



Chinese management guidelines for radioactive iodine-refractory differentiated thyroid cancer (2025 edition)

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Abstract

Purpose Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) has become a challenge in clinical practice, particularly in China with a high incidence and undesirable survival outcome. Since the publication of first China consensus on the diagnosis and treatment of RAIR-DTC in 2019, significant and rapid advances have occurred in the field both in China and internationally. This guideline aims to inform Chinese clinicians, researchers, patients, and health policy makers on the latest evidence and recommendations, to further standardize the clinical diagnosis and treatment of RAIR-DTC.

Methods The structured clinical questions addressed in this guideline were derived from clinical diagnostic and treatment processes, with references to study, prior guidelines, expert consensus, and systematic reviews, etc. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used for quantitative and qualitative evaluation of the evidence. The editorial process was completely independent of the guideline development group.

Results The guideline addressed 26 clinical questions and formed 35 recommendations. In this guideline, the definition criteria for RAIR-DTC was optimized, prediction and identification was based on evidence including molecular testing, dynamic biochemical changes, and multimodal imaging. Comprehensive pre-treatment clinical evaluation was emphasized and tailored for individualized decision-making. The combination of systematic therapy and surgery, and the redifferentiation followed by RAI therapy were also reviewed and updated. Molecular imaging plays a unique role in the pre-assessing and therapeutic response evaluation for RAIR-DTC.

Conclusions We have updated and developed evidence-based recommendations with the aim of providing scientific, rigorous, and comprehensive guidance for the clinical diagnosis and treatment of RAIR-DTC patients in China. We hope to share our guideline with colleagues out of China, with the expectation of further comments and suggestions.

Keywords Radioactive iodine-refractory differentiated thyroid cancer (RAIR-DTC) · Guideline · Committee Chinese Society of Clinical Oncology (CSCO) · Chinese Society of Nuclear Medicine (CSNM) · Thyroid oncology committee of China Anti-Cancer Association (CACA)

Preface

Up to two-thirds of patients with locally advanced and metastatic differentiated thyroid cancer (DTC) eventually develop radioactive iodine (RAI)-refractory or resistant DTC (RAIR-DTC), which usually progress rapidly with poor prognosis. Heterogenous and imbalanced management of such cases are noticed in China, which is considered to

be the main reason for the relatively low survival in China compared with US.

In 2019, the Thyroid Cancer Expert Committee of the Chinese Society of Clinical Oncology (CSCO) and three other societies jointly issued the first consensus on the diagnosis and treatment of RAIR-DTC, which has promoted the standardized management of RAIR-DTC across China [1]. Over the last 5 years, the advancement of molecular biological techniques has gradually promoted the molecular-based

management of RAIR-DTC, while new challenges are being encountered, such as timing or the priority of tyrosine kinase inhibitor (TKI), and considerations for TKI resistance. In response to these advancements and challenges, based on emerging research evidence, experts from various societies including the CSCO Nuclear Medicine Expert Committee and other six societies were gathered to formulate guidelines for the diagnosis and treatment of RAIR-DTC. The recommendations in these guidelines were developed using the Grading of Recommendations Assessment, Development, and Evaluation approach, providing a grading of recommendation strength and evidence quality (see Supplementary Table 1). Three aspects with a total of 26 clinical questions were addressed with 35 recommendations formed to further cover the whole management of RAIR-DTC.

It should be noted that due to space constraints of EJNM, this article provides a concise English synopsis of the Chinese 2024 RAIR-DTC Management Guideline (full text published domestically). The abridged version is intended to serve as an accessible reference for international readers. Key supplementary materials (e.g. evidence grading) are provided as attachments for transparency.

Definition of RAIR-DTC

Question 1. How to define RAIR-DTC?

Since the early 21st century, the term “RAIR-DTC” has emerged and defined in different clinical trials [2–6]. Under the premise of excluding thyroid remnant, inadequate thyroid-stimulating hormone (TSH) stimulation, and excessive levels of stable iodine in the body, which may diminish the ability of ^{131}I -whole body scan (^{131}I -WBS) to reflect the RAI-avidity of lesions, RAIR-DTC can be simplified by either of the followings (1) all known DTC lesions demonstrate non-RAI-avidity and (2) despite RAI-avidity in some or all lesions, disease progression occurs within 1 year after RAI therapy (RAIT). Disease progression can be characterized by the presence of at least one of the followings: increasing levels of thyroglobulin (Tg) or thyroglobulin antibody (TgAb), enlargement of the persistent lesion or emergence of new lesions, worsening of prior disease-related symptoms, appearance of new disease-related symptoms, or disease-related death.

Recommendation 1 RAIR-DTC involves structural lesions that do not exhibit RAI-avidity on ^{131}I -WBS or progress

within 1 year despite RAI-avidity. (**strong recommendation, high-quality evidence**).

Prediction and identification of RAIR-DTC

Question 2. How to predict RAIR-DTC through molecular testing?

To date, no specific histopathological features have been identified for RAIR-DTC, and its classification relies on a comprehensive assessment of tumor origin, morphology, differentiation, and biological behaviour.

The 5th edition of the WHO Classification of Thyroid Tumors integrated morphological, mutational, and transcriptomic features, and proposed *RAS*-like and *BRAF*-like tumors [7]. *BRAF*-like tumors are more prone to dedifferentiation and thus, they are more strongly associated with RAIR [8].

Differentiated high-grade thyroid carcinoma (DHGTC) and poorly differentiated DTC (PDTC) account for approximately 50% of RAIR-DTCs [9]. They typically evolve from DTC through a genetic multi-step process involving early driver gene variants such as *BRAF*, *RAS*, or gene fusions (often *RET* or *NTRK3*), followed by secondary mutations such as those in the *TERT* promoter, *TP53*, and *PIK3CA*, and other late molecular events [10]. Mutations in the *TERT* promoter, *PLEKHS1* promoter, and *TP53* or 9q deletion are linked to RAIR [7, 11].

Recommendation 2 Molecular testing is recommended for all DTCs, especially for DHGTC and PDTC, to guide the prediction of RAIR and subsequent treatment management (**strong recommendation, high-quality evidence**).

Question 3. How can RAIR-DTC be predicted through serological testing?

Serum Tg is an effective indicator for monitoring clinical outcomes in patients with distant metastatic DTC [12]. Studies have reported that, increasing levels of Tg after RAIT may indicated the possibility of progression to RAIR-DTC [13–15]. TgAb interferes with serum Tg measurement in vivo, and it should be tested simultaneously [16].

Recommendation 3 Insignificant decrease of Tg after RAIT may indicate the possibility of RAIR. (**weak recommendation, low-quality evidence**).

Question 4. The value of ultrasound, CT, and MRI in the diagnosis of RAIR-DTC

Though lack of specificity, ultrasound, CT, and MRI are commonly used to evaluate the progression and therapeutic response of local or distant lesions by reflecting the size, number, extent and exact relationships with adjacent vital organs. It is particularly useful to determine those RAIR-DTC who presented RAI uptake but with structurally progression [17–21].

Ultrasound is the mainstay for assessing lesions in the thyroid bed and cervical lymph nodes, while it is highly linked with the experience of the operator [18, 19]. It could be complemented by CT or MRI through reflecting extensive lymph node involvement and extra-thyroidal invasion [20, 21]. Chest CT is the preferred imaging method for assessing pulmonary metastases, whereas MRI has a unique advantage in assessing central nervous system metastases in RAIR-DTC. Both CT and MRI can be used to evaluate metastases in the mediastinum, abdomen, and bones.

Recommendation 4 Ultrasound, CT, and MRI are commonly used for assessing the progression and therapeutic response of local or distant lesions, and are helpful in determining those RAIR-DTC who presented RAI-avidity but with structural progression (**strong recommendation, high-quality evidence**).

Question 5. The value of nuclear medicine molecular imaging in diagnosing RAIR-DTC

^{131}I -WBS SPECT/CT is crucial for pre- and post-RAIT evaluation, accurate disease restaging, clinical decision-making, and prognosis prediction for DTC. Poorer differentiation is associated with greater aggressiveness, lower RAI-avidity and higher anaerobic glycolysis, resulting in an inverse relationship between RAI-avidity and ^{18}F -FDG affinity in DTC lesions, which is called the “flip-flop” phenomenon [22]. For patients with negative ^{131}I -WBS [absence of ^{131}I uptake indicating distant metastatic lesions observed in either diagnostic WBS (DxWBS) after administration of 3–5 mCi within 48 h or post-therapy WBS (RxWBS) after 5–7 days of RAI therapeutic dose of 100–200 mCi] and a stimulated Tg level > 10 ng/mL, ^{18}F -FDG PET/CT could be considered for identifying RAIR-DTC lesions, and its combination with ^{131}I -WBS SPECT/CT provides a comprehensive evaluation of the overall tumor burden [23].

In addition to ^{18}F -FDG PET/CT, emerging molecular radiotracers are increasingly employed for detecting RAIR-DTC. In cases with negative ^{18}F -FDG PET/CT results, integrin receptor-targeted RGD PET and prostate-specific membrane antigen (PSMA)-targeted ^{68}Ga -PSMA PET and fibroblast activation protein (FAP) inhibitors imaging may be useful for detecting RAIR-DTC lesions [24–27], and they might provide additional guidance for subsequent PSMA-targeted radionuclide therapy (e.g., ^{177}Lu -PSMA) [28]. Additionally, recent studies suggested that radioisotope-labelled somatostatin receptor (SSTR) analogues such as ^{68}Ga -DOTATATE or -DOTANOC and a novel amino acid transporter-targeted probe ^{18}F -FGln PET reflecting glutamine metabolism might also hold promise as complementary imaging modalities when ^{18}F -FDG imaging is negative [29–31].

Recommendation 5 ^{131}I -WBS SPECT/CT is useful for identifying RAIR-DTC in those with disease progression despite RAI-avidity (**strong recommendation, high-quality evidence**).

Recommendation 6 ^{18}F -FDG PET/CT is effective for assessing glucose metabolism in non-RAI-avid DTC lesions and indicates the likelihood of benefiting from RAIT. (**strong recommendation, high-quality evidence**).

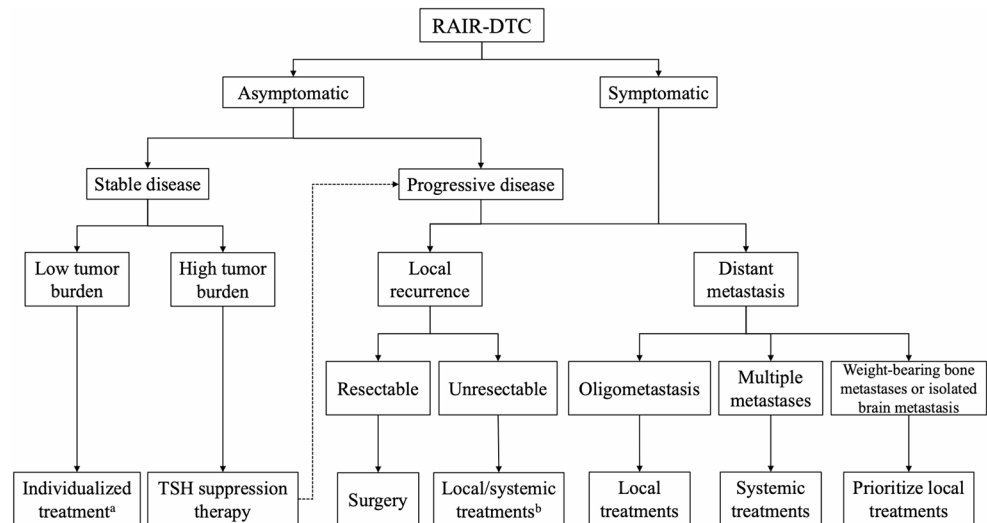
Comprehensive management of RAIR-DTC

Question 6. Pre-treatment clinical evaluation for RAIR-DTC

Patients with RAIR-DTC have various disease courses; therefore, a regularly comprehensive evaluation is needed to permit individualized treatment decisions (Fig. 1), which guarantees timely and effective medical care for patients with symptomatic or progressive disease and avoids over-treatment for those with stable or slowly progressive disease.

The clinical evaluation mainly includes several factors as follows: (1) Tumor burden. For patients with a low tumor burden (diameter ≤ 1 cm) and stable or slowly progressive disease, active monitoring under TSH suppression or sub-suppression therapy (see *Question 7* in detail) is advisable. For patients with a high tumor burden (single lesion diameter > 1–2 cm or the sum of diameter of target lesions ≥ 4 cm [32]), individualized management based on comprehensive considerations is suggested. (2) Tumor progression rate. For patients without measurable lesions, the serum Tg doubling time (Tg-DT) can indirectly reflect the tumor progression pace, and a short Tg-DT (< 1 year) generally indicates a rapid tumor growth rate [33]. For those with measurable

Fig. 1 Algorithm for the clinical management of patients with RAI-R-DTC. ^a Local or systemic treatments can be considered if disease progression presents with associated symptoms, organ dysfunctions, or even life-threatening situations. ^b Other local treatments (such as external-beam radiation therapy, ablation, and particle implantation, etc.), systemic therapy followed by surgery, and systemic treatments



lesions, the tumor volume doubling time (TV-DT) can evaluate the progression rate from a three-dimensional perspective, and TV-DT < 1 year usually indicates poor prognosis [34]. Therefore, active treatment is suggested for patients with disease progression within 1 year [2, 35], while regular (every 3–12 months) follow-up can be adopted in those with stable disease [36]. (3) Location and quantity of metastatic lesions. For patients with fewer metastases or oligometastases concentrated in a single organ, corresponding local treatments can be applied based on the specific lesion location. For patients with multiple lesions or multiple organs involved that cannot be treated with local interventions, systemic treatments should be considered. For some special circumstances, such as metastases in weight-bearing bones or isolated brain metastasis, it is recommended to prioritize local treatments. (4) Accompanying symptoms. When accompanied by tumor-related symptoms, active systemic treatment is primarily suggested. If there is a high risk of local complications, then local treatments could be conducted first.

Recommendation 7 Comprehensive clinical evaluations should be regularly performed in patients with RAI-R-DTC, and individualized management should be developed based on patient-related and disease-related factors (**strong recommendation, high-quality evidence**).

Recommendation 8 The comprehensive evaluation of patients with RAI-R-DTC is generally conducted from both biochemical and imaging aspects, including the tumor burden, tumor progression rate, presence of metastatic lesions,

and presence of accompanying symptoms, etc. (**strong recommendation, high-quality evidence**).

Active monitoring during TSH suppressive therapy

Question 7. The indication for active monitoring under TSH suppressive therapy

Active monitoring under TSH suppressive therapy is commonly suitable for the following situations: asymptomatic unresectable metastatic disease; low tumor burden; stable or minimally progressive disease; low likelihood of developing rapidly progressive disease in a short term; and no adverse impact of the disease burden [3]. A retrospective study revealed that patients with non-RAI-avid pulmonary metastatic PTC had a median Tg change rate of 0.03 ng/mL/month during TSH suppressive therapy alone, and median progression-free survival (PFS) reached 54.4 months [37]. Meanwhile, some studies argued that excessive TSH suppression may not be necessary in improving outcomes in patients with high-risk DTC and could potentially increase cardiac and bone-related risks [38, 39]. Sub-suppressive TSH therapy (0.1 to 0.5 mIU/L) may be more appropriate in such case.

Recommendation 9 For patients with RAI-R-DTC whose disease is stable or minimally progressive, active monitoring

under TSH suppressive therapy is recommended (**strong recommendation, moderate-quality evidence**).

Question 8. Degree of TSH suppression and adjustment of the thyroid hormone dosage

In patients with RAIR-DTC, initial TSH suppression to below 0.1 mIU/L is recommended, particularly for those with residual RAI-avid lesions. However, treatment adjustment is allowed considering the potential adverse effects of TSH suppression [3, 40]. Furthermore, regular monitoring of TSH is recommended for patients receiving TKIs [41]. Potential mechanisms include TKI-induced diarrhea leading to poor absorption of thyroid hormones and inhibition of monocarboxylate transporter 8-mediated thyroid hormones uptake, thereby diminishing their suppressive effect on the pituitary gland [42, 43].

Recommendation 10 For patients with RAIR-DTC, TSH levels should be maintained below 0.1 mIU/L (**strong recommendation, high-quality evidence**).

Recommendation 11 Surveillance and close monitoring during TSH suppressive therapy are recommended for patients with RAIR-DTC, and timely adjustments of the thyroid hormone dosage are essential to maintain appropriate TSH levels (**strong recommendation, high-quality evidence**).

Local treatments

Question 9. Indication and major strategies of local treatment for RAIR-DTC

The indications of local treatment for recurrent or metastatic RAIR-DTC mainly include: (1) respiratory tract obstruction; (2) gastrointestinal obstruction or bleeding caused by recurrent or metastatic lesions; (3) central nervous system invasion or compression; (4) symptomatic bone metastases or asymptomatic metastases in weight-bearing bones; (5) solitary distant metastasis; and (6) other cases with clinically significant symptoms or invasion of vital sites that might cause a significant risk [44–47].

Local treatments include surgical resection, external irradiation, ablation, ^{125}I seed implantation, etc [48–51]. Surgical treatment should be prioritized. For recurrent lesions involving important structures (e.g., trachea, esophagus, common carotid artery), multi-disciplinary discussion and collaboration are recommended to ensure patient safety. For patients who refuse surgery and those who are not candidates for reoperation, other modalities can be considered.

These treatments can be applied alone or in combination depending on the individual's characteristics.

Recommendation 12 For solitary lesions, lesions with local symptoms, or lesions with potential risks of invading important adjacent organs and tissues, local treatments can be considered (**strong recommendation, moderate-quality evidence**).

Recommendation 13 The local treatment strategies for RAIR-DTC include surgical resection, external irradiation, ablation, etc. Surgical treatment should be prioritized for patients who are indicated for surgeries (**strong recommendation, moderate-quality evidence**).

Question 10. Surgical management of RAIR-DTC

When evaluating and deciding on surgical treatment for RAIR-DTC, two situations should be distinguished:

- 1) For patients with non-RAI-avid local or distant metastatic lesions identified on ^{131}I -WBS after initial RAIT, active surgery should be performed if surgical indications exist [52].
- 2) For patients who have received multiple comprehensive treatments, including repeated RAIT, the decision on whether to surgically resect recurrent/metastatic lesions, as well as the appropriate surgical approach, requires thorough evaluation and cautious decision-making, and multi-disciplinary discussion is usually necessitated. They should primarily aim to alleviate life-threatening conditions and prolong overall survival (OS). For patients with significant threatening lesions that cannot undergo immediate surgery, conversion therapy with targeted drugs is a potential strategy [53].

Recommendation 14 Surgery is one of the comprehensive treatment modalities for the local control of RAIR-DTC, necessitating multi-disciplinary, comprehensive evaluation and careful decision-making (**strong recommendation, moderate-quality evidence**).

Question 11. External-beam radiotherapy (EBRT) in RAIR-DTC

EBRT is a valuable treatment option for the local control of RAIR-DTC [48], and it is mainly recommended for patients with recurrent or metastatic lesions that cannot be surgically removed or those with macroscopic or microscopic residues post-resection. EBRT is also the preferred local treatment for patients with brain or bone metastasis, especially for those with local pain or compression [54, 55].

Precision radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) are usually preferred [56–58]. Proton or heavy ion radiotherapy may further improve the efficacy via the “Bragg phenomenon” [59]. Either conventional fractionated or hypofractionated radiotherapy can be adopted, but the latter has remarkable biological and economic advantages.

Recommendation 15 EBRT can improve the local control of RAIR-DTC lesions, and it is the preferred local treatment for patients with brain or bone metastasis (**strong recommendation, moderate-quality evidence**).

Question 12. Ablation for RAIR-DTC

Ablation is mainly indicated in the following situations: recurrent or metastatic RAIR-DTC that cannot be surgically resected [49]; invasion of critical structures such as the trachea, esophagus, blood vessels, and nerves [50]; and patients with poor general condition who cannot tolerate surgery (e.g., severe chronic comorbidities, intolerance of anesthesia).

When performing ablation for RAIR-DTC lesions, the following factors should be considered:

- 1) Either a fixed-electrode or moving-shot technique can be chosen depending on the size of the lesion [60].
- 2) For lesions adjacent to critical cervical structures, liquid isolation is required to improve safety [61].
- 3) Contrast-enhanced ultrasound (CEUS) should be performed immediately after ablation to measure the ablated volume [62].

Recommendation 16 For recurrent or metastatic RAIR-DTC lesions that invade critical structures and cannot be surgically resected, palliative ablation can be considered (**weak recommendation, moderate-quality evidence**).

Question 13. Radioactive ^{125}I seed implantation for RAIR-DTC

Radioactive ^{125}I seed implantation is usually performed through image-guided percutaneous puncture. According to limited research evidence, ^{125}I seed implantation can be used in patients with unresectable cervical lymph nodes or soft tissue metastatic RAIR-DTC [51] or those with symptomatic bone metastases [63].

Several steps are required to ensure the standardized performance of ^{125}I seed implantation for RAIR-DTC: (1) First, multi-disciplinary collaboration is required. The implantation procedure should be guided by ultrasound, CT, or MRI. (2) The plan should be made preoperatively, according to

the treatment planning system (TPS). (3) Finally, therapeutic dosimetry should be verified postoperatively [64].

Recommendation 17 For unresectable recurrent or metastatic RAIR-DTC lesions, especially for those who may not be amenable to surgical resection, external irradiation, ablation, radioactive ^{125}I seed implantation could be considered (**weak recommendation, low-quality evidence**).

Systemic therapies

Question 14. Indication and commonly used strategy for systemic therapy for RAIR-DTC

For patients with symptomatic or rapidly progressive RAIR-DTC with multi-organ involvement or those whose lesions cannot be salvaged by local treatment, systemic therapy is the commonly used approach [65]. TKIs are the standard first-line treatments for RAIR-DTC. However, in the second-line setting, there is no standard option for Chinese patients, although cabozantinib has received regulatory approval in other countries [66]. In this circumstance, agents of the same class that were not used in the first-line setting could be utilized according to current evidence [67]. Given their favorable efficacy and safety, specific *RET* or *TRK* inhibitors are primarily recommended for patients with *RET* or *TRK* fusion. For immunotherapy, the evidence is insufficient to support their use in RAIR-DTC excluding a minority of patients with a high tumor mutational burden (TMB-H) [68].

Recommendation 18 Systemic therapy is indicated for patients with symptomatic or rapidly progressive RAIR-DTC with multi-organ involvement or those whose lesions who cannot be salvaged by local treatment (**strong recommendation, moderate-quality evidence**).

- Monotherapy modalities.

- a) Chemotherapy.

Question 15. Indication and strategy for chemotherapy for RAIR-DTC

Chemotherapy is only recommended as a palliative method for patients who will not benefit from other treatments or clinical trials because of its limited efficacy in RAIR-DTC [69]. Adriamycin is the only chemotherapeutic agent approved by the US Food and Drug Administration. In recent years, nanoparticles loaded with adriamycin have been expected to improve the efficacy of chemotherapy by

increasing their selective accumulation and retention at the tumor site [70].

Recommendation 19 Chemotherapy is only recommended when other systemic therapies are not applicable (**weak recommendation, moderate-quality evidence**).

Targeted therapy

Question 16. Pre-treatment evaluation and timing of targeted therapy for RAIR-DTC

A comprehensive evaluation should be performed before initiating targeted therapy for patients with RAIR-DTC. The detailed contents are shown in Table 1.

The timing for initiating targeted therapy is still controversial because of the lack of evidence, as well as heterogeneity regarding the molecular mechanisms, clinical features, and natural course of RAIR-DTC [71]. Some studies found that factors such as age, the pathological type, the size of lung metastasis, the tumor location, the neutrophil-to-lymphocyte ratio, tumor-related symptoms, the baseline tumor burden, and TV-DT might be associated with the efficacy of targeted therapy, suggesting the importance of incorporating these factors into decision-making [32, 35, 72, 76–78]. Integration of these factors to establish a scoring system will be helpful to precisely determine the initiation of targeted therapy, but further studies are warranted [79].

Recommendation 20 Comprehensive evaluation should be performed for patients with RAIR-DTC before targeted therapy, including assessments of the general condition, comorbidities, symptoms and signs, tumor location and burden, and progression rate, etc. (**strong recommendation, low-quality evidence**).

Recommendation 21 Targeted therapy should be considered in patients with rapidly radiographic progressive

(within 1 year) disease. (**strong recommendation, moderate-quality evidence**).

Recommendation 22 Genetic testing can be considered to identify the presence of specific genetic mutations or fusions to guide the selection of targeted agents (**weak recommendation, moderate-quality evidence**).

Question 17. Clinical benefit of multi-targeted TKIs in treating RAIR-DTC

Multi-targeted TKIs play important roles in treating RAIR-DTC. The main clinical research results and National Medical Products Administration (NMPA) approval status of multi-targeted TKIs such as lenvatinib, anlotinib, and donafenib are illustrated in Table 2 [2, 66, 73, 74, 80–82]. It is worth noting that most of the TKIs did not exhibit benefit in improving the OS, except for apatinib [2, 73, 74, 80].

Question 18. Clinical benefit of specific targeted drugs in treating RAIR-DTC

The main clinical research results and approval status of clinically accessible specific targeted drugs are summarized in Table 3 [83–89]. These specific targeted drugs have exhibited better efficacy and a lower incidence of adverse effects, thereby emerging as new targeted treatment options for RAIR-DTC [83–89].

Question 19. Principles of selecting targeted therapy for RAIR-DTC

Multi-target TKIs have demonstrated clinical benefits in treating RAIR-DTC with definite efficacy and manageable safety profiles [2, 66, 72–74, 80–82]. However, since these findings are primarily based on placebo-controlled studies, there is still a lack of randomized controlled trials that directly compare the efficacy of different targeted agents. As a result, the recommended preference of different targeted

Table 1 Contents of the evaluation and considerations before initiating targeted therapy for RAIR-DTC

Contents of evaluation	Factors need to be considered before initiating targeted therapy
General condition	ECOG performance status, nutritional status, and life expectancy should be evaluated [2, 71–74]
Comorbidities	Comorbid serious diseases that may increase the risk of adverse reactions, or conditions affecting drug intake and absorption should be discussed by multidisciplinary team [2, 72–74]
Symptoms and signs	The decision of initiating targeted therapy should be made in accordance of the impact of tumor-related symptoms and disease progression [75]
Laboratory testing	Cardiovascular, hepatic and renal functions are assessed to determine organ impairment induced by disease and previous therapies
Imaging examination	Radiographic progression within 1year, especially diffuse and rapid disease progression as opposed to focal progression, is an indication to initiate targeted therapy
Molecular testing	Identify the presence of specific genetic mutations such as <i>BRAF</i> mutation to guide the combination use of targeted agents (<i>BRAF</i> selective inhibitor and <i>MEK</i> inhibitor) or fusions to guide the selection of targeted agents.

ECOG: Eastern Cooperative Oncology Group

Table 2 Main clinical research results and approval status of multi-targeted TKIs

Drug and its corresponding trial	Progressive disease before enrolment (months)	Prior TKI treatment	Targets	Median PFS (months)	ORR	NMPA approval
Sorafenib [2] DECISION	Yes (14)	No	VEGFR1-3、PDGFR-β、RAF、RET	10.8 vs. 5.8	12.2% vs. 0.5%	Yes
Lenvatinib [80]	Yes (13)	No	VEGFR1-3、FGFR1-4、PDGFR-α、RET、KIT	23.93 vs. 3.7	69.9% vs. 0.0%	Yes
Anlotinib [81] ALTER01032	Not mandatory	No	VEGFR2-3、PDGFR、FGFR、KIT	40.54 vs. 8.38	59.2% vs. 0.0%	Yes
Donafenib [74] DIRECTION	Yes (14)	18.8% in donafenib arm, 17.5% in placebo arm	VEGFR、FGFR、RAF	12.9 vs. 6.4	23.3% vs. 1.7%	Yes
Apatinib [73] REALITY	Yes (12)	10.9% in apatinib arm, 6.5% in placebo arm	VEGFR-2	22.2 vs. 4.5	54.3% vs. 2.2%	Yes
Surufatinib [82]	Yes (12)	11.5% had received other treatment in DTC cohort ^a	VEGFR、FGFR-1、CSF-1R	11.1	21.7%	Yes
Cabozantinib [66] COSMIC-311	Yes	All received prior TKIs including sorafenib and/or lenvatinib	MET、VEGFR1-3、ROS1、RET、AXL、NTRK、KIT	Not reached vs. 1.9	15% vs. 0.0%	Yes

a: Patients had received treatments other than surgery, external radiation, and chemotherapy, but the specific use of TKIs was not clarified
DTC: differentiated thyroid cancer; NMPA: National Medical Products Administration; ORR: objective response rate; PFS: progression-free survival; TKI: tyrosine kinase inhibitor

Table 3 Main clinical research results and approval status of specific targeted drugs

Drug	Target	Corresponding clinical trial	Median PFS or PFS rate	ORR	NMPA approval
Pralsetinib [83]	<i>RET</i>	Global multi-center, open-label, phase I/II clinical trial	25.8 months	90.9%	Yes
Selpercatinib [84]	<i>RET</i>	Phase I/II clinical trial	1-year PFS rate: 64%	79%	Yes
Dabrafenib [85]	<i>BRAF</i>	Multi-center, randomized, open-label, phase II clinical trial	10.7 months	42%	Yes
Vemurafenib [86]	<i>BRAF</i> ^{V600E}	Global multi-center, non-randomized, open-label, phase I/II clinical trial	18.2 months (received no prior TKI)/ 8.9 month (received one prior TKI)	38.5% (received no prior TKI)/ 27.3% (received one prior TKI)	Yes
Larotrectinib [87]	<i>NTRK</i> rearrangement (<i>TRK</i> fusion)	Phase I/II clinical trial	81% (1-year PFS rate), 69% (2-year PFS rate)	71%	Yes
Entrectinib [88]	<i>NTRK</i> fusion	Phase II clinical trial	19.9 months	54%	Yes
Selumetinib [89]	<i>MEK1/2</i> receptor	Authorized as orphan drug in adjuvant therapy of stage III/IV DTC; Phase II trial of redifferentiation therapy for RAIR-DTC is ongoing	7.5 months	3%	Yes

NMPA: National Medical Products Administration; ORR: objective response rate; PFS: progression-free survival; TKI: tyrosine kinase inhibitor

Table 4 Comparison of safety data for commonly used targeted drugs

Safety Indicators	Sorafenib [2]	Lenvatinib [80]	Anlotinib [81]	Donafenib [74]	Apatinib [73]	Surufatinib [82]	Pralsetinib [83]	Selpercatinib [84]
Incidence of adverse events (AEs)	98.6%	100%	100%	99.2%	100%	100%	-	94%
Incidence of grade ≥ 3 AEs	-	87.4%	58.1%	43.8%	78.3%	-	54.0%	30%
Common grade ≥ 3 AEs	Hand-foot skin reaction, hypertension, hypocalcemia, diarrhea, etc.	Hypertension, proteinuria, hand-foot skin reaction, diarrhea, weight loss, etc.	Hypertension, hand-foot skin reaction, diarrhea, weight loss, etc.	Hypertension, hand-foot skin reaction, diarrhea, hypocalcemia, etc.	Hypertension, hand-foot skin reaction, proteinuria, diarrhea, etc.	Hypertension, proteinuria, hypertriglyceridemia, pneumonia	Hypertension, neutropenia, anemia, etc.	Dry mouth, hypertension, diarrhea, fatigue, elevated transaminases, vomiting, etc.
Dose adjustment rate related to AEs	Dose reduction (%)	64.3%	80.6%	32.3%	42.2%	37.0%	50.8%	46.0%
	Interruption (%)	66.2%	67.0%	-	-	-	54.0%	-
	Discontinuation (%)	18.8%	8.7%	16.1%	6.3%	6.5%	13.6%	4.0%

AE: adverse event

therapies remains undetermined. In a recent multi-centre retrospective study, treatment with lenvatinib, as a first-line TKI for progressive and symptomatic RAIR-DTC, exhibited longer PFS (median: 35.3 months vs. 13.3 months) and a higher objective response rate (ORR) (59% vs. 24%) than sorafenib [90].

For patients with RAIR-DTC harboring specific gene alterations (*RET* or *NTRK* fusions), targeted therapies such as selpercatinib, pralsetinib, larotrectinib, and entrectinib are preferred due to their higher clinical response rates and favorable safety profiles.

In addition to efficacy, safety is also a key factor in selecting targeted therapies. A comparison of safety data for commonly used targeted agents is provided in Table 4 [2, 73, 74, 80–84].

Therefore, the development of target therapy strategy that maximizes patient benefits for progressive RAIR-DTC should involve a comprehensive and multi-factor consideration, incorporating factors such as drug accessibility, socioeconomic considerations, patients' comorbidities, and their preference as well.

Recommendation 23 For patients with RAIR-DTC who present with symptoms or exhibit rapid disease progression,

multi-targeted TKIs are recommended as the first-line treatment (**strong recommendation, high-quality evidence**).

Recommendation 24 For symptomatic or rapidly progressing patients with *RET* or *NTRK* gene fusion-positive tumors, corresponding specific targeted kinase inhibitors are recommended (**strong recommendation, moderate-quality evidence**).

Recommendation 25 Apart from efficacy and safety profiles, other factors such as accessibility, socioeconomic considerations, patients' comorbidities and preference should also be considered to develop an individualized treatment plan (**weak recommendation, moderate-quality evidence**).

Question 20. Exploratory strategies for patients who failed first-line TKI therapy

Few studies have focused on the treatment of patients with RAIR-DTC who have failed first-line treatment with TKIs. The COSMIC-311 trial compared the efficacy and safety of cabozantinib and placebo in patients with RAIR-DTC that had progressed after lenvatinib and/or sorafenib, and PFS (not reached vs. 1.9 months) and ORR (15% vs. 0%) were significantly improved in the cabozantinib arm [66], which enabled cabozantinib as a standard second-line treatment. A

real-world study reported that salvage treatment with apatinib achieved a median PFS of 12.0 months and an ORR of 45.5% in patients with RAIR-DTC that progressed after sorafenib [91]. Subgroup analyses from SELECT and the DIRECTION trials revealed that, compared with placebo, lenvatinib and donafenib prolonged PFS in patients who had progressed after first-line anti-angiogenic therapy [72, 74]. While the recommended sequence of the aforementioned drugs cannot be determined at present due to limited evidence. Meanwhile, molecular testing for specific genetic alterations such as *RET* is recommended for patients resistant to first-line TKIs, and corresponding specific targeted agents can be considered as subsequent options upon positive results.

Prospective clinical trials provide an additional option for such patients, thus participating in clinical trials should be considered in situations in which there exists no available standard of care. Trial information can be obtained via www.clinicaltrials.org and www.chictr.org.cn, and the details can be further confirmed by directly contacting the trial sponsor.

Recommendation 26 For patients with RAIR-DTC who have disease progression on first-line TKI therapy, drugs of the same class that have not been exposed previously can be considered (**weak recommendation, moderate-quality evidence**).

Recommendation 27 For patients harboring specific genetic alterations such as *RET*, corresponding specific targeted agents can be applied as subsequent options after disease progression on first-line TKI therapy (**weak recommendation, moderate-quality evidence**).

Recommendation 28 Participating in clinical trials can be an additional option for patients with RAIR-DTC if no standard of care is available after the failure of first-line TKIs (**weak recommendation, moderate-quality evidence**).

Immunotherapy

Question 21. Clinical benefit of immunotherapy in RAIR-DTC

Thyroid cancer has been traditionally recognized as a “cold” tumor. Except for a handful of cases with TMB-H, the efficacy of immunotherapy has been observed to be limited in thyroid cancer, especially in DTC. The reported ORR is lower than 10% either with a programmed death protein 1 and its ligand 1 (PD-1/PD-L1) inhibitor alone, or with the combination of a PD-1/PD-L1 inhibitor and a cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitor

[92–94]. In a prospective phase II study, the combination of pembrolizumab and lenvatinib achieved an ORR of 62% and a 1-year progression-free rate of 74% in patients with RAIR-DTC. However, randomized controlled clinical trials are needed to prove whether this combined regimen is superior to lenvatinib monotherapy [95].

Recommendation 29 Except for a handful of cases with TMB-H, the clinical benefit of immunotherapy has not been verified in RAIR-DTC, either in monotherapy mode or in combination with targeted therapies (**weak recommendation, low-quality evidence**).

Other modalities

Question 22. Alternative treatment strategies for RAIR-DTC

In addition to the aforementioned conventional treatments, alternative strategies for RAIR-DTC, such as combined systemic pharmacological therapies, peptide receptor radionuclide therapy (PRRT), radioligand therapy (RLT), and traditional Chinese medicine, may be explored if appropriate. Clinical trials are increasingly exploring combinations of different targeted drugs, or immunotherapy with targeted therapies. RLT targeting FAP, PSMA, and PRRT targeting SSTR have also been trialed for RAIR-DTC management, albeit mostly as case reports or small exploratory studies [28, 96–99]. The traditional Chinese medicine was primarily indicated for improving complications after surgery and alleviating the treatment-related adverse events [100, 101].

For patients who are ineligible for active anti-tumor treatment, palliative care including pain relief, nutritional supplement, and complication management is warranted. Meanwhile, psychological support for both patients and their families is essential to alleviate negative emotions such as depression and anxiety, ensuring patients’ safety and comfort.

Recommendation 30 When no superior treatment options are available, combined pharmacological regimens, PRRT, RLT and traditional Chinese medicine may be considered

on the basis of a thorough evaluation by clinicians (**weak recommendation, low-quality evidence**).

Combined treatment

Question 23. Systemic therapy combined with surgery for locally invasive RAIR-DTC

For locally invasive RAIR-DTC, if R0/R1 resection is unlikely achievable upon initial evaluation, neoadjuvant/conversion therapy could be performed to improve the radical resection rate by reducing the tumor volume. As per individual situation, doxorubicin as chemotherapy [102, 103], lenvatinib or anlotinib as targeted therapy [53, 104], even surufatinib and toripalimab as combination of targeted therapy and immunotherapy [105], have been tried with improved R0/R1 resection rate. Nonetheless, certain questions in neoadjuvant therapy, such as drug selection, surgical indication, and medication regimen, remain to be addressed by large-scale prospective clinical trials.

Recommendation 31 For patients with recurrent or metastatic lesions invading or compressing vital organs, if potentially resectable, perioperative treatment consisting of systemic therapy combined with surgery can be considered. Clinical trials are recommended to address questions related to this treatment strategy (**strong recommendation, low-quality evidence**).

Question 24. Redifferentiation therapy followed by RAIT for RAIR-DTC

With increasing understanding of the molecular backgrounds of DTC, some specific targeted agents have been reported to enhance or restore RAI-avidity in RAIR-DTC. Inhibitors of *BRAF*, *MEK*, *RET*, and *NTRK* fusion have been reported to increase RAI uptake and enable subsequent RAIT [106–110]. Among these, dabrafenib combined with trametinib was the most studied, with promising results reported in a phase II trial. Partial response was observed in 38% of the patients 6 months after ^{131}I administration [111]. However, the long-term benefits of this treatment mode warrant further investigation because drug selection, the measurement of RAI uptake, efficacy evaluation, and the characteristics of enrolled patients varied among the studies.

Recommendation 32 Some specific targeted agents may enhance or restore RAI-avidity in RAIR-DTC, and patients may potentially benefit from the drug-induced redifferentiation and subsequent RAIT. However, current evidence is

insufficient to support this strategy as a standard therapeutic option (**weak recommendation, low-quality evidence**).

Monitoring and follow-up

Question 25. Efficacy evaluation in RAIR-DTC

Patients with RAIR-DTC who received local or systemic treatment should undergo regular biochemical and radiological monitoring to evaluate efficacy. The serum Tg can partially reflect the overall tumor burden and serve as a convenient method for efficacy monitoring and follow-up management of RAIR-DTC [112]. The Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) is also applicable for efficacy evaluation in RAIR-DTC [112].

^{18}F -FDG PET/CT has certain advantages in early efficacy evaluation. The Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST), which is based on the quantitative comparison of glucose metabolism changes in RAIR-DTC lesions [113], can be used to assess the response of RAIR-DTC to targeted therapies [114, 115], and its findings are associated with PFS [116].

Recommendation 33 RECIST 1.1 is recommended to evaluate therapeutic efficacy in RAIR-DTC (**strong recommendation, high-quality evidence**).

Recommendation 34 ^{18}F -FDG PET/CT hold certain value in the follow-up and efficacy monitoring for RAIR-DTC (**weak recommendation, moderate-quality evidence**).

Question 26. Monitoring and management of treatment-related adverse reactions

Previous studies indicated that the probability of adverse reactions related to targeted therapy may reach as high as 100%. Among certain drugs, the probabilities of grade 3 or higher adverse reactions, severe adverse reactions leading to dose reduction, treatment interruption, and discontinuation can reach as high as 87.4%, 80.6%, 76.0%, and 18.8%, respectively, with the treatment-related mortality rate ranging from 1% to 2.3% [2, 73, 74, 80–84]. The occurrence of adverse reactions to targeted therapy varies significantly among individuals.

Managing underlying conditions before treatment and close monitoring during treatment can reduce the probability of adverse reactions. The compensatory effect of bypass signaling in reticuloendothelial cells can induce tolerance, making early prevention and management of adverse reactions crucial for patient tolerance [117].

Graded treatment for adverse reactions should be strictly implemented. For grade 3 or higher adverse reactions or significant organ damage, timely discontinuation or dose reduction is required. Multi-disciplinary discussions are advised to evaluate the indications for re-administration. In brief, a concurrent strategy of prevention, monitoring, and graded treatment should be implemented [118].

Recommendation 35 Adverse reactions to targeted therapy exhibit significant individual differences, necessitating a concurrent strategy of prevention, monitoring, and graded treatment (**strong recommendation, moderate-quality evidence**).

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Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval This is guideline for management of radioactive iodine-refractory differentiated thyroid cancer and no ethical approval is required.

Consent to participate This is guideline for management of radioactive iodine-refractory differentiated thyroid cancer and no written informed consent is required.

Consent to publish Not applicable.

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