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Assessment of Total Body Atherosclerosis by PET/CT

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SYNOPSIS

Atherosclerotic burden has come in focus of cardiovascular risk assessment. PET/CT imaging with tracers ^{18}F-fluorodeoxyglucose and ^{18}F-sodium fluoride mirror arterial wall inflammation and microcalcification, respectively. Arterial uptake of both tracers is modestly age-dependent, but rarely overlaps in site and time. ^{18}F-sodium fluoride uptake is consistently associated with risk factors and more easily measured in the heart. Due to extremely high sensitivity, ultra-short acquisition, and minimal radiation to the patient, total body PET/CT provides unique opportunities for atherosclerosis imaging: disease screening and delayed and repeat imaging with global disease scoring and parametric imaging to characterize better atherosclerosis of the individual patient.

KEY POINTS

- The recently expressed view that the atherosclerotic burden should be in focus of cardiovascular risk assessment rather than characterizing the individual vulnerable plaque is what PET/CT imaging should express in essential parts of the arterial system.
- ^{18}F-fluorodeoxyglucose and ^{18}F-sodium fluoride, depicting arterial wall inflammation and microcalcification, respectively, are presently the only PET tracers that have been studied more extensively; their arterial uptake rarely overlap in site and time.
- Arterial uptake of both tracers is modestly age-dependent, albeit ^{18}F-sodium fluoride uptake is more consistently associated with risk factors than ^{18}F-fluorodeoxyglucose uptake and is more easily measured in the heart.
- Arterial ^{18}F-fluorodeoxyglucose uptake appears to come and go with time (months); recent preliminary data suggest that ^{18}F-sodium fluoride uptake may also be a more varying process than previously anticipated. These statements require confirmation in future prospective longitudinal studies.
- Total body PET provide unique opportunities for studying atherosclerosis and its management more profoundly due to much higher sensitivity, ultra-short acquisition, and minimal radiation to the patient; this allows for disease screening, delayed and repeat imaging with features such as global disease scoring and parametric imaging to characterize the individual patient much better then hitherto seen.

INTRODUCTION

The underlying premise of this forward-looking communication is the view put forth in recent years that the entire atherosclerotic process and disease burden should be in focus of cardiovascular risk assessment rather than characterizing the individual vulnerable plaque.[1-3] Until recently, there has been, and still is, an overwhelming interest in the vulnerable or rupture prone plaque, anticipating that if such plaques can be identified and passivated it would improve significantly the prognosis of patients suffering from advanced atherosclerosis. A shift to assessing instead the atherosclerotic burden in the heart, carotids, aorta, or other major arteries is a change of game that places great demand on available imaging techniques, as atherosclerotic arterial wall changes are often scattered, diffuse and mostly invisible by CT meaning that they are difficult to segment properly (Fig. 1).

Apart from being able to demonstrate subtle arterial wall changes, an imaging test for measuring the atherosclerotic burden and prediction of cardiovascular risk based on the global atherosclerotic burden comprising the heart and major arteries must be easy and fast to perform and so specific, accurate, and reproducible that any clinician would feel better off with that instead of conventional methods for assessment of diagnosis, prognosis, treatment triage or therapeutic efficacy in the individual patient.

The aim of this review was to elucidate and discuss potentials and challenges of a "transition from a focus on individual lesions to atherosclerotic disease burden in coronary and overall cardiovascular risk assessment", as Arbab-Zadeh and Fuster have put it,[2] – seen in light of novel total-body PET scanners and the rapid rise in artificial intelligence (AI) for interpretation of PET scans.

ATHEROSCLEROTIC DISEASE BURDEN OR VULNERABLE PLAQUE

Considerable effort has been put into modalities that can identify and characterize vulnerable plaques, which are considered responsible for thrombosis and occlusion leading to acute myocardial infarction (MI) and stroke. They have a thin cap on the luminal side and a lipid-rich and often necrotic core that rarely gives rise to severe stenosis, i.e., properties that hamper their detection and have called for diagnostic criteria, primarily based on CT, ultrasound or MRI,[4-12] none of which, however, have reached general clinical application.

No wonder, therefore, that arterial NaF-PET imaging, initiated in 2010 by Derlin et al. who started looking at the prevalence and topographic distribution of NaF uptake compared to CT calcification in major arteries,[13,14] sparked an interest in studying NaF uptake in vulnerable coronary and carotid plaques[15-18] to achieve improved plaque characterization, since CT-calcification could not characterize the individual patient very precisely.[19-21]

Post-mortem studies of patients dying from cardiac arrest and acute MI have indicated that the percent luminal area stenosis at sites of thrombus or at likely culprit lesions causing MI is very high (≥75%) and that only 10% of culprit lesions had a diameter of <50% after thrombosis removal.[22-24] In the heart, it is a limitation that even advanced approaches examine plaques exclusively in the proximal parts of the coronary tree[25,26] disregarding calcification in the distal and transmural branches supplying the subendocardial myocardial layers, where ischemia is more likely to trigger infarction and neuralgia. With global molecular imaging of the heart this limitation does not apply and, thus, results of PET imaging may be a better indicator of cardiac atherosclerotic burden.This, together with the observation that the atherosclerotic processes are more dynamic and changeable than previously thought,[27,28] has made leading cardiologists suggest that “our focus must remain on the entire atherosclerotic process and prevention of diffuse disease, and seeking individual plaques may not be the ultimate answer.”[29]

Arbab-Zadeh and Fuster conclude their review stating that “there is no conclusive evidence that individual plaque assessment better predicts acute coronary event risk than established risk factors, such as the extent and severity of coronary artery disease”. Since atherosclerotic plaque rupture occurs mostly without clinical symptoms, whereas the atherosclerotic disease burden is a consistent, strong predictor of adverse events, they suggest that instead of focusing on individual coronary lesions we must strive for “comprehensive risk assessment that integrates specific information on the atherosclerotic plaque burden and systemic factors that increase the risk for disease activity and vascular thrombosis and is tailored to specific patient populations and individual patients.”[2] Their point of view is reinforced by the fact that the literature on PET characterization of vulnerable plaques does not reveal such a close association between uptake of FDG or NaF and alleged vulnerability that it is possible to predict with a reasonable certainty the cardiovascular risk of the individual patient.[18,30] Therefore, there may indeed be a need for more elaborate schemes for risk assessment, taking into account, besides imaging results, also clinical, biochemical and genetic data. This calls for AI-based algorithms as discussed below.

Assessment of total body atherosclerosis is a new approach focusing on detection and grading of the extent and severity of disease, whether grading arterial wall inflammation (by FDG-PET) or micro-calcification (by NaF-PET) as indicators of early stage atherosclerosis or macro-calcification by CT as a representative of late stage atherosclerosis.[31] With PET, this has been done by manual segmentation, summarizing uptake in multiple adjacent axial slices to get a single number representing the atherosclerotic burden in, for instance, the aorta. This is a cumbersome and time consuming task; however, from experience in prostate cancer,[32,33] it seems that this can soon be done in atherosclerosis too in less than a minute or so by applying AI-based interpretation.[18,30] A major vision of this ap-

proach is to provide a means for monitoring effects of anti-atherosclerotic intervention. We describe some of the challenges that must be dealt with before assessment of total body atherosclerosis by molecular imaging can become a clinical reality.

PET TRACERS FOR ATHEROSCLEROSIS IMAGING

Surprisingly few tracers have been found to be clinically useful in the study of atherosclerosis. Most tracers studied over the years never reached beyond the animal testing stage. This goes for ^{18}F-labeled resveratrol offering some protection against atherosclerosis (including the inhibition of low-density lipoprotein),[34] ^{64}Cu-DTPA-CLIO-VT680, a ^{64}Cu-labeled triple reporter nanoparticle known to accumulate in macrophages located in inflamed lesions and carotid artery plaques after intravenous administration,[35] and ^{18}F-4V, a tetrameric linear peptide targeting atherosclerotic plaques and myocardial ischemic lesions.[36] Other probes are ^{68}Ga-NODAGA-AE105-NH2, a urokinase-type plasminogen activator receptor targeting molecule,[37] ^{18}F-AppCHFppA and ^{18}F-SB209670, identifying the adenosine nucleotide receptor,[38,39] and ^{18}F-ET-1, targeting the endothelin-1 receptor.[40] Common to these and many others are lack of specificity, since most of them target processes (like apoptosis) or elements (like metalloproteinases) of other types of disease, not least inflammation and cancer. When the *Molecular Imaging and Contrast Agent Database* (developed by the National Center for Biotechnology Information, at the National Institutes of Health) ceased in June 2013 to become updated, it contained only a single tracer that thus far had been used in humans for studies of atherosclerosis, namely FDG, whereas NaF was not mentioned for this purpose, nor for imaging of bone metastases.[41]

FDG AND NAF PET IMAGING IN ATHEROSCLEROSIS

Until now, only FDG and NaF have reached considerable human use, perhaps because they were early available for other primary purposes, i.e., studies of brain metabolism and bone mineral turn over, respectively.[42,43] FDG was first used by Yun at al. almost twenty years ago, while NaF as mentioned was introduced about 10 years later by Derlin et al.[44,45]Traditionally, in being a marker of glucose metabolism, FDG is known to mirror macrophage accumulation and thus inflammation, while NaF, in being adsorbed to microcalcifications of a size below 50 microns, is a sensitive and specific marker of local tissue necrosis.[31] However, their interrelationship, temporal and topographic relationship and connection to CT-detectable arterial macrocalcification are still not known in detail. It was hoped that one or both tracers could be used to identify early stage atherosclerosis and serve as precursors to the late appearing macrocalcification and plaque development that cause organ damage. Unfortunately, it appears that things are not that straightforward.

Recent reviews have pointed to NaF as perhaps the more valuable of the two, the reasons of which are twofold: (1) in animal studies, it mirrors some of the earliest changes observed in the atherosclerosis process;[46] (2) in human studies, it has, opposite to FDG, been consistently associated with cardiovascular risk in most parts of the arterial system.[18, 47-49] Unlike FDG, NaF uptake is more easily detected and quantified in the heart, where it is assumed to represent early coronary artery atherosclerosis; NaF is not detectable in the myocardium of atherosclerotic pigs,[46] and presumably not in the human myocardium either except in patients, who have suffered from a myocardial infarction.[50]

There appears to be is a missing link between arterial FDG uptake and existing or later developed CT-detectable macro-calcification. Thus, multiple studies showed a lack of

overlap between FDG uptake and CT-detectable plaque,[12, 50-54] while others could not demonstrate a significant correlation with cardiovascular risk factors.[54-57] In line with this, Meirelles et al. demonstrated that thoracic aorta FDG uptake in 100 consecutive cancer patients is a "waxing and waning process" as the authors put it. FDG uptake was seen in 70% of the patients on the first scan and changed on the second in 55% of the patients after in mean 7 months (range 21 days – 3 years). In 28 patients, vascular FDG uptake was less intense or had resolved on the second scan, while in 27 patients there was an increase at existing sites or appearance of new foci. There was a trend to unstable FDG uptake in older patients and in women, no correlation between risk factors for cardiovascular disease and FDG vascular uptake, and FDG uptake and calcifications were present at the same site in only two patients. Vascular calcifications were identified in 42 patients on the first or on the second PET/CT scan, were more commonly seen in older patients and were generally stable from scan to scan. None of the patients progressed over time from FDG vascular uptake to calcifications at the same location.[58]

Recently, similar observations were made for NaF uptake in the abdominal aorta. Cecelja et al. reported change in NaF uptake in the abdominal aorta of 21 postmenopausal women, who underwent NaF PET/CT for assessment of bone mineralization. They found no change in NaF target-to-background ratio after 3.8 (standard deviation: 1.3) years despite a significant 54% increase in abdominal aortic calcium volume.[59] Nakahara et al., who studied prostate cancer patients with at least three NaF PET/CTs over at least 1.5 years, observed variable NaF uptake in the abdominal aorta from scan to scan, while calcium volumes remained constant or increased between scans.[60]

Several studies demonstrating significant correlations between NaF uptake and characteristics like vulnerable or high-risk plaque used the term "prediction" for such associa-

tions,[54,59,61,62] as has been done multiple times in the past when a significant correlation was observed between coronary calcification and risk of future cardiovascular events.[63-71] However, none of these associations were sufficiently close to allow such an accurate prediction in the individual patient that it could be of use in the daily clinic. All demonstrated relationships were indicative rather than actually predictive, which leaves us in a limbo: despite increasing scientific activity, white spots remain on the map depicting the relationship between arterial wall FDG uptake, NaF uptake, and CT-detectable calcification. The unexplored areas call for longitudinal in-depth studies applying repeat FDG- and NaF-PET scans for comparison with CT-calcification. Right now, the essence of what we know and do not know about NaF uptake in atherosclerosis by March 2020[49] can be summarized as follows:

By targeting arterial microcalcification, NaF uptake appears to be a marker of early stage atherosclerosis that is slightly age dependent, albeit with a large scatter, and consistently associated with cardiovascular risk. Increased arterial NaF uptake is relatively uncommon in diabetics, as is NaF uptake in the renal arteries of hypertensive patients. Progression of arterial wall NaF uptake has been studied by retrospective analyses in the abdominal aorta only and indicates slow or variable progression over a period of some years despite constant or increasing calcium volumes. Therefore, it remains unknown, whether NaF uptake is a reliable harbinger of CT-detectable calcification and whether intervention can modify NaF-associated microcalcification.

PET EQUIPMENT FOR PART OR TOTAL BODY ASSESSMENT

With the advent of long-axial PET scanners with multiple detector rings that allow an elongated axial field of view of 70 or up to 200 cm, exemplified by the PennPET Explorer[72-74] and the United Imaging Explorer scanner,[75-79] respectively, we will soon be able to collect information on illness in major parts or all over the body in a way and with a speed that has never been possible before. Thanks to the much higher sensitivity of these instruments, in theory up to 40 times higher, in practice presumably 8-10 times as high, as with current PET/CT scanners, we can make part or total body acquisitions in seconds or in most cases probably a few minutes with the same, fixed bed position. This kind of equipment places new major demands on logistics and investments, not to speak of processing software, but offers benefits that healthcare will soon profit from. With regard to the physical characteristics and capabilities of these devices, reference is made to other literature;[72-77] here we will focus on their possible importance for clinical PET/CT imaging of atherosclerosis.

A wide range of conditions and restrains that we have not previously been able to take into account or deal with can now be addressed to optimize examination of the individual patient. One is delayed imaging to reduce the amount of background activity, which is a problem with FDG in particular; another is improved motion correction because acquisition is so fast that it can be done in held inhalation or during a few breaths and with high resolution, a third is full-body recordings to elucidate disease activity in more than one or just a few locations in the body, and a forth is dynamic recordings enabling parametric imaging to retrieve a number of essential disease parameters that have so far not been within practical reach. By means of dynamic imaging with high spatial and temporal resolution, total body PET will allow kinetic analysis in patients that we have hitherto only been able to obtain in advanced experimental animal and human studies, many of which need real-life validation in patients.[76,79] In atherosclerosis, like in many other diseases, this would yield

much more reliable estimates of metabolism, oxygen use, signal transduction, and pharmacodynamics than what we have so far been able to retrieve from static or conventional dynamic PET imaging within a limited field of view and insufficient time resolution.

Moreover, ultra-short acquisition times mean that patient placement on the scanner bed is more time consuming than the scan itself,[79] The much lower tracer doses needed result in effective doses to the patient that are well below the natural background radiation even in countries with low background levels. Such low effective patient doses mean that dual or triple tracer studies will become possible, whether performed in succession on the same day or on different days. Moreover, they will allow for disease screening and for repeat scans in longitudinal follow-up trials and studies monitoring therapy effect which requires a minimum of three scans, i.e., baseline and two or more follow-up scans, to ensure reliable results.[80] The automation and advanced processing software needed with these devices will offset the greater uncertainty that comes with repeated imaging because all sources of error are in play every time one makes a new scan.[81]

Thus, an entirely new series of possibilities open up with total-body PET imaging, e.g.:

- Mapping and quantification of atherosclerosis, its location and relative activity throughout the body, something that may have both prognostic and therapeutic implications.
- Screening for incipient, but threatening atherosclerotic processes in asymptomatic patients or patients with uncharacteristic symptoms including cerebral atherosclerosis, carotid atherosclerosis as a forerunner of stroke, and accelerated cardiac, aortic or peripheral arterial disease, all of which may be sensitive to early-onset therapy.
- Disease characterization with a number of different PET tracers in the same patient.

- Easy, fast, and risk-free monitoring of a variety of therapeutic interventions even in the same individual.
- Calculation of a single score, the global disease score, expressing the atherosclerotic burden in the body and its activity at diagnosis and as an easy, simple and reliable guidance for therapy.

ARTIFICIAL INTELLIGENCE-BASED INTERPRETATION

Artificial intelligence (AI)-based interpretation will become a necessity. Not only will it increase reproducibility and reduce differences due to different scanners and scanner manufactures; it will significantly increase diagnostic accuracy, since it will never stop learning and optimizing, meaning that AI-based reporting will sooner or later become superior to that of a standard physician. In addition, the AI approach will take into account a wide range of paraclinical and clinical factors all of which are not routinely considered or easy to interpret.[82-84] In the long run, high-level AI will probably reach beyond the role of advanced medical decision aid by providing intelligent computer generated suggestions for alternative diagnosis and treatment regimens. However, underlying paraclinical and clinical data must be permanently accessible to AI-based algorithms, and such data need to be updated continuously – a matter that in times of increased data protection formalities remains to be solved judiciously.

In practice, AI-based reporting will comprise calculation in seconds of quantitative parameters that are practically impossible for the individual physician to obtain, primarily because manual segmentation is too uncertain and slow, in particular when it comes to discrimination between soft tissues (Fig. 2). With AI, such measures can be calculated for the

entire body imaged by the UI Explorer scanner or for the torso, which is what the PennPET Explorer system with its 70 cm axial field of view can see in a single scan. The purpose is to provide the clinician with a tool, in this case a single number, that meets hers/his three most important needs when assessing the individual patient, i.e., knowledge of whether (a) the disease is present and how widespread and active it is, (b) guidance for proper treatment triage, and (c) ability to judge if the treatment is working or whether it is advisable to switch to another form of therapy. Total body PET with AI-based interpretation may well be the instrument, which will make this vision come true.

With total body PET, atherosclerosis development can be examined in known sites of predilection like the heart and major arteries long before this is possible in the course of disease with other modalities. In addition, atherosclerosis can be studied in places where it is rarely done or where it is poorly practiced, e.g., the brain, lungs, and arteries of smaller organs. However, to speculate further may be going too far as long as clinical total body PET/CT is still in its infancy and needed sophisticated hardware and software are still work in progress. Nonetheless, we believe that total body PET/CT has come to stay and that it will significantly change our perception, understanding, and treatment of many of our most important and debilitating diseases, including atherosclerosis.

COST-EFFECTIVENES

We foresee that total body PET will cause a complete change in the management of atherosclerosis from diagnosis of late-onset symptomatic lesions and their treatment, which as of today is more repair than actual therapy, towards detection in the early, symptom-free stages when there is a much greater chance of cure or inhibiting further development.

The economic and the patient-related benefits of such a strategy will be huge and difficult to estimate, although it will probably, as is customary with novel and advanced expensive equipment, be argued that this new technology is too complicated and costly to reach general clinical use. Only cost-effectiveness studies on top of or in prolongation to clinical studies will offer evidence to this end in the future. However, changing this is a matter of time. When these promising opportunities become apparent to colleagues, patients and authorities, the production and clinical use of total body PET will increase and reach a level, where its advantages will more than counterbalance its gradually decreasing costs.

CONCLUSION

Total body PET imaging will in atherosclerosis, like in many other diseases, cause a change of our conception of the illness, its development and association with other disorders. In addition, it will allow prevention and/or earlier, more individualized, and more effective anti-atherosclerotic intervention than what is common for the time being.

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Fig. 1

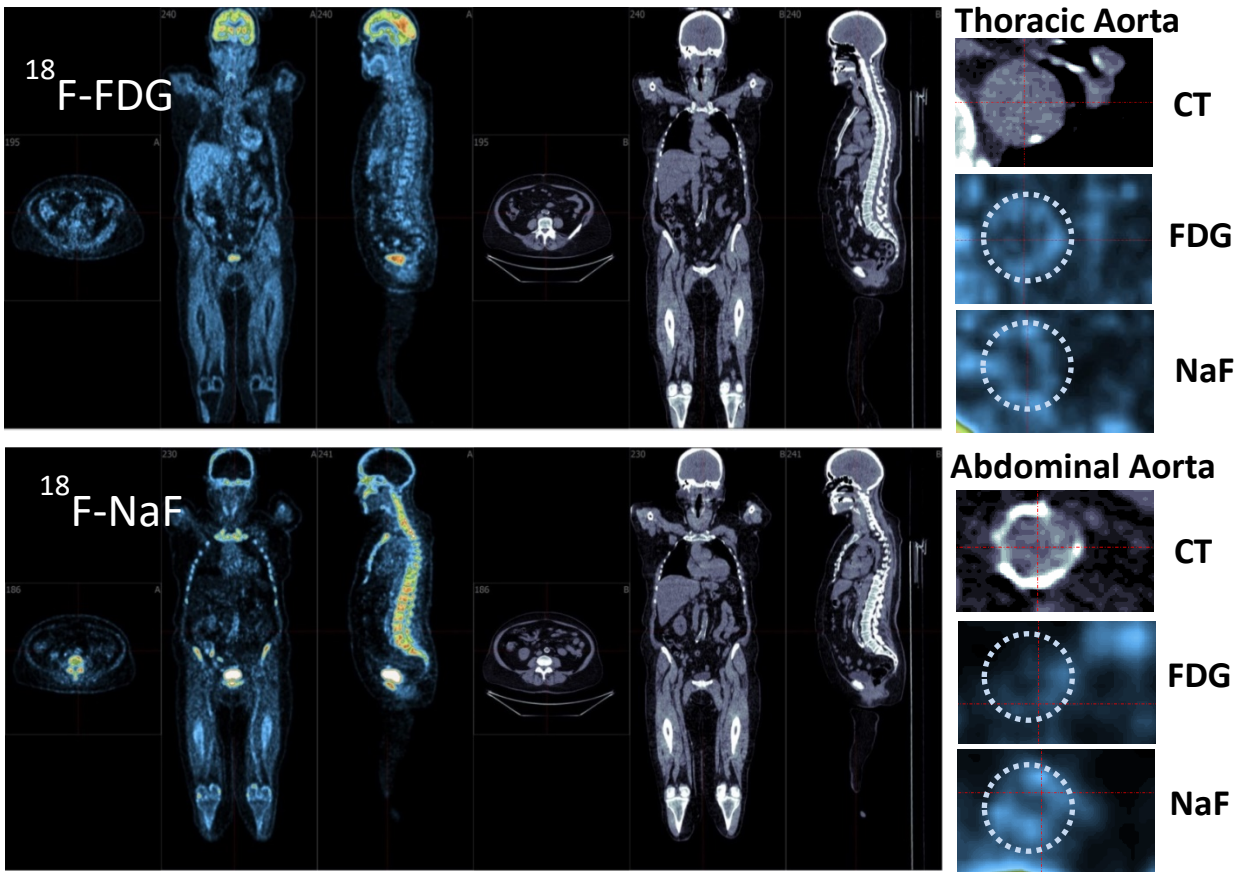
18F-FDG
18F-NaF
Thoracic Aorta
CT
FDG
NaF
Abdominal Aorta
CT
FDG
NaF

Fig. 2

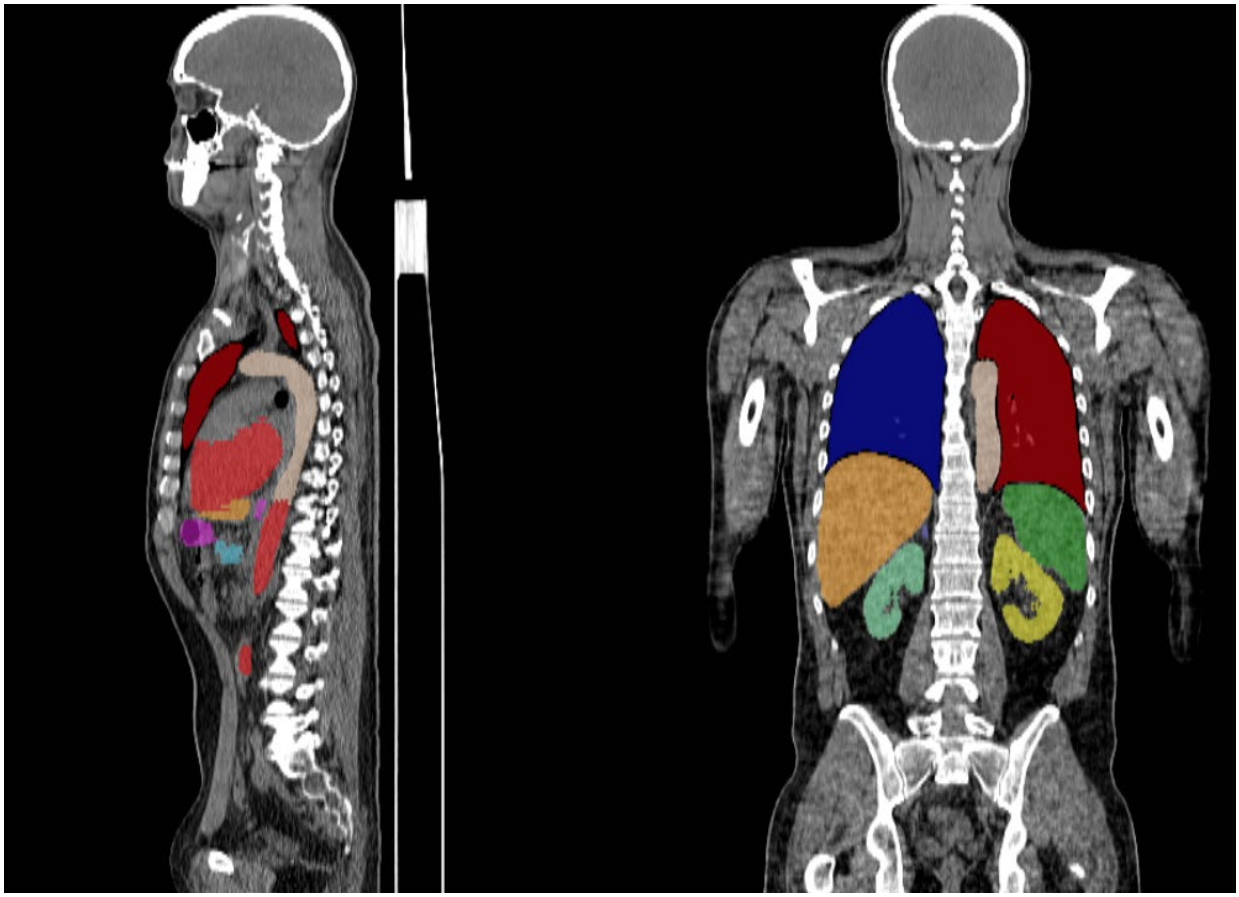

Figure legends

Fig. 1

Whole-body (from top of skull to below knee) uptake distribution of FDG and NaF in the axial, coronal, and sagittal planes displayed on composite PET/CT and CT images (left and right half, respectively, of the two major panels). Note the intense uptake of NaF in the bones on PET images in the lower panel. The small images to the right show what is displayed on axial slices of the thoracic aorta (upper three images) and the abdominal aorta (lower three images) by means of (from top to bottom) CT, FDG-PET/CT and NaF-PET/CT and illustrate some of the difficulties in delineating and segmenting the aortic wall correctly.

Fig. 2

AI-based segment of organs (color-coded). Note the heart (red), thoracic aorta (beige) and abdominal aorta (darker red).