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EDITORIAL COMMENTARY

Differentiated thyroid cancer incidentally detected by ^{18}F-FDG PET/CT: patient's future in a hot-spot?

Silvia Morbelli · Marcello Bagnasco

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In modern medicine, the term incidentaloma refers to a lesion that is discovered during an unrelated procedure either imaging or surgical [1]. In recent decades the chance of finding an incidentaloma has increased as a result of both imaging-based health screening programmes and improved resolution of diagnostic imaging modalities [2]. An increasing number of thyroid incidentalomas is certainly one of the causes of the so-called "thyroid cancer epidemic", i.e. the increase in the number of differentiated thyroid cancers (DTC) [3]. The widespread use of ultrasonography (US) and subsequent fine-needle aspiration biopsy undoubtedly coincided with the larger number of small, clinically occult thyroid cancers [3]. Another source of thyroid incidentalomas is the increasing rate of reporting of thyroid lesions during other nonthyroid imaging investigations (carotid US imaging, CT, ^{18}F-FDG PET [4]. In this context, incidentalomas discovered on US imaging have in particular been connected to possible overdiagnosis. In fact, the rising number of DTC may mainly refer to detection of cancers which would not have caused any relevant health problem if undetected [3, 5]. In contrast, given the exquisite functional/metabolic nature of ^{18}F-FDG PET, incidental discovery of DTC by means of PET may not provide a simple unexpected diagnosis of cancer. Together with the diagnosis, this PET finding may carry relevant prognostic information that could even be taken into account in the early and long-term management of the patient.

In the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging* Piccardo and colleagues [6] present the results of a multicentre study of the prognostic relevance of thyroid ^{18}F-FDG "hot-spots" whose reporting during scans performed for other reasons led to the incidental diagnosis of DTC. They analysed 54 patients in whom focal ^{18}F-FDG uptake on PET was due to a DTC and who were then clinically followed up over time. All the patients, independent of tumour size, staging or any other variable, underwent total thyroidectomy, ^{131}I remnant ablation (RAI) and levothyroxine suppressive therapy, and were followed up according to published guidelines both in case of recurrence as well as in case of non-evidence of disease [7]. The baseline scans which had originally resulted in the discovery of the DTC were retrospectively analysed. The ratio between SUVmax of DTC and SUVmean of the liver (SUV ratio) was recorded for each scan. All clinical data obtained during the follow-up were used to assess the response to initial therapy and patient outcome. The relationships among SUVmax, SUV ratio, disease persistence/progression and other risk factors (T, N, M and histological subtype) were evaluated. The SUV ratio of the incidentally discovered DTC was significantly higher in patients showing persistence of disease after initial treatment and in patients classified as high risk according to the European Thyroid Association (ETA) risk stratification system. Moreover, high ^{18}F-FDG uptake was found in the majority of DTC patients with T3/T4 primary tumour (70 %), locoregional involvement (67 %), distant metastases (75 %) and aggressive histological subtypes (64 %). In a univariate analysis, SUV ratio, tumour size, nodal status, distant metastases and histological subtype were all significantly associated with disease persistence/progression. Finally, when risk estimates were adjusted for all variables, tumour size remained the only independent predictor of persistence/progression. However, a trend toward a higher risk of disease persistence/progression was seen in patients with a SUV ratio ≥3.

Previous studies have demonstrated that the level of ^{18}F-FDG uptake by DTC lesions may have prognostic value especially in patients with metastases, as lesions with high

S. Morbelli (✉)
Nuclear Medicine Unit, IRCCS AOU San Martino – IST, Department of Health Sciences, University of Genoa, Genoa, Italy
e-mail: silviadaniela.morbelli@hsanmartino.it

M. Bagnasco
Autoimmunity Unit, IRCCS AOU San Martino – IST, Department of Internal Medicine, University of Genoa, Genoa, Italy

uptake tend to be less differentiated and to behave more aggressively [8, 9]. ^{18}F-FDG uptake by the primary DTC has also been linked with aggressive histological features, tumour size and lymph node metastases [10, 11]. In their analysis, Piccardo and colleagues have taken a step forward on these prognostic issues as they linked ^{18}F-FDG intensity of the thyroid hot-spot which resulted in the discovery of DTC with the future of the patients. These aspects are particularly interesting considering the increased emphasis given to individual and "ongoing" estimates of risk to guide both initial therapy and follow-up in DTC patients [12]. Indeed, both the ETA [7] and the American Thyroid Associations [13] risk stratification systems have proved to be a good starting point for initial decision making in DTC patients, but they are less accurate in predicting long-term outcome [14]. For these reasons, ongoing risk stratification has been proposed for adjusting the risk over time on the basis of accumulated clinical data [12, 15, 16]. As prognosis is good and response to treatment is high in most DTC patients, one of the goals proposed for such a risk-adapted approach is to identify and appropriately treat the nearly 30 % of patients who may experience a clinically significant recurrence [12]. In this context, the work of Piccardo and colleagues suggests the possibility of some type of early "discovery-related" risk stratification in DTC. Decision making in DTC patients starts with the extent of thyroid surgical resection and the use of RAI, and goes on with the intensity of follow-up and the modalities used to detect recurrent disease [12]. According to published guidelines [7, 13], near-total or total thyroidectomy is proposed even with tumours <1 – 1.5 cm if patients have regional or distant involvement. However metastases (notably, distant ones) may not be detected during presurgical staging. As Piccardo et al. found that a high SUV ratio characterizes the primary DTC in patients with distant metastases and locoregional involvement, the intensity of ^{18}F-FDG uptake might be taken into account in the surgical planning in patients with DTC incidentally discovered on PET.

Similarly, Law and Lang found that DTC incidentally detected by ^{18}F-FDG PET had significantly higher frequency of tumour bilaterality than DTC incidentally detected by US despite comparable tumour size, tumour multifocality, extrathyroidal extension and capsular invasion [15]. Accordingly, given the high frequency of tumour bilaterality and the poor ability of preoperative imaging to detect the contralateral tumour focus, these authors have proposed total thyroidectomy for ^{18}F-FDG PET-detected DTC even for tumour sizes <1 cm [15]. After surgery, published guidelines recommend the routine use of RAI in patients at high risk and but not in patients at very low risk; however, a relevant proportion of patients fall into a category where evidence for or against the use of RAI is conflicting, thus leaving the decision regarding its use to be made on an individual basis [12]. In DTC incidentally discovered on PET, the intensity of ^{18}F-FDG uptake might represent a new variable to be included in the equation for the appropriate use of RAI. This information would be available before treatment initiation (when it is actually useful for the clinician) and it might contribute to more objective decision making in cases where RAI use is only selective.

Given the lack of prospective data and the large number of patients with no evidence of disease after the first treatment, no paradigms have taken into account the impact of using ^{18}F-FDG PET in the follow up of DTC which are known to concentrate ^{18}F-FDG from baseline (as they were specifically discovered by means of PET). However, in this selected group of patients when relapse is suspected or proven, we could hypothesize a greater impact of ^{18}F-FDG PET with respect to what might be expected in the general population of patients with DTC. Given the known ^{18}F-FDG avidity of these primary DTC, several questions may concern the referring clinician if recurrence is present or suspected:

- Will the sites of recurrence be radioiodine-avid or ^{18}F-FDG-avid (or both), and will they produce sufficient amounts of thyroglobulin to allow detection of recurrent disease?
- Will the metastases become RAI-refractory more frequently or more quickly than in other patients?

Although performing ^{18}F-FDG PET scans in the restaging of this type of patient may answer these questions at the single patient level, prospective studies including a larger number of patients would be needed to clarify these issues. Finally, it has to be underlined that Piccardo and colleagues included patients with DTC incidentally discovered on PET and thus characterized by "visually" detectable uptake (hot-spots). As stated by the authors themselves, from a theoretical point of view, it would be more appropriate also to include patients with DTC with an available baseline PET scan performed for other reasons and with no ^{18}F-FDG avidity at the site of the primary DTC. To partially overcome this problem, Piccardo and colleagues broke down their patients according to the intensity of tracer uptake into low (SUV ratio <3) and high (SUV ratio ≥3) ^{18}F-FDG-avid primary DTC. Although this subgrouping was sufficient to show that the group with SUV ratio ≥3 have a risk of disease persistence about 12-fold higher than patients with SUV ratio <3, this finding needs to be further addressed with a proper case-control approach.

In conclusion the prognostic and diagnostic value of ^{18}F-FDG PET is well established in patients with metastatic lesions especially in not-iodine concentrating genotypes. By contrast, ^{18}F-FDG PET is not recommended in the presurgical staging of DTC. However, when levels of ^{18}F-FDG uptake by primary DTC are known from incidental discovery on PET, this information should not be neglected during a patients' management. The future behaviour of a

DTC might be somehow predicted from the intensity of ^{18}F-FDG uptake in the primary tumour. Further prospective studies are needed on this topic: it undoubtedly does not concern the majority of DTC patients, but a peculiar group of them who – not to be forgotten – are often afflicted with another neoplasia and whose age distribution is possibly peculiar as well. Nevertheless, considering ^{18}F-FDG uptake of the primary tumour in these patients does follow the modern path of individualizing the management and treatment of cancer patients.

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