REVIEW ARTICLE

# A review on imaging and treatment of thyroid cancer using radiopharmaceuticals

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## ABSTRACT

Thyroid cancer (TC) is the most frequent endocrine cancer worldwide. Early-stage TC is commonly asymptomatic but can proceed to cause major symptoms like neck swelling which leads to difficulty in swallowing. Thyroid glands are necessary for hormone production and for managing multiple bodily processes but malfunctioning may lead to thyroid malignancy. Precise diagnosis, typically, is the foundation of affective treatment and restoration of normal body functions. Focusing on radiopharmaceuticals, this review outlines the recent developments as well as the promising prospects for TC diagnostics and treatment. In addition to enhancing patient's treatment outcomes, the targeted diagnosis and medications make possible more effective individualized treatment plans. Examining current advancements in radiopharmaceuticals that improve treatment efficacy and diagnostic accuracy, the review also addresses potential future prospects for this field of study and clinical practice.

**Keywords:** Thyroid, radiopharmaceuticals, TSH, SPECT/CT, imaging.

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## Introduction

The abnormal proliferation in the thyroid gland causes thyroid cancer (TC). The gland is located in the front of the neck. Hormones secreted from the thyroid gland regulate heart beat rate, body temperature, high blood pressure, and abnormal metabolism. Thyroid hormone is vital to biological systems because it controls cell metabolism and modulates cell proliferation and division [1]. It might not show any symptoms in the beginning, but as it worsens, it may produce swelling in the neck, dysphonia, and dysphagia. TC too, may be the commonest human endocrine disease worldwide. In the past few years, there has been an upsurge in cancer development. All continents exhibit this pattern, with the notable exception of the African region, most likely as a result of improperly conducted relevant research investigations. Of all the endocrine malignancies, TC has the greatest annual death rate, which is widely spread among young people and accounts for 1%-2% of all cancers worldwide [2]. It is also continuously reported that the incidence rate is rising after each day, particularly in young adults, women, and children. Out of different subtypes, thyroid nodule malignancy is more common in younger people and arises more commonly in girls (2-4 times) in comparison to boys, and it rarely occurs in children and teenagers. Every year, 0.57 million cases of tumors on the thyroid are recorded globally. However, comparatively low mortality rates were recorded, ranging from 0.4 to 0.5 for each gender and 10.2 per 100,000 individuals, the prevalence rate was reported. The disease constitutes 5.1% of the overall cancer burden that women experience and is three-fold higher compared to that of men [3]. Predictably, a mix of hereditary and environmental factors, lack of awareness, and non-easy access to diagnostic and treatment centers are the primary causes of the growing prevalence of this cancer. TC originates in the Follicle epithelial cells. Diverse histological subtypes of TCs derived from follicular cells are observed; poorly differentiated thyroid (PDTC, <2%) cancer; anaplastic thyroid (ATC, <2%) cancer; and papillary TC (PTC, 80%-85%). PTC and follicular thyroid carcinoma (FTC) are some of the examples that represent a considerable percentage of thyroid malignancies that are collectively known as well-differentiated thyroid tumors (WDTC). The cells of this type of TC look like normal thyroid cells and are difficult to differentiate such as papillary, follicular, and oncocytic. Nearly 84% of TC cases are papillary thyroid malignant tumors. ATC and PDTCs are uncommon and aggressive forms of TC that can arise

from WDTC due to the appearance of genetic disorders inside the tumor. Furthermore, the parafollicular C cells contribute to about 4% of medullary thyroid tumors [4]. In short, all the thyroid gland-related cancers could be addressed precisely using well-systemized diagnostic and therapeutic procedures. Precise diagnosis, however, can lead to the design of a well-organized treatment procedure that remarkably controls the disease and mortality rate. Since the use of radioisotopes in medical practice various different kinds of radiotracers were introduced to diagnose and treat diseases; especially, the technetium-99m labeled compounds for infections and Iodine-123 (I-123) and Iodine-131 (I-131) for the diagnosis and treatment of TC. In this review article, we are presenting the recent trend in the use of iodine-based and other radionuclide-based radiopharmaceuticals for the diagnosis and treatment of TC and its effectiveness.

## Epidemiology

Worldwide, the prevalence of TC has been continuously rising during the last three decades. The highest rates per 100,000 persons per year have been reported as 15.5 persons in Lithuania, 13.5 persons in Italy, 12.4 persons in Austria, 11.4 persons in Croatia, and 11.1 persons in Luxembourg [5]. The increased diagnosis of DTCs and PTCs, particularly, is nearly solely responsible for the rising incidence rates. Over a period of three decades, the graph of the incidence rates of medullary thyroid cancer (MTC), ATC, and FTC recorded constant. Small and subclinical PTCs can easily be diagnosed using imaging methods and biopsy procedures such as fine-needle aspiration (FNA), and could easily be controlled through good medical surveillance, as well as better access to healthcare protocols.

## Types of TC

The most common endocrine malignant tumors are DTCs, which arise from thyroid follicular cells. Over 90% of individuals having TC show the three most prevalent types of differentiated thyroid cancers (DTCs): FTC, hürthle cell carcinoma, and PTC [6]. Globally, the overall prevalence of DTC has risen over the past few decades, with women having a 2.5-3 times greater risk than men [7]. About 80% of TC cases are of PTC, the most common form of DTC. It is recognized by unique nuclear characteristics such as grooves, pseudo inclusions, nuclear clearance, and papillary structures, and it arises from thyroid follicular cells [8]. Compared to PTC, FTC is less frequent, accounting for 10%-15% of TC occurrences. Although FTC typically grows slowly and has a good prognosis, it is more likely to spread to the advanced stage than PTC. The prevalence of FTC is 50% higher in women than in men. In contrast to PTC, FTC rates have remained relatively stable in recent years.

A rare kind of TC originating from the C cells of the thyroid gland, MTC accounts for 5%-10% of all thyroid malignancies. The non-follicular cell genesis and radioactive iodine resistance of this specific type of malignancy set it distinctive from other thyroid tumors [9]. About 75% of cases are sporadic MTC, which is more common but fortunately develops at a low rate of incidence of 2-3 cases per million people annually [10]. DTC begins in the thyroid's para-follicular neuroendocrine cells; endocrine cancer begins in the gland. Neck lymphadenopathy may be the first manifestation as the disease has a tendency to disseminate to cervical lymph nodes. At surgery, 70% of the people with PTC had evidence of metastases to cervical nodes [11]. Certain people display the typical symptoms of a thyroid nodule, particularly flushing and diarrhea, which might suggest the presence of extensive metastatic illness. Patients with a genetic multiple endocrine neoplasia syndrome account for 25% of occurrences of MTC [12].

Approximately 2% of all TC cases are ATC, a rare but very aggressive kind of TC. Since there are no obvious differences or particular thyroid markers, it is also known as undifferentiated TC. Usually seen as a big, quickly expanding tumor in the neck, anaplastic TC causes discomfort, hoarseness, and trouble swallowing. It is more prevalent in those patients who are over 65 years old and only makes up 1%-2% of thyroid malignancies. Prompt biopsy is necessary, since the majority of patients appear with a hard thyroid mass, occasionally accompanied by cervical lymphadenopathy. Evaluation frequently reveals distant metastases, particularly in the brain, bones, and lungs. ATC frequently results from pre-existing thyroid malignancies and can coexist with them, while it may advance on its own [13].

### *Risk factors*

Since the late 1980s, TC incidence has risen more among all types of cancers. Risk factors, such as radiation, alterations in lifestyle, and environmental pollutants, contribute to the increase in TC incidence is crucial. Ionizing radiation exposure in childhood is strongly linked with PTC, i.e., 1.3 - 35.1 cases per 10,000 persons per year have been registered [14]. Similarly, a higher risk of TC is linked to childhood exposure to $^{131}$I radioisotopes. Although other ionizing radiations, such as alpha particles from $^{238}$Pu, can also cause TC, the thyroid gland is especially susceptible to radioiodine exposure [15]. It is reported that 13,127 individuals under the age of 18 years who lived in Ukraine after the 1986 Chernobyl nuclear accident were evaluated for TC as part of a cohort study; conducted between 1998 and 2000, it was found 5.25 (95% CI, 1.70-27.5) times higher relative risk of TC per grey (Gy) of radiation exposure - there 45 cases of TC were found [16]. According to Tronko et al. [16] the mean age of TC occurrence is 35 years (with a range of 6-58 years). It was revealed that

the threat of thyroid carcinoma was highest among people under the age of ten, compared to other age groups. However, the risk substantially dropped as exposure age increased.

Data show that women who have already experienced TC before the age of 35 may be more vulnerable to developing again as a result of abortion and multiparty. There is an important connection between TC and the number of live births, pregnancies, incomplete pregnancy history, and use of fertility pills or alternative hormone replacement therapy, according to case-based research, carried out in Norway and Sweden. There was a significant connection between the first delivery, before the age of 20 or within 5 years of menstruation, there is an increased chance of TC. Further, TC risk is increased by irregular menstruation. Thyroid stimulating hormone (TSH) is thought to be a stimulant for TC and rises with puberty and fertility, which suggests that an increase at these stages may contribute to the genesis of TC. After all, a well-defined diagnosis can lead to design the smart and effective treatment protocol. The next sections will explain the possible diagnostic options of TC.

### *Diagnosis of TC*

A well-defined medical history and physical assessment are the first stages in the workup of a thyroid nodule, just like they are for any newly found malignancy elsewhere in the body. TC should be suspected if there is a strong Familial cancer background or if there has been previous radiation therapy for the head and neck. Thyroid lymphoma or Undifferentiated TC could be the cause of the thyroid nodule if it is growing quickly and exhibiting compressive symptoms [17]. Diagnostic tests are performed for growths or swelling in the neck, adjacent lymph nodes, and thyroid to check for lumps or nodules. Furthermore, the blood is tested for inappropriate TSH levels. Sufficient or inadequate TSH indicates improper thyroid gland activity. Therefore, it is important to examine a high level of calcitonin and other blood tests for MTC. The size, form, and fluid-filled or solid state of each nodule should be examined using an acoustic device. Fluid-filled nodules are typically not cancerous. Solid nodules could be cancerous. However, on the pre-treatment scan utilizing Iodine-123 ($^{123}$I) or Technetium-99m($^{99m}$Tc) pertechnetate for patients with hyperthyroidism, the majority of big centers undergoing isotopic thyroid tests will detect 2 incidental thyroid malignant tumors annually.

### *Ultrasound*

The primary method of selection for assessing thyroid nodules and distinguishing between benign and malignant nodules is ultrasound. Not only is ultrasound affordable and easily available, but it also spares patients from radiation exposure. Ultrasound-directed FNA is frequently used for biopsies of thyroid nodules with questionable attributes. In addition to being helpful in identifying primary neoplasms, ultrasound can assess locoregional lymph nodes for nodal metastases. To verify that any questionable nodule(s) and lymph nodes have been removed, ultrasound guidance is also widely implemented for surgical planning. Thyroid nodules are identified by their size, borders, eccentric position of solid section, hypoechogenicity, microcalcification, irregular shape, and the fact that the malignancy is taller than it is wide in diagnostic ultrasounds [18]. Based on FNA cytology, the Bethesda method for reporting thyroid cytopathology is a diagnostic classification method, which includes six diagnostic systems: benign, atypia of unknown importance or follicular lesion of unknown significance, follicular neoplasm or suspected for a follicular neoplasm, suspicious for malignancy, and malignant [19].

It should be remembered that ultrasounds cannot always be utilized in predicting cancers but in some cases due to their detection limitations. According to Ram et al. [20] ultrasonography has an 80% sensitivity and a 68% specificity for detection of cancer. Therefore, in people who have a high index of suspicion for primary or recurrent TC, a variety of imaging advanced protocles, including fine-needle aspiration cytology (FNAC), computed tomography, magnetic resonance imaging, single-photon emission computed tomography (SPECT), and so on, should be carried out to rule out disease.

### Fine-Needle Aspiration Cytology and Biopsy

The main goal of an FNAC is to distinguish differentiating benign and malignant malignancies according to prevent the need for an insufficient thyroidectomy. As FNAC is still the most reliable, economical, and accurate diagnostic method available for assessing nodules, it should be carried out if the preliminary investigation indicates a non-functioning nodule. FNAC can be carried out using ultrasound guidance. If suspicious lymph nodes are discovered, an FNA biopsy must be carried out on both the thyroid nodule and the lymph node. A biopsy on a subcentimeter nodule is not required for a patient who already has increased cancer risk, such as becoming exposed to radiations, with a background of TC, a previous hemithyroidectomy for TC, or favorable nodules seen by a PET scan. By correctly detecting nodules that are most likely malignant, Fine-Needle Aspiration Biopsy (FNAB), in addition which explaining the tissue structure and morphology, can reduce the number of needless procedures by nearly 50% [21]. It is especially effective for identifying ATC and PTC, which is critical for therapy planning.

However, the diagnostic reliability of FNAB is 70%-97% and is dependent on the competence of the person undertaking the technique and interpreting the result. FNAB is considered unsatisfactory between 17%-20% of samples sampled [22]. In addition, FNAB is a valuable tool for identifying PTC since it analyses individual

cellular properties rather than the nodule's general architecture. However, it is unable to identify parietal or vascular invasions by FTC. Consequently, while FNA may demonstrate some features that point to FTC, in up to 63% of the cases, definitive evidence of FTC can only be made after histopathological examination of the surgical specimen.

### *Radioiodine detection*

Scanning with radioiodine for a period of over 50 years, radioiodine has been employed for treating and diagnosing TC among individuals because the thyroid gland is capable of accepting iodide through the sodium iodide ($Na^+/I^-$) symporter. For both therapeutic and diagnostic causes, $^{131}I$ sodium iodide is the most frequently used radioisotope. The primary benefits of $^{131}I$ include its accessibility, affordability, and capacity for delayed imaging at the ideal tumor-to-background ratio. The high energetic photon emissions, however, have concerns for radiation safety and are not ideal for gamma camera imaging for diagnostic reasons [23]. In contrast with $^{131}I$, $^{123}I$ offers a number of benefits for the diagnosis of thyroid disorders. With a photon energy of 159 keV, it is a pure gamma emitter that is perfect for imaging via conventional scintillation gamma cameras. Furthermore, due to the increased activity of $^{123}I$ and the high photo peak of $^{131}I$, which may be administered, the photos are of superior quality contrasted to the tracer $^{131}I$. Since count statistics are essential for SPECT imaging, the higher count rate that may be acquired with $^{123}I$ in comparison with tracer $^{131}I$ is very relevant. Radiation exposure to the thyroid gland and the patient will be decreased due to the shorter half-life (13 hours) [24]. Because it is created using a cyclotron, it is costlier and less accessible. Like-wise because of the shorter half-life of $^{123}I$, tumors that accumulate over time radioiodine may go undetected [25]. $^{131}I$ or $^{123}I$ is typically used for testing and therapeutic purposes, depending on local choice and availability.

### *SPECT imaging*

SPECT is a nuclear imaging method that is employed extensively in medical diagnostics. Fundamentally, SPECT provides 3D visualization of the radioactive tracer's distribution (or probe) introduced into the bloodstream and subsequently absorbed by specific organs. $^{99m}Tc$ is the most frequently used isotope for SPECT, followed by $^{123}I$ and relatively rarely Indium-111. Clinicians choose an isotope based on what the scan is trying to detect, any risks to the patient, and of course, cost. Since $^{99m}Tc$ has a 6-hour half-life and high photon emission, scanning time can be shortened with lower radiation exposure to the target organ. That permits the usage of greater tracer doses, which gives sharper pictures with little additional increase in the patient's overall radiation exposure [26]. $^{123}I$, however, had 13 hours of much longer half-life which means that the target organ has a greater quantity of detectable iodine than the background. The organ receives a greater radiation dose as a result of the prolonged half-life and higher localized concentration. $^{99m}Tc$ is typically preferred for the majority of clinical applications because of its reduced radiation exposure, excellent imaging, and shorter scan duration. To determine if a suspicious or indeterminate thyroid nodule is "hot" (higher iodine uptake) or "cold" (lower thyroid uptake), whole-body scintigraphy (WBS) is frequently carried out using $^{123}I$ [27]. Preserved sodium iodide symporter has preferentially greater radioactive iodine accumulation in the neoplasm relative to normal thyroid tissue. Dedifferentiation of a thyroid neoplasm results in loss of the capacity to render lesions occult on radioiodine SPECT, an important false negative to be aware of. Radioiodine scan can be utilized to identify remaining thyroid tissue remaining after surgeries and/or recurrences at new metastatic sites in those who have had their thyroid removal, or lymph node dissection [28]. Because it emits both beta and gamma rays, $^{131}I$ is a suitable theranostics agent. To treat leftover thyroid tissue and local/distal metastases, $^{131}I$ is frequently given after thyroidectomy, without or after nodal dissection [28]. Moreover, response to $^{131}I$ radioablation can be assessed by SPECT because of $^{131}I$ gamma ray emission. Post ablation SPECT is often employed 5 to 9 days after the ablation, due to the boosted signal-to-noise ratio which improves overall sensitivity for detecting metastases at distant sites [28].

### *SPECT/CT imaging*

SPECT/CT imaging is a progressively developed method that is implemented along radioiodine scintigraphy to assess patients for TC is SPECT integrated with CT. The technique has shown promising potential for imaging target sites with 100% sensitivity. SPECT/CT creates patient-specific attenuation correction of tracer distribution and it also makes possible the structural and functional co-registration of data. Compared to planar imaging, this enables improved description of foci of increased tracer uptake and precise anatomical spatial localization.

This device allowed for the subsequent acquisition of CT and SPECT pictures while the detectors revolved around the patient. That performs this by combining a low-intensity X-ray tube with simultaneous gamma and X-ray detectors on the same slip-ring gantry. After the commercial achievement of PET/CT systems which combines multi-slice CT scanners with PET, new hybrid systems incorporating extremely expensive spiral CT scanners up to 64 slices with dual head gamma cameras have been developed to enhance image quality and reduce time to acquisition. Some of these systems utilized an ultrahigh resolution SPECT/CT system with an innovative digital detector, operated on cadmium zinc telluride

technology, where we get much better signal-to-noise ratio and counts [29]. $^{131}$I is often used among people with DTC not only for therapy but also for disease diagnosis and localization. Whole-body scintigraphy using $^{131}$I is often carried out 2-3 days following the administration of $^{131}$I for diagnostic purposes, and 5-10 days following the administration of $^{131}$I for the purpose of ablation of the postsurgical residue or treatment of metastatic disease.

This results in accurate localization of ambiguously located lesions and, as such, allows for the determination of the lesion which is benign or malignant, and consequently major impact on patient treatment by determination of the most suitable additional therapeutic technique as needed. In this sufficiently interesting clinical scenario, $^{131}$I SPECT/CT is able to open a novel route to a more precise staging of patients with DTC with a certified diagnosis of lymph node involvement at the time of thyroid remnant radioablation [30]. Numerous research works have examined the function and therapeutic advantages of $^{131}$I. SPECT/CT discovered that, as compared to planar imaging, SPECT/CT had another diagnostic benefit in 57% (41 of 71) of patients, having a significant influence on the clinical care of such patients. In reported data, 85% of foci incorrectly found unreliable on planar imaging were reliably defined by SPECT/CT, resulting in a shift in treatment in 47% of patients [31].

### *Radiopharmaceuticals for thyroid imaging applications*

In addition to radiotracers used for the diagnosis and treatment of TC, there are variety of different isotopes have been labeled with organic molecules to image and treat TC, particularly in situations where radioiodine is not available. These radiopharmaceuticals, which have proven especially helpful, include $^{201}$Tl (Thalium-201), $^{99m}$Tc-sestamibi, $^{99m}$Tc-methoxyisobutylisonitrile (MIBI), $^{99m}$Tc-tetrofosmin, $^{99m}$Tc-depreotide, and Indium-111 ($^{111}$In) labeled DOTA-octreotide [32]. It has been demonstrated that $^{201}$Tl scintigraphy is effective for recognizing differentiated thyroid carcinoma that has spread and was reported as radioiodine-negative. A study has been carried out comparing scintigraphy findings of $^{201}$Tl and fluorodeoxyglucose (FDG) uptake in patients with DTC underwent total thyroidectomy, which reveals that the FDG distribution pattern is similar to $^{201}$Tl distribution pattern [33]. $^{99m}$Tc-MIBI has been the subject of many decades of use in parathyroid and myocardial perfusion imaging (similar to pentavalent dimercaptosuccinic acid). In addition, it is tumor seeking. $^{99m}$Tc MIBI is being used more and more to assess thyroid nodules for benign and malignant characteristics. Given that the $^{99m}$Tc-MIBI-Hot/$^{123}$I-cold phenotype, however, is very specific for thyroid malignancy patients suffering from false positive parapyroid scintigraphy during surgery should be evaluated for TC. In addition, Rubello and associates have advocated the use of a $^{99m}$TcMIBI intraoperative gamma probe to detect and serve as a guide for the removal of recurrent locoregional malignancy in DTC patients with $^{131}$I negative locoregional metastatic foci [34]. In patients with cold thyroid nodules without a malignant suspicion on ultrasonography, or in patients with benign or unclear cytology, a $^{99m}$Tc- tetrofosmin scan may be useful in a decision regarding surgical treatment [35]. In this regard, Stokkel et al. also studied the role $^{111}$In-DOTA-octreotide scintigraphy in DTC patients with elevated thyroglobulin levels and negative $^{131}$I WBS and showed its 82% sensitivity to recognize DTC patients with distant metastases [36].

Another study showed the uptake to be correlated with survival and prognosis and showed an overall sensitivity of 74 % of $^{111}$In-DOTA-octreotide scintigraphy in identifying nonfunctioning DTC metastases [37]. HCC is a rare DTC that has a poorer prognosis and is more susceptible to distant spread areas, usually the soft tissues of the neck. Individuals that have recurrent HCC may benefit from evaluating the extent of their disease by way of a combination $^{131}$I & $^{99m}$Tc-tetrofosmin imaging as suggested by Bomanji et al. [38]. Currently, a wide range of cancers, including radioiodine-refractory DTC, can be detected by 2-[$^{18}$F]fluoro-2-deoxy-D-glucose, the most widely used PET-radiopharmaceutical [39]. Furthermore, the use of peptide-receptor radionuclide diagnosis and therapy in medullary TC is gaining ample attention [40].

### *Treatment*

Surgery is the initial choice for almost all people with TC, with some other alternatives available for managing TC. On the other hand, when the complete thyroid gland is surgically replaced, it is referred to as a total thyroidectomy. Radioactive iodine treatment, also known as radionuclide therapy, may be part of the post-thyroidectomy treatment strategy. Levothyroxine, the thyroid hormone is given orally daily to patients who are post total thyroidectomy with TC. The body's thyrocytes absorb radioactive iodine (RAI) which is termed as radioactive iodine therapy. As a consequence, RAI is absorbed by the patient's body as a fluid that aggregates in thyroid cells. The emitted beta radiation possesses a sufficient amount of energy that is able to destroy the malignant thyrocytes without causing any adverse side effects or harm to the other parts of the body. Levothyroxine pills are commonly prescribed since after a thyroidectomy, as the patient's body will not be able to produce thyroid hormone, which is a crucial metabolic regulator. External beam radiation therapy (EBRT) is another therapeutic option for TCs. EBRT uses high-energy emissions, or X-rays, to either annihilate cells that are malignant or stop their proliferation [41]. In practice, the type of radiation therapy indicated for DTCs patients is seldom suggested if a patient is thought to be a good responder to RAI. However, in reality, EBRT is often employed in the treatment of MTC and ATC patients.

## Treatment and Ablation with Radioactive Iodine

$^{131}$I has been a vital component of TC treatment and care since 1946. Together with thyroidectomy, $^{131}$I crucial to completely ablate the remnant thyroid tissue of the gland and get rid of any possible post-operative residual malignancy. In the thyroid cells, once $^{131}$I enters the cells, the sodium iodide transporters release beta rays that cause the cell to die quickly. This will result in another lower chance of relapse while the sensitivity of subsequent diagnostic methods, like serum thyroglobulin levels or WBS scan for detecting metastatic or residual illness, will also increase [42]. Most importantly it is very useful in DTC, which is responsible for up to 90%-95% of overall TC patients with a 90%-95% 10-year survival. This survival rate points to the need for recurrent observation and recurrence testing. Modeled after the current standard, $^{131}$I therapy has been used mostly as an adjuvant treatment but remains the accepted treatment for nonsurgical and, in part, respectable thyroid carcinomas including microscopic or metastatic disease. A patient should be started on $^{131}$I treatment after certain important factors have been addressed. Given that surgery is the first-line procedure in the therapy of cancer. Furthermore, the treatment using $^{131}$I allow $^{131}$I to enter into the body tissues, it is critical to measure the iodine avidity of the impacted tissues. Whole body PET scans and post-therapy scans are suggested for confirmation. The characteristics of the tumor and the disease site are crucial because they influence the outcome of $^{131}$I therapy. This is illustrated by the fact that well-differentiated malignancy histotypes and lung and soft tissue metastases have higher cure rates than brain metastases and poorly differentiated malignancies [43]. Those who have had tumors bigger than 4 cm; extra-thyroidal extension; and know of metastases would be treated with $^{131}$I ablation according to the American Thyroid Association guidelines. Cancers are also treated that may be small but have high-risk features (those with vascular invasion and aggressive histologies) [44]. On the other hand, for uni-focal or multifocal nodules less than 1 cm that do not have high-risk qualities, the guidelines advise do not favor the practice of $^{131}$I ablation [43].

Because $^{131}$I therapy commonly produces side effects such as excessively dry eyes (25%) and salivary gland dysfunction (>40%), transitory leukopenia (20%), and thrombocytopenia; that is why particular emphasis should be placed on the patient's general condition, as well as to his or her tolerance to the treatment [45]. In $^{131}$I therapy, the patients have to be put on a low-iodine diet for 4-6 weeks before administration or they are restricted to having an iodine intake of less than 50 µg/day for 2 weeks in advance to preclude competition between $^{131}$I and natural iodine [44]. In a similar vein, patients with high iatrogenic loads of iodine such as those undergoing contrast or amiodarone, are not eligible for therapy until their 24-hour urine iodine level drops to 100 µg [44]. Following that, patients begin a course of medication aimed at increasing blood TSH levels to 30 mU/l, which will improve $^{131}$I absorption and boost the quantity of sodium iodide symporters [43].

This can be accomplished in two ways: either by eliminating thyroid hormone or by employing the more current recombinant human thyroid stimulating hormone (rhTSH) [43]. Before $^{131}$I therapy in 2007, the US Food and Drug Administration approved the use of rhTSH, which was initially made accessible in 1998 for diagnostic purposes [46]. Iatrogenic hypothyroidism is a risk factor for thyroid hormone withdrawal that might last for many weeks. However, there are concerns over the utility of rhTSH. A recent study indicates that when paired with $^{131}$I thyroid residual ablation, rhTSH is just as effective as thyroid hormone deprivation. Patients experience less adverse effects before and during the surgery, along with a decrease in the overall radiation dose administered to the body [47]. After the correct level of TSH is reached, $^{131}$I is then given orally as a capsule, at a level of activity suggested.

Two to eight days after treatment, a whole-body scan is normally used to confirm the $^{131}$I uptake, and 6-12 months later, a follow-up scan is routinely performed [44]. At that time thyroid ultrasonography and stimulated thyroglobulin levels should also be done to monitor response. "Lower risk patients with negative thyroglobulin levels, however, may not require follow up scanning at all," says Prof Stevens. If the follow-up scan has low activated thyroglobulin and 0.1% $^{131}$I of uptake in the thyroid bed, the therapy is considered to be successful. On a neck ultrasound, then, there may be an empty thyroid bed, free of any new growths, expansions, or other new abnormalities that can be observable [44].

## External-Beam Radiation

EBRT is becoming more and increasingly well-known as a successful treatment for DTC, particularly when the carcinoma is locally progressed or cannot be surgically removed completely. Patients over 45 who have visible residual or unresectable locoregional illness, or who are more likely to have microscopic residual disease and a decreased response to RAI, are advised to undergo EBRT by the American Head and Neck Society. EBRT is not advised exclusively for cervical lymph node involvement or as an adjuvant treatment after the entire visible disease has been removed [48]. EBRT for TC is rarely used and usually reserved for a small number of patients, such as those suspected of having residual disease, including those with extra-thyroidal extension following thyroidectomy, although some guidelines support its use [49].

The Memorial Sloan-Kettering Cancer Centre states that studies show radioactive iodine treatment can still be successful in up to 85% of poorly differentiated malignancies since these tumors do have some iodine avidity. EBRT may be beneficial for patients with unrespectable

illness, partially resected tumors, or locoregional recurrence in a previously treated field [50]. When all other options, including radioactive iodine and surgery, have been exhausted, external-beam radiation is usually the last option.

### *Future prospects*

The employment of radiopharmaceuticals in diagnosing and treatment of TC appears to have a bright future fueled by developments in personalized medicine and molecular imaging. It is expected that continued research will enhance therapeutic efficacy and patient outcomes through the use of novel radiopharmaceuticals and theranostic protocols. For individuals with recurrent illness, research on retreatment with radioiodine following tumor re-differentiation seems encouraging. New theranostic drugs and radiolabeled antibodies are increasing therapeutic possibilities, especially for advanced and refractory cases. Combining radiopharmaceuticals with other forms of treatment could improve therapeutic results and lessen adverse effects. While new developments in radiopharmaceuticals present exciting opportunities, there are still certain obstacles to overcome, particularly in the areas of handling cases that do not respond to radioiodine and standardizing new diagnostic criteria. Overcoming these obstacles and giving patients the greatest care will require ongoing research and clinical trials. Therefore, in conclusion, with the advent of new molecules that can target specifically the biomarkers expressed over cancer cell surface can change the game and more patients can survive after a proper diagnosis of TC.

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