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Imaging of multiple endocrine neoplasia type 1 patients in the era of somatostatin receptor positron emission tomography–computed tomography: “no place to hide for neuroendocrine tumours”

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Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited autosomal dominant disease that predisposes to primary hyperparathyroidism, pituitary tumours, and duodenopancreatic neuroendocrine tumours (dP-NETs) as well as other less frequent tumours, such as adrenocortical tumours, lung/thymic NETs, and lipomas.¹ The dP-NETs (including gastrinomas, insulinomas, and non-functioning tumours) and thymic NETs account for 50% of disease-specific deaths.² The screening and lifelong surveillance programmes should provide accurate information on disease staging/restaging to guide decision-making, use non-invasive methods, and have acceptable cost burden. At present, guidelines for MEN1 patients do not promote the use of positron emission tomography–computed tomography (PET/CT).³ In recent years, somatostatin receptor (SSTR) PET/CT has gained an important role in the evaluation of NETs.

In the paper published by Kostianen et al., in the same issue of *European Journal of Endocrinology*, the authors performed a head-to-head comparison between SSTR PET/CT and anatomical pancreatic imaging (magnetic resonance imaging [MRI] or CT) in the real-life management of 58 MEN1 patients. Of note, the age at the time of SSTR PET/CT was high (40 years, 28–56), most likely due to the absence of guidance on the use of this imaging modality. They also found that SSTR PET/CT outperformed anatomical imaging in the detection of pancreatic neuroendocrine tumours (panNETs) (133 vs 44 pancreatic lesions, respectively, $P < .001$). Several studies, including 1 from our group that also evaluated endoscopic ultrasound, showed that SSTR PET/CT has a higher detection rate of panNETs in MEN1 patients (which are often multifocal) irrespective of the clinical scenario and can even detect extra-pancreatic primaries and metastases.^{4–8} Beyond tumour detection, the results from Kostianen et al. are strengthened by the important clinical impact induced by the use of SSTR PET/CT. The authors have reported a change in the

management in 27 (47%) patients, with half of the changes attributable to novel panNET discoveries requiring close follow-up, the remaining cases being attributed to therapeutic interventions. Active surveillance is a reasonable option for small (maximal diameter ≤ 2 cm) panNETs. It is estimated that 50%–70% of panNETs of 2–3 cm are associated with nodal metastases and that 25%–40% of those tumours with size greater than 4 cm have liver metastases.⁹ In the study by Kostianen et al., SSTR PET/CT was found to be more sensitive than MRI/CT in the detection of nodal involvement, most likely related to their small size that prevents any reliable characterization on anatomical imaging. This added value of SSTR PET/CT over anatomical imaging in this setting is of prime importance, since the presence of SSTR positive nodes dramatically impacts the management of patients, as illustrated in 3 cases in this cohort (patients 1 and 8 were referred for surgery, and patient 12 was treated by somatostatin analogues). These data, together with recent studies from other groups,^{4–8} provide a great impetus towards the use of SSTR PET/CT in the initial evaluation of MEN1 patients. Kostianen et al. also provide interesting results on the potential predictive value of SSTR PET/CT. They showed that in a subgroup of 10 patients with negative SSTR PET/CT, no panNET lesions occurred in all but one case in the subsequent imaging follow-up (median duration of follow-up of 38 months). Moreover, in 8 out of 15 patients with positive panNET on SSTR PET/CT with no corresponding lesions on conventional imaging, none of them developed clinically relevant tumours during follow-up (after a median period of 47 months). These data suggest that SSTR PET/CT could be used to personalize and in particular to space out the surveillance programme of MEN1 patients. If not performed initially, SSTR PET/CT should be performed during follow-up. Repeat SSTR PET/CT should be discussed on an individual basis in the setting of an interdisciplinary tumour board. It is

important to remember that drawbacks to any surveillance programme are the psychological consequences involved, subjecting patients to long-term anxiety, and uncertainties. In contrast, the level of confidence generated by reassuring patients that any abnormality would be rapidly diagnosed and treated is of paramount importance and helps with self-insurance. SSTR PET/CT is a reliable imaging tool for panNET detection in MEN1 patients. The CT/MRI or endoscopic ultrasound can complement SSTR PET/CT and is particularly useful for guiding biopsy or for preoperative planning due to its very high resolution: The anatomic structures can serve as roadmaps, and CT is also preferred by most surgeons who are trained in cross-sectional interpretation.¹⁰

As a general concept, functional (ie, molecular) imaging provides insights into tumour biology, which is closely linked to tumour location, genetic status, biochemical phenotype, and pathological grade, with all being intimately interconnected. High tumour uptake on SSTR PET/CT reflects the expression of somatostatin receptors subtype 2 (SSTR2) of NET, which is associated with a well-differentiated nature.¹¹ In MEN1 patients, an overwhelming majority of dP-NETs are well differentiated¹² and therefore can be potentially detected by SSTR PET/CT. However, some lung or thymic NETs may have a lower differentiation pattern and can be therefore missed by SSTR PET/CT and are also not eligible for SSTR-targeted peptide receptor radionuclide therapy.¹¹ In the study by Kostianen et al., 1 patient had widespread liver metastases from a lung NET with no uptake on SSTR PET/CT. In these scenarios, [¹⁸F]FDG can be positive. The term “flip-flop phenomenon” is usually used to illustrate the inverse relationship between SSTR expression and [¹⁸F]FDG uptake on dual tracer imaging.

Despite the potential added value of SSTR/PET CT, there is still a concern regarding diagnostic radiation exposure for MEN1 patients who require lifelong surveillance. In the study by Kostianen et al., the effective dose of SSTR PET/CT ranged from 4.5 to 7 mSv compared with 13 mSv for multi-phasic abdominal contrast-enhanced CT. It is anticipated that technological breakthroughs will continue to significantly decrease dose exposure. For example, the recently introduced ultra-extended field-of-view PET scanners (total body) allow to reduce radiation burden from PET to 1 mSv. Important improvements in physics and technology of time-of-flight (TOF) PET detectors are also expected in the next 2 decades under the umbrella of the “10 picoseconds TOF PET” challenge.¹³ These advancements will probably allow to reduce administrated activities with the objective to decrease effective dose by more than 200-fold (0.03 mSv per PET, below the exposure from a flight from London to NYC). These changes will probably dispel some of the controversies related to radiation exposure in the surveillance of patients with cancer predisposing syndromes.

In conclusion, MEN1 patients require a personalized and interdisciplinary management plan. In this regard, the value of SSTR PET/CT for providing an accurate assessment of disease extension at a whole-body scale and phenotypic information could position this modality as an important tool in the evaluation of MEN1 patients. This approach warrants inclusion in future clinical practice guidelines for MEN1 patients.

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