In reaction to

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Letter to the editor

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Dear Editor,

With interest we have read the SFA-AFCE-SFMN 2022 consensus on the management of thyroid nodules "section 5: what is the role of functional imaging and isotopic treatment?" by Thuillier et al. published ahead of print in *Annales d'Endocrinologie* [1]. What specifically drew our attention was the paragraph on the use of [^{18}F]FDG-PET/CT in the analysis of thyroid nodules with indeterminate fine-needle aspiration cytology (FNAC) including atypia of undetermined significance or follicular lesion of undetermined significance (Bethesda III, AUS/FLUS) and (suspicious for a) follicular neoplasm (Bethesda IV, FN/SFN) or Hürthle cell neoplasm (Bethesda IV, HCN/SHCN) [2,3].

The follicular lesions of which this group largely consists require histopathological assessment of capsular and vascular invasion to obtain a conclusive benign or malignant diagnosis [3]. Current international guidelines recommend repeat FNAC in Bethesda III nodules and consideration of clinical and ultrasound characteristics and patient preference in both Bethesda III and IV nodules, before deciding to proceed with either active surveillance or diagnostic surgery [3,4]. Alternative diagnostic approaches to prevent unnecessary diagnostic hemithyroidectomy are vast, with molecular diagnostics, assessing the genetic changes in these lesions, and molecular imaging using [^{99m}Tc]Tc-sestamibi scintigraphy or [^{18}F]FDG-PET/CT, as most promising techniques [5].

The authors of this French consensus document discuss the value of molecular imaging [1] including our meta-analysis [6] and modelled cost-effectiveness [7] of the diagnostic value of [^{18}F]FDG-PET/CT. Because the "excellent diagnostic performance" specifically in larger nodules are contradicted by more recent studies and meta-analyses, they come to the conclusion that both visual and quantitative "[^{18}F]FDG-PET/CT is not recommended for FNAC-indeterminate thyroid nodules (Bethesda 3–4), due to suboptimal NPV in recent studies and the lack of added value over and above combined ultrasound/cytology. Grade A ++" (Recommendation 5.7) [1]. The same observations have led the American Thyroid Association 2015-guideline on thyroid nodules "not to routinely recommend for the evaluation of thyroid nodules with indeterminate cytology" (Recommendation 18: Weak recommendation, Moderate-quality evidence) [4]. It seems therefore the authors have taken over this conclusion without re-assessing recent literature as we fully disagree with their conclusion.

Based on this lack of high-quality evidence, we have undertaken a nationwide randomised-controlled trial in 15 academic and non-academic centres ("Efficacy of [^{18}F]FDG-PET in Evaluation of Cytological indeterminate Thyroid nodules prior to Surgery (EfFECTS)", NCT02208544), the main results of which were published earlier this year [8–12]. We've randomised (2:1) 132 patients with centrally revised indeterminate cytology to either an arm driven by the result of centrally blindly read [^{18}F]FDG-PET/CT and an arm in which all patients underwent diagnostic hemithyroidectomy regardless the result of the [^{18}F]FDG-PET/CT. Patients managed without surgery (i.e. with negative [^{18}F]FDG-PET/CT) were followed up by their endocrinologists according to the risk of a benign nodule, including an ultrasonography after one year. We prospectively collected clinical data, healthcare usage, quality of life, direct and indirect costs of each of these patients.

The [^{18}F]FDG-PET/CT-driven approach indeed did reduce the number of futile surgeries by 40% (48% in non-Hürthlecell nodules). No malignant or borderline tumours were observed in patients under surveillance. Sensitivity, specificity, negative and positive predictive value, and benign call rate of [^{18}F]FDG-PET/CT were 94.1%, 39.8%, 95.1%, 35.2% and 31.1%, respectively, which was fully in line of our 2011 meta-analysis [6]. This observed high NPV fits the American Thyroid Association 2015-guideline statement that "one could surmise that [...] an ideal "rule-out" test would have a NPV similar to a benign cytologic diagnosis (96.3%) (predictive value estimates based on a recent meta-analysis of performance of the Bethesda system), and these would hold true with a reasonable degree of precision and reproducibility." [4].

None of the (few) patients crossing over in the study for fear of missed diagnosis or persistent obstructive complains of a nodule suffered from malignancy. Mean one-year societal costs, adjusted for imbalance in malignancy rate in both study arms despite successful stratification, were almost €7000 lower in the [^{18}F]FDG-PET/CT-driven approach. This included additional diagnostics and other costs due to incidental findings in the skull-base to aortic arch PET/CT-acquisition. Extending the one-year window to a life-long horizon confirmed that this imaging-driven approach is cost-effective both for direct and societal costs with almost €10,000 lifetime reduction in costs [10]. The reassurance of a negative [^{18}F]FDG-PET/CT resulted in sustained health-related quality of life throughout the first year of active surveillance. Diagnostic surgery for a nodule with benign histopathology resulted in more cognitive impairment and physical problems including cosmetic complaints, but improved goitre symptoms and anxiety. Anxiety was also reduced in patients with malignant histopathology [9]. Quantitative analyses confirmed that an [^{18}F]FDG-PET/CT-driven approach is specifically effective in non-Hürthle nodules, although it suggested that using a different cut-off of the Standardised Uptake Value in Hürthle nodules, might improve the diagnostic value of [^{18}F]FDG-PET/CT in this subcategory of patients [11]. We could not find image-based or immunohistochemical markers that explain the difference between true and false [^{18}F]FDG-positive nodules [8,11] and are currently preparing a manuscript on the comparative value of molecular imaging and molecular diagnostics in our cohort.

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Critics could dismiss our findings because of the relatively short follow-up of only one year, which was chosen due to rules set by the grant provider (Dutch Cancer Society). All patients are currently still in clinical follow-up (up to 5 years), and up-to-date no missed malignancies have been reported. Long-term analyses of our cohort are scheduled in 2025.

Thus we, truly believe that that data from the Dutch EfFECTS-trial confirm earlier publications by our group as well as others: the use of [^{18}F]FDG-PET/CT in cytologically indeterminate thyroid nodules prevents unbeneficial diagnostic thyroid surgery, is oncologically safe, cost-effective and preserves quality of life. Its use is practice changing, should be offered to any patients scheduled for diagnostic surgery for indeterminate thyroid FNAC, and will be part of the updated Dutch national guideline (expected end of 2023).

Author contribution

Lioe-Fee de Geus-Oei, Wim J.G. Oyen, and Dennis Vriens conceptualised the EfFECTS-study. Lioe-Fee de Geus-Oei was the project leader. Wim J.G. Oyen and Dennis Vriens were principal investigators. Elizabeth J. de Koster was the junior investigator. Dennis Vriens prepared the manuscript of this Letter. All authors contributed to data acquisition and the interpretation of the data of the EfFECTS-study, and critically reviewed this manuscript (and other EfFECTS-related manuscripts). All authors had full access to all the data in the study and approved any manuscript before submission. Dennis Vriens had final responsibility for the decision to submit for publication.

Disclosure of interest

The authors declare that they have no competing interest.

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References

[1] Thuillier P, Benisvy D, Ansquer C, Corvilain B, Mirallie E, Taieb D, et al. Section 5: what is the role of functional imaging and isotopic treatment? Ann Endocrinol (Paris) 2022;83:401-6, http://dx.doi.org/10.1016/j.ando.2022.10.008.
[2] Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS. The diagnosis and management of thyroid nodules: a review. JAMA 2018;319:914–24, http://dx.doi.org/10.1001/jama.2018.0898.
[3] Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid 2017;27:1341–6, http://dx.doi.org/10.1089/thy.2017.0500.
[4] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26:1–133, http://dx.doi.org/10.1089/thy.2015.0020.
[5] De Koster EJ, De Geus-Oei LF, Dekkers OM, Van Engen-Van Grunsven I, Hamming J, Corssmit EPM, et al. Diagnostic utility of molecular and imaging biomarkers in cytological indeterminate thyroid nodules. Endocr Rev 2018;39:154–91, http://dx.doi.org/10.1210/er.2017-00133.
[6] Vriens D, De Wilt JH, Van Der Wilt GJ, Netea-Maier RT, Oyen WJ, De Geus-Oei LF. The role of [18F]-2-fluoro-2-deoxy-d-glucose-positron emission tomography in thyroid nodules with indeterminate fine-needle aspiration biopsy: systematic review and meta-analysis of the literature. Cancer 2011;117:4582–94, http://dx.doi.org/10.1002/cncr.26085.
[7] Vriens D, Adang EM, Netea-Maier RT, Smit JW, De Wilt JH, Oyen WJ, et al. Cost-effectiveness of FDG-PET/CT for cytologically indeterminate thyroid nodules: a decision analytic approach. J Clin Endocrinol Metab 2014;99:3263–74, http://dx.doi.org/10.1210/jc.2013-3483.
[8] De Koster EJ, Van Engen-Van Grunsven ACH, Bussink J, Frielink C, De Geus-Oei LF, Kusters B, et al. [(18)F]FDG uptake and expression of immunohistochemical markers related to glycolysis, hypoxia, and proliferation in indeterminate thyroid nodules. Mol Imaging Biol 2022;online ahead of print, http://dx.doi.org/10.1007/s11307-022-01776-4.
[9] De Koster EJ, Husson O, Van Dam E, Mijnhout GS, Netea-Maier RT, Oyen WJG, et al. Health-related quality of life following FDG-PET/CT for cytological indeterminate thyroid nodules. Endocr Connect 2022;11(8):e220014, http://dx.doi.org/10.1530/EC-22-0014.
[10] De Koster EJ, Vriens D, Van Aken MO, Dijkhorst-Oei LT, Oyen WJG, Peeters RP, et al. FDG-PET/CT in indeterminate thyroid nodules: cost-utility analysis alongside a randomised controlled trial. Eur J Nucl Med Mol Imaging 2022;49:3452–69, http://dx.doi.org/10.1007/s00259-022-05794-w.
[11] De Koster EJ, Noortman WA, Mostert JM, Booij J, Brouwer CB, De Keizer B, et al. Quantitative classification and radiomics of [(18)F]FDG-PET/CT in indeterminate thyroid nodules. Eur J Nucl Med Mol Imaging 2022;49:2174–88, http://dx.doi.org/10.1007/s00259-022-05712-0.
[12] De Koster EJ, De Geus-Oei LF, Brouwers AH, Van Dam E, Dijkhorst-Oei LT, Van Engen-Van Grunsven ACH, et al. [(18)F]FDG-PET/CT to prevent futile surgery in indeterminate thyroid nodules: a blinded, randomised controlled multicentre trial. Eur J Nucl Med Mol Imaging 2022;49:1970–84, http://dx.doi.org/10.1007/s00259-021-05627-2.

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