Role of PET/CT In Molecular Imaging of Thyroid Cancer: A Comprehensive Review

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Abstract- Background: Thyroid cancer represents the most common endocrine malignancy, with a steadily increasing global incidence. While thyroidectomy followed by radioiodine therapy achieves effective disease control in most patients, a substantial subset develops recurrent, metastatic, or radioiodine-refractory disease requiring advanced imaging strategies. Positron emission tomography/computed tomography (PET/CT) has emerged as a key hybrid modality, combining metabolic information with precise anatomical localisation to enhance diagnostic accuracy.

Objective: This review evaluates the established and emerging roles of PET/CT across major thyroid cancer subtypes — differentiated thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, and radioiodine-refractory disease — with emphasis on radiotracer selection, clinical indications, diagnostic performance, impact on therapeutic decision-making, and theranostic potential.

Methods: A structured literature search was performed using databases including PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science for peer-reviewed studies published between January 2009 and February 2026. Search terms incorporated controlled vocabulary and keywords related to PET/CT, thyroid malignancies, molecular imaging, FDG, TENIS syndrome, radioiodine-refractory disease, medullary thyroid carcinoma, and fibroblast activation protein inhibitors. After applying predefined eligibility criteria, 42 studies were included for qualitative synthesis.

Results: FDG PET/CT was able to detect recurrent thyroid cancer with good accuracy, correctly identifying disease in most patients and helping doctors change treatment plans in about half of the cases. DOTATATE PET/CT showed useful detection rates in medullary thyroid cancer and helped in selecting patients for targeted radionuclide therapy. New FAPI-based tracers appear promising, especially in patients whose cancer does not take up iodine or is not clearly seen on FDG scans. Increasing TSH levels before FDG PET/CT improved the chances of finding cancer during follow-up of differentiated thyroid cancer.

Conclusion: Appropriate radiotracer selection guided by tumour biology and clinical context is critical for optimal PET/CT utilisation in thyroid oncology. Integration of PET/CT into multidisciplinary care pathways, adherence to evidence-based protocols, and expansion of theranostic strategies are expected to further improve patient outcomes. Future directions include artificial-intelligence-assisted image interpretation, receptor-targeted tracers, and broader application of PET/MRI in personalised thyroid cancer management.

Keywords: PET/CT; Thyroid Cancer; Molecular Imaging; FDG; TENIS Syndrome; Radioiodine-Refractory; DOTATATE; FAPI; Theranostics; Differentiated Thyroid Carcinoma; Medullary Thyroid Carcinoma; Nuclear Medicine

I.INTRODUCTION

Thyroid cancer ranks as the most prevalent endocrine malignancy worldwide, contributing approximately 3.4% of all incident cancer diagnoses annually. Its global incidence has increased nearly threefold over the past four decades — from 4.4 to 14.4 cases per 100,000 persons — a trend largely attributable to expanded diagnostic surveillance, widespread use of neck ultrasonography, and the incidental detection of sub-centimetre papillary microcarcinomas. In 2024, approximately 44,000 new thyroid cancer cases were estimated in the United States, where the disease constitutes the fifth most common malignancy in women.

Roughly 90% of thyroid cancers are classified as differentiated thyroid carcinoma (DTC), encompassing papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). The ten-year disease-specific survival following total thyroidectomy and radioiodine (131I) ablation exceeds 95% in most series. Nevertheless, 5–15% of DTC patients experience disease progression or biochemical recurrence, including the diagnostically challenging scenario of elevated serum thyroglobulin (Tg) with a negative 131I whole-body scan — a condition designated Thyroglobulin-Elevated Negative Iodine Scintigraphy (TENIS) syndrome. This pattern reflects tumour dedifferentiation characterised by loss of sodium-iodide symporter (NIS) expression and concurrent upregulation of glucose metabolism via the Warburg effect.

Medullary thyroid carcinoma (MTC), originating from parafollicular C-cells, accounts for 3–5% of all thyroid malignancies and presents unique diagnostic challenges owing to its distinct embryological derivation, reliance on calcitonin and carcinoembryonic antigen (CEA) as tumour markers, and resistance to radioiodine therapy. Anaplastic thyroid carcinoma (ATC), although representing fewer than 2% of thyroid cancers, is among the most lethal of all human solid tumours, with a median overall survival of 3–5 months. Both subtypes require specialised imaging approaches that extend beyond conventional radioiodine scintigraphy.

PET/CT — integrating the metabolic and functional resolution of positron emission tomography with the anatomical precision of multidetector computed tomography — has transformed oncological imaging practice. In thyroid cancer, PET/CT enables whole-body disease mapping, metabolic characterisation and dedifferentiation assessment, treatment response evaluation, and, increasingly, stratification of patients for targeted radionuclide therapy. The repertoire of available PET radiotracers has expanded considerably beyond 18F-fluorodeoxyglucose (18F-FDG) to encompass iodine-124 (124I), 68Gallium-labelled somatostatin receptor analogues, 18F-DOPA, and novel fibroblast activation protein inhibitor (FAPI)-based agents, each exploiting discrete molecular targets.

This review offers a systematic, evidence-based assessment of the current and evolving roles of PET/CT in thyroid cancer management. It encompasses all major histological subtypes and addresses radiotracer selection, guideline-concordant clinical indications, diagnostic performance data, management impact, theranostic applications, and emerging technological developments. It is intended as a practical resource for nuclear medicine physicians, diagnostic radiologists, endocrinologists, and thyroid oncologists.

II.MATERIALS AND METHODS

2.1 Search Strategy:

We performed a structured literature search in four major databases: PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science. The search included studies published between January 2009 and February 2026. We used combinations of keywords related to PET/CT, thyroid cancer, molecular imaging, FDG, TENIS syndrome, radioiodine-refractory disease, theranostics, DOTATATE, and FAPI.

Studies in all languages were considered, but papers without an English abstract were excluded.

2.2 Inclusion and Exclusion Criteria:

We included studies that Evaluated PET/CT in confirmed thyroid cancer patients Reported diagnostic accuracy results (such as sensitivity or specificity) were cohort studies with at least 20 patients, systematic reviews, meta-analyses, or major clinical guidelines from recognised organisations such as American Thyroid Association, European Association of Nuclear Medicine, European Society for Medical Oncology, National Comprehensive Cancer Network, and International Atomic Energy Agency.

We excluded case reports with very small numbers, conference abstracts without full text, studies focused only on incidental thyroid findings, and studies using PET without CT.

III.THYROID CANCER BIOLOGY RELEVANT TO PET IMAGING

3.1 Molecular Basis of Radiotracer Uptake:

How well a PET tracer works in thyroid cancer depends on the biology of the tumour. Well-differentiated thyroid cancers behave more like normal thyroid cells. They can absorb iodine, produce thyroglobulin, and respond to TSH.As the tumour becomes more aggressive and less differentiated, these normal thyroid functions gradually decrease. Genetic mutations drive this change. At the same time, the tumour shifts to a high-glucose-use metabolism. This increases glucose transporter activity, so the tumour takes up more FDG on PET scans. Because of this, there is an important pattern called the "flip-flop phenomenon." Well-differentiated tumours usually take up iodine but show low FDG uptake. Poorly differentiated or iodine-resistant tumours show high FDG uptake but low iodine uptake. This explains why FDG PET/CT is most helpful in patients whose disease is not clearly seen on radioiodine scans.

3.2 Molecular Subtypes and Genomic Classification:

According to the thyroid cancer study from The Cancer Genome Atlas, thyroid cancers can be broadly divided into two main molecular groups.

The first group is the BRAF-like type, which mainly includes classical papillary thyroid cancers. These tumours often lose their normal thyroid features over time and are more likely to become radioiodine-resistant or develop TENIS syndrome.

The second group is the RAS-like type, which includes follicular-pattern tumours such as follicular variant papillary cancer and follicular thyroid cancer. These tumours usually keep some ability to absorb iodine and remain more differentiated.

Understanding these molecular types is becoming important because they may help doctors choose the most suitable PET tracer and targeted therapy for each patient.

3.3 Pathological Classification and Imaging Implications;

The latest tumour classification from the World Health Organization (2022) introduced updated thyroid tumour categories. These include NIFTP (a low-risk tumour with very good prognosis) and newly defined high-grade follicular cell cancers. Poorly differentiated thyroid carcinoma lies between well-differentiated cancer and anaplastic cancer. It may sometimes absorb iodine, but it usually shows strong uptake on FDG PET scans. Anaplastic thyroid carcinoma is the most aggressive type. It loses almost all normal thyroid functions and does not take up iodine. Therefore, FDG PET/CT becomes the main imaging method for staging the disease and monitoring treatment response.

IV.PET RADIOTRACERS IN THYROID CANCER IMAGING

4.1 18F-FDG PET/CT:

How it works:

FDG is a sugar-like tracer. Cancer cells use more sugar than normal cells, so they take up more FDG. This is especially true for aggressive or poorly differentiated thyroid cancers.

Before the scan, the patient should fast for about 6 hours. The tracer dose is given based on body weight, and scanning is done about 1 hour later.

If TSH levels are increased before the scan (either by stopping thyroid hormone tablets or giving recombinant TSH injections), the tumour takes up more FDG. This can improve cancer detection by about 15–20%.

Use in TENIS syndrome:

FDG PET/CT is mainly used in patients whose thyroglobulin is high but radioiodine scan is negative (TENIS syndrome). In these patients, FDG PET/CT can detect disease in most cases and often changes treatment plans. It helps doctors find:

- local recurrence that can be removed surgically
- areas needing radiotherapy
- distant metastases where surgery is not useful

Prognostic value:

The intensity of FDG uptake also gives information about prognosis.

Higher FDG uptake usually means:

- more aggressive disease
- higher chance of progression

- possible need for targeted systemic therapy

4.2 Iodine-124 PET/CT:

Iodine-124 PET/CT is a special scan that shows iodine-absorbing thyroid cancer more clearly than traditional iodine scans.

It can detect very small lymph nodes and lung metastases that older scans may miss.

Its main use is to calculate how much radioiodine therapy a patient actually needs. This allows personalised treatment, avoiding unnecessarily high doses and reducing side effects.

4.3 68Ga-DOTATATE / DOTATOC PET/CT:

These tracers detect somatostatin receptors, which are commonly present in medullary thyroid cancer cells.This scan can find disease in many MTC patients and is particularly good for detecting liver metastases and small lymph nodes.Guidelines from European Society for Medical Oncology recommend this scan in patients with high calcitonin levels.An important advantage is that if the scan is positive, the same receptor can be targeted for treatment using radionuclide therapy (PRRT). This makes it both a diagnostic and therapeutic tool (theranostics).

4.4 18F-DOPA PET/CT:

DOPA PET/CT works by detecting amino-acid metabolism in tumour cells.

It is useful in medullary thyroid cancer and can sometimes detect small lymph node metastases better than FDG or DOTATATE scans.

It is also helpful in patients with MEN-related endocrine conditions where multiple tumours may be present.

4.5 FAPI PET/CT:

FAPI tracers are very new. Instead of targeting tumour cells directly, they target special supportive cells (fibroblasts) present around many cancers. These scans often produce very clear images with high tumour contrast. They may be especially useful in patients whose cancer is not seen on iodine scans or FDG PET.

Research studies suggest FAPI imaging may detect disease missed by other scans, and combined diagnostic-treatment approaches using FAPI are currently being tested in clinical trail

V.CLINICAL INDICATIONS BY THYROID CANCER SUBTYPE:ESTED IN CLINICAL TRIALS

5.1 High-Risk Differentiated Thyroid Cancer

Apart from TENIS syndrome, some types of differentiated thyroid cancer are known to behave more aggressively. These types need FDG PET/CT earlier in their management. Hurthle cell cancer, now recognised as a separate tumour type in the latest classification from the World Health Organization, usually does not absorb iodine well. Because of this, FDG PET/CT becomes very important for staging and follow-up.

Other aggressive variants, such as tall cell, hobnail, columnar cell, and widely invasive follicular cancers , also have a higher chance of recurrence and faster tumour progression.

When iodine scans are negative but doctors still suspect disease, PET/CT is recommended. This approach is supported by the risk-based guidelines of the American Thyroid Association.

5.2 Paediatric Thyroid Cancer:

In children, thyroid cancer (mostly papillary type) often spreads to neck lymph nodes and sometimes to the lungs. However, it usually still absorbs iodine well and responds to standard treatment.

FDG PET/CT is mainly needed in children when:

- tumour markers are high but iodine scans are negative, or
- disease progression is suspected but routine tests are unclear.

PET/CT can be performed safely in children when special low-dose protocols are used. These protocols follow radiation-safety recommendations such as those promoted by the Image Gently Alliance, which aim to minimise radiation exposure in paediatric imaging.

VI.DIAGNOSTIC PERFORMANCE

6.1 Factors Affecting PET/CT Accuracy:

Several factors can affect how well FDG PET/CT detects thyroid cancer:

- TSH level: Higher TSH levels improve scan accuracy. When TSH is stimulated, more tumours become visible.
- Thyroglobulin level: PET/CT works better when thyroglobulin levels are high, especially above 10 ng/mL, and detection becomes very high when levels are above 50 ng/mL.
- Tumour type: Aggressive cancers such as poorly differentiated or Hurthle cell cancers usually show stronger FDG uptake than typical papillary cancers.
- Patient preparation: Proper fasting, normal blood sugar, and avoiding exercise before the scan help reduce normal body uptake and improve image quality.
- Scanner quality: Newer digital PET scanners can detect smaller tumours more clearly than older machines.

6.2 Comparison with Conventional Imaging:

Studies show that FDG PET/CT is better than many routine imaging tests when iodine scans are negative (TENIS situation). PET/CT detects neck recurrence more accurately than ultrasound or CT. It can also find distant metastases that were not suspected before. When PET/CT is combined with neck ultrasound, detection becomes very high. In iodine-resistant disease, PET/CT works much better than iodine scans. PET/CT also gives clearer images and scans the whole body in one session compared with older nuclear imaging methods.

VII.PET/MRI HYBRID IMAGING IN THYROID CANCER

- PET/MRI combines PET scanning with MRI in one machine. It has some advantages over PET/CT in certain thyroid cancer situations.
- MRI gives much better soft-tissue detail than CT. Because of this, PET/MRI can more clearly show how cancerous lymph nodes are related to nearby blood vessels, which helps surgeons plan operations more safely.
- PET/MRI is also very useful for detecting brain metastases, especially now that patients are living longer due to modern targeted therapies.

However, PET/MRI also has some limitations. It is expensive, not widely available, takes longer to perform, and has some technical difficulties in image correction.

Because of these reasons, PET/MRI is not routinely used instead of PET/CT in thyroid cancer. It may be preferred in special situations such as:

- children (to reduce radiation exposure),
- suspected tumour spread near major blood vessels,possible liver or brain metastases.

VIII.ARTIFICIAL INTELLIGENCE IN THYROID CANCER PET/CT

Artificial intelligence (AI) is now being used in PET/CT imaging of thyroid cancer to help doctors analyse scans more quickly and accurately.

AI programs can help detect cancer lesions automatically. Some computer models perform almost as well as experienced nuclear medicine doctors in finding recurrent disease. This can save time and improve workflow in busy hospitals.

AI tools can also measure tumour activity automatically, such as metabolic tumour volume and total lesion glycolysis. These measurements are important because they help predict how aggressive the disease is and how the patient may respond to treatment.

Another growing field is radiomics, where many small imaging features are extracted from PET/CT scans and analysed using computer models. These features can help predict tumour behaviour, genetic mutations, risk of recurrence, and whether the cancer may become resistant to radioiodine therapy.

Recent research suggests that AI models combining imaging features with clinical data may help identify high-risk patients earlier, allowing doctors to choose better imaging methods and treatments sooner.

However, before AI tools can be used routinely in clinical practice, they still need large studies and validation in different patient populations.

IX.LIMITATIONS AND CURRENT CHALLENGES

9.1 Technical Limitations

Although PET/CT is very useful in thyroid cancer, it still has some technical limits.

Small tumours below about 5 mm may not be seen clearly on PET scans, which is important because thyroid cancer can spread as very tiny lung or lymph node metastases.

Sometimes PET/CT can also give false positive results. Increased FDG uptake may occur in normal or non-cancerous conditions such as:

- brown fat activity
- enlarged thymus in young patients after treatment
- inflamed or reactive lymph nodes
- healing surgical areas
- vocal cord overactivity after nerve injury
- infections like tuberculosis or sarcoidosis
- autoimmune thyroid inflammation
- Newer digital PET scanners can detect disease better, but they are expensive and not available in many centres worldwide.

9.2 Interpretation and Clinical Challenges

Reading PET/CT scans in thyroid cancer requires experience and knowledge of the patient's history.

Some common difficulties include:

- telling normal post-surgery uptake from true cancer in the neck
- judging treatment response in patients on targeted drugs, where PET may show improvement before CT does
- interpreting DOTATATE scans in medullary cancer, since some normal organs naturally show tracer uptake and may hide nearby metastases

9.3 Availability, Equity, and Cost Issues:

Not all PET tracers are easily available everywhere. FDG is widely accessible, but other tracers need special equipment or radiopharmacy support. Some newer tracers are still used only in research centres.Even with these limitations, studies show that PET/CT is still cost-effective in thyroid cancer because it:

- avoids unnecessary surgeries
- helps choose correct radioiodine dose
- prevents ineffective treatments

Overall, PET/CT may reduce total treatment costs by improving decision-making.

X. FUTURE DIRECTIONS

PET/CT technology for thyroid cancer is improving quickly in many ways.

New total-body PET scanners can scan the whole body at once with much higher sensitivity than older machines. They can produce clearer images, use very low radiation doses, and even show how tracers move through the body over time. This is especially useful in children, where reducing radiation exposure is important.

Researchers are also developing new PET tracers that target specific tumour markers, blood vessels, or immune proteins. These may help doctors select the best treatments for individual patients in the future.

Another important development is combining PET imaging with blood tests such as circulating tumour DNA. This may help detect treatment resistance earlier and personalise follow-up schedules.

Artificial intelligence is also expected to become part of routine PET/CT reporting. AI may help detect lesions automatically, measure tumour activity, generate structured reports, and compare scans over time.

International experts are also working to create standard reporting systems for thyroid PET/CT, similar to structured reporting systems already used in other cancers.

XI.CONCLUSION

PET/CT has greatly improved how thyroid cancer is diagnosed, staged, and monitored. It provides information about tumour location, activity, and behaviour that other imaging methods cannot offer alone. Choosing the correct PET tracer based on tumour type, treatment history, and clinical question is essential for getting the best results.

- FDG PET/CT remains the main scan for patients with suspected recurrence when iodine scans are negative.
- DOTATATE PET/CT is important in medullary thyroid cancer and helps identify patients suitable for targeted radionuclide therapy.
- Iodine-124 PET/CT allows personalised radioiodine treatment planning.
- New tracers such as FAPI may help detect disease that other scans miss.

For PET/CT to give maximum benefit, it should be used within multidisciplinary tumour boards and according to established guidelines from organisations such as the American Thyroid Association, European Association of Nuclear

Medicine, European Society for Medical Oncology, and National Comprehensive Cancer Network.

With advances in scanner technology, new tracers, AI tools, and theranostic treatments, PET/CT is expected to play an even bigger role in personalised thyroid cancer care in the coming years.

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