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Review Article

Appraisal of radioiodine refractory thyroid cancer: advances and challenges

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Abstract: The incidence of thyroid cancer ranks top among all endocrine cancers, which has increased worldwide. Some patients suffer from recurrent/residual diseases after primary treatment. The recurrent/residual disease often turns out to be radioiodine refractory and shows poor response to radioiodine therapy. A lot of studies have explored the precise appraisal of radioiodine refractory disease in recent years. The mechanism of iodine uptake and the definition of radioiodine refractory disease have been summarized and discussed. The advances in tumor characteristics, histologies, and mutant conditions have been explored for a more accurate method in the early-stage appraisal. We then offer a review of opinions in the evaluation of refractory disease during follow-up, including Tg doubling time, ^{18}F PET/CT, ^{131}I WBS, and others. The sensitivity and specificity have been compared between different diagnostic methods. Some novel methods may be introduced for more precise appraisal, such as a scoring system and RNA expression profiling. This review aims to provide physicians a broad insight into the appraisal of radioiodine refractory disease and to pave way for future study.

Keywords: Thyroid cancer, radioiodine, refractory disease, BRAF mutation, TERT promoter mutation, Tg doubling time, I-131 WBS, F-18 PET

Introduction

The incidence of thyroid cancer has increased to 5th place among all female cancers [1], partially due to the over-assessment of papillary thyroid cancers (PTCs) [2]. Though most cases can be cured with thyroid ablation and postoperative thyroid-stimulating hormone (TSH) suppression, around 20% of cases will develop regional recurrence or distant metastasis, two-thirds of which will then become radioactive iodine (RAI) refractory during follow-up [3]. Poor prognosis has been reported in these cases. The mean life span of RAI refractory disease is less than 5 years and the 10-year-survival rate is usually less than 10% [4].

The treatment of RAI refractory disease with targeted drugs has attracted many studies, while its diagnosis and evaluation have wide space for improvement. The current appraisal of RAI refractory disease is roughly divided into two stages [5]. The early stage is carried out shortly after thyroid ablation or fine needle aspiration biopsy (FNAB). The early appraisal is based on tumor characteristics and clinical presentation, including age, pathological subtype, locoregional invasion, and metastasis. Among these factors, BRAF and TERT promoter mutations are two promising predictors [6]. The presence of the two mutations is strongly indicative of loss of iodine uptake rate (IUR). Half of the wild-type tumors, however, are non-RAI avid as well, denoting a complicated mechanism underlying the dedifferentiation of thyroid cancer. An accurate perspective appraisal is thus in urgent need.

The late-stage is defined as the appraisal during follow-up. Thyroglobulin (Tg) doubling time in combination with ^{131}I whole body scanning (WBS) is deemed as the gold standard for the diagnosis of RAI refractory disease [7]. However, the ^{131}I WBS has met doubts for its fairly low resolution and contrast which might lead to false-positivity and false-negativity [8]. Micro

foci are hardly distinguishable among noise signals. On the other hand, Tg doubling time has a high sensitivity in predicting RAI refractory disease, but its specificity is unsatisfactory, with more than 60% of refractory cases showing negative results [9]. However, neither of them can be assessed in a short period. Many patients thus receive unnecessary RAI therapy for months or years until refractivity appears.

In the past 5 years, many studies have dedicated to improving the predicting efficacy for RAI refractory disease employing different prognostic factors. The aim of this review is thus to summarize the molecular mechanism underlying non-RAI avidity, the definition of RAI refractory disease, the association between clinical presentation and IUR, and finally to discuss the possibility of building up a scoring system with multiple predictors.

Mechanism of loss of radioiodine uptake

NIS

The sodium-iodide symporter (NIS) plays an essential role in the transmembrane transport of ^{131}I in the thyroid follicular epithelium. With the 'downhill' electrochemical gradient provided by the extra-membranal Na^+, NIS drives one I^- with two Na^+ inwards simultaneously [10]. RAI absorbed can release Beta ray for therapeutic approach and Gamma ray for diagnostic approach [11]. The expression of NIS will decrease during oncogenesis and dedifferentiation just as other thyroid-specific genes [12]. Several pathways have been reported to participate in the down-regulation, including MAPK and PI3K pathways [13]. Interestingly, the down-expression of NIS protein is not the only answer to refractivity. Over-expression of cytoplasmic NIS protein has been found in many papillary thyroid cancers [14]. The intracellular NIS has a non-pump, carcinogenetic role in thyroid cells via PTEN signaling [15]. In contrast, the NIS mRNA is more persuasive in predicting RAI refractory disease [13, 16].

TSH receptor

Thyroid-stimulating hormone (TSH) can bind to its receptor and promote the NIS expression via cAMP-dependent activation of the NIS upstream enhancer [17]. Interestingly, the TSH receptor is seldomly affected by dedifferentiation during tumorigenesis, which provides a theoretical foundation for postoperative TSH suppression therapy [18]. The decreased TSH receptor is robustly indicative of loss of RAI uptake and thus poor prognosis [19].

Age

Radioiodine uptake is influenced by many factors either physiological or pathological. Old age (over 55) is strongly indicative of poor iodine uptake [20]. IUR reduction correlates with increasing age in primary lesions as well as in metastases [21]. Adolescents and young adults are more likely to receive RAI for their unaffected RAI avidity. The phenomenon can be attributed to age-related reduced expression of NIS [22, 23].

BRAF mutation

Driver mutations are promising predictors in the evaluation of IUR. BRAF is the key protein in the MAPK signaling and $BRAF^{V600E}$ mutation has been confirmed to harm the transcription of the NIS gene [24, 25]. The classical mechanism of $BRAF^{V600E}$-induced down-regulation in NIS is via decreased paired box 8 (PAX8), which can thus inhibit the function of NIS upstream enhancer [13]. Some novel downstream signal pathways have been reported to modulate the NIS expression and posttranscriptional modification, including GPIT, TGF-β/SMAD3, and HDAC [26-28]. These novel signal pathways provide potential targets for drug development [29]. Clinical trials have demonstrated that the BRAF mutation in the primary lesion can act as an independent biomarker for non-RAI avid metastases, with a sensitivity of 84.2% and a specificity of 94.4% [30, 31]. BRAF mutation could also cooperate with ^{99m}Tc-MIBI scintigraph to improve the accuracy. Positive BRAF mutation in combination with negative ^{99m}Tc imaging is robustly associated with non-RAI avid loci [32]. The limited number of patients involved is a shortcoming in these studies.

TERT promoter mutation

TERT promoter mutation has been a hotspot since its first discovery in thyroid cancer [33]. TERT is a subunit of telomerase and the mutation of its promoter will lead to proliferating out of control. Although its underlying mechanism has not been elucidated, TERT promoter muta-

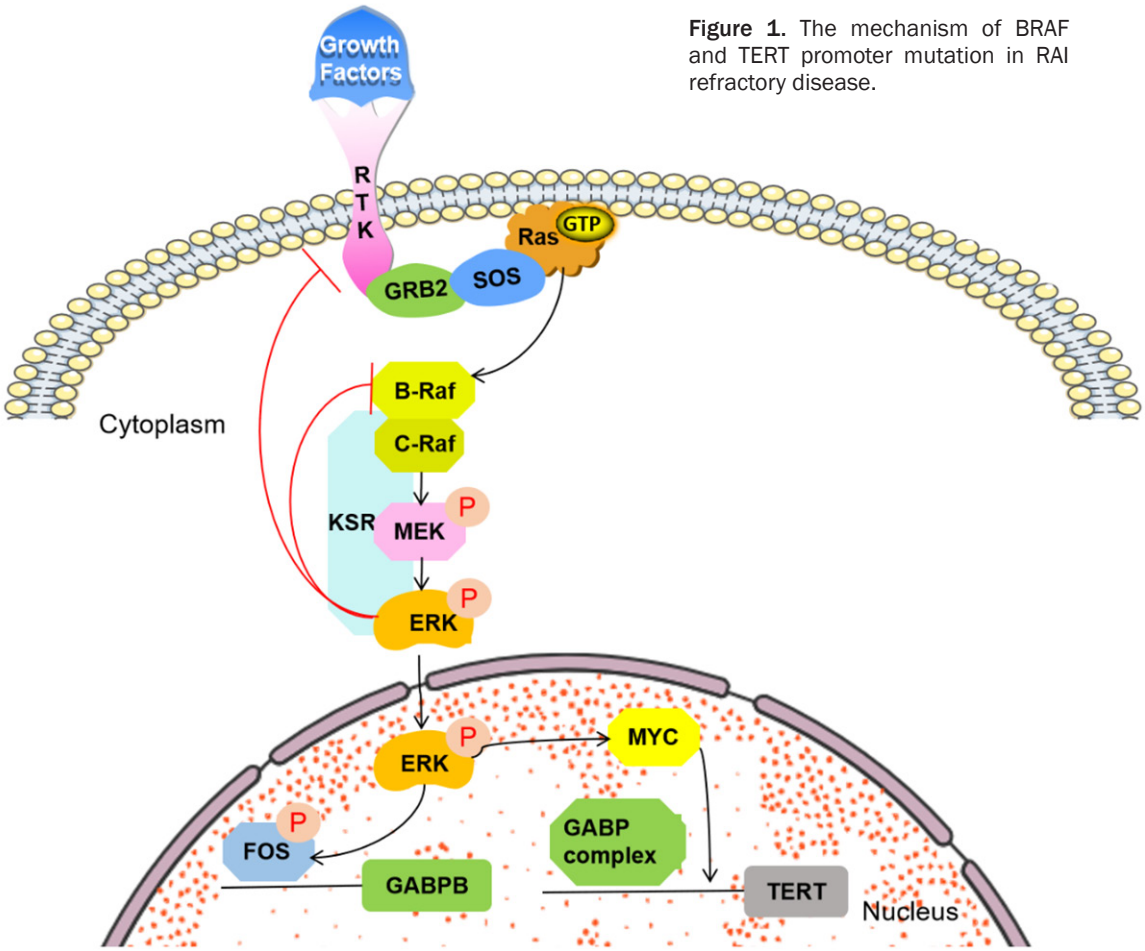

Figure 1. The mechanism of BRAF and TERT promoter mutation in RAI refractory disease.

tion has been confirmed to associated robustly with the loss of RAI avidity in recurrent thyroid cancers [34, 35]. TERT promoter mutation coexists with $BRAF^{V600E}$ mutation in many cases, which could be bridged in MAPK signaling [36] (**Figure 1**). If the two mutations are combined as one biomarker for RAI avidity, it could reach an astonishing sensitivity of 97.4% [6].

Besides, RAS, PTEN, and PI3K pathway mutations have been confirmed to inhibit the NIS expression [37-39]. However, none of them have been reported to be promising markers in clinical trials yet.

Definition of iodine refractory disease

According to the recent guidelines and studies, the radioiodine refractory disease can be classified into four groups based on clinical presentations: (I) the recurrent/metastatic lesion doesn't ever concentrate RAI since the first RAI treatment; (II) the recurrent/metastatic lesion gradually loses its ability to absorb RAI during treatment; (III) some lesions show RAI avid while others are not; and (IV) the recurrent/metastatic disease progresses even with substantial RAI uptake [40, 41]. The guidelines, however, are 'live' and some studies have discussed in different aspects (**Table 1**).

In fact, the former three criteria can be summarized as 'at least one lesion loses its capacity for RAI uptake at the first RAI treatment or during following treatment'. The dedifferentiation and heterogeneity of tumor cells account for definition II/III [42]. BRAF and TERT promoter mutations are more likely to be detected in non-RAI avid loci than avid ones [31, 43].

The last criterion is the so-called post-therapeutic definition and can be refined to the presence of incomplete response to RAI therapy of 600 mCi or more as cumulative activity [4]. Either elevated Tg values or persistent/newly-identified diseases on imaging are defined as

Table 1. Definition of radioiodine refractory disease

Main definitions
1 the recurrent/metastatic lesion doesn't ever concentrate RAI since the first RAI treatment
2 the recurrent/metastatic lesion gradually lose its ability to absorb RAI during treatment
3 some lesions show RAI avid while others are not
4 the recurrent/metastatic disease progresses even with substantial RAI uptake
Additional criteria
high uptake in ^{18}F PET/CT
aggressive histology
unresectable primary tumor
BRAF or TERT promoter mutation positive

incomplete response, which requires 1-2 years before a final diagnosis [44].

Besides, there are some additional criteria, including high uptake in ^{18}F PET/CT, aggressive histology, and unresectable primary tumor [45]. They tend to be suggestive of the loss of RAI, but the ultimate diagnosis still requires imaging of long-term follow-up.

The advances on evaluation methods

Tumor gross characteristics

Tumor characteristics are often suggestive rather than diagnostic. Large lump size and primary location in isthmus are two risk factors for RAI avidity in metastatic loci [46, 47]. Another adverse association has been found between extrathyroidal extension and RAI uptake in both pre- and post-surgical patients [48, 49]. The most suggestive predictor, however, is metastasis [50]. In two-thirds of cases, metastases are associated with radioiodine refractory disease. The most affected organs are central cervical lymph nodes, lung, and bones. But no matter to which organ the tumor cells spread, the IUR decreases in the process of metastasis due to further dedifferentiation [21, 51, 52]. As the tumor progresses, new metastatic sites are even less RAI-avid than primary ones [53], leaving patients with significantly shorter disease-specific survival. Interestingly, all the tumor characteristics above are co-results with poor RAI uptake to tumor aggressive behavior. Though not sensitive or specific enough to act as independent biomarkers, these characteristics are easily available. If a thyroid cancer patient is at old age or has cervical lymphadenopathy, the physician is expected to perform a further test before radioiodine irradiation.

Histology

Fine needle aspiration biopsy has facilitated the preoperative pathological stratification. It enables histological evaluation with minimal invasion. Thyroid cancer is categorized into four groups according to the microscopic appearance: papillary (PTC), follicular (FTC), medullary (MTC), and anaplastic (ATC). It has been widely recognized that MTC and ATC are closely related to radioiodine refractory disease [54, 55]. A current study has shown that FTC tends to respond better to RAI therapy in comparison with classical PTC and follicular variant of PTC [20]. The difference is even more significant in metastases. Age seems to have little impact on the iodine uptake in FTC, indicating the need to apply RAI in such patients. Despite a high tendency for vascular invasion and bone metastasis, FTC tumor cells are more conservative in their iodine uptake. One hypothesis emphasized $NRAS^{Q61D/R}$ and PAX8/PPARγ mutations, which are often the driver mutations for FTC, have less effect on the expression of NIS [56].

Tg and its doubling time

Tg used to be a powerful predictive factor for the postoperative appraisal (**Table 2**). Elevated Tg level several weeks after thyroid ablation was seen as a precarious signal of metastasis or remnant cancer tissue [57, 58]. Tg values >1 ng/ml without stimulation or Tg values >10 ng/ml with TSH-stimulation is defined as biochemical incomplete response [40]. Patients with biochemical incomplete response tend to have a better prognosis compared to those with structural incomplete response. A recent study, however, showed that Tg is not a stable and accurate predictor for RAI avidity because its post-

Table 2. Summary and comparison of several factors in predicting non RAI avidity

Author & Published year	Study type	Predictor	Tumor phenotype	N*	Sensitivity (%)	Specificity (%)	Statistic test
de la Fouchardiere, 2018	cohort	TERT promoter mutation	PDTC	63	70.8	66.7	P=0.004
Yang, 2017	cohort	TERT promoter mutation	DTC	66	100	64.7	P<0.001
Yang, 2014	cohort	$BRAF^{V600E}$ mutation	PTC	73	84.2	94.4	P<0.001
Liu, 2020	cohort	combination of BRAF and TERT mutations	PTC	164	97.4	N/A	P<0.001
Campenni, 2018	cohort	combination of BRAF and ^{99m}Tc-MIBI	PTC	15	5/5***	N/A	N/A
Castro, 2001	cohort	poor NIS expression	DTC	60	58.8	86.0	P=0.004
Min, 2001	cohort	poor NIS expression	DTC	40	100	50	N/A
Kelders, 2014	cohort	positve Tg doubling time	DTC	65	8/9***	N/A	N/A
Ozdemir, 2016	cohort	^{99m}Tc pertechnetate scintigraphy	DTC	717	72.2	70.5	P<0.001
Jung, 2015	cohort	^{99m}Tc pertechnetate scintigraphy	DTC	168	100	42.6	N/A
Santhanam, 2017	systematic review	^{124}I PET/CT	DTC	141	94	49	P<0.01
Liu, 2018	cohort	^{18}F-FDG PET/CT**	DTC	81	93.5	23.9	P=0.002
Zhu, 2019	cohort	^{18}F-FDG PET/CT	DTC	83	53.8	80.7	P<0.001

N/A: not available. *: number of patients involved in statistical analysis. **: The SUVmax of 4.0 was defined as a cut-off value. ***: insufficient sample for sensitivity.

surgical range varies widely [59]. The ablation approach and anti-Tg contribute to the variation to some degree [60]. But Tg doubling time proves to be a promising predictive tool [9]. Kelders et al found that the positive Tg doubling time is associated with ^{18}F-FDG-positive, ^{131}I-negative metastases whilst patients with negative Tg doubling time have a good chance of finding ^{131}I positive lesions [61]. Tg doubling time can thus be used as a precursor of ^{18}F FDG PET/CT and ^{131}I whole body scanning.

Nuclear imaging

Nuclear imaging has played an important role in the appraisal of RAI avidity of metastases and the diagnosis of thyroid recurrent disease. ^{123}I, ^{124}I, ^{99m}Tc pertechnetate, ^{18}F-fludeoxyglucose PET/CT have been used as imaging agents before RAI therapy.

Prognostic ^{131}I whole body scan: Prognostic ^{131}I WBS is regarded as the gold standard in assessing RAI avidity of metastases. Three criteria for RAI refractory disease are directly based on ^{131}I WBS. This common sense, however, has met challenges. Kang et al argued that there are disagreements between the results of prognostic ^{131}I WBS and patients' response to RAI therapy [62]. They also declared that FDG PET/CT is a better tool in predicting RAI therapy response and patients' prognosis. Low resolution and contrast of prognostic RAI WBS lead to a fairly high false-positivity and false-negativity [8]. The situation could be solved by either improving its resolution or introducing new pattern analysis techniques. A Korean group has adopted the pattern recognition technique and found that star-shaped intense uptake of RAI on WBS represents a good response to RAI treatment [63].

^{18}F-FDG PET/CT: ^{18}F-FDG PET/CT has become an accurate and versatile imaging method since its first adoption in thyroid cancer [64]. Not only can it examine the RAI uptake capacity of metastases, but tell useful information on prognosis. ^{18}F-FDG PET/CT combined with ^{131}I WBS has been recognized as an excellent standard in scanning distant metastases and examining their RAI avidity [65, 66]. Aggressive phenotypes tend to lose their tissue-specificity while they consume more sugar. ^{18}F-FDG positive and ^{131}I negative foci usually indicate the metastatic site with aggressive phenotypes, low NIS expression, poor response to RAI therapy, and thus gloomy prognosis. In fact, ^{18}F-FDG PET/CT alone can roughly tell the same thing due to its high negative correlation with the ^{131}I therapy response rate [62]. Some studies have tried to create a cut-off value of ^{18}F-FDG maximum standard uptake value (SUVmax), ranging from 4.0 to 5.85 [49, 67]. The agreement on a specific value has not been met, partly due to the variation of patient characteristics in different studies.

Other than iodine uptake, ^{18}F-FDG PET/CT can predict other characteristics of metastases, including tumor size and aggressive phenotypes [45]. Gaertner et al illustrated that ^{18}F-FDG PET/CT is even more predictive in long time survival than in RAI uptake [7]. Several groups were devoted to improving its predictive

ability. Manohar et al combined FDG PET with Tg doubling time to gain more accurate results for prognosis [68]. Ciappuccini et al improved the ability to detect recurrent disease by applying an additional head and neck PET [69]. The head and neck PET has an advantage of high resolution without increasing the scanning time significantly. Another group has examined ^{18}F-AIF-NOTA-PRGD2 as a substitute for ^{18}F-FDG in scanning but its results were inferior to the latter ones [70]. The relationship between appearance in ^{18}F PET and other clinical characteristics has become a hotspot.

^{99m}Tc pertechnetate scintigraphy: ^{99m}Tc pertechnetate scintigraphy has been widely applied in the evaluation of thyroid dysfunction, including thyroid cancers, hyperthyroidism, and thyroiditis [71]. It can predict the presence of remnant thyroid cancer tissue before a RAI ablation [72]. Tsai et al have elucidated that ^{99m}Tc pertechnetate scintigraphy can serve as an alternative to low dose ^{131}I scanning in post thyroidectomy patients [73]. Several groups have compared ^{99m}Tc pertechnetate scintigraphy with ^{131}I WBS in detecting remnant thyroid tissues and metastases before RAI therapy [74, 75]. Its sensitivity and specificity reach up to 72.2% and 70.5%, respectively. As mentioned above, more accurate results were obtained when ^{99m}Tc MIBI scintigraphy and BRAF^{V600E} mutation were combined [32].

Nuclear imaging with other isotopes of iodine: ^{123}I and ^{124}I are two isotopes of ^{131}I, both of which have the potentials to become alternative with less adverse effects in examining iodine uptake capacity. Their prognostic equivalence has been tested. ^{124}I have been confirmed to be a substitute for predicting the following ^{131}I therapy activities [76, 77]. Pettinato et al have demonstrated that a negative ^{124}I scan indicates poor RAI uptake, the oncoming useless RAI therapy can hence be avoided [78]. However, another study carried out by Khorjekar et al came to exactly the opposite, declaring the negative results of ^{124}I can not predict non-RAI avid metastases [79]. The disagreement may be explained by the levels of Tg in separate studies. Furthermore, ^{124}I scanning can also identify new lesions that are negative in ^{131}I scanning [80].

The introduction of ^{123}I in thyroid cancer is long before ^{124}I [81, 82]. Recently, Villani et al have proved that the combined use of recombinant human TSH and ^{123}I WBS as an accurate tool in evaluating RAI avidity and staging of diseases, which facilitates the oncoming therapeutic plan [83].

Novel appraisal approaches

microRNAs: Several microRNAs have been demonstrated to influence and predict the NIS expression and iodine uptake (**Table 3**). Among them, miR-122, and miR-375 are verified to be up-regulator in the NIS expression [84], while miR-146a, miR-146b, miR-339-5p, and miR-106a works oppositely [85-89]. Those down-regulators can directly bind to the 3' untranslated region of NIS and thus inhibit its expression. Some miRs may undergo somatic mutations during tumorigenesis, but significant difference needs further studies with sufficient sample to verify. Those previous studies suggest miRs can be promising predictors.

Circulating biomarkers in serum: Qiu et al verified that the count of circulating thyroid cells is negatively correlated with IUR and prognosis [90, 91]. Circulating thyroid cell count ≥5 is a predictor for distant metastasis and count >6 indicates a poor response to ^{131}I therapy with 73.7% sensitivity and 69.6% specificity. This group further studied the association between non-^{131}I avid metastases and long noncoding RNAs (lncRNAs) [92]. Four lncRNAs (ENST00000462717, ENST00000415582, TCON5_00024700, and NR_028494) were discovered to correlate negatively with RAI uptake in lung metastases with sensitivity and specificity of approximately 85%, indicating they can act as promising biomarkers for ^{131}I avidity in distant metastases.

Ultrasound: Ultrasound is an important tool in the screening, diagnosis, and follow-up of thyroid cancer. Several groups combined ultrasound with Tg to detect recurrent/residual disease with higher sensitivity [93]. The detectable serum Tg level is essential for recurrent PTC identification with ultrasound. Gao et al found that large lymph node size, multiple lesions, and less hyperechogenic punctuations under ultrasound can act as markers for cervical RAI refractory lesions [94]. Post-PET ultrasound was also found to improve the specificity of ^{18}F FDG PET/CT in detecting recurrent disease [95].

Table 3. Summary of microRNAs involved in the regulation of NIS expression and iodine uptake

Author & Published year	microRNAs	Mechanism	Change in thyroid cancer cells	Tumor phenotype	Material
Kotlarek, 2018	miR-146a	directly bind to and inhibit NIS	↑	fvPTC	Human cancer cells
Lakshmanan, 2015	miR-339-5p	directly bind to the 3'UTR of hNIS	↑	PTC	cell lines HEK293
Li, 2015	miR-146b	dysregulate the NIS-3'UTR activity	↑	FTC	cell line FTC-133
Qiu, 2015	miR-1249, miR-106a, miR-503, miR-34c-5p, miR-1281	N/A	↑	PTC	Human cancer cells
	miR-1915, miR-2861, miR-3196, miR-500, miR-572, miR-33b, miR-554, miR-18a		↓		
Reddi, 2013	miR-122 and miR-375	inactive AKT pathway	↓	FTC and ATC	cell lines BHT-101, FRO, C-643, KTC-2 and KTC-3*; mouse model Fox1$^{nu/nu}$
Riesco-Eizaguirre, 2015	miR-146b	bind to the 3'UTR of PAX8 and NIS	↑	PTC	Human cancer cells
Shen, 2016	miR-106a	directly target RARB 3'UTR	↑	PTC	Human cancer cells
Wachter, 2018	miR-146b	N/A	↑	PDTC and ATC	Human cancer cells

Abbreviation: PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; PDTC, poorly differentiated thyroid cancer; ATC, anaplastic thyroid cancer; fvPTC: follicular variant of papillary thyroid cancer; NIS: the sodium-iodide symporter; UTR: untranslated region; miR: microRNA; RARB: retinoic acid receptor beta; N/A, not available. *: The change of miR-122 and miR-375 could merely be detected in cell line BHT-101.

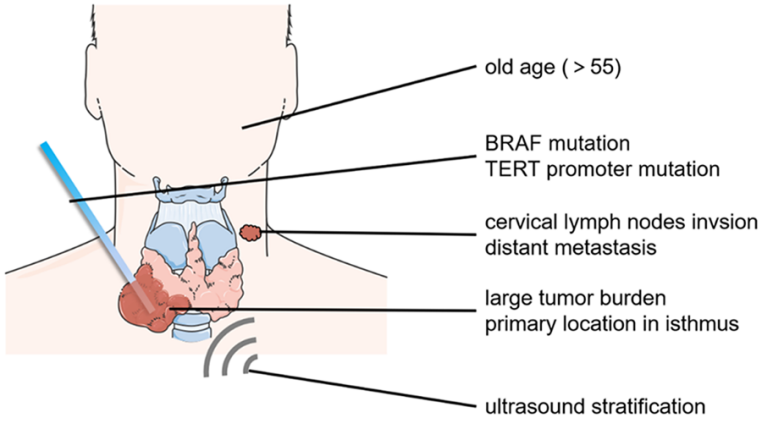

Figure 2. The possible biomarkers in thyroid cancer for a scoring system.

Other methods: Jung et al employed apoptosis imaging in predicting the NIS expression and ^{131}I uptake in thyroid tumor cell lines and rat models [96, 97]. They found that increased apoptosis is associated with high NIS expression and iodine uptake. Another group reported that autophagy activity is closely associated with NIS expression on the cell membrane and thus the response to RAI therapy [98]. Barbolosi et al created a mathematical model to predict RAI response in metastases [99]. The model was constructed based on several parameters, including tumor doubling time, the concentration of thyroglobulin produced by one tumor cell, the elimination rate of thyroglobulin from blood, etc. Tumor doubling time is the most informative parameters among them. And yet these findings have a long way from bench to bed.

Future perspectives

The precise prediction of iodine refractory disease has been a challenging problem. Though the discovery of BRAF and TERT promoter mutations have facilitated early-stage appraisal, the sensitivity and specificity have not met the clinical demand. Single biomarker seems incapable of telling prognosis with precision. A risk stratification scoring system may be introduced to solve the problem, which is based on tumor gross characteristics, pathological phenotypes, and mutant conditions (**Figure 2**). Some scoring system has been adapted in the appraisal of breast recurrent disease or survival rate, which shows good efficacy [100, 101]. Besides, RNA profiling may act as a promising biomarker in the appraisal of IUR, including miRNAs and lncRNAs [102, 103]. The DECISION trial now is exploring these predictors [104].

Follow up on time is essential in the late-stage appraisal (**Figure 3**). Now that Tg doubling time has been confirmed to be a stable factor, it may replace the elevated Tg as an easy-operative method in the evaluation of recurrent/remnant disease [61]. On the other hand, nuclear imaging needs to improve its resolution and eliminate its adverse effect. The biochemical equivalence of different iodine isotopes needs more studies to prove. The adaption of ^{18}F FDG PET/CT is a break-through in thyroid cancer. The relationship between ^{18}F PET/CT and tumor characteristics is a large field to explore.

Final remarks

It is of significant value for physicians to evaluate the patients' RAI avidity before RAI therapy. Several methods have been discussed and compared. Age and gross characteristics of tumors are easily available so that physicians can make preliminary judgments. More accurate judgments are based on laboratory and imaging tests. BRAF^{V600E} and TERT promoter mutations can be detected together on post-surgical pathological examination, which have a high sensitivity and specificity. Serum Tg plays a role in post-ablative follow-up, and its doubling time has a high correlation with recurrent diseases with non RAI-avid metastases. Nuclear imaging is more accurate in the prediction of RAI avidity. ^{18}F FDG PET/CT is versatile in thyroid cancer evaluation. Other nuclear imaging, including ^{99m}Tc pertechnetate scintigraphy and WBS with iodine isotopes, can also assess iodine uptake capacity with great accuracy.

A more precise appraisal approach is in need. The combination of several methods may lead to a more accurate diagnosis. How to combine these methods, however, has become a challenging problem. RNA expression profiling and scoring system may be introduced to solve the problem.

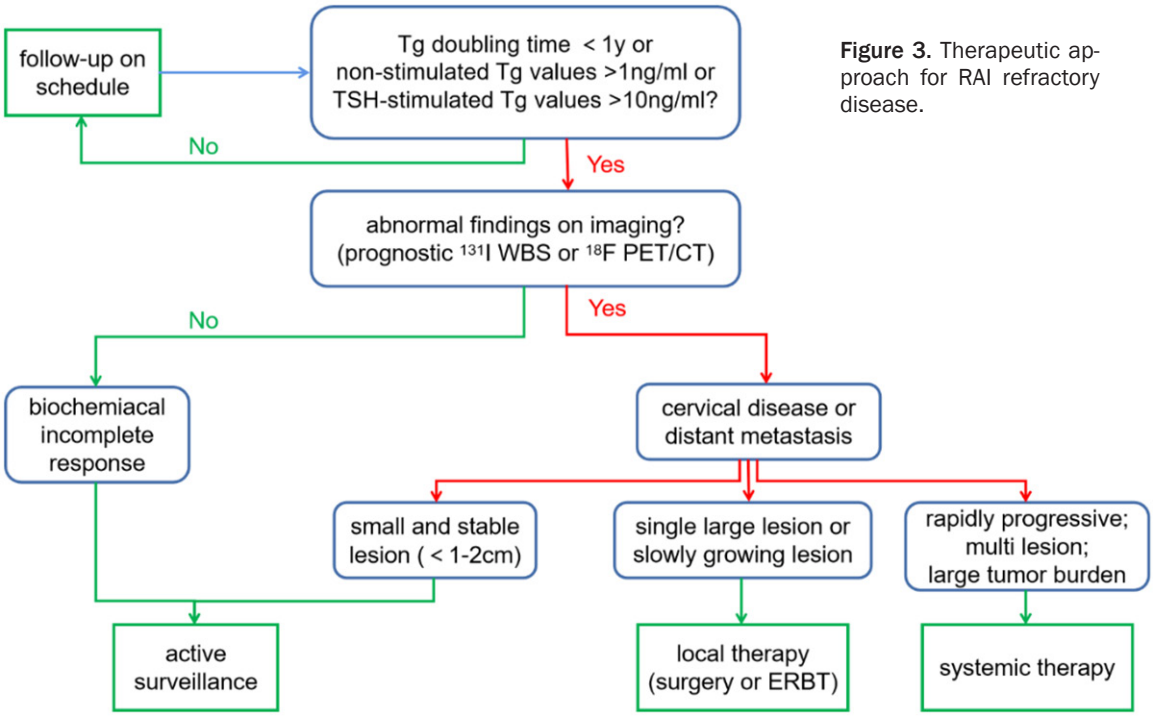

Figure 3. Therapeutic approach for RAI refractory disease.

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Disclosure of conflict of interest

None.

Abbreviations

ATC, anaplastic thyroid cancer; BRAF, B-raf oncogene; CT, computed tomography; FDG, fludeoxyglucose; FNAB, fine needle aspiration biopsy; FTC, follicular thyroid cancer; GPIT, ribosomal glycosylphosphatidylinositol transamidase; HDAC, histone deacetylase; IUR, I uptake rate; lncRNA, long noncoding RNA; MAPK, mitogen-activated protein kinase; MIBI, myocardial perfusion imaging test; miR, microRNA; MTC, medullary thyroid cancer; NIS, the sodium-iodide symporter; PAX8, paired box 8; PET, positron emission tomography; PI3K, Phosphoinositide 3-kinase; PTC, papillary thyroid caner; PTEN, phosphatase and tensin homolog; RAI, radioactive iodine; RAS, rat sarcoma; SUVmax, maximum standard uptake value; TERT, telomerase reverse transcriptase; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; WBS, whole body scanning.

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