OTHER POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY TRACERS IN DIFFERENTIAL THYROID CARCINOMA BEYOND THE USE OF 2-[¹⁸F] FDG

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Thyroid cancer is the most common endocrinology malignancy worldwide accounting for 3% of the global incidence of all cancers [1]. Differentiated thyroid carcinoma (DTC) is the most frequent subtype, being categorized by the World Health Organization (WHO) into four types derived from epithelial thyroid cells: the most frequent is papillary thyroid cancer (PTC) (85%), followed by follicular thyroid carcinoma (FTC), Hürthle cell carcinoma (HCC) and poorly differentiated thyroid carcinoma (PDTC) [2].

The diagnostic images on DTC are focused on primary detection, initial staging, treatment follow-up, and re-staging in case of recurrence [3].

Positron emission tomography / computed tomography (PET/CT), is a non-invasive imaging study that used the injection of radioactive compounds to provide functional information about tissues and organs [4].

The following article is a review about the PET/CT tracers different than 2-[¹⁸F] FDG in patients with diagnosed differentiated thyroid carcinoma.

MATERIALS AND METHODS

Initially, a structured literature search was performed in medical databases such as PubMed, Ovid, BMJ, Clinical Key, ScienceDirect, LILACS, Scielo, and Cochrane; DeCS and MeSH

* All authors have contributed to all phases of the construction of this manuscript. As it is a review article, it did not experiment on animals or people, so informed consent or approval from the ethics committee was not required. All authors read and approved the final version of the manuscript.

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terms were entered as Thyroid Cancer; papillary; Thyroid Neoplasms; Positron Emission Tomography Computed Tomography; PSMA; Tetrafluoroborate; 124-I; RGD2; choline; DOTA-TATE/TOC/NOC; FAZA; methionine; lectin Galectin-3 accompanied by Boolean operators AND, OR and NOT and the search was limited to the years 2015 to 2021.

After the previous exploration and eliminating duplicate articles, 42 results were found between cross-sectional studies, cohorts, systematic reviews with and without meta-analysis. For the election of the articles, it was taken into account that they had: introduction, methodology, results and discussion in addition to the bibliographical references. In the end, 42 articles were entered into this review.

Utility of PET/CT in patients with diagnosis of carcinoma differentiated from thyroids

A meta-analysis, systematic reviews, and narrative reviews [5–8] describe the use of PET/CT as an alternative to morphological images such as computed tomography (CT) or magnetic resonance imaging (MRI) when diagnosis imaging is inconclusive or negative to the suspicion of tumor persistence or recurrence, elevation of tumor markers, dedifferentiation thyroid carcinoma, non-conventional therapeutic options, and others.

Different studies have been reported 1/3 of patients with DTC don't concentrate radioactive iodine ([¹²⁴I] NaI), between 20 and 40 % of patients with lymph node metastases will show dedifferentiation of tumor cells during the disease [5], and 2/3 of patients with distant metastases eventually develop radiiodine-refractory thyroid cancer [5]. In the previous scenarios, PET/CT has proven an adequate imaging tool for the evaluation of behavioral in terms of tumor biology.

Traditionally, the use of 2-[¹⁸F] FDG PET/CT based on the «flip-flop phenomenon» [8] of tumor cells has been described, considering that have a high concentration of fluorodeoxyglucose (FDG) for positive regulation GLUT1 increased proliferation have decreased the possibility of concentrating [¹²⁴I] NaI, secondary to a reduction or loss of the expression/function of the sodium-iodide symporter (NIS). Despite the foregoing, due to the suspicion of disease due to serum elevation of the tumor marker with negativity anatomical and molecular imaging with [¹³¹I] NaI, an entity known as TENIS syndrome (thyroglobulin elevated and negative iodine scintigraphy). It is indicated 2-[¹⁸F] FDG PET/CT; but there are scenarios where this can be negative or inconclusive, for this reason, in recent years other PET tracers have been used, which will be discussed in the following sections.

[¹²⁴I] NaI PET/CT in differentiated thyroid carcinoma

[¹²⁴I] NaI is a radiopharmaceutical that a half-life of 4.18 days, in its decay, it generates X-rays, 63 % of gamma rays with an energy of 603 keV, and 22 % of positrons with maximum and means energies of 2.138 and 0.975 MeV respectively with a spatial resolution for tissue penetration between 5 to 6 mm [9, 10, 20]. Regarding its diagnostic role in differentiated thyroid carcinoma, the expression by cells of NIS is recognized as an uptake mechanism, which allows the uptake of [¹²⁴I] NaI, which carries out an organization process inside the cell [11].

Within the literature, the use of [¹²⁴I] NaI PET/CT has been recorded for:

- Pediatric and adult patients scheduled previously to [¹³¹I] NaI therapy, the [¹²⁴I] NaI establish locoregional and distant disease more effectively and better diagnostic certainty than [¹²³I] NaI and [¹³¹I] NaI SPECT and/or SPECT/CT scans [5, 12–14];
- Dosimetry before therapy with [¹³¹I] NaI [5, 13];
- Determination of non-radioiodine-avid lesion in the subject required other therapies different than [¹³¹I] NaI [5, 15];
- Better characterization between the persistence of pyramidal lobes or thyroid remnants versus adenopathy in the thyroid bed when compared with the images obtained with [¹³¹I] NaI SPECT and/or SPECT/CT [12, 15];
- Identification functional thyroid tissue without anatomical representation [12] and cases of tumor markers elevation for the better characterization of locoregio-
nal and distant radioiodine — avid lesion when comparing with $^{123}$I NaI and $^{131}$I NaI [13].

$^{[18F]}$Tetrafluoroborate PET/CT in differentiated thyroid carcinoma

Tetrafluoroborate (TFB) is an iodine analog that is associated with $^{[18F]}$TFB composes a radio-nuclide with a half-life of 109.8 min and in its disintegration, it generates up to 98% of positrons with energies of 0.64 MeV [16]. As an uptake mechanism, $^{[18F]}$TFB is trapped, but not organized by thyroid cells [17] entering through the NIS [18] which is a transmembrane glycoprotein that mediates the transport of active iodine to epithelial and follicular cells thyroid [19]. $^{[18F]}$TFB can be easily produced in a cyclotron and for PET/CT imaging it provides an excellent lesion/background ratio, additionally, it has a lower absorbed dose when compared to $^{[131]}$I NaI PET/CT [17, 18].

Among the studies available in the literature, its usefulness in differentiated thyroid carcinoma in these scenarios:

- In TENIS syndrome for detection of recurrences in a lymph node or distant metastases with greater precision compared to $^{[131]}$I NaI SPECT/CT [17, 20];
- Better detection of locoregional and/or distant metastatic lesions in case of minimally elevated tumor markers [17];
- Greater successful result for surgical resection of lesions in thyroid bed and/or lymph nodes compromises [17, 20] and monitoring response treatments such as $^{[131]}$I NaI PET/CT [17, 18].

In other cases, the combined use of 2-$^{[18F]}$FDG PET/CT and $^{[18F]}$TFB PET/CT allows better diagnostic for the determination of locoregional recurrences and/or distant metastases in addition to the presence of dedifferentiation diseases [17].

$^{[68Ga]}$Ga-NOTE-PRGD2 and $^{[18F]}$AIF-NOTE-PRGD2 PET/CT in the following DTC:

- Predict the efficacy and prognosis of therapy with tyrosine kinase inhibitors (ITK) in radioiodine-refractory thyroid cancer [21];
- Establish a prognosis patient undergoing therapy directed to the Vascular Endothelial Growth Factor (VEGF) / Vascular Endothelial Growth Factor receptor (VEGFR) pathway in cases of radioiodine-refractory thyroid cancer [21, 23];
- When the 2-$^{[18F]}$FDG PET/CT is negative in patients with radioiodine-refractory thyroid cancer, the $^{[68Ga]}$Ga-NOTE-PRGD2 is adequate imaging tool to detection of structural disease [21];
- Determination of surgically unresectable and distant metastases in patients with a diagnosis of radioiodine-refractory thyroid cancer [22, 24];
- Determine the presence of recurrent and/or distant disease in a patient with a diagnosis of TENIS syndrome [22].

A positive study $^{[68Ga]}$Ga-NOTE-PRGD2 or $^{[18F]}$AIF-NOTE-PRGD2 PET/CT can be used as a theragnostic agent to use treatment-based on $^{[177}$_Lu$^{Lu}$ RGD or other chemotherapeutic agents such as paclitaxel and doxorubicin bound to RGD [22-24].

$^{[68Ga]}$Ga-DOTA-FAPI PET/CT in differentiated thyroid carcinoma

Fibroblasts are cells that are physiologically located throughout the body. In recent years, it has been found that this type of cell can be contemplated in the tumor microenvironment of multiple neoplasms expressing fibroblast activation protein (FAP), which has exopeptidase
and endopeptidase activity [25]. This type of molecule has generated interest as a molecular target, for which it has been associated with an inhibitor (FAPI) presenting high uptake in the tumor stroma [26, 27].

Regarding the use of \[^{68}\text{Ga}\] Ga-FAPI PET/CT in DTC, the following utilities have been described:

- Determination of locoregional disease in case of suspected persistence or recurrence in the context of TENIS syndrome because having better injury/background ratio in terms of the presence of lymph node and distant lesions [26];
- Better monitoring lymph node metastases when compared with 2-\[^{18}\text{F}\] FDG PET/CT studies [26];
- Superior detection of bone metastases justified by the large component of activated fibroblasts and/or myofibroblasts [26].

The synchronous use of 2-\[^{18}\text{F}\] FDG and \[^{68}\text{Ga}\] Ga-DOTA-FAPI PET/CT has shown an opposite behavior in the lesions of interest. This may be related to tumor heterogeneity, for this reason, a lesion with low uptake of FDG and high uptake of FAPI may be cells that are in the initial stages of the dedifferentiation process [26].

\[^{18}\text{F}\] Fluorocholine or \[^{11}\text{C}\]C-Choline PET/CT in differentiated thyroid carcinoma

Choline is a precursor molecule for the formation of phosphatidylcholine, which is a major component of the cell membrane [28]. Within its uptake mechanism, choline is metabolized and internalized in cells by the enzyme choline kinase. It is known that there is an increase in the production of phosphatidylcholine in the case of tumor lesions to satisfy the demand on cell membranes [28, 29]. For this reason, in recent years, analogs of choline labeled with radiotracers such as \[^{18}\text{F}\] and \[^{11}\text{C}\] have been used [28, 29]. Some studies, explain the use of \[^{18}\text{F}\] FCH (fluorocholine) or \[^{11}\text{C}\] C-Choline in DTC in the cases of thyroid nodules because present a 90 % sensitivity and negative predictive value of 96 % for the prediction of malignancy [30]. On the other hand, have utility for detection of locoregional and/or distance metastasis in the case of DTC with a negative 2-\[^{18}\text{F}\] FDG PET/CT [29] and in the cases of high-risk differentiated thyroid carcinoma with non-aggressive subtypes and short thyroglobulin doubling with suspect of locoregional dissemination [29].

The combination of \[^{18}\text{F}\] FCH and 2-\[^{18}\text{F}\] FDG PET/CT has shown high sensitivity for the detection of structural disease in case of differentiated thyroid carcinoma to determine surgery in neck and mediastinum [29].

\[^{18}\text{F}\] or \[^{68}\text{Ga}\] Ga-PSMA PET/CT in differentiated thyroid carcinoma

The prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that in recent years has been expressed not only at the cell in malignant prostate neoplasms but also the level of the tumor neovascularure of other solid neoplasms, including radioiodine-refractory thyroid cancer [31, 32].

Regarding the expression of PSMA in this type of carcinoma, in recent years using immunohistochemical techniques, the tumor cells present dedifferentiation process develops more aggressive behavior, which requires generating neovascularure to provide sufficient supply to the tumor [31, 33, 34]. Similarly, the expression of the folate hydrolase 1 (FOLH1) gene, responsible for encoding the expression of PSMA, has been described in less than 5 % of DTC [34].

In the literature, the \[^{18}\text{F}\] or \[^{68}\text{Ga}\] Ga-PSMA PET/CT in DTC, the following utilities have been described for:

- Determination of locoregional (lymph node) or distant (pulmonary, bone, liver, leptomeningeal) lesions in case of radioiodine-refractory thyroid cancer [31, 33, 34];
- Assessment of distant lesions in poorly differentiated thyroid carcinoma [32].

For initial staging, the use of \[^{18}\text{F}\] or \[^{68}\text{Ga}\] Ga-PSMA PET/CT in patients with advanced-stage (III/IV) is a predictor of radioiodine-refractory thyroid cancer in addition to metastatic involvement, which may be considered as a criterion of aggressiveness [32, 33]. On the other hand, a positive study with \[^{18}\text{F}\] or \[^{68}\text{Ga}\] Ga-PSMA PET/CT gives a chance to use therapeutic agent treatment based on \[^{177}\text{Lu}\] Lu PSMA in case of radioiodine-refractory thyroid cancer [31, 33, 34].
**[68Ga] Ga DOTA-TATE/TOC/NOC/LAN PET/CT in differentiated thyroid carcinoma**

Somatostatin is a hormone responsible for regulating critical processes such as neurotransmission, hormonal secretion, and cell proliferation. The somatostatin receptors (SSTRs) are present on the surface of multiple cells in the body [35]. As a diagnostic tool, in recent years radiopharmaceuticals based on a positron emitter type [68Ga] have been developed, which is associated with a chelator (DOTA) and finally the somatostatin analog (TATE/TOC/NOC/LAN) [35]. As an uptake mechanism, it has been described that the cells in DTC associated with TENIS syndrome can show SSTR1 in 88.8% of cases followed by SSTR3 in 55.5%, SSTR2 in 44.4%, SSTR5 in 33.3%, and SSTR4 at 11.2% [36, 37]. Similarly, it has been described that the less aggressive variants present higher SSTR5 expression compared to the more aggressive ones with higher SSTR3 expression [36].

The use of [68Ga] Ga DOTA-TATE/TOC/NOC/LAN PET/CT has been described in the staging in case of suspected locoregional and/or distant recurrence in patients diagnosed with DTC associated with TENIS syndrome can show SSTR1 in 88.8% of cases followed by SSTR3 in 55.5%, SSTR2 in 44.4%, SSTR5 in 33.3%, and SSTR4 at 11.2% [36, 37]. Similarly, it has been described that the less aggressive variants present higher SSTR5 expression compared to the more aggressive ones with higher SSTR3 expression [36].

Among the studies with [18F]-FAZA PET/CT in patients with a diagnosis of DTC, uptake in locoregional or distant lesions with 2-[18F] FDG PET/CT and [18F]-FAZA PET/CT is related to the short-term progression of the disease in affected sites after therapy with [131I] NaI and increase uptake of FDG [40].

**L-[methyl-11C] methionine PET/CT in carcinoma differentiated from thyroids**

Methionine is an amino acid necessary for protein synthesis by donating the methyl group required for DNA methylation, transfer RNA, among other compounds [42]. As a diagnostic strategy, methionine has been bound together with the positron emitter [11C]. Regarding the uptake mechanism, it is known that methionine enters the interior of the cell through the L1-type amino acid transporter (LAT1) [43]. Regarding the use of these studies in DTC, there is a case report of a 66-year-old patient who indicated the study with L-[methyl-11C] methionine PET/CT to search for a lesion due to the diagnosis of primary hyperparathyroidism, finding incidental uptake in the isthmus and left lobe being taken to surgical resection with histopathological diagnosis of parathyroid adenoma and follicular thyroid carcinoma [42].

**[89Zr] DFO-PAS200-Fab PET/CT in differentiated thyroid carcinoma**

Galectin-3 (GAL3) is a member of the family of galactosidase-binding proteins that are found intra- and extracellular, fulfilling multifunctions.

This molecule expresses in multiple cells in the body, and recent work has evaluated its expression in thyroid carcinoma [44]. For this reason, αGAL3 has been linked to the deferoxamine chelator, PAS chain (Proline, Alanine,
and Serine), a Fab proteolytic antibody fragment, and the positron emitter $^{89}$Zr for PET/CT imaging [44]. The usefulness of this tracer in the DTC has been described for establishing recurrence of the disease after the surgical event [44] and determining the presence of probable micrometastases in the case of TENIS syndrome [44].

Finally, in Table 1 we summarize the different tracers described in the previous sections with their mechanism of action and possible use scenarios.

### Table 1

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Mechanism of action</th>
<th>Possible use scenarios</th>
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<tbody>
<tr>
<td>$[^{125}I]$ NaI</td>
<td>Expression tumoral cells NIS symporter</td>
<td>Establish locoregional and distant disease Dosimetry before therapy with $[^{131}I]$NaI Determination of non-radioiodine — avid lesion Identification of functional thyroid tissue without anatomical representation</td>
</tr>
<tr>
<td>$[^{18}F]$ Tetrafluoroborate</td>
<td>Expression tumoral cells NIS symporter</td>
<td>TENIS syndrome Detection of locoregional and/or distant metastatic lesions</td>
</tr>
<tr>
<td>$[^{68}Ga]$ Ga-NOTE-PRGD2 and $[^{18}F]$ AIF-NOTE-PRGD2</td>
<td>ovb3 and ovb5 integrins overexpressed in tumoral vasculature</td>
<td>Predict the efficacy and prognosis of therapy ITK Predict prognosis patients undergoing therapy VEGF / VEGFR Determination of surgically unresectable and distant metastases Theragnostic agent to used $[^{177}Lu]$Lu RGD or other chemotherapeutic agents</td>
</tr>
<tr>
<td>$[^{68}Ga]$ Ga-DOTA-FAPI</td>
<td>Tumor microenvironment expressing fibroblast activation protein</td>
<td>TENIS syndrome Monitoring lymph node metastases Detection of distant metastases (bone)</td>
</tr>
<tr>
<td>$[^{18}F]$ Fluorocholine or $[^{11}C]$ C-Choline</td>
<td>Increase production of phosphatidylcholine in the tumor lesions</td>
<td>Thyroid nodules prediction of malignancy Detection locoregional and distant metastases</td>
</tr>
<tr>
<td>$[^{18}F]$ or $[^{68}Ga]$ Ga-PSMA</td>
<td>Tumoral microvasculature expression</td>
<td>Detection locoregional and distant metastases Patients with advanced-stage (III/IV) is a predictor of radioiodine refractory diseases Theragnostic agent treatment based on $[^{177}Lu]$Lu PSMA</td>
</tr>
<tr>
<td>$[^{68}Ga]$ Ga DOTA-TATE/TOC/NOC/LAN</td>
<td>SSTR1 - SSTR2 - SSTR3 - SSTR4 - SSTR5 expression</td>
<td>TENIS syndrome Suspected locoregional and/or distant recurrence Staging poorly differentiated and Hürthle cell Theragnostic agent used treatment based on $[^{177}Lu]$Lu DOTA</td>
</tr>
<tr>
<td>$[^{18}F]$-FAZA</td>
<td>Hypoxia markers</td>
<td>locoregional or distant lesions short-term progression</td>
</tr>
<tr>
<td>L-[methyl-$^{11}C$] methionine</td>
<td>Amino acid necessary for protein synthesis introduce interior cell used LAT1</td>
<td>Incidental uptake in follicular thyroid carcinoma</td>
</tr>
<tr>
<td>$[^{69}Zr}$ DFO-PAS200-Fab</td>
<td>Galectin-3 expresses in tumoral cells</td>
<td>Recurrence disease after the surgical event</td>
</tr>
</tbody>
</table>
CONCLUSIONS

There are multiple radiopharmaceuticals different than 2-[18F] FDG, which can be adequate in the context of differentiated thyroid carcinoma: 2-[18F] FDG PET/CT negative, TENIS syndrome, radioiodine-refractory thyroid cancer suspected, thyroid dedifferentiated carcinoma, and some cases theragnostic tools.

REFERENCES

OTHER POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY TRACERS IN DIFFERENTIAL THYROID CARCINOMA BEYOND THE USE OF 2-[18F]FDG

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Thyroid cancer is a common endocrinological malignancy worldwide, accounting for 3% of the global incidence of all cancers. Meta-analyses, systematic reviews, and descriptive reviews mention the use of positron emission tomography / computed tomography (PET/CT) as an alternative to morphological imaging such as computed tomography or magnetic resonance imaging to clarify the diagnosis. The aim: analysis of positron emission tomography/computed tomography tracers in the differential diagnosis of thyroid carcinomas.

Materials and methods: Review about PET/CT tracers different than 2-[18F] fluorodeoxyglucose (FDG) in patients with diagnosed differentiated thyroid carcinoma.

Evidence Synthesis: PET/CT is an alternative to morphological diagnosis imaging when is inconclusive or negative due to the suspicion of tumor persistence or recurrence, elevation of tumor markers, dedifferentiation thyroid carcinoma, non-conventional therapeutic options. 2-[18F] FDG is the most uses a tracer, but there are scenarios where can be negative or inconclusive, for this reason, in recent years other PET tracers have been used: [123I] NaI, [18F] Tetrafluoroborate, [68Ga] Ga-NOTE-PRGD2 or [18F] AIF-NOTE-PRGD2, [68Ga] Ga-DOTA-FAPI, [18F] Fluorocholine or [11C] C-Choline, [18F] or [68Ga] Ga-PSMA, [68Ga] Ga DOTA-TATE/TOC/NOC/LAN, [18F]-FAZA, L-[methyl-11C] Methionine and [89Zr] DFO-PAS200-Fab.

Conclusions. There are multiple radiopharmaceuticals different than 2-[18F] FDG, which can be adequate in the context of differentiated thyroid carcinoma: 2-[18F] FDG PET/CT negative, TENIS syndrome, radioiodine-refractory thyroid cancer suspected, thyroid dedifferentiated carcinoma, and some cases theragnostic tools.

Keywords: Positron Emission Tomography / Computed Tomography, Thyroid Neoplasms, Radiopharmaceuticals.
Рак щитовидної залози є поширеним ендокринологічним злоякісним захворюванням у світі, на нього припадає 3 % глобальної захворюваності на всі види раку. Мета-аналіз, систематичні та описові огляди згадують використання позитронно-емісійної томографії/комп’ютерної томографії (ПЕТ/КТ) як альтернативу морфологічним зображенням, таким як комп’ютерна томографія або магнітно-резонансна томографія, для уточнення діагнозу.

Мета: аналіз радіофармпрепаратів для позитронно-емісійної томографії/комп’ютерної томографії при диференційній діагностиці карцином щитовидної залози.

Матеріали та методи. Огляд радіофармпрепаратів для ПЕТ/КТ, відмінних від 2-[18F] фтордезоксиглюкози (FDG), застосованих у пацієнтів з діагностованою диференційованою карциномою щитовидної залози.


Висновки. Існує кілька радіофармацевтичних препаратів, відмінних від 2-[18F] FDG, які можуть бути достатніми в такому контексті диференційованої карциноми щитовидної залози, як: 2-[18F]FDG ПЕТ/КТ-негативний синдром TENIS, підозра на стійкий до радіойоду рак щитовидної залози, дедиференційовану карциному щитовидної залози і в деяких випадках терапевтичні інструменти.

Ключові слова: позитронно-емісійна томографія, комп’ютерна томографія, новоутворення щитовидної залози, радіофармацевтичні препарати.