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EDITORIAL

Total-body [^{18}F]FDG PET/CT scan has stepped into the arena: the faster, the better. Is it always true?

Luca Filippi[1] · **Orazio Schillaci**[2,3]

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Technological development has always represented the essential core of nuclear medicine advancement. In particular, the introduction of hybrid imaging, combining morphological and functional data in a unique approach [1, 2], has definitely constituted a cornerstone culminated, more than twenty-two years ago, with the nomination of positron emission computed tomography (PET/CT) as the medical invention of the year 2000 by the Time Magazine. Since then, PET/CT has gained a well-established role in diagnosis, staging, and monitoring the response to treatment in many oncological conditions.

An innovative type of PET detectors, the silicon photomultiplier (SiPM)-based detectors, has been recently implemented into a novel PET/CT scanner, defined as digital PET/CT (dPET/CT), with an overwhelming impact on clinical practice [3]. In comparison with PET/CT equipped with photomultiplier tubes (PMTs), namely analogue PET/CT (aPET/CT), dPET/CT presents higher sensitivity, greater time resolution, and better spatial resolution. Recently published papers have underlined the usefulness of dPET/CT for improving the accuracy of PET imaging in oncological and non-oncological settings [4, 5]. The high sensitivity of dPET/CT paved the ground for the implementation of shorter time acquisition protocols. Imaging faster has a plethora of beneficial aspects, such as reduction of respiratory artifacts, avoiding sedation of certain kinds of patients (e.g., subjects affected by highly debilitating diseases or pediatric patients) and, last but not least, increasing the throughput per time-unit in a single diagnostic session. In a retrospective study performed by Alberts et al., twenty-one cancer patients, who had been previously submitted to dPET/CT, were randomly selected and their PET/CT scans were reconstructed in list-mode acquisition for a standard 2 min/bed position (bp), 1 min/bp, and 30 s/bp [6]. The various reconstructed PET/CT images were then interpreted by 2 nuclear medicine physicians, blind to clinical data, and compared for lesions detection: An almost perfect agreement was registered among the 3 reconstructed scans (K's $\alpha = 0.999$). Of note, PET-derived parameters (i.e., SUVmax, SUVmean, and TBR) resulted strongly comparable among the 3 reconstructions, even though longer acquisition time PET/CT presented a trend toward a higher TBR. Similar results have been reported by Lasnon and coworkers, who, notably, pointed out that optimization of reconstruction protocol is required when the very fast (i.e., 30 s/bp) acquisition time protocol is utilized [7]. Table 1 summarizes the different technologies cited in the present paper for fast or very fast acquisition protocols.

Standard PET/CT detectors cover an axial field of view (SAFOV) consisting of about 15–30 cm [8]; very recently, PET/CT technology has been pushed further by the implementation of the long axial field of view (LAFOV), covering 106–194 cm, suitable to scan the entire human body (total-body PET/CT). With respect to SAFOV, LAFOV PET/CT is characterized by increased sensitivity, due to the higher number of photons collected during acquisition, and allows for more accurate dynamic study [9]. Worthy of note, the ultra-sensitivity of total-body PET/CT scanners proved to dramatically increase the signal-to-noise ratio (SNR) of images, also in the setting of low or very low administered activity, therefore resulting particularly effective for the detection of small lesions located in organs characterized by a greater physiological background, such as brain or liver [10].

Liver cancer, of which hepatocellular carcinoma (HCC) is the most common form, represents a global health challenge,

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✉ Luca Filippi
lucfil@hotmail.com

[1] Department of Nuclear Medicine, Santa Maria Goretti Hospital, Via Canova, 04100 Latina, Italy

[2] Department of Biomedicine and Prevention, University Tor Vergata, Rome, Italy

[3] IRCCS Neuromed, Pozzilli, Italy

Table 1 Different technologies applied for fast or very fast PET/CT protocols

Authors/year	Device	AFOV	Detectors	Acq. protocols	Comments
Alberts et al. [6], 2021	Biograph-Vision 600 (Siemens Healthineers)	26.3 cm (SAFOV)	(SiPM)-based	Standard 2 min/bp *vs* reconstructed 1 min/bp and 30 s/bp	Lesions' detection was not hampered by fast acquisition protocols. Standard 2 min/ bp PET/CT showed higher TBR
Lasnon et al. [7], 2020	Vereos PET/CT (Philips)	16.4 cm (SAFOV)	(SiPM)-based PDPC	Standard 2–1.5 min/bp *vs* reconstructed 60 s/bp to 10 s/bp	Only 60 s/bp showed similar TBR to standard protocol. Inter-rater agreement resulted excellent for all the reconstructions
Hu et al. [19], 2021	uEXPLORER (United Imaging Healthcare) *vs* uMI780 (United Imaging Healthcare)	194 cm (LAFOV) 30 cm (SAFOV)	(SiPM)-based (SiPM)-based	LAFOV PET data reconstructed to emulate 30 s, 45 s, or 60 s acquisition duration vs 2 min/bp images obtained with SAFOV uMI780	A fast 30–45 s protocol with LAFOV provided equivalent image quality with respect to conventional digital SAFOV uMI780 at 2 min/bp
Hu et al. [17], 2022	uEXPLORER (United Imaging Healthcare) *vs* uMI780 (United Imaging Healthcare)	194 cm (LAFOV) 30 cm (SAFOV)	(SiPM)-based (SiPM)-based	LAFOV standard 15 min (1 bp) *vs* reconstructed 2 min (1 bp) LAFOV data (15 min and 2 min) *vs* 2 min/bp obtained with SAFOV uMI780	LAFOV data with a fast 2 min protocol did not hamper liver cancer detection with respect to conventional 15 min protocol and SAFOV PET/CT at 2 min/bp
Alberts et al. [20], 2021	Biograph Vision Quadra (Siemens Healthineers) *vs* Biograph-Vision 600 (Siemens Healthineers)	106 cm (LAFOV) 26.3 cm (SAFOV)	(SiPM)-based (SiPM)-based	LAFOV PET data reconstructed to emulate 10 min, 6 min, 4 min, 2 min, 1 min, and 0.5 min acquisitions *vs* 2 min/bp images obtained with digital SAFOV PET/CT	PET data reconstructed at acquisition under 2 min provided image quality comparable to 2 min/bp images obtained with digital SAFOV PET/CT

with Asian countries accounting for 75% of the overall number of HCC cases globally reported each year [11, 12]. In spite of the aforementioned epidemiologic issues, the potential of PET/CT for the management of liver cancer has not been fully investigated yet, since [^{18}F]FDG, the most commonly utilized tracer in oncology, has well-known limitations for the imaging of HCC, mainly due to the suboptimal target-to-background ratio [13]. In spite of the aforementioned drawback, [^{18}F]FDG PET/CT has been applied with encouraging results for prognostication, evaluation after loco-regional therapy, and follow-up after liver transplantation of hepatic tumors [14–16].

In the current issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, an elegant comparative study carried out by Dr. Hu and colleagues, from Fudan University (Shanghai, China), has further deepened the potential of a fast acquisition protocol for liver cancer detection through [^{18}F]FDG total-body PET/CT [17]. The authors retrospectively evaluated 78 patients with liver disease, submitted to total-body PET/CT through uEXPLORER (United Imaging Healthcare, Shanghai, China), a highly performing ultra-sensitive scanner, combining a LAFOV of 194 cm with last-generation SiPM-based detectors [18]. All subjects underwent total-body PET/CT with a conventional 15 min acquisition protocol (G15), then reconstructed with the data obtained from the first 2 min (G2). G15 and G2 PET images were independently evaluated by 2 nuclear medicine physicians for liver lesions detection; furthermore, PET-derived parameters (i.e., SUVmax, SUVmean, and tumor-to-liver ratio/TLR) were calculated both for G2 and G15 images. The results obtained with total-body PET/CT in the selected 78 subjects (both G2 and G15) were compared with those carried out in a matched cohort of 78 liver cancer patients (G780), submitted to the conventional whole-body (from skull base to mid-thigh) PET/CT scanner (uMI780, United Imaging Healthcare, Shanghai, China), characterized by an SAFOV of 30 cm and a speed of 2 min/bp. When the diagnostic performance of G15 and G2 was compared, no significant differences were found among them since they both detected 87 liver tumors, regardless of lesions' dimension. Notably, G15 identified more pathological lymph nodes in comparison with G2 (i.e., 59 vs 56, respectively), but this discrepancy did not meaningfully impact on PET-based TNM staging.

One of the most relevant merits of the study performed by Hu and collaborators [17] is represented by the correlation of PET/CT results with pathological findings. Among the 87 subjects with PET/CT positive findings, liver cancer was confirmed in 66 cases; therefore, the 2 different protocols (i.e., G2 and G15) showed a sensitivity of 95.45%, specificity of 75.0%, positive predictive value (PPV) of 95.45%, negative predictive value (NPV) of 75%, and accuracy of 92.31%. Noteworthy, no significant differences in PET-derived parameters were registered among G2 and G15, and at ROC analysis, SUVmax and TLR showed AUCs of 0.812 and 0.861, respectively. As far as it concerns, the results obtained through conventional whole-body PET/CT (G780), sixty-two of 78 subjects showed PET/CT positive findings for liver cancer, ten of whom also presenting lymph node metastases. Therefore, G780 presented a sensitivity of 96.88%, specificity of 64.29%, PPV of 92.54%, NPV of 81.82%, and diagnostic accuracy of 91.03%. On the one hand, the results achieved by Hu and coworkers support the feasibility of a short-time acquisition protocol for total-body PET/CT, as suggested by a phantom study previously carried out by the same group of research [19], and, on the other hand, indicate that lesions' detectability through total-body PET/CT is not meaningfully hampered by fast acquisition even in a challenging anatomical site, such as liver, characterized by high physiological background.

The results described by Hu et al. [17] are substantially in agreement with a previously published report by Alberts and colleagues [20], who assessed the diagnostic performance of total-body PET/CT (Biograph Vision Quadra PET/CT, Siemens) with respect to the conventional whole-body PET/CT (Biograph Vision 600, Siemens) through a head-to-head intra-individual comparison. The preliminary data reported by Alberts and collaborators suggest that a 2 min acquisition of total-body PET/CT would be as accurate as a standard 16 min conventional whole-body PET/CT [20], as then confirmed by the recently published research performed by Hu et al. [17]. However, it has to be highlighted that, when both LAFOV and SAFOV PET images were visually evaluated by experienced readers, although total-body PET/CT reconstructions emulating a shorter acquisition protocol (0.5 min) were considered adequate for lesions' detection, 10 min PET images provided the most satisfying image quality, especially in terms of SNR and TBR.

As specifically regards the potential of total-body PET/CT for HCC management, it has to be highlighted that several radiopharmaceuticals, other than [^{18}F]FDG, have recently emerged as useful molecular probes for liver cancer detection [14]. Among these, the ^{68} Ga-labeled tracer targeting prostate-specific membrane antigen (i.e., ^{68} Ga-PSMA-11), exploited as a biomarker of tumor-induced neovasculature, has shown particularly promising results: In a retrospective analysis performed on 40 HCC cases examined at staging, ^{68} Ga-PSMA-11 PET/CT showed higher accuracy than multiphase CT for the detection of extra-hepatic metastases, significantly impacting on subjects therapeutic management [21]. Furthermore, PSMA-expression by HCC paves the ground for possible theranostic applications through the utilization of ^{177}Lu-PSMA ligands [22]. From this perspective, it would be desirable to further investigate the possible application of total-body PET/CT with ^{68} Ga/^{18}F-labeled PSMA ligands in patients affected by advanced HCC,

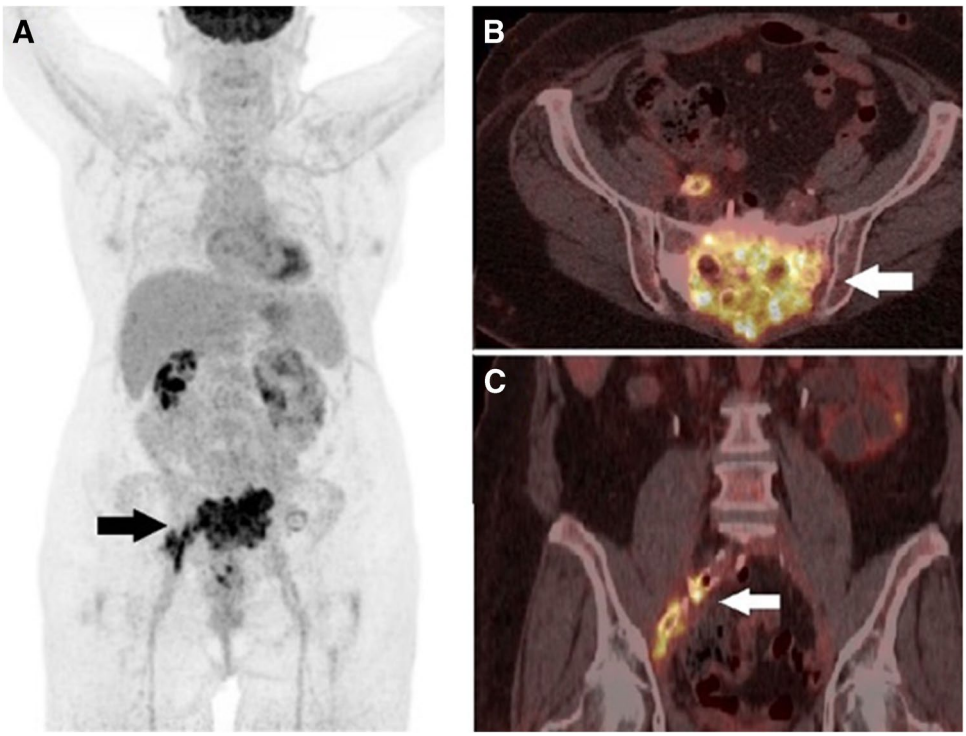

Fig. 1 An example of the fast protocol. A 65-year-old-female, affected by severely debilitating skeletal metastasis of the pelvis from anal cancer, previously submitted to vascular endoprosthesis of the right iliac artery, scheduled for restaging PET/CT. Supine posture was uncomfortable due to intense pelvic pain; therefore, after i.v. administration of 3.7 MBq/kg of [^{18}F]FDG, a fast protocol was used for digital PET/CT (Siemens Biograph Vision 450), with an axial FOV of 19.7 cm using continuous-bed motion with a bed speed equivalent to approximately 45 s/bp for a total time of 270 s. Image quality was excellent; no movement artifacts were registered: MIP showed intense tracer accumulation in the pelvis (**A**), fused axial PET/CT demonstrated ^{18}F-FDG uptake in the skeletal lesion (**B**, arrow), and coronal fused image well depicted tracer incorporation along the iliac endoprosthesis (**C**, arrow), highly suspected for coexisting cancer metastasis and endovascular infection

especially as far as it concerns the feasibility of fast acquisition protocols in this field of interest.

As the Roman philosopher Seneca the younger wrote, "*Omnia aliena sunt, tempus tantum nostrum est*," meaning that time is the only thing that we truly own, our most valuable and precious resource. This is particularly true in the case of cancer patients, who have to comply with repeated imaging sessions both to achieve a correct diagnosis and for the assessment of therapy response. According to the results reported by the previously cited papers [17, 20], one would wonder whether a fast or very fast acquisition always has to be preferred to the conventional (e.g., 15 min) protocol. Nevertheless, the clinical impact of total-body PET/CT with a fast acquisition protocol has to be fully determined yet, and as always, not all that glitters is gold. Firstly, the comparative study between total-body (G2 and G15) and conventional whole body (G780) was not a head-to-head comparison, since patient populations, although matched as closely as possible, presented distinct demographic and clinical features, thus introducing a bias potentially hampering the results of the study. Secondly, arms were differently positioned when patients underwent PET/CT with the 2 different scanners: along the body for total-body PET/CT and above the shoulders for G780. The different scanning posture might represent an explanation for the discrepancy in calculated SUVmean: higher for total-body than for whole-body PET/CT. Finally, as far as it concerns the detection of distant metastases, G2 acquisition missed 3 metastatic lymph nodes, characterized by relatively low [^{18}F]FDG incorporation that was indeed visualized by G15. Since the cohort of included liver cancer patients was relatively small, it is difficult to gauge how much this discrepancy might impact on larger populations. Finally, particular attention should be paid when low-dose or very fast acquisition protocols are applied for total-body PET/CT in patients with high body mass index that might require dedicated algorithms of reconstruction to obtain images of satisfying quality [23]. Although it has received an enthusiastic welcome from the scientific community, further studies – ideally larger, prospective and possibly standardized – should be carried out to obtain robust and reproducible information on the clinical impact of total-body PET/CT with different acquisition time protocols.

We can conclude that total-body PET/CT represents an extremely valuable tool, providing a wide range of technical opportunities to optimize acquisition protocol according to patients' needs. In the case of cancer patients with good performance status, a conventional 15 min scan time should be preferred, but in well-selected cases (e.g., pediatric patients, claustrophobia, severely debilitated subjects), as shown in Fig. 1, fast acquisition protocols may be feasible without meaningfully hampering image quality. In this perspective, a paradigm shift is needed: As the same drug does not always work properly for everyone, the same is true for technology. Therefore, every single Nuclear Medicine center should inflect its available facilities to minimize patients' discomfort, at the same time achieving the best diagnostic result possible. It is time to move forward and say welcome to the era of "personalized technology."

Author contribution The authors equally contributed.

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Declarations

Ethics approval and consent to participate Not applicable.

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