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EDITORIAL COMMENTARY

Evaluation of ^{124}I PET/CT and ^{124}I PET/MRI in the management of patients with differentiated thyroid cancer

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In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Binse and colleagues report the results of ^{124}I PET/MRI in comparison with those of ^{124}I PET/CT in patients with differentiated thyroid cancer (DTC). The two separate PET acquisitions explored the neck, 24 h after ^{124}I intake. This elegant study showed the superiority of the PET component associated with the MRI device over the PET component associated with the CT device as it detected more iodine-positive metastases (72 vs. 60 tumour lesions, $p = 0.002$) and identified additional patients with at least one tumour lesion (21/65 vs. 17/65 patients, $p =$ n.s.) using a 2-min acquisition time. The assumed explanation was better lesion-to-background contrast due to an improved PET device (better geometry of the detector systems and sensitive area of the crystals), which allowed better detection of thyroid tumour foci, taking advantage of their unique prolonged ^{124}I accumulation. In fact, two acquisitions were performed with PET/MRI: a 30-minute PET acquisition covered the neck MRI acquisition time and increased the detection rate of tumour lesions by 22 % in comparison with the previously cited 2-min PET acquisition (88 vs. 72, $p = 0.07$). The conclusion of this study was that ^{124}I PET/MRI shows no substantial advantage over ^{124}I PET/CT for the detection of tumour lesions in the neck when using similar PET devices and that the MRI component does not significantly improve sensitivity or specificity in the detection of neck lesions as compared to the CT component.

Dosimetry by ^{124}I PET

In some centres DTC patients are treated with a fixed standard activity of radioiodine. In others an individualized radioiodine activity is used based on dosimetry to deliver higher radiation doses to lesions and/or doses that will not induce damage to organs at risk. A theoretical model based on literature data has shown that individualized therapy could enhance the overall response rate by 8 % (70 % vs. 62 %) while saving an average of 0.9 GBq per patient (7 vs. 6.1 GBq) [1] in comparison with a 7-GBq fixed standard therapy. One major aim of ^{124}I PET could be the determination of the ^{131}I activity to be used in DTC treatment.

The dosimetry method based on lesion dosimetry estimates the radiation dose to the lesion by taking into account the volume of the lesion, the initial concentration of radioiodine and its effective half-life in the lesion. One theoretical benefit over a standard activity is that higher activities result in higher radiation doses to tumour foci which may be associated with higher tumour-response to ^{131}I therapy [2]. Studies by Maxon and colleagues have indeed shown that tumour absorbed doses greater than 8.5, 10 and 14 Gy to lymph node metastases are associated with ablation rates of 74 %, 80 % and 86 %, respectively [3–5]. Additionally, doses to metastases above 80 Gy are successful in most cases. The second dosimetry method is based on theoretical models calculating a maximal tolerated dose that avoids bone marrow and lung toxicity. Bone marrow suppression can be avoided if the ^{131}I dose delivered to the bone marrow or blood is less than 2 Gy. Pulmonary fibrosis can be avoided if the ^{131}I retention in the lungs is less than 2.95 GBq at 48 hours [2].

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In clinical practice, dosimetry is not recommended for the postsurgical administration of radioiodine in patients with low-risk thyroid cancer after complete surgical resection. The same ablation rate [6] and lower costs [7] have been observed after administration of a standard low ^{131}I activity of 1.1 GBq in comparison with 3.7 GBq. Dosimetry by ^{124}I PET may be used in patients with high-risk thyroid cancer. However, the benefits of an individualized activity over a standard activity of ^{131}I therapy remain to be determined because current models are time consuming and highly complex, and no prospective trials have demonstrated better results in terms of disease-free survival or overall survival rates.

The limits and inaccuracies of dosimetry by ^{124}I PET should also be considered. The radiosensitivity of tumour cells is not taken into account in current models. Its importance is, however, emphasized by the nonlinear relationship between the absorbed radiation dose in a lesion estimated by ^{124}I PET and its subsequent response to ^{131}I therapy because low estimated ^{124}I radiation doses might be associated with a complete response to ^{131}I [8]. The complex ^{124}I PET dosimetry models are also challenged by the heterogeneous iodine metabolism in tumour foci because the ^{124}I concentration and effective half-life show a broad variability among lesions even in the same patient [9–13], and iodine-negative lesions associated with a poor outcome are ignored. Finally, there are significant physical limits. The volume of lesions is inaccurately estimated without morphological correlates, partial volume effect correction can only be applied in lesions larger than 1.3 times the PET spatial resolution [14], and most tumour responses are observed in patients with metastases smaller than 1 cm in diameter [15]. A simple protocol based on two acquisitions after administration of ^{124}I (24 and 96 hours) allows acceptable estimation of the volume, the uptake and half-life of ^{124}I in each metastatic lesion [10]. However, the reference protocol (five PET acquisitions at 4, 24, 48, 72, and 96 hours) is associated with an estimated physics-related error range of 20 – 30 % [10], and the added inaccuracy of simpler protocols (<16 %) may not be negligible.

Dosimetry by MRI

Dosimetry by MRI is feasible but remains a technical challenge. CT scan clearly outperforms this procedurefor attenuation correction, which is a key role of morphological imaging. This study used a T1-weighted water-only 3D Dixon sequence and a T1-weighted fat-only 3D Dixon sequence prior to contrast agent administration. This allowed segmentation of the attenuation map into four automatically generated classes: background, lung, fat and soft tissue. This segmentation did not lead to differences in clinical interpretation but changed the measurement of SUV (estimating ^{124}I uptake in lesions), especially for bone and neck lesions [16, 17]. This needs to be considered when ^{124}I PET is performed to optimize dosimetry planning that may thus require a CT scan.

Another hypothesis, which is not supported by the results of Binse and colleagues, is that MRI could minimize radiation exposure by allowing better detection and classification of the lesions. This was suggested by the combination of intrinsically coregistered ^{124}I PET/CT and software coregistered ^{124}I PET/MRI images for the diagnosis and dosimetry of thyroid remnant tissues and lymph node metastases in patients with DTC [18]. The ^{124}I PET-positive lesions were classified as thyroid remnants (58 %) or lymph nodes (27 %). A morphological correlate between ^{124}I PET and CT was observed in 26 % of thyroid remnants and 62 % of metastatic lymph nodes. A morphological correlate between ^{124}I PET and MRI was observed in 54 % of thyroid remnants and 83 % of metastatic lymph nodes. MRI was especially helpful in lesions <10 mm and improved pretreatment dosimetry by improving the characterization of lesions unclassified by ^{124}I PET alone (15 %). Indeed, two thirds of lesions visible on MRI and not on CT were classified as thyroid remnant tissue, and redoing dosimetry based on the volume information from MRI for these small lesions would have allowed the activity to be decreased in 5 of 33 patients.

As a conclusion, one potential advantage of MRI is minimizing radiation exposure of patients by substituting the CT scan by MRI. However, the low-dose radiation delivered by CT must be put into perspective in patients with DTC who are going to be treated with high-activity ^{131}I. The choice of the reference standard will remain a problem in further studies: MRI may be false-negative and may also be false-positive due to the inflammatory process after thyroidectomy. Additionally, further studies are needed to evaluate the robustness and reproducibility of dosimetry by ^{124}I PET/MRI as compared to ^{124}I PET/CT. They also should compare the combination of neck ultrasonography with either ^{124}I PET/CT or ^{124}I PET/MRI because, in clinical practice, ultrasonography is the procedure routinely used to detect and characterize lymph node metastases and might also detect thyroid remnants.

Detection of tumour lesions by ^{124}I PET/CT

^{124}I PET is also of potential interest for the localization of tumour lesions. ^{124}I PET/CT is indeed highly specific and seems to be the most accurate procedure for the staging of iodine-positive lesions. As mentioned by the authors, the detection of additional metastases might be crucial for optimal treatment planning, especially in patients with locally limited DTC in whom surgical treatment may be performed with curative intent. The diagnostic value of ^{124}I PET/CT in DTC is better than that of low-activity diagnostic ^{131}I scans [19]. The detection of disseminated iodine-avid lung metastases remains a challenge in ^{124}I PET/CT and this may only partially be

addressed by the lung-to-background ratio [20]. The CT component is the most sensitive tool for detecting lung micrometastases that are often not visualized by MRI. ^{124}I PET/CT reveals more lesions which are more visible and it adequately predicts findings on subsequent posttreatment ^{131}I scans [21] and ^{131}I SPECT/CT [22]. However, the clinical significance of such additionally detected lesions with low iodine uptake remains to be determined and most studies were performed in a limited number of patients and did not relate their discovery to the outcome of patients. Indeed, ^{124}I PET fails to detect metastases that show no iodine uptake whose presence may indicate thyroid cancer refractory to ^{131}I treatment.

The design of the study by Binse et al. did not allow the determination as to whether the morphological imaging component (MRI or CT) was able to accurately detect metastases with no iodine uptake. The reference standards were ^{124}I PET/CT at 96 hours and posttherapy ^{131}I whole-body SPECT/CT rather than pathology. However, in patients with high-risk DTC and elevated serum thyroglobulin (>10 ng/ml) and negative radioiodine imaging, the current guidelines of the American Thyroid Association (ATA) recommend the use of ^{18}F-FDG PET [23]. Several reports have indeed shown the superiority of ^{18}F-FDG PET over morphological imaging [24] and its excellent diagnostic accuracy in DTC lesions without ^{131}I uptake (sensitivity 83 %, specificity 84 %) [25]. These conclusions are strengthened by several facts. Firstly, a combination of ^{18}F-FDG PET and ^{124}I PET has proved that one third of recurrent DTC lesions in patients with negative neck ultrasonography and increased serum thyroglobulin and/or thyroglobulin antibodies demonstrate pathological tracer uptake with both modalities, while two thirds are positive with only one of these two modalities [26]. Secondly, in such patients ^{18}F-FDG PET/CT is superior to postempirical ^{131}I whole-body scan for the detection of suspicious recurrent or persistent disease [27].

Detection of tumour lesions by MRI

In the current ATA guidelines, MRI is recommended in only a limited number of indications for the assessment of the locoregional extent of DTC. MRI provides better diagnostic information than CT for the delineation of any demonstrated or suspicious lesion of the aerodigestive tract or of the suprahyoid region [23]. MRI is indeed considered as the reference-standard in head and neck assessment because it provides high-resolution images and an excellent lesion to soft tissue contrast. However, in thyroid cancer patients, neck ultrasonography is the clinical reference-standard. Additionally, MRI relies on the injection of a noniodinated contrast enhancement product, which is a major advantage over CT because the injection of iodinated contrast agent will delay the administration of radioiodine for at least 4 weeks.

The study of the potential role of MRI in the detection of locoregional metastases is of interest because, as highlighted by the authors, there are some discrepancies in the literature. Some studies have shown poor sensitivity of MRI in diagnosing metastatic cervical lymphadenopathy [28]. Others have shown that PET images retrospectively coregistered with MRI images is beneficial in the management of iodine-positive DTC [18, 29]. Binse and colleagues demonstrate that there is no evident benefit in using MRI over a low-dose CT scan without iodinated contrast agent for lesion detection or lesion characterization. MRI did not lead to a significant increase in the detection rate of DTC lesions nor did it improve significantly the characterization of lesions. This conclusion was strengthened by two facts: inconclusive lesions were observed in 13 of 65 patients on PET/MRI vs. 14 of 65 patients on PET/CT; PET/MRI categorized as metastasis or thyroid remnant only 5 of 21 lesions which were classified as inconclusive on PET/CT.

The 30-minute acquisition only explores the neck, and thus the accuracy of PET/MRI for the detection of distant metastases was not evaluated. However, there are some reports in the literature suggesting that the diagnostic accuracy of PET/MRI might not outclass that of PET/CT. Current MRI sequences are indeed less sensitive than CT for the detection of lung micronodules [23], and FDG PET/CT outperforms FDG PET/MRI for the diagnosis of pulmonary metastases in DTC [30]. Additionally, dedicated MRI sequences are not more accurate than FDG PET/CT for the detection of bone involvement in DTC [31]. Finally, Dixon sequences acquired on MRI for attenuation correction are insufficient to provide anatomical information because of low spatial resolution. Thus, additional MRI sequences might be necessary [17] and may lead to an unreasonable acquisition time.

Functional MRI

As explained by Binse and colleagues, the anatomical and functional capabilities of MRI combined with the molecular information provided by PET are expected to provide new insights into disease phenotype and biology. It is an enticing hypothesis: MRI sequences might provide information such as perfusion and diffusion. Further studies are needed to determine the clinical benefit of these sequences and whether MRI may predict tumour behaviour and/or improve the clinical management of patients. However, we have to keep in mind that despite the excellent resolution of MRI, most iodine-positive lesions were not detectable and thus not evaluable with MRI alone. Thus, the functional information provided by MRI might be less sensitive and informative than a combination of ultrasonography, FDG PET/CT and ^{124}I PET/CT.

Clinical use of ^{124}I PET/MRI

The potential benefits of ^{124}I PET/CT and PET/MRI do not preclude more general questions about patient accessibility and acceptability, the impact on patient outcome and the cost-effectiveness for healthcare systems. MRI suffers from several contraindications, which should be carefully screened for. The acquisition time is 30 minutes for an evaluation of the neck only, whereas a whole-body CT acquisition lasts less than 1 minute, and modern PET devices are able to perform a whole-body acquisition in less than 10 minutes. The duration of the procedure is an important point to consider for the patient (especially in those with potential claustrophobia) and for the healthcare system (a whole-body PET/CT scan with a coregistered MRI scan of the neck is certainly more cost-effective).

Conclusion

The work of Binse and colleagues points out that there are probably some research perspectives for the use of ^{124}I PET/CT and PET/MRI in patients with DTC. It shows that there is no substantial advantage of ^{124}I PET/MRI over ^{124}I PET/CT for the detection of tumour lesions in the neck when using similar PET devices. It confirms the superiority of ^{124}I PET over CT and MRI for the detection of iodine-positive lesions. It demonstrates that the use of a more sensitive PET device and a longer acquisition time leads to the detection of more lesions.

^{124}I PET is a promising research tool [23] for pretherapy dosimetry, the evaluation of response to ^{131}I treatment and the staging of recurrent or residual disease [32]. The recognized advantages of MRI are the evaluation of aerodigestive tract lesions and suprahyoid region lesions. The coregistration of MRI and ^{124}I PET/CT might thus be more convenient than ^{124}I PET/MRI (shorter time of acquisition, better cost-effectiveness and more accurate attenuation correction). The benefits of these procedures in terms of patient outcome, and for the clinician and the healthcare system remain to be determined.

Compliance of ethical standards

Conflicts of interest None.

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