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 methodsof such patients.

Key Words: *Thyroid Neoplasms; Iodine Radioisotopes; Molecular Imaging*

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

Paris, France, an international panel defined RAIR-DTC as a combination of at least one lesion which does not show RAI uptake on a RAI whole-body scan (WBS) or clinical evidence that RAI no longer provides a benefit to the patient.[11] In September 2012 in Pisa, RAIR-DTC was complementally considered as one or more metastatic lesions failing to take up RAI and continuing to grow.[12] Tuttle et al.[13] detailed factors associated with suboptimal RAI avidity in 2014: a negative post-treatment WBS (RxWBS) after a properly administered RAI therapy, structural disease progression or rising serum thyroglobulin (Tg) 6-12 months after previous RAI therapy. In 2015, Sacks and Braunstein[14] further proposed that the lack of RAI avidity in one or more lesions even using diagnostic ^{131}I-WBS (DxWBS) was considered RAI-refractory disease. Subsequently, the 2015 ATA guidelines classified RAIR-DTC in the following basic ways: 1) when malignant/ metastatic tissue does not concentrate RAI (no uptake outside the thyroid bed at the first RxWBS), 2) the tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination), 3) RAI is concentrated in some lesions but not in others; and 4) metastatic disease progresses despite a significant concentration of RAI.[15]

Although the definition of RAIR-DTC has been developed over time, some controversies remain, particularly as to its clinical implication. Meanwhile, it is noteworthy that novel perspectives have been put forward recently.

The first controversy is the debate over the value of negative ^{131}I-WBS imaging in RAIR-DTC proof. Negative ^{131}I-WBS could be a fundamental indicator for RAIR-DTC identification, while it may not be a gold standard. Plenty of factors affect the reliability of ^{131}I-WBS, including low-iodine preparation, prescribed activity, ^{131}I-WBS acquisition timing, imaging techniques, RAI isotopes, etc. Furthermore, it has been claimed that the RAI activity of DxWBS might not detect all of the RAI-avid lesions. As many as 25% to 80% of patients with negative DxWBS were spotted with RAI-avid foci by RxWBS.[16] While relevant studies suggested limited benefit from additional RAI treatments in patients with negative DxWBS but positive RxWBS.[17,18] Moreover, the interval between ^{131}I-WBS acquisition and RAI administration could impact the detection of RAI-avid metastases.[19-21] Either earlier or later scans after administration of a ^{131}I therapy may falsely classify RAI-avid metastasis as non-RAI-avid.[22] Concerning imaging techniques, the superiority of PET to deliver images for detecting RAI-avid disease have been demonstrated compared with planar and SPECT.[23,24] Similarly, [124]I showed a superior ability to detect RAI-avid lesions than ^{131}I did. Notably, growing evidence has suggested that the RAI-avid metastatic lesions spotted on a [124]I scan wouldn't guarantee more effective ^{131}I treatment.[25,26]

The second debate among nuclear medicine physicians is over patients with multiple metastases displaying imaging heterogeneity, which means avid and no-avid RAI metastases coexistence in one DTC patients. As it has been suggested in such cases, a combined strategy toward heterogeneous foci seems more reasonable, for example, a local treatment for RAI-refractory lesions (e.g. surgery, radiotherapy, radiofrequency ablation, etc.) and ^{131}I therapy for RAI-avid tumors.[27] Nevertheless, it has been questioned whether it really provide precise benefits for such patients. The potential risk of thyrotropin (TSH) stimulation to non-RAI-avid lesions during ^{131}I therapy preparation is also cause for concern. Meanwhile, the probable contribution of the tumor burden by certain non-RAI-avid or RAI-avid lesions should be taken into account when tailoring the subsequent RAI therapy. Thus, the rationality of ^{131}I therapy should be further evaluated and balanced in terms of benefit and risk.

Concerning the cumulative activity of RAI therapy, it may not be rational to take 22.2 GBq (600mCi) as a cut-off value of RAIR-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 RAIR-DTC.[9,28] 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".[15] 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 RAIR-DTC have been put forward as follows. 1) Patients with disease progressing whereas complementary total thyroidectomy is no longer beneficial merely for demonstrating RAIR-DTC by ^{131}I-WBS. Such patients could be identified as RAIR-DTC by alternative molecular imaging other than ^{131}I-WBS. 2) Benefits from RAI therapy in aggressive DTC histology (such as poorly differentiated, insular or Hürthle Cell variants).[29] 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, RAIR-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 unclearness in defining RAIR-DTC, it is not easy to confirm the RAI-refractory status. Further evaluation and more neutral approaches should be tailored to identify RAIR-DTC.

CURRENT APPROACHES TO IDENTIFY RAIR-DTC

1. ^{131}I -WBS

Due to the expression of sthe odium iodide symporter (NIS), the unique property of thyroid follicular cells to trap and concentrate iodine was also reserved in DTC, which allows RAI (generally ^{131}I) to be an effective agent of imaging and therapy of DTC and its metastases. ^{131}I-WBS can localize to the remnant thyroid issue and residual or recurrent RAI-avid lesions and provide evidence for subsequent ^{131}I treatment. The accuracy of a DxWBS can reach up to 90%, especially with high specificity (91%-100%) and relatively low sensitivity (27-55%).[30-33] 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 ^{131}I uptake initially or gradually.[9] According to Durante et al.[9] and Song et al.,[34] patients without ^{131}I uptake in their metastases presented significantly higher disease-specific mortality and drastically decreased 10-year survival rate, compared with those with ^{131}I uptake. In addition, one retrospective analysis indicated that ^{131}I uptake grade of metastatic disease was an independent prognostic factor.[35] Adequate attention needs to be paid to patients with negative imaging of ^{131}I-WBS (despite DxWBS or RxWBS) and abnormally elevated serum Tg level, which always suggests the presence of RAI-refractory disease (Fig. 1).

2. ^{18}F-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. ^{18}F-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.[36] 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 ^{18}F-FDG-PET/CT in DTC patients with elevated serum Tg after thyroidectomy and negative ^{131}I-WBS, the pooled sensitivity and specificity of ^{18}F-FDG PET/CT were 93.5% (95% confidence interval [CI], 87.0%-97.3%) and 83.9% (95% CI, 72.3%-92.0%), respectively.[37] There has been a variety of reports demonstrated that the sensitivity of ^{18}F-FDG PET/CT findings increased with the Tg level.[38-42] ^{18}F-FDG PET metabolic parameters have been confirmed to be prognostic factors in several studies.[43-46] In a study of 62 metastatic RAIR-DTC patients, Manohar et al.[43] found that patients with overall metabolic tumor volumes (MTV)s 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, ^{18}F-FDG PET/CT was recommended for high-risk DTC patients with elevated Tg levels (generally stimulated Tg>10 ng/mL) and negative RAI imaging.[15] A recent prospective study showed that at a
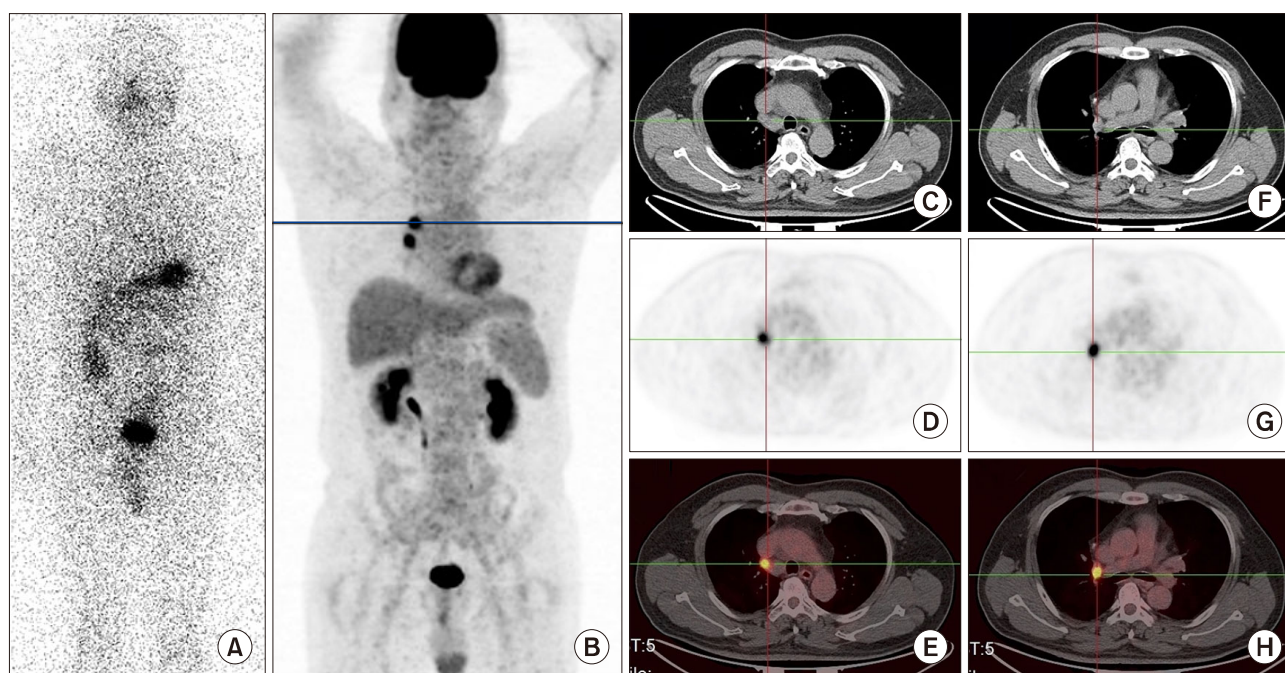
FIG. 1. A 52-year-old man with DTC with negative ^{131}I-WBS and positive ^{18}F-FDG PET/CT. The patient had an elevated serum Tg but negative ^{131}I-WBS. ^{18}F-FDG PET/CT was recommended and displayed two right hilar lymph nodes with metastatic carcinoma. (A) ^{131}I-WBS, (B) PET MIP imaging, (C, F) CT, (D, G) PET, (E, H) fusion.

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 thedisease. 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, that 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 BRAF[V600E] mutation is correlated with the recurrence and poor clinicopathological outcomes.[51-53] The BRAF[V600E] 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, BRAF[V600E] mutation promotes NIS silence by histone deacetylation (HDAC) of NIS promoter,[57] on the other hand, the BRAF[V600E] mutation upgrades the secretion of transforming growth factor β (TGFβ), which, through the activation of SMADs (the family of intracellular transducers that act downstream of receptors for TGFβ family members) and sequential 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 BRAF[V600E] 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 BRAF[V600E] 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 BRAF[V600E] 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-
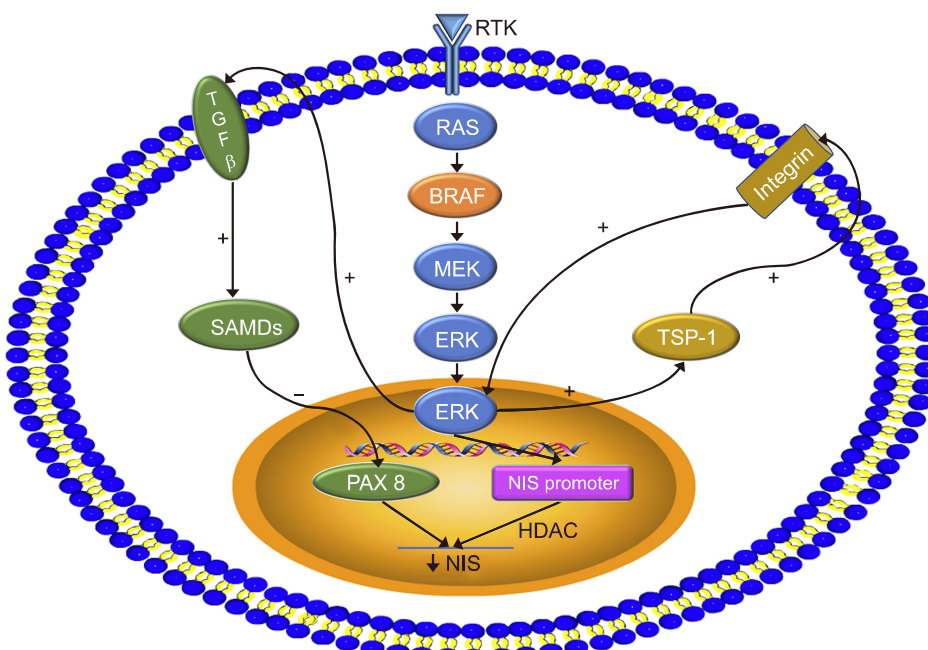
FIG. 2. The mechanism of BRAFV600E mutation negatively regulates sodium iodide symporter (NIS) and Integrin targeted imaging. On the one hand, BRAFV600E mutation promotes NIS silence by histone deacetylation (HDAC) of NIS promoter, on the other hand, BRAFV600E mutation promotes the secretion of transforming growth factor β (TGFβ), which, through the activation of SMADs and consequent impairment of the thyroid-gene transcription factor PAX8. BRAF oncoprotein can activate ERK1/2 signal through mitogen-activated protein kinase (MAPK) pathway, then thrombospondin-1 (TSP-1) was upregulated, TSP-1 further positively regulates the expression of integrin, which in turn increases the level of ERK1/2 signal, forming a positive feedback.

able to detect all of the foci. Regarding further studies, refreshing specific radiotracer uptake showed potential benefits for identifying RAIR-DTC. The BRAF oncoprotein can activate ERK1/2 signal through the MAPK pathway, then thrombospondin-1 (TSP-1) is upregulated. TSP-1 positively regulates the expression of a cell membrane receptor, integrin, which in turn increases the level of ERK1/2 signal, forming positive feedback (Fig. 2).[68] Therefore, Integrin can be a potential imaging target for the estimation of tumor angiogenesis. Integrin $\alpha_v\beta_3$ has been proposed as a molecular marker for radiolabeled RGD peptides. Our previous study showed that all the targeted RAIR-DTC metastatic lesions were identified as positive on ^{99m}Tc-3PRGD2 SPECT images in 10 DTC Patients, which provided hopeful imaging for the localization and growth evaluation of RAIR-DTC lesions.[69] In one prospective research study, 81.1% of patients showed positive ^{99m}Tc -3PRGD2 uptake by SPECT/CT in 37 DTC patients who had negative ^{131}I-WBS, but elevated Tg levels. The sensitivity and positive predictive value (PPV) were respectively 96.6% and 93.3% and increased with growing serum Tg levels.[70] ^{68}Ga- DOTA-RGD PET imaging has higher sensitivity and resolution than ^{18}F-FDG PET, which is more beneficial to the quantitative analysis of the lesions.[71] Additionally, Chernaya et al. reported different expression levels of integrin receptors and their ligands in different DTC subtypes and could be affected by the BRAF mutation, which indicated that it is possible to more accurately select RGD imaging under individual clinical and pathological conditions.[72]

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.[73,74] 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.[75,76] It is compelling that ^{68}Ga-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 ^{68}Ga-PSMA PET, compared 23/32 positive lesions on ^{18}F-FDG PET/CT. Particularly, 21 (70%) of the 30 lesions showing PSMA expression were localized to the bones.[77] Verburg et al.[78] provided imaging evidence of PSMA expression in DTC using ^{68}Ga PSMA-HBED-CC PET/CT. Recently in a study by Lütje et al.,[79] 6 patients with ^{131}I-WBS-negative and ^{18}F-FDG-positive metastasized DTC received ^{68}Ga -labeled PSMA ligands and underwent PET/CT. The results demonstrated that ^{68}Ga-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.[80-83] Radiolabeled somatostatin analogs, such as ^{68}Ga-DOTA-octreotide and ^{68}Ga-DOTA-lanreotide
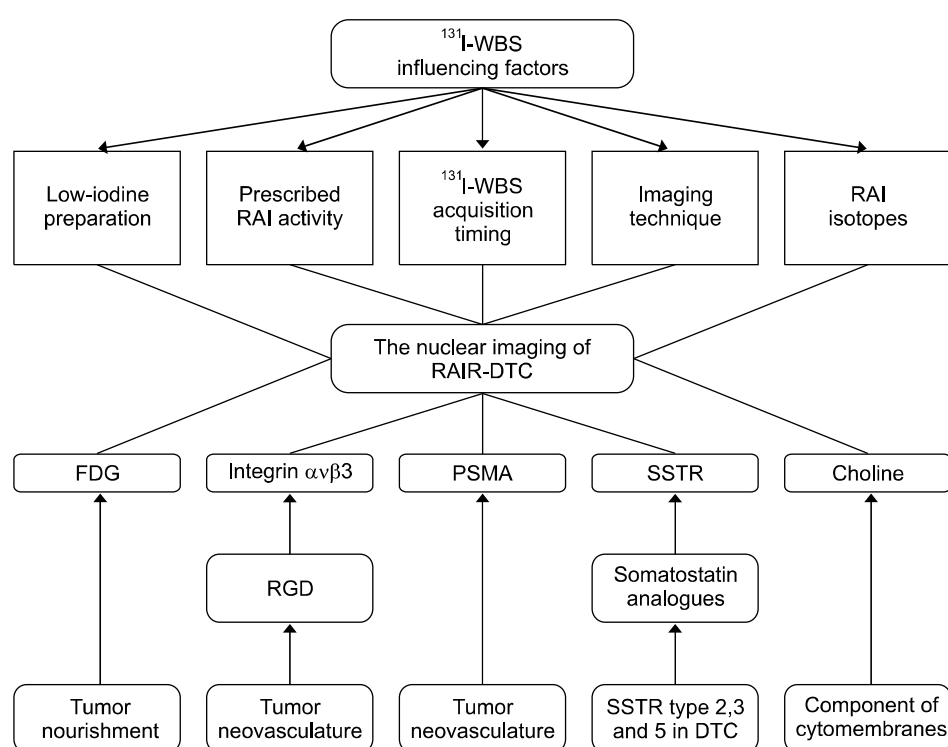
FIG. 3. The nuclear imaging for identifying RAIR-DTC. Negative ^{131}I-WBS act as fundamental indicator for RAIR-DTC identifying, while there still are plenty of influencing factors. Other nuclear imaging modalities could be complements with progressed researches. ^{131}I-WBS: ^{131}I-whole-body scan, 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.

(LAN), have drawn worldwide attention because of their superior pharmacokinetic characteristics and better spatial resolution of PET technology.[84-86] However, the diagnostic value of radiolabeled somatostatin analogues in RAIR-DTC remains conflicting. In a study by Traub-Weidinger et al.,[87] lesions showing aerobic glycolysis on ^{18}F-FDG PET were found in 24 (86%) of 28 patients with corresponding positive results with ^{68}Ga-DOTA-LAN in 35% and with ^{68}Ga-DOTA-Tyr^3-octreotide in 29%. Kundu et al.[88] also confirmed ^{68}Ga-DOTA-NOC PET-CT is inferior to ^{18}F-FDG PET-CT at the lesion-based level in DTC with raised Tg and negative ^{131}I-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 ^{18}F-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 ^{18}F-FDG PET/CT. Wu et al.[89] successfully identified thyroid carcinoma using ^{11}C-choline PET/CT in 4 patients with thyroid carcinomas, while the lesions in 3 of 4 patients were missed by previous ^{18}F-FDG PET. In a case report by Piccardo et al.,[90] it concluded that ^{18}F-choline PET/CT could detect lethal DTC recurrences, thus choline PET/CT may complement ^{18}F-FDG PET/CT in identifying DTC lesions. Given the absence of convincing evidence, the effectiveness of ^{11}C-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-^{131}I 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 ^{131}I 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

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CONFLICT OF INTEREST STATEMENT

None declared.

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