Kurdish Studies
Jan 2024
Volume: 12, No: 1, pp.4479-4492
ISSN: 2051-4883 (Print) | ISSN 2051-4891 (Online)
www.KurdishStudies.net

Received: October 2023 Accepted: December 2023
DOI: https://doi.org/10.58262/ks.v12i1.322

The Role of Molecular Imaging in the Clinical Assessment of Well-Differentiated and Poorly Differentiated Thyroid Cancer

Layal Jambi[1], Zainab Aldawood[2], Haitham Alahmad[3], Ohoud Almuyid[4], Lulah Qysi[5], Ghadi Alahmadi[6], Mohammed Mostafa[7], Mohammed Alnafea[8]

Abstract

Non-invasive medical imaging modalities has become a standard /unique tool for the diagnosis and staging of numerous diseases. Molecular imaging plays an important role in the evaluation and management of thyroid cancer. Hyperthyroidism, Hypothyroidism, Thyroid cancer are a mixture of endocrine group disease that can be ruled out using hybrid-imaging technique. An emerging role of molecular imaging is in providing information that directly influences on the mode of delivery of detection, diagnosis and treating cancer patients. This study was conducted to compare well-differentiated and poorly differentiated thyroid carcinoma using Hybrid imaging modalities in thyroid carcinoma imaging using literature review proved research from 2008-2022. There are specific case examples of patients with thyroid cancer who appear to have benefited from imaging with Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET). Positron Emission Tomography / Computed Tomography (PET/CT) improves both disease detection and management in patient diagnosed with poorly differentiated thyroid carcinoma and consider as the best assessment method in cases with high serum Thyroglobulin (Tg) and negative Whole Body Iodine Scan (WBIS) using 131-Iodine Single Photon Emission Computed Tomography / Computed Tomography (^{131}I-SPECT/CT) imaging. In the context of modern oncology science both molecular imaging and Theranostic imaging plays an integral role in the clinical management and the evaluation of thyroid cancer and endocrine disorders. Treatment options depends on the thyroid malignancy staging. PET/CT improves both disease detection and management in-patient diagnosed with poorly differentiated thyroid carcinoma like Hürthl cell carcinoma. At initial evaluation at the time of radioiodine ablation therapy, 18-Fluorine (^{18}F-FDG) PET/CT should be performed in patients with intermediate-to-high-risk thyroid cancer owing to excellent prognostic capabilities.

Key words: *Thyroid disorders, Thyroid Carcinoma, differentiated thyroid cancer, Well differentiated, poorly differentiated, ^{18}F-PET/CT.*

Introduction

Endocrine system consists of network glands each released specific chemical hormones act as messenger through the blood stream which help in coordinating, control and regulate the blood

[1] Department of Radiological Science, collage of Applied Science, King Saud University, Riyadh 11433, Kingdom of Saudi Arabia
[2] Department of Radiological Science, collage of Applied Science, King Saud University, Riyadh 11433, Kingdom of Saudi Arabia
Department of Medical Imaging, Almana General Hospital Dammam, Kingdom of Saudi Arabia
[3] Department of Radiological Science, collage of Applied Science, King Saud University, Riyadh 11433, Kingdom of Saudi Arabia
[4] Diagnostic Radiology Department, Applied Medical Sciences College, King Khalid University
[5] Aldarb general Hospital, Jazan, Saudi Arabia
[6] AlGad International College for Applied Medical Sciences, Radiological Sciences, Jeddah, Saudi Arabia
[7] Department of Radiologic Technology, collage of Applied Science, Qassim University, Buraidah 51452
[8] Department of Radiological Science, collage of Applied Science, King Saud University, Riyadh 11433, Kingdom of Saudi Arabia

circulation, body glucose level, body temperature and growth and metabolism function to reach targeting organs. Human body have endocrine and exocrine glands which excrete the substances inside and outside the body like hypothalamus, pancreas, adrenal, thyroid and parathyroid. The pituitary (master gland) that influence both thyroid and parathyroid glands. Endocrine disorders are classified into two main reasons first due to hormone imbalance either the excessive or less secretion and second due to development of nodular or tumor lesions. The symptoms are widely depending specifically on the gland involved. Thyroid is a butterfly glandular tissue shape measured about 5 cm in diameter located in the lower neck region. Triiodothyronine (T3), Thyroxin (T4) and calcitonin are the three major metabolic hormones produced and secreted by thyroid gland after absorbing iodine into blood stream [1]. Both T3 and T4 hormones are play an integral role in regulating the body metabolic rate, bone metabolism, influence the cardiovascular system, growth and it is very important for the normal development of nervous system. Genetic disorders multiple endocrine neoplasia syndromes, failure of stimulating and producing enough hormones, endocrine glands injuries or tumors are all considered as endocrine disorders as mixed group of disease that affect the body system organization [1, 2].

Thyroid cancer incidence has rapidly increased in highly income countries in the past 30 years. This is observed especially in females in the United States of America (USA), Japan, Finland and Singapore and Chinese populations. In Europe France and Romania, have the highest rates in females followed by Italy and Iceland respectively. A high incidence of thyroid cancer has been observed in Iceland and in native Alaskan women also. Among men, the highest rate was seen in Iceland followed by Filipinos in Hawaii. Filipino men also have rates higher than most other groups. On the other hand, in India and the United Kingdom (UK) the rates have remained steady over the past 30 years. Age standardized rate in females were always higher than in males in all countries. The rates in females were more than twice the rates in males in most of the population studied. Cancer of thyroid in children has been observed and reported from all over the world. Though its incidence is low throughout the world. However, the highest for thyroid cancer in children among females were reported from African Americans in Los Angeles, USA.

A risk factor is anything that increases a person's chance of getting a cancer. Different cancers have different risk factors. For example, unprotected exposure to strong sunlight is a risk factor for skin cancer, and smoking is a risk factor for cancers of the lungs, mouth, throat and esophagus. Several authors have found a few risk factors that make a person more likely to develop thyroid cancer. However, even if a patient with thyroid cancer has one or more risk factors, it is impossible to know exactly how much that risk factor may have contributed to causing the cancer. Of the few factors that are suspected as high risk for thyroid cancer are exposure to radiation, iodine intake and certain diets. Of these, radiation exposure has been regarded as consistent with a causal role for thyroid cancer. Therapeutic radiation, radiation fall out from nuclear weapon testing and radiations from nuclear accidents have been observed as risk factors.

Increased risk of second primary malignancy (SPM) in papillary thyroid cancer (PTC) has been reported in several cancer registry and epidemiologic clinical studies. Women are affected by thyroid cancer more than men with a female-to-male ratio that may reach to 3:1 [4,5]. Patient might present with different symptoms like weight loss, sleep disorders, bilateral neck pain or neck swelling, heart palpitation and other cardiovascular complications [2-4, 7]. Based on the World Health Organization (WHO) and the American Thyroid Association (ATA), thyroid carcinoma classification is mainly divided into three main risky groups low, intermediate and high [5]. In pathological molecular tumor profile terminology, well differentiated used to describe the cancerous cell which have less likely look similar to the normal features of healthy surrounding cells. It is grown and spread slowly to the body part. In contrast, poorly differentiated and undifferentiated cell types are more aggressive and spread quickly through human body. Moderately differentiated term is used in describing the clearly abnormal cells seen microscopy comparing into the surrounding cells shape but still having the same features [5-6]. Currently, the initial assessment of thyroid cancer starting with serum Thyroid Stimulating Hormone (TSH) and calcitonin laboratory medicine tests and four main medical imaging modalities presenting a great special distribution and structural and functional attribution using high resolution ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) scan contrast studies which can provide valuable information on tumor size, location, and local invasion. However, these imaging techniques have limitations in assessing tumour biology and predicting disease behaviour. Molecular imaging and nuclear medicine scintigraphy on the other hand, both can offer a unique approach to visualize and quantify specific molecular processes that is associated with tumour development and progression. By targeting specific molecular markers, molecular imaging techniques can provide insights into tumour aggressiveness, risk of recurrence, and response to therapy, as well as the therapeutic ablation dose in the determination, identification and evaluation of thyroid bed tissue residual or any recurrence as well as any iodine avidity and distance metastasis [8, 9]. From the pathology view, the thyroid cancer according to WHO world organization the new classification has divided thyroid tumors into several new categories. The first is benign followed by malignant and low risk for a clearer understanding of the cell of origin and its biological behavior, pathologic features (cytopathology and histopathology), molecular classification. The most common thyroid cancers, papillary and follicular, have a cure rate of 97%. Follicular cell-derived tumors constitute the majority of thyroid neoplasms [5-7]. Differentiated cancer raised from follicular cells and divided into four main groups Papillary (PTC), Follicular (FTC), Medullary (MTC) and Anaplastic (ATC) discussed in Fig. 1.

In the context of thyroid cancer, molecular imaging plays a pivotal role in the clinical assessment of both Well-differentiated thyroid cancers (WDTCs) and papillary thyroid carcinoma (PDTCs). For WDTCs, radioiodine scintigraphy remains the gold standard for evaluating iodine uptake and identifying remnant thyroid tissue or metastatic lesions. Additionally, [^{18}F] fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has emerged as a valuable tool for detecting and characterizing aggressive WDTCs, particularly those with radioiodine-refractory disease. [10-12].

Management of Differentiated Thyroid Cancer

Based on Histopathology type, fine needle aspiration (FNA) is the most common method to differentiate between thyroid carcinoma and adenoma with high sensitivity and cost effectiveness. There are two factors must be considered in FNA nodule cytology: vascular or capsular invasion and the involvement of extra thyroidal spread, lymph node. In ultrasound imaging biopsy the appearance and nature solitary, cold, or solid nodules often requires biopsy to roll out suspicion as well as malignancy [10, 11, 44].

1. Differentiated Thyroid Cancer

Differentiated thyroid cancer is a type of thyroid cancer in which the cancer cells look similar to normal thyroid cells when viewed under a microscope. Most differentiated thyroid cancers form in the follicular cells of the thyroid gland. They tend to grow slowly, can be treated, and can usually be cured.

1.1 Papillary Thyroid Carcinomas

Papillary thyroid cancer is the most common type of well-differentiated thyroid malignancy. It affects about 8 out of 10 people with thyroid cancer also, adult in-group age between 20-60. It usually grows very slowly and often spreads to the lymph nodes in the neck region and rarely spreading to the lungs or bone. It affects women three times more than men; it has excellent prognosis and 90% overall survival rate [12, 13].

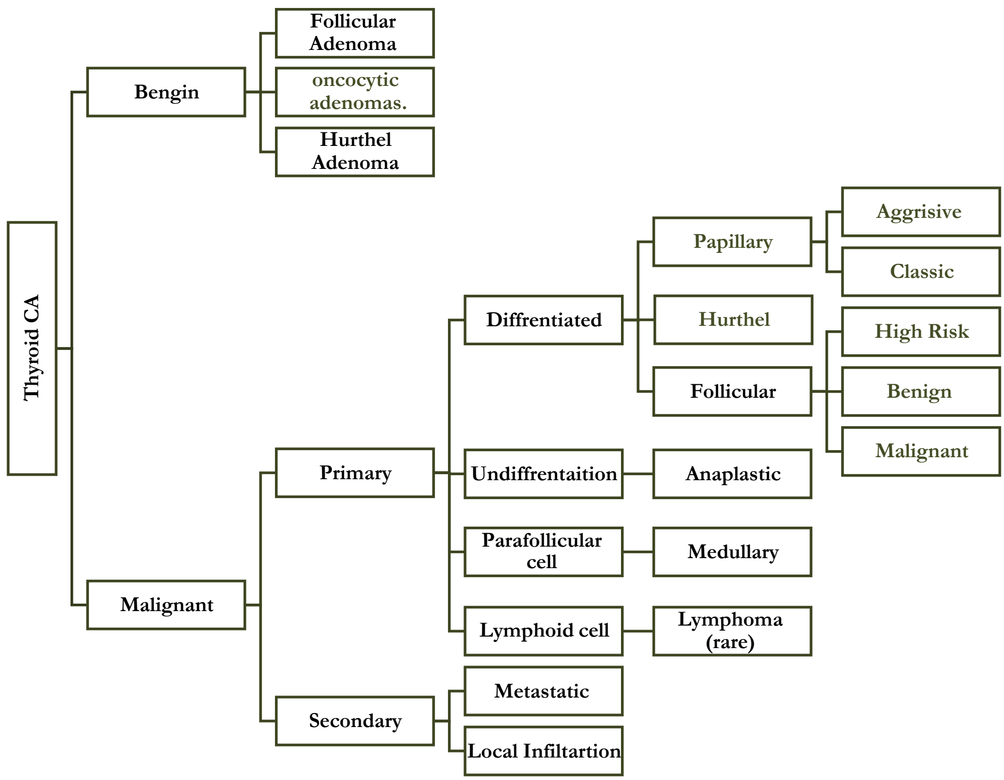

Fig. 1: 5th Edition of Thyroid Cancer Neoplasm Classification Features in World Health Organization 2022 based on Biological, Cellular Origin, Molecular and Pathological Characteristics. Follicular Cell Derived Tumors, which make up most Thyroid Neoplasms, are Now Classified as Benign, Low-Risk, Or Malignant. Finally, Poorly Differentiated Carcinomas, as well as High-Grade, Differentiated Thyroid Carcinomas, are Considered as High-Grade Follicular Cell Derived Malignancies Because of their Shared Characteristics.

1.2 Follicular Cell Carcinoma

Follicular adenocarcinoma is the second most common type of well-differentiated thyroid carcinoma after papillary type and usually diagnosis using FNA and capsular or vascular invasion histology workout. Follicular neoplasm represents heterogeneous of lesion groups like follicular adenoma, benign follicular hyperplasia and Follicular lesion with Hürthl cell carcinoma changes. The majority of diagnosed cases as per surgeon recommended go under total thyroidectomy surgery [14-16].

1.3 Hürthl Cell Carcinoma

In facts, Hürthl cell carcinoma of thyroid in histology is very rare and aggressive compared into follicular generally, drive from the follicular epithelial and very rich with mitochondria bodies. Whole Body Imaging Scan (WBIS) take place within 6-8 weeks post-surgery (total thyroidectomy) then followed by hormonal therapy Levothyroxine. The most prevalent sites of metastases with this type are skeleton, Central Nervous System (CNS) and lungs [14, 15-17].

2. Medullary Thyroid Carcinoma

Is the third most common form of thyroid carcinoma originated from Para follicular cell (C cell) that produce, secrete and release calcitonin hormone through blood stream. Considering as non-well differentiated thyroid cancer, not absorbing iodine and more aggressive compared to well differentiate thyroid carcinoma (WDTC). It might spread through lymphatic system into brain, lung, liver and bone. Thyroidectomy and hormonal therapy baseline treatment after the final diagnosis. PET/CT is the best modality in assessing medullary and anaplastic thyroid cancer [18, 19].

3 Undifferentiated Thyroid Carcinoma - Anaplastic Thyroid CA (ATC)

In histopathology, Anaplastic Thyroid CA (ATC) classified as one of the most of undifferentiated form, aggressive and rare type of thyroid cancer with prevalence of 2%. It has a unique morphological feature. Moreover, it is associated with worse prognosis compared to WDTC. Total thyroidectomy, neck dissection and radio-chemotherapy very helpful in the management of ATC [20].

4. Less Common - Primary Thyroid Lymphoma (PTL)

Primary thyroid lymphoma (PTL) is a rare primary thyroid malignancy, characterized by lymphomatous involving the thyroid gland only, without contiguous spread or distant involvement of other organs or tissues, as shown in this case. PTL is usually manifested by a rapidly growing and painless thyroid masses in patients with a history of Hashimoto's thyroiditis. Surgical resection used to be the mainstay of treatment. However, combined chemo radiation is increasingly utilized as the first line of therapy, often with a favorable and sustainable response [21, 22].

Imaging Technique Protocol

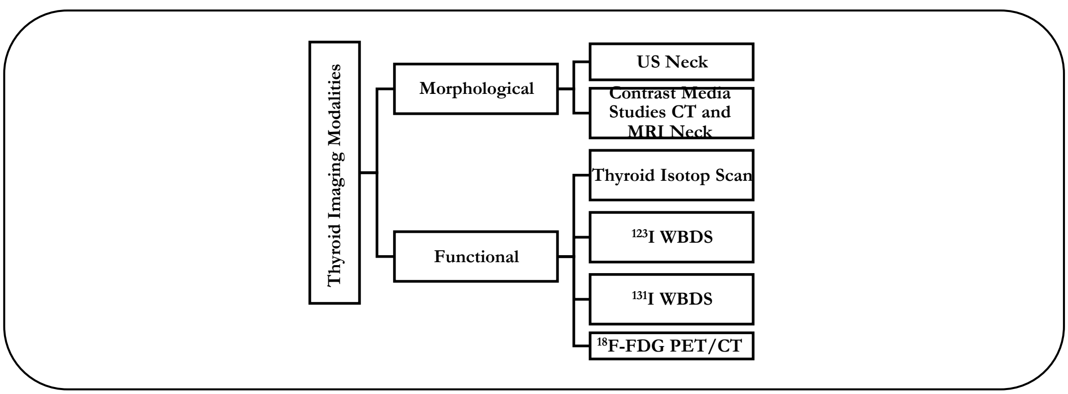

Fig.2: Thyroid Imaging Modalities Assessment Map Using Neck Ultrasonography and Contrast Medical Imaging Like CT and MRI in Diagnostic Radiology move through Thyroid Isotope Scan as well as WBIS Using ^{131}I And ^{123}I- Capsule or WB ^{18}F-FDG If Post Therapy Scan Using ^{131}I Is Negative in Hybrid Imaging.

Ultrasonography and Contrast Media Studies

In the 1980s, determining serum levels of thyroglobulin and neck ultrasonography became available in routine practice as a comprehensive method and key factor in the evaluation of neck nodules and fine needle aspiration biopsy needed. In this imaging technique, the ultrasound waves transmitted into the patient neck and lymph node tissue using special ultrasound probe frequency range in-between 3-12 MHz [24, 25]. Ultrasound can clearly evaluate the internal structure of the imaged organs, tissue margins, and the blood flow and tissue vascularity. These feature morphologies helped in distinguishing between both benign and malignant lesions. However, the primary role of using Cross sectional anatomy modalities using computed tomography and magnetic resonance imaging with high soft tissue contrast in the assessment of small lesions, lymph nodes, lytic lesion as well as suspected recurrence [26, 27].

Hybrid Imaging Using Single Photon Emission Computed Tomography (SPECT/CT)

Hybrid imaging modalities using PET/CT and SPECT/CT are mainly combines the best/ penitential in function and structure to provide accurate localization, characterization and diagnosis. Morphological cross-sectional imaging used Computed Tomography and MRI techniques play significant role in the evaluation of loco regional staging and restaging of endocrine cancer [28, 29]. Differentiated thyroid cancer is the most frequent subtype of thyroid cancer and in most patients the standard treatment (surgery followed by either radioactive iodine or observation) is effective [30, 31].

The role of nuclear medicine in thyroid cancer started in 1942. Radioactive iodine (^{131}I) is a unique isotope, which emits two types of radiation beta particles as well as gamma rays. It produces by nuclear reactor in the form of capsule. Its energy 364 KeV with gamma ray emission, Physical half live is 8.1 days with 0.8 mm range in tissue is as shown in Table 1 [31].

Table 1: The Main Isotopes and Appropriate Collimator Used in SPECT/CT Modality.

Radio nuclide	Physical $T_{1/2}$	Energy KeV	Collimator	Imaging Purposes	Tarping and organification	Cost
^{99m}Tc	6 h	140	Low Energy	Diagnostic	Yes -No	Low
^{123}I	13.5 h	159	Low Energy	Diagnostic	Yes-Yes	Low
^{131}I	8.1 D	364.5	High Energy	Diagnostic / Therapeutic	Yes-Yes	High

In patient diagnosed with Well Differentiated Thyroid Carcinoma management radioiodine planar imaging using iodine-123 (^{123}I) and radioiodine-131 (^{131}I) tracers play cure role and remains the gold standard in the follow-up after initial surgery and radioactive iodine ablation dose in the evaluation of the residual thyroid cancerous tissue with association of Tg and ATg lab test. Iodine has normal physiological uptake clearly seen in liver, Gastrointestinal (GI) tract and salivary gland [28, 29]. Radioactive iodine uptake (RAIU) is measuring the function of iodine trapping and accumulation in thyroid tissue using active transport mechanism. Patient must follow low Iodine preparation protocol in both diagnostic and therapeutic procedure. No iodine contrast study using MRI or CT scan studies allowed 6-8 weeks to thyroid isotope scan, ^{123}I and ^{131}I WBIS, low iodine diet, supplement hormonal medication and common sources of iodine food like ionized salt, diary product and seafood must be stopped at least for 2 weeks before the procedure to improve iodine uptake.

Written consent, base line carcinoma biomarker like serum TG, ATg and CBC must be obtained before therapeutic procedure. Pregnancy test and breastfeeding must be confirmed for female patient, Hormonal therapy must be stopped 3-4 weeks and elevated TSH serum [45].

The advantages of using SPECT/CT over planer SPECT clearly seen in improving the overall diagnostic performance moreover in the detection and localization of ectopic thyroid tissue, thyroid adenoma cases. SPECT/CT has higher specificity 96% and sensitivity 70% compared into planner gamma and baseline ultrasound. Serum TSH, thyroglobulin (Tg), and anti-Tg antibodies (TgAb) were measured immediately before administration the therapeutic dose of ^{131}I as seen in Fig 3 (A-E).

Alternatively, SPECT and PET images represent the distribution of activity concentrations (per voxel) of a single photon (SPECT) or a positron (PET) emitter. There are two main categories for Image Reconstruction (IR) algorithms in CT, SPECT and PET: analytical reconstructions and iterative reconstructions [40, 41].

Case (1)

Fig (3): 41Y/O-F, known case of malignant thyroid papillary neoplasm post total thyroidectomy and neck discussion, FU 6 months neck US showed a tissue, FU rhTSH-stimulated serum thyroglobulin were still elevated. After a good preparation following stoppage of levothyroxine suppressive treatment for 2 weeks, low iodine diet regimen, her TSH level was 33.8 uIU/mL, she received a therapeutic dose of 191.1 mCi RAI-131.

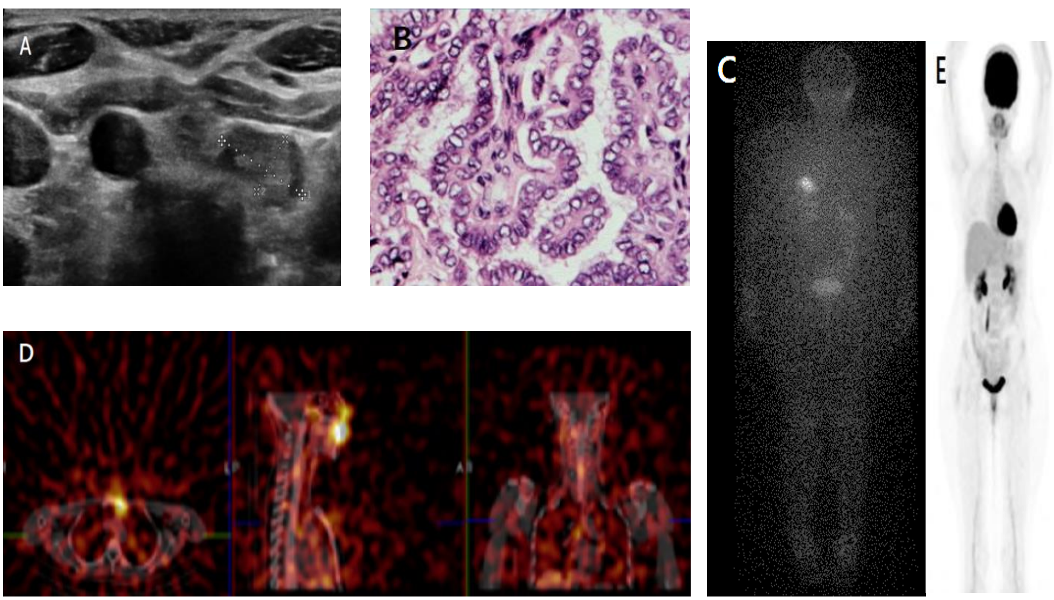

Fig.3: A: Neck US Showed Lt Thyroid Lobe Measured 0.5×0.7 Cm with Minimal Vascularity Maybe Recurrence and Mildly Suspicious Left Thyroid Bed Lymph Nodules. Fig.3B: Microscope Histopathology Confirmed Carcinoma Papillary Thyroid Type (PTC). Fig.3C: RAI-131 Post Therapy WBS Using SPECT/CT Hybrid Imaging. Showed Bilateral Cervical Lymph Nodes Showing Preserved Shape and Hila, The Largest Measures about 2.2×0.7 Cm. Fig.1D: SPECT/CT Fused Image in Coronal, Sagittal and Axial Views Showed Enhanced Radiotracer Uptake at the Bed of the Thyroid Gland Lateralized to the Lt. And Enhanced Radiotracer Uptake Lateralized to the Rt. At the Upper Part of the Neck. Fig.3E: FDG PET/CT (MIP) Showed Low-Grade FDG-Avid Two Small Nodules at the Surgical Bed of Left Thyroid Lobe, And Bilateral Discrete Cervical Lymph Nodes Predominantly Small with Variable Metabolic Activities and FNA from Left Cervical and Supraclavicular Lns was Positive for Metastatic Thyroid Neoplasm.

Hybrid Imaging – Positron Emission Tomography ^{18}F-FDG PET/CT

PET/CT is one of the hybrid imaging modalities techniques used for the initial diagnosis, re-assessment and monitoring patient response. In the clinical practice ^{18}F-FDG is the most attractive and ideal tracer used in positron imaging to roll out various types of disease like lymphoma, lung, breast and endocrine carcinoma [33-35].

Moreover, ^{18}F-FDG is widely used as a unique PET radioactive tracer has also obtained a significant role in the management of patients with metastatic/recurrent differentiated thyroid cancer and negative ^{131}I WBS [36, 37]. The exact localization of the thyroid metastases is essential in this subgroup of patients as there may be a change in therapeutic planning. The alternative treatments available for these patients are surgery, external radiation therapy, and chemotherapy and dedifferentiation therapy [37, 39, 40]. Contraindication to a planned surgery may be deduced from the results of ^{18}F-FDG PET. The usefulness of further radioiodine therapy comes under scrutiny if WBS negative sites exist (at more important sites) along with WBS positive tumor sites [36, 37, 40, 41]

Case (2)

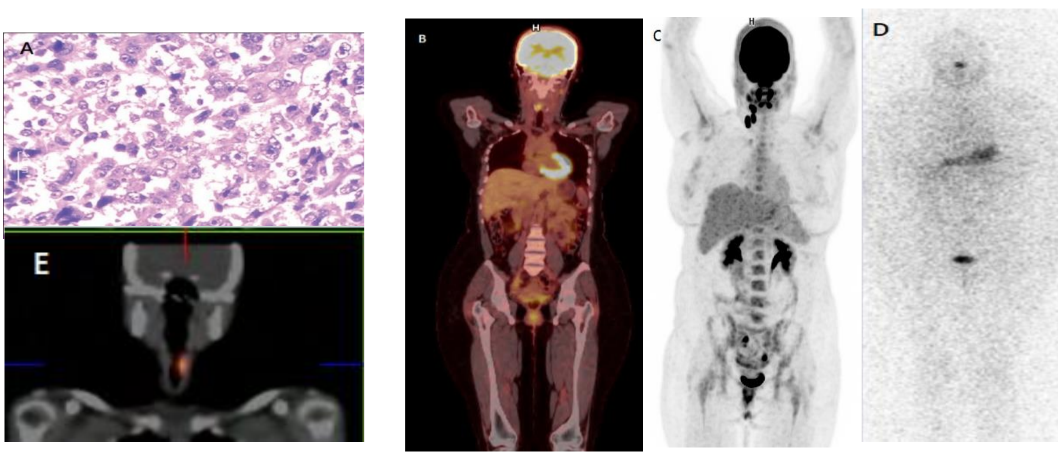

Fig (4): 43 Y/O F, Diagnosed with Poorly Differentiated Thyroid Carcinoma. Positron Emission Computed Tomography Imaging Using ^{18}F-FDG Demonstrate High Accuracy Compare into Other Medical Imaging Modalities in the Assessment of Local or Distance Metastases as well as Recurrence of Thyroid CA with Elevated TSH and Negative WBIS Using ^{131}I.

A. Microscopic Histopathology showed Follicular PDTC, persisting pathological focal lesion around 1 cm in the area of retro-laryngeal at the posterior end of thyroid cartilage.
B. Demonstrate Baseline WB ^{18}F-FDG for recurrence Thyroid CA PDC, Thyroid surgical bed shows FDG avidity of (SUV max 9.35), small cervical lymph nodes and diffuse physiological uptake in the soft palate and tongue.
C. Demonstrate WB ^{18}F-FDG MIP image with normal uptake in brain, heart muscle, liver and urinary system as well as the multiple metastatic LNs
D. Radioactive WBIS was negative with normal physiologic distribution of tracer in nasal mucosa, stomach, urinary bladder, and background. In comparison with ^{18}F-FDG imaging PET showed local recurrence associated with mildly elevated TSH-stimulated and biomarker lab serum Tg.
E. SPECT/CT Fusion demonstrate multiple small bilateral discrete upper and lower deep cervical LNs with low-grade or no corresponding pathological radioiodine avidity.

Result and Discussion

The clinical presentation of thyroid cancer is a spectrum including the incidental, asymptomatic, small, solitary nodule, in which the exclusion of cancer is the major concern. For the patient who presents with a nodule, the main concern is to exclude the possibility of thyroid cancer, even though the vast majority of nodules are benign. The initial evaluation should include measurement of the serum thyrotropin level and a fine-needle aspiration, preferably guided by ultrasonography. If the patient has a family history of medullary thyroid carcinoma, the serum calcitonin level should also be checked. If the thyrotropin level is suppressed, radionuclide scanning should be performed. PET camera is a unique functional method for assessing thyroid and parathyroid glands disorders. Overall, in this review 60 scientific papers and summary guidelines have been summarized which were published in PubMed, JNM. The papers discuss the clinical imaging acquisition and imaging criteria, patient preparation and the value of single photon emission computed tomography SPECT/CT in well-differentiated thyroid cancer (WDT). One of the first findings are papillary carcinoma and medullary thyroid carcinoma (MTC) are the most common thyroid cancers to metastasize to lymph nodes, whereas nodal metastases are uncommon in follicular carcinoma. Nodal masses may be the first presentation for papillary carcinoma and MTC. The second main finding of this study is that the measurement of serum Tg is of limited value in the diagnosis of primary thyroid tumour but is very useful in post-operative management of differentiated thyroid carcinoma. The sensitivity and the specificity of Tg determination is comparable to that obtained with WBS, however, both are complimentary.

The thyroid uptake and scan are radiologic diagnostic tool used to determine the thyroid function and pathologies. The thyroid scan checks for the even spread of the tracer in the gland. Clinicians use different radionuclides for diagnostic and treatment purposes. More than 20 radioactive tracers exist, of which two isotopes of iodine ^{123}I and ^{131}I and ^{99m}Tc-technetium Pertechnetate, are the usual agents used in this test. ^{131}I has a longer half-life than ^{123}I, so ^{123}I is used more frequently than ^{131}I due to less radiation exposure to the body. ^{99m}Tc-pertechnetate is an analog of iodine, so it gets transported to the thyroid gland similarly to iodine. The test uses a radioactive tracer, which is a protein, or a molecule attached to radioactive material. The radioactive tracer is administered into the patient, and a probe measures the amount of iodine uptake by the thyroid gland. Thyroid isotope scan plays an integral role in the initial diagnosis of thyroid function, malignancy and benign lesion, thyroid gland disorders like goiter and hyperthyroidism. The normal values of thyroid uptake of radiotracer are 3 to 15% at 6 hours and 7 to 25% at 24 hours. These values may change according to laboratory standard techniques or patient dietary habits. The thyroid gland can uptake more or less than normal. If it is more than normal uptake of radioactive iodine by the thyroid gland indicates hyperactive thyroid. On the other hand, if less than normal uptake infers hypoactive thyroid gland.

Clinicians usually perform the thyroid uptake and scan in the outpatient setting. The patient should be prepared well for these as certain foods and medications interfere with radiotracer uptake in the thyroid gland. Communication with the clinician is important before performing a contrast CT scan in a patient with known thyroid malignancy. In many cases, a noncontract study is preferred because the free iodide load of contrast medium injections interferes with iodide uptake in the thyroid for at least 6 weeks. The patient can be allergic to the radiotracer, so careful evaluation is necessary. If a patient is taking antithyroid medications such as methimazole or propylthiouracil, they should receive instructions to hold these medications for at least five days. Prior studies of the thyroid gland and baseline TSH and free T4 levels are necessary before the test. In thyroid cancer patients, thyroglobulin and thyroglobulin antibodies may also need to be checked. Diagnostic whole body iodine scan using oral ^{123}I capsules. In medical laboratory science, Free T4 serum is a useful tool in clinical routine of thyroid gland assessment and it should be measured in parallel with TSH in detection and monitoring of thyroid disorders and thyroid suppressive therapy [1, 5].

SPECT/CT is a powerful diagnostic imaging tool using fused images that allows better detection and further characterization of lymph node and distant metastasis of well-differentiated thyroid carcinoma compared to WBS planar imaging alone. The newly diagnosed cases as well as the follow up cases with history of thyroid carcinoma must be follow specific preparation starting from stopping the hormonal therapy levothyroxine for 3-4 weeks, starting low iodine diet for two weeks. ATG, TG, TSH thyroid lab test must be reviewed before patient admission for therapeutic dose [10, 27, 29]. SPECT/CT and MRI can play an important role in preoperative and post-treatment assessment of thyroid malignancy. It is very important that the radiologist should be aware of the pathological behavior of thyroid carcinoma, and the characteristic imaging appearance of the primary tumor and metastases. The radiologist should also be aware of the scenarios in which thyroid malignancy can be imaged with CT and MRI and how to approach a thyroid nodule and nodal disease with these modalities.

Low-grade tumors are classified under well-differentiated group. When cervical lymph node calcification is present, immediate surgery is required. Thyroglobulin and anti-thyroglobulin primarily used as tumor marker in-patient with diagnosis of Differentiated Thyroid Carcinoma. Measurement of serum Tg is very useful in detecting any recurrence of DTC following surgical resection or radioactive iodine ablation dose as seen in Fig. 3. The potential localization of tumor in differentiated thyroid cancer (DTC) patients who are radioiodine whole body scan (WBS) negative and thyroglobulin (Tg) positive. Also of value is the identification of patients unlikely to benefit from additional ^{131}I therapy and identification of patients at highest risk of disease-specific mortality, which may prompt more aggressive therapy or enrollment in clinical trials as discussed in Fig.4 (A-E).

Conclusion

Currently, thyroid cancer has become one of the most endocrine health challenges in human societies. The early detection of multi endocrine disorders play a prominent role in the level of diagnosis and treatment plan. In medical imaging, there are different types of thyroid imaging modalities starting from high-resolution ultrasonography, computed tomography as well as magnetic resonance imaging for neck evaluation. Moreover, Hybrid imaging modalities ^{18}F-FDG PET/CT imaging, planar radioiodine imaging scintigraphy in the form of WBS ^{131}I or ^{123}I SPECT/CT and post therapy scan PTS has a fundamental role in the management and survival of differentiated thyroid cancer.

In summary, molecular imaging has revolutionized the clinical assessment of thyroid cancer by providing a non-invasive means to evaluate tumour biology and predict disease behaviour. This information is essential for tailoring treatment strategies and optimizing patient outcomes. As molecular imaging techniques continue to evolve, their role in the management of thyroid cancer is expected to expand further, providing personalized and effective care for patients with this complex disease [53-56]. FDG-Positron Emission Computed Tomography considered as valuable imaging modality in the detection/re-assessment of patients diagnosed with proven histopathology well differentiated follicular and Papillary Thyroid CA, elevated

TG lab test and negative whole body iodine therapy but not for routine positive whole body iodine therapy scan. The most valuable role of ^{18}F-FDG-PET is in the work-up of differentiated thyroid cancer in patients with increasing serum thyroglobulin (Tg) levels and a negative diagnostic radioiodine scan [57-60].

Acknowledgement

The authors would like to extend their sincere appreciation to the Researchers supporting program for funding this work under Researchers Supporting Project number (RSPD2023R780), King Saud University, Riyadh, Saudi Arabia. Radiological Sciences Department, College of Applied Medical Sciences, King Saud University, P.O. Box 145111, Riyadh 4545, Saudi Arabia.

References

[1]. Kirsten, D. "The thyroid gland: physiology and pathophysiology." *Neonatal network: NN* vol. 19,8 (2000): 11-26. doi:10.1891/0730-0832.19.8.11.

[2]. Zia Sherrell, M. P. H. Thyroid Gland: Function, Location, and More. 29 July 2021, https://www.medicalnewstoday.com/articles/thyroid-gland-function.

[3]. Miller B, Kolonel LN, Bernstein L, et al. Racial/ethnic patterns of cancer in the United States 1988–1992. Cancer Institute NIH Pub 1996; No 96–4104. (Bethesda, MD.)

[4]. Cabanillas, Maria E et al. "Thyroid cancer." Lancet (London, England) vol. 388,10061 (2016): 2783-2795. doi:10.1016/S0140-6736(16)30172-6.

[5]. Baloch, Zubair W et al. "Overview of the 2022 WHO Classification of Thyroid Neoplasms." Endocrine pathology vol. 33,1 (2022): 27-63. doi:10.1007/s12022-022-09707-3

[6]'Thyroid Cancer'. American Thyroid Association, 9 Sept. 2015, https://www.thyroid.org/thyroid-cancer/.

[7]. Wouter, P., et al., editors. Pampaloni6 & Insoo Suh Use of PET Tracers for Parathyroid Localization: A Systematic Review and Meta-Analysis.

[8]. Nusynowitz, M L. "Thyroid imaging." *Lippincott's primary care practice* vol. 3,6 (1999): 546-55; quiz 556-8.

[9]. Intenzo, Charles M et al. "Imaging of the thyroid in benign and malignant disease." *Seminars in nuclear medicine* vol. 42,1 (2012): 49-61.doi: 10.1053/j.semnuclmed.2011.07.004

[10] Giovanella, L.; Deandreis, D.; Vrachimis, A.; Campenni, A.; Petranovic Ovcaricek, P. Molecular Imaging and Theragnostics of Thyroid Cancers. *Cancers* 2022, *14*, 1272. https://doi.org/10.3390/cancers14051272

[11] Petranović Ovčariček, P.; Campenni, A.; de Keizer, B.; Deandreis, D.; Kreissl, M.C.; Vrachimis, A.; Tuncel, M.; Giovanella, L. Molecular Theranostics in Radioiodine-Refractory Differentiated Thyroid Cancer. *Cancers* 2023, *15*, 4290. https://doi.org/10.3390/cancers15174290

[12] Sheikh A, Polack B, Rodriguez Y, Kuker R. Nuclear Molecular and Theranostic Imaging for Differentiated Thyroid Cancer. Mol Imaging Radionucl Ther. 2017 Feb 9;26(Suppl 1):50-65. doi: 10.4274/2017.26.suppl.06

[13] Oh, J.M.; Ahn, B.-C. Molecular mechanisms of radioactive iodine refractoriness in differentiated thyroid cancer: Impaired sodium iodide symporter (NIS) expression owing to altered signaling pathway activity and intracellular localization of NIS. *Theranostics* 2021, *11*, 6251–6277

[14] Giovanella, L.; Avram, A.M.; Iakovou, I.; Kwak, J.; Lawson, S.A.; Lulaj, E.; Luster, M.; Piccardo, A.; Schmidt, M.; Tulchinsky, M.; et al. EANM practice guideline/SNMMI procedure standard for RAIU and thyroid scintigraphy. *Eur. J. Nucl. Med. Mol. Imaging* 2019, *46*, 2514–2525

[15] Avram, A.M.; Zukotynski, K.; Nadel, H.R.; Giovanella, L.M. Management of differentiated thyroid cancer: The standard of care. *J. Nucl. Med.* 2022, *63*, 189–195

[16] Maghsoomi, Z.; Emami, Z.; Malboosbaf, R.; Malek, M.; Khamseh, M.E. Efficacy and safety of peptide receptor radionuclide therapy in advanced radioiodine-refractory differentiated thyroid cancer and metastatic medullary thyroid cancer: A systematic review. *BMC Cancer* 2021, *21*, 579

[17] Ho, A.S.; Luu, M.; Ba, L.B.; Balzer, B.L.; Bose, S.; Fan, X.; Walgama, E.; Clair, J.M.-S.; Alam Bs, U.; Shafqat, I.; et al. Prognostic Impact of histologic grade for papillary thyroid carcinoma. *Ann. Surg. Oncol.* 2021, *28*, 1731–1739

[18]. Buzdugă, C M et al. "Thyroid fine-needle biopsy: aspiration versus capillary." *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi* vol. 119,1 (2015): 45-50.

[19]. Bakhos, R et al. "Fine-needle aspiration of the thyroid: rate and causes of cytohistopathologic discordance." *Diagnostic cytopathology* vol. 23,4 (2000): 233-7. doi:10.1002/1097-0339(200010)23:4<233: aid-dc3>3.0.co;2-l

[20]. Caron, Nadine R, and Orlo H Clark. "Papillary thyroid cancer." *Current treatment options in oncology* vol. 7,4 (2006): 309-19. doi:10.1007/s11864-006-0040-7

[21]. Ajiboye, Tolu. 'An Overview of Papillary Thyroid Cancer'. Verywell Health, 2 Apr. 2019, https://www.verywellhealth.com/papillary-thyroid-cancer-4588220.

[22]. Carling, Tobias, and Robert Udelsman. "Follicular neoplasms of the thyroid: what to recommend." *Thyroid: official journal of the American Thyroid Association* vol. 15,6 (2005): 583-7. doi:10.1089/thy.2005.15.583

[23]. McHenry, C R, and B A Sandoval. "Management of follicular and Hürthle cell neoplasms of the thyroid gland." *Surgical oncology clinics of North America* vol. 7,4 (1998): 893-910.

[24]. Baloch, Zubair W et al. "Overview of the 2022 WHO Classification of Thyroid Neoplasms." *Endocrine pathology* vol. 33,1 (2022): 27-63. doi:10.1007/s12022-022-09707-3

[25]. Asa, S. L. 'My Approach to Oncocytic Tumours of the Thyroid'. *Journal of Clinical Pathology*, vol. 57, no. 3, BMJ, Mar. 2004, pp. 225–232, https://doi.org10.1136/jcp.2003.008474.

[26]. Carcangiu, M. L., et al. 'Poorly Differentiated ("insular") Thyroid Carcinoma. A Reinterpretation of Langhans' "Wuchernde Struma"'. *The American Journal of Surgical Pathology*, vol. 8, no. 9, Sept. 1984, pp. 655–668, https://doi.org10.1097/00000478-198409000-00005.

[27]. Bartz-Kurycki, Marisa A et al. "Medullary thyroid carcinoma: recent advances in identification, treatment, and prognosis." Therapeutic advances in endocrinology and metabolism vol. 12 20420188211049611. 8 Oct. 2021, doi:10.1177/20420188211049611

[28]. Molinaro, Eleonora, et al. 'Anaplastic Thyroid Carcinoma: From Clinicopathology to Genetics and Advanced Therapies'. *Nature Reviews. Endocrinology*, vol. 13, no. 1, Springer Science and Business Media LLC, Nov. 2017, pp. 644–660, https://doi.org10.1038/nrendo.2017.76.

[29]. Pavlidis, Efstathios T, and Theodoros E Pavlidis. "A Review of Primary Thyroid Lymphoma: Molecular Factors, Diagnosis and Management." *Journal of investigative surgery: the official journal of the Academy of Surgical Research* vol. 32,2 (2019): 137-142. doi:10.1080/08941939.2017.1383536

[30]. Stein, Stephanie Aleskow, and Leonard Wartofsky. 'Primary Thyroid Lymphoma: A Clinical Review'. *The Journal of Clinical Endocrinology and Metabolism*, vol. 98, no. 8, The Endocrine Society, Aug. 2013, pp. 3131–3138, https://doi.org10.1210/jc.2013-1428

[31]. Ratcliffe, J G et al. "The measurement of serum thyroglobulin in the presence of thyroglobulin antibodies." *Clinical endocrinology* vol. 15,5 (1981): 507-18. doi: 10.1111/j.1365-2265.1981tb00695.

[32]. Schlumberger, M. et al. Follow-up of low-risk patients with differentiated thyroid carcinoma: a European perspective. *Eur. J. Endocrinol.* 50, 105–112 (2004).

[33]. Guo, Rongrong et al. "Ultrasound Imaging Technologies for Breast Cancer Detection and Management: A Review." *Ultrasound in medicine & biology* vol. 44,1 (2018): 37-70. doi: 10.1016/j.ultrasmedbio.2017.09.012

[34]. Azizi, Ghobad et al. "Diagnosis of Thyroid Nodule with New Ultrasound Imaging Modalities." *VideoEndocrinology* vol. 7,1 ve.2020.0173. 30 Mar. 2020, doi:10.1089/ve.2020.0173

[35]. Ahmed, Najeeb et al. "Hybrid SPECT/CT Imaging in the Management of Differentiated Thyroid Carcinoma." *Asian Pacific journal of cancer prevention: APJCP* vol. 19,2 303-308. 26 Feb. 2018, doi:10.22034/APJCP.2018.19.2.303

[36]. Aide, N., et al. 'Clinical Relevance of Single-Photon Emission Computed Tomography/Computed Tomography of the Neck and Thorax in Post Ablation (131) I Scintigraphy for Thyroid Cancer'. *J Clin Endocrinol Metab*, vol. 94, 2009, pp. 2075–2084.

[37]. Caron, Nadine R, and Orlo H Clark. "Papillary thyroid cancer." *Current treatment options in oncology* vol. 7,4 (2006): 309-19. doi:10.1007/s11864-006-0040-7

[38]. Bockisch, Andreas et al. "Hybrid imaging by SPECT/CT and PET/CT: proven outcomes in cancer imaging." *Seminars in nuclear medicine* vol. 39,4 (2009): 276-89. doi: 10.1053/j.semnuclmed.2009.03.003

[39]. Lee, Jandee et al. "Effectiveness of [(124) I]-PET/CT and [(18)F]-FDG-PET/CT for localizing recurrence in patients with differentiated thyroid carcinoma." *Journal of Korean medical science* vol. 27,9 (2012): 1019-26. doi:10.3346/jkms.2012.27.9.1019

[40]. Lee, Jandee et al. "Effectiveness of [(124) I]-PET/CT and [(18)F]-FDG-PET/CT for localizing recurrence in patients with differentiated thyroid carcinoma." *Journal of Korean medical science* vol. 27,9 (2012): 1019-26. doi:10.3346/jkms.2012.27.9.1019

[41]. Wang, Guobao, and Jinyi Qi. "PET image reconstruction using kernel method." *IEEE transactions on medical imaging* vol. 34,1 (2015): 61-71. doi:10.1109/TMI.2014.2343916

[42]. Alessio, A., and P. Kinahan. 'PET Image Reconstruction'. *Nucl Med*, vol. 1, 2006, pp. 1–22, https://doi.org10.1088/0031-9155/54/12/007.Iterative.

[43]. The Royal College of Radiologists et al. "Evidence-based indications for the use of PET-CT in the United Kingdom 2016." *Clinical radiology* vol. 71,7 (2016): e171-88. doi: 10.1016/j.crad.2016.05.001

[44]. Lerch, H et al. "Survival of differentiated thyroid carcinoma studied in 500 patients." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* vol. 15,5 (1997): 2067-75. doi:10.1200/JCO.1997.15.5.2067

[45]. Feine, U. "Fluor-18-deoxyglucose positron emission tomography in differentiated thyroid cancer." *European journal of endocrinology* vol. 138,5 (1998): 492-6. doi:10.1530/eje.0.1380492

[46]. Farahati, J et al. "Differentiated thyroid cancer. Impact of adjuvant external radiotherapy in patients with perithyroidal tumor infiltration (stage pT4)." *Cancer* vol. 77,1 (1996): 172-80. doi:10.1002/(SICI)1097-0142(19960101)77:1<172: AID-CNCR28>3.0.CO;2-1

[47]. Glastonbury, Christine M. "Head and Neck Squamous Cell Cancer: Approach to Staging and Surveillance." *Diseases of the Brain, Head and Neck, Spine 2020–2023: Diagnostic Imaging*, edited by Juerg Hodler et. al., Springer, 15 February 2020.pp. 215–222. doi:10.1007/978-3-030-38490-6_17

[48]. Hall, Nathan C, and Richard T Kloos. "PET imaging in differentiated thyroid cancer: where does it fit and how do we use it?." *Arquivos brasileiros de endocrinologia e metabologia* vol. 51,5 (2007): 793-805. doi:10.1590/s0004-27302007000500017

[49]. Marinelli LD, Trunnell JB, et al. Factors involved in the experimental therapy of metastatic thyroid cancer with I131; a preliminary report. Radiology. 1948;51(4):553–7.

[50]. Jelinek, J., Young, R., Smith, L.O., Burman, K.D. (2016). MR and CT Imaging of Thyroid Cancer. In: Wartofsky, L., Van Nostrand, D. (eds) Thyroid Cancer. Springer, New York, NY. https://doi.org/10.1007/978-1-4939-3314-3_45.

[51]. Baloch, Z. W., Asa, S. L., Barletta, J. A., Ghossein, R. A., Juhlin, C. C., Jung, C. K., LiVolsi, V. A., Papotti, M. G., Sobrinho-Simões, M., Tallini, G., & Mete, O. (2022). Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocrine pathology, 33(1), 27–63. https://doi.org/10.1007/s12022-022-09707-3.

[52]. Meier, D. A., Brill, D. R., Becker, D. V., Clarke, S. E., Silberstein, E. B., Royal, H. D., Balon, H. R., & Society of Nuclear Medicine (2002). Procedure guideline for therapy of thyroid disease with (131) iodine. Journal of nuclear medicine: official publication, Society of Nuclear Medicine, 43(6), 856–861.

[53] Hao Fu, Ri Sa, Lin Cheng, Yuchen Jin, Xian Qiu, Min Liu, Libo Chen, Updated Review of Nuclear Molecular Imaging of Thyroid Cancers, Endocrine Practice, 27 (5), 494-502, 2021,

[54] Verburg, F.A.; Flux, G.; Giovanella, L.; Van Nostrand, D.; Muylle, K.; Luster, M. Differentiated thyroid cancer patients potentially benefitting from postoperative I-131 therapy: A review of the literature of the past decade. *Eur. J. Nucl. Med. Mol. Imaging* 2020

[55] Suzuki, C.; Kiyota, N.; Imamura, Y.; Goto, H.; Suto, H.; Chayahara, N.; Toyoda, M.; Ito, Y.; Miya, A.; Miyauchi, A.; et al. Exploratory Analysis to Predict Optimal Tumor Burden for Starting Lenvatinib in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer. *Front. Oncol.* 2021, *11*, 638123

[56] Kersting, D.; Seifert, R.; Kessler, L.; Herrmann, K.; Theurer, S.; Brandenburg, T.; Dralle, H.; Weber, F.; Umutlu, L.; Führer-Sakel, D.; et al. Predictive factors for RAI-refractory disease and short overall survival in PDTC. *Cancers* 2021, *13*, 1728

[57] Bible, K.C.; Kebebew, E.; Brierley, J.; Brito, J.P.; Cabanillas, M.E.; Clark, T.J., Jr.; Di Cristofano, A.; Foote, R.; Giordano, T.; Kasperbauer, J.; et al. 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021, 31, 337–386

[58] Tiedje, V.; Stuschke, M.; Weber, F.; Dralle, H.; Moss, L.; Führer, D. Anaplastic thyroid carcinoma: Review of treatment protocols. *Endocr.-Relat. Cancer* 2018, *25*, R153–R161

[59] Lorusso, L.; Cappagli, V.; Valerio, L.; Giani, C.; Viola, D.; Puleo, L.; Gambale, C.; Minaldi, E.; Campopiano, M.; Matrone, A.; et al. Thyroid cancers: From surgery to current and future systemic therapies through their molecular identities. *Int. J. Mol. Sci.* 2021, *22*, 3117

[60] Kim, H.J.; Chang, H.-S.; Ryu, Y.H. Prognostic role of pre-treatment [18 F]FDG PET/CT in patients with anaplastic thyroid cancer. *Cancers* 2021, *13*, 4228