BJR

https://doi.org/10.1259/bjr.20180136

Received: 01 February 2018 | Revised: 17 September 2018 | Accepted: 20 September 2018

Cite this article as:
Choudhury PS, Gupta M. Differentiated thyroid cancer theranostics: radioiodine and beyond. *Br J Radiol* 2018; **91**: 20180136.

THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

Differentiated thyroid cancer theranostics: radioiodine and beyond

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ABSTRACT

The term theranostics is the combination of a diagnostic tool that helps to define the right therapeutic tool for specific disease. It signifies the "we know which sites require treatment (diagnostic scan) and confirm that those sites have been treated (post-therapy scan)" demonstrating the achievable tumor dose concept. This term was first used by John Funkhouser at the beginning of the 90s, at the same time the concept of personalized medicine appeared. In nuclear medicine, theranostics is easy to apply and understand because of an easy switch from diagnosis to therapy with the same vector. It helps in maximizing tumor dose and sparing normal tissue with high specific and rapid uptake in metastasis. The oldest application of this concept is radioactive iodine I-131 (RAI). The first treatment based on the theranostic concept was performed on thyroid cancer patients with RAI in 1946. From then on management of differentiated thyroid cancer (DTC) has evolved on the multimodality concept. We now use the term "our" patient instead of "my" patient to signify this. However, the initial surgical management followed by RAI as per the theranostics has remained the mainstay in achieving a cure in most of DTC patients. The normal thyroid cells metabolise iodine, the principle of which is utilized in imaging of the thyroid gland with isotopes of iodine. RAI treatment of DTC is based on the principle of sodium iodide symporter (NIS) expressing thyroid cells with DTC cells having the ability of trapping circulating RAI successfully helping in treatment of residual and metastatic disease. NIS is usually negative in poorly differentiated cells and is inversely proportional to Glucose transporter receptor Type 1 expression. Both positive and negative NIS are the key components of the theranostic approach in treatment of DTC. Presence or absence of NIS is documented by either whole body iodine scintigraphy (WBS) or 2-deoxy-2(^{18}F) fludeoxyglucose (FDG) positron emission tomography computed tomography (PET-CT). Currently, single photon emission CT and CT (SPECT-CT) has significantly improved the precision and sensitivity of whole body iodine scintigraphy with its capability of accurate localization of disease foci whether iodine avid or non-avid. This has helped in a more personalized approach in treatment. This review will give an overview of the role of NIS in the theranostic approach to management with RAI, its current status and also the molecular approach to treatment in RAI refractory disease.

CLINICAL PRESENTATION OF DIFFERENTIATED THYROID CANCER

Majority of thyroid cancer patients present with a solitary thyroid nodule which is detected most of the time incidentally. The thyroid nodule can be associated with lymph nodes in the neck. Rarely, it may present as hoarseness of voice or symptoms of distant metastasis at presentation.[1] The first investigation is the ultrasound (USG) of neck which can characterize the solitary nodule as cystic, solid or indeterminate. In addition, the vascularity of the nodule can also be assessed with ultrasonography or scintigraphy. USG is capable of detecting other non-palpable nodules which will also help to ascertain the probability of a benign or malignant outcome.[2–7]

INITIAL TREATMENT OF DIFFERENTIATED THYROID CANCER

Differentiated thyroid cancer (DTC) are the tumors arising from the cells lining the thyroid follicles which includes papillary (PTC), follicular (FTC) and Hurthle cell carcinoma (HTC). It generally excludes the tumors arising from para follicular cells. DTC are the commonest type of thyroid malignancy. In recent years, the incidence of these tumors seems to be rising.[8] While surgical resection has remained the gold-standard for their initial treatment, controversies still exist regarding the extent of surgery because of indolent nature of majority of these tumors.[9–16] The study of various prognostic factors has enabled the endocrine surgeons to develop a risk stratification system in order to arrive at

some consensus regarding the extent of thyroidectomy.[4] Based on these, the risk of death, from thyroid cancer were classified.[17] Total (TT)- or near total thyroidectomy (NTT)_ is considered as the procedure of choice for most of the DTCs.[9,18–21] A major advantage of total thyroidectomy is that it facilitates detection of metastatic disease by whole body iodine scintigraphy (WBS) followed by the use of radioactive iodine (RAI) as adjuvant therapy whenever necessary. Disease surveillance by estimation of serum thyroglobulin levels (Tg) during follow-up is another advantage of NTT or TT. Lymphnodes in the neck are frequently involved in PTC in 20–90% across literature. Microscopic metastasis is also common in about 38–45% undergoing prophylactic central compartment dissection (CND).[22]

American Thyroid Association (ATA) recommends prophylactic CND in PTC with locally advanced primary tumors (T3 and T4) only. CND is not recommended for small T1 and T2, noninvasive, clinically node negative PTC and most FTC, as such patients have lower risk of lymph node metastasis and are less likely to benefit from additional surgery. The European thyroid cancer taskforce recommend prophylactic CND only in patients with suspected and/or intraoperatively proven lymph node metastasis.[23] Few technical advancements in surgery include endoscopic thyroid surgery and robotic surgery[21,24–29]

SODIUM IODINE SYMPORTER (NIS) AIDED THERANOSTIC CONCEPT IN TREATMENT OF THYROID CANCER WITH RADIOIODINE

The NIS is an intrinsic plasma membrane protein that mediates active iodine transport into the thyroid gland and into several extrathyroidal tissues.[30] RAI treatment of DTC is based on the principle of NIS expressing thyroid cells and is the cornerstone of treatment by this method.[31] This was in fact the first ever application of the theranostic concept in the 1940s. The RAI therapy is based on the fact that thyroid follicular cells and DTC are efficient in trapping circulating radioiodine than other tissues.[32,33] RAI has remained the key player in treatment of DTC since many decades and has been used successfully for the treatment of both local and disseminated disease. Expression of NIS is, however, not entirely specific for thyroid cancer and can be seen also in either breast or GI cancers as well.[34,35] NIS is found to be expressed more in differentiated thyroid cancer tissue[36] and is usually negative in poorly differentiated tissues like in oxyphilic change and anaplastic transformation. Glucose transporter receptor Type 1 (GLUT−1) expression was more observed in NIS negative cases and vice versa,[37–39] thus leading to the concept of personalized treatment by the theranostic approach. NIS expression may also be helpful in predicting response and enhance patient management. DTC cells expressing NIS usually takes up more RAI and respond better to therapy[40,41]

RISK STRATIFICATION FOR PRECISE POST-SURGICAL MANAGEMENT WITH RADIOIODINE

A staging system that incorporates both standard clinical risk factors and an evaluation of response to therapy is more predictive of important clinical outcomes than a system based on clinical risk factor alone. During the last few years, strong emphasis has been given to individual risk stratification for guiding further management and future follow up in DTC. This is in the form of post-operative staging and a further dynamic ongoing risk stratification[23,42] amenable to change during the course of treatment and follow-up. Earlier several risk stratification strategies have been put forward which estimated risk to guide both initial therapy and follow-up. Most of these had always been to predict death.[43–46] Since most of the DTCs are of indolent nature and have a long disease free interval it becomes more important to predict risk of recurrence rather than risk of death. To overcome the limitation of such staging system, ATA published its guidelines[47] pointing more towards predicting the risk of recurrence which were divided into three categories namely low, intermediate and high. These guidelines were predominantly based on the pTNM status integrated with other clinical parameters, the histological variant, the results of first post-therapy WBS and serum Tg measurement were also an integral part of the risk stratification system. European thyroid association (ETA) guidelines[48] were slightly different than the ATA guidelines. This risk stratified the patients as very low, low- and high risk group. Multiple parameters were included in the initial risk stratification which included the age at diagnosis, histologic features, size of the primary tumor, lymph nodal status, multifocally, vascular invasion, extrathyroidal extensions completeness of resection, distant metastatic lesions and the post-operative Tg values. These guidelines were subsequently modified to include other parameters like additional clinical or follow-up investigational data which had been termed as ongoing risk stratification and is a very important component in the management of DTC. It has also been suggested to include the outcome of first RAI therapy in the parameters of risk stratification termed as delayed risk stratification[49,50]

Applying this concept, it was found that a significant number of patients moved to the low risk category from intermediate or high risk category and had a significantly better positive-predictive value or negative-predictive value in predicting the final outcome as compared to standard guidelines. This helped in moving to a less aggressive approach in a significant number of patients and still keeping the rate of recurrence as low. The authors concluded that the initial risk stratification at the time of initial treatment should be used to only decide whether the patient needs RAI ablation or not. The subsequent strategy and follow up should be based on ongoing and delayed risk stratification[49,51]

PATIENT PREPARATION FOR RADIOIODINE THERAPY WITH RECOMBINANT TSH

High levels of thyroid stimulating hormone (TSH) is essential for effective ablation of remnant tissue as it stimulates RAI uptake by thyroid cells. Traditionally, this high level has been achieved by withholding thyroxine therapy for 4–6 weeks after NTT or TT, causing endogenous TSH to rise.[52,53] The resultant hypothyroidism can impact the patients quality of life (QoL) and imbalance of several biochemical parameters especially in the elderly[54–58] A highly purified, recombinant form of the naturally occurring human protein TSH, rhTSH, has been developed and used as an alternative to withholding thyroxine to facilitate RAI ablation.[53,59] It is a highly purified, recombinant form of the naturally occurring human protein TSH (rhTSH), produced by recombinant DNA technology.[60] Recombinant

human thyrotropin is currently approved by many international authorities including the United States Food and Drug Administration and Health Canada for use in patient preparation for RAI remnant ablation in patients who have undergone a NT or TT for DTC and who do not have evidence of distant metastases.

RADIOIODINE ABLATION AND TREATMENT BASED ON THERANOSTICS

The role of post-thyroidectomy RAI ablation is mainly to eliminate residual thyroid tissue left after surgery visualized in the WBS.[61] The availability of hybrid imaging technology like single photon emission CT/CT (SPECT-CT) has significantly increased the precision and accuracy of detection of residual disease or metastasis in the diagnostic WBS. SPECT-CT provides incremental diagnostic value to the WBS in correctly localizing the iodine avid disease sites helping in more precise treatment. This is most helpful in localizing the lymph nodal metastasis in the neck accurately especially those in the vicinity of extremely iodine avid residual thyroid tissue. The increase in the sensitivity of detection and localization of radioiodine at the sites of disease are clearly documented. SPECT-CT improves detection and characterization of RAI avid disease and helps in localization of thyroid bed, lymph nodal and distant metastatic sites thereby either upstaging or at times downstaging patients post-NTT or TT facilitating correct decision-making and management enhancing the accuracy of treatment by RAI[62] This also helps in the detection of early recurrence and increase the sensitivity of Tg values with RAI scan and serum Tg assays.[63] RAI can also be considered as adjuvant treatment to eliminate microscopic disease and other unsuspected disease in the neck outside the thyroid bed, lymph nodes, lungs and bones.[64,65] These unsuspected disease can be detected on post-therapy WBS and the patient can be further risk stratified based on "treating what has been seen and confirming what has been treated concept". Therefore, the role of RAI ablation and adjuvant treatment can reduce the risk of recurrence and mortality and also become a part of ongoing risk stratification.[66–68] These findings are however seen in patients who have a tumor >1.5 cm and have disease outside the thyroid bed post-surgery. No such benefits were, however, seen in lower risk group of patients.[69–71]

In a primary tumor of 1 cm size which is intrathyroidal or showing microscopic multifocality, RAI is usually not recommended as it will not decrease the risk of recurrence or death. This may, however, facilitate initial post-operative staging and long term follow-up. Not much data are available in cases of tumor upto 4 cm in this group as to whether it can reduce the risk of recurrence. Therefore, selective use of RAI is recommended. Tumors >4 cm and in patients <55 years of age RAI is definitely recommended. In patients >55 years of age, there is evidence that radioiodine decrease the risk of recurrence and should be administered. In cases of lymph nodal disease, selective use of radioiodine is recommended keeping in view the other tumor-related factors.[72–77] The recommendations for the use of RAI in DTC has not been substantially changed in the current guidelines.[7] In this, there is an almost clear demarcation as to which patients should be considered for RAI ablation and who should not be. These have been based on the general oncological principles of remnant ablation, adjuvant treatment and therapy for metastatic disease. Patients having adjuvant therapy are one with higher risk and are expected to have a reduced rate of recurrence post-RAI. Treatment of metastatic disease by the theranostic concept will have the best chance of disease control. The main idea is to limit the use of RAI in patients who are unlikely to benefit and use it effectively in the patient subgroup who have a maximum chance to benefit[78] In operated patients with low or intermediate risk DTC without extensive lymph node involvement (*i.e.* T1–T3, N0/Nx/N1a, M0), in whom RAI remnant ablation or adjuvant therapy is planned, preparation with rhTSH stimulation is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation as it provides better short-term QoL, comparable ablation efficacy, and no significant difference in long-term outcomes.[79] We use rhTSH for early ablation post-NTT or TT predominantly to maintain the QoL of patients undergoing radioisotope ablation within 7–10 days post-surgery. Comparable outcomes with regards to ablation has been seen in patients with either methods of preparation. However, the QoL has been found to be better (statistically significant $p < 0.05$) by rhTSH method of patient preparation. This eventually also saves many man hours and money for the patient[80]

DECIDING THE DOSE OF RADIOIODINE FOR REMNANT ABLATION

The objective of RAI ablation post initial NTT or TT has been different in different stages of the disease. In low risk group, the ablation of residual tissue post-surgery has been to facilitate follow up by eliminating post-surgical thyroid remnant and increase the sensitivity of Tg values. It can also be used to treat residual disease outside the thyroid bed as an adjuvant therapy. In metastatic disease higher therapeutic dose of RAI is needed to be administered. Diagnostic WBS plays an important role in this setting.

Based on the objectives of treatment, the functions of the first dose of radioiodine could be termed either ablation or therapeutic whereas the clinical outcomes can be defined as either to prevent recurrence or predict survival. Histopathological features are also an important factor for deciding the need and the dose of radioiodine where non-papillary histologies and invasive nature of the tumor also needs to be considered. Other factors of consideration are clinical judgment and experience in handling such cases.

Although remnant ablation of low-risk DTC patients after NTT or TT has been used as a standard of care for the last six decades, the most effective dose of RAI required for this purpose still remains controversial. It has been suggested across many studies in the literature that adequate remnant ablation could be achieved in upto 80% of the cases with a dose of 25–50 mCi. Further increasing the dose did not better the ablation rate. Few meta analysis[81–83] suggested some different facts. There was evidence of marginal increase in rate of successful ablation when the dose was increased from 30 mCi (54%) to 77–100 mCi (73%). There was no conclusive evidence that 30 mCi had a similar or lower ablation rate compared with 100 mCi in these meta analysis. There was also a risk of development of second malignancy with higher dose of RAI and suggested that the lowest possible

effective dose should be delivered to minimize the risk of second malignancy.[84] A recent randomized equivalence trial to determine the optimum dose radioiodine for remnant ablation[85] did not find any statistically significant differences in ablation rates among the different ablation groups in the proportion of patients with successful ablation with a standard treatment of 100 mCi compared with those who underwent experimental treatment of 50 and 25 mCi. The authors concluded that a first dose I-131 ablation rate with 25 mCi is not inferior to using 50 or 100 mCi[85–88] A lower dose of 30 mCi has been recommended in the current guidelines for remnant ablation to reduce the risk of side effects like xerostomia, epiphora etc. in the majority of patients with low or intermediate risk of recurrence.[78]

DOSIMETRY

The term theranostics describes the use of hybrid imaging for planning radionuclide therapy and the prediction of absorbed doses with the same or allied tracers thereby making the therapy safer and more efficacious. In thyroid cancer, both I-123 and I-124 can be used in pre-therapeutic dosimetry as a substitute for I-131. Among the two isotopes, I-124 has been preferred as it emits positrons and thus positron emission tomography (PET) imaging can be performed which has better resolution than SPECT images using I-123. The longer T1/2 of I-124 also permits quantitation many days after administration. It is well-known that for the treatment of metastatic disease it is ideal to deliver a tumoricidal radiation dose to the disease sites. In such situations, there can be two aspects to the concept of dosimetry. It is assumed that increasing the radioiodine dose will deliver a higher absorbed dose to the metastatic sites. Therefore, a balance between the maximum tolerated dose and the therapeutic benefit needs to be derived. In this case, whole body or blood clearance dosimetry can be done to find out the maximum tolerated activity. The other way is to calculate the absorbed dose to the lesion which can predict the response to radioiodine treatment. In dose–response relationship assessed by I-124, it was found that there was statistically significant difference in lesion absorbed dose between a complete and partially responding lesion with the lesion absorbed dose of the completely responding lesion much higher than the other. This was 90 Gy for the remnant and 40 Gy for metastasis.[89] The American thyroid association guideline task force acknowledged the theoretic advantage of dosimetry but did not find sufficient evidence in the literature to recommend this approach.[90] It was suggested that while lesion absorbed dose is important, the effectiveness of RAI therapy was also associated with other clinicopathological factors[78,90] In a large study comparing the treatment of patients with RAI avid distant metastasis, in two different institutions, it was found that the whole body and blood clearance dosimetry approach did not provide significant survival benefit over the fixed dose protocol.[91] Clinical benefit was, however, reported in the dosimetric approach as compared to a fixed dose.[92] It was suggested that higher dose of RAI may be more efficient in disease control than lower fractionated activity. The patient treated with dosimetric approach were 70% less likely to progress and more likely to achieve complete response. Complete response was significantly higher with the dosimetric approach in the patients with locally advanced DTC. The frequency of side effects were, however, not significantly different between the groups. Thus, high efficacy and similar safety profile makes the individually prescribed activity approach more logical in high risk patients and radioiodine avid metastatic disease in DTC.[91] The mean absorbed doses for individual tumors were in the range of 1.2–540 Gy and was obtained with three-dimensional dosimetry in individual patients using I-124.[93,94] It was found that the mean absorbed dose for ablation was >300 and >80 Gy was required for treatment of metastatic disease in other studies.[95] . Dosimetry is certainly an integral part of the theranostic concept and has been successfully performed with I-124 and I-131 pair in the pre-therapeutic setting during treatment of DTC with RAI. However, in modern times most of the therapy is performed with the fixed dose concept, the RAI dose for ablation being lower than that used for metastatic disease. The selection of individual dose now depends on the oncological principles like the stage, histopathology and risk stratification for a particular patient rather than the absorbed dose concept

TREATMENT OF METASTATIC DISEASE IN DTC

PTC has the least potential to metastasize followed by the papillary follicular variant, FTC and HTC. Bone metastasis is more frequent in FTC (7–28%) as compared to PTC (1.4–7%) with axial skeleton being the primary target.[96] WBS remains the cornerstone of diagnosis of metastatic disease in thyroid cancer which is amenable to treatment with RAI having the expression of NIS intact.[97] RAI has been used in the treatment of metastatic disease in DTC after surgery and has been proved to be effective in long-term follow-up. Younger patients with PTC histology and more extensive thyroidectomy in the form of initial treatment showed better prognosis.[98] The 10 years survival rate in DTC drops by almost 50% in presence of metastatic disease. Bone metastasis at presentation before initial RAI demonstrated poorer prognosis than if detected later in the course. The treatment of metastasis from DTC was feasible with RAI and could continue till the alleviation symptoms, regression or disappearance of lesions. Majority of patients having metastatic disease are diagnosed using WBS along with SPECT-CT with high specificity along with other ancillary findings in structural imaging.[99] This also aids in the assessment of therapeutic benefit by the theranostic concept. The survival drops to 14% in patients older than 40 years old with macronodular lung metastasis or multiple bone metastasis.[100]

RAI treatment outcomes in patients with bone, lung and lymph node metastasis depend on factors like volume of disease, total administered RAI dose and age of the patient at the time of treatment among other factors. Total or partial remissions were more common in patients <45 years with lower dose of RAI 62.5 *vs* 49.5%.[101–103] Low volume disease and predominantly microscopic disease burden in younger patients has better outcome. Positive pre-therapy WBS and a negative chest X-ray had better results than the one with both WBS and X-ray chest being positive. The metastatic disease with high tumor rate of differentiation loses the NIS expression and metabolises glucose. Fludeoxyglucose (FDG) shows preferential tracer uptake in malignant cell with high glucose metabolism. In thyroid cancer, FDG is now routinely used for detection of disease foci in cases of high Tg and negative WBS. Few studies have reported the use of Ga-68

DOTATOC scan and combined FDG/MRI in these cases.[104–107] Complete remissions can be seen in lesser number of metastatic sites.[103] Local treatment modalities like surgery or external beam radiotherapy (EBRT) can be combined with systemic treatment like RAI in selected cases. Bone metastasis having persistent pain, poor uptake of RAI, spinal instability or cord compression can be stabilized with surgery before attempting RAI. Few studies have investigated the role or RFA or ethanol in selected cases. However, these are still in the investigational stage.[108]

Similarly bone metastasis not amenable to treatment with RAI may be given EBRT for pain palliation or to prevent pathological fracture and cord compression. Predominantly, partial pain relief is obtained in more than 80% of patients and upto 6 months of sustained pain relief is seen in approximately 50% of such patients. Combination of localized EBRT and systemic RAI treatment has also been found to be useful[109] A variety of chemotherapeutic regimes have been used in metastatic DTC with inconsistent results.[110,111] Unfortunately, no provision of systemic treatment was available for poorly DTC in earlier times but is currently available.[112]

The use of rhTSH stimulation for patient preparation prior to treatment of metastatic disease has not been approved by FDA yet. However, few institutions have recommended its use in properly selected patients, especially with bone metastasis. In our experience, the treatment of bone metastasis with radioiodine is feasible post-rh TSH stimulation.

In bone metastasis, the RAI avidity and Tg values simulate the results of standard hormone withdrawal protocol which is the universal standard. However, no morbid symptoms and signs which were seen during thyroxine withdrawal were encountered post-rhTSH which resulted in better patient compliance, performance status and QoL. It is expected that the outcome of treatment in bone metastasis should be better as the window period of TSH stimulation is short and hardly results in disease flare as happen with the other method. [113]

ROLE OF FDG IN DTC

FDG-PET-CT is currently being used in the management of DTC mainly to detect sites of disease which may not be RAI avid or as a result of tumor heterogeneity, which is more common in high risk patients and where FDG avid and non-avid disease may co-exist. The localization of FDG in DTC depends on a number of factors. It is known that GLUT receptors are abundantly expressed on thyroid cells. GLUT1 is particularly found in aggressive variety of thyroid cancer cells. This aggressive variety also overexpresses hexokinase1 and HIF1α which promotes FDG uptake. In high risk disease, FDG-PET can identify clinically relevant sites of disease, assess serially the progress or response to treatment, identify the need for additional local intervention like EBRT, excision or RFA and response to targeted therapies. FDG-PET can also be used during initial staging in high risk patients with advanced T stage, distant metastasis at diagnosis and aggressive histological subtypes. Most of the bulk of disease in such cases do not show RAI avidity and may not benefit from the theranostic approach of treatment.[114] The most common indication of FDG-PET-CT in DTC has been in patients with elevated Tg levels and a negative RAI scan or the RAI scan is not corroborating with the expected disease burden in the patient. The disease in the latter group of patients undergo gradual de-differentiation with activation of cellular glucose metabolism. This has been termed as a "flip flop" phenomenon. Over the time, we have realized that this phenomenon is not absolute and both RAI avid and RAI refractory (FDG avid) can co-exist in the same patient. FDG has good sensitivity of detection in this setting and it varies between 70 and 90% across literature. In specific clinical situations, it can affect patient management in 20–40%. In addition to the diagnostic indications, FDG-PET provides significant prognostic information.[115] It has been seen that high FDG uptake in metastatic DTC is usually seen in de-differentiated, aggressive variety with poor prognosis and reduced survival. In such cases and high risk DTC, total volume of FDG positive disease is the strongest prognostic indicator of survival. Low or no FDG uptake in RAI negative disease has better prognosis and in fact thyroxine suppression is adequate in the absence of any active management. FDG-PET-CT has also been utilized in Hurthle cell carcinoma,[116] poorly differentiated carcinoma, anaplastic carcinoma and incidentalomas.

TREATMENT OF RADIOIODINE REFRACTORY METASTATIC DISEASE

Although RAI treatment has remained the success story in the treatment of metastatic thyroid cancer, about 25–50% of patient with locally advanced or metastatic disease become refractory to RAI.[117,118] Limited treatment options are available for patients with advanced or RAI refractory disease. Many genetic alterations have been seen in the molecular pathogenesis of DTC, most commonly RET/PTC translocations and $BRAF^{V600E}$ point mutations in PTC and RAS point mutations in FTC and poorly DTC. Elevated expression of vascular endothelial growth factor and its receptors may play a role in thyroid carcinoma. Studies of the tumor biology of DTC has led to the development of targeted therapies based on the theranostic concepts. It has been found that like other solid tumor, many pathways are involved in tumor angiogenesis, growth and progression. Few agents have been developed to inhibit these inappropriately activated pathways within the cells. Currently, based on the findings of multicentre, randomized, double blind placebo controlled Phase III studies, two agents, Sorafenib and Lenvatinib has been approved in USA and Europe for the treatment of this group of thyroid cancer. These small molecular tyrosine kinase inhibitors have shown clinical benefit in this group. The DECISION and SELECT trials showed that Sorafenib and Lenvatinib has significant benefit in terms of progression free survival over placebo. Sorafenib is an oral multityrosine kinase inhibitors and shows inhibitory activity against the VEGFR- 1,–2,–3, platelet derived growth factor receptor B, RAF-1 RET and BRAF.[119] Lenvatinib is a multityrosine kinase inhibitor of the VEGFRs 1,2 and 3 FGFRs 1 through 4, platelet derived growth factor receptor α RET and KIT signaling networks, also showing significantly improved PFS against placebo. Current studies have shown that the PFS, with these targeted therapies have been 10.8–18.3 *vs* 5.8–3.6 months as compared to placebo.[119,120] It is still unclear when these form of treatment needs to be started during the course

of the disease and more so in asymptomatic patients with metastatic disease. It can be started in RAI refractory disease documented by a negative WBS and a positive FDG-PET-CT scan and this can also be used for objective response evaluation by PERCIST. The measurable lesion should be evaluated by both RECIST and PERCIST criteria. So far these drugs have shown promising results in terms of disease control, regression or stable disease. It must be however remembered that these agents are associated with side effects most commonly being hand/foot skin reactions, rash, fatigue, mucositis, hypertension diarrhea, ECG changes and weight loss. The severity of the symptoms of side effects and the potential benefit needs to be critically evaluated before starting this form of treatment. [121,122]

PTC with BRAF mutations are associated with significantly reduced expression of genes involved in the metabolism of iodine including genes for NIS, Tg and thyroperoxidase. On the other hand, BRAF mutated tumors exhibit higher GLUT-1 receptors levels. These play an important part in the tumor dedifferentiation reducing efficacy of RAI.[123–125] The extensive mechanism of actions of these mutations are beyond the scope of the review and can be found elsewhere.

ROLE OF THYROGLOBULIN AND ITS INERPRETATION IN DTC

Tg is a tissue specific 660 kDa protein, that serves as a precursor in thyroid hormone biosynthesis.[126] It is synthesized by both thyroid follicular cells and differentiated cancer cells. Tg is thus a sensitive marker to detect recurrence or persistent disease. High serum Tg in the follow-up DTC patients after adequate surgery and RAI treatment with negative imaging results is suspicious of recurrence. A Tg value of 2 ng ml^{-1} suggests persistent disease or possibility of distant metastasis. In a series of 256 patients, a high recurrence rate has been seen using this as a cut off value[127,128] Other studies have used a range of values as a predictor of recurrent disease. A Tg value of 5–10 ng ml^{-1} had a lower rate of recurrence with a PPV of 42% in comparison to 53% of patients with serum Tg >10 ng ml^{-1}. We have seen that a Tg value upto 11 ng ml^{-1} and negative WBS in a low risk patient during the first follow-up after RAI do not always warrant an aggressive approach[129] The measurement of Tg autoantibodies (TgAb) has become a routine with measurement of serum Tg to check the presence or absence of TgAb interference in the follow up of patients with DTC. Although detection of TgAb is crucial in the follow up of DTC, its measurement is cumbersome and high intermethod variability is reported. Although the different methods of detection, as compared to the reference standard and the significance of various ranges of detection are beyond the scope of this article, it is important to determine the TgAb upper limit to be considered when following up a case of DTC as the TgAb tends to mask recurrence.[130,131] Serum TgAb are reported to be present in approximately 25–30% of the patients. It depends on the assay used and the cut-off employed to differentiate patient as positive or negative.

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT) OF DTC

One of the treatment options which has been recently proposed for RAI refractory thyroid cancer has been peptide receptor radionuclide therapy (PRRT) based on the theranostic concept. PRRT is a unique way of targeting somatostatin receptors over expression on tumor cells in many cancer including thyroid.[132–135] Although quite a few studies are available, the number of patients treated are not very large till now. In a study of 16 patients with RAI refractory thyroid cancer patients treated by PRRT with 90-Yttrium and/or 177-Lutetium labeled somatostatin analogs, the results have not been so encouraging. Stable disease was seen in 36.4%, partial response in 18.2% and progressive disease in 45.6% with an overall PFS of 25 months.[136] In another study where 68-Ga-DOTATOC PET/CT was used to select such patients for PRRT as well as treatment response and toxicity,PR and SD was seen in approx. 60% of the treated patients with duration of response being 3.5–11.5 months.[137] Main adverse events were nausea, asthenia, and transient hematologic toxicity. At this point of time and with the available literature, PRRT shows variable results in the form of partial remission or stable disease in approx. 50% of the treated patients. However, the currently available results cannot be treated as sufficient evidence for recommending this form of treatment in iodine refractory DTC.

CONCLUSION

Surgery followed by radioiodine has remained the treatment of choice over the last six decades in DTC with a favorable outcome. SPECT-CT has added precision to the WBS aiding proper staging and choosing RAI dose. Over the years, we are seeing an increasing trend in iodine refractory metastatic disease. Availability of FDG-PET- CT imaging has helped in early detection of these lesions, helping multimodality management protocols. Similarly, the study of tumor biology has led to the development of targeted therapies based on the gene mutations and receptor expression which is showing promising results in this group. The future will focus on the detection, management and response evaluation of radioiodine refractory metastatic disease. Combination therapies will play a bigger role as the tumor heterogeneity in the form of both RAI avid and RAI refractory disease can exist in the same patient. In time to come, both FDG-PET-CT and WBS will probably be more frequently used in the high risk patients for precise treatment planning. Further long-term studies will be needed before PRRT can be established as an option in the treatment of RAI refractory metastatic DTC.

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