

## My Approach to Evaluation of Cardiac Masses Using FDG PET/CT

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### Abstract

Cardiac masses represent solid formations of various origins, with accurate diagnosis being crucial, particularly for those of a malignant nature, which are typically associated with a worse prognosis. Given this diversity, a comprehensive approach often involves the integration of multiple imaging modalities. Conventional cardiovascular imaging techniques such as transthoracic echocardiography, magnetic resonance imaging (MRI), and cardiac tomography offer insights into anatomical features and hemodynamic implications associated with these masses. However, due to its limitations, greater precision in the etiological investigation of these masses can be achieved by combining Nuclear Medicine with complementary methods, notably positron emission tomography combined with computed tomography using fluorodeoxyglucose-Fluorine-18 (FDG PET/CT). This approach aids in effectively assessing cardiac masses' metabolic activity, particularly when distinguishing between benign and malignant masses, guiding optimal biopsy site selection, and facilitating comprehensive staging. The Standardized Uptake Value (SUVmax) serves as a quantitative measure of FDG uptake by the mass, with elevated SUVmax values indicating malignancy. Clinical and conventional imaging data should complement the interpretation of FDG PET/CT findings for a more conclusive diagnosis. Thus, a multimodal strategy, particularly incorporating FDG PET/CT, enables a more precise differentiation between benign and malignant cardiac masses, ultimately optimizing patient management.

### Cardiac masses

Cardiac masses are solid formations of variable etiology resulting from a wide of causes, such as tumors (benign and malignant, primary or secondary), thrombi, vegetations, or pseudotumors.<sup>1</sup> Given this etiological diversity, a comprehensive approach often involves the integration of

### Keywords

Nuclear Medicine; Fluorodeoxyglucose F18; Positron Emission Tomography Computed Tomography.

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multiple imaging modalities. In this article, we will discuss this approach by emphasizing the contributions of Nuclear Medicine (Central Figure).

While not commonly encountered in clinical practice, the detection of cardiac masses has risen with the advancement and increased utilization of cardiovascular imaging modalities.<sup>2</sup> Symptoms are varied, ranging from asymptomatic scenarios to manifestations resulting from alterations in cardiac mechanics (such as flow obstruction and the occurrence of arrhythmias), mass embolization (thromboembolic phenomena for the pulmonary or systemic circulation) or constitutional symptoms such as fever, weight loss, fatigue, those related to the pro-inflammatory and hypermetabolic effect of the tumor or paraneoplastic syndromes. In many cases, regardless of the etiology, these repercussions resulting from the mass under investigation will be key to the patient's prognosis.<sup>3,4</sup>

When considering neoplasms as a diagnostic possibility, it is imperative to distinguish between primary and secondary cardiac tumors stemming from metastatic spread to the heart. Primary cardiac tumors, despite having fewer incidents, are generally benign (75% of cases), with emphasis on myxoma.<sup>1,2</sup> Among primary malignant tumors, sarcoma and lymphoma are the most prevalent. In contrast, secondary neoplasms are much more common than primary neoplasms.<sup>2-4</sup> These are malignant tumors that originate from other parts of the body and infiltrate the heart. The types of cancer that most commonly lead to cardiac metastases include lung, breast, esophageal, lymphoma, leukemia, and melanoma.<sup>2-4</sup>

Intracavitary thrombi, primarily composed of fibrin and platelets, can be mistaken for masses and should therefore be considered in the evaluation. The main associated risk is systemic embolization, particularly in patients with a heart condition, who are more predisposed to their formation.<sup>4</sup> Vegetations, characterized by abnormal tissue growth on heart valves, primarily arise from bacterial infections and are frequently observed in patients with infective endocarditis. Conversely, pseudotumors represent non-neoplastic formations that can simulate genuine cardiac tumors, stemming from inflammatory processes, reactive changes, or anatomical anomalies.<sup>2</sup>

### Imaging methods

Associated with clinical history, imaging exams are essential for morphological and diagnostic definition. Traditionally, the investigation begins with transthoracic echocardiography, a widely available, radiation-free exam that provides general data such as location, effects on the patient's hemodynamics, and relationship with adjacent tissues, such

Central Illustration: My Approach to Evaluation of Cardiac Masses Using FDG PET/CT

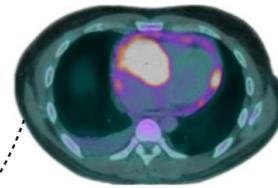


### How to evaluate cardiac masses: the role of FDG PET/CT

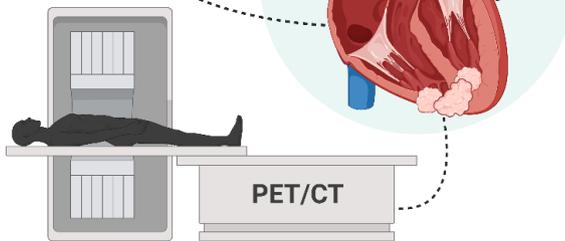
Cardiac masses are solid formations of variable etiology, and it is crucial to identify those of malignant nature (associated with worse prognosis).



- The PET/CT is a hybrid exam that provides molecular and anatomical informations.
- Fluorodeoxyglucose-F-18 (FDG) is the most commonly used radiopharmaceutical in the study of cardiac masses.
- As a glucose analogue, its degree of uptake is directly related to the glycolytic metabolism of the mass.



- Conventional methods allow for the characterization of anatomical aspects and hemodynamic repercussions.
- PET/CT adds to the diagnostic assessment by evaluating the metabolism of the lesion and its staging, as well as aiding in the selection of more appropriate sites for biopsy.



- In preparation for the examination, instituted measures aim to suppress the physiological consumption of glucose by the myocardium.
- Additionally, analysis is performed by comparing the uptake of the mass with the blood pool, enhancing the specificity of FDG uptake patterns.

#### Key points in FDG PET/CT evaluation

- Patient's clinical history;
- Assessment of FDG uptake degree in the mass;
- Search for other lesions with uptake in cardiac or extra-cardiac topography;

#### Primary considerations

- The cardiac lesion does not show uptake, and there are no other lesions in the body: consider a **benign lesion**;
- The cardiac lesion shows uptake, and there are no other lesions in the body: consider a **malignancy** confined to the heart;
- The cardiac lesion shows uptake, and there are other lesions in the body: consider **metastatic implants**.

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The role of FDG-PET/CT in evaluating and diagnosing cardiac masses of variable etiologies. PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose labeled with fluorine-18. Image made with BioRender.com.

as the pericardium.<sup>2</sup> However, despite providing relevant information, the method has certain technical limitations, such as dependence on the operator's expertise and an adequate patient window, as well as difficulties in evaluating the migration of the mass to other organs. The study can be complemented with additional tools from echocardiography itself, such as transesophageal, three-dimensional assessment, use of strain or contrast. These tools enhance diagnostic accuracy while facilitating a comprehensive evaluation of valve lesions and the spatial relationship between the mass and adjacent anatomical structures.<sup>2,4,5</sup>

Cardiac magnetic resonance (CMR) imaging is generally the next imaging method employed. Their primary advantage lies in their ability to offer morphological insights from multiple perspectives, coupled with superior spatial and temporal resolution, thereby enabling more precise characterization of tissue anatomy compared to echocardiography.<sup>2</sup> However, their main drawbacks include lengthy acquisition times, limited availability, potential challenges for claustrophobic patients, and the risk of nephrogenic systemic fibrosis associated with gadolinium-based contrast agents in individuals with severe renal impairment, as well as incompatibility with certain metallic devices.<sup>2,6</sup>

The study by Paolisso et al.,<sup>6</sup> using an observational cohort of 167 patients undergoing echocardiography, CMR, and histological analysis or serial radiological examinations (in the case of cardiac thrombi), showed a significantly greater accuracy of CMR when compared to echocardiography. In this study, the mass' morphological characteristics (non-left location, sessile, lobulated, heterogeneity, infiltration and pericardial effusion) and tissue characteristics (first-pass perfusion and heterogeneity enhancement) were identified as independent predictors of malignancy.<sup>6</sup>

Cardiac tomography (CT) is also important, especially in evaluating coronary arteries, calcified masses, and tumor staging. However, its major disadvantages include the radiation exposure, the risk of contrast-induced kidney injury with iodinated contrast, lower temporal resolution compared to CMR, and restricted tissue assessment capabilities.<sup>2,7</sup>

Positrons Emission Tomography associated with Computed Tomography (PET/CT) represents a nuclear medicine technique that examines specific physiological processes, aiding in the understanding and comprehensive characterization of lesions. PET's sensitivity, rooted in molecular-level changes, surpasses that of purely anatomical exams, as functional alterations often precede morphological ones.<sup>4,5</sup> The most frequently used

radiopharmaceutical in clinical practice is fluorodeoxyglucose labeled with fluorine-18 (FDG). FDG is a glucose analogue that reflects the degree of glycolytic metabolism in lesions. This radiopharmaceutical emits radiation captured by PET detectors, generating three-dimensional images of FDG uptake patterns. Additionally, as a hybrid method, PET/CT also provides anatomical information through CT scans.<sup>2,7</sup>

In summary, FDG PET/CT provides metabolic and anatomical information, contributing to better characterization of the mass.<sup>2</sup> The degree and pattern of FDG uptake aids in the differentiation between benign and malignant masses.<sup>5,8</sup> Moreover, given its whole-body coverage, the examination allows for the assessment of disease extension to other tissues (in cases of malignant masses) or the potential presence of septic emboli (in the scenario of vegetation due to endocarditis).<sup>7</sup> PET can also be integrated with magnetic resonance imaging (PET/MRI) equipment instead of CT, potentially making it the optimal method for evaluating cardiac masses, providing comprehensive information from both PET and MRI in a single examination. However, the use of PET/MRI in clinical practice is still extremely limited due to its low availability and high cost.<sup>9</sup>

### Preparation for the exam

Physiologically, glucose is metabolized in the myocardium. Consequently, without specific preparation for the exam, the analysis loses specificity. Therefore, it is necessary to suppress myocardial glycolytic metabolism, thereby increasing the accuracy of the findings. To this end, a fasting period of at least 12 hours (preferably 18 hours) is recommended, along with dietary adjustments in the 24 hours prior, with a lower supply of carbohydrates and greater availability of fats, increasing the cardiac consumption of fatty acids.<sup>2,7,10</sup>

Additional requirements include avoiding vigorous physical activity and good sleep the night before the exam. In certain medical centers, an intravenous dose of unfractionated heparin (50 IU/kg) is administered 15 minutes before FDG injection as an adjunctive measure, provided there are no contraindications.<sup>10</sup> For diabetic patients, it is recommended not to administer insulin on the morning of the examination, as insulin promotes glucose uptake (and subsequently FDG uptake) by muscle cells via glucose transporters in the cell membrane, which could potentially interfere with analysis results. Additionally, it is advisable to maintain blood glucose levels ideally below 180 mg/dL.<sup>10</sup> Despite adherence to these protocols, the uptake level may still be influenced by factors such as medication usage and the patient's comorbidities (e.g., diabetes or ischemic heart disease). Therefore, in addition to analyzing the degree of mass uptake alone by the FDG standardized uptake value (SUV), strategies like comparing with cardiac SUV and blood pool SUV contribute to the accuracy of image analysis.

### Cardiac mass investigation algorithm

After discovering the cardiac mass, diagnosing its etiology and establishing the prognosis are essential. Biopsy of the lesion is considered the gold standard; however, it is not always feasible due to the procedure's risk and sometimes the low local expertise.<sup>1</sup> When echocardiography and CMR

cannot accurately determine the nature of the mass, FDG PET/CT can help with differentiation. The particularities of this exam in evaluating benign and malignant masses will be discussed below.

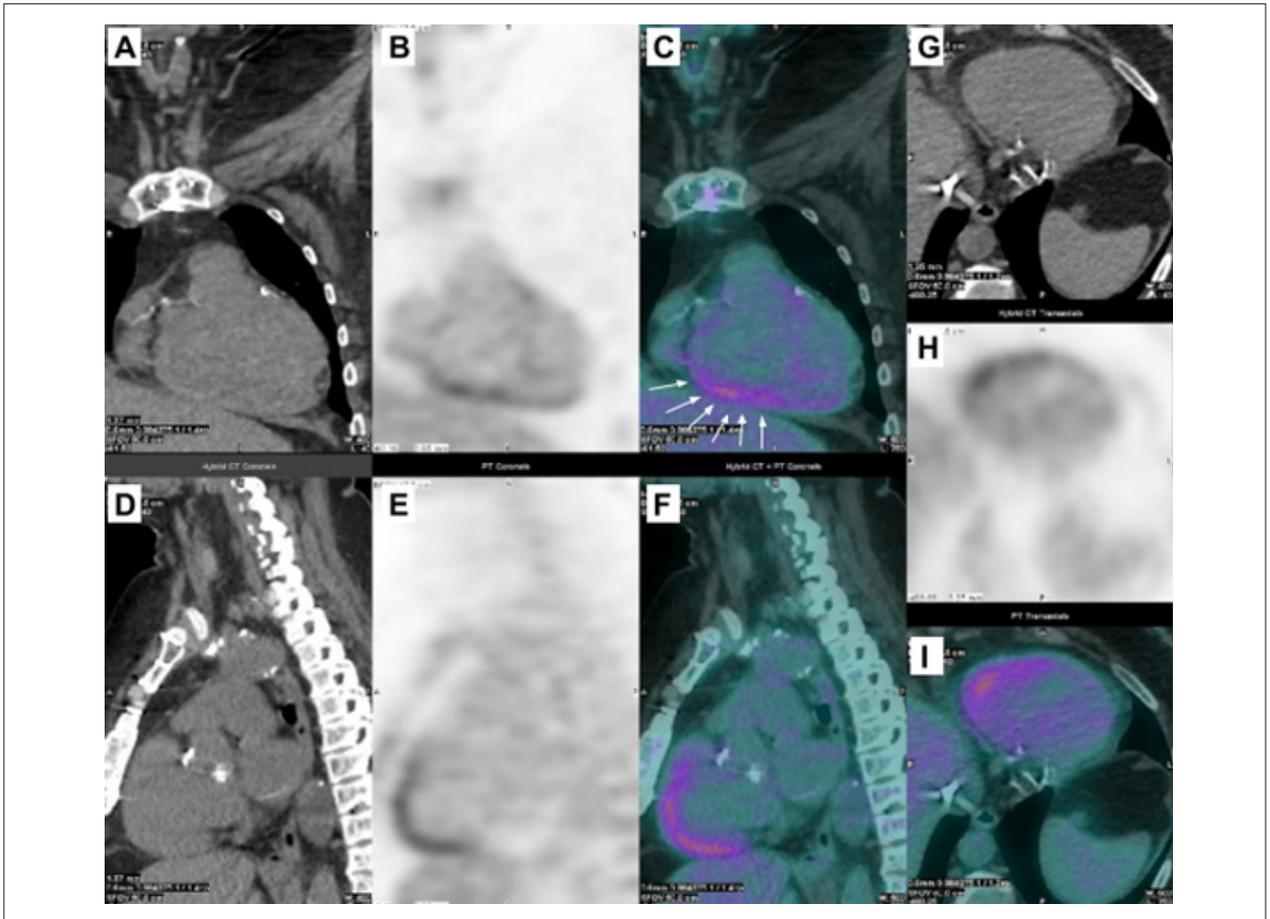
The majority of primary cardiac tumors are benign, with myxoma being the predominant etiology in adults, followed by lipoma and hemangioma.<sup>4</sup> Cardiac myxoma typically manifests as an intracavitary mass easily detectable by echocardiography and tomography. Lipomas, on the other hand, are well-circumscribed, homogeneous, and predominantly immobile benign tumors that are better characterized through CT and CMR examinations.<sup>1</sup> Hemangioma, an exceedingly rare subtype, presents diagnostic challenges due to limited data.

Generally, these three tumors exhibit low or negligible FDG uptake, except in specific scenarios such as increased brown fat content in lipomas. Studies<sup>4,5</sup> demonstrate that the absence of significant FDG uptake, indicated by a maximum SUV of the lesion below 2.5, coupled with the absence of lesions in other tissues, effectively excludes malignancy (Figure 1).

Primary malignant cardiac tumors are exceptionally rare, accounting for approximately 5% of cardiac masses. Sarcoma is the predominant subtype (with more than two thirds of cases), followed by lymphoma and mesothelioma.<sup>4</sup> Sarcomas typically have high FDG uptake, with a maximum mean SUV of 12,<sup>2</sup> markedly surpassing that of benign tumors and physiological myocardial uptake. This heightened metabolic activity facilitates their detection and classification with high sensitivity and specificity using FDG PET/CT. Among sarcomas, angiosarcoma is the most common histopathological subtype, known for its aggressiveness and propensity for metastasis<sup>11</sup> (Figure 2).

Secondary cardiac tumors, primarily associated with metastatic spread from primary cancers, are more prevalent than primary cardiac tumors. Melanomas are the most frequent malignancies involving the heart, although thoracic carcinomas predominate due to their higher incidence. In these cases, FDG PET/CT is extremely useful in initial staging and evaluating response to treatment. In extracardiac tissue metastases, the high avidity for FDG allows its rapid detection, as well as helping to indicate more suitable sites for histological analysis from biopsy, with a lower rate of complications compared to performing the procedure in the heart.<sup>12</sup>

The role of FDG PET/CT in determining the malignancy of lesions has been reinforced by several studies. Rahbar et al.<sup>8</sup> and Shao et al.<sup>5</sup> evaluated FDG uptake patterns, tomographic findings and histological diagnosis of cardiac tumors in 23 and 24 patients, respectively. Both studies concluded that the higher the SUV of the lesion, the greater the risk of malignancy, with a cutoff point between 3.5 and 4. Isolated, this criterion determined malignancy (non-invasively) with a sensitivity of 100% and a specificity of 86%. Within the framework of a multimodal investigation commonly employed in these cases, the aggregation of tomographic data yielded a diagnostic accuracy nearing 96%, with a 100% negative predictive value.



**Figure 1** – Amorphous tumor. PET/CT images at the cardiac level. Top row, coronal sections. Bottom row, sagittal sections. On the right, from top to bottom, axial cuts. Tomographic images (A, D and G). PET images (B, E and H). PET/CT images (C, F and I). Female, 41 years old, chronic kidney disease on dialysis, with severe pulmonary arterial hypertension and cor pulmonale due to chronic pulmonary thromboembolism. Two years ago, the patient underwent cardiac surgery to remove an amorphous tumor in the left atrium. It evolved with the emergence of a new mass on the roof of the left atrium, with poorly defined edges (30x19mm). PET/CT was requested to evaluate the mass better. On examination, no focal area of pathological increase in FDG was observed in the left atrium, suggesting benignity of the lesion. However, a right ventricle with an increased volume is observed, with increased glycolytic metabolism in its walls, probably due to chamber overload due to pulmonary hypertension (white arrows in Figure C). Source: Authors' personal archive.

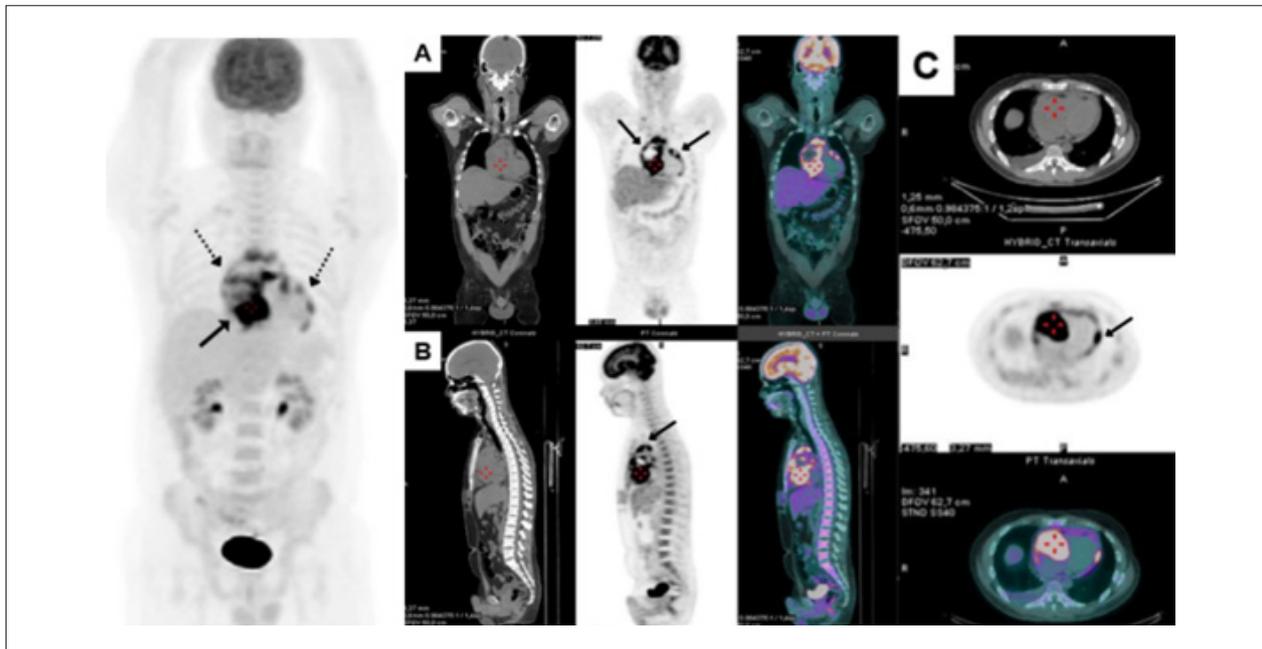
In the study conducted by D'Angelo et al.,<sup>7</sup> a cohort of 60 cases underwent CT and FDG PET/CT assessed eight morphological CT signs alongside the pattern and intensity of FDG uptake (as indicated by maximum SUV, mean, and mass uptake volume) as diagnostic markers for malignancy in cardiac masses. The presence of at least five tomographic signs identified malignant masses. However, in cases of diagnostic uncertainty (where only 3 or 4 signs were present), the presence of at least one FDG uptake assessment variable proved sufficient to accurately classify malignant tumors, with a 100% positive predictive value. Conversely, all patients with benign masses exhibited FDG uptake values below the defined cutoff points for malignancy.

In summary, considering the nuances added by clinical history and multimodal studies to the analysis, benign lesions typically demonstrate minimal FDG uptake, with no other lesions exhibiting uptake elsewhere in the body. The primary cardiac malignant mass, without distant

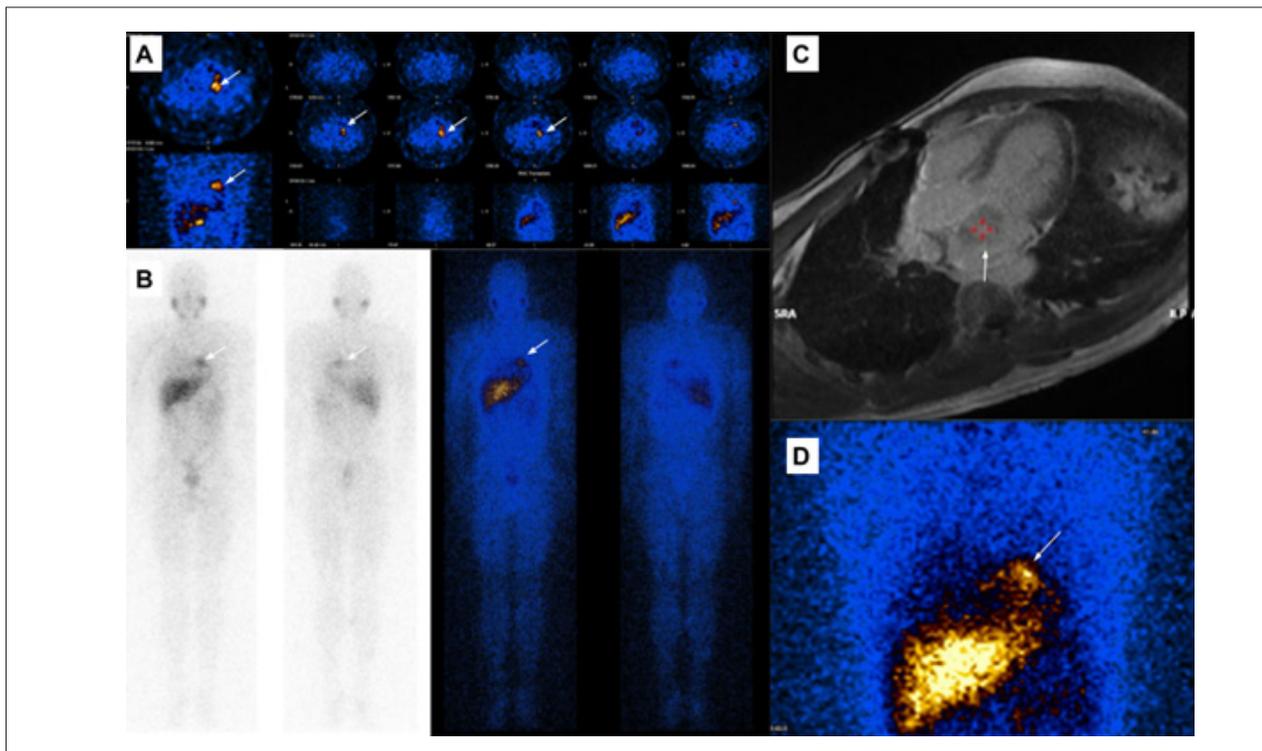
dissemination, presents high FDG uptake, without uptake lesions in the rest of the body. In contrast, metastatic implants (secondary cardiac lesions) manifest as lesions with substantial uptake both in the heart and other body regions. Through evaluation of morphological characteristics and lesion distribution, inference regarding the primary site can be made.

#### Radiopharmaceuticals other than FDG

While FDG is widely used due to its ability to evaluate the glycolytic metabolism of tumor cells, other radiopharmaceuticals offer complementary approaches in some specific cases. Gallium-68 labeled somatostatin analogues (68Ga-DOTATATE, 68Ga-DOTATOC, 68Ga-DOTANOC)<sup>13</sup> are widely used to assess neuroendocrine tumors due to their high affinity for the somatostatin receptors in these lesions, which can provide valuable information about the biology and extent of tumors.



**Figure 2** – Cardiac angiosarcoma. Male, 39 years old, hospitalized with cardiac tamponade. The patient underwent pericardiocentesis and biopsy of a fixed mass adhered to the lateral wall of the right ventricle, right atrium and posterior tricuspid leaflet. FDG PET/CT examination (A, coronal sections, B, sagittal and C, axial) reveals a cardiac mass with an epicenter in the right atrium of heterogeneous density, presenting glycolytic hypermetabolism (SUV maximum of 19.6) that extends to the entire pericardium (arrows). There is no evidence of distant metastases on whole-body images. Source: DA SILVA, et al.<sup>[11]</sup>.



**Figure 3** – Cardiac paraganglioma. Male, 39 years old, with inoperable left atrial paraganglioma. Images from scintigraphy with metaiodobenzylguanidine-Iodine<sup>131</sup> for staging and evaluation of possible treatment with radionuclide. The scintigraphic images reveal a moderate focal increase in radiotracer concentration within the left atrial region (arrow) while demonstrating physiological distribution in other anatomical segments. These findings suggest the presence of a neuroendocrine tumor localized within the cardiac region, with no discernible lesions detected outside the primary focus. A shows chest tomographic images obtained from scintigraphy (SPECT); B shows full-body scan images captured in anterior and posterior projections; C shows the CMR image (T1-weighted sequence) indicating the tumor (arrow); and D shows the static image of the anterior chest from the scintigraphy indicating the tumor (arrow) and the physiological uptake of the radiotracer in the liver. Source: Authors' personal archive.

These tumors evidence the role of metaiodobenzylguanidine labeled with iodine-123 or iodine-131 (mIBG). mIBG, a norepinephrine analogue, selectively accumulates in adrenergic cells, enabling the visualization of tumors expressing norepinephrine transporters such as pheochromocytomas, paragangliomas, and neuroblastomas.<sup>14</sup> Radioactive mIBG therapy (mIBG-131) remains a viable therapeutic option, particularly in advanced disease stages (Figure 3).

Finally, prostate-specific membrane antigen (PSMA), primarily employed to detect prostate epithelial cells, finds increasing use in PET/CT evaluation for prostate adenocarcinoma.<sup>15</sup> While its application in assessing cardiac masses is experimental, initial findings suggest promising sensitivity and specificity in identifying cardiac metastases from prostate, breast, and lung cancers.<sup>15</sup>

## Conclusion

A multimodal approach, integrating various cardiovascular imaging techniques alongside consideration of clinical history, is pivotal for accurate diagnosis and effective management of cardiac masses. It provides a comprehensive understanding of the morphological and functional characteristics of these lesions. The primary objective is the prompt identification of malignant lesions, given their association with poorer patient prognosis.

In such context, where conventional exams fall short in determining lesion nature, FDG PET/CT stands out due to its heightened sensitivity and specificity. In addition to FDG uptake intensity by the mass, the presence of hyperuptake lesions in tissues distant from the myocardium serves as a crucial parameter for differential diagnosis. While FDG remains the most widely used radiopharmaceutical in clinical practice, nuclear medicine provides a spectrum of other valuable radiopharmaceuticals tailored for tumor

evaluation in specific contexts. Expanding the availability of these resources, however, remains an important challenge.

## Author Contributions

Conception and design of the research: Brandão SCS, Sobrinho JMDR, Leão EDLM, Carreira LCTF, Brito ASX; acquisition of data, analysis and interpretation of the data and writing of the manuscript: Brandão SCS, Sobrinho JMDR, Leão EDLM; critical revision of the manuscript for intellectual content: Brandão SCS, Carreira LCTF, Brito ASX.

## Potential Conflict of Interest

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

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## Study Association

Brandão SCS is affiliated with the Graduate Program in Surgery at the Federal University of Pernambuco. Sobrinho JMDR is a medical student at the Federal University of Pernambuco and a PROPEQ PIBIC/UFPE/CNPq research student. Leão EDLM is a medical student at the Federal University of Pernambuco.

## Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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