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EDITORIAL COMMENTARY

Predictive medicine: towards a multi-parametric imaging for a personal risk stratification

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Ischemic stroke is a major public health issue with, per 100,000 persons, an incidence rate of 44-176, a disability-adjusted life-year of 80-597, and a mortality rate of 27-42 [1]. The total excess direct and indirect cost would correspond to €1.5 billion, only considering first-ever strokes [2]. Consequently, large financial offsets are expected, both in the healthcare sector and in the social service sector, if the incidence of stroke could be reduced. In this line, a study randomizing 3000 asymptomatic patients showed that successful carotid endarterectomy reduced 10-year stroke risks [3].

Prediction of subsequent ischemic stroke is thus a critical challenge, precisely to identify asymptomatic high-risk patients who would benefit from intervention before rupture of nascent plaques. Beside the well-known risk factors of atherosclerosis, the exact relationship with cancer remains debated [4, 5], the concurrence of the two diseases leading to a more dismal prognosis [5].

Functional imaging, by establishing tools for personal risk stratification, could help to better select asymptomatic high-risk patients requiring an early intervention. Over the past years, public health has indeed greatly benefited from precise and early diagnosis and screening of diseases, which are otherwise incurable or difficult to treat at later stages; as well as from early and precise post-therapeutic evaluation, especially both not to delay another treatment that may be more effective and not to cause unnecessary side effects and/or complications. More recently, medical models have evolved towards a personalized concept, proposing customization of healthcare for each patient with tailored approaches. In this line, imaging PET and SPECT biomarkers are implemented for select individual patients, as well as to guide, predict, and evaluate the most appropriate treatments according to the molecular signature of the disease and of the lesions, in particular in oncology [6] and more recently in neurology [7].

In the present publication of the *EJNMMI*, Jahae Kim et al. [8] studied 18 F-FDG PET/CT imaging biomarkers that predict ischemic stroke found in 30 of 134 patients initially explored for a cancer, and clinically followed-up during one year. This original study first extends previous findings obtained in a non-tumour population. In this line, Figueroa et al. followed 513 patients without symptomatic cardiovascular disease for a mean of 4.2 years, and found that 18 F-FDG uptake within the wall of the ascending aorta was an independent predictor of future cardiovascular events [9]. The carotid plaque inflammation, as measured by 18 F-FDG PET and correlated with the degree of macrophage infiltration and plaque erosion [10], has been also associated with a high risk of early stroke recurrence, independently of the degree of stenosis [11], and may, thus, be a useful imaging biomarker for high-risk carotid plaque [10, 12], especially in case of imminent vascular event [11, 13], and for yet symptomatic plaques [14].

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In tumour populations, previous studies had also shown a specific association between FDG uptake and vascular events, however, with a weak incidence of 0.5-1.6 % [15, 16], by contrast with those of 7.6 % reported here, and specifically for ischemic stroke, by Jahae Kim et al. [8]. This could be due to the fact that these last patients were included from a Department of Neurology, and had all neurological antecedents (but no stroke). It is, of course, thus uncertain whether the findings of Jahae Kim et al. would apply to an asymptomatic cohort in the absence of neurological antecedents.

In addition to its clinical value for this specific population of patients with cancer and neurological antecedents, the multi-parametric and multimodal approach proposed by Jahae Kim et al. [8] appears here as originally, leading to the multivariate validation of a combination of PET and CT biomarkers. In detail, the authors demonstrated the predictive value of arterial multisite FDG uptake (Tissue-to-Background Ratio, TBR, of carotid arteries and abdominal aorta), presence of metabolic PET active tumours, and visceral adipose tissue CT proportions. This model takes advantage of non-specific pathophysiological uptake of FDG for tumour and inflammatory diseases [17]; of whole-body imaging which is particularly adapted for systemic diseases, and here to explore inflammatory processes of atherosclerosis affecting multiple vascular territories; and of hybrid morpho-functional imaging, using CT not only for attenuation correction and anatomical localization but for its own biomarker value.

With a similar approach, dual properties of 18 F-FDG and an opportunity for whole-body imaging have been previously used to concomitantly explore other inflammatory diseases, such as infectious diseases, and cancer, for example for infective endocarditis, to detect both extra-cardiac embolisms [18], and associated tumours [19]. Moreover, multi-parametric PET imaging has been extended to dynamic and dual-phase acquisitions, to distinguish between tumour and inflammatory lesions [20], with a gradually increasing trend of 18 F-FDG uptake over time in malignant cells, and a decreasing or constant trend in inflammatory/infectious processes [21]. On the other hand, several studies had also combined PET and CT biomarkers to improve predictive performance, and especially for further ischemic strokes, using, for example, calcified plaque sum or vessel volume in addition to 18 F-FDG uptake [15, 22]. More recently, Hyafil et al. took advantage of simultaneous acquisition of high-resolution MRI and 18 F-FDG PET imaging to better characterize lesion type and plaque composition [23].

Interestingly, the findings of Jahae Kim et al. [8] point out other morphological parameters, the visceral adipose tissue CT proportions, as a new predictor for ischemic stroke in patients with cancer. As mentioned by the authors, this is of course not surprising given that obesity is a well-known risk factor for atherosclerosis. Pro-inflammatory cytokine secretion associated with obesity could indeed adversely affect endothelial cells, arterial smooth muscle cells, and macrophages in the vessel wall [24].

Beyond aspects developed in this report, and also the possible implication of several radiopharmaceuticals to characterize multiple biological targets [25], multi-parametric imaging nowadays also integrates development and applications of innovative methods of image processing and analysis. While usual metrics such as Standardized Uptake Value (SUV) or Metabolic Tumor Volume (MTV), or even TBR, are known to not fully describe the entire properties of pathological lesions, other properties such as shape and uptake heterogeneity may reflect different biological profiles associated with aggressiveness, or degree of response to a specific treatment, and, consequently, with the prognosis as recently proposed in oncology [26]. Such multi-parametric quantifications could provide complementary indices with higher clinical value in stratifying patients, probably also in non-oncologic diseases.

On the whole, combined PET/CT multi-parametric imaging has now exceeded the initial concept of "anatometabolic" imaging [27], and the only quantification of SUV, by currently proposing new innovative protocols and biomarkers to individually impact healthcare management, and especially for improving personal risk stratification in oncologic and non-oncologic diseases. The study of Jahae Kim et al. [8] highlights this evolution with the identification of original 18 F-FDG PET/CT biomarkers to predict ischemic stroke in patients with cancer.

Compliance with Ethical Standards

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