

## PET-CT <sup>18</sup>F-FDG applications in cardiac tumors

### Aplicações da PET-TC <sup>18</sup>F-FDG nos tumores cardíacos

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#### ABSTRACT

Cardiac neoplasms are divided into primary and secondary. Secondary neoplasms are 20 to 40 times more common than the primary ones. Although rare, primary cardiac neoplasms may be benign or malignant. Benign neoplasms are responsible for 75% of the cases. The main objectives of cardiovascular imaging are to define tumor morphology and etiology, identify potential complications and assist in the establishment of treatment. For the diagnosis of cardiac neoplasms, positron emission tomography combined with computed tomography (PET-CT) with fluorodeoxyglucose-F18 (<sup>18</sup>F-FDG) is a technique that is still little used, especially in primary cardiac tumors. However, it can help differentiate between malignant and benign tumors, thus preventing cardiac biopsies and unnecessary invasive treatments. For this review, we searched the PubMed database, considering the publications on this topic in the past 10 years. PET-CT <sup>18</sup>F-FDG is a useful test to differentiate benign from malignant heart masses according to the higher degree of glycolytic metabolism found in malignant neoplasms. Moreover, in malignant tumors, PET-CT <sup>18</sup>F-FDG plays a central role in disease staging and may help assess treatment response.

#### Introduction

Cardiac tumors were first described in the 16<sup>th</sup> century,<sup>1</sup> but the first excision of an intrapericardial teratoma was conducted as late as in 1936.<sup>2</sup> In 1955, Crafoord, using cardiopulmonary bypass, performed the first resection of an atrial myxoma. Surgical removal of cardiac tumors represents an uncommon yet important cause of cardiac interventions in large specialized centers.<sup>1</sup>

Cardiac neoplasms can be divided into primary and secondary. Secondary neoplasms are 20 to 40 times more common, mostly corresponding to lung, breast, esophagus, lymphoma, leukemia and melanoma metastases.<sup>4</sup> Primary tumors, with an approximate incidence of 0.001 to 0.03%, include benign and malignant tumors, with benign tumors accounting for 75% of the cases.<sup>5</sup> The main benign tumor is

myxoma, accounting for half of benign neoplasms in adults. Among malignant neoplasms, sarcoma is the most prevalent one, followed by lymphoma.<sup>5</sup>

#### Diagnosis

Diagnosis is based on clinical history data, physical examination findings and complementary cardiovascular imaging methods.<sup>6</sup> In recent years, with the progress of non-invasive methods, there has been a considerable increase in the number of cardiac tumors diagnosed, incidentally found in asymptomatic patients as well.<sup>4</sup>

The main objectives of cardiovascular imaging are to define tumor morphology and etiology, identify potential complications and help establishing treatment.<sup>6</sup> It is essential to define tumor malignancy before any surgical planning, as many are not accessible for biopsy through catheter.<sup>7</sup> For this purpose, many techniques can be used and are able to identify tumor location, size and vascularization, and to evaluate hemodynamic impairment and myocardial or pericardial infiltration.<sup>6</sup>

Transthoracic Echocardiography (TTE) is the initial modality, with techniques that can add up to diagnostic information such as contrast TTE, three-dimensional TTE and strain.<sup>6</sup> In addition to TTE, Cardiac Magnetic Resonance Imaging (CMRI) and Computed Tomography (CT) provide additional information on myocardial infiltration and tumor tissue characteristics.<sup>6</sup>

#### PET-CT <sup>18</sup>F-FDG

Recently, Positron Emission Tomography associated with CT (PET-CT) has been used as a tomographic scintigraphy technique that provides molecular images corresponding to tumor cell metabolism.<sup>6</sup> This method represents progress for the diagnosis, staging and restaging of tumors, as it detects biochemical abnormalities even before anatomical abnormalities.<sup>6</sup> The most commonly used marker is <sup>18</sup>F-Fluorodeoxyglucose (<sup>18</sup>F-FDG), a glucose-like molecule that has a high affinity for malignant cells. This effect was demonstrated by Otto Warburg in 1931, comparing glycolytic metabolism of embryonic, normal mature, carcinoma and sarcoma tissues.<sup>8</sup>

For the diagnosis of cardiac neoplasms, PET-CT is still little used, with limited experience in the natural clinical course of the disease, especially primary tumors. Regarding metastatic extracardiac cancers, known to be the most common ones, PET-CT <sup>18</sup>F-FDG is an established technique.<sup>6</sup>

#### Cardiac uptake of fluorodeoxyglucose

For the correct diagnosis of cardiac neoplasms, consideration should be given to the physiology and patterns of myocardial

#### Keywords

Heart Neoplasms; Review; Positron-Emission Tomography.

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FDG uptake, which depend on the levels of glucose, free fatty acids and plasma insulin. In fasting situations, insulin levels drop, with increased lipolysis in peripheral tissues and high plasma levels of fatty acid. This decreases glycolytic metabolism and myocardial glucose uptake/FDG.<sup>9</sup>

For PET-CT <sup>18</sup>F-FDG in cancer patients, 6-hour fasting is recommended to reduce myocardial FDG uptake. However, even with adequate fasting, it is still difficult to predict the degree of cardiac uptake suppression, with no clear correlation with fasting duration and serum glucose level. Besides the situations mentioned above, certain drugs and diets may also alter myocardial FDG uptake. For practical purposes, as the physiological activity of myocardial FDG is not uniform, it can be defined as absent, diffusely increased (heterogeneous or not), focally increased (e.g.: in papillary muscles) or regionally increased.<sup>9</sup>

When there is no myocardial FDG activity, normal residual blood pool activity can be viewed. This depends on kidney function and usually after 1 hour of intravenous FDG injection, blood pool activity presents Standard Uptake Value (SUV) of 1.5 to 2.5.<sup>9</sup>

### Differentiation between benign and malignant tumors

Diagnostic approach of cardiac masses via PET-CT <sup>18</sup>F-FDG, especially in the differentiation between malignant and benign tumors, is a recurring theme of great importance these days. A search on the PubMed database, considering publications from the last 10 years, found 39 case reports,<sup>10-48</sup> three case series,<sup>49-51</sup> two review articles<sup>9,52</sup> and two retrospective studies.<sup>7,53</sup>

The two main studies addressing this theme were conducted by Rahbar et al.<sup>7</sup> and Shao et al.<sup>53</sup> Both aimed to evaluate the diagnostic value of PET-CT <sup>18</sup>F-FDG over CT in differentiating malignant and benign cardiac tumor masses.<sup>7</sup> However, the study by Shao et al. also included pericardial masses in the analysis.<sup>53</sup>

Table 1 shows the case reports. Among case series, Kikuchi et al., in a retrospective analysis of 17 cases, described three benign tumors (lipoma, fibroma and one benign granular cell tumor); five diffuse large B-cell lymphomas; seven secondary tumors; granulocytic sarcoma and spindle cell

sarcoma.<sup>51</sup> In the series reported by Puranik et al., there are four cases of cardiac metastasis of upper respiratory and digestive tract tumors. In all reports, cardiac masses were asymptomatic and were discovered via PET-CT <sup>18</sup>F-FDG, emphasizing the importance of the method in the detection and staging of malignant tumors.<sup>50</sup> Elsayad et al. reported three primary angiosarcomas diagnosed via PET-CT <sup>18</sup>F-FDG and PET-MRI treated with surgery, radiotherapy and adjuvant chemotherapy.<sup>49</sup>

Rahbar et al., in their study Differentiation of Malignant and Benign Cardiac Tumors Using <sup>18</sup>F-FDG PET/CT, evaluated 24 consecutive patients with <sup>18</sup>F-FDG PET/CT (11 men and 13 women with mean age 59±13), studied before treatment, between 2004 and 2010. Patients were divided according to the histological subtype of the tumors, obtained by surgical resection<sup>16</sup> and biopsy,<sup>8</sup> resulting in primary benign tumors (n=7), primary malignant tumors (n=8) and secondary malignant tumors (n=9). Subsequently, they were grouped together in malignant tumors (n=17) and benign tumors (n=7), and FDG uptake was compared between the groups to assess sensitivity and specificity in the diagnosis of malignancy.<sup>7</sup>

Shao et al., in their study Differentiation of Malignant from Benign Heart and Pericardial Lesions using Positron Emission Tomography and Computed Tomography, retrospectively evaluated 23 patients (14 men and nine women, mean age 55 years, ranging from 16 to 86), including 13 malignant and ten benign tumors. Sixteen patients had pericardial lesions and seven intracardiac lesions. Histological diagnosis was obtained by surgery, pericardiocentesis, lymph node biopsy or lesion biopsy.<sup>53</sup>

Image analysis in both studies was conducted similarly. Firstly, the morphological characteristics of the lesions observed at CT were evaluated. The study by Rahbar et al. also classified the lesions as malignant and benign based on CT, according to pre-established criteria, namely: (1) contrast uptake; (2) tumor infiltration into the epicardium; (3) irregular tumor margin; (4) presence of necrosis; (5) presence of pericardial effusion; (6) tumor involving more than one chamber; and (7) tumor infiltration into the neighboring tissue. By obtaining three or more characteristics of these described, the tumor was classified as malignant at CT.<sup>7</sup>

In both studies, diagnosis of PET-CT <sup>18</sup>F-FDG was based on the calculation of Maximum Standardized Uptake Value

**Table 1** - Case reports published in the PubMed database from 2009 to 2019, of patients with cardiac masses undergoing F18-fluorodeoxyglucose PET-CT scans.

Case reports on PET-CT <sup>18</sup> F-FDG	n	Etiology	SUVmax (Mean ± SD)
Metastasis <sup>12-15,20,22,25,26,30,31,34,35,39-41,43,46,47,54</sup>	19	Lung cancer; melanoma; non-Hodgkin lymphoma; diffuse large B-cell lymphoma (DLBCL); squamous carcinoma; renal carcinoma; adrenocortical carcinoma; urothelial carcinoma; adrenal angiosarcoma; thyroid carcinoma; osteosarcoma; Ewing's sarcoma; pleomorphic sarcoma; intravenous leiomyomatosis; pancreatic cancer; Askin's tumor	8.3 ± 10.29
Primary <sup>10,11,16-18,20,23,24,28,29,32,33,36-39,42,44,45,55</sup>	20		
Benign <sup>16,17,33</sup>	3	Myxoma, hemangioma	2.5 ± 1.65
Malignant <sup>10,11,18,20,23,24,28,29,32,36-39,42,44,45,55</sup>	17	Angiosarcoma; lymphoma; sarcomas	12 ± 7.04

<sup>18</sup>F-FDG: fluorodeoxyglucose-F18; SUVmax: maximum standardized uptake value; SD: standard deviation; DLBCL: diffuse large B-cell lymphoma.

(SUVmax) of FDG of three-dimensional volume covering the tumor mass.<sup>7,53</sup> This parameter was obtained to compare FDG uptake between blood pool, normal myocardium and the tumor. Fasting preparation was performed to keep physiological myocardial FDG uptake at a low level. Mean SUVmax was  $2.1 \pm 0.6$  in the normal myocardium;  $1.6 \pm 0.4$  in the blood pool; and  $7.5 \pm 3.7$  in the tumors, ranging from 1.6 to 16.7,<sup>7</sup> allowing the differentiation of hypermetabolic tumors and normal myocardium.

## Myocardial masses

### Benign

These are the most common primary heart masses. Although benign, they may have significant symptoms, depending on their location and size. The main complications are flow obstruction, arrhythmia, valve dysfunction and embolism, originating from the neoplasia itself or from adjacent thrombus.<sup>4</sup>

The most common mass is myxoma, easily diagnosed on CT and usually showing little or no FDG uptake.<sup>9</sup> In addition to myxoma, lipoma is a well-circumscribed spherical mass, homogeneously composed of fat and showing no FDG uptake. However, interatrial septal lipomatous hypertrophy may present increased FDG activity. In these cases, FDG uptake (SUVmax) has ranged from 0.48 to 3.48, probably due to the amount of brown fat that metabolizes FDG.<sup>9</sup>

In the study by Rahbar et al., among benign tumors (n=7), glucose uptake was low (mean SUVmax was  $2.8 \pm 0.6$ ). These tumors do not usually have positive contrast to normal myocardium and are only seen on morphological images,<sup>7</sup> as shown in Figure 1.

On CT, according to the criteria of malignancy, only one

benign lesion was mistakenly classified as malignant, but it was a hemangioma located in the epicardial fat near the origin of the left coronary artery, which had three characteristics of malignancy: increased contrast, epicardial fat involvement and pericardial effusion.<sup>7</sup> However, PET-CT did not show any significant FDG uptake, thus favoring the diagnosis of benignity (Figure 2).

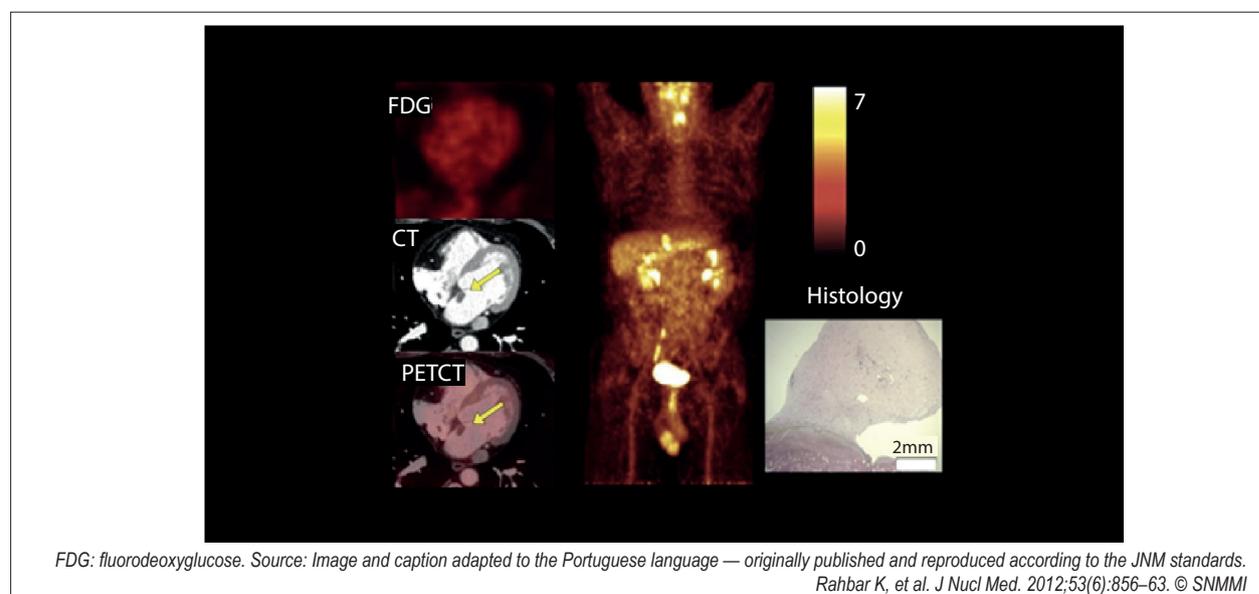
In the study by Shao et al., establishing a cut-off value of SUVmax of up to 4.0, benign tumors appeared below this point, except for one case of active pericardial tuberculosis, which presented high FDG uptake. In such cases, care must be taken and clinical examination must be correlated with PET and CT imaging.<sup>53</sup>

Among the case reports found, only three involved benign masses, two hemangiomas and one myxoma.<sup>16,17,33</sup> As shown in table 1, mean SUVmax of the lesions was 2.5, with 1.65 standard deviation. In the series published by Kikuchi et al., of the 17 cases, three were benign, one lipoma with SUVmax of 0.9, one fibroma with 6.8 uptake, and one benign granular cell tumor with 2.6 SUVmax.<sup>51</sup>

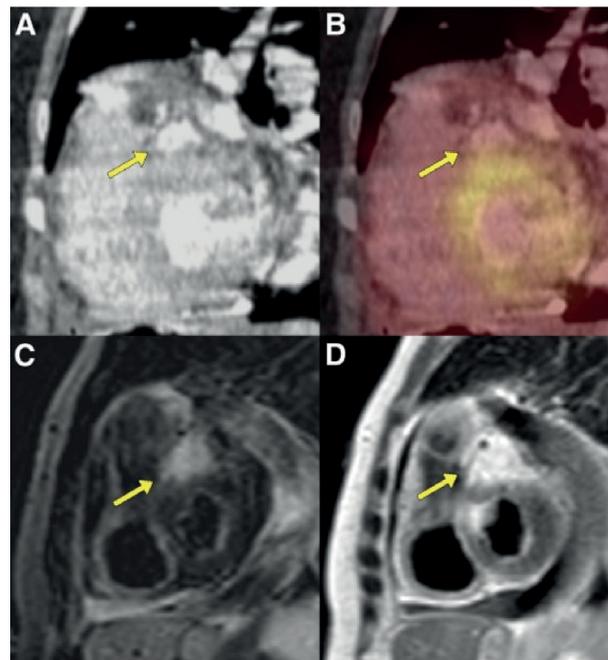
### Primary malignant tumors

Sarcomas are the most common primary cardiac neoplasms and have high FDG uptake, with angiosarcoma being the most prevalent entity.<sup>9</sup> It tends to appear mainly in the right atrium, as shown in Figure 3, or in the atrioventricular sulcus.<sup>7,9</sup> However, its identification can be difficult when myocardial FDG activity is high, and should, therefore, be correlated with tomographic images.<sup>9</sup>

In the study by Rahbar et al., according to the CT morphological criteria, 14 of 17 malignant lesions were correctly diagnosed, showing 82% sensitivity for CT. Three malignant tumors were poorly classified as benign on CT: one liver metastasis of hepatocellular carcinoma, one metastatic



**Figure 1** – Incidental mass in the left atrium of 48-year-old man (yellow arrows) on echocardiography. On PET-CT, no significant fluorodeoxyglucose uptake or distance injury was seen (full-body image in the middle). Histology: myxoma (in the lower row, to the right).



Source: Image and caption adapted to the Portuguese language — originally published and reproduced according to the JNM standards. Rahbar K, et al. *J Nucl Med.* 2012;53(6):856–63.(7). © SNMMI.

**Figure 2** – 59-year-old woman with pleural and pericardial effusion and chest pain. CT scan showed left ventricular epicardial tumor (A); cardiac magnetic resonance imaging showed hyperintense T2-weighted (C) hyperventricular tumor and T1-weighted contrast-enhanced (D) tumor and major pericardial effusion. On PET-CT images (B), the tumor has low uptake of fluorodeoxyglucose (arrow). Diagnosis: benign tumor (hemangioma).

pancreas adenocarcinoma and one liposarcoma. However, PET helped correctly classify these masses by the high FDG uptake.<sup>7</sup>

In PET-CT <sup>18</sup>F-FDG, the SUVmax of primary malignant lesions ranged from 5.3 to 10.7, showing an uptake significantly higher than that of benign lesions (SUVmax =  $2.8 \pm 0.6$ ), also higher than the normal myocardium ( $2.1 \pm 0.6$ ) and blood pool ( $1.6 \pm 0.4$ ).<sup>7</sup> In Shao et al., malignant lesions had SUVmax above 4.0, a cutoff point that helped correctly diagnose all malignant lesions.<sup>53</sup>

In the case reports, of the 17 primary malignant tumors, SUVmax was described in nine articles only, with mean SUVmax of 12.0, standard deviation of 7.04, and a predominant etiology of angiosarcomas, followed by lymphomas and other sarcomas. In the Kikuchi series, three large diffuse B-cell lymphomas were observed with SUVmax of 26.6, 29.0, and 22.2, which is significantly higher than that found in granulocytic and spindle cell sarcomas, with uptakes of 15.2 and 4.4, respectively.<sup>51</sup> Elsayad et al. addressed three primary angiosarcomas whose uptake (SUVmax) were 36.0, 8.8 and 17.0.<sup>49</sup>

### Secondary malignant tumors

Secondary heart masses are usually associated with disseminated metastatic disease.<sup>9</sup> PET-CT <sup>18</sup>F-FDG can identify the primary lesion with high sensitivity and specificity as it assesses the entire body and is very useful in differential diagnosis.<sup>9</sup> Figure 4 shows a case of disseminated melanoma with cardiac metastasis.

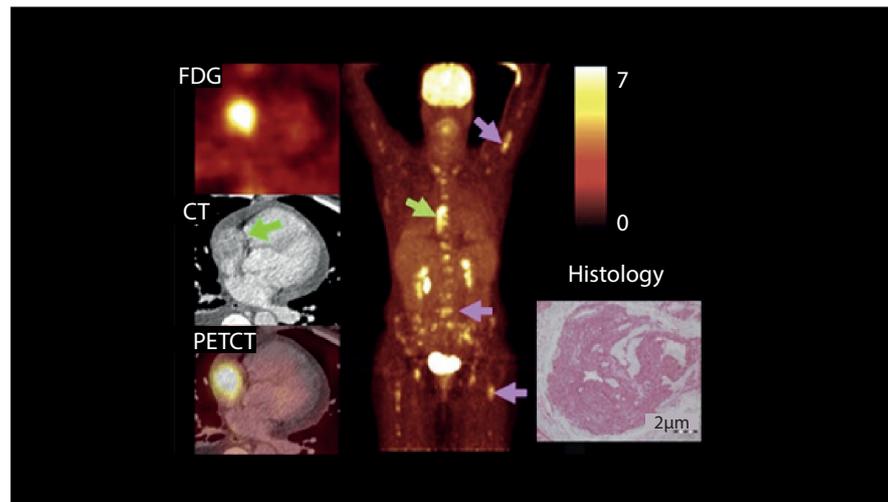
In lymphoma, PET-CT <sup>18</sup>F-FDG is often used at initial staging and post-treatment evaluation (Figure 5). Cardiac involvement is present in 15 to 30% in non-Hodgkin lymphomas, although any lymphoma may manifest as a primary cardiac injury, especially in immunocompromised patients.<sup>9</sup>

Shao et al. showed seven cases of lymphoma and leukemia correctly diagnosed by PET-CT <sup>18</sup>F-FDG.<sup>53</sup> confirmed by pathology or on clinical grounds, were analyzed in this study. All lesions were evaluated semi-quantitatively using maximum standard uptake values (SUV(max) Rahbar et al. showed mean FDG SUVmax of  $10.8 \pm 4.9$ , ranging from 3.4 to 16.7 in nine cases of secondary cardiac tumors.<sup>7</sup>

Of the 19 case reports addressing metastatic masses, 12 had the SUVmax measurement, with mean 8.3 and standard deviation 10.29. The series of four cases published by Puranik et al. showed asymptomatic metastases from the upper airway/gastrointestinal tract, esophageal cancer, oral mucosa, tongue and vallecula. Although they did not report mass uptake, there were cases in which PET-CT <sup>18</sup>F-FDG was of paramount importance in the diagnosis and choice of therapeutic option, ruling out surgery as an option and introducing palliative measures.<sup>50</sup>

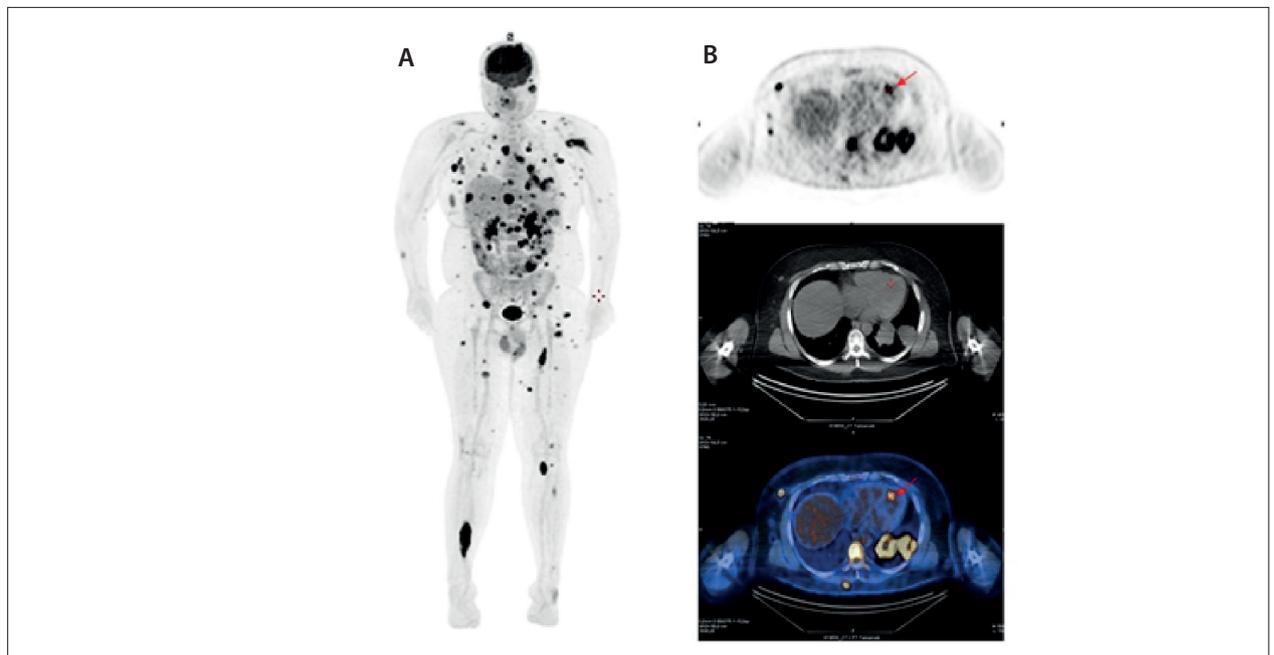
### Cut-off point of maximum standard uptake value in cardiac tumor diagnosis by PET-CT <sup>18</sup>F-FDG

Rahbar et al. exposed the established SUVmax values according to the tumor characteristic on a chart (Figure 6). Uptake is low in the blood pool and normal myocardium,



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**Figure 3** – 48-year-old woman with dyspnea and pleural effusion. Tomography showed right atrium mass (green arrow) and PET-CT showed intense fluorodeoxyglucose uptake, in addition to multiple bone metastases (lilac arrows on full-body images at the center). Histology (lower right row): primary cardiac angiosarcoma.

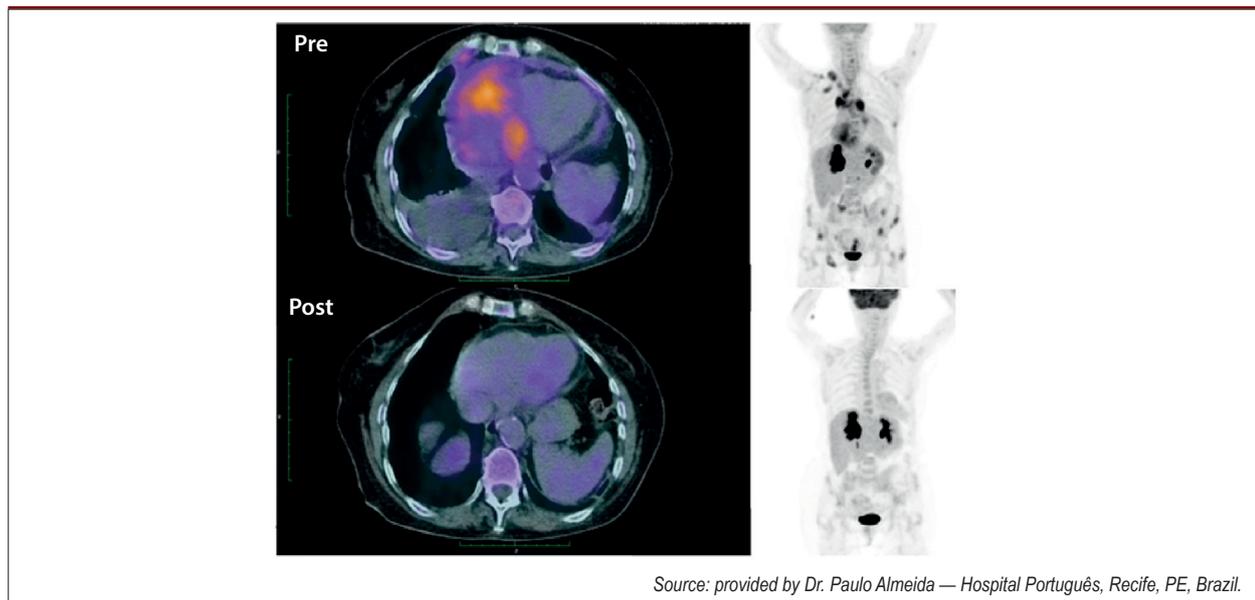


**Figure 4** – Male, 37 years old, diagnosed in 2016 with melanoma in the right pectoral region. At the time, he underwent surgical treatment with negative sentinel lymph node. After 3 years, he returns with multiple subcutaneous metastases. Fluorodeoxyglucose-F18 PET-CT was performed for restaging and showed metastases throughout the body. (A) Full-body images, including focal metastasis in the left ventricular septal apical (arrow) segment (B), with maximum standard uptake value of 8.7. This patient died 30 days after this scan.

and significantly high in malignant primary tumors compared to the benign ones. Uptake in secondary malignant tumors is comparable to that of primary malignant tumors, but with considerably greater SUVmax variation.<sup>7</sup>

To determine a cut-off point for malignancy determination using PET-CT <sup>18</sup>F-FDG, the study included an analysis using

the Receiver Operating Characteristic (COR) curve, obtaining SUVmax of 3.5 and reaching 100% sensitivity, 86% specificity (a benign tumor was misdiagnosed, so it was not 100%), positive predictive value of 94% and negative predictive value of 100%. On CT, using four morphological criteria instead of three, the positive predictive value reached 100%.<sup>7</sup> On



Source: provided by Dr. Paulo Almeida — Hospital Português, Recife, PE, Brazil.

**Figure 5** – 77-year-old man with non-Hodgkin lymphoma who underwent fluoroxyglucose-F18 PET-CT for basal staging (images at the top — PRE) and evaluation of response during treatment (images at the bottom — POST). In the images during treatment, there is a complete metabolic response of the lesions, with significant reduction in uptake in cardiac lesions and previously affected lymph node chains.

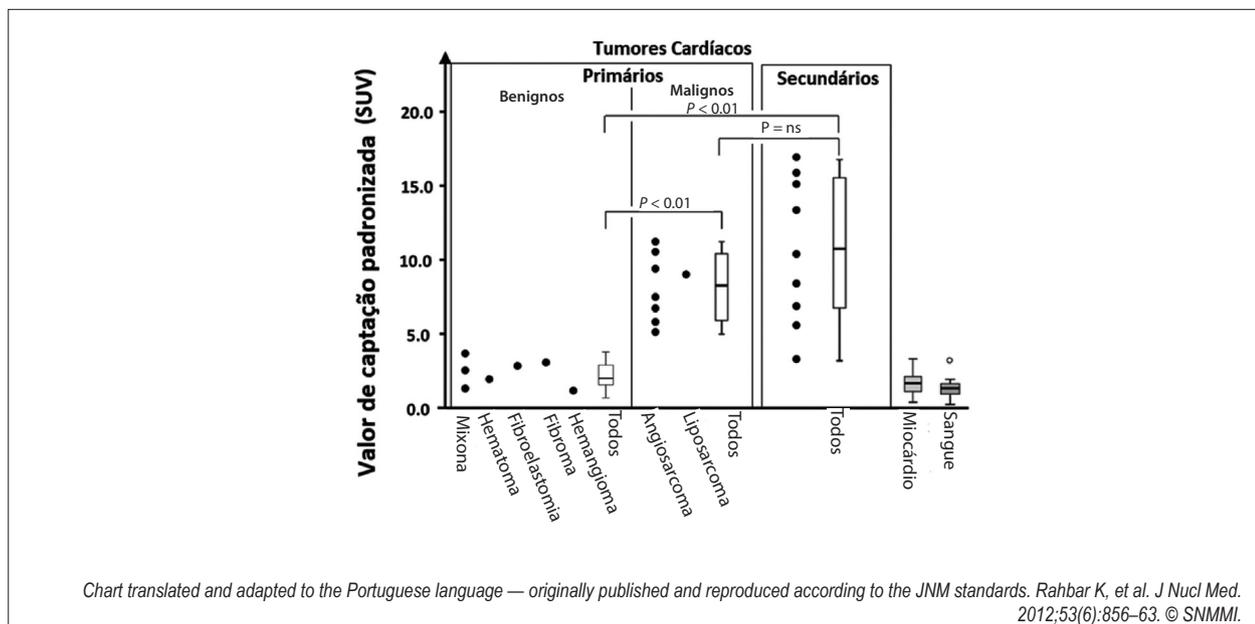


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**Figure 6** – Glucose uptake quantified by fluorodeoxyglucose-F18 PET (standard uptake value) in multiple cardiac, myocardial, and blood tumors. Uptake is low in myocardium and blood. Uptake in primary malignant cardiac tumors is higher than in benign tumors. Secondary malignant tumors show average uptake comparable to primary malignant tumors, but with greater variation.

PET FDG, increasing the SUVmax cutoff to 4.6, specificity increased to 100%, positive predictive value to 100% and sensitivity to 94%.

Shao et al. concluded that SUVmax of 3.5 to 4.0, or SUVmax ratio between lesion and blood pool of 1.3 to 2.0 achieved 100% sensitivity, 90% specificity, 95.7% accuracy, positive predictive value of 92.9% and negative predictive

value of 100% for the diagnosis of a malignant cardiac tumor.<sup>53</sup>

Regarding sensitivity, specificity and accuracy in distinguishing malignant from benign masses, PET-CT <sup>18</sup>F-FDG improved sensitivity and accuracy in differential diagnosis, while specificity was higher in CT.<sup>53</sup> All ten patients with benign lesions were correctly diagnosed with CT, while PET-TC <sup>18</sup>F-FDG classified one case of tuberculosis as malignant.

Of the 13 malignant tumors, PET-CT <sup>18</sup>F-FDG correctly diagnosed all of them, while CT did so in ten, misclassifying a chondrosarcoma, an angiosarcoma and a metastatic pericardial tumor.

Observing the cut-off points generated in the two previously detailed studies and establishing the SUVmax cutoff of 3.5 (7.53) the noninvasive determination of malignancy and metastatic spread is of major interest to stratify patients and to select and monitor therapies. In the diagnostic work-up, morphologic imaging modalities such as echocardiography or magnetic resonance tomography offer information on, for example, size, invasiveness, and vascularization. However, preoperative assessment of malignancy may be unsatisfactory. The aim of this study was to evaluate the diagnostic value of (18, most of the masses described in the case reports and case series would be correctly diagnosed, with some exceptions — one myxoma with SUVmax of 5.2<sup>17</sup> and one fibroma with SUVmax of 6.8.<sup>51</sup> None of the malignant tumors was below the cutoff point, although the sample did not correspond to all cases due to lack of data. This corroborates the findings in the aforementioned analyses and helps to construct the profile of cardiac masses in the PET-CT <sup>18</sup>F-FDG approach.

## Perspectives

PET and MRI are two well-established and widespread imaging scans for the investigation of cardiovascular diseases.<sup>56</sup> Cardiac MRI provides high-resolution information about tissue anatomy, morphology, function and characteristics, while PET shows the physiological processes by labeling biological compounds with positron-emitting radionuclides. It is a noninvasive method for accessing myocardial perfusion, tumor metabolism and cardiac inflammation/infection.<sup>56</sup>

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In cardiac applications, these two combined methods (PET-MRI) may have synergistic value deriving from combined image recording, motion correction and reduced ionizing radiation compared to PET-CT.<sup>56</sup>

Regarding the cardiac masses, one study analyzed 20 patients undergoing PET-MRI for the evaluation of cardiac tumors.<sup>57</sup> FDG uptake was high in malignant tumors and, by using the hybrid PET-MRI method, establishing a 5.2 SUVmax cutoff point, both specificity and sensitivity were 100%.<sup>57</sup> In this context, this tool appears to be quite promising as long as it is more widely availability and affordable.

## Conclusion

PET-CT <sup>18</sup>F-FDG is a well-established test recommended for patients with various types of cancer. In metastatic heart tumors, more common than primary malignant tumors, it is a very useful tool. It is also an effective means of differentiating primary cardiac tumors from malignant and benign tumors, and staging malignant tumors. This test can also be used to evaluate treatment response, showing early metabolic improvement in successful therapies.

## Authors' contribution

Data acquisition: Brandão S, Dompieri L. Data analysis and interpretation: Brandão S, Dompieri L. Manuscript writing: Dompieri L. Critical revision of the manuscript for important intellectual content: Brandão S.

## Conflict of interest

The authors declare that there is no conflict of interest regarding this manuscript.

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