

## REVIEW

# Molecular imaging in thyroid cancer

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### Abstract

Molecular imaging plays an important role in the evaluation and management of thyroid cancer. The routine use of thyroid scanning in all thyroid nodules is no longer recommended by many authorities. In the initial work-up of a thyroid nodule, radioiodine imaging can be particularly helpful when the thyroid stimulating hormone level is low and an autonomously functioning nodule is suspected. Radioiodine imaging can also be helpful in the 10–15% of cases for which fine-needle aspiration biopsy is indeterminate. Therapy of confirmed thyroid cancer frequently involves administration of iodine-131 after surgery to ablate remnant tissue. In the follow-up of thyroid cancer patients, increased thyroglobulin levels will often prompt the empiric administration of <sup>131</sup>I followed by whole body radioiodine imaging in the search for recurrent or metastatic disease. <sup>131</sup>I imaging of the whole body and blood pharmacokinetics can be used to determine if higher doses of <sup>131</sup>I can be given in thyroid cancer. The utility of [<sup>18</sup>F]fluorodeoxyglucose (FDG) positron emission tomography (PET) is steadily increasing. FDG is primarily taken up by dedifferentiated thyroid cancer cells, which are poorly iodine avid. Thus, it is particularly helpful in the patient with an increased thyroglobulin but negative radioiodine scan. FDG PET is also useful in the patient with a neck mass but unknown primary, in patients with aggressive (dedifferentiated) thyroid cancer, and in patients with differentiated cancer where histologic transformation to dedifferentiation is suspected. In rarer types of thyroid cancer, such as medullary thyroid cancer, FDG and other tracers such as <sup>99m</sup>Tc sestamibi, [<sup>11</sup>C]methionine, [<sup>111</sup>In]octreotide, and [<sup>68</sup>Ga]somatostatin receptor binding reagents have been utilized. <sup>124</sup>I is not widely available, but has been used for PET imaging of thyroid cancer and will likely see broader applicability due to the advantages of PET methodology.

**Keywords:** Thyroid cancer; PET/CT; molecular imaging; papillary thyroid cancer; follicular thyroid cancer; FDG; nuclear medicine.

### Introduction

Molecular imaging plays an important role in the evaluation and management of thyroid cancer. Varying radioisotopes of iodine, most notably <sup>131</sup>I, <sup>123</sup>I, and to a lesser extent, the positron emitter <sup>124</sup>I, are useful from a diagnostic and therapeutic standpoint. [<sup>18</sup>F]Fluorodeoxyglucose (FDG) is helpful in the diagnosis of an unknown primary and in staging and restaging metastatic disease when other imaging tests are negative or inconclusive. Other radionuclide agents are also useful in selected clinical situations. In order to help clinicians put the role of molecular imaging into perspective, this review covers the epidemiology, biology, clinical work-up, and the general management of thyroid cancer.

The proper role and emerging opportunities for molecular imaging in thyroid cancer are discussed within this context.

### Epidemiology

Although thyroid nodules are common, thyroid cancer is a relatively uncommon malignancy. Overall, palpable thyroid nodules occur in about 5% of women and 1% of men, however, the prevalence is much higher in parts of the world where iodine is deficient. The estimated incidence of thyroid cancer currently is around 0.01% to 0.03% per year. Of all thyroid nodules, only about 1% to 5% are malignant resulting in an overall cancer

incidence of about 30 out of 100,000 people per year. Thyroid cancer is less common than breast, colon, lung, and malignant skin cancer and lung cancer but slightly more common than brain malignancies. Thyroid cancer is about 3 times more common in women than in men<sup>[1]</sup>.

The thyroid gland is particularly susceptible to radiation. Internal radiation from radioisotopes released from atomic bomb blasts and the Chernobyl reactor accident resulted in a marked increase in thyroid cancer particularly in children and adolescents<sup>[2]</sup>. External radiation, previously used to treat a variety of minor conditions such as tonsillitis and thymic enlargement also increases the risk and possibly the aggressiveness of thyroid cancer<sup>[3,4]</sup>. The increased risk is seen as early as 5 years after exposure, and patients remain at an increased risk of thyroid cancer for at least 30–40 years after radiation exposure<sup>[5]</sup>.

## Histology

There are several types of thyroid cancer, but the vast majority are differentiated. About 80–90% of thyroid cancers are differentiated thyroid cancer (DTC), consisting primarily of papillary carcinoma (~70% of DTC), follicular carcinoma (~20% of DTC), and Hurthle cell (~10%)<sup>[6]</sup>. The two other major thyroid cancers are anaplastic and medullary, which tend to be more aggressive and deadly. Although rare, primary lymphoma also can arise in the thyroid gland and is a consideration in the differential diagnosis.

Papillary carcinoma is the most common thyroid cancer, being responsible for about 60–70% of all thyroid cancers. Women are affected about 2–3 times more often than men. Although it occurs more frequently in the young, it is more malignant in the elderly. A history of radiation exposure increases the risk of the disease. Papillary carcinoma is the most benign form of thyroid cancer and with proper medical care is usually associated with a normal life span. It tends to spread via the lymphatic system.

Follicular carcinoma accounts for about 15% of all thyroid cancers. It is more common in the elderly and more malignant than papillary carcinoma. It tends to spread hematogenously to the lungs and bone. Prior radiation exposure increases the risk of the disease and is more common in women than in men. Follicular carcinoma also tends to be relatively benign, and associated with a normal life span.

Anaplastic carcinoma accounts for 10% or less of thyroid cancers. It is more common in the elderly and slightly more common in women than in men. It is characterized by a rapid growth rate and painful enlargement. About 80% of patients with anaplastic carcinoma die within 1 year. A rapidly growing thyroid nodule also raises the suspicion for thyroid lymphoma, particularly when the patient has increased levels of thyroid peroxidase antibodies and has Hashimoto's thyroiditis.

Medullary carcinoma occurs infrequently. It may be a sporadic disease, but also can be familial, being transmitted as an autosomal dominant trait. Medullary cancer arises from the parafollicular calcitonin producing C cells. It usually presents as an asymptomatic thyroid nodule, although it is also frequently discovered during routine screening of patients with multiple endocrine neoplasia type IIA or IIB. Metastatic spread is via the lymphatic system. Long-term survival is common.

## Clinical evaluation

In order to make an assessment of the appropriate role of molecular imaging in the diagnosis, staging, and restaging of thyroid cancer, it is important to know how thyroid cancer typically presents.

The diagnosis of a primary thyroid cancer typically starts with the finding of a nodule on self-examination. Nodules noted on self-examination should be brought to the attention of a medical professional because of the wide variety of presentations that thyroid cancer can take. A neck mass, which may be confused for a thyroid nodule, has a large differential diagnosis including congenital, inflammatory, and neoplastic diseases. When evaluating a thyroid nodule, the presumption initially is malignancy unless proven otherwise. Certainly, routine physical examination can also detect such nodules.

Thyroid nodules are also frequently discovered incidentally on imaging studies performed for an unrelated medical reason. Incidentalomas occur in up to 15% of thyroid ultrasound studies, with about 10–30% of these being malignant<sup>[7–9]</sup>. On FDG dual PET, incidentally found focal uptake of the tracer in the thyroid gland is found in about 1–4% of scans. This is an important finding, with about 25% upwards to 50% being malignant<sup>[10]</sup>. The intensity of FDG uptake can overlap substantially between malignant and benign thyroid nodules.

Factors increasing the likelihood of malignancy are young age (although the elderly have a worse prognosis), male gender (women get more nodules, but a nodule in a man is more likely to be malignant), a solitary nodule instead of multiple nodules, recent or rapid enlargement, and a stony hard consistency.

The patient is asked to estimate the time course of the condition and a rough growth rate. Associated symptoms such as hoarseness, stridor, palpitations, fatigue, and night sweats are noted. The patient's cardiovascular history is obtained. Close attention is paid to any history of radiation exposure and the presence of any other cancer.

The clinical examination is then performed, and includes an estimation of the thyroid gland's overall size. The nodule itself is then assessed for size, location, hardness, tenderness, and attachment to underlying structures. Regional lymph nodes are examined. Since thyroid nodules are often hyperfunctional, the patient's vital signs are closely evaluated along with a thorough cardiovascular examination.

Berry's sign of malignant thyroid enlargement is the absence of the carotid pulsation on inspection and palpation. This occurs because a malignant tumor tends to encase the carotid, masking its pulsation. Benign thyromegally generally does not encase the vessel or mask the carotid pulsation<sup>[11]</sup>.

## Laboratory evaluation

The laboratory work-up of a patient with a thyroid nodule typically starts with an evaluation of the patient's thyroid function tests and thyroid antibodies. For some nodules, it is appropriate to do a fine-needle aspiration (FNA) biopsy before doing additional testing. However, FNA is non-diagnostic in about 10% of cases, thus requiring further evaluation. An increased level of serum calcitonin increases the chances of medullary thyroid cancer.

In patients with known thyroid cancer who are status post thyroidectomy and post surgical radioiodine ablation, thyroglobulin levels are routinely obtained. An increased thyroglobulin level indicates recurrence of the thyroid cancer, prompting further evaluation to localize the site of recurrence.

## Conventional imaging

In most cases, the initial imaging procedure is ultrasonography. Ultrasonography is helpful in the differentiation of nodules versus cysts, however, it will not distinguish between benign and malignant nodules. High-resolution linear array transducers with frequencies between 7.5 and 15 MHz are usually used. Characteristics of malignancy on ultrasonography include a solid echo structure, hypoechogenicity, fine calcification, and an ill-defined margin<sup>[12]</sup>.

Positron emission/computed tomography (PET/CT) and magnetic resonance imaging (MRI) have a limited role in the evaluation of thyroid disease. They may be more sensitive than radionuclide imaging in the evaluation of intrathoracic goiters, especially when the goiters are poorly radiotracer avid because they contain minimal amounts of functioning tissue. CT and MRI can help plan the surgical approach when a substernal goiter requires surgical removal. For thyroid cancer, they can demonstrate tumor extent, extracapsular spread, and local invasion due to associated compressive symptoms. Unenhanced CT imaging is typically utilized, because the use of iodine contrast interferes with radioiodine imaging and therapy.

For nodules found to be indeterminate on FNA, radionuclide scintigraphy with [<sup>99m</sup>Tc]pertechnetate (assesses cellular uptake of iodine) or <sup>123</sup>I (assesses both uptake and organification) can be helpful. Nodules showing increased tracer uptake by either tracer almost always represents non-malignant disease, especially in the setting of a low level of thyroid stimulating hormone (TSH). Whole body radioiodine scans are also useful in the

staging and restaging of thyroid cancer. After a therapeutic dose of <sup>131</sup>I, any residual uptake of radioiodine more than 6 months later most likely represents residual or recurrent disease.

Other gamma emitting radionuclide agents are infrequently used. Thallium-201 has been utilized to detect recurrence of differentiated thyroid carcinoma in patients with increased serum thyroglobulin levels and negative results on radioiodine scanning. Thyroid tissue, both benign and malignant, takes up thallium-201, however benign lesions show a faster washout of the tracer<sup>[13]</sup>. [<sup>99m</sup>Tc]Sestamibi is taken up by thyroid tissue (both benign and malignant), and has been utilized in the evaluation of patients post thyroidectomy. However, it is of limited usefulness since [<sup>18</sup>F]FDG has been shown to be more sensitive for the detection of metastatic disease<sup>[14,15]</sup>.

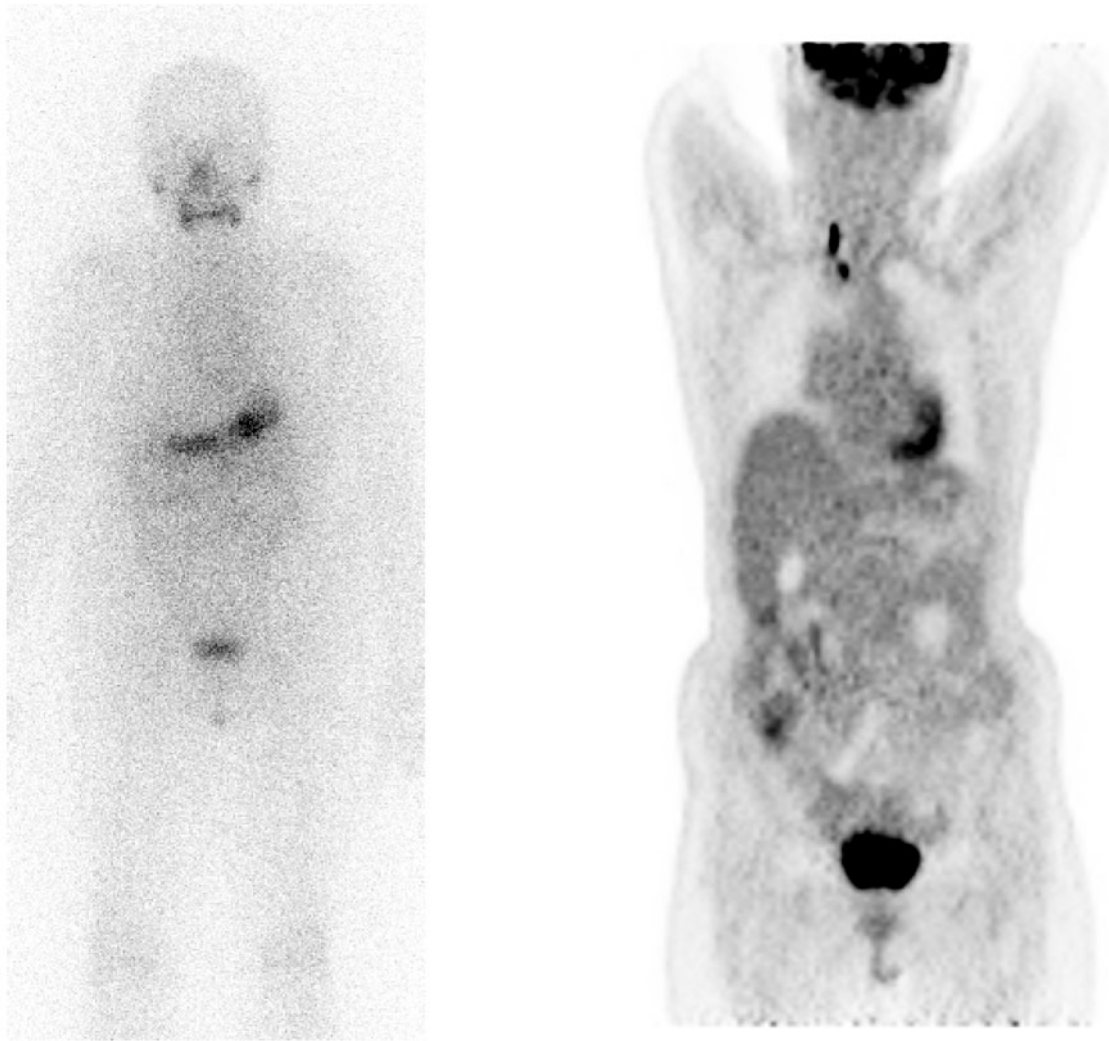
The role for gamma emitting radionuclide imaging in medullary thyroid carcinoma is primarily to assist in the detection of recurrent and metastatic disease<sup>[16]</sup>. Radioiodine labeled meta-iodobenzylguanidine (MIBG) is taken up by some medullary thyroid cancers, and by metastatic disease from medullary thyroid cancer<sup>[17]</sup>. Somatostatin receptors are abundant in medullary thyroid cancers, however their distribution is heterogeneous making somatostatin receptor scintigraphy of limited usefulness<sup>[18]</sup>. One very small study found that the sensitivity of [<sup>111</sup>In]octreotide for detection of metastatic medullary thyroid carcinoma was 100%<sup>[19]</sup> whereas another study found a sensitivity of only 37%<sup>[20]</sup>. The use of [<sup>99m</sup>Tc]dimercaptosuccinic acid (DMSA) for imaging occult disease, however, has been progressively replaced by superior agents, primarily by [<sup>111</sup>In]octreotide and positron emitting radiotracers<sup>[17]</sup>.

Radiolabeled monoclonal anti-carcinoembryonic antigen antibodies have also been used in medullary thyroid cancer. Sensitivity has been shown to be upwards of 75%, with improved sensitivity in more aggressive disease<sup>[21-23]</sup>.

Hybrid SPECT/CT imaging has been shown to improve diagnostic accuracy compared with standard planar gamma imaging<sup>[24]</sup>. It has been shown to optimize the localization of <sup>131</sup>I uptake to lymph nodes compared with remnant thyroid tissue, lung compared with mediastinal metastases, and to the skeleton<sup>[25]</sup>. Hybrid SPECT/CT imaging in endocrine neoplasm scintigraphy has been shown to outperform side-by-side imaging of separately acquired scintigraphic and CT images<sup>[26]</sup>.

## Positron emission tomography

Hybrid imaging with PET/CT in the evaluation of a neck mass is generally performed with [<sup>18</sup>F]FDG. FDG is normally not taken up by the thyroid gland since free fatty acid is the main source of energy for thyroid function. Diffuse uptake of FDG generally indicates thyroiditis<sup>[27,28]</sup>. Focal uptake of FDG in the thyroid gland represents malignancy in 30% or more of cases<sup>[29-34]</sup>.



**Figure 1** This patient with thyroid cancer had a radioiodine negative scan (left image) but positive [ $^{18}\text{F}$ ]FDG PET scan (right image).

FDG PET/CT is not sufficiently accurate to eliminate the need for surgery in patients with a non-diagnostic biopsy.

FDG is primarily taken up by undifferentiated thyroid tumors, which tend to concentrate radioiodine poorly. Thus, FDG PET/CT is of particular benefit in patients with a negative radioiodine scan in spite of suspected recurrent disease (Fig. 1). It is also helpful in the patient with known or suspected aggressive disease. In these patients, FDG PET/CT can help identify the site of recurrent or metastatic disease. FDG uptake, since it is taken up primarily by undifferentiated thyroid cells, is a poor prognostic sign and associated with more aggressive tumors.

It is important to keep in mind that thyroid cancers are characterized by polymorphism and often changes in histological type over time. Thus, FDG PET/CT should be routinely considered even in the patient who was initially diagnosed with DTC<sup>[35]</sup>.

Iodine-124 is a positron emitter with a 4.2-day half-life. Where available, it has been used for the purpose of lesion-specific dosimetry<sup>[36,37]</sup> and to enhance diagnostic sensitivity due to its high spatial and contrast resolution compared with conventional techniques<sup>[38,39]</sup>.

Indications for PET scanning are summarized in Table 1.

TSH stimulation can be helpful in imaging residual thyroid tissue or recurrent thyroid cancer, particularly in patients with DTC. TSH stimulation can be accomplished by withholding the patient's replacement (exogenous) synthroid or synthetic TSH can be used to increase tissue uptake of the radioiodine. A TSH level of greater than 30 mU/L is recommended prior to radioiodine scanning for recurrent disease. TSH stimulation in patients undergoing FDG PET/CT also may be of benefit, although the effect is not as clear as with radioiodine scanning and may vary by lesion.



**Table 1** Common indications for PET scanning in thyroid cancer

1. Diagnosis
  - (a)  $^{124}\text{I}$  PET can be utilized as an alternative to gamma scintigraphy with  $^{123}\text{I}$
  - (b) Patients who remain with an unknown primary malignancy after ultrasonography, FNA, and radionuclide gamma scintigraphy
2. Staging
  - (a) Thyroid cancer patients with increased thyroglobulin but a negative radioiodine whole body scan
  - (b) Patients with known or suspected aggressive (undifferentiated) thyroid cancer

**Table 2** Clinical aspects of thyroid cancer

1. Presentation
  - (a) Chief complaint
    - (i) Thyroid nodule on self-examination, usually asymptomatic
    - (ii) Hoarseness
    - (iii) Incidentaloma on previous imaging study
  - (b) History of present illness
    - (i) Growth rate
    - (ii) Neck pain or tenderness
    - (iii) Respiratory complaints
    - (iv) Dietary iodine level
  - (c) Past medical history
    - (i) Radiation exposure
    - (ii) Family history of thyroid cancer
2. Factors associated with a poor prognosis
  - (a) Histopathologic grade: anaplastic
  - (b) Age >45 years
  - (c) Male sex (frequency of poor histology is higher)
  - (d) Low radioiodine accumulation (indicates poor differentiation)
  - (e) Large initial size of the nodule
  - (f) Local invasion
  - (g) Metastatic disease
  - (h) Rapid growth
3. Clinical examination
  - (a) Evaluate for obstructive symptoms (e.g. inspiratory stridor)
  - (b) Palpate thyroid and assess for nodule size, hardness, tenderness, and attachment to underlying structures
  - (c) Assess for regional lymph node enlargement
  - (d) Cardiovascular examination
    - (i) Vital signs
    - (ii) Cardiac auscultation (murmurs)
    - (iii) Peripheral pulse quality
4. Laboratory tests
  - (a) Thyroid function tests are obtained on all patients with a nodule
  - (b) Thyroglobulin. Occasionally thyroglobulin levels will be unreliable due to the presence of antithyroglobulin antibodies
  - (c) FNA pathology

**Table 3** Molecular imaging in thyroid cancer

1. Diagnosis
  - (a) Ultrasonography with FNA as appropriate is almost always done prior to any other imaging test
  - (b) Scintigraphy: when the serum TSH is low in order to evaluate for an autonomous nodule
  - (c)  $^{123}\text{I}$  or  $^{99\text{m}}\text{Tc}$  pertechnetate
    - (i) When FNA is contraindicated due to anticoagulant use
    - (ii) For suspicious or indeterminate FNA results
    - (iii) Almost all nodules showing increased tracer uptake will be benign
      - (A) About 20% of cold nodules will be malignant
      - (B) Follicular and Hurthle cell cancers cannot be distinguished cytologically from follicular and Hurthle cell adenomas. The result is that 15–20% of all FNA biopsies are classified as suspicious or indeterminate
  - (d) [ $^{18}\text{F}$ ]FDG indications
    - (i) Unknown primary
    - (ii) Possibly useful in cytologically indeterminate nodules<sup>[41]</sup>
    - (iii) When a neck mass separate from the thyroid is found
2. Staging
  - (a)  $^{123}\text{I}$  or  $^{124}\text{I}$  to help with dosimetry estimates prior to high-dose  $^{131}\text{I}$  therapy
  - (b)  $^{131}\text{I}$  whole body scan 3–10 days after high-dose  $^{131}\text{I}$  therapy to identify metastatic disease
  - (c) [ $^{18}\text{F}$ ]FDG
    - (i) Poorly differentiated tumors (often radioiodine negative)
    - (ii) High-risk patients
    - (iii) Patients with an increased thyroglobulin but negative high-dose radioiodine scan (occurs in about 15–20% of patients), especially in patients with an unstimulated serum thyroglobulin level above 20 ng/ml
    - (iv) Hurthle cell carcinoma
  - (d) Miscellaneous agents
    - (i)  $^{201}\text{Tl}$ : may be useful in patients with an increased Tg but negative radioiodine scan
    - (ii)  $^{123}\text{I}$  MIBG,  $^{111}\text{In}$  octreotide, radiolabeled monoclonal antibodies: may be helpful in medullary thyroid cancers to identify recurrent or metastatic disease
    - (iii)  $^{99\text{m}}\text{Tc}$  sestamibi: use has been replaced by [ $^{18}\text{F}$ ]FDG PET/CT imaging which is more sensitive for the detection of metastatic disease
  - (e) Role of TSH stimulation
    - (i) Performed prior to obtaining a follow-up thyroglobulin level in patients without antithyroglobulin antibodies
    - (ii) Increases sensitivity of radioiodine and also possibly [ $^{18}\text{F}$ ]FDG scintigraphy when restaging patients
    - (iii) rhTSH is more convenient for patients than stopping exogenous thyroid hormone replacement therapy, but is significantly more expensive
    - (iv) TSH should be >30 mU/L prior to imaging

medullary thyroid cancer. Limited metastatic disease should be resected. Reoperations are not uncommon.

## Treatment

In the great minority of cases where the nodule ends up being malignant, medical treatment usually entails a total thyroidectomy with regional lymph node dissection. This is often followed by radioiodine treatment to ablate any remnant cancerous cells, especially in higher risk patients. Neck dissection is frequently performed in

## Clinical course

Most thyroid cancers are papillary, with a 10-year survival of 90% when confined to the thyroid gland. The 10-year survival drops to about 60% when extrathyroidal disease is present. Follicular carcinoma also has a 10-year survival of about 90% when there is minimal angioinvasion present, but only 35% when moderate to extensive

angioinvasion is present. Medullary thyroid cancer also has a 90% 10-year survival when nodal metastases are absent, and a 40% 10-year survival if nodal metastases are present. Anaplastic carcinoma of the thyroid has an average survival time of 6–12 months, with a 5-year survival of 5%<sup>[40]</sup>.

## Conclusion

Thyroid cancer frequently responds well to the proper medical therapy. Molecular imaging helps ensure that patients get the optimal medical therapy for their disease. Although gamma scintigraphy with radioiodine and [<sup>99m</sup>Tc]pertechnetate can be useful in the initial work-up of a patient with a thyroid nodule, there is also an important role for [<sup>18</sup>F]FDG PET/CT in the evaluation of patients with an aggressive histology, an unknown primary, and in suspected histologic transformation from low risk to high risk. An overview of the clinical features of thyroid cancer is outlined in Table 2 and clinical indications for imaging in thyroid cancer, with an emphasis on molecular imaging techniques, is outlined in Table 3.

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