Preoperative stratification of cytologically indeterminate thyroid nodules by [18F]FDG-PET: can Orpheus bring back Eurydice?

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LETTER TO THE EDITOR

Preoperative stratification of cytologically indeterminate thyroid nodules by [^{18}F]FDG-PET: can Orpheus bring back Eurydice?

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Dear Sir,

According to Virgil's ancient myth, the legendary lyrist Orpheus of Thrace decided to descend to the Underworld to see his wife Eurydice after a snake bite had caused her untimely death. Singing his grief with his lyre, he convinced Hades and Persephone to ascend into the world of the living together with Eurydice. The sole condition was that she would follow him without him looking back as they walked. Unable to hear her footsteps, Orpheus feared the Gods had fooled him. At the verge of the underworld's exit, just before bright daylight would have embodied Eurydice's shade, Orpheus lost faith and turned around, only to see Eurydice vanish, now eternally trapped in Hades' reign.

Thyroid nodules are increasingly diagnosed, mainly due to the increased use of medical imaging. To rule out malignancy, cytologic analysis of fine-needle aspiration biopsy (FNAB) material is the primary modality for initial evaluation [1]. In 2007, the National Cancer Institute convened a conference to define consistent thyroid cytology terminology, including the risk of malignancy (RoM). This resulted in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which has since been widely adopted [2]. More recently, nodules diagnosed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and follicular tumour of uncertain malignant potential (FTUMP) were defined as benign yet potentially premalignant lesions, for which surgery is considered justified. Additionally, ultrasound-based risk-stratification systems such as Thyroid Imaging Reporting and Data System (TI-RADS) are finding their way into the clinic, aiding to the decision which nodules need to be biopsied and guiding the location of the sampling [1].

TBSRTC stratifies FNAB samples to five categories of increasing RoM, after excluding nondiagnostic or unsatisfactory FNAB (Bethesda I, RoM 5–10%) which require a repeat US-guided biopsy. At the lower end of the spectrum, benign lesions (Bethesda II, RoM 0–3%), require only clinical and sonographic follow-up. At the higher end, lesions suspicious for malignancy (Bethesda V, RoM 50–75%[1]) or malignant (Bethesda VI, RoM 97–99%[1]), require near-total thyroidectomy or lobectomy. For the intermediate, rather heterogeneous group of nodules with indeterminate cytology, the TBSRTC does not provide clear answers. This includes cytology with atypia or follicular lesion, both of undetermined significance (Bethesda III, RoM 10–30%[1]) and cytology (suspicious for a) follicular or Hürthle cell neoplasm (Bethesda IV, RoM 25–40%[1]). Bethesda III and IV nodules require repeat FNAB (Bethesda III only), molecular diagnostics and/or diagnostic lobectomy. In a recent large series, the nodules that were selected for biopsy by TI-RADS showed an indeterminate outcome in 14%, in unselected nodules even 20% [3].

This article is part of the Topical Collection on Editorial.

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[1] For presented RoM's, NIFTP is counted as malignancy. When NIFTP is considered benign, the RoM for Bethesda III, IV, V and VI is 6-18%, 10-40%, 45-60% and 94-96%, respectively [2].

Thus, thyroid nodules with indeterminate cytology are posing a frequent and difficult dilemma for clinical decision-making. Different preoperative approaches including ex vivo analysis of cytology and in vivo clinical imaging have been investigated to further stratify these nodules and to prevent futile diagnostic lobectomies with associated complications as well as financial and quality-of-life-related sequelae [4]. Of these stratifying tests, molecular diagnostics and molecular imaging using [^{99m}Tc]Tc-sestamibi and [^{18}F]FDG seem the most promising.

After first, somewhat disappointing report of 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) imaging of thyroid tumours using a conventional Anger camera in 1988 [5], two follow-up studies in 1993 successfully showed that imaging of [^{18}F]FDG using positron emission tomography (PET) could discern malignant from malignant nodules [6, 7]. Encouraged by our own pre-Bethesda experience [8], a meta-analysis of available literature [9] and modelled cost-effectiveness [10], it was concluded that a negative [^{18}F]FDG-PET, obtained in 37% of patients, shows sufficient negative predictive value (NPV, 96%) to rule-out malignancy while being cost-effective, specifically for nodules larger than 15 mm when using the PET systems available up to 2010. The remaining RoM of 3.6% was very comparable to that of a Bethesda II nodule, the definition of an "ideal rule-out test" according to actual guidelines [1]. Despite these findings, in their 2015 guidelines, the American Thyroid Association does not routinely recommend [^{18}F]FDG-PET imaging for the evaluation of thyroid nodules with indeterminate cytology (Recommendation 18: Weak recommendation), and therefore, the guideline neither endorses nor discourages its use [1]. The reasoning was rather limited, moderate-quality evidence, likely fed by co-existent variable and sometimes conflicting data [11–16].

Several causes have been attributed to the disappointing findings following initial promising work. These include improved cytology classification, inclusion of smaller lesions and shift from PET-only to hybrid PET-CT imaging. As earlier work was from the pre-TBSRTC-era, it is likely that improved stratification between Bethesda II and Bethesda V/VI may leave less aggressive histopathological diagnosis and thus less [^{18}F]FDG-avid variants in the indeterminate cytology group [17]. Another explanation of decreasing NPV over time include the increasing number of smaller malignancies reported in studies. Indeed, false-negative [^{18}F]FDG-PET-CT is often observed for sub-centimetre lesions [18, 19] and a positive relation between nodule size and NPV has been described [9]. Technical advances in PET-hardware and reconstruction algorithms have led to improvement in imaging resolution and signal-to-background ratio. This development, including the fact that most recent studies exclude sub-centimetre nodules and consider (sub) millimetric carcinomas a coincidence rather than a false-negative malignancy, however, has not led to less false-negative cases and still malignancies up to 20 mm have been described to be [^{18}F]FDG-nonavid [17].

The third cause, the transition from PET-only to hybrid PET/CT imaging, was specifically addressed by two recent meta-analysis, analysing over 1000 nodules in over 20 independent cohorts. These show large ranges in observed sensitivities (0–94%, pooled: 73–74%) and specificities (41–91%, pooled: 56–58%) [15, 16]. A better performance of [^{18}F]FDG-PET-only studies as compared to hybrid PET-CT studies is reported, mainly due to better sensitivity (pooled 95% versus 73%) but comparable specificity (pooled 58% versus 56%) [16]. NPVs should be interpreted with caution as post-test probabilities, including predictive values and benign call rates, not only depend on test characteristics (i.e., sensitivity and specificity) but also pre-test probability (i.e., RoM) which varied widely from 4.2 to 50% among studies included. Pooled NPV was 99% for PET-only imaging, but varied from 74 to 91% for PET/CT with rather robust but limited positive predictive values similar to previous work (34–37%) [15, 16] and similar to the RoM of [^{18}F]FDG-incidentalomas in random patients [20, 21]. Also, the prevalence of a negative test, i.e., the benign call rate, varied between 37 and 92% between studies [15, 16]. The variation in RoM clearly reflects heterogeneity of the study populations including whether or not to include FTUMP and NIFTP as benign lesions; the variation in sensitivities reflects large differences in methodology. Drilling down in the three studies with strikingly high false-negative rates of 8–19% [18, 22, 23] suggests that at least the inclusion of incidental, clinically irrelevant carcinomas in the millimetre range contributed in one study [23]. Qichang et al. tried to explain the apparent difference in the performance of PET-only versus hybrid PET-CT by speculating that atypical [^{18}F]FDG uptake in the neck (tonsils, pharynx, cervical lymph nodes and other thyroid nodules) may have been falsely attributed to a nearby false-negative thyroid nodule under study on PET-only imaging, which would not have been the case if hybrid PET-CT was performed. Furthermore, they argue that the definition of a positive PET was less strict in the earlier PET-only studies, causing this misinterpretation to occur more often [16].

The call for large, prospective, multicentre studies with unified image interpretation protocols, incorporating the evolving TBSRTC and uniform appraisal of lesion such as FTUMP and NIFTP encouraged us to design and execute 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 were published earlier this year in EJNMMI [24–26]. We randomised 132 patients with indeterminate (Bethesda III and IV) cytology to either the experimental arm (diagnostic hemithyroidectomy only when the nodule was FDG-positive) or standard of care (diagnostic hemithyroidectomy regardless of the result of the [^{18}F]FDG-PET/CT). Patients

in the experimental arm who were managed without surgery (i.e., 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.

The [^{18}F]FDG-PET/CT-driven approach indeed did reduce the number of futile surgeries by 40% (48% in non-Hürthle cell 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 [24]. This was fully in line of our 2011 meta-analysis [9] and the observed high NPV fits the American Thyroid Association 2015-guideline statement on an ideal "rule-out test" [1].

In the group of patients with a negative FDG-PET/CT, very few patients crossed over in the study from watchful waiting to surgery for fear of missed diagnosis or persistent obstructive complains of a nodule. None of these had a malignancy. The 2/132 [^{18}F]FDG-PET/CT scans considered a false-negative were difficult to classify and required next-generation sequencing to determine the nature of the nodule [24]. Mean 1-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 1-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 [26]. 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 [27]. Quantitative analyses confirmed that an [^{18}F]FDG-PET/CT-driven approach is specifically effective in non-Hürthle cell nodules, although it suggested that using a different cutoff of the Standardised Uptake Value in Hürthle cell nodules might improve the diagnostic value of [^{18}F]FDG-PET/CT in this subcategory of patients [25]. We could not find image-based or immunohistochemical markers that explain the difference between true and false [^{18}F]FDG-positive nodules [25, 28] and are currently preparing a manuscript on the comparative value of molecular imaging and molecular diagnostics in our cohort.

Admittedly, initial follow-up was relatively short with a final evaluation after only 1 year, which was chosen due to rules set by the grant provider (Dutch Cancer Society). However, all patients remained in clinical follow-up up to 5 years, and to date, no missed cancer diagnoses have been reported. Long-term analyses of our cohort are scheduled in 2025. Secondly, during the execution of the trial, TI-RADS stratification of thyroid nodules by ultrasound characteristics was not routinely performed in the Netherlands. As it is currently being incorporated in routine clinical care, it might influence the RoM of selected cytologically indeterminate thyroid nodules and thus benign call rate and NPV of [^{18}F]FDG-PET/CT.

In conclusion, 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).

We call to push forward now and not to look back until the role of [^{18}F]FDG-PET/CT in cytologically indeterminate thyroid nodules has embodied in the bright daylight of guidelines. Looking back too soon might send back Eurydice to the Underworld forever and even Orpheus was not able to undertake a return trip to Hades a second time.

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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 Editorial. 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.

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Data availability The study protocol and datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. Data requestors will need to sign a data access agreement and in keeping with patient consent for secondary use and obtain ethical approval for any new analyses.

Declarations

Ethical approval The EfFECTS trial was conducted according to the principles of the Declaration of Helsinki (version of the 59th WMA General Assembly, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO), the European Union (EU) General Data Protection Regulation (GDPR), the National Thyroid Cancer guideline and the local (hospital) guidelines.

Consent to participate Written informed consent was obtained from all participants prior to any study activity. The study protocol was approved by the Medical Research Ethics Committee on Research

Involving Human Subjects region Arnhem-Nijmegen, Nijmegen, the Netherlands. The trial was overseen by a trial steering committee and an independent study safety committee. The funder of the study had no role in its design, data collection and analysis, or writing of this report.

Competing interests The authors declare no competing interests.

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