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Response to the Letter to the Editor entitled "THYROPET study: is biology or technology the issue?"

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Dear Editor,

Thank you for the opportunity to respond to the letter to the editor by Pattison et al.,[1] regarding our manuscript presenting the results of the Thyropet study.[2] In this study we showed that ^{124}I PET/CT after preparation with rhTSH was not able to predict the outcome of the post-therapy ^{131}I scan after thyroid hormone withdrawal (THW) in patients suspected of differentiated thyroid cancer recurrence. In our manuscript we discussed several factors potentially causing these disappointing results; both technical issues regarding ^{124}I PET/CT acquisition and biological matters were put forward.

Pattison et al. argue in their letter to the editor that in their opinion the biological explanations are most probably causing the false negative ^{124}I PET/CT scans. We fully agree that the method of preparation with rhTSH on the ^{124}I PET/CT versus THW before the ^{131}I therapy and post-therapy scan is a very likely cause of the false negative ^{124}I PET/CT scans. Data from our study and as well results from others support this hypothesis.[2-4] Prospective studies with intra-patient comparisons of rhTSH- and THW-stimulated ^{124}I PET/CT are warranted to confirm this.

Notably, the one important downside of ^{124}I PET/CT scanning after THW as a diagnostic tool is the reduced quality of life during the period of THW.[5]

Whether technical issues can be ruled out as factor, as argued by Pattison et al., is in our opinion not definite. The sensitivity of ^{124}I PET/CT is shown to be confined by specific scanner characteristics (eg. no time-of-flight and no point-spread function)[6]. New scan protocols and new generation scanners will - in greater or lesser degree - improve sensitivity of ^{124}I PET/CT. Similarly, higher administered doses of ^{124}I (eg. 222 MBq as applied by Ho et al.[7]) might improve lesion detection. Currently, it is not known whether the lesions detected by improved sensitivity of ^{124}I PET/CT can be treated with an administered dose of ^{131}I required to deliver a curative dose without exceeding safety limits for bone marrow. Future studies on this matter are needed to elucidate this.

In conclusion, we agree with Pattison et al. that the method of preparation on the ^{124}I PET/CT with rhTSH is probably the most important factor causing false negative ^{124}I PET/CT scans. However, it is too early to state that it is the *only* factor.

REFERENCES:

1. Pattison D, Hicks R. THYROPET study: is biology or technology the issue? *J Nucl Med*.

2. Kist JW, de Keizer B, van der Vlies M, 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(5):701-707. doi:10.2967/jnumed.115.168138.

3. Van Nostrand D, Khorjekar GR, O'Neil J, et al. Recombinant human thyroid-stimulating hormone versus thyroid hormone withdrawal in the identification of metastasis in differentiated thyroid cancer with 131I planar whole-body imaging and 124I PET. *J Nucl Med*. 2012;53(3):359-362. doi:10.2967/jnumed.111.096016.

4. Freudenberg LS, Jentzen W, Petrich T, et al. Lesion dose in differentiated thyroid carcinoma metastases after rhTSH or thyroid hormone withdrawal: 124I PET/CT dosimetric comparisons. *Eur J Nucl Med Mol Imaging*. 2010;37(12):2267-2276. doi:10.1007/s00259-010-1565-3.

5. Nygaard B, Bastholt L, Bennedbæk FN, Klausen TW, Bentzen J. A Placebo-Controlled, Blinded and Randomised Study on the Effects of Recombinant Human Thyrotropin on Quality of Life in the Treatment of Thyroid Cancer. *Eur Thyroid J*. 2013;2(3):195-202. doi:10.1159/000354803.

6. Beijst C, Kist JW, Elschot M, et al. Quantitative Comparison of 124I PET/CT and 131I SPECT/CT Detectability. *J Nucl Med*. 2016;57(1):103-108. doi:10.2967/jnumed.115.162750.

7. Ho AL, Grewal RK, Leboeuf R, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. *N Engl J Med*. 2013;368(7):623-632. doi:10.1056/NEJMoa1209288.