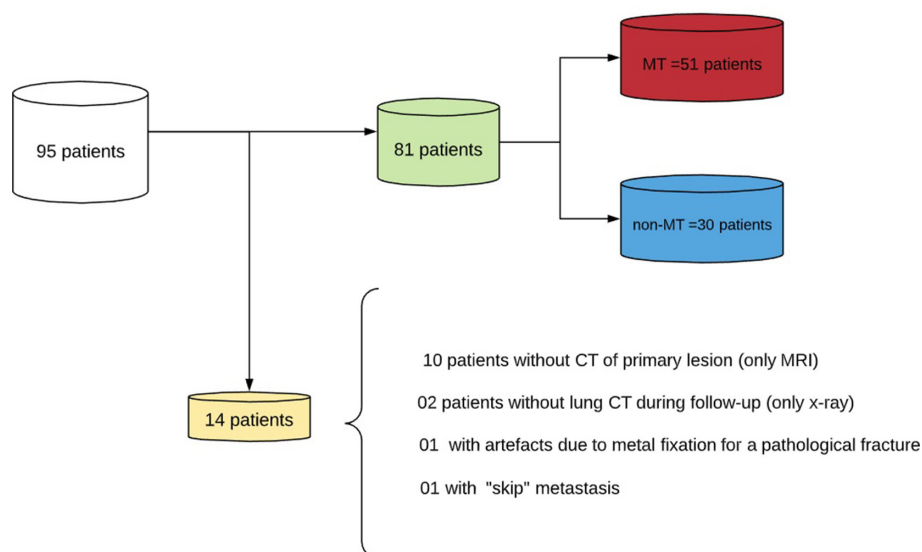


Figure 3. Flowchart for the selection of eligible patients.



(MT) if their predicted probability for each patient had a cutoff value of 0.5 or more. The performance of algorithms was also assessed in terms of accuracy, sensitivity, and specificity.

RESULTS

From a total of 95 patients diagnosed with a high-grade OS, the following patients have been excluded: ten patients without NECT of the primary lesion (only MRI), two without CT of the chest during follow-up (only chest X-ray), one with artifacts due to metal fixation for a pathological fracture and one with skip metastasis. In the end, a total of 81 patients with (MT, $n = 51$) and without (Non-MT, $n = 30$) lung metastases were eligible for the study. (Figure 3)

Out of 51 patients in the MT group, 32 patients already had pulmonary metastases and were classified as stage III, and 19 patients developed pulmonary metastases during 2-year follow-up. (Supplementary Material 1)

No significant differences in age, sex, and anatomical site of the tumor were found between the MT and non-MT groups. The knee region was the most frequent site of involvement in both groups. The majority of patients (58%) were classified as stage II B by the MSTs system. The characteristics of the patients included in this series are described in Table 1.

Except for one patient who died of complications after chemotherapy, non-MT patients were alive until the end of this study's observation period. In the MT group, patients with metastases' survival curve rate at the time of initial diagnosis were worse than the curve of patients who developed metastases during follow-up. (Figure 4).

Intra- and interobserver DSC were 0.88 and 0.83, respectively.

The training set had 48 patients ($n = 18$ non-MT and 30 MT), and after SMOTE, it was balanced ($n = 30$ non-MT x 30 MT). The test

set had 33 patients ($n = 12$ non-MT and 21 MT). A total of 943 features were extracted from the balanced training set. They were divided into four types, including shape features ($n = 14$), histogram or first-order features ($n = 19$), texture features or second-order ($n = 75$), and higher order using Laplacian Gaussian ($n = 92$) and wavelet filters ($n = 743$). (Supplementary Material 2)

Among the 943 features, 67 features had ICC < 0.75 , and they were excluded. Out of 876 features, only four had a high correlation coefficient with the class, though still uncorrelated with each other and fitted the final training model.

All four radiomics features that fitted the model (radiomics signature) derived from filters, two from Laplacian of Gaussian filters (sigma value of 3) (*GLCM-Sum Squares* and *GLSZM-Size ZoneNonUniformityNormalized*) and two from wavelet filters (*HLL - First order- 90 Percentile* and *LLH- NGTDM- Strength*) [H – high pass and L – Low pass sub-bands]. The boxplot of the features in radiomic models is illustrated in Figure 5.

Random Forest algorithm showed higher metrics than naïve Bayes and multilayer perceptron algorithms in the training and test set to evaluate non-MT and MT patients (Table 2 and Supplementary Material 3).

DISCUSSION

In the present study, we could predict the risk of developing lung metastasis in patients with a high-grade OS using machine learning-based CT radiomics features, at least in a 2-year follow-up period. The model proved to be reproducible and with high accuracy among patients using similar protocols and scans.

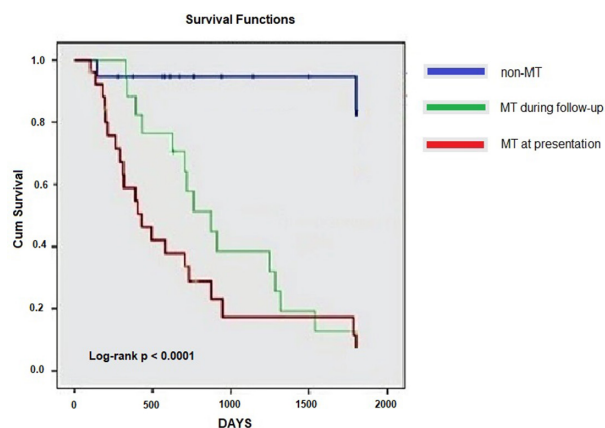
Approximately 20% of patients with osteosarcoma present with metastatic disease at the time of the initial diagnosis.^{2,12,13} Our study observed higher rates (39%) of lung metastases in the primary osteosarcoma's initial diagnosis (stage III). Because our institutions are tertiary reference centers in the treatment

Table 1. Demographics of the study participants

	Lung Metastasis			
	Yes (<i>n</i> = 51)	No (<i>n</i> = 30)	<i>t</i> / χ^2 value	<i>p</i> -value
Age (years)				
Mean $\pm$ SD	22 $\pm$ 12	21 $\pm$ 14	652.5 ^a	0.35
Range	4–63	6–58		
Gender				
Male	34	15	2.2 ^b	0.12
Female	17	15		
Anatomical location				
Distal femur	23	14		
Proximal femur	4	5		
Distal tibia	2	2		
Proximal tibia	13	6	4.32 ^b	0.56
Proximal humerus	6	1		
Proximal fibula	2	1		
Scapula	1			
Calcaneus		1		
Staging at presentation	(MTST) ^c			
I A; IB	N/A ^d	N/A		
II A	1	1		
II B	18	29		
III	32			

^aMann-Whitney^bChi-square test^cMusculoskeletal Tumor Society staging^dNot applicable

Figure 4. Kaplan-Meier curves for 5 years survival (*n* = 62) of patients without pulmonary metastases (non-MT) and with pulmonary metastases (MT) at presentation and pulmonary metastases arising during follow-up. In the Kaplan-Meier analysis, significantly shorter survival was observed in the MT group, mainly those with pulmonary metastases at presentation (log-rank *p* < 0.0001).

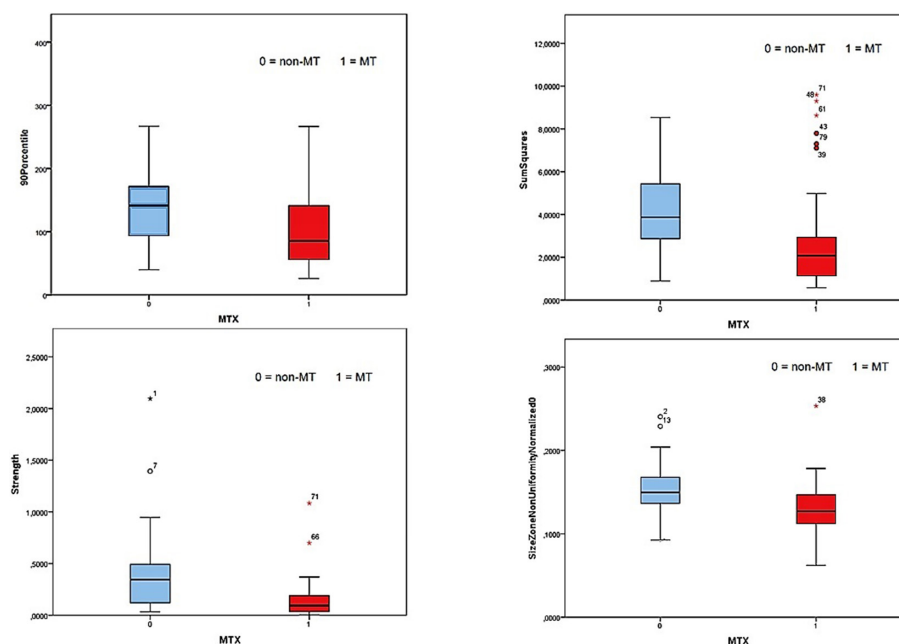


of sarcomas, more complex patients are referred for follow-up. Furthermore, we confirmed previous literature findings^{14,15} that age, sex, and anatomical location of the tumor are not different between MT and non-MT groups and should not be prognostic factors for the occurrence of pulmonary metastases.

As with other malignancies, the presence of metastases during the initial clinical investigation gives the patient with high-grade osteosarcoma a worse prognosis.¹⁶ Our study confirmed that patients with metastatic disease at presentation have a considerably higher risk of mortality than patients without metastatic disease. Hence, the construction of a prediction model would benefit the treatment and prognosis evaluation.

Segmentation is the most “critical, challenging, and contentious component” for radiomics analysis.¹⁷ In one previous study, the results of manual and semi-automatic segmentation of bone sarcoma using MRI showed high similarity (DSC >0.7) and an important reduction in segmentation time when using the semi-automatic method.¹⁸ The absolute value of DSC is difficult to interpret, but according to Zijdenbos et al¹⁹ and Bartko²⁰ DSC value is considered as low agreement <0.7, good agreement >0.7 or <0.8, and high agreement >0.8. According to

Figure 5. Boxplots show difference between patients without lung metastasis (0) and with lung metastasis in radiomics signature based on NECT images.



our findings (DSC >0.8), the semi-automatic method seems to be a reliable tool for the segmentation of bone sarcoma in the CT-based radiomics model.

Out of 943 features in our study, only four features fitted the model, two of them derived from wavelet filters. We achieved

high precision, accuracy, sensitivity, and specificity from CT images to predicting lung metastases. One previous study extracts texture features from bone computed radiography (CR) images to evaluate osteosarcoma's recognition rate using the wavelet features, and the accuracy, sensitivity, specificity, and ROC curves were higher than using the features derived from

Table 2. Performance of radiomics models for predicting lung metastases of osteosarcoma based on the operating point cutoff of 0.5 probability

Model	Training set			
	(n = 48) [non-MT = 18, MT = 30]			
	(n = 60 after SMOTE) [non-MT = 30, MT = 30]			
	Accuracy	Sensitivity	Specificity	AUC
	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Naives Bayes	78%	87% [26/30]	70% [21/30]	0.88
	(66–88%)	(69–96%)	(51–85%)	(0.79–0.96)
Random Forest	85%	83% [25/30]	87% [26/30]	0.93
	(73–93%)	(65–94%)	(69–96%)	(0.86–0.99)
Multilayer Perceptron	78%	77% [23/30]	80% [24/30]	0.79
	(66–88%)	(58–90%)	(61–92%)	(0.67–0.90)
Model	Test set (n = 33) [non-MT = 12, MT = 21]			
	Accuracy	Sensitivity	Specificity	AUC
	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Random Forest	73%	71% [15/21]	75% [9/12]	0.79
	(54–87%)	(48–89%)	(43–94%)	(0.62–0.96)

AUC, Area Under the Curve; CI, Confidence Interval; MT, with lung metastases; non-MT, without lung metastases.

the GLCM method.²¹ In another study, a delta-radiomics nomogram was used to evaluate pathologic responses after neoadjuvant chemotherapy in patients with high-grade osteosarcoma. Out of eight selected features, seven were derived from wavelet filters.²² Finally, a recent study analyzed survival prediction in high-grade osteosarcoma using radiomics of diagnostic CT. The five features most associated with the survival status were selected, three of them wavelet features.²³ Therefore, the use of wavelet features seems to play an essential role in texture analysis in osteosarcoma research.

As metastases is one the most important prognostic factor impacting the survival rate of patients with osteosarcoma,²⁴ several studies using clinical,²⁵ radiomics,^{10,26} and genomics²⁷ tried to predict pulmonary metastases. In the radiomics studies, one found a high prediction rate for pulmonary metastasis using FDG-PET and MRI in the extremities' soft tissue sarcomas.¹⁰ The other had substantial AUC, specificity, accuracy, and fair sensibility predicting osteosarcoma metastases from ¹⁸F-FDG-PET scans.²⁶ To the best of the authors' knowledge, a non-enhanced CT and machine learning method to predict pulmonary metastases in patients with osteosarcoma, reaching high performance, has not previously been well established in the literature. CT is a diagnostic method available worldwide,

cheaper than FDG-PET and MRI, and generally used in institutional protocols for staging and biopsy guidance of osteosarcoma. So, it should also be considered an excellent method to predict metastases.

There are several limitations to the present research. First, the study was retrospective, and the number of patients was relatively small. Second, there was an imbalance of the classes and simulated data with an oversampling technique. However, over-sampled techniques as SMOTE have been promising in imbalanced cancer data.²⁸ Briefly, for each sample of the minority class, the nearest neighbors of the same class were identified, and one was randomly chosen. The new synthetic sample lies on a random point of the line joining the two original samples.²⁹ Third, all exams used similar protocols and the same scanner manufacturer, so reproducibility among other scanners is not assured. Finally, a baseline reference study's lack of comparison limits understanding the radiomic model's added value.

In conclusion, artificial intelligence and machine learning strategies have gained attention in medical imaging research. They have provided insight into osteosarcoma metastases prediction, leading to diagnostic and therapeutic implications, bringing radiologists to the center of this discussion.

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