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Role of [^{18}F]FDG PET/CT in the management of follicular cell-derived thyroid carcinoma

Klaudia Zajkowska[1*], Paulina Cegla[1] and Marek Dedecjus[1]

Abstract
Follicular cell-derived thyroid carcinomas constitute the majority of thyroid malignancies. This heterogeneous group of tumours includes well differentiated, poorly differentiated, and undifferentiated forms, which have distinct pathological features, clinical behaviour, and prognosis. Positron emission tomography with 2-[^{18}F]fluoro-2-deoxy-D-glucose combined with computed tomography ([^{18}F]FDG PET/CT) is an imaging modality used in routine clinical practice for oncological patients. [^{18}F]FDG PET/CT has emerged as a valuable tool for identifying patients at high risk of poor clinical outcomes and for facilitating individualized clinical decision-making. The aim of this comprehensive review is to summarize current knowledge regarding the role of [^{18}F]FDG PET/CT in primary diagnosis, treatment, and follow-up of follicular cell-derived thyroid carcinomas considering the degree of differentiation. Controversial issues, including significance of accidentally detected [^{18}F]FDG uptake in the thyroid, the role of [^{18}F]FDG PET/CT in the early assessment of response to molecular targeted therapies, and its prognostic value are discussed in detail.

Keywords PET/CT, [^{18}F]FDG, Thyroid cancer, Dedifferentiation, Thyroid incidentaloma, TENIS syndrome

Background

Follicular cell-derived malignant neoplasms constitute the majority of thyroid malignancies. In the latest 5th edition of the World Health Organization (WHO) Classification of Thyroid Neoplasms, these tumours are classified according to pathological features, molecular background, and biological behaviour [1]. Follicular thyroid carcinoma (FTC) and invasive encapsulated follicular variant of papillary thyroid carcinoma (IEFVPTC) are characterized by a high incidence of *RAS*-like molecular alterations, whereas papillary thyroid carcinoma (PTC) and its numerous subtypes belong to the *BRAF*-like family of malignancies. Oncocytic carcinoma of the thyroid (OCA) (formerly Hürthle cell carcinoma) is considered a distinct entity because it has unique clinicopathologic and molecular characteristics. FTC, IEFVPTC, PTC, and OCA are traditionally referred to as well-differentiated thyroid carcinomas (WDTC), and are distinguished from other less differentiated types. In the latest edition of the WHO classification, a new category of high-grade non-anaplastic follicular-derived carcinomas was introduced for the first time; it includes poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (high-grade PTC, high-grade FTC, and high-grade OCA), which are characterized by the presence of tumour necrosis and/or increased mitotic activity, with an intermediate prognosis between well- and undifferentiated (anaplastic) carcinomas. Anaplastic thyroid carcinoma (ATC) remains the most dedifferentiated form of thyroid cancer. It is characterized by an extremely aggressive biological behaviour and poor prognosis [1].

*Correspondence:
Klaudia Zajkowska
km.zajkowska@gmail.com
[1]Department of Endocrine Oncology and Nuclear Medicine, Maria Skłodowska-Curie National Research Institute of Oncology, Roentgena Street 5, Warsaw 02-781, Poland

Iodine-131 whole-body scan ([^{131}I]I WBS) plays a pivotal role in the management of patients with WDTC. It is used in the postoperative evaluation of residual thyroid tissue, the detection of distant metastases, the determination of eligibility for radioactive iodine (RAI) therapy, and the assessment of treatment response [2]. During the process of dedifferentiation, thyroid cancer cells lose the capacity for RAI uptake and organification, which significantly limits the possibilities of using this radioisotope not only in diagnostics, but also for treatment, making the management of such patients challenging.

The introduction of positron emission tomography combined with multi-row computed tomography (PET/CT) into clinical practice has significantly changed the management of oncological patients. This scan allows simultaneous assessment of the patient's organ anatomy and the location of pathological radiotracer uptake. Among several PET radiotracers with different targets and metabolic pathways, 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is the best-characterized and most widely used. The value of [^{18}F]FDG PET/CT has been confirmed in numerous studies, including in patients with follicular cell-derived thyroid carcinoma, particularly in poor- and undifferentiated types [3–6].

Dedifferentiation of thyroid cancer cells is a multi-step process that involves "early" and "late" genetic alterations, as well as epigenetic modifications [7]. This process entails a decrease or loss of sodium iodide symporter (NIS) expression and the upregulation of glucose transporter 1 expression [8]. This phenomenon results in an inverse relationship between RAI and [^{18}F]FDG uptake ("flip-flop phenomenon") in patients with thyroid cancer [9]. Most WDTCs are slow-growing tumours that can show negative [^{18}F]FDG uptake [10]. The exception is OCA, which, more frequently than other WDTCs, does not take up RAI but shows positive [^{18}F]FDG PET/CT results [11]. Next in the WHO classification, high-grade non-anaplastic thyroid carcinomas develop resistance to RAI and exhibit increased avidity in [^{18}F]FDG PET in approximately 50% of cases [12, 13]. Finally, ATC consistently demonstrates high [^{18}F]FDG uptake [14]. A graphical representation of the relationship between RAI and [^{18}F]FDG uptake in follicular cell-derived thyroid carcinomas according to the degree of differentiation and the presence of high-grade features is shown in Fig. 1.

The aim of this comprehensive review is to summarize the most recent evidence on the role of [^{18}F]FDG PET/CT in the primary diagnosis, treatment, and follow-up of patients with follicular cell-derived thyroid carcinoma.

[^{18}F]FDG-avid thyroid incidentaloma

The widespread use of [^{18}F]FDG PET/CT has increased the frequency of incidental diagnosis of [^{18}F]FDG-avid thyroid nodules, so-called thyroid incidentaloma. The incidental detection of radiotracer uptake within the thyroid gland during [^{18}F]FDG PET/CT performed for purposes other than thyroid evaluation occurs in 1.9–4.3% of [^{18}F]FDG PET/CT scans [15–19]. Radiotracer uptake in the thyroid gland can occur in a diffuse or focal pattern. Diffuse [^{18}F]FDG uptake is associated with chronic thyroiditis, hypothyroidism, and Graves' disease; it can also occur in patients without thyroid disease (considered a normal variant) [20, 21], where it is an indication for evaluation of thyroid function and anti-thyroid antibody levels, whereas fine needle aspiration biopsy (FNAB) is not required [2, 20].

By contrast, focal [^{18}F]FDG uptake within the thyroid gland raises suspicion of malignancy, especially in lesions with a high standardized uptake value (SUV) [20]. In a recent meta-analysis by De Leijer et al. that included 50 studies and 640,616 patients, the pooled prevalence of focal [^{18}F]FDG-avid thyroid incidentaloma was 2.22%, and the cumulative risk of malignancy was 30.8% [22]. Among malignant focal thyroid incidentalomas, the most common is PTC (82.6%), whereas other types including FTC, medullary thyroid carcinoma, ATC, lymphoma, and metastases to the thyroid account for 7%, 2.2%, 0.7%, 0.8% and 6.1%, respectively [22]. Approximately 21–26%

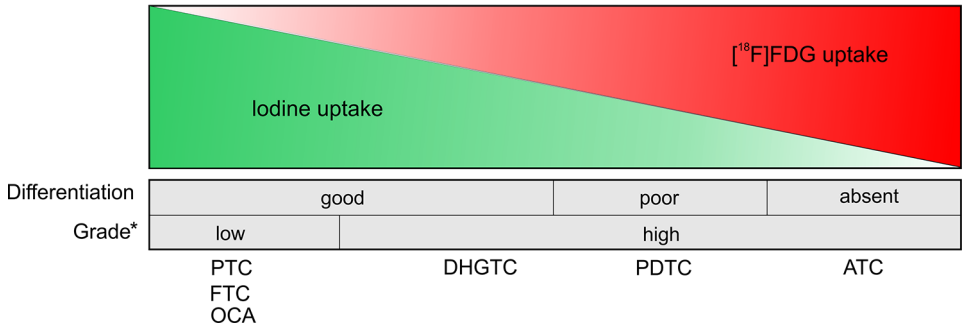

Fig. 1 The "flip-flop" phenomenon of radioactive iodine and [^{18}F]FDG uptake in follicular cell-derived thyroid carcinoma. Well-differentiated thyroid carcinomas with no high-grade features show high radioactive iodine uptake and low [^{18}F]FDG uptake. By contrast, dedifferentiated (anaplastic) thyroid carcinomas are characterized by high [^{18}F]FDG uptake and lack of radioactive iodine uptake. Differentiated high-grade thyroid carcinomas and poorly differentiated thyroid carcinomas may exhibit heterogenous uptake of both radiotracers. *mitotic activity, tumour necrosis

of focal [^{18}F]FDG PET thyroid incidentalomas subjected to FNAB yield nondiagnostic or indeterminate cytology results (Bethesda categories I, III, or IV) [22, 23].

The guidelines for the management of incidentally detected focal [^{18}F]FDG-avid thyroid nodules are inconsistent. The 2015 American Thyroid Association (ATA) guidelines recommend the use of ultrasonography to confirm the presence of a nodule and FNAB for nodules ≥ 1 cm in size [2]. The British and Polish guidelines recommend FNAB for all nodules showing increased [^{18}F]FDG uptake on PET regardless of size, although consideration of the clinical context is suggested [24, 25]. The recently published European Thyroid Association (ETA) guidelines recommend evaluating all incidentally detected PET-avid nodules according to standard thyroid nodule management principles, and making decisions regarding FNAB based on this evaluation [26].

An interesting voice in the discussion on thyroid incidentaloma is the consensus statement of a multidisciplinary group of experts led by Jonathan Wadsley on the management of incidentally discovered [^{18}F]FDG-avid thyroid nodules in patients being investigated for other cancers [27]. The authors recommended that if a patient is unlikely to survive 5 years as a result of their age, long-term prognosis or co-morbidities, further investigation is unlikely to be warranted. Exceptions include suspected metastasis to the thyroid that could affect the treatment of the known cancer, a thyroid incidentaloma larger than 4 cm, and concern that local progression of an undiagnosed thyroid malignancy may cause significant morbidity [27]. A less invasive approach seems reasonable given that the majority of PET-avid thyroid malignancies are PTCs, which are characterized by slow growth and a good prognosis [22]. Furthermore, the risk of thyroid cancer-related death in patients undergoing evaluation for another malignancy is extremely low [28].

[^{18}F]FDG PET/CT in the management of thyroid nodules with indeterminate cytology

The gold standard for the diagnosis of thyroid nodules is ultrasound examination, and in selected cases, FNAB. PET imaging, as well as CT or magnetic resonance imaging (MRI), are not recommended during the initial evaluation [2, 25, 26]. The primary limitation of FNAB is the occurrence of indeterminate results such as atypia of undetermined significance (Bethesda III category) and follicular neoplasm (Bethesda IV category) [29], which collectively account for 14–20% of all FNAB results [30, 31]. In such cases, repeat biopsy (only for Bethesda III), molecular diagnostics, or diagnostic surgery is recommended [29]. The estimated risk of malignancy is 22% for atypia of undetermined significance and 30% for follicular neoplasm [29], suggesting that many patients are overtreated and undergo unnecessary surgical treatment for benign lesions. Increasing evidence suggests that [^{18}F]FDG PET/CT may be a cost-effective and clinically efficient alternative to conventional approaches [32–37].

The prospective, multicentre, randomized, controlled clinical trial *EfFECTS* showed that in patients with Bethesda III and IV thyroid nodules, [^{18}F]FDG PET/CT is a highly accurate method to rule-out malignancy, with a sensitivity of 94% and a negative predictive value (NPV) of 95%. However, it is not suitable as a rule-in test [specificity, 40%; positive predictive value (PPV), 35%]. [^{18}F]FDG PET/CT-based management (surveillance for [^{18}F]FDG-negative nodules and diagnostic surgery for [^{18}F]FDG-positive nodules) prevented 40% of futile diagnostic surgeries for benign nodules and 48% of surgeries in patients with non-oncocytic thyroid nodules [32]. In patients with oncocytic thyroid nodules, PET is not beneficial because nearly all nodules are [^{18}F]FDG-positive [32, 38]. The conclusions drawn from the *EfFECTS* study are consistent with previous research demonstrating the high NPV of [^{18}F]FDG PET/CT in the evaluation of nodules with indeterminate cytology results [33–35]. A recently published study by the same authors comparing the performance of [^{18}F]FDG PET/CT with that of molecular diagnostics in Bethesda III and IV thyroid nodules indicated that the two methods are equally accurate for ruling out malignancy; however, their concordance was only 63% [39]. Finally, PET-based treatment is cost-effective compared with standard approaches, at least in the European setting, where the availability of multi-gene molecular tests is limited [36, 37].

In the preoperative evaluation of thyroid nodules with indeterminate cytology results, other radiopharmaceuticals, including [^{18}F]fluorocholine ([^{18}F]FCH) and [^{99m}Tc]Tc-methoxyisobutylisonitrile ([^{99m}Tc]Tc-MIBI), may also be useful. Studies have demonstrated that both [^{18}F]FCH PET/CT and [^{99m}Tc]Tc-MIBI scintigraphy exhibit high sensitivity and NPV, but poor specificity and PPV for predicting malignancy in indeterminate thyroid nodules [40–43]. The primary limitation of [^{18}F]FCH is its high cost and reduced worldwide availability [44]. Conversely, [^{99m}Tc]Tc-MIBI scintigraphy is a readily available and cost-effective procedure, but it is characterized by lower resolution and observer-dependent interpretation of results [41]. Interestingly, similar to [^{18}F]FDG, both [^{18}F]FCH and [^{99m}Tc]Tc-MIBI, despite their differing uptake mechanisms, exhibit lower diagnostic performance in oncocytic thyroid nodules [40, 41].

[^{18}F]FDG PET/CT for preoperative evaluation

Preoperative evaluation of differentiated thyroid carcinoma (DTC) consists primarily of a thorough ultrasound examination of the neck with assessment of the thyroid gland and lymph nodes of the central and lateral neck compartments [2]. Ultrasound-detected suspicious

lymph nodes should undergo FNAB prior to surgical treatment, and measurement of thyroglobulin (Tg) in the FNAB washout may also be helpful. Cross-sectional imaging scans (CT, MRI) should be performed in patients with locally advanced disease, e.g., in cases of vocal cord paresis; suspected infiltration of the trachea, oesophagus or major cervical vessels; and in patients with a large, rapidly growing tumour and suspected mediastinal lymphadenopathy, which may significantly affect the surgical treatment plan [2, 45]. [^{18}F]FDG PET/CT is not recommended for routine preoperative evaluation of DTC [2, 25].

A meta-analysis by Kim et al. [46] showed that [^{18}F]FDG PET/CT has low sensitivity (30%) despite its high specificity (94%) in detecting metastases of DTC to the lymph nodes of the neck. Another meta-analysis showed that [^{18}F]FDG PET/CT has lower PPV, NPV and accuracy for cervical lymph node metastasis compared with the inexpensive and non-invasive neck ultrasound scan [47]. To the best of the authors' knowledge, there are no reports on the usefulness of [^{18}F]FDG PET/CT for the assessment of locoregional invasion of DTC. However, it is likely that PET will be inferior to contrast-enhanced CT and MRI, as indicated in studies of other head and neck cancers [48, 49]. [^{18}F]FDG PET/CT is a highly sensitive and specific modality for detecting distant metastases of DTC [50, 51]. Nonetheless, when performed during preoperative assessment, it has a limited impact on clinical management. Patients with distant metastases detected during initial evaluation still undergo total thyroidectomy to facilitate subsequent RAI treatment [52]. This approach differs from that in most other malignancies, in which surgical treatment of the primary tumour in patients with metastatic disease is generally not recommended.

In contrast to DTC, in ATC, [^{18}F]FDG PET/CT plays a crucial role in determining the extent of disease, as well as in the surgical decision-making process. According to ATA guidelines, [^{18}F]FDG PET/CT is the preferred imaging modality for the initial assessment of patients with ATC [53]. [^{18}F]FDG PET/CT is more sensitive than contrast-enhanced CT in the detection of metastatic lymph nodes in the neck (100% vs. 57%) and mediastinum (100% vs. 56%), and metastasis to the lungs (100% vs. 83%), and it is more sensitive than bone scintigraphy for detecting bone metastases [14]. These findings were confirmed by Kim et al. [54], who performed [^{18}F]FDG PET/CT on 40 patients with ATC for pretreatment evaluation. Distant metastases were detected exclusively by [^{18}F]FDG PET/CT in 15 patients (37.5%), of which 7 had lung metastases, 6 had bone metastases, 5 had them in extra-regional lymph nodes, and 1 in the brain [54]. However, [^{18}F]FDG PET/CT is considered inferior to contrast-enhanced MRI for detecting brain metastases. Therefore, patients presenting with clinical symptoms suggesting the presence of brain metastases should undergo contrast-enhanced MRI as part of the initial staging [53]. Additionally, [^{18}F]FDG PET/CT performed without intravenous contrast is insufficient for accurately assessing the extent of local invasion into the trachea, oesophagus, and great vessels, which is essential for evaluating the feasibility of surgical treatment. In patients with only locoregional disease (stage IVA/IVB), decisions regarding tumour resection should depend on the possibility of achieving satisfactory resection (R0/R1) and consider the patient's quality of life and preferences. Extensive resections (including laryngectomy, tracheal resections, oesophageal resections, and major vascular or mediastinal resections) are generally not recommended because of the poor prognosis of ATC [53]. The results of [^{18}F]FDG PET/CT have a direct impact on clinical management in 25–50% of patients with ATC [14, 55]. Examples of [^{18}F]FDG PET/CT performed during the initial evaluation of patients with ATC are presented in Fig. 2.

[^{18}F]FDG PET/CT for postoperative staging and risk stratification

Postoperative staging of DTC is performed according to the latest edition of the Tumour-Node-Metastasis (TNM) Classification by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC), which provides the most accurate estimation of disease-dependent survival [56]. In most centres that treat thyroid cancer, the risk of a poor clinical outcome is assessed using the classification proposed by the ATA, which incorporates data from the histopathological report (e.g., extent of tumour resection, histological subtype, presence of vascular invasion and extrathyroidal extension, and size of lymph node metastases), as well as the first clinical tests conducted after surgery and RAI treatment, if applicable [2]. The combined assessment of postoperative Tg levels and the result of the first WBS performed after the administration of the diagnostic or therapeutic dose of [^{131}I]I enables early detection of metastases in 86.2% of patients [57]. However, expecially in patients with high-grade tumours, post-therapeutic scintigraphy can provide false-negative results and may not reveal the actual extent of the disease. In these cases, [^{18}F]FDG PET/CT performed during RAI ablation therapy provides a more accurate assessment of disease extent, which facilitates changes in the treatment strategy and adequate monitoring of patients [58–62].

The largest published study evaluating the clinical utility of [^{18}F]FDG PET/CT in the postoperative assessment of DTC is a retrospective study by Lee et al. that included 286 patients classified as intermediate or high risk according to ATA criteria [58]. All patients had [^{18}F]FDG PET/CT scan performed concurrently with RAI

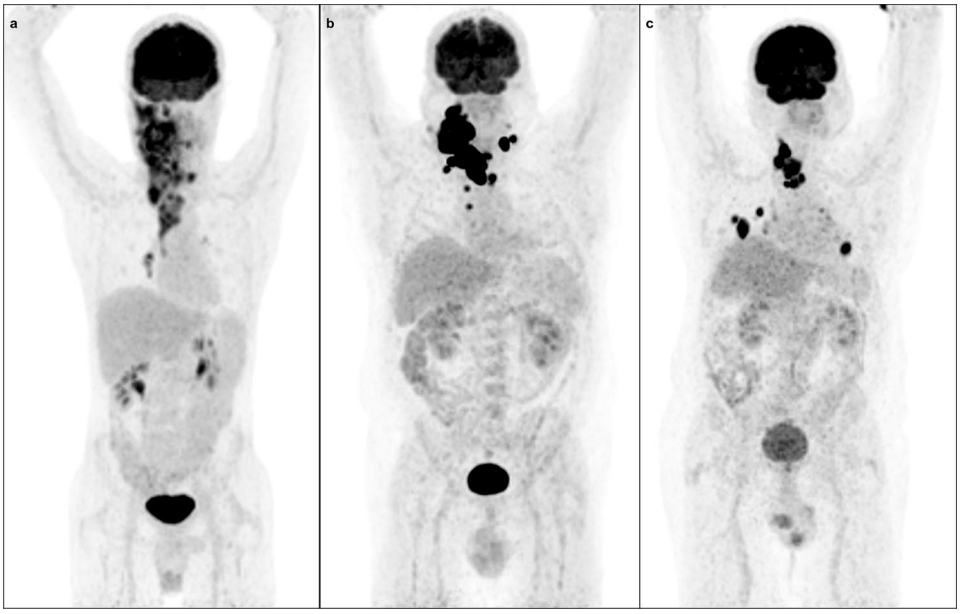

Fig. 2 [^{18}F]FDG PET/CT performed during initial evaluation. (**a**) A 34-year-old man with anaplastic thyroid carcinoma with metastases to the lymph nodes in the right lung hilum. (**b**) A 56-year-old man with squamous cell carcinoma of the thyroid (classified as anaplastic thyroid carcinoma according to the new WHO classification) with metastases to the mediastinal lymph nodes. (**c**) A 74-year-old man with anaplastic thyroid carcinoma with metastases to the lungs, mediastinal lymph nodes and lung hilum

treatment. In 39 (14%) patients, the [^{18}F]FDG PET/CT scan detected additional recurrent or metastatic lesions that were not detected in the post-therapeutic [^{131}I] I WBS, leading to a change in the treatment plan in 30 patients (10%). Both tumour stage and size were predictive of a positive [^{18}F]FDG PET/CT result, and the highest frequency of additional PET-avid lesions was observed in patients with recurrent DTC (46%) and in patients with stage T3–T4N1 and tumour size > 2.0 cm (25%) [58].

Another study evaluated 38 patients with aggressive histological subtypes of DTC and PDTC without known persistent disease or distant metastases who had [^{18}F] FDG PET/CT performed during postoperative RAI ablation [59]. Of 86 lesions detected in 20 (53%) patients, 41% were visible in [^{18}F]FDG PET/CT only, 31% in the post-therapeutic [^{131}I]I WBS only, and 28% in both modalities. The only statistically significant risk factor for a positive [^{18}F]FDG PET/CT result was a stimulated Tg concentration measured at ablation > 10 ng/ml [59]. Other studies have also confirmed the clinical benefit of [^{18}F]FDG PET/CT performed during ablative RAI therapy in high-risk patients, with suspected metastases or high postoperative Tg levels; this has led to a change in clinical management in 20–36% of patients [4, 60–64].

[^{18}F]FDG PET/CT during follow-up after initial treatment

The follow-up of patients after initial treatment (surgery +/- RAI treatment) of DTC aims to identify individuals with local recurrence or distant metastases; it consists of neck ultrasound examination, measurement of Tg levels together with anti-Tg antibodies (TgAb) and, in selected cases, diagnostic [^{131}I]I WBS and other cross-sectional imaging studies [2]. The risk of thyroid cancer recurrence is estimated at 4.3% for PTC, 13.6% for FTC, and up to 39% for PDTC [65–67]. Furthermore, the risk of recurrence depends on tumour stage: patients in early stages (stages I and II) have significantly lower recurrence rates than those in advanced stages (stages III and IV) according to the AJCC/UICC TNM classification (7.2 vs. 28.2%, $p < 0.05$) [68]. Most recurrences occur within the first 5 years of follow-up, although recurrences after several decades of surgical treatment are also possible [69, 70].

As recommended by scientific societies, patients presenting with elevated serum Tg levels after effective initial treatment of DTC should undergo a neck ultrasound and diagnostic [^{131}I]I WBS first [2, 71]. In most patients, this approach is sufficient. However, approximately 10% of patients exhibit elevated Tg levels without detectable lesions on the [^{131}I]I WBS, a clinical situation referred to as thyroglobulin elevated negative iodine scintigraphy (TENIS) syndrome, which is an indication for [^{18}F] FDG PET/CT [72]. According to meta-analysis, [^{18}F] FDG PET/CT has the pooled sensitivity and specificity of 87% and 89%, respectively [51], in the detection of recurrence in patients with TENIS syndrome and is superior to conventional imaging studies [50]. [^{18}F]FDG PET/CT performed in this context leads to changes in clinical management in 42–79% of patients, which most often consist of the cancellation of the next cycle of RAI

therapy and a referral to surgical treatment, radiotherapy, or initiation of molecular targeted therapy [73–75].

Most scientific societies, including ATA, recommend the [^{18}F]FDG PET/CT scan in DTC patients with serum Tg>10 ng/ml [2, 25, 76]. However, the usefulness of [^{18}F]FDG PET/CT in patients with lower Tg levels has been suggested [77, 78]. The National Comprehensive Cancer Network guidelines suggest considering [^{18}F]FDG PET/CT when the stimulated Tg level is greater than 2–5 ng/ml [71].

In addition to the absolute level of Tg, the growth dynamics of this marker are important. Giovanella et al. indicated that the accuracy of [^{18}F]FDG PET/CT increases significantly when the unstimulated Tg levels are >5.5 ng/ml or when the Tg doubling time (TgDT) is <1 year [77]. Conversely, Albano et al. identified TgDT≤2.5 years as a predictive factor of positive [^{18}F]FDG PET/CT results (sensitivity, 93%; specificity, 87%; AUC=0.911) and demonstrated that it is a more effective criterion for selecting patients for PET imaging than absolute Tg level [79]. A recent meta-analysis confirmed the value of TgDT as a predictive factor for [^{18}F]FDG PET results, as well as for response to treatment, disease recurrence, and overall survival (OS) in patients with DTC [80]. Examples of [^{18}F]FDG PET/CT results in patients with TENIS syndrome are presented in Fig. 3.

The indication for [^{18}F]FDG PET/CT in patients with TENIS syndrome should be determined after considering the clinical context. Firstly, low serum Tg levels do not always indicate a small tumour burden; in PDTC and certain aggressive histological subtypes of DTC, Tg expression can be decreased, resulting in lower production and secretion of Tg [81, 82]. Secondly, in TgAb-positive patients, the measurement of Tg levels is unreliable due to Tg assay interference [83]. In this situation, TgAb can serve as an imprecise surrogate tumour marker [84]. Total thyroidectomy followed by RAI treatment should eliminate the antigens required for TgAb production, leading to a gradual decrease in TgAb levels, with their disappearance typically occurring within a median of 3 year [85]. Thus, the presence of TgAb, and especially increasing serum TgAb levels, might indicate persistent and/or recurrent disease [86]. The diagnostic performance of [^{18}F]FDG PET/CT for the detection of recurrence in DTC patients with negative [^{131}I]I WBS and increased TgAb levels appears to be as high as in classic TENIS syndrome, as indicated by the meta-analysis by Bang et al. [51]. Another recent meta-analysis by Albano et al. reported pooled sensitivity and specificity of [^{18}F]

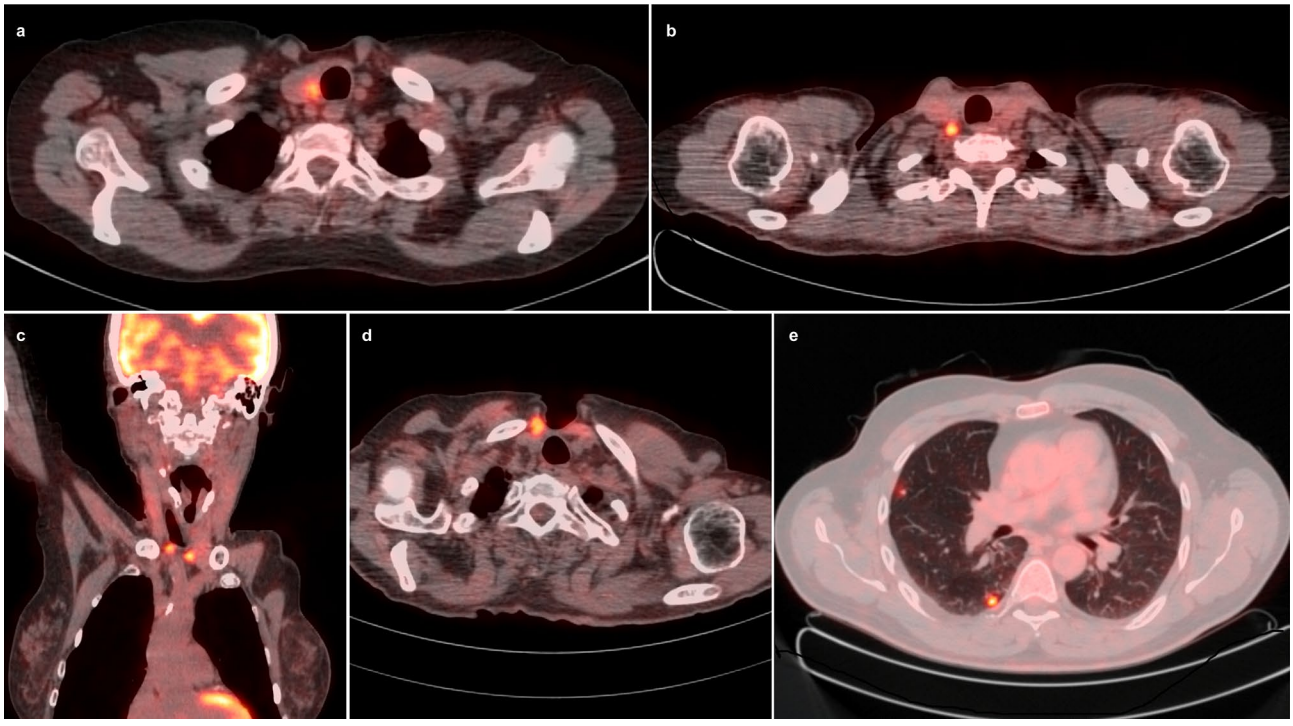

Fig. 3 Examples of [^{18}F]FDG PET/CT scans performed in patients with TENIS syndrome. (**a**) 70-year-old woman with papillary thyroid carcinoma with thyroglobulin level 17.28 ng/ml. PET scan detected an [^{18}F]FDG-avid metastatic lesion in the thyroidectomy bed. (**b**) A 61-year-old woman with papillary thyroid carcinoma and thyroglobulin level 4.03 ng/ml. PET scan showed [^{18}F]FDG-avid metastasis to the lymph node in the lateral neck compartment. (**c**, **d**) A 73-year-old woman with thyroid follicular carcinoma and thyroglobulin level 53.81 ng/ml. PET scan showed [^{18}F]FDG-avid recurrent foci in subcutaneous tissue and muscles. (**e**) A 42-year-old man with thyroid follicular carcinoma and thyroglobulin level 202.60 ng/ml. PET scan detected [^{18}F]FDG-avid lung metastases

FDG PET/CT in this clinical scenario to be 84% and 82%, respectively [87]. Several studies proposed potential cut-off value of TgAb level with best accuracy to predict [^{18}F]FDG PET/CT results, but their findings vary considerably and are difficult to compare due to the use of different TgAb assays [88, 89].

The impact of TSH (thyroid stimulating hormone) stimulation on the diagnostic value of [^{18}F]FDG PET/CT in patients with DTC remains controversial. A meta-analysis by Ma et al. demonstrated that [^{18}F]FDG PET performed under TSH stimulation identifies a greater number of patients with PET true-positive lesions, a higher number of PET-detected lesions, and a higher tumour-to-background ratio than [^{18}F]FDG PET under TSH suppression. Moreover, PET scans performed under TSH stimulation alter the clinical management in 9% of patients [90]. However, more recent analyses involving a larger number of patients did not show statistically significant differences in the diagnostic accuracy of [^{18}F]FDG PET/CT after stratifying patients according to TSH stimulation status [51, 91].

Up to half of patients with PDTC and a significant proportion of patients with high-grade DTC become resistant to RAI during the follow-up period, which markedly limits the utility of [^{131}I]I WBS and thereby increases the importance of [^{18}F]FDG PET/CT in the management of these patients [6, 12]. Yang et al. assessed the utility of [^{18}F]FDG PET/CT in high-risk DTC patients in various clinical settings; the greatest clinical benefits from [^{18}F]FDG PET/CT were obtained in patients with lesions detected on [^{131}I]I WBS that did not correspond to conventional imaging findings or were not proportional to stimulated Tg level, as well as in those with aggressive histological subtypes of DTC [5]. [^{18}F]FDG PET/CT performed within 6 months after RAI therapy in patients with high-risk DTC and PDTC helps predict the treatment response, has a high impact on TNM staging and clinical management, and enables the early introduction of multimodal treatment [6, 92, 93]. An example of the use of [^{18}F]FDG PET/CT in a patient with high-risk DTC during follow-up after initial treatment is shown in Fig. 4.

In addition, in some cases of OCA, conventional monitoring approaches including neck ultrasound, serum Tg measurement, and [^{131}I]I WBS may be insufficient. Lopez-Penabad et al. reported that only 38% of patients

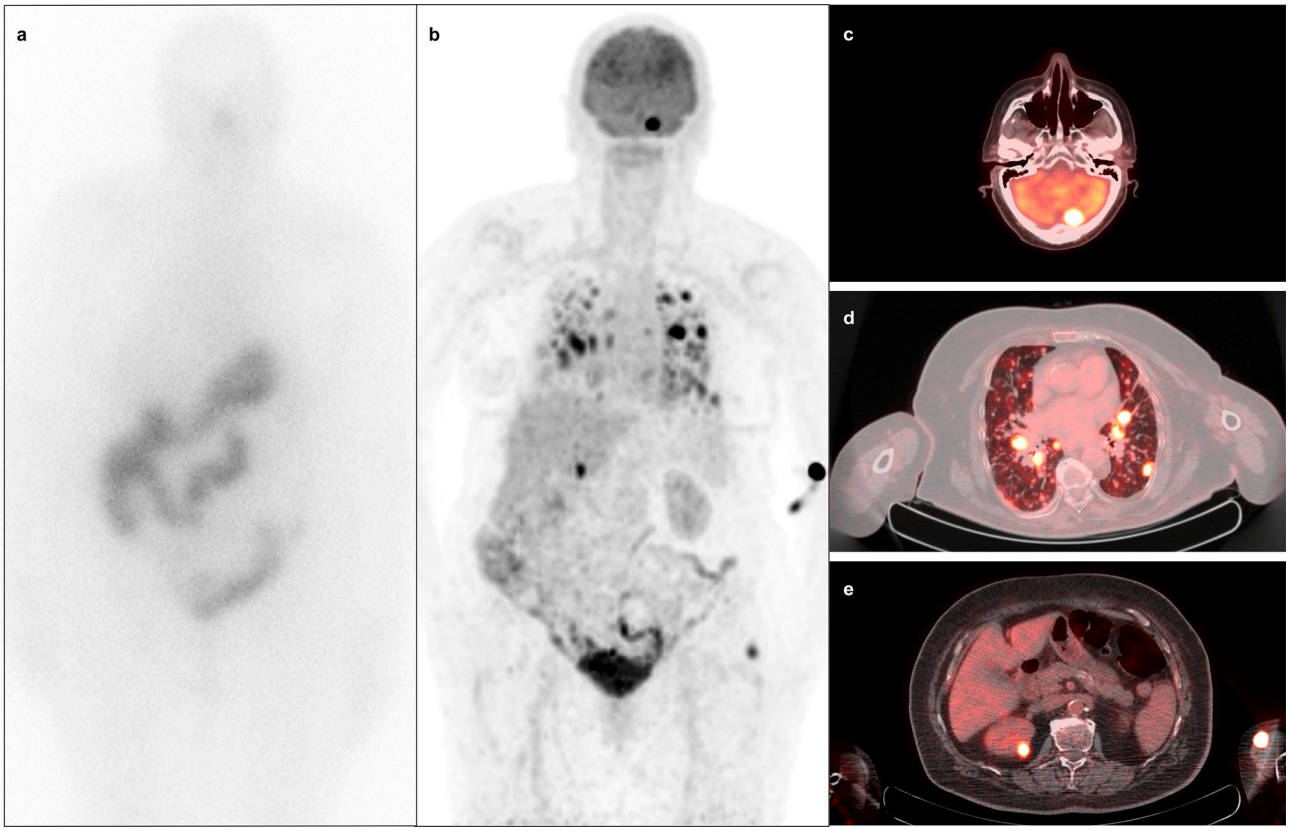

Fig. 4 A 79-year-old female presented with high-risk papillary thyroid carcinoma after total thyroidectomy and central neck lymph node dissection, radiotherapy to the neck and upper mediastinum, and multiple cycles of [^{131}I]I therapy with a total activity of 22.6 GBq. Post-therapeutic [^{131}I]I WBS performed during the last radioiodine treatment was negative (**a**). The patient had an [^{18}F]FDG PET/CT scan performed due to elevated thyroglobulin levels (202.3 ng/ml), which revealed [^{18}F]FDG-avid metastatic lesions in the cerebellum, lungs, and right kidney (**b**-**e**)

with known OCA metastases show RAI uptake, and in patients with known lung or bone metastases, the uptake rate is <10% [11]. Furthermore, patients with OCA may have distant metastases despite undetectable Tg levels and negative neck ultrasound results [94]. By contrast, [^{18}F]FDG PET/CT demonstrates excellent diagnostic accuracy in patients with OCA, overperforming both [^{131}I]I WBS and morphological imaging [95–97]. Plotkin et al. reported that [^{18}F]FDG PET/CT detects OCA recurrence with a sensitivity of 92%, specificity of 80%, PPV of 92%, and NPV of 80% [97]. Many authors support the routine use of [^{18}F]FDG PET/CT in both, the initial postoperative staging and the follow-up of OCA patients [95–97].

Role of [^{18}F]FDG PET/CT in novel targeted therapies for metastatic thyroid cancer

Understanding the signalling pathways involved in thyroid tumorigenesis has led to the development of novel molecular targeted therapies — tyrosine kinase inhibitors (TKIs) [98]. Multikinase inhibitors (MTKIs) have multiple targets associated with the pathogenesis of thyroid cancer (e.g., RET, KIT, BRAF, MET and EGFR) and neoangiogenesis processes (e.g., VEGFR and PDGFR). MTKIs include sorafenib, lenvatinib and cabozantinib, which are used in the treatment of advanced RAI-refractory DTC. Newer selective inhibitors target specific protein kinases such as RET kinase (selpercatinib and pralsetinib) and tropomyosin-related kinase (larotrectinib and entrectinib), and are used in tumours harbouring RET and neurotrophic tyrosine receptor kinase gene fusions. Additionally, combined inhibition of MEK and BRAF using dabrafenib and trametinib is an effective therapeutic option for BRAF V600E-mutated ATC. Evidence from the literature suggests that [^{18}F]FDG PET/CT may serve as a valuable tool for patient qualification and evaluation of treatment response to these innovative drugs.

Marotta et al. [99] evaluated the role of [^{18}F]FDG PET/CT performed prior to and 15 days after initiating sorafenib treatment in patients with advanced RAI-refractory DTC. Baseline mean SUVmax values in target lesions were significantly higher in patients who showed disease progression than in those who responded to treatment (p=0.001). Early [^{18}F]FDG PET/CT scans performed 15 days after the initiation of sorafenib showed that average SUVmax values decreased to a greater extent in patients who showed a clinical benefit from treatment than in non-responders (p=0.002). However, there was no significant correlation between baseline and early [^{18}F]FDG PET/CT results and progression-free survival (PFS). The authors concluded that baseline [^{18}F]FDG PET/CT assessment may predict the radiological response to treatment, whereas early [^{18}F]FDG PET/CT evaluation is effective for the rapid identification of non-responding patients, thereby preventing unnecessary therapy [99].

Another group of researchers analysed the role of [^{18}F]FDG PET/CT in the evaluation of metabolic response and outcome prediction in patients with progressive RAI-refractory DTC treated with lenvatinib [100]. In most patients, the greatest metabolic response to lenvatinib was observed at the first [^{18}F]FDG PET/CT scan, performed 4 weeks after the initiation of treatment; however, in some patients, this response was observed later during follow-up. The metabolic response detected by the [^{18}F]FDG PET/CT scan performed after 4 weeks of lenvatinib was significantly correlated with the morphological response obtained in the CT performed after 8 weeks of treatment and later during follow-up. This enabled the early identification of patients who would not benefit from therapy. Moreover, patients with a positive metabolic response at the [^{18}F]FDG PET/CT scan performed after 4 weeks of lenvatinib had a significantly longer median OS than non-responders (36.53 vs. 11.28 months) [100].

Additional studies have further validated the prognostic role of [^{18}F]FDG PET in the early assessment of thyroid cancer patients treated with MTKIs [101–105]. Functional tumour response assessment by [^{18}F]FDG PET outperforms morphological response assessment by CT because the therapeutic effect of TKIs is detected earlier by PET than by CT as a decline in PET-semiquantitative parameters [101, 102]. However, the optimal timing for [^{18}F]FDG PET after the initiation of treatment remains controversial. Takeuchi et al. reported that the decrease in [^{18}F]FDG uptake is already visible in PET scans performed 1 week after the initiation of lenvatinib therapy, thus enabling the prediction of treatment outcomes [101]. By contrast, the previously cited study by Valerio et al. suggests that a positive metabolic response may occur even after more than 4 weeks of treatment [100].

TKIs such as selumetinib, lenvatinib, trametinib, dabrafenib, vemurafenib and larotrectinib can restore the radioiodine uptake in RAI-refractory thyroid cancer patients [106–110]. Short-term (3–6 weeks) therapy with these TKIs restored or increased radioiodine uptake in 35–60% of patients, thus allowing subsequent RAI therapy [106–110]. In these studies, [^{18}F]FDG PET/CT was used to determine the indication for redifferentiation therapy, for assessment of treatment response, and as follow-up [106, 107, 109, 111]. Weber et al. suggested that [^{18}F]FDG PET/CT can serve as a predictive factor of the response to redifferentiation therapy [108]. These researchers evaluated the efficacy of redifferentiation therapy through genotype-guided MAPK inhibition: BRAF*V600E*-wild type patients were treated with

trametinib, whereas patients with the BRAF*V600E* mutation received combination treatment with trametinib and dabrafenib. Redifferentiation was achieved in 7 of 20 (35%) patients. Subsequent RAI therapy led to a decrease in Tg levels in 57% (4/7) of the patients. The peak standardized uptake value (SUVpeak) of metastatic lesions on baseline [^{18}F]FDG PET/CT significantly predicted the redifferentiation rate: redifferentiation was successful in 6 of 9 (66.7%) patients with a mean SUVpeak < 10 and unsuccessful in all 11 patients with a higher SUVpeak ($p=0.01$) [108].

To date, there are no large-scale studies evaluating the role of [^{18}F]FDG PET in patients with ATC treated with molecular targeted therapies. Only case reports and case series are available, suggesting that [^{18}F]FDG PET/CT is effective for the qualification and assessment of treatment response with these drugs [112–116]. A case series of three patients with stage IVB and IVC ATC used short-term mutation-based "neoadjuvant" therapy [116]. One patient with a BRAF mutation received combination therapy with dabrafenib and trametinib, whereas the two BRAF-wild type patients were treated with a combination of pembrolizumab and lenvatinib for 4 weeks. Whole-body [^{18}F]FDG PET/CT scans were performed at diagnosis and after 4 weeks of "neoadjuvant" treatment. Restaging PET showed significant tumour reduction and reduced glucose uptake in all three patients, who subsequently underwent surgical resection of the primary tumour; R0 resection status was achieved in two patients and R1 in one patient [116]. The efficacy of [^{18}F]FDG PET for monitoring ATC patients treated with targeted therapies needs to be confirmed in larger patient cohorts.

Prognostic value of [^{18}F]FDG PET/CT

According to ATA guidelines, [^{18}F]FDG PET/CT should be considered as a prognostic tool in thyroid cancer patients with metastatic disease to identify both lesions and patients at the highest risk of rapid progression and disease-specific mortality [2]. Uptake of [^{18}F]FDG in metastatic lesions is a recognized negative prognostic factor for OS, whereas RAI uptake is prognostic for stable disease [64, 96, 117, 118]. In a multivariate analysis of 400 patients with follicular cell-derived thyroid carcinoma, only age > 45 years and [^{18}F]FDG uptake in metastatic lesions were statistically significant predictive factors of OS, whereas initial stage, histology, serum Tg and RAI uptake were not. A significant inverse relationship was found between survival and both the glycolytic rate of the most active lesion (SUVmax) and the number of [^{18}F]FDG-avid lesions [119]. In OCA, the 5-year OS is 92% in patients with SUVmax < 10 and 64% in patients with SUVmax > 10, and each increase in SUVmax of one unit is associated with a 6% increase in mortality ($p<0.001$) [96]. Masson-Deshayes et al. found that PFS is significantly worse in patients with metastatic DTC with > 10 [^{18}F]FDG-avid lesions and a standardized uptake value corrected for lean body mass (SUL) peak > 5 [120]. Other PET-derived semiquantitative parameters evaluated by various authors that could be useful for the dynamic risk stratification of patients with RAI-refractory DTC include metabolic tumour volume (MTV), total lesion glycolysis (TLG) and the location of PET-positive lesions [121–123].

Wijewardene et al. proposed a new scoring system, I-PET, which identifies patients who have or are likely to become refractory to RAI [124]. I-PET combines information from [^{131}I]I WBS and [^{18}F]FDG PET imaging, assigning the results to one of four categories: I-PET [0]: Iodine −/FDG −, I-PET [1]: Iodine +/FDG −, I-PET [2]: Iodine +/FDG + and I-PET [3]: Iodine −/FDG +. Patients with [^{18}F]FDG-positive lesions (I-PET [2] and I-PET [3]) were further classified into groups A and B according to SUVmax ≤ 5 or > 5, respectively. After a median follow-up of 40 months, disease progression was observed in 22% of patients with I-PET [0], 40% with I-PET [1], 63% with I-PET [2] and 74% of patients with I-PET [3]. I-PET [2B] and I-PET [3B] were associated with progression rates of 88% and 78%, respectively. Patients classified as I-PET [3B] had an 8-fold greater mortality ($p=0.003$) and were 9.6-fold more likely to initiate multikinase inhibitor therapy ($p=0.001$) than patients in other I-PET groups [124].

The prognostic value of [^{18}F]FDG PET/CT has also been demonstrated in the context of ATC. Poisson et al. identified the volume of [^{18}F]FDG uptake (≥ 300 ml) and the intensity of [^{18}F]FDG uptake (SUVmax ≥ 18) as significant prognostic factors for survival, whereas the number of involved organs did not have a prognostic role [14]. Similar conclusions were drawn by Kim et al., who showed that [^{18}F]FDG PET/CT parameters such as SUVmax, MTV, and TLG were significantly associated with poor prognosis ($p<0.001$, $p=0.002$ and $p<0.001$, respectively) [54].

Limitations

This narrative review aims to provide an overview of the current knowledge on the role of [^{18}F]FDG PET/CT in the management of follicular cell-derived thyroid carcinoma. The primary limitation of narrative reviews is the subjectivity in the selection of studies, their interpretation, and the synthesis of available evidence. Therefore, it should not be considered as clinical guidelines, and patient care and treatment should always be based on official recommendations from scientific societies, considering the individual clinical context. Nonetheless, the authors believe that this review offers a comprehensive understanding of the topic, highlights gaps in the available evidence, and serves as a starting point for future research.

Conclusions

[^{18}F]FDG PET/CT is a valuable tool in almost every step of thyroid cancer diagnosis and treatment, from the evaluation of indeterminate thyroid nodules, through the planning of surgical treatment and RAI therapy, to the assessment of patients with biochemical recurrence, and has a tangible impact on clinical management. Its importance increases with the degree of tumour dedifferentiation. In DTC, its application is limited to a small subset of patients in whom disease has eluded the standard approach. However, in poorly differentiated and undifferentiated forms, it represents one of the most effective diagnostic modalities. [^{18}F]FDG PET/CT has recently acquired an increasingly important role in the assessment of response to treatment with molecular targeted therapies. Metabolic response, expressed as a decrease in semiquantitative PET parameters, is detectable earlier than structural response. This enables the early identification of patients who will not benefit from a therapy burdened with numerous adverse events. Finally, [^{18}F]FDG PET/CT serves as a powerful prognostic tool capable of identifying both lesions and patients at high risk of rapid disease progression and disease-specific mortality, which can lead to the design of treatment and monitoring strategies tailored to the specific needs of individual patients.

Abbreviations

AJCC/UICC	American Joint Committee on Cancer/Union for International Cancer Control
ATA	American Thyroid Association
ATC	Anaplastic thyroid carcinoma
CT	Computed tomography
DHGTC	Differentiated high-grade thyroid carcinoma
DTC	Differentiated thyroid carcinoma
ETA	The European Thyroid Association
[^{18}F]FCH	[^{18}F]fluorocholine
[^{18}F]FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose
FNAB	Fine needle aspiration biopsy
FTC	Follicular thyroid carcinoma
IEFVPTC	Invasive encapsulated follicular variant papillary thyroid carcinoma
[^{131}I]I WBS	Iodine-131 whole-body scan
MRI	Magnetic resonance imaging
MTKI	Multitargeted tyrosine kinase inhibitors
NCCN	The National Comprehensive Cancer Network
NIS	Sodium/Iodide symporter
NPV	Negative predictive value
OCA	Oncocytic carcinoma of the thyroid
OS	Overall survival
PDTC	Poorly differentiated thyroid carcinoma
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
PPV	Positive predictive value
PTC	Papillary thyroid carcinoma
RAI	Radioactive iodine
SUL	Standardized uptake value corrected for lean body mass
SUV	Standardized uptake value
TBR	Tumour-to-background ratio
[^{99m}Tc]Tc-MIBI	[^{99m}Tc]Tc-methoxyisobutylisonitrile
TENIS	Thyroglobulin elevated negative iodine scintigraphy
TgAb	Anti-thyroglobulin antibodies
TgDT	Thyroglobulin doubling time
TKI	Tyrosine kinase inhibitor
TNM	Tumour-Node-Metastasis
TSH	Thyroid stimulating hormone
WDTC	Well-differentiated thyroid carcinoma

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References

1. Baloch ZW, Asa SL, Barletta JA, Ghossein RA, Juhlin CC, Jung CK, et al. Overview of the 2022 WHO classification of thyroid neoplasms. Endocr Pathol. 2022;33(1):27–63.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, 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.
3. Vogel J, Sekler J, Gückel B, Pfannenberg C, Nikolaou K, La Fougère C, et al. How [18F]FDG-PET/CT affects the management of patients with differentiated thyroid carcinoma in clinical routines. Cancers. 2024;16(3):588.
4. Rosenbaum-Krumme SJ, Görges R, Bockisch A, Binse I. 18F-FDG PET/CT changes therapy management in high-risk DTC after first radioiodine therapy. Eur J Nucl Med Mol Imaging. 2012;39(9):1373–80.
5. Yang JH, Maciel RMB, Nakabashi CCD, Janovsky CCPS, Padovani RP, Macellaro D, et al. 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):416–25.
6. Grawe F, Cahya A, Fabritius MP, Beyer L, Wenter V, Ruebenthaler J, et al. Course of Disease and Clinical Management of patients with poorly differentiated thyroid carcinoma. Cancers. 2021;13(21):5309.
7. Volante M, Lam AK, Papotti M, Tallini G. Molecular Pathology of poorly differentiated and anaplastic thyroid Cancer: what do pathologists need to know? Endocr Pathol. 2021;32(1):63–76.
8. Grabellus F, Nagarajah J, Bockisch A, Schmid KW, Sheu SY. Glucose transporter 1 expression, Tumor Proliferation, and Iodine/Glucose uptake in thyroid Cancer with emphasis on poorly differentiated thyroid carcinoma. Clin Nucl Med. 2012;37(2):121–7.
9. Feine U, Lietzenmayer R, Hanke JP, Held J, Wöhrle H, Müller-Schauenburg W. Fluorine-18-FDG and iodine-131-iodide uptake in thyroid cancer. J Nucl Med off Publ Soc Nucl Med. 1996;37(9):1468–72.
10. Saif MW, Tzannou I, Makrilia N, Syrigos K. Role and cost effectiveness of PET/CT in management of patients with cancer. Yale J Biol Med. 2010;83(2):53–65.

11. Lopez-Penabad L, Chiu AC, Hoff AO, Schultz P, Gaztambide S, Ordoñez NG, et al. Prognostic factors in patients with Hürthle cell neoplasms of the thyroid. Cancer. 2003;97(5):1186–94.
12. De La Fouchardière C, Decaussin-Petrucci M, Berthiller J, Descotes F, Lopez J, Lifante JC, et al. Predictive factors of outcome in poorly differentiated thyroid carcinomas. Eur J Cancer. 2018;92:40–7.
13. Rivera M, Ghossein RA, Schoder H, Gomez D, Larson SM, Tuttle RM. Histopathologic characterization of radioactive iodine-refractory fluorodeoxyglucose-positron emission tomography-positive thyroid carcinoma. Cancer. 2008;113(1):48–56.
14. Poisson T, Deandreis D, Leboulleux S, Bidault F, Bonniaud G, Baillot S, et al. 18F-fluorodeoxyglucose positron emission tomography and computed tomography in anaplastic thyroid cancer. Eur J Nucl Med Mol Imaging. 2010;37(12):2277–85.
15. Thuillier P, Roudaut N, Crouzeix G, Cavarec M, Robin P, Abgral R, et al. Malignancy rate of focal thyroid incidentaloma detected by FDG PET–CT: results of a prospective cohort study. Endocr Connect. 2017;6(6):413–21.
16. Piek MW, De Boer JP, Vriens MR, Van Leeuwaarde RS, Stokkel M, Hartemink KJ, et al. Retrospective analyses of ^{18} FDG-PET/CT thyroid incidentaloma in adults: incidence, treatment, and Outcome in a Tertiary Cancer Referral Center. Thyroid. 2021;31(11):1715–22.
17. Soelberg KK, Bonnema SJ, Brix TH, Hegedüs L. Risk of malignancy in thyroid Incidentalomas detected by ^{18} F-Fluorodeoxyglucose Positron Emission Tomography: a systematic review. Thyroid. 2012;22(9):918–25.
18. Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid Incidentalomas. J Clin Endocrinol Metab. 2012;97(11):3866–75.
19. Roddy S, Biggans T, Raofi AK, Kanodia A, Sudarshan T, Guntur Ramkumar P. Prevalence of incidental thyroid malignancy on routine 18F-fluorodeoxyglucose PET-CT in a large teaching hospital. Eur J Hybrid Imaging. 2020;4(1):21.
20. Agrawal K, Weaver J, Ngu R, Krishnamurthy Mohan H. Clinical significance of patterns of incidental thyroid uptake at 18F-FDG PET/CT. Clin Radiol. 2015;70(5):536–43.
21. Karantanis D, Bogsrud TV, Wiseman GA, Mullan BP, Subramaniam RM, Nathan MA, et al. Clinical significance of diffusely increased 18F-FDG uptake in the thyroid gland. J Nucl Med. 2007;48(6):896–901.
22. De Leijer JF, Metman MJH, Van Der Hoorn A, Brouwers AH, Kruijff S, Van Hemel BM, et al. Focal thyroid incidentalomas on 18F-FDG PET/CT: a systematic review and Meta-analysis on prevalence, risk of malignancy and inconclusive fine needle aspiration. Front Endocrinol. 2021;12:723394.
23. Scappaticcio L, Piccardo A, Treglia G, Poller DN, Trimboli P. The dilemma of 18F-FDG PET/CT thyroid incidentaloma: what we should expect from FNA. A systematic review and meta-analysis. Endocrine. 2021;73(3):540–9.
24. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81(s1):1–122.
25. Jarząb B, Dedecjus M, Lewiński A, Adamczewski Z, Bakuła-Zalewska E, Bałdys-Waligórska A, the National Oncological Strategy. Diagnosis and treatment of thyroid cancer in adult patients — Recommendations of Polish Scientific Societies and. 2022 Update. Endokrynol Pol. 2022;73(2):173–300.
26. Durante C, Hegedüs L, Czarniecka A, Paschke R, Russ G, Schmitt F, et al. 2023 European thyroid Association Clinical Practice guidelines for thyroid nodule management. Eur Thyroid J. 2023;12(5):e230067.
27. Wadsley J, Balasubramanian SP, Madani G, Munday J, Roques T, Rowe CW et al. Consensus statement on the management of incidentally discovered FDG avid thyroid nodules in patients being investigated for other cancers. Clin Endocrinol (Oxf). 2023;cen.14905.
28. Pattison DA, Bozin M, Gorelik A, Hofman MS, Hicks RJ, Skandarajah A. ^{18} F-FDGthyroidhincidentalomasalthesimportancertance of Contextual Interpretation. J Nucl Med. 2018;59(5):749–55.
29. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda System for Reporting Thyroid Cytopathology. Thyroid®. 2023;thy.2023.0141.
30. Vuong HG, Ngo HTT, Bychkov A, Jung CK, Vu TH, Lu KB, et al. Differences in surgical resection rate and risk of malignancy in thyroid cytopathology practice between western and Asian countries: a systematic review and meta-analysis. Cancer Cytopathol. 2020;128(4):238–49.
31. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for reporting thyroid cytopathology: a Meta-analysis. Acta Cytol. 2012;56(4):333–9.
32. De Koster EJ, De Geus-Oei LF, Brouwers AH, Van Dam EWCM, Dijkhorst-Oei LT, Van Engen-van Grunsven ACH, et al. [18F]FDG-PET/CT to prevent futile surgery in indeterminate thyroid nodules: a blinded, randomised controlled multicentre trial. Eur J Nucl Med Mol Imaging. 2022;49(6):1970–84.
33. Piccardo A, Puntoni M, Dezzana M, Bottoni G, Foppiani L, Marugo A, et al. Indeterminate thyroid nodules. The role of 18F-FDG PET/CT in the era of ultrasonography risk stratification systems and new thyroid cytology classifications. Endocrine. 2020;69(3):553–61.
34. Rosario PW, Rocha TG, Calsolari MR. Fluorine-18-fluorodeoxyglucose positron emission tomography in thyroid nodules with indeterminate cytology: a prospective study. Nucl Med Commun. 2019;40(2):185–7.
35. Merten MM, Castro MR, Zhang J, Durski J, Ryder M. Examining the role of Preoperative Positron Emission Tomography/Computerized Tomography in Combination with Ultrasonography in discriminating Benign from Malignant Cytologically Indeterminate thyroid nodules. Thyroid. 2017;27(1):95–102.
36. De Koster EJ, Vriens D, Van Aken MO, Dijkhorst-Oei LT, Oyen WJG, Peeters RP, et al. FDG-PET/CT in indeterminate thyroid nodules: cost-utility analysis alongside a randomised controlled trial. Eur J Nucl Med Mol Imaging. 2022;49(10):3452–69.
37. Vriens D, Adang EMM, Netea-Maier RT, Smit JWA, De Wilt JHW, Oyen WJG, et al. Cost-effectiveness of FDG-PET/CT for cytologically indeterminate thyroid nodules: a decision Analytic Approach. J Clin Endocrinol Metab. 2014;99(9):3263–74.
38. Pathak KA, Klonisch T, Nason RW, Leslie WD. FDG-PET characteristics of Hürthle cell and follicular adenomas. Ann Nucl Med. 2016;30(7):506–9.
39. De Koster EJ, Morreau H, Bleumink GS, Van Engen-van Grunsven ACH, De Geus-Oei LF, Links TP, et al. Molecular Diagnostics and [18 F]FDG-PET/CT in indeterminate thyroid nodules: complementing techniques or Waste of Valuable resources? Thyroid®. 2024;34(1):41–53.
40. Ciappuccini R, Edet-Sanson A, Saguet-Rysanek V, Gauthé M, Bardet S. Thyroid incidentaloma on 18F-fluorocholine PET/CT and 68Ga-PSMA PET/CT revealing a medullary thyroid carcinoma. Clin Nucl Med. 2019;44(8):663–5.
41. Saggiorato E, Angusti T, Rosas R, Martinese M, Finessi M, Arecco F, et al. ^{99m} Tcimagingmaging in the Presurcharacterizationzatithyroidhfollicularineoplasmsplrelationshiponship to Multresistancesproteinrexpressionession. J Nucl Med. 2009;50(11):1785–93.
42. Giovanella L, Suriano S, Maffioli M, Ceriani L, Spriano G. ^{99m} Tc-sestamibi scanning in thyroid nodules with nondiagnostic cytology. Head Neck. 2010;32(5):607–11.
43. Hurtado-López L, Arellano-Montaño S, Torres-Acosta E, Zaldivar-Ramirez F, Duarte-Torres R, Alonso-de-Ruiz P et al. Combined use of fine-needle aspiration biopsy, MIBI scans and frozen section biopsy offers the best diagnostic accuracy in the assessment of the hypofunctioning solitary thyroid nodule. Eur J Nucl Med Mol Imaging [Internet]. 2004 Sep;31(9):1286-91.
44. Treglia G, Piccardo A, Paone G, Trimboli P, Imperiale A. [18F]Fluorocholine PET/CT as First-Line vs. Second-Line Imaging Method to localize parathyroid adenomas in primary hyperparathyroidism: game, set, and Match. Eur J Nucl Med Mol Imaging. 2024;51(12):3596–9.
45. Yeh MW, Bauer AJ, Bernet VA, Ferris RL, Loevner LA, Mandel SJ, et al. American Thyroid Association Statement on Preoperative Imaging for thyroid Cancer surgery. Thyroid. 2015;25(1):3–14.
46. Kim DH, Kim SJ. Diagnostic role of F-18 FDG PET/CT for preoperative lymph node staging in thyroid cancer patients; a systematic review and metaanalysis. Clin Imaging. 2020;65:100–7.
47. Kim K, Shim SR, Lee SW, Kim SJ. Diagnostic values of F-18 FDG PET or PET/CT, CT, and US for Preoperative Lymph Node staging in thyroid Cancer: a Network Meta-Analysis. Br J Radiol. 2021;94(1120):20201076.
48. Tantiwongkosi B. Role of ^{18} F-FDG PET/CT in pre and post treatment evaluation in head and neck carcinoma. World J Radiol. 2014;6(5):177.
49. Li H, Kong Z, Xiang Y, Zheng R, Liu S. The role of PET/CT in radiotherapy for nasopharyngeal carcinoma. Front Oncol. 2022;12:1017758.
50. Schütz F, Lautenschläger C, Lorenz K, Haerting J. Positron Emission Tomography (PET) and PET/CT in thyroid Cancer: a systematic review and Meta-analysis. Eur Thyroid J. 2018;7(1):13–20.
51. Bang JI, Park S, Kim K, Seo Y, Chong A, Hong CM, et al. The diagnostic value of ^{18} F-Fluorodeoxyglucose Positron Emission Tomography/Computed tomography in differentiated thyroid Cancer patients with elevated Thyroglobulin/Thyroglobulin antibody levels and negative iodine scintigraphy: a systematic review and Meta-analysis. Thyroid®. 2023;33(10):1224–36.
52. Sampson E, Brierley JD, Le LW, Rotstein L, Tsang RW. Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer. 2007;110(7):1451–6.
53. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ, et al. 2021 American Thyroid Association Guidelines for Management of patients with

anaplastic thyroid Cancer: American thyroid Association anaplastic thyroid Cancer Guidelines Task Force. Thyroid. 2021;31(3):337–86.
54. Kim HJ, Chang HS, Ryu YH. Prognostic role of pre-treatment [18F]FDG PET/CT in patients with anaplastic thyroid Cancer. Cancers. 2021;13(16):4228.
55. Bogsrud TV, Karantanis D, Nathan MA, Mullan BP, Wiseman GA, Kasperbauer JL, et al. ^{18} F-FDG PET imanagementgemepatientstientsanaplasticlthyroidh-carcinomacinoma. Thyroid. 2008;18(7):713–9.
56. Brierley JD, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. Eighth edition. Chichester, West Sussex, UK Hoboken, NJ: John Wiley & Sons, Inc; 2017.
57. Filesi M, Signore A, Ventroni G, Melacrinis FF, Ronga G. Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. J Nucl Med off Publ Soc Nucl Med. 1998;39(9):1542–6.
58. Lee JW, Lee SM, Lee DH, Kim YJ. Clinical utility of ^{18} F-FDG PET/CT concurrent with ^{131} I therapy in intermediate–to–high-risk patients with differentiated thyroid Cancer: dual-center experience with 286 patients. J Nucl Med. 2013;54(8):1230–6.
59. Nascimento C, Borget I, Al Ghuzlan A, Deandreis D, Hartl D, Lumbroso J, et al. Postoperative fluorine-18-Fluorodeoxyglucose Positron Emission Tomography/Computed tomography: an important imaging modality in patients with aggressive histology of differentiated thyroid Cancer. Thyroid. 2015;25(4):437–44.
60. Rendl G, Rettenbacher L, Schweighofer-Zwink G, Hehenwarter L, Pirich C. Pre-ablation rhTSH-Stimulated F-18 FDG PET/CT changes patient management in increased-risk thyroid Cancer. Horm Metab Res. 2020;52(03):158–67.
61. Gaertner FC, Okamoto S, Shiga T, Ito YM, Uchiyama Y, Manabe O, et al. FDG PET performed at thyroid remnant ablation has a higher predictive value for long-term survival of high-risk patients with Well-differentiated thyroid Cancer Than Radioiodine Uptake. Clin Nucl Med. 2015;40(5):378–83.
62. Rizzo A, Perotti G, Zagaria L, Lanni V, Racca M, Palestini N et al. 18F-FDG PET/CT concurrent with first radioiodine post-therapeutic scan in high risk differentiated thyroid cancer: a useful tool or just an expensive diversion? Q J Nucl Med Mol Imaging. 2023 May;67(2):141-8. Available from: [URL if needed]. [cited 2024 Feb 21].
63. Liu M, Cheng L, Jin Y, Ruan M, Sheng S, Chen L. Predicting 131I-avidity of metastases from differentiated thyroid cancer using 18F-FDG PET/CT in postoperative patients with elevated thyroglobulin. Sci Rep. 2018;8(1):4352.
64. Matsuo M, Baba S, Hashimoto K, Isoda T, Kitamura Y, Kogo R, et al. Utility of FDG PET at the initial Radioiodine Therapy in differentiated thyroid Cancer. Anticancer Res. 2023;43(1):183–90.
65. De Ywata A, Kohler HF, Gomes CC, Vartanian JG, Kowalski LP. Predictive factors for recurrence of papillary thyroid carcinoma: analysis of 4,085 patients. Acta Otorhinolaryngol Ital. 2021;41(3):236–42.
66. Grønlund MP, Jensen JS, Hahn CH, Grønhøj C, Von Buchwald C. Risk factors for recurrence of follicular thyroid Cancer: a systematic review. Thyroid. 2021 Jul 5;31(7):1017-29. https://doi.org/10.1089/thy.2020.0921.
67. Hescot S, Al Ghuzlan A, Henry T, Sheikh Alard H, Lamartina L, Borget I et al. Prognostic of recurrence and survival in poorly differentiated thyroid cancer. Endocr Relat Cancer. 2022 Aug;29(8).
68. Sun JH, Li YR, Chang KH, Liou MJ, Lin SF, Tsai SS, et al. Evaluation of recurrence risk in patients with papillary thyroid cancer through tumor-node-metastasis staging: a single-center observational study in Taiwan. Biomed J. 2022;45(6):923–30.
69. Pałyga I, Rumian M, Kosel A, Albrzykowski M, Krawczyk P, Kalwat A, et al. The frequency of differentiated thyroid Cancer recurrence in 2302 patients with excellent response to primary therapy. J Clin Endocrinol Metab. 2024;109(2):e569–78.
70. Kunogi H, Naoi Y, Matsumoto T, Ozaki Y. Late recurrence of a papillary thyroid carcinoma 37 years after hemithyroidectomy: Solitary, left cervical lymph node metastasis evident on fluorodeoxyglucose positron-emission tomography/computed tomography images revealing nodular uptake. World J Nucl Med. 2020;19(02):155–8.
71. Haddad RI, Bischoff L, Ball D, Bernet V, Blomain E, Busaidy NL, et al. Thyroid carcinoma, Version 2.2022, NCCN Clinical Practice guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(8):925–51.
72. Hoe Khoo A, Fong L, Hamzah F. A review of TENIS syndrome in Hospital Pulau Pinang. Indian J Nucl Med. 2018;33(4):284.
73. Boktor RR, Lee ST, Berlangieri SU, Scott AM. Impact of 18F-FDG PET/CT on treatment of patients with differentiated thyroid carcinoma, negative 131I whole body scan and elevated serum thyroglobulin. Asia Ocean J Nucl Med Biol. 2022;10(1):20–7.
74. Filippi L, Frantellizzi V, Monari F, Lodi Rizzini E, Tabacchi E, Pirisino R, et al. Usefulness of PET/CT with 18F-FDG in patients with differentiated thyroid carcinoma after Radioiodine Therapy: an Italian Multicenter Study. Diagnostics. 2021;11(7):1264.
75. Zhi Y, Higuchi T, Hackenberg S, Hagen R, Stöth M, Scherzad A et al. [18F] FDG PET/CT can trigger relevant oncological management changes leading to favorable outcome in iodine-negative thyroid cancer patients. Endocr [Internet]. 2023 Dec 22.
76. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(12):1856–83.
77. Giovanella L, Trimboli P, Verburg FA, Treglia G, Piccardo A, Foppiani L, 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(6):874–80.
78. Lebbink CA, de Vries LH, Borel Rinkes IHM, Braat AJAT, van Leeuwaarde RS, Lodewijk L, et al. FDG PET/CT in differentiated thyroid cancer patients with low thyroglobulin levels. Eur J Endocrinol. 2022;187(1):101–10.
79. Albano D, Tulchinsky M, Dondi F, Mazzoletti A, Lombardi D, Bertagna F, et al. Thyroglobulin doubling time offers a better threshold than thyroglobulin level for selecting optimal candidates to undergo localizing [18F]FDG PET/CT in non-iodine avid differentiated thyroid carcinoma. Eur J Nucl Med Mol Imaging. 2021;48(2):461–8.
80. Giovanella L, Garo ML, Albano D, Görges R, Ceriani L. The role of thyroglobulin doubling time in differentiated thyroid cancer: a meta-analysis. Endocr Connect. 2022;11(4):e210648.
81. Nilsson JN, Siikanen J, Hedman C, Juhlin CC, Ihre Lundgren C. Pre-therapeutic measurements of Iodine Avidity in Papillary and poorly differentiated thyroid Cancer Reveal associations with Thyroglobulin expression, histological variants and Ki-67 index. Cancers. 2021;13(14):3627.
82. Kalshetty A, Basu S. Thyroglobulin 'Nonsecretor' metastatic poorly differentiated thyroid carcinoma with Noniodine concentrating Disease and Aggressive Clinical Course: a clinical Case Series. Indian J Nucl Med IJNM off J Soc Nucl Med India. 2018;33(3):218–23.
83. Barbesino G, Algeciras-Schimnich A, Bornhorst J. Thyroglobulin Assay interferences: clinical usefulness of Mass-Spectrometry methods. J Endocr Soc. 2022;7(1):bvac169.
84. Verburg FA, Luster M, Cupini C, Chiovato L, Duntas L, Elisei R, et al. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid Cancer: a clinical position Statement. Thyroid. 2013;23(10):1211–25.
85. Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med. 2003;139(5Part1):346.
86. Durante C, Tognini S, Montesano T, Orlandi F, Torlontano M, Puxeddu E, et al. Clinical aggressiveness and long-term outcome in patients with papillary thyroid Cancer and circulating Anti-thyroglobulin autoantibodies. Thyroid. 2014;24(7):1139–45.
87. Albano D, Piccardo A, Rizzo A, Cuzzocrea M, Bottoni G, Bellini P et al. Diagnostic performance of 2-[18F]FDG PET/CT in recurrent differentiated thyroid cancer and elevated antithyroglobulin antibodies: an updated systematic review and bivariate meta-analysis. Endocrine [Internet]. 2024 Sep 9.
88. Kingpetch K, Pipatrattana R, Tepmongkol S, Sirisalipoch S, Chaiwatanarat T. Utility of 8F-FDG PET/CT in well differentiated thyroid carcinoma with high serum antithyroglobulin antibody. J Med Assoc Thail Chotmaihet Thangphaet. 2011;94(10):1238–44.
89. Qiu ZL, Wei WJ, Shen CT, Song HJ, Zhang XY, Sun ZK, et al. Diagnostic performance of 18F-FDG PET/CT in papillary thyroid carcinoma with negative 131I-WBS at first Postablation, negative tg and progressively increased TgAb level. Sci Rep. 2017;7(1):2849.
90. Ma C, Xie J, Lou Y, Gao Y, Zuo S, Wang X. The role of TSH for 18F-FDG-PET in the diagnosis of recurrence and metastases of differentiated thyroid carcinoma with elevated thyroglobulin and negative scan: a meta-analysis. Eur J Endocrinol. 2010;163(2):177–83.
91. Qichang W, Lin B, Gege Z, Youjia Z, Qingjie M, Renjie W, et al. Diagnostic performance of 18F-FDG-PET/CT in DTC patients with thyroglobulin elevation and negative iodine scintigraphy: a meta-analysis. Eur J Endocrinol. 2019;181(2):93–102.
92. Triviño Ibáñez EM, Muros MA, Torres Vela E, Llamas Elvira JM. The role of early 18F-FDG PET/CT in therapeutic management and ongoing risk stratification of high/intermediate-risk thyroid carcinoma. Endocrine. 2016;51(3):490–8.

93. Kersting D, Seifert R, Kessler L, Herrmann K, Theurer S, Brandenburg T, et al. Predictive factors for RAI-Refractory disease and short overall survival in PDTC. Cancers. 2021;13(7):1728.
94. Chindris AM, Casler JD, Bernet VJ, Rivera M, Thomas C, Kachergus JM, et al. Clinical and molecular features of Hürthle Cell Carcinoma of the thyroid. J Clin Endocrinol Metab. 2015;100(1):55–62.
95. Lowe VJ, Mullan BP, Hay ID, McIver B, Kasperbauer JL. 18F-FDG PET of patients with Hürthle cell carcinoma. J Nucl Med off Publ Soc Nucl Med. 2003;44(9):1402–6.
96. Pryma DA, Schöder H, Gönen M, Robbins RJ, Larson SM, Yeung HWD. Diagnostic accuracy and prognostic value of 18F-FDG PET in Hürthle cell thyroid cancer patients. J Nucl Med off Publ Soc Nucl Med. 2006;47(8):1260–6.
97. Plotkin M, Hautzel H, Krause BJ, Schmidt D, Larisch R, Mottaghy FM, et al. Implication of 2–^{18} Fluor-2-Deoxyglucose Positron Emission Tomography in the Follow-Up of Hürthle cell thyroid Cancer. Thyroid. 2002;12(2):155–61.
98. Puliafito I, Esposito F, Prestifilippo A, Marchisotta S, Sciacca D, Vitale MP, et al. Target therapy in thyroid Cancer: current challenge in clinical use of tyrosine kinase inhibitors and management of Side effects. Front Endocrinol. 2022;13:860671.
99. Marotta V, Ramundo V, Camera L, Prete MD, Fonti R, Esposito R, et al. Sorafenib in advanced iodine-refractory differentiated thyroid cancer: efficacy, safety and exploratory analysis of role of serum thyroglobulin and FDG - PET. Clin Endocrinol (Oxf). 2013;78(5):760–7.
100. Valerio L, Guidoccio F, Giani C, Tardelli E, Puccini G, Puleo L, et al. [18F]-FDG-PET/CT correlates with the response of Radiorefractory thyroid Cancer to Lenvatinib and Patient Survival. J Clin Endocrinol Metab. 2021;106(8):2355–66.
101. Takeuchi S, Hirata K, Magota K, Watanabe S, Moku R, Shiiya A, et al. Early prediction of treatment outcome for lenvatinib using 18F-FDG PET/CT in patients with unresectable or advanced thyroid carcinoma refractory to radioiodine treatment: a prospective, multicentre, non-randomised study. EJNMMI Res. 2023;13(1):69.
102. Ahmaddy F, Burgard C, Beyer L, Koehler VF, Bartenstein P, Fabritius MP, et al. 18F-FDG-PET/CT in patients with Advanced, Radioiodine refractory thyroid Cancer treated with Lenvatinib. Cancers. 2021;13(2):317.
103. Gay S, Raffa S, Di De'Luca A, Bauckneht M, Vera L, Miceli A, et al. 2-[18F]FDG PET in the management of Radioiodine Refractory differentiated thyroid Cancer in the era of thyrosin-kinases inhibitors: a real-life Retrospective Study. Diagnostics. 2022;12(2):506.
104. Treistman N, Nobre GM, Tramontin MY, Silva GMWD, Herchenhorn D, Araujo LHDL et al. Prognostic factors in patients with advanced differentiated thyroid cancer treated with multikinase inhibitors – a single Brazilian center experience. Arch Endocrinol Metab [Internet]. 2021 Apr 29;65(2):163-71..
105. Carr LL, Mankoff DA, Goulart BH, Eaton KD, Capell PT, Kell EM, et al. Phase II study of Daily Sunitinib in FDG-PET–Positive, iodine-refractory differentiated thyroid Cancer and metastatic medullary carcinoma of the thyroid with functional imaging correlation. Clin Cancer Res. 2010;16(21):5260–8.
106. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced Radioiodine Uptake in Advanced thyroid Cancer. N Engl J Med. 2013;368(7):623–32.
107. Dotinga M, Vriens D, Van Velden FHP, Stam MK, Heemskerk JWT, Dibbets-Schneider P, et al. Reinducing Radioiodine-Sensitivity in Radioiodine-Refractory thyroid Cancer using Lenvatinib (RESET): study protocol for a Single-Center, open label phase II trial. Diagnostics. 2022;12(12):3154.
108. Weber M, Kersting D, Riemann B, Brandenburg T, Führer-Sakel D, Grünwald F, et al. Enhancing Radioiodine Incorporation into Radioiodine-Refractory thyroid Cancer with MAPK inhibition (ERRITI): a single-center prospective two-arm study. Clin Cancer Res. 2022;28(19):4194–202.
109. Dunn LA, Sherman EJ, Baxi SS, Tchekmedyian V, Grewal RK, Larson SM, et al. Vemurafenib Redifferentiation of *BRAF* Mutant, RAI-Refractory thyroid cancers. J Clin Endocrinol Metab. 2019;104(5):1417–28.
110. Groussin L, Theodon H, Bessiene L, Bricaire L, Bonnet-Serrano F, Cochand-Priollet B, et al. Redifferentiating effect of Larotrectinib in *NTRK* -Rearranged Advanced Radioactive-Iodine refractory thyroid Cancer. Thyroid. 2022;32(5):594–8.
111. Iravani A, Solomon B, Pattison DA, Jackson P, Ravi Kumar A, Kong G, et al. Mitogen-activated protein kinase pathway inhibition for redifferentiation of Radioiodine Refractory differentiated thyroid Cancer: an evolving protocol. Thyroid. 2019;29(11):1634–45.
112. Cabanillas ME, Ferrarotto R, Garden AS, Ahmed S, Busaidy NL, Dadu R, et al. Neoadjuvant BRAF- and Immune-Directed Therapy for anaplastic thyroid carcinoma. Thyroid. 2018;28(7):945–51.
113. Fazeli S, Paal E, Maxwell JH, Burman KD, Nylen ES, Khosla SG. Salutary response to targeted therapy in anaplastic thyroid Cancer. J Investig Med High Impact Case Rep. 2019;7:232470961989094.
114. Arıkan R, Telli TA, Demircan NC, Başoğlu T, Ercelep Ö, Atasoy BM, et al. Rechallenge with dabrafenib plus trametinib in anaplastic thyroid cancer: a case report and review of literature. Curr Probl Cancer. 2021;45(2):100668.
115. Wang JR, Zafereo ME, Dadu R, Ferrarotto R, Busaidy NL, Lu C, et al. Complete Surgical Resection Following Neoadjuvant Dabrafenib Plus Trametinib in $BRAF^{V600E}$ -Mutated Anaplastic Thyroid Carcinoma. Thyroid. 2019;29(8):1036–43.
116. Maurer E, Eilsberger F, Wächter S, Riera Knorrenschild J, Pehl A, Holzer K, et al. Mutation-based, short-term neoadjuvant treatment allows resectability in stage IVB and C anaplastic thyroid cancer. Eur Arch Otorhinolaryngol. 2023;280(3):1509–18.
117. Deandreis D, Al Ghuzlan A, Leboulleux S, Lacroix L, Garsi JP, Talbot M, et al. Do histological, immunohistochemical, and metabolic (radioiodine and fluorodeoxyglucose uptakes) patterns of metastatic thyroid cancer correlate with patient outcome? Endocr Relat Cancer. 2011;18(1):159–69.
118. Jannin A, Lamartina L, Moutarde C, Djennaoui M, Lion G, Vantyghem MC, et al. 1921P prognostic impact of [18F]FDG-PET/CT in differentiated thyroid cancer with bone metastasis: a French TUTHYREF study. Ann Oncol. 2020;31:S1089.
119. Robbins RJ, Wan Q, Grewal RK, Reibke R, Gonen M, Strauss HW, 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(2):498–505.
120. Masson-Deshayes S, Schvartz C, Dalban C, Guendouzen S, Pochart JM, Dalac A, et al. Prognostic value of 18F-FDG PET/CT metabolic parameters in metastatic differentiated thyroid cancers. Clin Nucl Med. 2015;40(6):469–75.
121. Manohar PM, Beesley LJ, Bellile EL, Worden FP, Avram AM. Prognostic value of FDG-PET/CT metabolic parameters in metastatic radioiodine-refractory differentiated thyroid Cancer. Clin Nucl Med. 2018;43(9):641–7.
122. Roy M, Edet-Sanson A, Lefebvre H, Vera P, Decazes P. Using 18F-FDG-PET/CT Metrics to Predict Survival in Ra-Dio-Iodine Refractory thyroid cancers. Diagnostics. 2022;12(10):2381.
123. Albano D, Dondi F, Mazzoletti A, Bellini P, Rodella C, Bertagna F. Prognostic role of 2-[18F]FDG PET/CT metabolic volume parameters in patients affected by differentiated thyroid carcinoma with high Thyroglobulin Level, negative 131I WBS and positive 2-[18F]-FDG PET/CT. Diagnostics. 2021;11(12):2189.
124. Wijewardene A, Hoang J, Maw AM, Gild M, Tacon L, Roach P et al. I-PET score: Combining whole body iodine and ^{18} F-FDG PET/CT imaging to predict progression in structurally or biochemically incomplete thyroid cancer. Clin Endocrinol (Oxf). 2022;cen.14804.

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