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## **Factors Associated with a Myocardial Uptake on Oncologic Somatostatin-Positron Emission Tomography Investigations and Differentiation from the Myocardial Uptake of Acute Myocarditis**

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## Abstract

Myocardial somatostatin-PET uptake is observed in most patients with acute myocarditis (AM) but also in some oncology patients referred for routine somatostatin-PET. This raises concerns about the specificity of somatostatin-PET for detecting myocarditis. The current study aims to identify (i) factors associated with the detection of myocardial uptake on somatostatin-PET recorded for oncology indications and (ii) differential PET criteria that characterize myocardial uptake in AM patients.

**Methods.** We analyzed i) factors associated with the detection of myocardial [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC uptake in 508 [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC PETs from 178 patients, performed for a confirmed or suspected oncologic disease (Onc-PET group) and ii) PET criteria that could differentiate myocardial [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC uptake in 31 patients with an MRI-ascertained AM (AM-PET group) from the Onc-PET group.

**Results.** Significant myocardial uptake was detected in 137 (26.9%) Onc-PETs and was independently associated with somatostatin analog treatment (Exp(Beta) (95 %CI): 0.805 (0.728-0.890),  $p < 0.001$ ) and age (1.005 (1.001-1.009),  $p = 0.012$ ). A comparable model was selected for predicting the myocardial/blood SUVmax ratio (i.e. somatostatin analog treatment ( $p < 0.001$ ) and history of coronary artery disease (CAD)  $p = 0.022$ ). Myocardial uptake was detected in 12.9% (25/193) of Onc-PETs from patients treated with somatostatin analogs but in 43.4% (59/136) of untreated patients over the median of 64 years of age.

Myocardial uptake was apparent in all 31 AM-PETs, with volume and intensity of uptake dramatically higher than in the 137 Onc-PETs showing myocardial uptake. A myocardial/blood SUVmax ratio threshold of 2.20 provided a sensitivity of 87% (27/31) and a specificity of 88% (44/50) for differentiating myocardial uptake between AM-PETs and an Onc-PET group restricted to patients with comparable clinical characteristics to the AM group ( $\leq 64$  years of

age, no CAD history, no somatostatin agonists). A myocardial uptake volume threshold of  $18 \text{ cm}^3$  provided a comparable diagnostic accuracy (sensitivity: 84% (26/31), specificity: 94% (47/50)).

**Conclusion.** Myocardial uptake is detected in 26.9% of somatostatin-PETs recorded for oncology indications. This rate is decreased by somatostatin analog treatments and increased in older individuals. However, somatostatin-PET, analyzed with the quantitative criterion of uptake intensity or volume, is able to identify acute myocarditis and to differentiate it from myocardial uptake of other origins.

## Introduction

Myocarditis is far from being infrequent; it sometimes mimics an acute coronary syndrome, with some cases presenting or evolving toward left ventricular (LV) dysfunction, heart failure, and arrhythmia (1).

An endomyocardial biopsy, analyzed using the Dallas Criteria, remains the gold standard for myocarditis diagnosis, even though it has a low sensitivity for detecting focal forms (2).

Magnetic resonance imaging (MRI) is an efficient noninvasive diagnostic tool when analyzed using the 2018 revised “Lake Louise” criteria (3). However, MRI suffers from a low sensitivity for detecting subacute or chronic myocarditis, characterized by cardiomyopathy-like or arrhythmia presentations (4).

[<sup>68</sup>Ga]-DOTA peptides were developed for Positron Emission Tomography (PET) imaging of somatostatin receptor (SSTR) subtypes to diagnose/monitor neuroendocrine tumors. However, SSTRs are also overexpressed in lymphocytes and activated macrophages, the primary cell subsets involved in myocarditis (1,2).

Previous pilot somatostatin-PET studies have reported myocardial radiopeptide uptake in most patients with acute myocarditis (AM) (5–10). However, for reasons that are still poorly understood, myocardial uptake is also observed in numerous patients undergoing somatostatin-PET for routine oncology indications (11–13), raising concerns about the specificity of somatostatin-PET to identify AM.

This study aims to identify the factors associated with myocardial uptake observed on somatostatin-PET recorded for routine oncology indications and define differential PET criteria that characterize myocardial uptake in AM patients.

## Materials and Methods

### Study Populations

This study analyzed a retrospectively constituted group of consecutive [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC PET/CT recorded in our Nuclear Medicine department between January 2019 and December 2023 (Onc-PET group). Patients were referred from the Regional University Hospital of Nancy or the neighboring Regional Oncology Center (Institut de Cancerologie de Lorraine) to investigate conventional oncology indications. PET/CT from patients with carcinoid syndrome or a cardiac tumor location were excluded.

We extracted variables listed in Table 1 from the electronic medical databases, including age, sex, tumor data, previous history of oncologic and cardiac interventions, ongoing oncologic treatments, and cardiovascular risk factors.

We analyzed a second group of [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC PET/CT recorded between July 2020 and April 2023 as part of a prospective study of AM ascertained by MRI according to the 2018 Lake Louis Criteria (AM-PET group) (3) (see supplemental file for cardiac MRI methodology).

Both the AM-PET and Onc-PET study protocols were approved by dedicated ethics committees ("Comité de Protection des Personnes - Ouest IV" and "Comité d'Éthique du CHRU de Nancy," respectively) and released on the clinical.trial.gov site under identifiers NCT03347760 and NCT05478733, respectively. All participants from the AM prospective study signed an informed consent to participate. The requirement to obtain informed consent was waived for the Onc-PET patients but they had previously been informed that their medical data could be retrospectively used for research purposes.

### PET/CT Recording and Analysis

All PETs were recorded 60 min after the intravenous injection of 2 MBq/kg of [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC on a digital PET/CT system (Vereos, Philips, Cleveland, Ohio). In patients treated with

somatostatin analogs, the PET/CT procedures were scheduled just before the monthly treatment dose (14).

Both Onc-PETs and AM-PETs were reconstructed with cubic 2 mm voxels, a similar iterative algorithm, and additional corrections detailed elsewhere (5). However, a 3-minute PET recording was scheduled per bed position for Onc-PET and a single 15-minute cardiac-centered bed position for AM-PET.

Areas of LV myocardial uptake of [<sup>68</sup>Ga]Ga-DOTA-TOC were detected visually with a 0-to-≤3 Standardized Uptake Value (SUV) scaling range (5) and localized according to a 17-segment LV division (supplemental Figure 1). These uptake areas were only considered significant when they (i) involved at least two contiguous LV segments, (ii) were associated with a myocardial/blood SUVmax ratio > 1.5 with this ratio being determined with 2 cm diameter spherical volumes of interest, and a right atrium center location for blood activity and (iii) were located at more than 1 cm from liver activity (5).

In addition, a myocardial PET uptake volume was quantified using isocontours and the same criteria as those used for the visual analysis (i.e. myocardial/blood SUVmax ratio > 1.5 and > 1 cm distance from liver activity). This volume was considered to be zero when no myocardial uptake was detected visually.

### **Statistical Analysis**

Continuous variables are represented as medians, with interquartile ranges, and categorical variables as frequencies and percentages. Two-group comparisons were performed with i) chi-square tests (or Fisher's exact tests when more appropriate) for categorical variables and ii) Mann-Whitney. Receiver Operating Characteristics (ROC) curves were additionally performed for continuous variables, and associations between continuous variables were tested with the non-parametric Spearman's rank correlation method. The significance

threshold was set at  $p < 0.05$ , and the closest-to – (0,1) corner approach was used to define the optimal threshold value from ROC curves.

In the Onc-PET group, Generalized Linear Mixed-effects Models (GLIMMIX SAS procedure) for repeat measurements were used to identify factors associated with significant myocardial [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC uptake (dichotomous variable), among those listed in Table 1, and linear mixed-effects models for repeat measurements (Mixed SAS procedure) to determine factors associated with the log-transformed Myocardial/blood SUVmax ratio. This log transformation was required to meet the normality assumptions of the linear models. Odds ratios (GLIMMIX) and Exp(Beta) (Mixed) with 95% confidence intervals were reported, and p values of 0.15 and 0.05 were used as thresholds for, respectively, entering and removing variables from the models. Log linearity/linearity assumptions for continuous variables in GLIMMIX/Mixed models were checked using the restricted cubic splines method and with knot locations based on Harrell's recommended percentiles (15).

All analyses were conducted using SAS<sup>®</sup> software version 9.4 (SAS Institute, Cary, NC, USA).

## Results

### Analysis of the Oncologic (Onc)-PET Group

A total of 511 consecutive [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC PETs/CTs were considered, 3 were excluded because of a confirmed or suspected cardiac metastasis or a technical PET problem, leaving 508 [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC PET recordings from 178 patients in the current analysis. Seventy-six patients had a single PET, 56 had 2-3 PETs, and 46 patients had > 3 PETs.

As detailed in Table 1, 423 of Onc-PETs (83.1 %) were recorded from patients with a confirmed neuroendocrine tumor and only 40 (7.9 %) with a history of coronary artery disease (CAD) (myocardial infarction or coronary revascularization). Oncology surgery was documented in 266 (52.3 %) cases, and the Onc-PETs were recorded during periods of analog somatostatin treatment in 193 (37.9 %) cases.

A significant myocardial uptake was detected in 137 (26.9%) Onc-PETs and, as detailed in Table 2, the multivariate predictors of this uptake were somatostatin analog treatment (Exp(Beta) (95 %CI): 0.805 (0.728-0.890),  $p < 0.001$ ) and age (1.005 (1.001-1.009),  $p = 0.012$ ). A comparable model was selected for predicting the logarithm of the myocardial/blood SUVmax ratio – i.e. somatostatin analog treatment ( $p < 0.001$ ) and coronary artery disease history ( $p = 0.022$ ).

The detection rate of myocardial uptake was only 12.9% (25/193) in somatostatin analog-treated patients. This rate was higher, 29.4% (53/180), when the absence of somatostatin analog treatment was associated with an age of  $\leq 64$  years, which was the median of the Onc-PET population, and even higher, 43.4% (59/136), when associated with the older age group. These data are illustrated in the Graphical Abstract.

### **Analysis of the Acute Myocarditis (AM)-PET Group**

Thirty-one patients were recruited at the time of AM diagnosis, with elevated plasma troponin I levels (median peak [interquartile range]: 12.0 [6.9-17.4] ng/mL) and chest pain in 27 cases. Symptoms evocative of a gastrointestinal or respiratory tract infection were documented for 15 of these patients, and a recent ( $\leq 3$  days) history of mRNA-based COVID-19 vaccination for three other patients. Ten AM patients had an abnormal LV ejection fraction ( $< 50\%$ ) on MRI. The PET scan was performed a median 4 [3-5] days after peak troponin.

As detailed in Figure 1, the PET parameters considered (myocardial/blood SUVmax ratio, myocardial uptake volume) were unrelated to the MRI parameters used for tissue characterization (T1, T2, number of segments with late gadolinium enhancement). However, the LV ejection fraction, determined by MRI, was inversely correlated to the myocardial/blood SUVmax ratio ( $p = 0.008$ ), and myocardial PET uptake volume ( $p = 0.013$ ).

### **Comparison Between the Onc-PET and AM-PET Groups**

As shown in Table 1, men were overrepresented in the AM-PET group compared to the Onc-PET group with myocardial uptake. Patients in the AM-PET group were also younger and had lower rates of most CV risk factors. None of the AM-PET patients had any history of cancer or cardiac disease.

Significant myocardial uptake was detected in all 31 AM-PETs, with the volume and intensity of uptake dramatically higher compared to the 137 Onc-PETs with myocardial uptake. The respective medians in these two groups were 2.80 [2.29-3.00] and 2.00 [1.76-2.18] ( $p < 0.001$ ) for the myocardial/blood SUVmax ratio and 47.3 [24.0-135.0]  $\text{cm}^3$  and 2.2 [0.6-9.5]  $\text{cm}^3$  ( $p < 0.001$ ) for the myocardial uptake volume (Figure 2). Higher rates of myocardial uptake were also observed in the AM-PET group compared to the Onc-PET group in a per-segment analysis, with the difference particularly marked for inferior and inferior-lateral segments (Figure 2).

On the ROC curve analysis shown in Figure 3, both the myocardial uptake volume and the myocardial/blood SUVmax ratio were able to differentiate myocardial uptake in the AM-PET group from that of the Onc-PET group, with areas under the curves (95% confidence intervals) of 0.888 (0.817-0.960) and 0.879 (0.814-0.944) respectively. The criteria of a myocardial/blood SUVmax  $> 2.2$  (blue arrow) allowed to differentiate myocardial uptake between AM-PET and Onc-PET groups with a sensitivity of 87% (27/31) and a specificity of

77.4% (106/137). The criteria of a myocardial uptake volume  $> 18 \text{ cm}^3$  provided comparable results (sensitivity: 84% (26/31), specificity: 83% (114/137)).

Specificities of 88% (44/50) for the criteria of a myocardial/blood SUVmax ratio  $> 2.2$  and of 94% (47/50) for that of a myocardial uptake volume  $> 18 \text{ cm}^3$  were obtained when the Onc-PET group with myocardial uptake was restricted to a subgroup with more comparable characteristics to the AM group (i.e. age  $\leq 64$  years, no CAD history, and not somatostatin agonists).

Representative AM-PET and Onc-PET group scans are shown in Figure 4.

## Discussion

Our study found that as many as 26.9% somatostatin-PETs recorded for routine oncology indications show significant myocardial uptake. This is consistent with the prevalence reported in the literature (11-13). The uptake detection rate was decreased by somatostatin analogs and increased with patient age. Moreover, uptake in oncology cases was generally less intense and less extensive than uptake measured in AM, which supports the notion that somatostatin-PET may be able to specifically detect AM.

Results obtained in our AM-PET group, where [ $^{68}\text{Ga}$ ]Ga-DOTA-TOC PET was recorded in MRI-ascertained AM cases, confirm our previously published preliminary results (5) – i.e. a consistently observed increased myocardial uptake relative to the blood activity on at least two contiguous LV segments, associated with a marked decrease in blood activity, and with myocardial uptake predominantly localizing to inferior and inferior-lateral LV segments (Figure 2). The main technical limitations remain (i) the relatively low activity of the

myocardial uptake areas (mean SUVmax was 1.8 in the present AM-PET group) and (ii) the inability to analyze certain inferior LV segments proximal to liver activity.

In [<sup>68</sup>Ga]Ga-DOTA-TOC PETs recorded for oncology indications, differences in SUVmax between organs from the same patient were previously shown to correlate with differences in SSTR expression (16). However, tissue-to-blood SUV ratios of [<sup>68</sup>Ga]Ga-DOTA-TOC are known to be a more accurate measure of somatostatin receptor density than SUV (17), and in the present study, the myocardial-to-blood SUVmax ratio was a much better predictor of acute myocarditis than SUVmax. The lower blood SUVmax observed in the AM-PET group compared to the Onc-PET group is also likely to further enhance the difference in myocardial/blood SUVmax ratio between the two groups.

The specificity of detecting AM could be undermined by the frequent observation of myocardial uptake in somatostatin-PET recordings of common oncology indications. Such incidental observations were previously found to correlate with older patient age, a CAD history, and cardiovascular risk factors (11). In our large sample of [<sup>68</sup>Ga]Ga-DOTA-TOC PETs recorded for an oncology indication, we also found a significant correlation between age and the detection of myocardial uptake, as well as between a CAD history and the myocardial/blood SUVmax ratio. However, these two cardiac PET parameters were primarily associated with an ongoing somatostatin antagonist treatment. Somatostatin analogs were prescribed in as many as 37.9% of Onc-PET group cases, which is in line with their anti-proliferative and anti-secretory action in neuroendocrine tumors.

The myocardial uptake rate was only 12.9% in Onc-PETs recorded in patients treated with somatostatin analogs. According to current recommendations (14), an Onc-PET was scheduled a few days before the monthly administration of somatostatin agonists and, thus, as long as four weeks after the last administration. Nevertheless, such long-acting treatments

are known to decrease tracer uptake in somatostatin-PET for up to 25 days after their administration (18), and a primary consequence of this reduced uptake is an apparent increase in blood activity (see the Graphical Abstract).

The detection rate of significant myocardial uptake was thus even higher when only considering the population not treated with somatostatin analogs and specifically the older subgroup of this cohort (43.4% uptake in the > 64-year-old subgroup). This observation is not fully understood, although it is supported by the general concept that cardiovascular aging involves an overall increased level of heart inflammation (19).

Consistent with previous reports (6,20), we also observed myocardial uptake in patients with a history of myocardial infarction (Figure 3). The previous observations of SSTR expression in fibroblasts could explain the detection of a Somatostatin-PET uptake within myocardial scars (21,22). However, of the 24 Onc-PETs from patients that presented a history of myocardial infarction, myocardial uptake was only documented in 10 cases. Certain areas of somatostatin-PET uptake could also occur within the atherosclerotic plaques of coronary arteries, as previously reported (23). Notably, the anterior and anterior-septal segments, located in the basal and median part of the LV, exhibited the slightest difference in the uptake rate between AM-PET and Onc-PET (see Figure 1 and yellow arrows in Figure 3). However, this uptake location was previously considered to correspond to the atheromatous left anterior descending arteries (24) (Figure 1).

The main finding of the present study is that AM-PET is best differentiated from Onc-PET based on the objective quantitative criteria of uptake intensity and volume – i.e. myocardial/blood SUVmax ratio and myocardial uptake volume. These parameters were strongly interrelated in the present study population (see Figure 1), and by using optimized thresholds, respective sensitivities of 87% and 84% were achieved. The respective

specificities were 88% and 94% when the Onc-PET group with myocardial uptake was further restricted to a subgroup with more comparable clinical characteristics to the AM group. Patients from this subgroup did not exhibit factors previously shown to affect myocardial uptake in our Onc-PET population, factors which are unlikely to be present in acute myocarditis patients (> 64 years old, somatostatin analog treatment, history of coronary artery disease).

Our results appear to be more satisfactory than those previously published with [<sup>18</sup>F]-FDG PET for detecting myocarditis (25), this is most likely due to the difficulties of suppressing physiologic myocardial [<sup>18</sup>F]-FDG uptake, despite diet or fasting. No preparation is recommended before a cardiac somatostatin-PET except the withdrawal of any corticosteroid or somatostatin analog treatment.

Finally, the pathological significance of the myocardial/blood SUVmax ratio and the myocardial uptake volume are further strengthened by our additional observations of inverse associations with the LV ejection fraction in myocarditis patients (Figure 1).

Our results need to be confirmed in other populations and require a dedicated cardiac somatostatin-PET recording protocol for control groups. It would be interesting to determine whether this PET methodology could also detect cardiac sarcoidosis or chronic forms of myocarditis and to what extent our findings may be extrapolated to other somatostatin-PET tracers, such as [<sup>68</sup>Ga]Ga-DOTA-NOC (26).

## Conclusion

A significant myocardial uptake is observed in as many as 26.9% of somatostatin-PETs recorded for routine oncology indications. This rate is even higher in the absence of somatostatin agonist treatments, particularly in older individuals. However, somatostatin-PET, analyzed with the objective quantitative criterion of uptake intensity or volume, is able to identify acute myocarditis and differentiate it from myocardial uptake of other origins.

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## Key Points

**Question:** What are the parameters associated with the detection of a myocardial uptake on somatostatin-PET recorded for routine oncology indications, and what are the PET criteria for differentiating from acute myocarditis?

**Pertinent findings:** A myocardial uptake is frequently detected on oncologic somatostatin-PET, especially in older patients not treated with somatostatin analogs, but this uptake is mostly less extensive and intense than that observed in acute myocarditis.

**Implication for patient care:** Somatostatin-PET, analyzed with the objective quantitative criterion of uptake intensity or volume, has the potential to diagnose acute myocarditis and differentiate it from myocardial uptake of other origins.

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**Table 1:** Main data recorded at the time of the PET/CT in the overall Onc-PET group, in the Onc-PET subgroup with myocardial uptake, and in the AM-PET group. P values relate to the comparison between the AM-PET group and the Onc-PET group with myocardial uptake.

|   | Onc-PET            |                                   | AM-PET             | P value  |
|---|--------------------|-----------------------------------|--------------------|----------|
|   | Overall<br>(n=508) | With myocardial<br>uptake (n=137) | (n=31)             |          |
| Age (years)                                 | 64.0 [54.8-72.0]   | 65.7 [55.0-73.4]                  | 26.5 [21.9-33.8]   | <0.0001  |
| Women                                       | 246 (48.3 %)       | 64 (46.7 %)                       | 1 (3.2 %)          | <0.0001  |
| Body mass index (kg/m <sup>2</sup> )        | 25.5 [22.5-29.1]   | 26.1 [23.1-29.5]                  | 24.9 [23.2-27.7]   | 0.27     |
| <b>CV history and risk factors</b>          |                    |                                   |                    |          |
| Coronary artery disease history             | 40 (7.9 %)         | 14 (10.2 %)                       | 0 (0%)             | 0.075    |
| Myocardial infarction history               | 24 (4.7 %)         | 9 (6.6 %)                         | 0 (0%)             | 0.21     |
| Number of CV risk factors                   | 1 (0 - 2)          | 1 (0 - 2)                         | 0 (0 - 1)          | 0.005    |
| Active smoking                              | 7 (1.4 %)          | 2 (1.5 %)                         | 7 (22.6 %)         | 0.0001   |
| Obesity                                     | 102 (20.1 %)       | 29 (21.3 %)                       | 5 (16.7 %)         | 0.80     |
| Treated hypertension                        | 207 (40.7 %)       | 58 (42.3 %)                       | 1 (3.2 %)          | <0.0001  |
| Treated dyslipidemia                        | 78 (15.3 %)        | 20 (14.6 %)                       | 1 (3.2 %)          | 0.13     |
| Treated diabetes                            | 102 (20.0 %)       | 26 (19.0 %)                       | 0 (0 %)            | 0.005    |
| <b>Oncologic data</b>                       |                    |                                   |                    |          |
| Diagnosed cancer                            | 466 (91.5%)        | 124 (90.5 %)                      | _____              | _____    |
| Diagnosed NET                               | 423 (83.1 %)       | 111 (81.0 %)                      | _____              | _____    |
| ≥ 2 tumor grade                             | 275 (54.3 %)       | 68 (49.6 %)                       | _____              | _____    |
| External radiotherapy history               | 100 (19.6 %)       | 28 (20.4 %)                       | _____              | _____    |
| Internal radiotherapy history               | 87 (17.1 %)        | 17 (12.4 %)                       | _____              | _____    |
| Oncologic surgery history                   | 266 (52.3 %)       | 62 (45.3 %)                       | _____              | _____    |
| Current chemotherapy                        | 61 (12.0 %)        | 26 (19.0 %)                       | _____              | _____    |
| Current immunotherapy                       | 67 (13.2 %)        | 14 (10.2 %)                       | _____              | _____    |
| Somatostatin analog treatment*              | 193 (37.9 %)       | 25 (18.2 %)                       | _____              | _____    |
| <b>CV PET/CT data</b>                       |                    |                                   |                    |          |
| Presence of a myocardial uptake             | 137 (26.9%)        | 137 (100%)                        | 31 (100 %)         | 1        |
| Number of segments with myocardial uptake   | 0.0 [0.0-3.0]      | 6.0 [3.0-9.0]                     | 15.0 [10.0 – 17.0] | < 0.0001 |
| Myocardial uptake volume (cm <sup>3</sup> ) | 0.0 [0.0-0.09]     | 2.2 [0.6 -9.5]                    | 47.3 [24.0-135.0]  | < 0.0001 |
| Myocardial/blood SUVmax ratio               | 1.44 [1.25-1.79]   | 2.00 [1.76-2.18]                  | 2.80 [2.29-3.00]   | < 0.0001 |

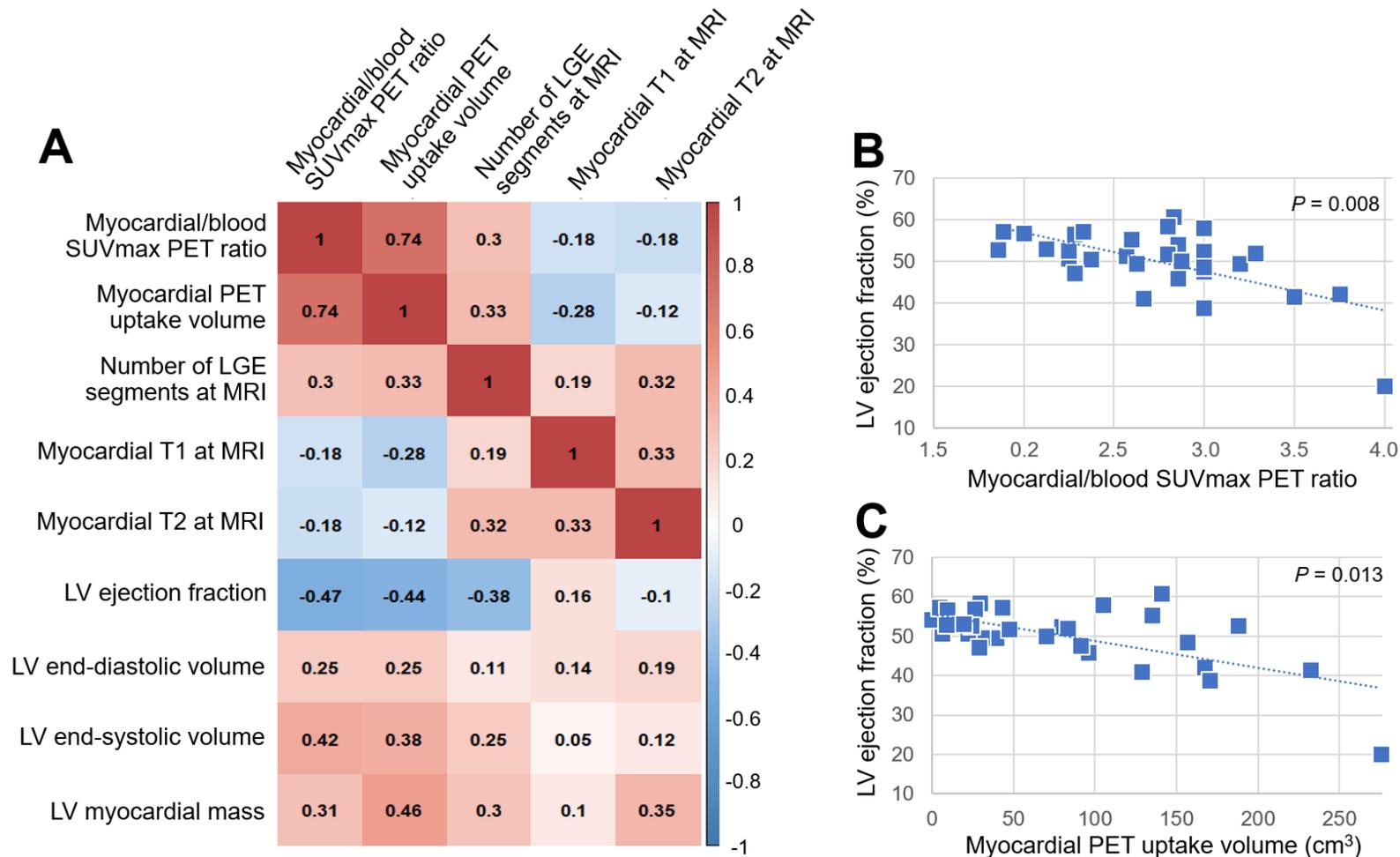
CV: cardiovascular; LV: left ventricle; NET: neuroendocrine tumor; SUVmax: maximal standardized uptake value

\*: Somatostatin analogs were not administered in the four weeks preceding PET

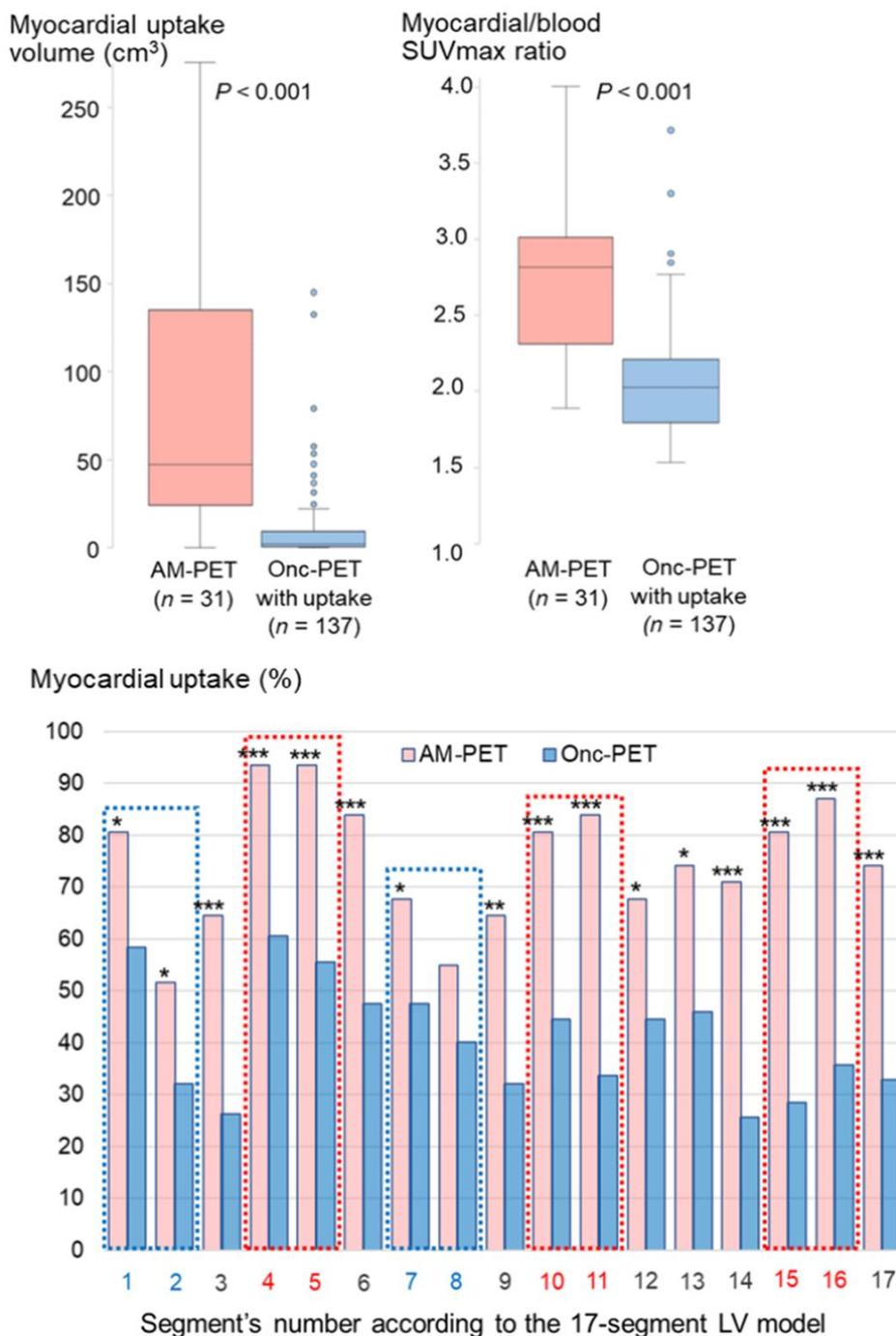
**Table 2:** Univariate and multivariate predictors of myocardial uptake and the log-transformed myocardial/blood SUVmax ratio in the Onc-PET group.

|  | Myocardial uptake         |          |                           |          | Ln (SUVmax ratio)         |          |                           |          |
|--|---------------------------|----------|---------------------------|----------|---------------------------|----------|---------------------------|----------|
|  | Univariate                |          | Multivariate              |          | Univariate                |          | Multivariate              |          |
|  | <i>Exp(Beta) (95 %CI)</i> | <i>P</i> | <i>Exp(Beta) (95 %CI)</i> | <i>P</i> | <i>Exp(Beta) (95 %CI)</i> | <i>P</i> | <i>Exp(Beta) (95 %CI)</i> | <i>P</i> |
| Age (years)                            | 1.018 (0.993-1.044)       | 0.16     | 1.005 (1.001-1.009)       | 0.012    | 1.003 (0.999-1.006)       | 0.16     |                           |          |
| Women                                  | 1.070 (0.620-1.848)       | 0.81     |                           |          | 0.973 (0.877-1.079)       | 0.60     |                           |          |
| Body mass index (kg/m <sup>2</sup> )   | 1.049 (0.995-1.106)       | 0.075    |                           |          | 1.006 (0.996-1.015)       | 0.23     |                           |          |
| <b>CV history and risk factors</b>     |                           |          |                           |          |                           |          |                           |          |
| Coronary artery disease history        | 1.646 (0.758-3.572)       | 0.21     |                           |          | 1.184 (1.024-1.369)       | 0.023    | 1.177 (1.024-1.353)       | 0.022    |
| Myocardial infarction history          | 1.887 (0.717-4.964)       | 0.20     |                           |          | 1.214 (1.015-1.451)       | 0.034    |                           |          |
| At least one CV risk factor            | 0.970 (0.587-1.602)       | 0.91     |                           |          | 1.015 (0.922-1.118)       | 0.76     |                           |          |
| Active smoking                         | 0.962 (0.127-7.285)       | 0.97     |                           |          | 1.007 (0.676-1.500)       | 0.97     |                           |          |
| Obesity                                | 1.329 (0.723-2.442)       | 0.36     |                           |          | 1.043 (0.944-1.152)       | 0.41     |                           |          |
| Treated hypertension                   | 1.076 (0.619-1.871)       | 0.80     |                           |          | 0.957 (0.862-1.063)       | 0.42     |                           |          |
| Treated dyslipidemia                   | 1.045 (0.482-2.264)       | 0.91     |                           |          | 1.064 (0.924-1.225)       | 0.39     |                           |          |
| Treated diabetes                       | 0.872 (0.433-1.756)       | 0.70     |                           |          | 1.036 (0.910-1.178)       | 0.59     |                           |          |
| <b>Oncologic data</b>                  |                           |          |                           |          |                           |          |                           |          |
| Diagnosed cancer                       | 0.829 (0.380-1.805)       | 0.64     |                           |          | 0.881 (0.769-1.009)       | 0.069    |                           |          |
| Diagnosed NET                          | 0.730 (0.383-1.391)       | 0.34     |                           |          | 0.978 (0.870-1.099)       | 0.70     |                           |          |
| ≥ 2 tumor grade                        | 0.839 (0.481-1.463)       | 0.54     |                           |          | 0.869 (0.783-0.963)       | 0.008    |                           |          |
| External radiotherapy history          | 1.090 (0.500-2.378)       | 0.83     |                           |          | 1.044 (0.911-1.195)       | 0.54     |                           |          |
| Internal radiotherapy history          | 0.532 (0.264-1.071)       | 0.078    |                           |          | 0.950 (0.848-1.065)       | 0.38     |                           |          |
| Oncologic surgery history              | 0.771 (0.459-1.297)       | 0.33     |                           |          | 0.900 (0.820-0.989)       | 0.028    |                           |          |
| Current chemotherapy                   | 1.639 (0.712-3.772)       | 0.25     |                           |          | 1.008 (0.888-1.145)       | 0.90     |                           |          |
| Current immunotherapy                  | 0.820 (0.399-1.686)       | 0.59     |                           |          | 1.053 (0.939-1.180)       | 0.38     |                           |          |
| Current somatostatin analog treatment* | 0.325(0.171-0.619)        | 0.0007   | 0.805 [0.728-0.890]       | <.0001   | 0.759 (0.695-0.830)       | <.0001   | 0.761 (0.698-0.831)       | < 0.001  |

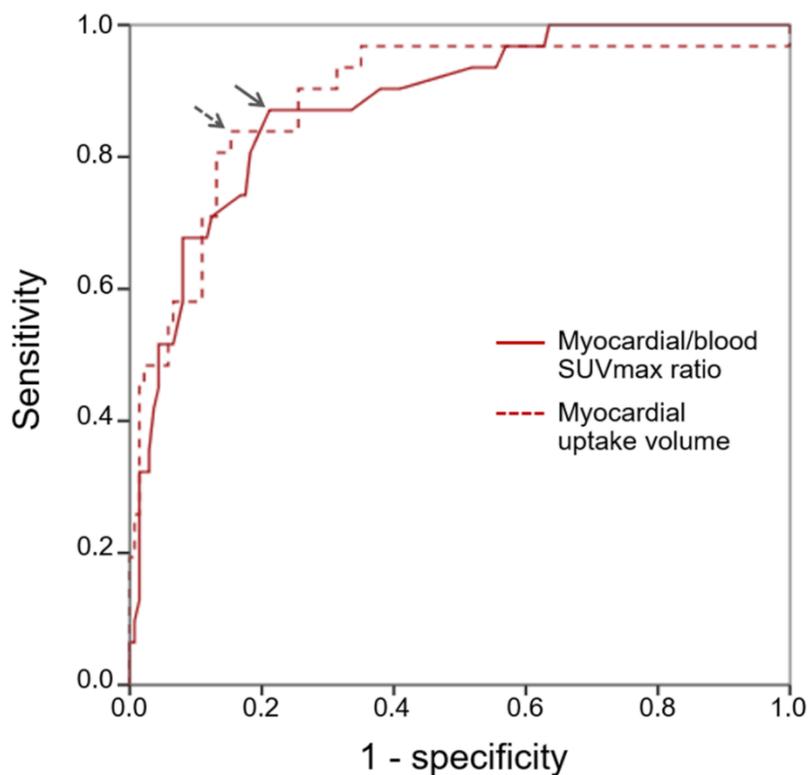
Abbreviations and footnotes are the same as in Table 1.



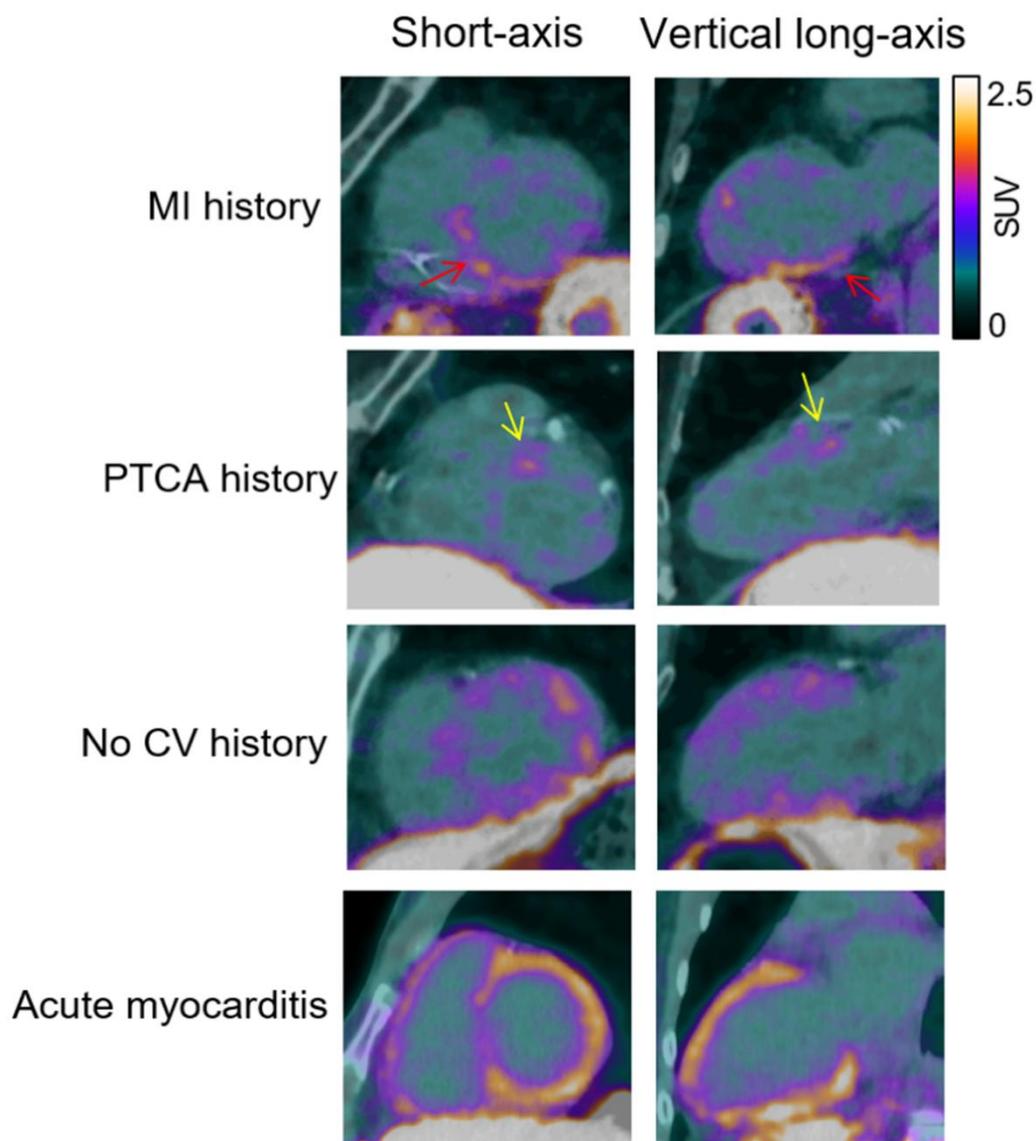
**Figure 1:** Left panel: Spearman correlation coefficients for associations between (i) tissue characterization parameters provided by PET (myocardial/blood SUVmax ratio, myocardial uptake volume) and MRI (T1, T2, number of late gadolinium enhancement LV segments) and (ii) all considered PET and MRI variables (left panel). Right panel: the relationship between LV ejection fraction and myocardial/blood SUVmax ratio as well as myocardial uptake volume.



**Figure 2:** Comparison of myocardial uptake in the AM-PET and Onc-PET groups in terms of (i) myocardial uptake volume (upper left panel), (ii) myocardial/blood SUVmax ratio (upper right panel) and (ii) myocardial uptake detection rate on each of the 17 LV-segments (lower panel). Note that the difference in uptake detection rates between AM-PET and Onc-PET groups is particularly marked ( $p < 0.001$ ) in the inferior and inferior-lateral segments (columns delimited with dashed red lines) and weaker ( $p$  values around 0.05) in the anterior and anterior-septal segments located in the basal and median parts of the LV (columns delimited with dashed blue lines).

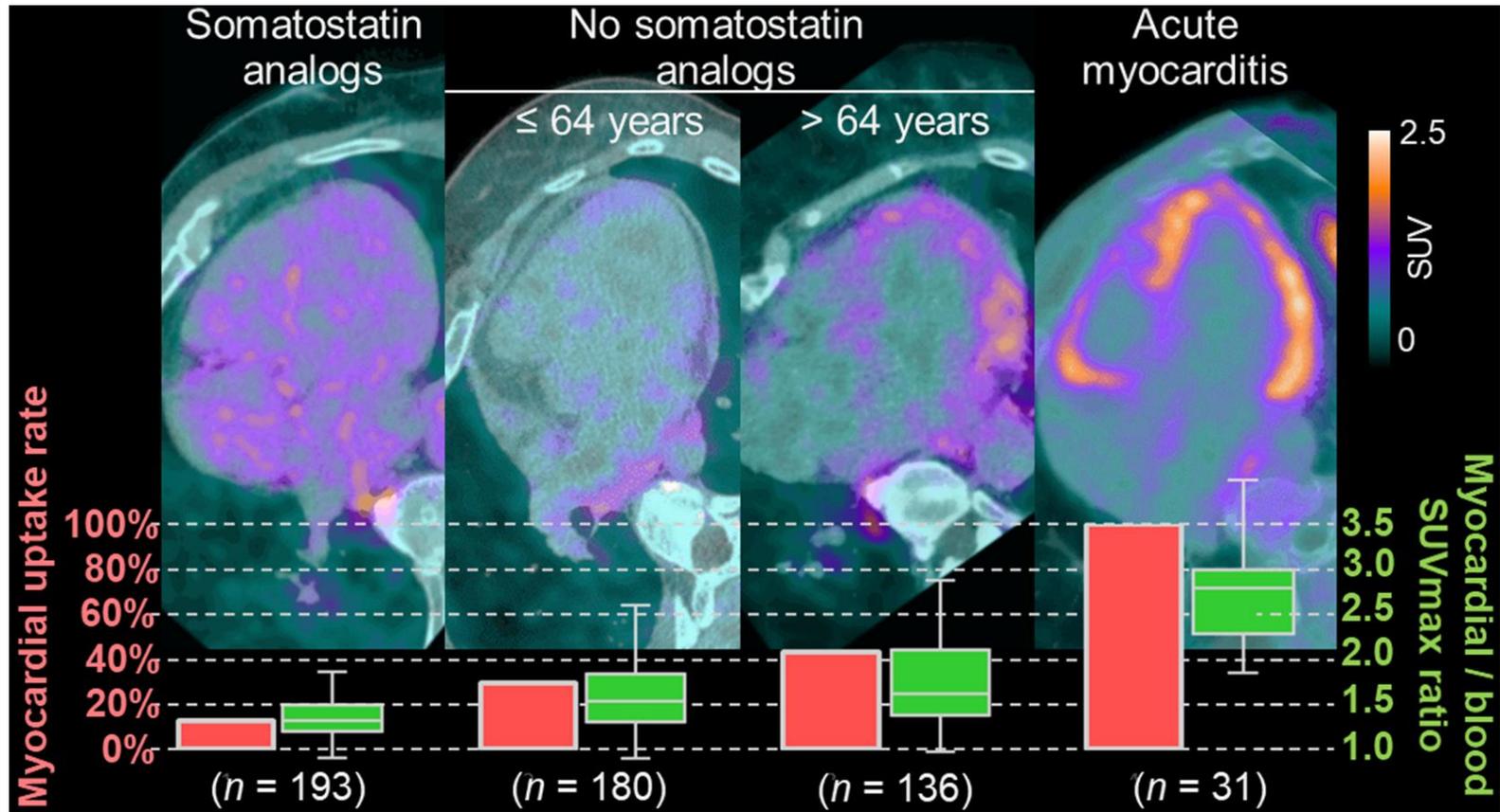


**Figure 3:** Receiver operating characteristic curves (ROC) optimized to differentiate the AM-PET from the Onc-PET group based on the myocardial/blood SUVmax ratio and the myocardial uptake volume. According to the closest-to – (0,1) corner approach, we selected thresholds of 2.2 for myocardial/blood SUVmax ratio and 18 cm<sup>3</sup> for myocardial uptake volume (grey arrows).



**Figure 4:** Representative fused PET/CT slices, represented on a 0-to-2.5 SUV scale, of an AM-PET group 41-year-old man (Acute myocarditis; see the diffuse and intense LV uptake) and of three Onc-PET patients with myocardial uptake: a 71-year-old man and a 76-year-old woman with respective previous histories of inferior myocardial infarction (MI history; see the uptake on inferior and inferoseptal segments (red arrows)) and percutaneous transluminal angioplasty (PTCA history; see the uptake on the proximal parts of the anterior and septal walls (yellow arrows)), as well as an Onc-PET group 81-year-old man with no cardiovascular history (No CV history; see the diffuse LV uptake).

The myocardial/blood SUVmax ratio was 4.0 in the AM-PET patient and ranged from 2.13 to 2.18 in the three Onc-PET patients.



Graphical Abstract