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THYROPET study: is biology or technology the issue?

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LETTER TO THE EDITOR:

We read with interest the results of the recently published THYROPET study[1], a prospective multicentre diagnostic cohort study testing the hypothesis that a recombinant human (rh)-TSH stimulated I-124 PET/CT can identify patients with a negative thyroxine withdrawal (T4WD) post-therapy I-131 scan and avoid futile treatment in patients with suspected recurrence of differentiated thyroid carcinoma. The trial was terminated prematurely due to a high number of false negative rh-TSH stimulated I-124 PET/CT scans that would preclude potential therapeutic benefit from I-131 therapy. Whilst this may be interpreted as a rebuttal of the theranostic approach and affirmation of the established practice of empiric I-131, we agree with the authors' conclusion that 'I-124 PET/CT remains the most rational strategy to reduce futile I-131 therapies' despite this statement being in conflict with their actual study findings. The explanation of this result will be critical to guide the use of I-124 PET/CT for management of advanced thyroid cancer.

In particular, we would like to focus on the very different clinical implications arising from the possible technical and biologic explanations for the false negative rh-TSH stimulated I-124 results. Radioiodine imaging is a classic theranostic investigation, whereby the distribution of iodine uptake and retention within tumour is used to predict the response to a therapeutic administered activity of I-131. A key advantage of I-124 PET/CT imaging is the opportunity to perform prospective dosimetry to more accurately predict this response[2]. In this context, it is highly unlikely that a necessarily faint focus of uptake below the resolution of I-124 PET but visible on post I-131 imaging would deliver a clinically meaningful dose of radiation. Thus if technical differences were the only explanation for the high false negative rate of I-124 PET/CT, then it remains an appropriate screening investigation for this indication as the risks of high dose I-131 therapy are likely to outweigh the modest benefits due to unfavourable radiation dosimetry.

However, a recently published phantom study[3] confirms that there is no appreciable technical difference in detectability for even small spheres (<10mm) at this administered activity (74MBq I-124) on scanners using

point-spread function model-based resolution recovery and time-of-flight technology. We note that some, but not all THYROPET study centres had time-of-flight technology and thus knowledge of the number of patients imaged using this protocol is necessary to better interpret the results of this study. Different imaging times are another potential technical explanation for uptake on delayed post-therapy scans (5 days) missed on early (24 hour) I-124 imaging[4], however this is unlikely to be relevant due to the dual time-point 24 and 96 hour acquisitions utilised in the THYROPET study.

In contrast, it remains plausible that the false negative I-124 PET/CT scans reflect different biologic tumour responses to TSH stimulation from rh-TSH and thyroxine withdrawal. The authors appropriately discuss this possibility with numerous published intra-patient case studies. We also note that in one of the subset of THYROPET cases whom underwent I-124 PET/CT after both rhTSH and T4WD there was 23 times greater I-124 retention after T4WD. If confirmed in a large prospective intra-patient I-124 study this would have profound clinical implications for the management of metastatic thyroid cancer, given the widespread use of 'off-label' rh-TSH stimulation for both diagnostic I-124 and therapeutic I-131 therapy in this setting.

We believe it is more plausible that biologic differences between rh-TSH and T4WD stimulation of recurrent thyroid cancer explain the THYROPET results with significant clinical impact. To the extent that technical factors associated with I-124 imaging explain the THYROPET study findings, we believe that they are unlikely to impact its role as a theranostic test in this setting.

REFERENCES:

[1] Kist JW, de Keizer B, van der Vlies M, Brouwers AH, Huysmans DA, van der Zant FM, et al. 124I PET/CT to Predict the Outcome of Blind 131I Treatment in Patients with Biochemical Recurrence of Differentiated Thyroid Cancer: Results of a Multicenter Diagnostic Cohort Study (THYROPET). *J Nucl Med* 2016; 57: 701-707.

[2] Wierts R, Brans B, Havekes B, Kemerink GJ, Halders SG, Schaper NN, et al. Dose-response Relationship in Differentiated Thyroid Cancer Patients Undergoing Radioiodine Treatment Assessed by Means of 124I PET/CT. *J Nucl Med* 2016; 57: 1027-1032.

[3] Beijst C, Kist JW, Elschot M, Viergever MA, Hoekstra OS, de Keizer B et al. Quantitative Comparison of 124I PET/CT and 131I SPECT/CT Detectability. *J Nucl Med* 2016; 57: 103-108.

[4] Freudenberg LS, Jentzen W, Müller SP, Bockisch A. Disseminated iodine-avid lung metastases in differentiated thyroid cancer: a challenge to 124I PET. *Eur J Nucl Med Mol Imaging* 2008; 35: 502-508.