Identification of Radioactive Iodine Refractory Differentiated Thyroid Cancer

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Most differentiated thyroid cancer (DTC) patients have an excellent prognosis. However, about one-third of DTC patients with recurrent or metastatic disease lose the hallmark of specific iodine uptake initially or gradually and acquire radioactive iodine-refractory DTC (RAIR-DTC) with poor prognosis. Due to the potentially severe complications from unnecessarily repeated RAI therapy and encouraging progress of multiple targeted drugs for advanced RAIR-DTC patients, it has become crucial to identify RAIR-DTC early. In this review, we focus on the progress and controversies regarding the defining of RAIR-DTC, further with subsistent approaches and promising molecular nuclear medicine imaging in identifying RAIR-DTC, which may shed light on the proper management methods of such patients.

Key Words: Thyroid Neoplasms; Iodine Radioisotopes; Molecular Imaging

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INTRODUCTION

The incidence of thyroid cancer has increased rapidly. 567,233 new cases of thyroid cancer occurred globally in 2018, accounting for 3.1% of all tumors.1 Differentiated thyroid cancer (DTC), including papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), Hürthle cell carcinoma, and poorly differentiated thyroid cancer (PDTC), arise from follicular cells and make up more than 95% of all of thyroid cancers.2 Irrespective of excellent prognoses in most DTC patients, the prevalence of distant metastasis ranges widely from 5%-25%,3,7 which leads to a 5-year survival rate that can be as high as approximately 50%.8 However, about one-third of DTC patients with recurrence or metastasis lose the hallmark of specific iodine uptake initially or gradually, presenting as a RAI-refractory state.9 The 5-year survival rate was merely 19% for such patients.9 Inadequate response to RAI poses a great challenge RAI-refractory DTC (RAIR-DTC) management.

According to the 2015 American Thyroid Association (ATA) guidelines, the RAI therapy should be discontinued once the patient has been recognized as RAIR-DTC. Although the recognition of RAIR-DTC has been more and more clear over time, the diagnostic criteria are still based on imaging manifestation and RAI response, which is more or less influenced by the physician’s objective judgment. There isn’t a well-recognized definition of RAIR-DTC. Furthermore, along with the encouraging progress of molecular pathogenesis over the recent decades, multiple drugs targeted on genetic and epigenetic alterations, and aberrant signal pathways, notably tyrosine-kinase inhibitors (TKIs), have been developed with promising results and have begun to meaningfully impact clinical practice. With the advent of these new treatment options, practitioners are faced with important decisions in determining which patients are appropriate for systemic treatments and the proper timing to initiate the treatment. Thus, it has become crucial to early identify and even predict RAIR-DTC. Herein, we aim to address RAIR-DTC as follows: 1) the definition of and controversies surrounding RAIR-DTC; 2) subsistent approaches to recognize RAIR-DTC; and 3) promising molecular nuclear medicine imaging in identifying RAIR-DTC.

CONTROVERSIES OF THE DEFINITION

Paterson et al.10 reported the phenomenon of non-RAI avidity as early as 1952. However, no explicit statement had been clearly defined about RAIR-DTC until September 2010 during the 14th International Thyroid Congress in
Moreover, the interval between 131I-WBS acquisition and planar and SPECT. Similarly, 124I showed a superior RAI-avid disease have been demonstrated compared with questions, the superiority of PET to deliver images for detecting metastases coexistence in one DTC patients. As it has been growing heterogeneity, which means avid and no-avid RAI developed over time, some controversies remain, particularly as administration of a 131I therapy may falsely classify RAI-avid metastasis as non-RAI-avid. Concerning the cumulative activity of RAI therapy, it may not be rational to take 22.2 GBq (600mCi) as a cut-off value of RAI-DTC’s definition. Given the increased risk of secondary cancers and leukemias with RAI activity accretion, patients with a cumulative dose of more than 22.2 GBq are not recommended for RAI therapy and classified as RAI-DTC. However, it is noticeable that parts of such patients are still with visible RAI uptake in lesions which have neither been cured nor progress according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, which might be regarded as a kind of response as “stable disease”. In cases like these, it is debatable whether additional RAI treatment should be recommended for such patients. The 2015 ATA guidelines suggest that subsequent RAI treatment should be based on the meaningful response, which is “generally associated with a significant reduction in serum Tg and/or in the size or rate of growth of metastases or structurally apparent disease”. Therefore, how to define response to RAI therapy is more crucial in such a scenario, rather than the argument of a specific cut-off value of RAI dosages.

Furthermore, novel perspectives about defining RAI-DTC have been put forward as follows. 1) Patients with disease progressing whereas complementary total thyroidectomy is no longer beneficial merely for demonstrating RAI-DTC by 131I-WBS. Such patients could be identified as RAI-DTC by alternative molecular imaging other than 131I-WBS. 2) Benefits from RAI therapy in aggressive DTC histology (such as poorly differentiated, insular or Hürthle Cell variants). There is no sufficient evidence to determine whether RAI is likely to be effective in such a situation. Significant uptake of RAI and benefits still could be seen in up to 20% of patients with either Hürthle cell carcinoma or poorly differentiated phenotypes. Conversely, RAI-DTC would occur even in classic PTC. Therefore, it is tough to judge the benefits of RAI therapy in patients with aggressive histology variants. Further evaluation remains necessary to determine whether it is refractory to iodine indeed. Given the unclarity in defining RAI-DTC, it is not easy to confirm the RAI-refractory status. Further evaluation and more neutral approaches should be tailored to identify RAI-DTC.
CURRENT APPROACHES TO IDENTIFY RAIR-DTC

1. ¹³¹I-WBS

Due to the expression of the sodium iodide symporter (NIS), the unique property of thyroid follicular cells to trap and concentrate iodine was also reserved in DTC, which allows RAI (generally ¹³¹I) to be an effective agent of imaging and therapy of DTC and its metastases. ¹³¹I-WBS can localize to the remnant thyroid issue and residual or recurrent RAI-avid lesions and provide evidence for subsequent ¹³¹I treatment. The accuracy of a DxWBS can reach up to 90%, especially with high specificity (91%-100%) and relatively low sensitivity (27-55%). Nevertheless, the neoplastic cells may dedifferentiate and lose certain characteristics associated with normal thyroid follicular cells, notably the diminished NIS expression and/or intracellular retention. About one-third of DTC patients with recurrence or metastases show negative ¹³¹I uptake initially or gradually. According to Durante et al. and Song et al., patients without ¹³¹I uptake in their metastases presented significantly higher disease-specific mortality and drastically decreased 10-year survival rate, compared with those with ¹³¹I uptake. In addition, one retrospective analysis indicated that ¹³¹I uptake grade of metastatic disease was an independent prognostic factor. Adequate attention needs to be paid to patients with negative imaging of ¹³¹I-WBS (despite DxWBS or RxWBS) and abnormally elevated serum Tg level, which always suggests the presence of RAI-refractory disease (Fig. 1).

2. ¹⁸F-FDG PET/CT

Because of the rare iodine avidity of RAIR-DTC foci, research interest into other effective imaging modalities has been aroused by the time. ¹⁸F-FDG, the most well-known functional radiotracer, also plays a crucial role in RAIR-DTC management, including the foci detection, efficacy evaluation and prognosis prediction (Fig. 1). Feine et al. first reported an inverse relationship between RAI and FDG uptake in thyroid carcinoma (the so-called ‘flip-flop phenomenon’), which was thought to be attributed to the loss of ability to concentrate RAI during dedifferentiation, along with an increased demand for glucose of tumor cells. In a meta-analysis of the diagnostic accuracy of ¹⁸F-FDG PET/CT in DTC patients with elevated serum Tg after thyroidectomy and negative ¹³¹I-WBS, the pooled sensitivity and specificity of ¹⁸F-FDG PET/CT were 93.5% (95% confidence interval [CI], 87.0%-97.3%) and 83.9% (95% CI, 72.3%-92.0%), respectively. There has been a variety of reports demonstrated that the sensitivity of ¹⁸F-FDG PET/CT findings increased with the Tg level. ¹⁸F-FDG PET metabolic parameters have been confirmed to be prognostic factors in several studies. In a study of 62 metastatic RAIR-DTC patients, Manohar et al. found that patients with overall metastatic tumor volumes (MTVs) higher than 9.08 mL and total lesion glycolysis (TLG) higher than 49.1 had poorer overall survival (OS) (p=0.06) and progression-free survival (PFS) (p=0.007) rates. According to the 2015 ATA guidelines, ¹⁸F-FDG PET/CT was recommended for high-risk DTC patients with elevated Tg levels (generally stimulated Tg>10 ng/mL) and negative RAI imaging. A recent prospective study showed that at a...
cut-off value of 4.0 in SUVmax, the sensitivity and specificity of $^{18}$F-FDG PET/CT predicting $^{131}$I-avidity could reach to 75.3% and 56.7%, respectively, which indicates that $^{18}$F-FDG PET/CT before $^{131}$I therapy is of great value in the prediction of the RAI-avidity of metastases.47

3. Tg relevant indicators

Tg is a protein produced by thyroid follicular cells. Under the condition of negative anti-Tg antibody, Tg is an important additional parameter in the determination of remission and monitoring of the disease’s progress. The increasing trend or very high Tg levels after total thyroid ablation may suggest a recurrence and/or metastasis of the disease. From a retrospective study of 137 patients with PTC after total thyroidectomy, Miyauchi et al.48 found that Tg-doubling time (Tg-DT) was a prominent independent predictor of prognosis. Patients with Tg-DT shorter than 1 year showed a 10-year-survival rate of 50%, which is significantly less than 95% of those with Tg-DT for 1-3 years. Yet, one study aiming at progressive or recurrent DTC patients drew a different conclusion that Tg-DT alone was not an independent survival predictor, but instead, the highly significant difference in survival rates was revealed in patients with high tumor loads (Tg > 100 ng/mL).49 The discrepancies between these studies might result from the different patient constitution and cohort comparison. Another assessment of Tg trends provides a brand-new perspective on Tg dynamic evaluation. It analyzed the ratio of the pre-ablative, stimulated Tg in the first 2 RAI therapies (pstim-Tg2/Tg1) and the ratio of suppressed Tg before and after the second RAI therapy (sup-Tg2/Tg1) from pulmonary metastatic DTC patients, which indicated that the higher Tg2/Tg1 value above the cutoff point (0.544 for pstim-Tg2/Tg1, 0.972 for sup-Tg2/Tg1), the greater possibility of RAIR-DTC.50

4. Closely related genetic characteristic

It is well known that the BRAFV600E mutation is correlated with the recurrence and poor clinicopathological outcomes.51-53 The BRAFV600E mutation negatively regulates iodine metabolism genes (NIS, TSHR, Tg, TPO, etc) via the abnormal activation of the mitogen-activated protein kinase (MAPK) pathway.54-56 On the one hand, BRAFV600E mutation promotes NIS silence by histone deacetylation (HDAC) of NIS promoter,57 on the other hand, the BRAFV600E mutation upgrades the secretion of transforming growth factor β (TGFβ),58 which, through the activation of SMADs and consequent impairment of the thyroid-gene transcription factor PAX8, is a potent repressor of NIS in thyroid cells (Fig. 2)58,59. Our previous study found that the BRAFV600E mutation was associated with the non-RAI-avid of DTC lesions in distant metastases.60 Similarly, the TERT mutation also closely associates with non-RAI-avid DTC within distant metastases, it offers a greater negative influence on RAI avidity when compared with the BRAFV600E mutation. Meanwhile, the TERT mutation could be used as an early predictor RAIR status.61 Several studies have further found that coexistence of the TERT and BRAFV600E mutations may trigger more aggressive clinicopathologic characteristics.62-67

PROMISING MOLECULAR NUCLEAR MEDICINE APPROACHES TO IDENTIFY RAIR-DTC

1. RGD imaging targeted on integrin

$^{18}$F-FDG PET/CT is usually considered one of the most important alternative imaging strategies, which is still un-
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FIG. 3. The nuclear imaging for identifying RAIR-DTC. Negative 131I-WBS act as fundamental indicator for RAIR-DTC identifying, while there still are plenty of influencing factors. Other nuclear imaging modalities could be complements with progressed researches. 

131I-WBS: 131I-whole-body scan, RAI: radioactive iodine, RAIR-DTC: radioactive iodine refractory differentiated thyroid cancer, FDG: fluorodeoxyglucose, RGD: Arg-Gly-Asp, PSMA: prostate-specific membrane antigen, SSTR: Somatostatin receptors.

2. Prostate-specific membrane antigen (PSMA) imaging

The prostate-specific membrane antigen (PSMA) is a new target for radionuclide imaging and therapy of prostate cancer in recent years. Overexpression of PSMA has also been demonstrated on the cell membrane of endothelial cells of tumor neovasculature in several other malignancies such as renal cell carcinoma, colon carcinoma, neuroendocrine tumors, melanoma, and breast cancer.

It is compelling that 68Ga-PSMA PET/CT imaging can also identify RAIR-DTC potentially. In a prospective research study including 10 patients of metastatic DTC harboring 32 lesions, all patients showed substantial PSMA uptake with 30/32 total lesions detected by 68Ga-PSMA PET, compared 23/32 positive lesions on 18F-FDG PET/CT. Particularly, 21 (70%) of the 30 lesions showing PSMA expression were localized to the bones. In a study by Lütje et al., 6 patients with 131I-WBS-negative and 18F-FDG-positive metastasized DTC received 68Ga labelled PSMA ligands and underwent PET/CT. The results demonstrated that 68Ga-HBED-CC-PSMA PET/CT might be suitable for staging patients with RAI-negative DTC metastases and identifying patients who might be eligible for PSMA-targeted radionuclide therapy.

3. Somatostatin receptors (SSTR) imaging

Numerous studies have demonstrated the expression of somatostatin receptors (SSTR) type 2, 3 and 5 in DTC in variable percentages. Radiolabeled somatostatin analogs, such as 68Ga-DOTA-octreotide and 68Ga-DOTA-lanreotide...
(LAN), have drawn worldwide attention because of their superior pharmacokinetic characteristics and better spatial resolution of PET technology. However, the diagnostic value of radiolabeled somatostatin analogues in RAIR-DTC remains conflicting. In a study by Traub-Weidinger et al., lesions showing aerobic glycolysis on 18F-FDG PET were found in 24% of 28 patients with corresponding positive results with 68Ga-DOTA-LAN in 35% and with 68Ga-DOTA-Tyr3-octreotide in 29%. Kundu et al. also confirmed 68Ga-DOTA-NOC PET-CT is inferior to 18F-FDG PET-CT at the lesion-based level in DTC with raised Tg and negative 131I-WBS.

4. Choline imaging

The role of radiolabeled choline PET/CT has been fully verified in the diagnosis of prostate cancer. Incidental thyroid uptake has been reported by authors in 18F-choline PET/CT prostate cancer scintigraphy. Some researchers have reported that radiolabeled choline PET/CT may be useful in hunting metastases of thyroid cancer which were negative on 18F-FDG PET/CT. Wu et al. successfully identified thyroid carcinoma using 11C-choline PET/CT in 4 patients with thyroid carcinomas, while the lesions in 3 of 4 patients were missed by previous 18F-FDG PET. In a case report by Piccardo et al., it concluded that 18F-choline PET/CT could detect lethal DTC recurrences, thus choline PET/CT may complement 18F-FDG PET/CT in identifying DTC lesions. Given the absence of convincing evidence, the effectiveness of 11C-choline imaging needs to be further verified with large-scale research (Fig. 3).

FUTURE PERSPECTIVES

The management of RAIR-DTC has been a huge challenge for clinical physicians. There are still many controversies on the definition of RAIR-DTC. The current advancements in RAIR-DTC diagnosis are limited to post-131I therapy evaluation, in which the patients may have been exposed to unnecessary RAI radiation and missed the opportunity to receive more effective interventions. There is a need to be able to predict RAIR-DTC before 131I therapy and make individualized treatment decisions. Thus, continuous improvement in molecular imaging and molecular pathology are surely needed in future research and should focus on RAI-refractory prediction, treatment targets selection, determining the optimal timing for treatment initiation and making second and even third-line treatment schedules.

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AUTHOR CONTRIBUTIONS

Zhuan-Zhuang Mu: Literature search and review, manuscript writing, and editing. Xin Zhang: Manuscript writing and editing. Yan-Song Lin: manuscript writing and editing, and content planning.

CONFLICT OF INTEREST STATEMENT

None declared.

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