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SPOTLIGHT

Radiolabeled fibroblast activation protein inhibitor (FAPI) PET in oncology: has the time come for ^{18}F-fluorodeoxyglucose to think to a well-deserved retirement?

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Since the first application in human studies in 1976,^{18}F-fluorodeoxyglucose (FDG) has gained importance over the decades in Nuclear Medicine departments, becoming at present the most used radiotracer not only in oncological studies but also in the management of several neurological entities, as well as in the assessment of myocardial viability. Despite the well-recognized role and the wide application of FDG in cancer imaging, many limitations have continuously emerged in these years, accounting for low sensitivity in well-differentiated cancers or in some histological types of tumors, as well as for poor detection rate in districts with high physiological uptake.

These unmet needs have led in recent years to the development of a new class of radiopharmaceuticals, targeting the fibroblast activation protein (FAP), a type II membrane bound glycoprotein belonging to the dipeptidyl peptidase 4 family, which is able to activate cell signaling and contributes to tumor cell migration, invasion and tumor angiogenesis. This protein is highly expressed in cancer-associated fibroblasts of many epithelial carcinomas, especially in those characterized by a strong desmoplastic reaction, as they can comprise up to 90% of the tumor mass. Among these neoplasms, the most relevant are colorectal, breast, ovarian, pancreatic, and hepatocellular carcinomas [1, 2].

The new radiotracers are based on the FAP-specific inhibitor (FAPI) protein and several quinoline-based FAPIs labeled with positron emitters. Most recently, FAPI-04 and FAPI-02 labeled with ^{68}Ga showed a rapid renal clearance and provided PET images with high tumor-to-background ratios in patients across a wide array of cancers, suggesting high potential for FAPI-targeted diagnostics [3]. Another tracer of this class, ^{68}Ga-FAPI-46, emerged as the most promising tracer for therapeutic clinical application due to its high tumor uptake and retention, and lower uptake in normal organs compared with FAPI-04 [4].

Furthermore, because the ^{68}Ga-FAPI tracers contain the universal DOTA-chelator, a theragnostic approach seems also an achievable goal [5]. In 2018, in fact, a first therapeutic application of ^{90}Y-FAPI-04 had been published in a patient with advanced breast cancer [6]. A significant improvement in symptoms was achieved with a single administration and no toxicities were observed. However, due to a relatively fast clearance of FAPI-04 from tumor tissue, limiting the achievable radiation dose, the effectiveness of FAP-directed radionuclide therapy can probably be improved by ligands with longer retention in tumor tissues.

But why do the FAPI-based tracers appear so promising compared to FDG, mainly in oncological setting?

First, as DOTA-FAPI is labeled with ^{68}Ga obtained from a ^{68}Ge/^{68}Ga generator, the radiotracer can be produced on-site, also in departments without an on-site cyclotron, making it feasible at lower costs even in small centers. At the same time, the usable ^{68}Ga activity from a generator is limited by the amount of activity loaded on the generator, the interval between elutions and the maximum number of them, as well as by the ever-increasing price of generators. For these reasons, there has been increasing interest in the production of ^{68}Ga using medical cyclotrons via the ^{68}Zn(p,n)^{68}Ga reaction, as recently described by IAEA [7].

Second, there is no need for fasting or for any dietary preparation, as no glucose-related metabolic pathways are involved, allowing for a high compliance of the patients and

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making the PET examination feasible also in diabetic individuals with high serum glucose levels.

Third, the uptake time can be reduced up to 10 min, certainly an advantage for patients, because of a shorter waiting time, which can be relevant in sick patients, as well as for the department's workflow. As a consequence, the radiation burden of the examinations might be reduced if the injected activity can be lessened due to a faster uptake time.

Finally, the normal-tissue biodistribution of ^{68}Ga-FAPI ligands in comparison to FDG showed a lower brain, liver, and oral mucosa uptake. Therefore, primary or metastatic lesions in these organs can be easily identified.

Regarding the clinical performance in detecting malignant lesions, a study from Chen and colleagues [8] aimed to directly compare ^{68}Ga-DOTA-FAPI-04 and FDG PET/CT in a population of 75 patients with newly diagnosed cancers ($n=54$) or suspected relapse ($n=21$) and 20 different types of tumors. Interestingly, in the depiction of primary tumors, ^{68}Ga-DOTA-FAPI-04 showed a sensitivity of 98.2% compared to a sensitivity of 82.1% for FDG. Also, for the detection of metastatic lymph nodes using biopsy or lymphadenectomy as the reference standard, the sensitivity and accuracy of ^{68}Ga-DOTA-FAPI-04 were significantly higher than those for FDG PET/CT, conversely the specificity was lower, although not statistically significant. Alongside oncology applications, FDG is known to accumulate in acute inflammation, however, recent studies have demonstrated that FAP activation is typical of chronic inflammation already causing a fibrotic reaction [9].

For the depiction of distant metastases ^{68}Ga-DOTA-FAPI-04 outperformed better than FDG especially in liver, peritoneum, mesentery, omentum, brain and axial skeleton, confirming the abovementioned data that ^{68}Ga-DOTA-FAPI-04 was better than FDG in some organs.

Since the introduction of radiolabeled FAPI PET applied to human scans, several studies and case reports have been published in literature, showing a broad applicability of this new class of radiotracers both in oncological and non-oncological settings [3, 4, 7, 9]. Described by some authors as a pan-tumor radiopharmaceutical, a direct competition with FDG is therefore unavoidable. Especially in oncological patients with inconclusive FDG PET/CT findings, ^{68}Ga-DOTA-FAPI may have a complementary role in discriminating malignant from benign lesions, locating the primary site of unknown malignancy, modifying tumor staging, and detecting disease recurrence. Nevertheless, a careful attention should be paid for the interpretation of ^{68}Ga-DOTA-FAPI PET/CT images in tumors complicated with inflammation and further comparison studies with FDG are inevitably necessary to better comprehend the best field of application of each radiotracer.

However, the limited availability of the tracer and the small number of available research data, require further evaluation mainly in different patient populations and in new contexts, in order to obtain a "significant" panel of advantages and hopefully scarce pitfalls.

After all these considerations, the key question is: promising freshman or uproariously meteor? Time will tell and, at least for now, FDG can sleep peacefully.

Compliance with ethical standards

Conflict of interest Priscilla Guglielmo and Luca Guerra declare that they have no conflict of interest.

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

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