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, diagnostic 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 18F-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

Résumé

La tomographie par émission de positons couplée à la TDM (TEP-TDM) est une imagerie fonctionnelle avec support anatomi que pouvant être utilisée aux différentes étapes de la prise en charge des cancers thyroïdiens. Le 18Fluorodeoxyglucose (18F-FDG) est capté en grande quantité par les cellules en division rapide. La TEP-TDM utilisant le 18F-FDG reflète donc l’agressivité des tumeurs. Elle est un examen de référence pour le bilan d’extension des cancers de souche folliculaire métastatiques et/ou avec histologie agressive, leur évaluation pronostique et leur suivi sous traitement. Elle peut être indiquée devant une persistance biochimique de la maladie. Sa sensibilité est cependant dépendante de la masse résiduelle mais surtout du type histologique. La TEP à l’iode 124 est en cours d’évaluation, pour sa valeur diagnostique et pour la dosimétrie. La TEP à la 18F-FDOPA est à ce jour le plus sensible des tracers pour les cancers médullaires thyroïdiens (CMT) persistants ou récidivants. Sa sensibilité est cependant dépendante de la concentration sérique de calcitonine, avec une valeur seuil autour de 150 pg/mL. La TEP au 18F-FDG garde une valeur pronostique et peut être utilisée en cas de temps de doublage court de la calcitonine ou de l’ACE.

Mots clés : Cancer thyroïden ; TEP-FDG ; Iode-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...
3.1. called thyroid incidentaloma. Diffuse and homogeneous tracer uptake is usually related to thyroiditis. In contrast, intrathyroidal 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 ($^{131}$I) in absence of identified resectable tumor mass. In this situation, it is not uncommon to get no abnormal $^{131}$I focus on post-therapy whole body scintigraphy ($^{131}$I PT-WBS). $^{18}$F-FDG-PET can play a role in the diagnosis of tumor persistence/recurrence. In this setting, Lebouleux et al. found 16% sensitivity for $^{131}$I scan vs 88% for $^{18}$F-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 $^{131}$-I administration was 47 ng/mL (range: 4–3230; mean: 290). Only one patient had a normal $^{18}$F-FDG-PET and an abnormal $^{131}$I PT-WBS. Therefore, the authors suggest to start with $^{18}$F-FDG-PET and to proceed to empiric $^{131}$I treatment only in case of negative $^{18}$F-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 $^{18}$F-FDG-PET with a therapeutic impact [3–5]. $^{18}$F-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 $^{131}$I WBS, reported a $^{18}$F-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 $^{18}$F-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 $^{18}$F-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 $^{18}$F-FDG-PET remains unclear as there has been no study reporting a significant impact of stimulation on $^{18}$F-FDG-PET sensitivity. Lebouleux 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 $^{18}$F-FDG-PET should not be systematically performed. However, concomitant $^{18}$F-FDG-PET can complete stimulated $^{131}$I 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 $^{18}$F-FDG-PET and 31% on $^{131}$I PT-WBS [9].

The lack of sensitivity of $^{131}$I scan can be partially corrected by high resolution iodine-124 PET ($^{124}$I-PET). As expected, studies such as Van Nostrand’s showed a superiority of $^{124}$I-PET when compared to diagnostic planar $^{131}$I WBS [15]. In contrast, when $^{124}$I-PET is compared to $^{131}$I 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 $^{131}$I PT-WBS but totally missed on $^{124}$I-PET [21]. So far, two studies compared $^{124}$I-PET and $^{131}$I 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 $^{124}$I-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 $^{131}$I WBS and 63.9 MBq $^{124}$I-PET. When patients underwent $^{131}$I therapy, $^{131}$I PT-WBS demonstrated suspicious foci in 10/12 patients. Therefore, a negative $^{124}$I-PET failed to rule out the need of empiric radioiodine therapy.

The first explanation could be related to the too low amount of injected activity. $^{124}$I 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 $^{124}$I PET/CT and $^{131}$I SPECT/CT and, hence, whether the administered $^{124}$I 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, $^{124}$I activities as high as 170 MBq may be warranted to obtain equal detectability.

The second explanation could also be the way of stimulation before $^{124}$I 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 $^{124}$I-PET when compared to rhTSH stimulation [15]. The percentages of patients having positive foci detected on the 62.9 MBq rhTSH $^{124}$I-PET and THW $^{124}$I-PET scans were 29% (7/24) and 63% (10/16), respectively ($P < 0.03$), which was also observed with the 74 MBq $^{131}$I 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 consequences 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].
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-FDG-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-FDOPA 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-FDOPA 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 radionuclide 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.

Table 1
Use of PET for thyroid cancers.

<table>
<thead>
<tr>
<th>Thyroid Cancer Type</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Follicular thyroid carcinoma</td>
<td>18F-FDG-PET</td>
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<tr>
<td>Medullary thyroid cancer</td>
<td>18F-FDOPA PET for metastases diagnostic when CT &gt; 150 pg/mL 18F-FDG-PET for metastatic disease prognosis in case of CT or CEA doubling time &lt; 1 year</td>
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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


