Differentiation of soft tissue and bone sarcomas from benign lesions utilizing ^{18}F- FDG PET/CT-derived parameters

Bo Chen
The first hospital of dalian medical university
Hongbo Feng
The first hospital of dalian medical university
Jinghui Xie
the first hospital of dalian medical university
Chun Li
the first hospital of dalian medical university
Yu Zhang
the second hospital of dalian medical university
Shaowu Wang (wsw_2018@163.com)
The second hospital of Dalian medical university

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Abstract

Background: Accurate differentiation between malignant and benign in soft tissue and bone lesions is essential for the prevention of excessive pathological biopsy and unplanned surgical resection. However, it remains a challenge and a standard diagnosis modality is urgently needed. The purpose of this study is to evaluate the usefulness of ^{18}F- FDG PET/CT-derived parameters to differentiate soft tissue sarcoma (STS) and bone sarcoma (BS) from benign lesions.

Methods: Patients who underwent pretreatment ^{18}F-FDG PET/CT imaging and subsequent biopsy to confirm malignant (STS and BS, n=37) and benign (n=33) soft tissue and bone lesions were retrospectively reviewed. The tumor size, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG) and heterogeneous factor (HF) of each lesion were measured. Univariate analysis and multivariate logistic regression analysis were performed to screen the significant risk factors to distinguish STS and BS from benign lesions. To establish a regression model based on independent risk factors, receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performances.

Results: Univariate analysis results showed that tumor size, SUVmax, MTV, TLG and HF of ^{18}F-FDG PET/CT imaging in STS and BS group were all higher than benign lesions group, the difference were statistically significant (all *P* value were<0.01). However, the multivariate regression model only included SUVmax and HF as independent risk factors, odds radios were 1.135(95%CI: 1.026~1.256, *P* =0.014), 7.869(95%CI: 2.119~29.230, P =0.002), respectively. The regression model was as follow: Logit (*P*) = -2.461+0.127SUVmax+2.063HF. The area under the ROC was 0.860 (95%CI: 0.771~0.948, *P* <0.001) higher than SUVmax 0.744(95%CI: 0.628~0.860, *P* <0.001) and HF 0.790 (95%CI:0.684~0.896, *P* <0.001).

Conclusion: The regression model including SUVmax and HF based on ^{18}F-FDG PET/CT imaging may be useful for differentiating STS and BS from benign lesions.

Background

Soft tissue sarcoma (STS) and bone sarcoma (BS) are a rare group of mesenchymal origin diseases, account for approximately 1% of adult malignant tumors [1]. Computed tomography and magnetic resonance imaging are the preferred imaging techniques for clinical evaluation [2-3]. However, there are more than 200 diverse subtypes for soft tissue and bone tumors, many lesions have non-specific morphologic appearance, discrimination between malignant and benign tumors only using the conventional imaging modality often lead some overlaps [4-5]. Accurate discrimination between malignant and benign soft tissue and bone tumors are essential for the prevention of excessive pathological biopsy examination and unplanned surgical resection.

^{18}F-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/ CT) as a molecular imaging technology is considered capable of noninvasively quantify the tumors glycolytic metabolism in vivo, which is widely utilized in clinical assessment for tumors detection, staging, efficacy evaluation and prognosis prediction[6-8]. Maximum standardized uptake (SUVmax), metabolic tumor volume (MTV) and total glycolysis volume (TLG) are commonly used semi-quantitative parameters. However, in practice, using only one of the parameters mentioned above can't always facilitate to distinguish between malignant and benign lesions, there are remained some conflicting results, a standard diagnosis modality is urgently needed [9]. Recently, a quantitative intratumoral glucose metabolic heterogeneity indicator which is defined as heterogeneity factor (HF)

and obtained by calculating metabolic volume-threshold function has aroused widely attention [10]. Although numerous studies show that HF is closely related to the therapeutic response and prognosis of malignant tumors [11-13], few feasibility of studies have investigated involved HF in discrimination malignant and benign in soft tissue and bone tumors.

Therefore, this study aimed to perform univariate and multivariate analysis to evaluate the usefulness of multiple ^{18}F-FDG PET/CT-derived parameters（tumor size, SUVmax, MTV, TLG and HF）and establish a multifactorial regression model for accurately discriminating STS and BS from benign lesions.

Methods

Patients and Data Management

This study was approved by the institution's ethics review board. We retrospectively reviewed consecutive patients with soft tissue and bone lesions, who had examined ^{18}F-FDG PET/CT at our hospital from April 2012 to December 2019, all patients were confirmed by histopathological examination. Excluding neoadjuvant therapy before PET/CT examination or tumor size＜1cm (partial volume effect is obvious), a total of 70 patients were finally participated in this study. Among the patients 39 were female and 31 were males. The median age of patients was 58.5 (55.3±13.8) years. The subjects were then divided into malignant group (STS and BS, n=37) and benign group (n=33) based on the 2013 WHO classification of soft tissue and bone tumors [14], pathological subtypes were shown in Table1.

Image acquisition

PET/CT imaging were performed with a Biograph True-Point PET/CT scanner (Siemens Medical Systems, Germany). After patients fasted for at least 6 hours, they were injected with 5.55 MBq/kg ^{18}F-FDG. Keep lying in a quiet room for approximately 60 minutes, and then emptied the bladder. PET/CT scan was collected from the skull base to the proximal leg. If necessary, both upper limbs or/and lower limbs were included. Ordered the patient to breathe quietly. CT scanning was first performed, with 120 kV tube voltage and 60-80 mA tube current (Care Dose), then PET imaging adopts 3-dimensional acquisition mode with 1.5-2minutes per bed position. PET image data sets were reconstructed by subset expectation maximization, with CT image for attenuation correction.

Image processing

The ^{18}F-FDG PET/CT images were processed at a standard workstation (MMWP, Siemens) by two experienced nuclear medicine physicians. The measurement of the tumor size was performed by referring the PET/CT fusion image to confirm the tumor boundary, and the largest plane (coronal plane, sagittal plane or coronal plane) of the tumor was selected to measure its maximum diameter for tumor size. Semi-automatic method was utilized to delineate the tumor volume of interest (VOI) based on the threshold SUV, If necessary, it should be manually adjusted to cover the whole tumor tissue in three planes, and the normal tissue around the tumor and physiological uptake should be excluded as far as possible, as shown in Fig 1. The SUVmax was defined as the point of highest glucose metabolism within the VOI. MTV was determined as the sum of voxel volumes of ≥40%SUVmax. TLG was calculated by MTV and SUVmean multiply [15]. Calculated the derivative (dV/dT) of the metabolism volume-threshold function from 40 to 80% of SUVmax in linear regression curve [15], because of the derivative values pose negative values, the calculated derivative values were transferred to absolute values, which

represented the HF values [10,15] ,The closer the derivative value was to the negative value or the greater the HF values was, the greater the heterogeneity of the tumor tissue was.

Statistical analyses

The comparisons of continuous variables between malignant group and benign group via the Mann-Whitney U test. The chi-square test was utilized to analyze the Intergroup difference of the categorical variables. Multivariable logistic regression was adopted to identify independent predictors for malignant tumor. Only the variables with P <0.05 in the univariable analysis were included in logistic regression model. Area under the curve of the receiver operator characteristic (AUC) were performed, cutoff value was evaluated by the maximum Youden's index. All statistical analysis was performed using SPSS 26.0 (IBM, Chicago, USA), P <0.05 was considered statistically significant.

Result

First, univariate analysis results showed that tumor size(malignant vs benign: 7.5±4.2 vs 4.8±5.2, P <0.001), SUVmax(12.4±9 vs 7±5.2, P <0.001), MTV(57.7±54.9 vs18.8±16.5, P =0.001), TLG(26.3±513.8 vs 81.1±119.8, P <0.001) and HF(1.39±1.31 vs 0.38±0.35, P <0.001) in STS and BS group were all significantly higher than benign lesions group, but there were not statistically significant difference in age (P =0.911)and sex (P =0.336), were shown in Table 2.

Whereafter,the variables (including tumor size SUVmax, MTV, TLG and HF) which statistically significant differences were included in multivariate logistic regression analysis. The multivariate logistic regression analysis result revealed that only SUVmax and HF were identified as independent risk factors for malignant tumor, and could be incorporated into the logistic regression predictive model, the odds radios were 1.135(95%CI: 1.026~1.256, P =0.014), 7.869(95%CI: 2.119~29.230, P =0.002), respectively. Based on the above findings, regression predictive model was constructed using the following expression: Logit (P) = -2.461+0.127SUVmax+2.063HF. The P value represent the "probabilistic" which was generated from the regression model.

The ROC curve was plotted for regression model P value, SUVmax and HF (shown in Fig 2). The area under the curve (AUC)for regression model P values (AUC: 0.860, 95%CI: 0.771~0.948, P <0.001) was superior to SUVmax (AUC: 0.744, 95%CI: 0.628~0.860, P <0.001) and HF (AUC: 0.790,95%CI:0.684~0.896, P <0.001).The cutoff value to discriminate malignant group tumors from benign ones were 0.47, 5.95, 0.46 for regression model P value, SUVmax and HF, with 6/33, 9/33,10/33 false-positive benign lesions and 6/37, 9 /37, 10/37 false-negative malignant lesions, respectively. The regression prediction model combined with SUVmax and HF diagnostic performance increased considerably. When compared with observed value in SUVmax and HF, 8 false-positive benign lesions(1 each of inflammatory myofibroblastic tumor, giant-cell tumor of bone, langerhans histiocytosis, eosinophilic granuloma, inflammatory granuloma and organizing hematoma) and 6 false-negative malignant lesions (1 liposarcoma, 3 undifferentiated/unclassified sarcomas, 2 each of chondrosarcomas and spindle cell sarcoma) by utilizing regression model were extra correctly diagnosed. Representative cases were presented in Fig 3 and Fig 4.

Discussion

^{18}F–FDG PET/CT is widespread used to characterise tumor glycolytic activity, which is a valuable marker of tumor biological behavior [16-17]. In this study, we assessed the usefulness of ^{18}F–FDG PET/CT in differentiating soft tissue sarcoma (STS) and bone sarcoma (BS) from benign lesions. Numerous studies investigated that PET-derived semiquantitative estimation parameters such as SUVmax, MTV and TLG are considered for meaningful indicators. SUVmax represents the glucose metabolism of single integrin in the tumor. MTV and TLG can reflect the overall tumor burden. Nonetheless, the ability of individual parameters for discriminate malignant from benign in soft tissue and bone tumors are not always feasibly. Soft tissue and bone tumors are highly heterogeneous group of tumors, delay in diagnosis will form a negative impact on patients outcome [18].Finding a simple and reliably Imaging model to characterize the biological behavior is critical to overcome many overlapping features. HF as an additional parameter obtained through PET image was reported to be a method to reflect the intratumorally structure heterogeneity of ^{18}F-FDG uptake [19-20]. In this study, we comprehensively evaluate the feature parameters of ^{18}F–FDG PET/CT imaging and finally constructed a well-established model based on SUVmax and HF for differential diagnosis between malignant and benign in soft tissue and bone tumors.

Alipour R, et al. [21] research showed that HF in malignant parotid tumors were higher than benign ones, concluded that HF is a reliable value in distinguishing benign from malignant parotid. Kim SJ, et al. [22] research claimed that HF could be a predictor for characterization of thyroid nodule. But these studies only relied on the univariate analysis and neither further performed the multivariate analysis to remove the interaction among variables nor deeply explore the combined application value of parameters. The present study, the significant feature parameters between malignant and benign group were screened according to the results of univariate analysis, including the tumor size, SUVmax, MTV, TLG and HF (all *P* value were<0.01). Furthermore, multivariate logistic regression analysis result revealed that the SUVmax and HF were both identified as independent risk factors for malignant tumor and can be implemented to established regression prediction model, the odds radios of SUVmax and HF were 1.135(95%CI: 1.026~1.256, *P* =0.014), 7.869(95%CI: 2.119~29.230, *P* =0.002), respectively. The results demonstrated that the prediction function of the model was accurate and feasible. Nakajo M, et al. [23] also conduct a univariate analysis in 63 cases of musculoskeletal tumors by using cumulative SUV-volume histogram (CSH) method [24], and the results showed the area under curve of CSH in malignant tumors was higher than benign ones, the conclusion is similar to our results. However, this method is equivalent to the concept of dose-volume histogram for evaluating radiotherapy regimen which applied to PET/CT functional imaging data, the clinical practicality is extremely limited.

Regarding the different growth rate, vascular distribution, and necrosis characteristics of each tumor cell population, are found to be different in biological behaviors [25]. In our study, the area under the curve (AUC)for regression model was 0.860 (95%CI: 0.771~0.948, *P* =0.000) was higher than SUVmax (AUC: 0.744, 95%CI: 0.628~0.860, *P* =0.000) and HF (AUC: 0.790,95%CI:0.684~0.896, *P* =0.000).The cutoff value to discriminate malignant group tumors from benign ones were 0.47, 5.95, 0.46 for regression model *P* value, SUVmax and HF, with 6/33, 9/33,10/33 false-positive benign lesions and 6/37, 9 /37, 10/37 false-negative malignant lesions, respectively. It follows that the regression prediction model combined with SUVmax and HF has higher diagnostic performance. In general, ^{18}F-FDG uptake is not homogeneous within tumors, the biological characteristics of tumors are determined not only by tumor cells but also tumor microenvironment, including immune cells, endothelial cells and tumor-related fibroblasts [26-27]. SUVmax reflects the highest glucose metabolism in tumor cells, HF reflects the intratumorally spatial heterogeneity of glucose metabolism, the combination of SUVmax and HF can be considered as an incorporation of intertumoral structures from point to surface, which can more

comprehensively reflect the glucose metabolism inside the tumor and characterize the biological behavior of tumors, so as to more accurately characterize malignancy and benign classification of tumors and further reducing the overlap of differential diagnosis.

Despite in previous research tumor size and volume are often considered as an indicator of malignancy tumor [27-28]. However, in our study multivariate logistic analysis results showed that when SUVmax and HF were introduced simultaneously to the regression model , the tumor size, MTV and TLG became no statistical significance, demonstrates there were some overlap and existed interactions among the parameters. Or perhaps the predictive value of tumor size and volume in a single space is limited, the tumor develop rapidly along with period incremental moving forward, such as tumor doubling time maybe higher likelihood of malignancy [29].

Of course, this study has certain limitations, First, the sample number of this study is not big enough, such phenomenon is due to some pathological classification of STTs are relatively rare. Second, this paper is a retrospective study, the collection of histopathology data was limited, minority of the pathological classification of the samples were confirmed only by biopsy pathology and the histological subtype of several cases were not clearly defined. Nevertheless, we believe that our results are qualified to be utilized for reference. This paper proposes a new concept, which can effectively integrate the metabolic information of ^{18}F-FDG PET/CT imaging, and help to the clinical standardized management of soft tissue and bone tumors. A large sample of prospective cohort studies that involves imaging characteristic parameters and histopathology factors is recommended.

Conclusion

The logistic regression prediction model established based on SUVmax and HF of ^{18}F-FDG PET/CT may help to distinguish soft tissue and bone sarcoma from benign lesions, which can be used as an auxiliary diagnostic method to provide more reference information before treatment.

Abbreviations

STS: soft tissue sarcoma; BS: and bone sarcoma; ^{18}F-FDG:^{18}F-fluorodeoxyglucose; PET/ CT : positron emission tomography/computed tomography; SUVmax: maximum standardized uptake value; MTV: metabolic tumor volume; TLG: total lesion glycolysis; HF: heterogeneous factor; AUC: Area under receiver-operating characteristic curve; CSH: cumulative SUV-volume histogram.

Declarations

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Availability of data and materials
The datasets used and/or analyzed of this study are available from authors on reasonable request.

Authors' contributions
BC conceived the research, data collection, PET/CT interpretation, statistical analysis and drafting of the manuscript. HF software operation, data collection, PET/CT interpretation, statistical analysis. SW conceived the research, statistical analysis, clinical review of the manuscript and drafting of the manuscript. JX data collection, PET/CT interpretation and clinical review of the manuscript. CL and YZ helped for data collection and draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All involved human participants in this study were conform to the ethical standards of the institutional research committee (the First Affiliated Hospital of Dalian Medical University YJ-KY-FB-2020-04) . This retrospective study was approved by Institutional Review Board (the First Affiliated Hospital of Dalian Medical University), and the need for informed consent was waived own to the retrospective design.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Tables

Table 1. Histologic Type of the Tumors

Malignant tumors	n=37	Benign tumors	n=33
Liposarcoma	4	Schwannoma	7
Myxofibrosarcoma	4	Fibroma	5
Synovial sarcoma	4	Inflammatory myofibroblastic tumor	2
Hemangiosarcoma	5	Giant cell tumor of tendon sheath	2
Leiomyosarcoma	1	Giant-cell tumor of bone	2
Rhabdomyosarcoma	1	Soft tissue hemangioma	1
Undifferentiated sarcoma	4	PHAT* of soft parts	1
Pleomorphic sarcoma	1	Kaposi hemangioendothelioma	1
Spindle cell sarcoma	7	Langerhans histiocytosis	1
Osteosarcoma	2	Eosinophilic granuloma	1
Chondrosarcoma	4	Others	10

* for pleomorphic hyalinizing angiostatin tumor

Table 2. Comparisons of each Parameters between Malignant and Benign Groups

Characteristic	Grouping		Total	Statistical Magnitude	*P* value
	Malignant	Benign			
Age(y)	59(55.8±14.1)	56(54.8±13.6)	58.5(55.3±13.8)	*Z*=-0.112	0.911
Sex				*c2*=1.322	0.336
Male	23(58.97%)	16(41.03%)	39		
Female	16(51.61%)	15(48.39%)	31		
Size (cm)	7(7.5±4.2)	3.8(4.8±5.2)	5.3(6.2±4.9)	*Z*=-3.490	<0.001
SUVmax*	8.7(12.4±9)	4.7(7±5.2)	6.9(9.8±7.9)	*Z*=-3.507	<0.001
MTV† (cm^3)	36(57.7±54.9)	15(18.8±16.5)	24.8(39.4±45.6)	*Z*=-3.406	0.001
TLG‡	251.4(426.3±513.8)	37.6(81.1±119.8)	102.4(263.6±417.7)	*Z*=-4.159	<0.001
HF§	0.84 (1.39±1.31)	0.54(0.38±0.35)	0.56(0.92±1.1)	*Z*=-4.171	<0.001

* for maximum standardized uptake value, † for metabolic tumor volume , ‡ for total lesion glycolysis, § for heterogeneous factor, statistical description by n (%) or median (`*c±s*)

Figures

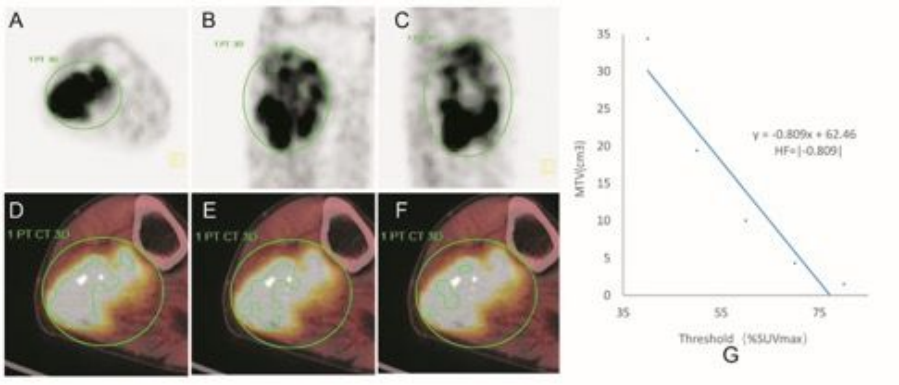

Figure 1

PET images depicting manually drawn VOI on three planes and the method to calculate HF. (A) Axial plane. (B) sagittal plane. (C) coronal plane. (D, E, F) The MTV decreasing gradually with the change of increasing threshold (40%, 50%, 60% of SUVmax, respectively). (G) The slope of the threshold-volume function curve was calculated as HF.

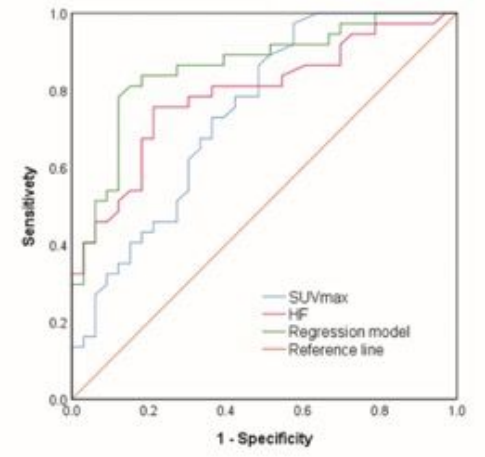

Figure 2

ROC curves of SUVmax, HF and logistic regression predictive model for differentiating malignant (STS and BS) and benign lesions. The AUC of SUVmax, HF and regression model were 0.744 (95%CI: 0.628~0.860, P <0.001) , 0.790 (95%CI:0.684~0.896, P <0.001), 0.860 (95%CI: 0.771~0.948, P <0.001), respectively.

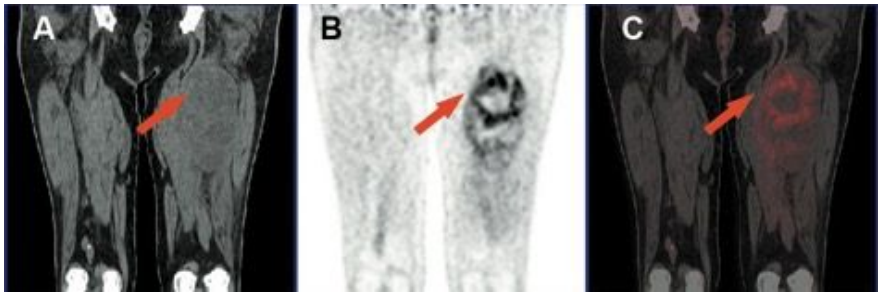

Figure 3

Liposarcoma of the left thigh. (A) CT- coronal plane. (B) PET- coronal plane. (C) PET/CT fusion image. As shown by the red arrow the density of the mass was equal or slightly lower than that of adjacent muscle tissue, the uptake of 18F-FDG was heterogeneously and observably increased, tumor size=16.9cm,SUVmax=8.3, HF=2.93, TLG=519.1, MTV=123.6cm3, P value=0.99.

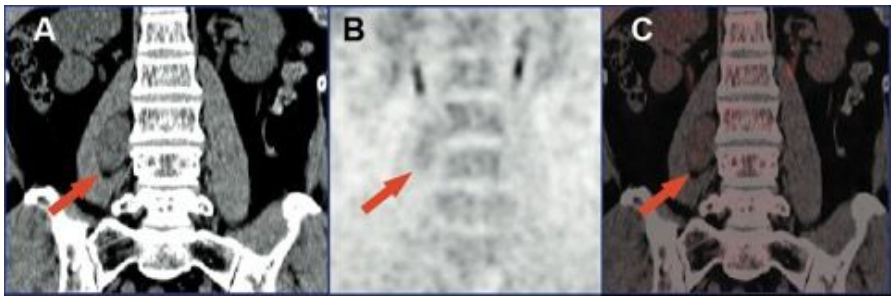

Figure 4

Schwannoma of the right psoas major. (A) CT- coronal plane. (B) PET- coronal plane. (C) PET/CT fusion image. As shown by the red arrow the density of the mass was slightly lower than that of adjacent muscle tissue, the uptake of 18F-FDG was homogeneously and moderately increased, tumor size=2.5cm, SUVmax=3, HF=0.36, TLG=25.5, MTV=15cm3, P value=0.21.