PET imaging for thyroid cancers: Current status and future directions

Imagerie TEP dans les cancers thyroïdiens : position actuelle et perspectives

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Abstract

Positron emission tomography–computed tomography (PET/CT) combines both functional and anatomic information and provides in vivo molecular information on biological processes that can be useful at different steps of evolution of thyroid cancers. 18F-Fluorodeoxyglucose being highly trapped in rapidly dividing cells makes 18F-FDG-PET recommended in the staging, prognostic evaluation and follow-up of metastatic and/or of poorly differentiated thyroid carcinomas. 18F-FDG PET/CT can help in the localization of persistent/recurrent disease. However, its sensitivity depends widely on tumor burden and histology. Iodine 124 (124I) is currently under evaluation for diagnosis and pretherapeutic dosimetry planning. PET/CT using 124I-FDOPA is the most sensitive radiopharmaceutical for localizing persistent/recurrent medullary thyroid carcinoma (MTC). However, its sensitivity depends on calcitonin levels, with a threshold value of around 150 pg/mL. 18F-FDG PET/CT can also be used in MTC with short calcitonin or CEA doubling time.

Keywords: Thyroid carcinoma; FDG-PET; Iodine-124; FDOPA

1. Introduction

Despite complete initial treatment, some thyroid cancer patients may have persistent disease or recurrent disease, with possible distant metastases. PET/CT is a high-resolution functional imaging technique that can guide thyroid cancer patient management. We will discuss thyroid incidentaloma detected by 18F-FDG-PET, the role of 18F-FDG-PET in thyroid cancers of follicular origin and the use of PET imaging for medullary thyroid carcinoma (MTC).

2. Thyroid incidentaloma on 18F-fluorodeoxyglucose PET (18F-FDG-PET)

It is not uncommon to identify intrathyroid 18F-FDG uptake on PET examinations performed in oncology context or not, also
called thyroid incidentaloma. Diffuse and homogeneous tracer uptake is usually related to thyroiditis. In contrast, intrathyroid focal uptake must be further investigated since it can be due to a primary thyroid carcinoma in about a 1/3 of cases, even in a context of extrathyroid oncology [1]. It warrants cytologic documentation in case of supra-centimeter lesion and if a specific treatment would be consistent with the patient prognosis.

3. PET for thyroid cancer of follicular cell origin

3.1. Stadiﬁcation and restadiﬁcation

During disease follow-up, the rise or persistence of abnormal thyroglobulin (Tg) level most often corresponds to lymph node metastases. It may lead to an empiric treatment with iodine-131 (131I) in absence of identiﬁed resectable tumor mass. In this situation, it is not uncommon to get no abnormal 131I focus on post-therapy whole body scintigraphy (131I PT-WBS).

18F-FDG-PET can play a role in the diagnosis of tumor persistence/recurrence. In this setting, Leboulleux et al. found 16% sensitivity for 131I scan vs 88% for 18F-FDG-PET [2]. This study gathered 34 patients, including 50% of stage III disease and 24% of aggressive histology sub-types. The median Tg level (in the absence of TgAb) measured after thyroid hormone withdrawal (THW) on the day of the empiric 131I administration was 47 ng/mL (range: 4–3230; mean: 290). Only one patient had a normal 18F-FDG-PET and an abnormal 131I PT-WBS. Therefore, the authors suggest to start with 18F-FDG-PET and to proceed empirically with 131I treatment only in case of negative 18F-FDG-PET finding.

We will now focus on the factors inﬂuencing the pre-test probability.

In most of the studies, a non-stimulated Tg level greater than 10 μg/L is often recognized as having a sufﬁcient pretest probability to get information on 18F-FDG-PET with a therapeutic impact [3–5]. 18F-FDG-PET sensitivity varies with Tg level, reﬂecting tumor burden in the majority of cases. Indeed, studies reported values rising from 53 up to 85% when Tg varies from 5.5 up to 29 μg/L [5–7]. A meta-analysis gathering 25 studies including 789 patients with biochemical residual disease but negative 131I WBS, reported a 18F-FDG-PET sensitivity and speciﬁcity of 88.5% and 84% respectively [8]. The pre-test probability increases in case of aggressive histology (mostly tall cell papillary carcinoma) [9], a locally advanced disease [10], Tg level and a short Tg level doubling time [10–12] or presence of persistent anti-Tg antibodies [13].

As 18F-FDG uptake is not speciﬁc of neoplastic lesions, inﬂammatory nodes in the neck may be responsible of false positive results. Therefore, cytology examination and Tg measurement in (ultrasound guided) ﬁne-needle aspiration is warranted on suspected lesions before surgical resection. When Tg is highly increased, a thoracic scan should complete 18F-FDG-PET in order not to miss small pulmonary nodules that may not be seen on the CT component of PET-CT performed in spontaneous breathing, or would be responsible of false negative on PET imaging due to partial volume effect.

The role of rhTSH before 18F-FDG-PET remains unclear as there has been no study reporting a signiﬁcant impact of stimulation on 18F-FDG-PET sensitivity. Leboulleux et al. observed more lesions per organ in the rhTSH arm but not more patients, leading to a change in disease management in only 6% of the patients [14]. Therefore, rhTSH stimulation before 18F-FDG-PET should not be systematically performed. However, concomitant 18F-FDG-PET can complete stimulated 131I PT-WBS [10]. Indeed, in a group of 38 patients with aggressive thyroid carcinoma (45% tall cells and 42% poorly differentiated), 41% of the lesions were only seen on 18F-FDG-PET and 31% on 131I PT-WBS [9].

The lack of sensitivity of 131I scan can be partially corrected by high resolution iodine-124 PET (124I-PET). As expected, studies such as Van Nostrand’s showed a superiority of 124I-PET when compared to diagnostic planar 131I WBS [15]. In contrast, when 124I-PET is compared to 131I PT-WBS, the results are highly variable [16–20]. Discrepancies are observed especially on cervical lymph nodes, but more surprisingly in case with miliary lung dissemination obviously seen on 131I PT-WBS but totally missed on 124I-PET [21]. So far, two studies compared 124I-PET and 131I PT-SPECT-CT [19,20]. In the study from de Pont et al. including 20 patients, per-patient analysis found 5% complete discordance and 45% partial discordances between both imaging modalities and 124I-PET was still the most sensitive imaging modality but missed one lung miliary. On the other side, Ruhlmann et al. gathered 137 patients and found a 95% level of agreement. Khorjekar et al. [18] reported the most surprising results with 12 patients having high stimulated Tg (median: 60 ng/mL; min 0.2–max 2480) but normal “diagnostic” no abnormal focus on 74 MBq 131I WBS and 63.9 MBq 124I-PET. When patients underwent 131I therapy, 131I PT-WBS demonstrated suspicious foci in 10/12 patients. Therefore, a negative 124I-PET failed to rule out the need of empiric radiiodine therapy.

The first explanation could be related to the too low amount of injected activity. 124I administered activities vary from 28 up to 74 MBq, and is injected or ingested. Beijst et al. investigated on phantoms whether the reported discrepancies may be ascribed to a difference in lesion detectability between 124I-PET/CT and 131I SPECT/CT and, hence, whether the administered 124I activity is sufﬁcient to achieve equal detectability estimated with the detectability equivalence percentage (DEP) [22]. An activity of 90 MBq is sufﬁcient to achieve similar detectability for lesion diameters of up to 17 mm on PSF TOF PET, with DEPs up to 1.8%. On the basis of DEPs of 3.5% for lesion diameters of up to 17 mm on no-PSF no-TOF PET, 124I activities as high as 170 MBq may be warranted to obtain equal detectability.

The second explanation could also be the way of stimulation before 124I PET/CT. Van Nostrand et al. found in a limited number of patients that thyroid hormone withdrawal would signiﬁcantly enhance the number of foci on 124I-PET when compared to rhTSH stimulation [15]. The percentages of patients having positive foci detected on the 62.9 MBq rhTSH 124I-PET and THW 124I-PET scans were 29% (7/24) and 63% (10/16), respectively (P < 0.03), which was also observed with the 74 MBq 131I WBS.
When $^{18}$F-FDG-PET and $^{124}$I-PET are performed in patients with elevated Tg level but no lesion identified on neck ultrasound, discrepancies were observed in 2/3 of the 20 included patients [23]. Sensitivities were 80% for $^{124}$I-PET, 70% for $^{18}$F-FDG-PET and 91% respectively for both modalities combination.

However, we do need to remind that most thyroid cancers have a good prognostic and that repeated examinations during patient follow-up has been found to be increased these last decade without any change on patients overall survival [24].

### 3.2. Prognostic value

In 10% of patients, metastases may occur at initial stage or during patient follow-up. An intense $^{18}$F-FDG tumors uptake phenotype is associated with resistance to $^{131}$I and in consequence worsens patient survival, as first demonstrated by Robbins [25,26]. Indeed, Lazar et al. demonstrated a decrease in iodine/sodium symporter expression whilst an increase in glucose transporter Glut1 in dedifferentiated thyroid tumor cells, also called on functional imaging a “Flip-flop” phenomena (Fig. 1) [27]. Poorly differentiated often demonstrate intense $^{18}$F-FDG tumor uptake [28,29], up to 100% of anaplastic thyroid carcinoma [30]. $^{18}$F-FDG-PET is the reference for imaging disease extension of poorly differentiated carcinoma and to metabolically characterize metastases. Once again, it completes $^{131}$I WBS and therefore can be systematically performed concomitantly to $^{131}$I therapy in case of bad prognosis histology.

### 3.3. Therapeutic monitoring

Patients with progressive refractory thyroid cancer should be treated with tyrosine kinase inhibitors (TKI) which also act as antiangiogenic agents. $^{18}$F-FDG-PET scans may help in evaluating treatment response. Thus, RECIST 1.1 criteria consider as progressive disease, the occurrence of a new focus of $^{18}$F-FDG uptake which has to be confirmed on CT or MRI. The next step will be the systematic use of PERCIST criteria into clinical trials [31].

### 3.4. Perspectives

The “Flip-Flop phenomena” can be reversible. Indeed, NIS expression inhibition related to MAP-kinase activations can be blocked by some TKI such as a MEK inhibitor [32,33]. After 1-month treatment with selumetinib, $^{124}$I-PET demonstrated a significant increase in iodine uptake in 12/20 iodine refractory patients, allowing for new $^{131}$I treatment in 8 patients following dosimetry studies. In one patient presenting with BRAF mutated tumors, lung metastases and one cervical node even became $^{124}$I avid after treatment leading from negative to highly positive $^{124}$I-PET.

Dosimetry studies rely on quantification and estimation of residence time of the radioactivity in the tumors and normal organs. Quantification is more established with PET/CT than with SPECT/CT imaging, and iodine 124 has a 4.2 days period allowing for repeated acquisitions over a few days to evaluate residence time. This makes $^{124}$I-PET the best tool for dosimetry studies as described by Freudenberg [34]. There are 2 different ways of dosimetry planification and to calculate the $^{131}$I activity to be administrated. The first is to define the most efficient absorbed dose in the tumors to reach tumor lysis (mostly 100 Gy for distant metastases). The second is to give the greatest $^{131}$I activity limited by the threshold of toxicity defined in normal tissues (exemple: 2 Gy to the bone marrow). Sgouros et al. have recently integrated radiobiological data about radiosensitivity of different tissues obtained from external beam radiation [35].

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![Fig. 1. “Flip-flop phenomena”: complementarity of $^{18}$F-FDG-PET and post-therapeutic Iodine 131 scan. a. Patient presenting with bone metastases in the right temporal bone and right humeral head demonstrating intense Iodine 131 uptake (1.a.1) but no $^{18}$F-FDG uptake (1.a.2). b. Patient presenting with lymph-nodes and lung metastases demonstrating no Iodine 131 uptake (1.b.1) but an intense $^{18}$F-FDG uptake (1.b.2).](image)
4. Medullary thyroid carcinoma (MTC)

MTC often metastasizes in cervical nodes leading to iterative surgical resections. Unfortunately, persistent disease is observed in many cases despite these approaches. The patient is then monitored with repeated multimodal imaging including cervical-thoracic calcitonin (CT), liver and bone marrow MRI, due to the risk of diffuse multiple organ extension [36]. The rhythm for surveillance depends on markers (CT and/or CEA) doubling time. A less than 1 year doubling time is associated with worse prognosis. Only in that situation, 18F-FDOPA-PET can reveal significant tracer uptake in metastases, stressing again the prognostic value of 18F-FDG-PET [37].

18F-FDOPA-PET was expected to help in the diagnosis of metastatic sites. However, its sensitivity varies from 47% up to 83% as reported by Treglia [38], depending on CT levels. As reported in the review by Slavikova, 18F-FDOA accuracy becomes significant if CT is greater than 150 pg/mL [39]. In the study of Archier et al., none of the 10 patients having only abnormalities on 18F-FDOA in nodal necks normalized CT level after surgery [40]. The lymph node compartment-based sensitivity of 18F-DOPA PET/CT was 100% but lesion-based sensitivity was only 24%. Early acquisitions are mandatory as a tumors wash-out is often observed [41]. 18F-FDOPA PET might also reveal a synchronous pheochromocytoma in MEN2 patients. Somatostatin analogues radiolabeled with Gallium 68 have been even less successful [42,43]. However, it may select patients for peptide radionucleide therapy (PRRT) in case of significant lesions uptake. Treglia has compared the 3 different radiotracers, and 18F-FDOPA remains the most sensitive tool [38,42].

Calcitonin remains a highly sensitive biomarker, highly more sensitive than any radiological examination. Therefore, stable high level of CT without detectable lesions would not alter patient short-term outcome, and should lead to a loose surveillance. Furthermore, apart from general symptoms such as profuse uncontrolled diarrhea, TKI are only indicated in case of supra-centimetric lesions visible on conventional imaging, and having a significant progression on RECIST over the last 12 months. At present, this still limits the value of functional imaging for the management of MTC.

5. Conclusion

In conclusion, PET imaging complements morphological imaging in the management of thyroid cancer of follicular origin, mainly for aggressive histologic subtypes (Table 1). Its role for medullary thyroid carcinoma is still debated and not well positioned.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

References


