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REPLY

How to scan who: the delicate balance between selecting the patient and selecting the imaging protocol

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In this issue of the EJNMMI, Spadafora et al. propose shortening the FDG PET/CT acquisition for evaluating a solitary pulmonary nodule. The rationale is to design a strategy with a better cost-effectiveness ratio. There is a lot to like in the paper, as it discusses various aspects highly relevant to clinical nuclear medicine, such as clinical impact, patients' selection, imaging methodology, radiation safety, and costs. The objective is quite ambitious, as the proposed strategy could increase the number of FDG PET/CT performed for characterizing lung nodules, improve its effectiveness while reducing the cost and the radiation burden, and finally, increase the diagnostic accuracy. While some of these objectives may very well be achieved through this new strategy, it appears difficult to reach all, and there remain many question marks preventing the straight passage from the idea to the routine implementation.

The first issue is the patient's selection. The current guidelines essentially use two criteria for deciding whether FDG PET/CT is indicated: the size of the nodule and the pre-test probability. It is important to note that the strategies discussed here exclusively concern solid nodules. FDG PET/CT should be performed for characterizing nodules > 8 mm in diameter with a pretest probability of malignancy that is low to moderate (5–65 %) [1] or ≥ 10 % [2]. The European guidelines are more complex, as it is recommended that indeterminate SPNs should be assessed, in light of all relevant information, including patient, epidemiological and procedure-related factors by expert multidisciplinary boards who will apply criteria such as those proposed by the Fleischner Society, which recommends considering PET in lesions > 8 mm [3, 4]. In patients with a very high risk of cancer, the indication becomes staging rather than characterization [1]. Spadafora et al. imply that whole-body imaging is not indicated in T1 tumours, thanks to the low incidence of distant metastases in these early-stage lesions. This contradicts every international guideline for staging lung cancer [5–7], including small-cell lung cancer [8]. Indeed, even though lung cancer is increasingly diagnosed at an earlier stage, the majority of NSCLC patients have distant metastases at the time of diagnosis [9]. Even though the occurrence and distribution of distant metastases may occur following specific patterns, it remains practically impossible to predict such occurrence in individual patients [10]. Even in T1 tumors, the incidence of metastases is not negligible, as M1 disease has been reported in 13–14 % of the cases [11, 12]. It is of primary importance that these patients are correctly identified in order to receive the optimal treatment, which may lead to prolonged survival in a subgroup presenting with synchronous oligometatastic NSCLC, i.e. with maximum five metastatic lesions [13]. PET/CT won't recognize all distant lesions, in particular the brain is not appropriately explored with PET alone. However, although the exact figure of extracerebral metastases that occur in T1 tumors is not known, it is too risky a gamble to remove PET/CT altogether from the staging of these patients. Furthermore, the time to treatment is an important parameter in early-stage NSCLC. Surgery or other ablative therapies should not be delayed as the median survival is only 13 months in untreated T1 tumors [14].

Hence, the question is not whether early-stage cancer patients could benefit from a shortened PET/CT procedure, but rather how we could better identify those patients who are unlikely to have a PET-positive lesion. The large programmes that evaluated low-dose CT as a screening tool for lung cancer have yielded much valuable information [15]. From these,

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probability models have been developed, such as the Brock University cancer prediction equation, which is fully integrated in the BTS guidelines [2]. This model considers the size of the nodule and the following parameters: age, gender, family history of cancer, emphysema, location, number, and CT appearance of the nodule. The cancer probability for an 8-mm nodule in a 65-year-old individual ranges from 1.9 to 20.8 %, depending on the number of risk factors that are present. It ranges from 25.9 to 82.8 % for a 30-mm nodule. Since whole-body PET/CT is recommended as a staging procedure for high-risk nodules, how could we define the very-low risk nodules that would benefit from a shortened PET/CT? In any case, these are nodules larger than 8 mm, but with a very low pretest likelihood of malignancy. Gould et al. suggest a likelihood lower than 5 % [1], which would include nodules between 8 and 11 mm in men, 8 and 10 mm in women, provided than none of the other risk factors are present. In a 65-year-old individual, male or female, all 10-mm nodules in the upper lobe or showing speculations on CT carry a risk of malignancy greater than 5 %. The exact number of patients who could safely benefit from a shortened PET/CT cannot be known with precision, but it is likely to be rather limited. More importantly, the process for identifying those patients need to be rigorously established, as one cannot solely rely on the size criterion. Completing the study with a subsequent acquisition centered over the abdomen and pelvis presents several disadvantages, in terms of logistics and practicability. Such on-the-fly decisions may be very disruptive for the PET schedule, leading to an increase in the uptake time for the following patient and increasing the variability of the quantity of FDG that needs to be ordered. The former, by increasing the variability of the uptake period across patients, decreases the overall quality of the PET service [16], and the later carries the risk of purchasing more FDG than actually needed, hence increasing the overall costs. Furthermore, adding the missing bed position requires an overlap with the initial study, which means that in these patients the radiation dose resulting from the CT will be slightly higher than in a one-step, whole-body study.

Considering the benefits of such shortened PET/CT, Spadafora et al. mention a) decreasing the effective dose and the cancer risk; b) reducing scanning time and improving workflow; c) decreasing costs; and d) improve SPN characterization with 4D PET/CT or dual time point imaging. Obviously, these objectives may be mutually exclusive. As d) increases the overall scanning time, it cannot be achieved with b), and c). However, although each of these objectives taken separately is desirable, the question is whether it is worth the trouble. The entire nuclear medicine community would surely agree that controlling the radiation dose delivered to our patients must be on top of our preoccupations. However, the numbers cited in the paper, such as 29,000 cancers resulting from CT and a 0.62 % of excess cancer death are unnecessarily alarming, not directly related with the procedure being discussed, and remain highly debated. With FDG, the effective radiation dose resulting from the PET component is 0.019 mSv/MBq, i.e. 3.8–5.7 mSv with 200–300 MBq [16]. The biological effects of a low-dose rate irradiation and of a higher rate exposure to X-rays are different, so let us focus on the latter, since it is the component that would be decreased in every case of shortened protocol. Indeed, the radiation dose resulting from FDG would be decreased only if one choses to increase the scanning time. The effective dose resulting from the CT component greatly varies depending on the acquisition protocol and body habitus of the patient. It was reported to be comprised between 1.3 and 4.5 mSv using a now outdated generation of PET/CT scanners [17]. In our institution, for a non-enhanced whole-body study performed with an algorithm of dose modulation, the DLP ranges from 150 to 450 mGy*cm. Using a k value of 0.015, the E_{dlp} is comprised between 2.25 and 6.75 mSv [18]. This is the compromise, between radiation dose and image quality, that we have adopted for scanning adult patients in oncological indications. Decreasing the length of the CT by 50 % would thus reduce the effective radiation dose associated to the X-rays irradiation by 0.65 to 3.4 mSv. How many radiation-induced cancers and how many deaths would be spared with such a reduction? The truth is that we do not know, but the current body of evidence indicates that the figure is very low, and possibly nil in the adult population being investigated with PET/CT for a SPN [19–21]. The estimation of the risk of radiation-induced cancer is based upon the BEIR VII model [22], which is far from being unanimously accepted [23]. Discussing the linear no-threshold risk model for low-dose radiation is far beyond the scope of this article. Suffice it to say that the benefit in terms of risk reduction is largely hypothetical and that seeking a dose reduction without carefully weighing the actual risk/benefit may actually be harmful [24].

Other potential benefits of a shortened PET/CT are improved throughput and reduced costs. One has to be careful when claiming cost-effectiveness. The effectiveness is generally easier to quantify than the cost aspect, which greatly varies across countries. The approach proposed by Spadafora et al. cannot significantly reduce the overall costs for the FDG: Dividing one dose by 2, in the midst of a complete PET/CT schedule, i.e. 15 to 20 patients, would only have a marginal impact on the FDG bill. Reducing the scanning time improves the comfort of the patient, and overall may improve the image quality by reducing the movements of the patients. In theory, it may also lead to an increase in the number of studies that could be performed with the same quantity of FDG. The net benefit would be removing 5–10 min from a 10–20-min acquisition time, for which the manipulation of the patient and the preparation of the study take a non-compressible time. Although this is certainly valuable, it is debatable whether this would translate into significant cost savings at year's end.

In summary, the objectives of tailoring the PET/CT acquisition to the clinical indication are undoubtedly commendable. Yet, it appears that it is not possible to reach all targets at the same time, and that choices have to be made. Identifying the patients who could benefit from such a protocol remains a challenge, and the real benefit does not appear certain, at least it is not quantified. The key question may be not so much whether those patients with a centimetric nodule and a very low pre-test probability of cancer would benefit from a shortened PET/CT as whether they should undergo PET/CT at all. Indeed, repeat low-dose CT at 3 months may well prove equally effective and less costly. On the other hand, if the objective is to improve the diagnostic accuracy, the methodology should be adapted, probably using respiratory gating whose clinical impact remains largely hypothetical [25], albeit further technological progresses have been made [26]. All in all, there is only one recommendation that could be made when fronted with new ideas, new technologies or new algorithms: just test it, in a sound scientific fashion.

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