EDITORIAL

Clinical perspectives for the use of total body PET/CT

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Introduction

In the last decade, PET scanners have benefited from new technologies such as the TOF system, PSF correction, and SiPM detectors. More recently, the increase of detector number allowed an axial FOV as large as a human body length in a total-body PET (TB-PET) system. Two different scanners called Quadra© and uEXPLORER© have been respectively proposed by Siemens Healthineers and United Imaging Healthcare. These TB-PET have two major advantages over actual systems on the market: a gain in detection sensitivity and a possibility of whole-body dynamic multiple organs analysis [1, 2]. More than reducing drastically the acquisition duration and/or injected activities, these systems open up very interesting clinical perspectives to address specific issues encountered in routine clinical practice and thus improve patient care.

We aimed in this brief communication to highlight some situations for whom a TB-PET might help to settle current clinical issues.

High temporal resolution whole-body dynamic imaging

4D dynamic PET (dynPET) acquisition methods have been proposed for extracting quantitative parameters from the temporal analysis of the radiotracer distribution in voxels [3, 4]. It allows to estimate kinetic parameters such as the tracer uptake rate Ki (slope) using a Patlak-based analysis modeling, after a plasma input function estimation from the images [5, 6]. Several studies have demonstrated its superiority (vs the usual 3D-approach) for

characterizing different solid tumors and distinguishing inflammation vs malignancy [7, 8]. Nevertheless, the first studies assessing dynPET acquisition only concerned one step (15–20 cm), constituting a limit in the evaluation of multiorgans cancerous or inflammatory pathologies.

Recently, multistep dynPET acquisition protocols have been developed, making possible a whole-body (WB) Ki-based analysis but with the condition of an iterative bed motion in the PET system and with the limitation of a low temporal sampling (WB in 5–10 min).

New TB-PET prototypes allow to increase the quality of 4D-quantification with excellent temporal sampling (WB in 10–20s), suggesting the resolution of the following clinical research issues.

Differentiation of benign/pathological processes

Pseudo-progression vs progression to immunotherapy

Immunotherapy with checkpoint inhibitors (ICI) has been a highly developed therapeutic strategy in recent years in oncology. Particularly, the first studies showed remarkable efficacy of anti-PD1-type molecules (nivolumab, pembrolizumab) in metastatic melanoma (mM) or lung cancer (mLC), with respective response rates of 40% [9, 10] and 20% [11, 12].

Nevertheless, these innovative therapies present certain problems hitherto unknown with chemotherapy and in particular the concept of pseudo-progression (PP). This phenomenon is defined as an initial increase in tumor size or a new lesion appearing, followed by a decrease in tumor burden.

18FDG-PET/CT can be proposed to assess tumor response after treatment by systemic therapy of mM or mLC [13]. However, this particular response profile has led to the establishment of new evaluation criteria in imaging with the integration of the notion of "unconfirmed progression" [14]. Consequently, the real response to treatment must be assessed several weeks after, in order to eliminate with certainty a PP linked to the tumor infiltration by lymphocytes, inducing on the contrary a loss of time in the diagnosis of confirmed progression (CP) with consequences for patient care and public health costs.

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Thus, TB-PET might have an interest in early differentiating the CP from the PP of such metastatic cancers treated by ICI.

Residual disease vs post-treatment tissue distortions

For certain cancers, 18FDG-PET/CT shows high diagnostic performance for the post-treatment residual disease (RD) assessment [15, 16] because post-radiation or post-surgical tissue changes reduce the specificity of CT or MRI examinations [17]. For example, it can be proposed for the post-treatment evaluation of head-neck or cervical carcinoma [13]. However, a period of 3 months after treatment must be observed for limiting the false positive risk linked to the early local inflammation (LI). Its negative predictive value in these indications is excellent (~100%), but the positive predictive value remains imperfect because certain interpretations leave doubt between the minimal RD and the absence of complete LI extinction [18]. Now, as above-mentioned, kinetic parameters extracted from dynPET acquisition are significantly different in malignant and inflammatory processes, thereby an optimized dynamic signal analysis with TB-PET could be of interest to differentiate minimal RD and post-therapeutic LI of such cancers.

Insufficient suppression of myocardial signal vs inflammatory process

18FDG-PET/CT can be useful for the diagnosis of inflammatory cardiovascular diseases (CD) such as atherosclerosis, sarcoidosis, or subacute myocarditis [19]. However, it remains relatively low used in clinical routine practice because it has certain limitations.

First of all, despite the recent improvement in double-gated PET and CT acquisition techniques, cardiac motion induces a low tissue-to-blood pool ratio (TBR) in case of moderate inflammatory process with a higher risk of false negative [20]. Moreover, even if the specific cardiac free fatty acid consumption diet has been respected, an insufficient suppression of physiological myocardial uptake (PMU) is found in approximately 1/3 of cases [21]. Recently, the Ki approach in PET has been suggested to be more efficient than the SUV-based one for the differentiation of a real inflammatory process to an insufficient suppression of PMU [20]. In addition to facilitate this physiological/pathological uptake, TB-PET might also play a role for such dedicated cardiovascular PET studies to improve inflammatory CD diagnosis by optimizing TBR quantification.

Simultaneous information collection with tracer cocktail injection

The concept of "cocktail" injection of PET tracers, consisting in administering 2 radiopharmaceuticals before a single PET acquisition procedure, has already been evaluated [22–24]. However, it has not been implemented in routine practice due to several limitations such as the lack of consensus for dose proportion and the difficulty in separating the signal of both tracers. Recently, a feasibility study has suggested that WB-dynPET could quantitatively extract the two separate tracer kinetics and also analyze different processes [25].

The application of this "two in one" approach in TB-PET might improve the characterization of several cancers in optimizing radiation exposure and patient comfort and in maximizing the cost-effectiveness strategy.

Its high sensitivity could be also a solution to reduce in this single scan the injected dose of "cocktail," as in the following examples.

Bone extension of osteophilic cancers

PET imaging with various radiopharmaceuticals can provide specific information for osseous remote extension of solid cancers. Indeed, 18FDG is a marker of glucose metabolism which is often increased in lytic metastasis, whereas 18FNa is a marker of osteoblastic activity with high potential for detecting condensing metastases. Combining the strengths of the two tracers would also improve osseous metastases detection rates in case of mixed presentation; and separating signal of these two phenomena remains essential for therapeutic and prognostic considerations, FDG-avid lesions being more aggressive [26].

One of the most frequent examples concerns breast cancer. 18FDG-PET/CT is recommended for initial staging in patients with clinical stage≥IIB [13]. Nevertheless, its performances in osseous extension assessment are lower in case of invasive lobular subtype (around 15% of breast cancers), due to the mixed presentation of metastatic lesions [26] so that 18FDG/18FNa cocktail studies would be interesting.

Aggressiveness and secretion of neuroendocrine tumors

The characterization of neuroendocrine tumors (NETs) can be done by functional PET imaging with different tracers depending on the location of the primary tumor and the histological grade. 68Ga-DOTATOC-PET/CT is thus indicated in G1-G2 NETs while 18FDG PET in G3 NETs [27–29]. However, it has been shown that 18FDG-PET/CT was very sensitive to detect certain so-called "borderline" G2 tumors with a Ki67index >10% [30]. Furthermore, among G1-G2 NETs, some studies have suggested that 18F-DOPA-PET/CT is more effective than somatostatin-receptor imaging for the midgut primary lesions [31]. As a result, patients may have to undergo 2 (even 3) PET scans with different tracers to explore distinct biological phenomena from their disease.

Aggressiveness and hormone-receptor expression of cancers

In the same way, several new agents targeting hormone-receptors could improve management of hormone-dependent cancers [32]. The most studied was the 18FES for breast cancers presenting estrogen receptors (ER) [33]. This tracer can be used to determine tissue levels of ER expression and thereby map hormone-sensitive lesions.

In this case, a cocktail of 18FDG/18FES could be important to obtain complementary information for such cancers with high intra-lesion heterogeneity that impact treatment success.

Improvement of intra- and inter-tumoral heterogeneity assessment

Many cancers present a high-level inter-tumor and intra-tumor heterogeneity (different cell populations of variable proliferation rates and areas of angiogenesis, hypoxia, necrosis or fibrosis, etc.), making the therapeutic choice difficult [34].

Among them, NETs constitute a network of tumors of common embryological origin but capable of developing in multiple organs and of secreting different hormones, which may thus lead to varied clinical presentations [35]. Moreover, despite its low incidence, more than 25% of patients are diagnosed at metastatic stage for which numerous treatments with different pharmacokinetics can be proposed (somatostatin analogues, targeted therapies, polychemotherapy, peptide-receptor radionuclide therapy, etc.).

So, it is crucial to search for surrogate markers in PET/CT to early predict treatment response.

The first dynPET studies showed the absence of a linear correlation between SUV and Ki values, suggesting additional quantitative information from kinetic data and opening new perspectives for the prognostic assessment of NETs [36]. But as above-mentioned, these preliminary reports concerned a one-step analysis, a limiting factor for multimetastatic and multiorgans diseases assessment. More recently, digital systems have validated the WB-dynPET approach but with an iterative constraint of bed motion in the machine [37].

The TB-PET could probably improve the predictive value of treatment response in such multimetastatic disease with a WB parametric Ki map reflecting the temporal inter-/intra-lesions biodistribution of tracer.

Phenotypic or molecular approaches

Phenotypic imaging of inflammation

As part of the ICI-induced inflammation during tumor PP, there is a recruitment of B and T lymphocytes [38]. On the contrary, in a post-surgical situation, there is an infiltration of inflammatory cells (macrophages and dendritic cells) into the operated site [39]. The post-radiation inflammation is of mixed presentation, the macrophages presenting the antigens of the destroyed tumor cells to the lymphocytes [40].

It is therefore conceivable to hypothesize that 18FDG uptake is different within these inflammatory processes and that TB-PET, beyond its usefulness for inflammation/tumor differentiation, could become a real phenotypic imaging capable of characterizing different inflammatory phenomena.

Likewise, it would be of potential interest for the differential diagnosis of rheumatic pathologies or systemic diseases mediated by different inflammatory cells.

Molecular imaging of thrombus

Molecular imaging has emerged as a new method of in vivo imaging allowing better visualization, characterization, and measurement of biological processes.

Venous thromboembolic disease (VTE) represents the 3rd cause of cardiovascular disease. The risk of death from untreated pulmonary embolism (PE) is approximately 30%. Anticoagulant treatment is effective but presents a significant risk of hemorrhage that can also be fatal [41]. For now, pulmonary SPECT lacks surrogate markers of PE recurrence at diagnosis.

The different constituents of the active venous thrombus (i.e., activated platelets, fibrin network) are potential specific targets for molecular imaging that may provide supplementary information for treatment management. In this context, few series have investigated its feasibility in SPECT [42–44] but reported limitations due to the intrinsic performances of system. To date, none of the tracers studied is used in clinical routine, not for lack of specificity but of detection sensitivity.

In this illustrative example, the high-resolution of TB-PET with dynamic analysis capabilities could allow a better characterization of such specific biological processes to improve a disease recurrence prediction and therefore the therapeutic management of patients.

Ultrahigh sensitivity imaging

Optimization of radiomic analysis

Tumor heterogeneity characterization is a major issue in oncology to improve therapeutic management and move towards a personalized medicine adapted to each patient. The textural analysis (radiomic) in PET imaging corresponds to an analysis of the spatial distribution of voxels and allows the calculation of numerous indices reflecting this heterogeneity. Nevertheless, the quality of this textural analysis is dependent on the noise (therefore on the intrinsic system performance) and remains limited for the small lesions [45].

The TB-PET could enable image reconstructions with a noise-limited high-resolution matrix, improving especially

radiomic analysis of small and/or moving lesions such as in the following examples.

Characterization of small size incidentalomas

Thyroid (TI) and adrenal (AI) incidentalomas are lesions fortuitously discovered on imaging with respective prevalence of around 2% and 5%. The search for predictive factors of malignancy in PET therefore appears interesting. Numerous studies have sought the interest of several quantitative parameters such as SUV, MTV, and TLG [46, 47], but no real threshold with high diagnostic performance has been proposed. A few studies have examined the radiomic analysis value in TI and AI characterization, concluding its difficult application in routine practice due to their too small size [47, 48], that high-sensitive TB-PET could solve.

Signal quantification of moving lesions

Numerous studies have shown the prognostic value of 18FDG-PET textural analysis in solid tumors, including lung cancer [49].

Nevertheless, radiomic analysis is limited for small lesions in the pulmonary bases (partial-volume effect) [50]. Several respiratory gating algorithms have been developed but are not sufficient to overcome these limits [45]. In this context, the TB-PET could allow shorter image acquisitions in apnea (several seconds) to exceed these detrimental effects of respiratory movement on radiomic analysis.

Ultra-fast acquisition for motion correction

In addition to obvious clinical considerations such as for patients with pain, claustrophobia, or restlessness, possibilities of ultra-fast breath-hold acquisitions in TB-PET might be useful to correct signal processing in moving regions. For example, it could become an interesting quantitative tool to assess more precisely lung function (LF).

Indeed, the physiological tests currently used give a global LF result. And providing spatial information on LF is one of the major challenges in pulmonology. Indeed, having a map of regional LF in ventilation/perfusion (V/Q) could have an impact in different clinical applications.

In the context of PE, several studies have shown that the index of vascular obstruction in V/Q SPECT is a prognostic factor [51]. Moreover, LF mapping could also have an impact on the patient management before surgery or radiotherapy planning of lung cancer [52]. However, SPECT quantification remains relative, and no tool is actually consensual.

The V/Q PET/CT with 68Ga-radiolabeled tracers is a new imaging technique allowing a SUV-based quantification more precise than in SPECT with absolute results [52]. However, respiratory motion remains a major intrinsic limit to a precise,

reliable, and reproducible definition of these volumes that TB-PET fast acquisitions might solve. As previously mentioned, respiratory synchronization techniques exist in PET but remain limited in case of irregular respiratory rhythm [53].

High precision characterization of cancer micro-environment

The high sensitivity of TB-PET could provide high-resolution noiseless images, leading to a detectability improvement, especially for low contrast uptakes. Thus, it would enhance images the diagnostic performance of lymph node micro-invasion or micro-metastasis of solid cancer, as in the following illustrative situations.

Peritoneal micro-metastasis

The diagnosis of peritoneal carcinomatosis (PC) is sometimes difficult to establish by imaging, and the lesions may be very small and scattered throughout the abdominopelvic cavity. In the case of ovarian cancer, its evaluation is essential at the initial staging to assess the possibilities of tumor resectability and the interest of neoadjuvant chemotherapy. Currently, two predictive scores are used (Fagotti or Sugarbaker during laparoscopy or laparotomy, respectively) to assess PC but remain probabilistic and imperfect [54], for that TB-PET could provide additional information before treatment decision.

Lymph node micro-invasion

Conventional CT and/or MRI imaging has limited performance in the assessment of lymph node extension of solid cancers in case of micro-invasion. Functional PET imaging could improve this detection, in particular by using specific tracers of tumor types.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein specifically overexpressed on the surface of prostate cancer cells. Recent studies report a higher performance of radiolabeled PSMA-ligands PET/CT to conventional imaging for assessing the initial extension of prostate cancers [55]. Nevertheless, it remains imperfect especially for the evaluation of histologically proven lymph node micro-infiltration that have an impact on the treatment management.

Imaging of tracer with low abundance emission and/or long half-life

One of the particularly promising aspects of TB-PET imaging is the possibility of imaging under conditions of very low statistics, by the use of isotopes with low branching ratio and long half-time (89Zr, 64Cu, 90Y).

For example, selective internal radiotherapy (SIRT) by intra-arterial injection of 90Y microspheres is a therapeutic

alternative for inoperable primary and secondary liver cancers [56]. The most recent studies highlight the importance of the tumor absorbed dose, significantly associated with overall survival, but also of the dose delivered to healthy organs, a source of radiation-induced side effects [57].

It is necessary to precisely anticipate the distribution of 90Y before SIRT by a work-up and to know its distribution after the procedure, in order to predict the treatment efficacy [58]. Currently, imaging before and after SIRT is performed in SPECT. Nevertheless, PET imaging after SIRT is possible, 90Y being a positron emitter with a very low-emission abundance (0.0032%) limiting its use in clinical practice with actual PET systems.

The TB-PET would also allow much more precise absolute quantification through its high sensitivity detection, optimizing the dosimetry approach in such internal radionuclide therapy for even more precise personalized medicine. It could also be an interesting tool to improve SNR in delayed imaging of such long half-time isotopes.

Ultralow-dose imaging for cancer screening

With the reported significant gain in sensitivity, ultralow-dose imaging procedures could obviously be considered, in particular for pediatric indications.

But in another exiting context, TB-PET could become a real imaging tool for systematic cancer screening (CS) in radically reducing injected activity. Indeed, systematic CS by CT or PET imaging is currently limited by the irradiation of patient. Recently, a randomized trial showed that lung CS by CT among high-risk persons (current/former smokers) resulted in substantially lower mortality than in no screened one [59]. 18FDG-PET/CT has already been reported as an interesting CS tool in the management of unprovoked venous thromboembolism [60]. Thus, iterative ultralow-dose TB-PET scans could be considered in the future for a CS strategy in a selective population of patients with risk factors.

Conclusion

TB-PET technology gives multiple opportunities to address clinical issues currently unsolved in clinical practice and opens up perspectives of use as a low-dose radiation imaging tool for cancer screening.

Declarations

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