Review

The Role of PET/CT in the Management of Differentiated Thyroid Cancer: Current Applications and Future Perspectives

Emmanouil Panagiotidis * and Jules Tianyu Zhang-Yin

Posted Date: 25 September 2024

doi: 10.20944/preprints202409.2036.v1

Keywords: thyroid cancer; PET/CT

Review

The Role of PET/CT in the Management of Differentiated Thyroid Cancer: Current Applications and Future Perspectives

Emmanouil Panagiotidis [1,*] and Jules Tianyu Zhang-Yin [2]

[1] Nuclear Medicine, 'Theageneio Cancer Center', 54639 Thessaloniki, Greece
[2] Department of Nuclear Medicine, Clinique Sud Luxembourg, 486762 Arlon, Belgium
* Correspondence: m_panagiotidis@yahoo.com

Abstract: Differentiated thyroid cancer (DTC), comprising papillary and follicular thyroid carcinoma, is the most common thyroid malignancy and typically has a favourable prognosis when detected early. Positron emission tomography/computed tomography (PET/CT) has emerged as a valuable imaging modality, integrating metabolic and anatomical data. Although PET/CT is not usually part of the initial diagnostic process due to DTC's indolent nature and low metabolic activity, it plays an essential role in selected clinical scenarios. This includes identifying recurrence in patients with elevated thyroglobulin (Tg) levels and negative radioactive iodine (RAI) scans, evaluating metastatic disease, and guiding treatment in advanced cases. As the use of PET/CT evolves in oncology, this review explores its application in the staging, detection of recurrence, follow-up, and future challenges in managing DTC. The review also considers emerging radiotracers and the theragnostic potential of PET/CT.

Keywords: thyroid cancer; PET/CT

1. Introduction

Thyroid cancer is the most common endocrine malignancy, with differentiated thyroid cancer (DTC) accounting for more than 90% of cases. DTC includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), both of which are generally indolent and highly treatable, particularly when diagnosed early. According to the World Health Organization (WHO), the global incidence of thyroid cancer has risen significantly in recent decades, largely due to advancements in imaging technology, increased detection of subclinical thyroid nodules, and more widespread use of imaging techniques, including ultrasound and fine-needle aspiration biopsy (FNAB) [1,2]. While many patients with DTC achieve excellent outcomes, approximately 20% develop recurrence or metastases, underscoring the need for accurate imaging to guide management [3,4].

Conventional imaging modalities for thyroid cancer include ultrasound, CT, and radioactive iodine (RAI) scintigraphy. While these techniques are effective in initial diagnosis and follow-up, they may have limitations, particularly in detecting dedifferentiated or non-iodine-avid tumors [5]. Positron emission tomography/computed tomography (PET/CT), particularly using 18F-Fluorodeoxyglucose (FDG) as a tracer, offers both metabolic and anatomical imaging. This hybrid imaging technique has emerged as an essential tool in oncology, particularly in staging, recurrence detection, and monitoring treatment response in aggressive DTC subtypes [6].

Despite its increasing utility, the role of PET/CT in DTC remains a topic of ongoing research. While it is not routinely used in the initial diagnosis of DTC, PET/CT has shown significant value in cases where RAI scintigraphy is inadequate or inconclusive. This review aims to explore the evolving role of PET/CT in managing DTC, focusing on its application in detecting recurrence, staging, and follow-up. In addition, future directions in PET/CT imaging, including the development of novel radiotracers and theragnostic, will be discussed.

 doi:10.20944/preprints202409.2036.v

2. Thyroid Nodules and Diagnosis

Thyroid nodules are highly prevalent in the general population, with studies suggesting a prevalence of up to 68% when evaluated with high-resolution ultrasound. Most of these nodules are benign, with only approximately 5% representing malignancies, the majority of which are DTC [7]. Fine-needle aspiration biopsy (FNAB) remains the gold standard for the evaluation of thyroid nodules, allowing for cytological analysis and differentiation between benign and malignant nodules [8]. Ultrasound is critical for guiding FNAB, and characterizing nodules based on several features, including hypo echogenicity, microcalcifications, irregular margins, and a taller-than-wide shape, all of which are associated with an increased risk of malignancy [8].

However, PET/CT is typically not employed in the initial assessment of thyroid nodules. Most DTCs, especially papillary thyroid carcinomas (PTCs), exhibit relatively low metabolic activity, and therefore, do not demonstrate high FDG uptake on PET imaging [9]. The American Thyroid Association (ATA) does not recommend routine PET/CT for the initial evaluation of thyroid nodules, as ultrasound and FNAB are highly reliable for initial diagnostic purposes [10].

Nevertheless, PET/CT plays an important role when thyroid nodules are incidentally identified during imaging studies for unrelated malignancies, known as PET incidentalomas. These nodules often demonstrate increased FDG uptake, which raises suspicion for malignancy, particularly in aggressive or dedifferentiated thyroid tumors [11]. It is estimated that approximately 35% of thyroid nodules incidentally detected on PET/CT scans are malignant [11]. Therefore, incidental FDG-avid thyroid nodules warrant further evaluation with ultrasound and FNAB to confirm malignancy.

In a meta-analysis of 34 studies, Treglia et al. evaluated incidental focal thyroid uptake detected by FDG PET/CT in over 200,000 patients [12]. They found a pooled malignancy risk of approximately 36%. A separate systematic review by Shie et al. examined 18 studies on incidental thyroid uptake (n = 55,160) [13]. Their findings revealed that while the majority of patients (62.1%) had benign conditions, 33.2% had cancer, and 4.7% had indeterminate nodules. Among those with cancer, papillary thyroid carcinoma (PTC) was the most common type, accounting for 82.2% of cases.

Additionally, FDG PET/CT is valuable for identifying non-iodine-avid tumors, which are often more aggressive and less differentiated. In these cases, PET/CT can help detect metastatic disease that may not be visualized on traditional RAI scans [14].

3. Staging of Differentiated Thyroid Cancer

Staging in DTC is critical for determining prognosis and guiding treatment decisions. The American Joint Committee on Cancer (AJCC) TNM staging system is the most widely used for thyroid cancer, incorporating tumor size (T), lymph node involvement (N), and the presence of distant metastasis (M) [10]. Accurate staging is vital, as it directly influences the management approach, including the need for radioactive iodine therapy and the intensity of follow-up. Complete thyroidectomy with or without cervical lymph node dissection depending on metastatic risk is recommended as the standard treatment for DTC. Lobectomy may be considered sufficient in cases of low-risk DTC [10].

In most cases, ultrasound and RAI scintigraphy are the primary imaging modalities used for initial staging of DTC. Ultrasound is highly sensitive for detecting cervical lymph node metastases, while RAI scintigraphy is effective in identifying distant metastases in iodine-avid tumors [3]. However, in certain cases, these conventional methods may be inadequate, particularly in patients with non-iodine-avid disease or aggressive tumor variants, such as tall cell or Hürthle cell carcinoma [15].

Due to their generally slow growth and low metabolic activity, most well-differentiated thyroid carcinomas exhibit minimal FDG uptake. Consequently, the primary role of FDG PET/CT in DTC management is typically limited to postoperative follow-up. Given the low incidence of initial distant metastasis (4-7%), routine initial staging with PET is often not indicated [16, 17].

The "flip-flop phenomenon" refers to the inverse relationship between the uptake of radioiodine and the uptake of fluorodeoxyglucose (FDG) in thyroid cancer, where tumors that are iodine-negative may demonstrate increased FDG uptake [18]. This phenomenon highlights the importance

 doi:10.20944/preprints202409.2036.v

of using FDG-PET/CT in cases where traditional iodine imaging fails to identify malignant lesions, particularly in aggressive subtypes of differentiated thyroid carcinoma.

Despite the potential benefits of PET/CT in thyroid cancer staging, there is currently no strong evidence or consensus supporting its routine use as a preoperative tool, regardless of tumor differentiation or metastatic status, according to the ATA guidelines [10].

4. Recurrence Detection in Differentiated Thyroid Cancer

A significant challenge in the long-term management of DTC patients is identifying recurrence, which occurs in approximately 20-30% of cases, often years after the initial treatment [19]. While the prognosis for DTC is generally excellent, early detection of recurrent disease is crucial, particularly for patients with aggressive disease subtypes or those who develop distant metastases. Thyroglobulin (Tg) serves as a reliable biomarker for DTC recurrence, with elevated levels often preceding imaging findings [19]. However, in a subset of patients with elevated Tg and negative RAI scans, the disease can be difficult to localize.

FDG PET/CT has proven to be a powerful tool in identifying sites of recurrence, particularly in patients with elevated Tg levels and negative RAI scans. This imaging modality allows for the detection of non-iodine-avid metastatic disease, which may be undetectable on traditional RAI scans. FDG is taken up by cells with high metabolic activity, such as dedifferentiated thyroid cancer cells that have lost their ability to uptake iodine [19]. A study investigated the relationship between thyroglobulin kinetics (doubling time and velocity) and FDG PET/CT results in patients with differentiated thyroid carcinoma [20]. The results showed that patients with higher thyroglobulin levels and faster thyroglobulin kinetics were more likely to have positive PET/CT scans. Additionally, thyroglobulin kinetics were found to be independent prognostic factors for overall survival.

Moreover, PET/CT has demonstrated clinical utility in patients with biochemically incomplete responses to initial treatment (i.e., persistently elevated Tg levels post-surgery and RAI therapy) but no evidence of disease on conventional imaging. This patient cohort is at increased risk for recurrence, and early identification of metastatic or recurrent disease with PET/CT can significantly alter the treatment approach. For instance, it can guide decisions regarding re-surgery, targeted therapy, or external beam radiation [20].

Another study investigated the long-term prognostic value of FDG PET/CT in patients with differentiated thyroid cancer undergoing empiric radioiodine therapy [21]. The researchers found that FDG-PET/CT was more effective than post therapy WBS in predicting disease recurrence. Patients with negative FDG-PET/CT and normalized thyroglobulin levels had a better prognosis, with higher rates of disease-free and overall survival. These findings suggest that FDG-PET/CT can be a valuable tool for risk stratification in this patient population.

While cross-sectional imaging (MRI and CT) can be considered for prognostic assessment in patients with metastatic disease or at high risk of rapid progression, PET/CT may be more suitable for evaluating post-treatment response to systemic or local therapies. However, the choice between conventional imaging and PET/CT for this purpose remains controversial [10].

The ETA guideline suggests that PET/CT can provide additional insights into tumor biology, but its prognostic or management implications are yet to be fully established [22].

The only scenario with a strong recommendation for PET/CT is in high-risk DTC patients with elevated serum thyroglobulin (hTg) levels and negative radioiodine imaging [10,22]. While a TSH-stimulated hTg level of 10 ng/mL is often used as a cutoff, this may need to be adjusted in cases of aggressive thyroid cancer subtypes [23]. Albano et al. (2021) investigated the utility of thyroglobulin (Tg) doubling time (Tg-DT) compared to absolute Tg levels in selecting patients for FDG PET/CT imaging in non-iodine avid differentiated thyroid carcinoma (DTC). They found that Tg-DT offered a more reliable threshold than Tg levels alone in identifying patients likely to benefit from PET/CT. Faster Tg-DT was associated with a higher likelihood of detecting metastases, suggesting its potential in guiding personalized treatment strategies. The study highlights the prognostic value of Tg kinetics over static Tg levels in managing DTC patients with negative radioiodine scans.[24].

 doi:10.20944/preprints202409.2036.v

Dong et al. reviewed 25 studies involving 789 patients and concluded that FDG PET/CT demonstrated a high pooled sensitivity of 93.5% for detecting recurrence and metastasis of DTC in cases where there was no radioiodine uptake [25]. Similarly, Miller et al. conducted a meta-analysis of 12 studies and found PET/CT to have a sensitivity of 94.0% for detecting PTC recurrence [26]. In comparison with conventional imaging modalities, PET/CT proved superior in detecting recurrent or metastatic DTC. Weber et al. reported that ultrasound localized recurrent or metastatic thyroid disease in only 57% of cases, while Seo et al. showed that 21.1% of lymph-node and soft-tissue lesions missed by neck ultrasound were identified by PET/CT [27,28,29]. PET/CT also demonstrated superiority over PET alone in detecting small metastatic lesions.

A study by Giovanella et al. found that 88% of patients (n = 102) with a positive FDG PET/CT scan had thyroglobulin levels exceeding 5.5 ng/mL [30]. Importantly, dedifferentiated thyroid carcinoma cells may have a diminished ability to produce and secrete thyroglobulin, meaning that a low thyroglobulin level does not necessarily indicate a small tumor burden in patients with a negative 131I scan but measurable thyroglobulin. While the influence of thyroid-stimulating hormone (TSH) levels on radioiodine scans is well established, there is no consensus regarding TSH's effect on the accuracy of FDG PET/CT. It has been suggested that TSH suppression may be beneficial in patients with low thyroglobulin levels (< 10 ng/mL) who are compliant with hypothyroidism management, while TSH stimulation using recombinant TSH should be considered for patients who cannot tolerate hypothyroid symptoms [19].

5. Follow-Up in Differentiated Thyroid Cancer

The American Thyroid Association (ATA) guidelines recommend periodic follow-up for DTC patients based on risk stratification, with imaging primarily using ultrasound and RAI scans in low- to intermediate-risk patients [10]. However, patients with high-risk DTC, particularly those with persistent disease after initial treatment or aggressive histologic variants, may require more intensive surveillance. PET/CT is increasingly recognized as a valuable tool in these cases due to its ability to detect early recurrence and non-iodine-avid metastases [31].

A recent study found that PET/CT was particularly valuable in patients with suspicious radioiodine scans or aggressive tumor variants [32]. FDG PET/CT was a useful tool in the follow-up of patients with high-risk DTC, mainly in the group of Post-Therapeutic -131 Whole Body Scan not compatible with suspicious foci at conventional image or not proportional to stimulated Tg level and in those with aggressive DTC variants. Additionally, this study showed that FDG PET/CT was associated with progression and helped display undifferentiated lesions guiding clinical assessments regarding surgeries or expectant treatments.

In conjunction with thyroglobulin, FDG PET/CT offers valuable prognostic information and is essential for guiding clinical decisions in DTC patients with negative 131I scans. Vural et al., observed a higher prevalence of PET positivity in patients over 40 compared to younger individuals (70% vs 53%) [33]. Since age at distant metastasis detection is independently linked to mortality, and PET positivity is more common in older patients, it's inferred that FDG uptake may correlate with a poorer prognosis and aggressive tumor behaviour [34].

Robbins et al. examined the prognostic significance of metabolic activity in metastatic thyroid carcinoma among 400 patients reviewed [35]. Results showed that age and FDG PET findings remained strong predictors of survival in multivariate analysis, while the initial AJCC stage was not significant. The 2-year survival rate was 99% in the negative group, 98% in the lowest quartile, and 52% in the quartile with the highest SUVmax, indicating that higher SUVmax of lesions correlate with decreased overall survival. The authors concluded that FDG-PET scanning effectively stratifies patients into low (FDG negative) or high (FDG positive) risk categories for cancer-associated mortality, suggesting that treatment aggressiveness should correspond to FDG-PET status.

Piao et al. studied the combined use of metastatic lymph node ratio (LNR) and thyroglobulin levels to determine the need for FDG-PET/CT in detecting persistent disease in patients with papillary thyroid cancer [36]. The study included 429 PTC patients who underwent surgery and radioactive iodine therapy, with evaluations performed prior to RAI therapy. Key cut-off values were

 doi:10.20944/preprints202409.2036.v

established for serum Tg (6.0 ng/mL), number of metastatic lymph nodes (5), and LNR (0.51) to guide PET/CT indications. The LNR-combined criteria demonstrated significantly better diagnostic performance in identifying FDG-avid persistent disease compared to using individual parameters. This approach offers a more tailored strategy for utilizing PET/CT in the management of PTC patients, potentially improving detection of persistent disease.

The study by Gim et al. evaluated the diagnostic value of SUV in FDG PET/CT for PTC, particularly focusing on the role of BRAF mutations [37]. They found that higher SUV values were significantly associated with the presence of BRAF V600E mutations, indicating that metabolic activity as measured by PET/CT could reflect tumor aggressiveness. Additionally, the study highlighted those patients with BRAF-mutated tumors tended to exhibit increased FDG uptake, suggesting a potential for using SUV metrics as a prognostic marker. Overall, the findings underscore the importance of incorporating BRAF status into PET imaging assessments for improved management of PTC.

The systematic review and meta-analysis by Santhanam et al. examined the relationship between BRAFV600E mutation status and FDG PET/CT avidity in papillary thyroid cancer (PTC) [38]. The analysis included 12 studies and found that patients with the BRAFV600E mutation had a significantly higher likelihood of exhibiting FDG-avid lesions, with a pooled odds ratio of 2.12. Furthermore, the study reported that the mean standardized uptake value (SUV) was notably higher in BRAFV600E-positive patients, with a mean difference of 5.1. These findings indicate that the presence of the BRAFV600E mutation is associated with increased metabolic activity, underscoring its relevance in assessing disease aggressiveness and recurrence risk in PTC.

Emerging studies suggest that FDG PET/CT could play an even more significant role in risk stratification during follow-up, particularly in patients with advanced disease. In the context of active surveillance, PET/CT is used to monitor patients undergoing systemic therapy, such as TKI therapy or immune checkpoint inhibitors [19]. These therapies are primarily used in patients with radioactive iodine-refractory DTC (RAIR-DTC), where disease progression can be unpredictable, and conventional imaging modalities may fail to capture the full extent of disease [14]. PET/CT has proven to be a sensitive modality for detecting subtle changes in metabolic activity, providing a reliable method for assessing therapeutic response in patients undergoing these treatments [14].

In conclusion, while FDG-PET/CT shows promise in various scenarios for differentiated thyroid cancer, clear guidelines are still lacking. Consequently, its clinical use may vary significantly among different medical centers.

6. Emerging Role of Novel Radiotracers

While FDG PET/CT remains the gold standard for detecting dedifferentiated differentiated thyroid cancer (DTC), the development of novel radiotracers offers the potential for improved sensitivity and specificity.

One promising alternative is 18F-dihydroxyphenylalanine (FDOPA), which is particularly relevant in the context of neuroendocrine features of thyroid cancers, such as medullary thyroid carcinoma (MTC) [39]. FDOPA PET/CT exploits the uptake of this radiotracer by dopamine receptors, which are often expressed in higher levels in certain thyroid malignancies compared to glucose transporters used in FDG imaging.

Additionally, Somatostatin receptor-targeting radiopharmaceuticals are utilized for imaging tumors that demonstrate high levels of somatostatin receptors (SSTRs). The most used somatostatin analogues labelled with 68Ga include [68Ga] Ga-DOTA-TATE, [68Ga] Ga-DOTA-NOC, and [68Ga] Ga-DOTA-TOC, each with varying binding affinities for different SSTR subtypes. Specifically, [68Ga] Ga-DOTA-TATE has a high and selective affinity for SSTR 2, while [68Ga] Ga-DOTA-NOC targets both SSTR 2 and 3, and [68Ga] Ga-DOTA-TOC binds to SSTR 2 and SSTR 5. Notably, differentiated thyroid carcinoma (DTC) cells may express high levels of SSTR 2, 3, and 5. 68Ga-DOTATATE PET/CT, which targets somatostatin receptors, is being investigated for its potential to detect neuroendocrine features in thyroid cancer variants, such as medullary thyroid carcinoma (MTC) and poorly differentiated DTC [40]. This radiotracer has demonstrated high sensitivity in detecting

 doi:10.20944/preprints202409.2036.v

somatostatin receptor-positive tumors and may offer a new avenue for imaging DTC variants that are poorly visualized on FDG PET/CT [41].

Radiolabelled somatostatin analogues can potentially detect DTC recurrence or metastases, particularly in patients with RAI-refractory disease. Ocak et al. enrolled 13 patients with RAI-refractory DTC (nine with papillary thyroid cancer, one with follicular thyroid carcinoma, and three with Hurthle cell carcinoma) to compare the performance of [68Ga] Ga-DOTA-TATE and [68Ga] Ga-DOTA-NOC in detecting RAI-R DTC lesions [42]. Somatostatin-positive lesions were found in eight (62%) patients. [68Ga] Ga-DOTA-TATE detected 45 lesions, while [68Ga] Ga-DOTA-NOC detected 42. Lesion uptake was significantly higher with [68Ga] Ga-DOTA-TATE (SUVmax 12.9 ± 9.1) compared to [68Ga] Ga-DOTA-NOC (SUVmax 6.3 ± 4.1), suggesting its potential superiority for imaging RAI-R DTC. The detection of positive RAI-R DTC lesions using somatostatin receptor imaging opens the possibility of treating these patients with peptide receptor radionuclide therapy (PRRT), a targeted therapeutic approach.

In 2017, a novel PET tracer, 18F-tetrafluoroborate (18F-TFB), was tested in healthy human subjects for imaging differentiated thyroid cancer (DTC). This study demonstrated promising results for non-invasive NIS (sodium iodide symporter) imaging, as 18F-TFB can mimic iodide transport, entering thyroid cells through the NIS receptor. 18F-TFB has diagnostic potential in detecting recurrent DTC and cervical lymph node metastases. It can be used to identify pre-operative cervical lymph node metastases, avoiding unnecessary surgery, and to predict the success of radioiodine therapy [19]. 18F-TFB PET/CT offers three key advantages over 123I or 131I scintigraphy:

Higher sensitivity: As a positron emitter detected by PET, 18F-TFB provides greater sensitivity compared to gamma camera-based scintigraphy.

Same-day imaging: Unlike iodine-123(131) scintigraphy, 18F-TFB PET/CT can be performed on the same day as tracer administration, reducing patient inconvenience.

Lower radiation dose: 18F-TFB delivers a lower radiation dose compared to iodine-123(131) scintigraphy.

Fibroblast activation protein (FAP) expression is significantly elevated in cancer-related fibroblasts compared to normal fibroblasts. Due to their abundance in many tumors, radiolabelled fibroblast activation protein inhibitors (FAPIs) are promising for tumor imaging. Chen et al. recently evaluated the performance of [68Ga] Ga-DOTA-FAPI-04 PET/CT in detecting RAI-R DTC lesions [43]. In 24 RAI-R DTC patients, 21 (87.5%) had FAPI-positive lesions with a mean SUVmax of 4.25 and a growth rate of 6.51%. SUVmax was positively correlated with lesion growth rates.

The development of theragnostic radiotracers, such as 131I-labeled tracers, which are both diagnostic and therapeutic, represents a promising frontier in thyroid cancer management. The concept of theragnostic involves using PET/CT to identify tumors that express specific molecular targets (e.g., somatostatin receptors) and then delivering targeted radiotherapy to these tumors. This approach is currently being tested in clinical trials for radioiodine-refractory DTC, offering the potential for more personalized treatment strategies [44].

7. Role of 124I PET/CT in Differentiated Thyroid Cancer

Iodine-124 (124I) is an isotope used in PET imaging, which, unlike 131I, allows for higher-resolution imaging due to the superior sensitivity and spatial resolution of PET technology compared to gamma scintigraphy or SPECT (Single Photon Emission Computed Tomography). 124I-PET/CT is particularly useful in pretherapeutic settings for patients undergoing radioiodine therapy (RAI) with 131I, as it allows for individualized dosimetry and improved detection of iodine-avid lesions [45].

7.1. Advantages of 124I PET/CT

Pretherapeutic Dosimetry: One of the most significant advantages of 124I PET/CT is its ability to provide personalized dosimetry. By using 124I-PET imaging before administering therapeutic doses of 131I, clinicians can accurately measure the iodine uptake in both the primary tumor and metastatic sites, allowing for the calculation of optimal therapeutic doses. This is particularly valuable in patients with RAI-refractory DTC or those at risk of over- or under-treatment with standard 131I

 doi:10.20944/preprints202409.2036.v

dosages [46]. 124I-PET allows for precise quantification of RAI uptake in metastatic sites, which can significantly impact treatment decisions. For example, it can guide the decision to escalate or de-escalate the dose of 131I or determine whether RAI therapy is even appropriate for patients with low uptake [47].

High Sensitivity for Metastatic Disease: In contrast to conventional 131I imaging, 124I-PET/CT provides a higher resolution, enabling the detection of smaller metastases and more precise localization of iodine-avid lesions. Studies have shown that 124I PET/CT can detect micro metastases, particularly in lymph nodes and pulmonary metastases, which might be missed by SPECT/CT with 131I [47].

Combination with FDG PET/CT: In certain cases, a combined approach using 124I-PET/CT and FDG PET/CT may be employed to evaluate both iodine-avid and non-iodine-avid metastatic sites, particularly in patients with advanced, aggressive variants of DTC. This dual imaging strategy provides a more comprehensive view of the disease burden, especially for patients with heterogeneous metastatic disease (i.e., both iodine-avid and non-avid lesions) [48].

Assessment of Radioiodine-Refractory DTC (RAIR-DTC): One critical application of 124I-PET/CT is in evaluating the extent of disease and functional status of metastatic lesions in RAIR-DTC patients. By accurately assessing iodine uptake, 124I-PET/CT helps identify patients who are unlikely to benefit from further RAI therapy and may need alternative treatments, such as TKIs or external beam radiotherapy [49].

124I-PET/CT is increasingly utilized in staging and treatment planning for patients with extensive metastatic thyroid cancer. By assessing iodine uptake in metastatic sites, 124I-PET/CT enables clinicians to tailor RAI therapy based on tumor-specific dosimetry. This personalized approach can improve treatment outcomes by increasing the likelihood of complete response and reducing the risk of radiation-induced toxicity. Additionally, 124I-PET/CT can identify non-iodine-avid metastases, guiding the selection of alternative treatments like surgery, external radiation, or systemic therapies. Moreover, by distinguishing metabolically active tumors from non-functional tissue, 124I-PET/CT can aid in differentiating active metastatic disease from benign or fibrotic changes post-treatment. Several studies have demonstrated the effectiveness of 124I-PET/CT in optimizing RAI therapy dosing and improving patient outcomes [50].

7.2. Emerging Applications of 124I PET/CT

Recent research is exploring the use of 124I-PET/CT in combination with other molecular imaging techniques and novel tracers. Theragnostic using 124I-labeled molecules offers a glimpse into the future of personalized thyroid cancer therapy. By combining PET imaging with targeted radioisotope therapy, clinicians may be able to treat specific tumor sites while sparing healthy tissue, a key goal in advancing the management of RAIR-DTC.

7.3. Despite Its Numerous Advantages, There Are Some Limitations to 124I-PET/CT

Availability and Cost: The use of 124I is limited by its high cost and the need for specialized equipment and expertise in dosimetry calculations. These factors make it less accessible in resource-constrained settings [50].

Radioactive Half-Life: 124I has a shorter half-life (approximately 4 days) compared to 131I, meaning the window for imaging is shorter, and some patients may require repeated scans to accurately measure iodine kinetics and calculate dosimetry.

Radiation Dose: Although 124I provides high-resolution imaging, it also delivers a higher radiation dose to patients compared to diagnostic doses of 131I, which may limit its use, particularly in paediatric or low-risk patients [49].

8. Future Challenges and Perspectives

Advances in molecular imaging, particularly the development of novel radiotracers that target specific molecular pathways, offer significant promise in overcoming current limitations in thyroid cancer management. For instance, iodine-124 PET/CT has shown considerable potential in improving the detection of iodine-avid metastatic disease, particularly in radioiodine-refractory differentiated

 doi:10.20944/preprints202409.2036.v

thyroid cancer (RAIR-DTC) patients. This imaging modality provides more accurate dosimetry and enables the visualization of smaller metastases that may be missed by traditional radioiodine (RAI) scans . Additionally, theragnostic approaches, which combine diagnostic imaging with targeted radionuclide therapy, are emerging as a highly personalized treatment strategy for advanced DTC. This dual-function approach could further refine the role of PET/CT in treatment planning, offering the ability to both detect disease and deliver therapy based on molecular characteristics, such as somatostatin receptor expression or glucose transporter (GLUT) upregulation.

Another significant challenge lies in the integration of PET/CT into the current clinical management guidelines for DTC. While PET/CT is increasingly used in specific clinical contexts, such as in cases of elevated thyroglobulin (Tg) levels but negative conventional imaging, its role remains largely supplementary to established imaging methods, such as ultrasound and conventional RAI scintigraphy. Further research and large-scale studies are required to establish standardized criteria for the optimal use of PET/CT in DTC management. Studies like the THYROPET study have already highlighted the potential of combining 124I PET/CT and FDG PET/CT in preventing futile RAI therapies [48]. Moreover, transcriptomic analysis in papillary thyroid cancer (PTC) patients, as shown in recent studies, indicates that tumor size and metabolic activity (SUVmax) are associated with distinct gene expression profiles, providing a potential avenue for PET/CT to be used in more personalized treatment approaches [51].

Future challenges in managing differentiated thyroid cancer (DTC) involve integrating molecular insights from SUVmax and gene expression profiles into clinical practice. SUVmax is associated with tumor aggressiveness, glucose metabolism, and pathways related to DNA replication, with distinct molecular characteristics observed in high SUVmax tumors. Based on subgroup analysis, genes like PSG5, TFF3, SOX2, SL5A5, SLC5A7, HOXD10, FER1L6, and IFNA1 were significantly associated with tumor aggressiveness [52]. Both high SUVmax PTMC and macro-PTC are enriched in pathways of DNA replication and cell cycle, while gene sets for purine metabolism are enriched only in high SUVmax macro-PTC. These findings highlight the molecular characteristics of high SUVmax tumors and the metabolism involved in DTC growth. However, challenges remain in standardizing advanced imaging like FDG-PET/CT and identifying patients who would benefit most. Further research and advances in molecular imaging and theragnostic are crucial to refine personalized treatment strategies for aggressive DTC.

Future perspectives should also focus on improving access to novel imaging technologies, such as [68Ga] Ga-DOTA-based PET/CT tracers, which are currently used for imaging somatostatin receptor-positive neuroendocrine tumors and may also be beneficial in select cases of DTC with neuroendocrine differentiation. As molecular imaging continues to evolve, its integration into routine clinical practice for DTC will depend on robust evidence demonstrating improved patient outcomes and cost-effectiveness.

While studies suggest that PSMA PET/CT may outperform FDG PET/CT in detecting bone and lung lesions, and FAPI-based tracers show promise in identifying radioiodine-refractory disease, their clinical utility must be validated through larger trials [44]. Moreover, 18F-TFB's potential for non-invasive NIS imaging presents a valuable opportunity for improved cervical lymph node metastasis detection. However, the limitations of current literature—such as small sample sizes, variability in study designs, and the potential omission of relevant studies—underscore the challenge of drawing definitive conclusions. The observed heterogeneity among studies further complicates the establishment of clear guidelines for clinical application. Therefore, future research should prioritize head-to-head comparisons of these tracers to enhance diagnostic accuracy and optimize patient stratification in the evolving landscape of DTC management.

Advances in molecular imaging, such as the development of novel radiotracers that target specific molecular pathways in thyroid cancer, may overcome some of these limitations. For example, iodine-124 PET/CT has shown promise in improving the detection of iodine-avid metastatic disease, offering a potential alternative to traditional RAI scans. Additionally, theragnostic, combining diagnostic imaging and targeted therapy, is an emerging field that could further refine the role of PET/CT in the management of DTC.

 doi:10.20944/preprints202409.2036.v

Another challenge is the integration of PET/CT into the current management guidelines for DTC. While PET/CT is increasingly used in certain clinical situations, its role remains largely supplementary to conventional imaging methods such as ultrasound and RAI scanning. Further research is needed to establish standardized criteria for its use and to determine which patients are most likely to benefit from PET/CT.

9. Conclusions

PET/CT is increasingly recognized as a valuable tool in managing differentiated thyroid cancer, particularly in detecting recurrent or metastatic disease in patients with non-iodine-avid tumors or elevated Tg levels. While it is not typically part of the initial diagnostic process, its role in staging, recurrence detection, and monitoring treatment response is expanding. Future developments in novel radiotracers and theragnostic applications may further enhance the utility of PET/CT in thyroid cancer, offering the potential for more personalized and effective treatment strategies. However, challenges related to cost, availability, and standardization must be addressed to fully realize the potential of PET/CT in routine clinical practice.

Table 1. PET/CT Applications in Differentiated Thyroid Cancer.

Stage of DTC	PET/CT Role
Initial Diagnosis	Limited role, mainly for incidental thyroid nodules
Staging	Supplementary to conventional imaging in selected cases (e.g., non-iodine-avid tumors)
Recurrence Detection	Valuable for identifying recurrent or metastatic disease, especially in patients with elevated Tg and negative RAI scans
Follow-up	Essential for monitoring patients with high-risk DTC, particularly those with aggressive subtypes or persistent disease

Table 2. Emerging Radiotracers for PET/CT in Thyroid Cancer.

Radiotracer	Target	Potential Applications
18F-FDOPA	Dopamine receptors	Medullary thyroid carcinoma
68Ga-DOTA-TATE/NOC/TOC	Somatostatin receptors	Neuroendocrine features in DTC
18F-TFB	Sodium iodide symporter (NIS)	Non-invasive NIS imaging, recurrence detection, pre-operative evaluation
68Ga-DOTA-FAPI-04	Fibroblast activation protein	Detection of RAI-refractory DTC lesions

Abbreviations

DTC	Differentiated Thyroid Cancer
PTC	Papillary Thyroid Carcinoma
FTC	Follicular Thyroid Carcinoma
WHO	World Health Organization
FNAB	Fine-Needle Aspiration Biopsy
RAI	Radioactive Iodine
PET/CT	Positron Emission Tomography/Computed Tomography
FDG	18F-Fluorodeoxyglucose
ATA	American Thyroid Association
AJCC	American Joint Committee on Cancer
Tg	Thyroglobulin
RAIR-DTC	Radioactive Iodine-Refractory Differentiated Thyroid Cancer
PRRT	Peptide Receptor Radionuclide Therapy
NIS	Sodium Iodide Symporter
FAP	Fibroblast Activation Protein
SUV	Standardized Uptake Value

 doi:10.20944/preprints202409.2036.v

References

1. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013;2013:965212.
2. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. JAMA. 2006 May 10;295(18):2164-7.
3. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994 Nov;97(5):418-28.
4. Sherman SI. Thyroid carcinoma. Lancet. 2003 Feb 8;361(9356):501-11.
5. Schlumberger M, Brose M, Elisei R, Leboulleux S, Luster M, Pitoia F, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. Lancet Diabetes Endocrinol. 2014 May;2(5):356-68.
6. Pește an C, Pavel A, Piciu D. The Role of SPECT/CT and PET/CT Hybrid Imaging in the Management of Ectopic Thyroid Carcinoma—A Systematic Review. *Diagnostics*. 2021;11(7):1234. doi:10.3390/diagnostics11071234.
7. Tata Memorial Centre. Thyroid and parathyroid cancers. In: Tata Memorial Centre Textbook of Oncology. [Internet]. 2024 [cited 2024 Aug 30]. p. 437–50
8. Jasim S, Dean DS, Gharib H. Fine-needle aspiration of the thyroid gland. *Thyroid*. 2020;30(8):1079-1093.
9. Wang H, Dai H, Li Q, Shen G, Shi L, Tian R. Investigating 18F-FDG PET/CT parameters as prognostic markers for differentiated thyroid cancer: A systematic review. *Front Oncol*. 2021;11:648658. doi: 10.3389/fonc.2021.648658. PMCID: PMC8158293. PMID: 34055616.
10. Haugen BR, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133. doi: 10.1089/thy.2015.0020.
11. Pattison DA, et al. 18F-fluorodeoxyglucose-avid thyroid incidentalomas: the importance of contextual interpretation. J Nucl Med. 2017;Oct 12:pii: jnumed.117.198085.
12. Treglia G, Bertagna F, Sadeghi R, Verburg FA, Ceriania L, Giovanella L. Focal thyroid incidental uptake detected by 18F-fluorodeoxyglucose positron emission tomography: meta-analysis on prevalence and malignancy risk. Nuklearmedizin 2013; 52:130–136
13. Kim H, Kim SJ, Kim IJ, Kim K. Thyroid incidentalomas on FDG PET/CT in patients with nonthyroid cancer: a large retrospective monocentric study. Onkologie 2013; 36:260–264
14. Tang X, Shi L, Zhao Z, Wang J, Yang R, Huang Y, et al. Clinical role of 18F-FDG PET/CT for detection of radioactive iodine refractory differentiated thyroid cancer. *Medicine (Baltimore)*. 2023 Jun 16; 102(24): e33878. doi: 10.1097/MD.0000000000033878. PMCID: PMC10270557. PMID: 37327310.
15. Zhou X, Zheng Z, Chen C, Zhao B, Cao H, Li T, Liu X, Wang W, Li Y. Clinical characteristics and prognostic factors of Hurthle cell carcinoma: a population-based study. *BMC Cancer*. 2020 May 12;20(1):407.
16. Schlumberger M, Tubania M, De Vathaire F, et al. Long-term results of treatment of 283 patients with lung and bone metastases from differentiated thyroid carcinoma. J Clin Endocrinol Metab 1986; 63:960–967
17. Karpinski S, Martineau P, Zeng W. 18F-FDG PET/CT imaging and the characterization of synchronous primary lung cancer versus intrapulmonary metastasis and primary versus metastatic lung cancer: a narrative review. *Can J Med Imaging*. 2024;6:1-12.
18. Bongiovanni M, Paone G, Ceriani L, Pusztaszeri M. Cellular and molecular basis for thyroid cancer imaging in nuclear medicine. Clin Transl Imaging. 2013;1:149–61.
19. Df Zampella E, Klain M, Pace L, Cuocolo A. PET/CT in the management of differentiated thyroid cancer. *Diagn Interv Imaging*. 2021;102(9):515-523.
20. Albano D, Tulchinsky M, Dondi F, Mazzoletti A, Bertagna F, Giubbini R. The role of Tg kinetics in predicting 2-[18F]-FDG PET/CT results and overall survival in patients affected by differentiated thyroid carcinoma with detectable Tg and negative 131I-scan. Endocrine. 2021;74(2):332–339
21. Df Salvatore B, Klain M, Nicolai E, D'Amico D, De Matteis G, Raddi M, et al. Prognostic role of FDG PET/CT in patients with differentiated thyroid cancer treated with 131-iodine empiric therapy. Medicine (Baltimore). 2017;96(42). doi: 10.1097/MD.0000000000008344.
22. Fugazzola, L.; Elisei, R.; Fuhrer, D.; Jarzab, B.; Leboulleux, S.; Newbold, K.; Smit, J. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. Eur. Thyroid J. 2019, 8, 227–245.

 doi:10.20944/preprints202409.2036.v

23. Bertagna, F.; Albano, D.; Bosio, G.; Piccardo, A.; Dib, B.; Giubbini, R. 18F-FDG-PET/CT in Patients Affected by Differentiated Thyroid Carcinoma with Positive Thyroglobulin Level and Negative 131I Whole Body Scan. It's Value Confirmed by a Bicentric Experience. Curr. Radiopharm. 2016, 9, 228–234.
24. Albano, D.; Tulchinsky, M.; Dondi, F.; Mazzoletti, A.; Lombardi, D.; Bertagna, F.; Giubbini, R. Thyroglobulin doubling time offers a better threshold than thyroglobulin level for selecting optimal candidates to undergo localizing [(18)F]FDG PET/CT in non-iodine avid differentiated thyroid carcinoma. Eur. J. Nucl. Med. Mol. Imaging 2021, 48, 461–468.
25. Dong MJ, Liu ZF, Zhao K, et al. Value of 18F-FDG-PET/PET-CT in differentiated thyroid carcinoma with radioiodine-negative whole-body scan: a meta-analysis. Nucl Med Commun 2009; 30:639–650
26. Miller ME, Chen Q, Elashoff D, Abemayor E, St John M. Positron emission tomography and positron emission tomography-CT evaluation for recurrent papillary thyroid carcinoma: meta-analysis and literature review. Head Neck 2011; 33:562–565
27. Weber T, Ohlhauser D, Hillenbrand A, Henne-Bruns D, Reske SN, Luster M. Impact of FDGPET computed tomography for surgery of recurrent or persistent differentiated thyroid carcinoma. Horm Metab Res 2012; 44:904–908
28. Seo JH, Lee SW, Ahn BC, Lee J. Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: special emphasis on using 18F-FDG PET/CT. Clin Endocrinol (Oxf) 2010; 72:558–563
29. Bertagna F, Biasiotto G, Orlando E, Bosio G, Giubbini R. Role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in patients affected by differentiated thyroid carcinoma, high thyroglobulin level, and negative 131I scan: review of the literature. Jpn J Radiol 2010; 28:629–636
30. Giovanella L, Trimboli P, Verburg FA, et al. Thyroglobulin levels and thyroglobulin doubling time independently predict a positive 18F-FDG PET/CT scan in patients with biochemical recurrence of differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging 2013; 40:874–880
31. Zoller M, Kohlfuerst S, Igerc I, et al. Combined PET/CT in the follow-up of differentiated thyroid carcinoma: what is the impact of each modality? Eur J Nucl Med Mol Imaging 2007; 34:487–495
32. Yang JH, Maciel RMB, Nakabashi CCD, Janovsky CCPS, Padovani RP, Macellaro D, Camacho CP, Osawa A, Wagner J, Biscolla RPM. Clinical utility of 18F-FDG PET/CT in the follow-up of a large cohort of patients with high-risk differentiated thyroid carcinoma. Arch Endocrinol Metab. 2017;61(5):416-425. doi: 10.1590/2359-3997000000285. PMCID: PMC10522253. PMID: 28977157.
33. Vural GU, Akkas BE, Ercakmak N, Basu S, Alavi A. Prognostic significance of FDG PET/CT on the follow-up of patients of differentiated thyroid carcinoma with negative 131I whole-body scan and elevated thyroglobulin levels: correlation with clinical and histopathologic characteristics and long-term follow-up data. Clin Nucl Med 2012; 37:953–959
34. Schönberger J, Rüschoff J, Grimm D, et al. Glucose transporter 1 gene expression is related to thyroid neoplasms with an unfavorable prognosis: an immunohistochemical study. Thyroid 2002; 12:747–754
35. Robbins RJ, Wan Q, Grewal RK, et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab 2006; 91:498–505
36. Piao HH, Jeon S, Yoo SW, Ryu YJ, Kim DY, Pyo A, Bom HS, Min JJ, Kwon SY. A stepwise approach using metastatic lymph node ratio-combined thyroglobulin for customization of [18F]FDG-PET/CT indication to detect persistent disease in patients with papillary thyroid cancer. Diagnostics. 2021;11(5):836. doi:10.3390/diagnostics11050836.
37. Gim H, Lee DK, Park HS, Jeong YJ. Diagnostic value of SUV in 18F-FDG PET/CT for papillary thyroid cancer. Int J Thyroidol. 2020;13(1):37-42. doi:10.11106/ijt.2020.13.1.37.
38. Santhanam P, Khthir R, Solnes LB, Ladenson PW. The relationship of BrafV600E mutation status to FDG PET/CT avidity in thyroid cancer: a review and meta-analysis. Int J Thyroidol. 2018;24(1):21-26. doi:10.11106/ijt.2018.24.1.21.
39. Araz M, Soydal Ç, Demir Ö, Gökcan MK, Küçük NÖ. The Role of 18F-FDOPA PET/CT in Recurrent Medullary Thyroid Cancer Patients with Elevated Serum Calcitonin Levels. J Clin Endocrinol Metab. 2021;106(4):1234-1241. doi:10.1210/clinem/dgaa947.
40. Pajak C, Cadili L, Nabata K, Wiseman SM. 68Ga-DOTATATE-PET shows promise for diagnosis of recurrent or persistent medullary thyroid cancer: A systematic review. Am J Surg. 2022;224(6):1260-7. doi: 10.1016/j.amjsurg.2022.03.046.

41. Pajak C, Cadili L, Nabata K, Wiseman SM. The role of Ga-DOTATATE PET/CT and F-FDG PET/CT in the follow-up of patients with medullary thyroid cancer. Hellenic J Nucl Med. 2022;25(1):12-18.
42. Ocak M, Demirci E, Kabasakal L, Aygun A, Tutar RO, Araman A, Kanmaz B. Evaluation and comparison of Ga-68 DOTA-TATE and Ga-68 DOTA-NOC PET/CT imaging in well-differentiated thyroid cancer. Nucl Med Commun. 2013;34(11):1084–9. doi: 10.1097/MNM.0b013e328364eaab.
43. Chen Y., Zheng S., Zhang J., Yao S., Miao W. 68Ga-DOTA-FAPI-04 PET/CT Imaging in Radioiodine-Refractory Differentiated Thyroid Cancer (RR-DTC) Patients. Ann. Nucl. Med. 2022;36:610–622. doi: 10.1007/s12149-022-01742-8.
44. Coerts HI, de Keizer B, Verburg FA. Advances in the development of positron emission tomography tracers for improved detection of differentiated thyroid cancer. Cancers (Basel). 2024 Apr;16(7):1401. doi: 10.3390/cancers16071401. PMCID: PMC11010999. PMID: 38611079.
45. Lubberink M, Abdul Fatah S, Brans B, Hoekstra OS, Teule GJ. The role of (124)I-PET in diagnosis and treatment of thyroid carcinoma. Q J Nucl Med Mol Imaging. 2008 Mar;52(1):30-6.
46. Wierts R, Brans B, Havekes B, Kemerink GJ, Halders SG, Schaper NN, et al. Dose-Response Relationship in Differentiated Thyroid Cancer Patients Undergoing Radioiodine Treatment Assessed by Means of 124I PET/CT. J Nucl Med. 2016 Jul;57(7):1027-32. doi: 10.2967/jnumed.115.168799
47. Kuker R, Sztejnberg M, Gulec S. I-124 imaging and dosimetry. Mol Imaging Radionucl Ther. 2017 Feb 9;26(Suppl 1):66-73. doi: 10.4274/2017.26.suppl.07. PMCID: PMC5305300.
48. Kist JW, de Keizer B, Stokkel MP, Hoekstra OS, Vogel WV; THYROPET study group. Recurrent differentiated thyroid cancer: towards personalized treatment based on evaluation of tumor characteristics with PET (THYROPET Study): study protocol of a multicenter observational cohort study. BMC Cancer. 2014 Jun 5;14:405. doi: 10.1186/1471-2407-14-405. PMCID: PMC4058699.
49. Petranović Ovčariček P, Campenni A, de Keizer B, Deandreis D, Kreissl MC, Vrachimis A, Tuncel M, Giovanella L. Molecular Theranostics in Radioiodine-Refractory Differentiated Thyroid Cancer. Cancers (Basel). 2023 Sep;15(17):4290. doi: 10.3390/cancers15174290. PMCID: PMC10486510. PMID: 37686566.
50. Lee J, Nah KY, Kim RM, Oh YJ, An YS, Yoon JK, An GI, Choi TH, Cheon GJ, Soh EY, Chung WY. Effectiveness of [(124)I]-PET/CT and [(18)F]-FDG-PET/CT for localizing recurrence in patients with differentiated thyroid carcinoma. J Korean Med Sci. 2012 Sep;27(9):1019–26. doi: 10.3346/jkms.2012.27.9.1019.
51. Soyluoglu S, Tastekin E, Andac B, et al. Tumor Microenvironment Features as Predictive Biomarkers in Metastatic Differentiated Thyroid Cancer and Their Relationship With 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG PET/CT) Metabolic Parameters. Cureus. 2023 Sep 5;15(9) doi:10.7759/cureus.44751
52. Ju S-H, Lee SE, Yi S, Choi NR, Kim KH, Kim SM, Koh J-Y, Kim S-K, Kim S-Y, Heo JY, Park JO, Park S, Koo BS, Kang YE. Transcriptomic characteristics according to tumor size and SUVmax in papillary thyroid cancer patients. *Sci Rep.* 2024;14:11005. doi: 10.1038/s41598-024-61839-0. PMCID: PMC11094162. PMID: 38745021.