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REVIEW ARTICLE

# Consensus on the management of advanced radioactive iodine-refractory differentiated thyroid cancer on behalf of the Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and Spanish Rare Cancer Working Group (GETHI)

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**Abstract** Thyroid cancer is the single most prevalent endocrine malignancy; differentiated thyroid cancer (DTC) accounts for more than 90 % of all malignancies and its incidence has been rising steadily. For more patients, surgical treatment, radioactive iodine (RAI) ablation, and thyroid-stimulating hormone (TSH) suppressive therapy achieve an overall survival (OS) rate of 97.7 % at 5 years. Nevertheless, locoregional recurrence occurs in up to 20 % and distant metastases in approximately 10 % at 10 years. Two-thirds of these patients will never be cured with radioactive iodine therapy and will become RAI-refractory, with a 3-year OS rate of less than 50 %. Over the last decade, substantial progress has been made in the management of RAI-refractory DTC. Given the controversy in some areas, the Spanish Task Force for Thyroid Cancer on behalf of Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and the Spanish Rare Cancer Working Group (GETHI) have created a national joint task force to reach a consensus addressing the most challenging aspects of management in these patients. In this way, multidisciplinary management should be mandatory and nuclear medicine targeted therapy, novel molecular targeted agents, and combinations are currently changing the natural history of RAI-refractory DTC.

**Keywords** Differentiated thyroid cancer · Lenvatinib · Radioactive iodine-refractory thyroid cancer · Review · Sorafenib · Targeted therapy · Thyroid cancer

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## Introduction

Thyroid cancer is the single most prevalent endocrine malignancy and its incidence has been rising steadily over the past three decades [1]. Thus, thyroid cancer is currently the fifth most common new cancer diagnosis in women and the eighth most common new cancer diagnosis overall in the USA [2]. For most patients, surgical treatment, radioactive iodine (RAI) ablation, and thyroid-stimulating hormone (TSH) suppressive therapy achieve an overall survival (OS) rate of 97.7 % at 5 years [3]. Nevertheless, locoregional recurrence occurs in up to 20 % and distant metastases in approximately 10 % at 10 years. Two-thirds of these patients will never be cured with radioactive iodine therapy and will become RAI-refractory, with a 3-year OS rate of less than 50 %.

Differentiated thyroid cancer (DTC) accounts for more than 90 % of all thyroid cancers. The dominant histotypes are papillary and follicular cancers, while Hürthle cell thyroid cancer (a follicular thyroid cancer subtype) and poorly differentiated thyroid cancer are less common variants. Around one-third of DTC patients with structurally-evident locoregional and/or metastatic disease becomes RAI-refractory. This phenomenon is defined more by intrinsic behavior of thyroid follicular cells than specific histopathology. Surprisingly, although anaplastic thyroid cancers have higher mortality rates than DTC, most of the estimated deaths from thyroid cancer will be in patients with RAI-refractory DTC [2].

Over the last decade, substantial progress has been made in the management of RAI-refractory DTC. Given the controversy in some areas, the Spanish Task Force for Thyroid Cancer on behalf of Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and the Spanish Rare Cancer Working Group (GETHI) have created a national joint task force to develop a DTC consensus statement to aid practitioners and develop a series of clinically relevant points. They selected nine chairpersons to lead the task force and membership on the panel was based on expertise and previous contributions to this field. The topics to be addressed were assigned to two specialists (JC and GR) to write the manuscript that was later reviewed and approved by all the experts. They used their knowledge and expertise of the subject, as well as a systematic search using MEDLINE (PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), for primary references, reviews, and other materials available prior to June 2016, to set down a series of recommendations. In preparing this consensus, we addressed the characteristics, molecular biology, diagnosis, treatment goals and management options including watchful waiting, local therapy, multikinase inhibitors, and RAI reinduction strategy for advanced radioactive iodine-refractory DTC. All drafts were reviewed and edited by the members of the panel for consistency and returned to the primary authors for review. The authors include specialist physicians in Endocrinology and Medical Oncology. The medical opinions expressed in this consensus are those of the authors. The SEEN and SEOM Boards approved the final document.

## Consensus

### The true incidence and prevalence of RAI-resistant DTC in Spain

The lack of national registries for thyroid cancer patients in Spain precludes an accurate estimation of the number of new diagnoses per year and the percentage of patients who become RAI-refractory. Available data reveal incidence rates of 2.12 per 100,000 males and 6 per 100,000 females in 2004 [4, 5]. If we extrapolate European incidence rates of new diagnoses, 2000–2500 new cases of thyroid cancer diagnoses can be expected in Spain per year; 90 % being DTCs and 10 % of those become RAI-resistant. Thus, approximately 180–200 new patients per year could be diagnosed with RAI-refractory DTC in Spain.

### The best definition of RAI-refractory DTC

Several terms such as "refractory," "resistant," "nonresponsive," or "non-avid" have been used to characterize DTC patients with locoregional and/or distant metastases for whom RAI therapy provides no further clinical benefit. The first three terms all imply that RAI therapy has not yielded a clinical benefit despite cells' possible avidity for RAI. "Non-avid" indicates tumors that fail to absorb any RAI whatsoever on diagnostic or post-therapy scintigraphy. Therefore, tumors may retain RAI avidity yet not receive sufficient radiation from therapy to result in medical benefit.

In routine clinical care, patients with appropriate TSH stimulation and iodine preparation can be defined as RAI-refractory if they meet any of the following criteria (Table 1): (1) No uptake of RAI at the initial diagnosis of distant metastases or locoregional recurrence. (2) Progressive loss of RAI uptake after several sessions of RAI therapy. (3) Evidence of various foci of distant metastases, some of which are RAI avid, while others are not on body scan. (4) Tumor progression after suitable RAI treatment, despite substantial prior RAI uptake. DTC classification as refractory translates as not indicated for further RAI treatment.

Despite the consensus with respect to these criteria, other vaguer situations exist and agreement within multidisciplinary teams is needed before considering RAI-refractory disease and potential candidates for systemic therapy (Table 1): (1) Total cumulative RAI doses exceeding 600 mCi, when increased risk of leukemia and myelodysplastic syndromes are observed; (2) significant uptake on integrated 2-deoxy18-fluoro-D-glucose positron emission tomography ($^{18}$FDG-PET) clearly associated with significant decrease on uptake of RAI body scan; (3) unresectable primary thyroid cancer tumors should be managed as RAI-refractory DTC, as RAI therapy is not feasible (this status could change if tumor reduction and thyroid excision are achieved); (4) aggressive DTC histologies (e.g. poorly differentiated, insular, Hürthle cell carcinomas) associated with lower probability of RAI uptake.

**Table 1** Clinical criteria defining RAI-refractory DTC

| Main criteria defining RAI-refractory DTC |
|---|
| No uptake of RAI at the initial diagnosis of distant metastases or locoregional recurrence |
| Progressive loos of RAI uptake after several sessions of RAI therapy |
| Evidence of different foci of distant metastases, some of them with RAI uptake and others without RAI uptake on the body scan |
| Tumor progression after adequate RAI treatment even with previous substantial iodine uptake |
| **Other suggested criteria** |
| Significant uptake on $^{18}$FDG-PET |
| Total cumulative doses of RAI over 600 mCi |
| Unresectable primary tumors of DTC |
| Aggressive DTC histologies (such as poorly differentiated, insular, Hürthle cell carcinomas) |

*DTC* differentiated thyroid cancer, *$^{18}$FDG-PET* 2-deoxy18-fluoro-D-glucose positron emission tomography, *mCi* millicurie, *RAI* radioactive iodine

## Patients with RAI-refractory metastatic DTC eligible for monitoring without additional therapy: watchful waiting

RAI-refractory metastatic DTC can be asymptomatic for long periods of time. Hence, overtreatment is a great challenge if we do not discriminate properly and anticipate the natural course of the disease. Watchful waiting should be contemplated in patients with an indolent clinical course; asymptomatic, unresectable metastatic cancer; low tumor burden; stable or minimally progressive; low likelihood of developing rapidly progressive disease, and no adverse impact from disease burden (Table 2). No further treatment beyond TSH suppression and active surveillance are needed in these subjects.

There are three clinical situations for which sufficient evidence for aggressive therapies is lacking and watchful waiting may be an option. One is the presence of small (<5–8 mm), asymptomatic metastatic lymph nodes following RAI ablation, particularly after previous neck compartmental dissection. In such cases, surgery or other local therapies have not demonstrated any benefit in improving macroscopic clinical disease recurrences or disease-specific survival. Secondly, some patients with small (usually <1 cm) pulmonary metastatic slowly or non-progressive disease can be followed with TSH suppression. The third case is when there are asymptomatic, stable bone metastases that do not threaten nearby critical structures.

Despite the slow evolution of their disease, these patients must be carefully and thoughtfully followed by a multidisciplinary team with imaging studies every 3–6 months together with an assessment of current or potential symptoms. In addition to thyroglobulin levels and neck ultrasound, attention must be directed toward asymptomatic metastatic disease, quantifying its extent by $^{18}$FDG-PET, Magnetic Resonance Imaging (MRI), CT, and the rate of progression of radiologically evident lesions using Response Evaluation Criteria In Solid Tumors (RECIST). Often, RAI-refractory status is defined by $^{18}$FDG-PET after increased thyroglobulin and negative RAI body scan are detected. In this circumstance, disease progression status by RECIST is difficult to define, as there tend to be no previous images available for comparison. In addition to imaging, assessing current or potential symptoms and understanding co-morbidities, patient age and life expectancy can inform decision-making during follow-up.

## RAI-refractory DTC patients eligible for local therapies

The indication for local therapies in RAI-refractory DTC is conditioned by the location and number of metastases, tumor burden, and technical feasibility. Locoregional recurrences are the most common location in DTC, followed by lung, extracervical lymph nodes, bones, and brain. Local therapies include surgery, external beam radiation (EBRT) or radiosurgery, radiofrequency or ethanol ablation, and (chemo)embolization, to circumvent damage to vital structures, such as the aerodigestive tract, central nervous system (CNS), or central neck compartment [6]. However, most clinical evidence has shown that a small fraction of patients may benefit from some of these locoregional treatment approaches, such as radiofrequency ablation [7], ethanol ablation [8], or embolization [9].

In the case of locoregional relapse, surgery is the first option, even when RAI uptake is present. Therapeutic compartmental central and/or lateral neck dissection,

**Table 2** Treatment options in RAI-refractory DTC

| | Watchful waiting | Local therapies | Systemic therapies |
|---|---|---|---|
| Clinical and radiological criteria | Non or minimally progressive<br>No symptoms<br>Low risk of compression<br>Unresectable, not feasible for local therapies | High risk of local compression aerodigestive tract or CNS<br>Single distant metastases<br>Local pain | Rapidly progressive<br>Symptomatic or immediately life-threatening<br>No candidate to other local therapies |
| Therapeutic recommendations | Surveillance every 3–12 months: Tg, US, functional and cross-sectional imaging<br>Assessment of symptoms severity<br>TSH suppression with levothyroxine | Surgical resection<br>External beam radiation<br>Radiofrequency ablation<br>(locoregional lymph node)<br>Chemoembolization (liver metastases)<br>Bisphosphonates (bone metastases)<br>TSH suppression with levothyroxine | Antiangiogenic multitargeted kinase inhibitors (i.e. Sorafenib, lenvatinib)<br>Kinase inhibitors with reinduction of NIS-mediated RAI uptake<br>Chemotherapy<br>TSH suppression with levothyroxine |

*NIS* sodium iodide symporter, *RAI* radioactive iodine, *Tg* thyroglobulin, *US* ultrasound

sparing uninvolved vital structures, is recommended. More limited surgery is reasonable in cases of prior comprehensive neck dissection and/or EBRT. In contrast, treatment of locoregional disease has not demonstrated benefit in the presence of intractable, distant metastases, except to possibly palliate symptoms or prevent aerodigestive obstruction. For tumors that invade the upper aerodigestive tract, surgery combined with EBRT is generally recommended.

In selected patients with pulmonary metastases, consideration must be given to local therapies, such as metastasectomy, endobronchial laser ablation, or EBRT to alleviate symptomatic intrathoracic lesions (e.g., obstructing or bleeding endobronchial masses), and pleural or pericardial drainage for symptomatic effusions.

Although some bone metastases are RAI avid, RAI therapy is rarely curative long term and patients will require further interventions. Complete surgical resection of isolated symptomatic metastases has been associated with improved survival and should be considered, especially in young patients with slowly progressive disease or in skeletal metastases in weight-bearing extremities. EBRT and concomitant glucocorticoids to minimize potential TSH-induced and/or radiation-related tumor enlargement should be fully weighed when bone lesions arise in locations where acute swelling may produce severe pain, fracture, or neurological complications. Intravenous bisphosphonate (pamidronate or zoledronic acid) or the RANKL inhibitor denosumab and embolization are options for symptomatic bone metastases [9].

## RAI-refractory DTC patients who should be considered and eligible for multikinase inhibitor therapy

A current consensus exists in that multikinase inhibitors (MKI) therapy should be considered only in RAI-refractory DTC patients with progressive and/or symptomatic metastatic disease not otherwise amenable to local therapies. The reasons for such limitations arise from trials demonstrating clinical benefit from MKI, albeit at the expense of drug toxicity and patient eligibility restrictions.

MKI and other targeted agents have substantially changed how advanced RAI-refractory DTC is currently treated (Table 3). These drugs, mainly MKIs with antiangiogenic effect, have now been assessed in phase I-III trials and some have been associated with more than 50 % partial response and stable disease. Of note, prolongation of progression-free survival (PFS) has been demonstrated in the two, phase III trials comparing sorafenib or lenvatinib with placebo (Table 4) [10, 11]. Both drugs have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in patients with RAI-refractory metastatic disease. In DECISION phase III trial, PFS was significantly superior in patients treated with sorafenib vs. those receiving placebo (10.8 vs. 5.4 months; HR 0.49; $p < 0.0001$) and in SELECT phase III study, patients treated with lenvatinib had also a significantly longer PFS than those treated with placebo (PFS: 18.3 vs. 3.6 months; HR 0.21; $p < 0.001$). There are some differences between any of the alternative drugs, sorafenib

**Table 3** Results of clinical trials of targeted therapies in RAI-refractory DTC

| Drug (study phase) | Targets | Number of clinical trials | Number of patients in clinical trials | PFS (months) |
|---|---|---|---|---|
| Multitargeted kinase inhibitors | | | | |
| Sorafenib | VEGFR, PDGFR, c-KIT, RET, RAF | 5 (one phase III trial) | 538 | 10–18 |
| Lenvatinib | VEGFR, FGFR, c-KIT, RET, PDGFR | 3 (one phase III trial) | 377 | 12–18 |
| Sunitinib | VEGFR, PDGFR, c-KIT, RET, FLT3 | 2* | 59 | NR |
| Vandetanib | VEGFR, EGFR, RET | 1* | 145 | 11 |
| Axitinib | VEGFR, PDGFR, c-KIT, RET | 1* | 45 | 18 |
| Cabozantinib | VEGFR, RET, c-MET, FLT3, TEK | 1** | 15 | NR |
| Pazopanib | VEGFR, PDGFR, c-KIT | 1* | 37 | 12 |
| Motesanib | VEGFR, PDGFR, c-KIT, RET | 1* | 93 | 9 |
| Single targeted kinase inhibitors | | | | |
| Vemurafenib | BRAFV600E | 1** | 3 | NR |
| Selumetinib | MEK1/2 | 1* | 32 | NR |
| Dabrafenib | BRAFV600E | 2* | 24 | 11 |

*NR* not referred, *PFS* progression-free survival

* Phase II studies, ** Phase I study

and lenvatinib that should be considered when deciding which is the best option for each patient. Thus, the rate of response was 12.2 % for sorafenib and 64.8 % for lenvatinib. More than 60 % of patients required dose reductions or interruptions with both drugs illustrating that the safety profile is unfavourable. The main severe adverse events (grade 3–4) is hand-foot syndrome for sorafenib and hypertension for lenvatinib with incidence rates of 20 % and 42 %, respectively. Both act on common targets, VEGFR, PDGFR, c-KIT and RET and each one has a specific target, RAF for sorafenib and FGFR for lenvatinib. Moreover, sorafenib improved OS relative to placebo in patients with BRAF mutation (HR 0.32; $p = 0.03$) while lenvatinib improve OS in patients with any grade of hypertension (HR 0.43; $p = 0.0003$).

Based on published phase II trials, other orally available MKIs such as sunitinib, axitinib, cabozantinib, or pazopanib may provide some clinical benefit in this setting; however, only the results of the concluded phase III study with vandetanib are expected [12].

Despite these promising results, there are limitations to using MKIs in advanced RAI-refractory DTC. The most important one is patient selection, as no biological or genetic biomarker has yet been elucidated to predict tumor response or patient outcome. The indolent course of the disease could jeopardize the efficacy of starting treatment early and increase the risk of toxicity. However, waiting for high tumor burden or for the onset of symptoms can compromise patient survival [10]. Additionally, some complete responses are beginning to be seen with MKIs in this setting, as well as trends toward increased OS in some subgroup analyses. These results are found even with the crossover design of placebo-controlled clinical trials, suggesting the ability to alter the natural history of this disease [11, 13].

Still, drug-related side effects are common and can affect patients' quality of life and increase the risk of drug-related deaths; hence, these agents should be limited to specialists experienced in their use. Optimal management of adverse events is clinically relevant, especially in view of the fact that these treatments require long-term administration in most cases. The most common side effects include fatigue, hand-foot syndrome, hypertension, diarrhea, skin rashes and erythema, weight loss, and thromboembolic events.

In summary, MKI therapy should be limited to cases with progressive, metastatic, and clinically relevant tumor burden disease that is not amenable to palliation with surgery or locoregional approaches (Fig. 1). Patients with advanced, progressive, RAI-refractory DTC should also be referred to experienced centers that can offer interdisciplinary expertise in customizing treatment and participation in clinical trials. Further research is needed to determine when to initiate targeted therapy and how to use agents sequentially and in combination without causing additive toxicity.

## Sodium iodide symporter restoration and subsequent RAI reinduction strategy in RAI-refractory DTC patients

Advanced RAI-refractory DTC show negligible $^{131}$I uptake due to loss of functional sodium iodide symporter (NIS) SLC5A5 expression. RAI selectively targets and destroys

**Table 4** Sorafenib and lenvatinib phase III studies: DECISION and SELECT

| Clinical trial and patient population | Study description | Efficacy data | Safety data and quality of life |
|---|---|---|---|
| DECISION Phase III<br>NCT00984282<br>RAI-refractory, locally advanced or metastatic DTC with progression in the prior 14 months (local assessment)<br>Patients had not been previously treated with other<br>MKIs or chemotherapy | Treatment: SORAFENIB (800 mg daily) vs. placebo<br>Number of patients: 417<br>Randomized 1:1<br>Main objective: PFS<br>Secondary objectives: RR, safety, quality of life, and OS<br>Crossover to sorafenib was allowed in patients who had initially received placebo | PFS: 10.8 vs. 5.4 months; HR 0.49; 95 % CI 0.39–0.61; $p < 0.0001$)<br>RR: 12.2 vs. 0.5 % ($p < 0.0001$)<br>OS: correction for the effect of switching from placebo to sorafenib on OS using the rank-preserving structural failure time method (HR 0.69; 95 % CI 0.49–0.99) and the iterative parameter estimation method (HR 0.79; 95 % CI 0.56–1.11)<br>Subgroup analyses: Sorafenib improved OS relative to placebo in patients with BRAF mutation (HR 0.32; $p = 0.03$) | Grade ≥3 adverse events (sorafenib)<br>Hand-foot syndrome: 20.3 %<br>Hypertension: 9.7 %<br>Hypocalcemia: 5.8 %<br>Weight loss: 5.8 %<br>Diarrhea, fatigue: 5.3 %<br>Rash/desquamation: 4.8 %<br>Shortness of breath: 4.8 %<br>Dose reduction: 64.3 %<br>Dose interruption: 66.2 %<br>FACT-G and EQ-5D scores were numerically lower with sorafenib relative to placebo at treatment initiation due to side effects, but remained stable during treatment period |
| SELECT Phase III<br>NCT01321554<br>RAI-refractory, locally advanced or metastatic DTC that had progressed in the previous 13 months (centrally reviewed)<br>One prior treatment with other MKIs or chemotherapy was allowed | Treatment: LENVATINIB (24 mg daily) or placebo<br>Number of patients: 392<br>Randomized 2:1<br>Main objective: progression-free survival<br>Secondary objectives: RR, safety, and OS<br>Crossover to lenvatinib was allowed in patients who had initially received placebo | PFS: 18.3 vs. 3.6 months; HR 0.21; 95 % CI, 0.14–0.31; $p < 0.001$<br>RR: 64.8 vs. 1.5 % ($p < 0.0001$)<br>OS: a non-significant trend was observed (HR 0.73; 95 % CI 0.5–1.0; $p = 0.10$)<br>Subgroup analyses: lenvatinib improved OS in patients with any grade of hypertension (HR 0.43; 95 % CI 0.27–0.69), $p = 0.0003$ | Grade ≥3 adverse events (lenvatinib):<br>Hypertension: 42 %<br>Proteinuria: 10 %<br>Thromboembolic effects: 6.5 %<br>Renal failure: 1.9 %.<br>QT prolongation: 1.5 %<br>Hepatic failure: 0.4 %<br>Dose reductions: 67 %<br>Dose interruption: 82 % |

*CI* confidence interval, *EQ-5D* EuroQOL five-dimension index questionnaire, *FACT-G* Functional Assessment of Cancer Therapy–General score, *HR* hazard ratio, *OS* overall survival, *PFS*: progression-free survival, *RR* response rate

any remnant or metastatic NIS-expressing thyroid cancer cells. Therefore, decreased expression of NIS and/or impaired targeting of NIS on the thyroid cancer cell membranes are the mechanisms underlying RAI-refractory disease. NIS gene cloning and characterization have made it possible to study the molecular mechanisms leading to loss of NIS function, potentially providing novel approaches to DTC therapy, in an attempt to restore NIS-mediated iodide accumulation.

NIS is a key target for novel thyroid cancer therapies. Although traditional therapies (e.g. retinoic acid) have shown some reinduction of RAI, such therapies have never sufficed to achieve a therapeutic effect [12]. Notably, novel therapies, particularly single kinase inhibitors, have paved the way to significant RAI reinduction (Table 3). The MEK inhibitor selumetinib was the first drug to reinduce iodide uptake enough to exert a RAI-induced cytotoxic effect [14]. In a prospective clinical trial with 20 patients with RAI-refractory DTC, 12 patients showed significant RAI uptake and 8 exhibited partial responses. Efficacy was especially conspicuous in RAS-mutated tumors, as all five mutant tumors displayed increased RAI uptake (four partial responses and one stable disease). Only one patient of the nine with a BRAFV600E-positive tumor showed significant RAI uptake.

Dabrafenib, a selective inhibitor of mutant BRAF, has been the second agent to show promising results [15]. Six out of 10 patients (60 %) with BRAF V600E-mutant RAI-

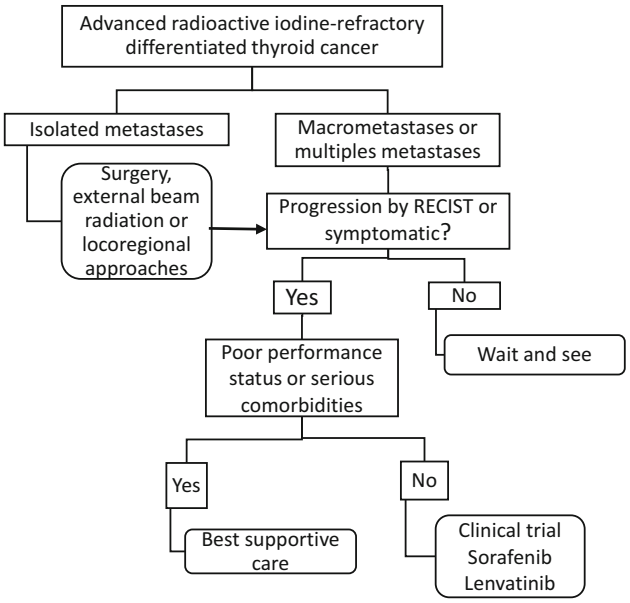


**Fig. 1** Algorithm for the management of advanced radioactive iodine-refractory differentiated thyroid cancer

refractory papillary thyroid cancer (PTC) showed significant RAI uptake and 2 presented a partial response; 4 patients had stable disease. A potential advantage of this treatment strategy (vs. long-term MKI treatment) is that timewise, kinase inhibitor therapy is short (45 days), which could lessen side effects. Nonetheless, this approach is not without its limitations, including the risk of hematological toxicity with accumulative doses of RAI therapy and the uncertainty surrounding the relation between reinduction of iodine uptake and long-term responses. Two international phase II and III efficacy studies are currently evaluating selumetinib in RAI-sensitive metastatic disease, as well as in adjuvant setting.

In any case, further evidence is needed before RAI reinduction strategy can be recommended in the treatment of RAI-refractory DTC patients.

## Implications of DTC's molecular biology for research on RAI-refractory disease treatment

Greater insight into the main molecular steps leading to the transformation of normal follicular cells into invasive thyroid carcinoma has prompted the development of several translational and clinical studies that have sparked greater optimism in treatment for these patients. Thyroid carcinogenesis has become one of the most fascinating multistep models and a particularly promising paradigm for targeted therapy.

One of the most important activating genetic aberrations in the signal transduction pathways of thyroid cancer development involves the RET (rearranged during transfection)/PTC-RAS-RAF-MAPK axis, with mutations in protein kinase RAS and BRAF in more than half of all DTC patients. This, added to the proangiogenic environment described in advanced thyroid cancer, have facilitated MKI development targeting angiogenic and lymphangiogenic-related tyrosine kinases, BRAF and RET proteins showing significant results [16]. Specifically, sorafenib, a RET, BRAF, c-KIT, vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) inhibitor, and lenvatinib, a RET, c-KIT, VEGFR, PDGFR, and fibroblast growth factor receptor inhibitor (FGFR), have demonstrated a significant impact, increasing median PFS in advanced RAI-refractory DTC.

The PI3 K-AKT-mTOR pathway is a major oncogenic driver of follicular thyroid carcinomas (FTC) and the follicular variant of PTC, and facilitates the identification of targets for new kinase inhibitors. RAS mutations, the most frequent genetic abnormalities in FTC, are dual activators, as they are capable of stimulating both the PI3 K-AKTmTOR and MAPK pathways. The former pathway is also activated by inactivating mutations in the tumor suppression gene PTEN or by activating PI3 KCA and AKT1 mutations, commonly found in FTC, particularly in its most aggressive forms, and in poorly differentiated and anaplastic carcinomas. Moreover, simultaneous activation of both pathways becomes more frequent in advanced RAI-refractory DTC with metastatic disease. Given this activation of the PI3K-AKT-mTOR pathway, phase II trials with mTOR inhibitors (everolimus and temsirolimus), alone or in combination with MKIs, are underway in patients with advanced RAI-refractory DTC [17, 18].

ALK translocations are uncommon in DTC (1.6 %), but present in 9 % of poorly differentiated thyroid cancers. As opposed to EML4–ALK fusions in lung cancer, the most common fusion-gene partner for ALK in thyroid cancer is STRN (encoding striatin), which results in constitutive ALK-mediated activation of the RAS/RAF/MEK/ERK pathway. STRN–ALK fusions appear to be mutually exclusive with respect to oncogenic BRAF and RAS mutation and ALK should be a therapeutic target in patients with ALK-mutated or ALK-rearranged advanced-stage disease [20].

VB-111, an engineered non-replicating adenovirus, is a novel targeted approach that is being assessed in a phase II trial in patients with advanced, progressive, RAI-refractory DTC [19].

Thyroid cancer, like melanoma, is composed of highly immunogenic tissues. Thyroiditis is the most common autoimmune disease coexisting with DTC and is induced by the anti-CTLA-4 monoclonal antibody ipilimumab and the anti-PD-1 antibody nivolumab. This suggests that the thyroid gland (and by extension, DTC) might be a relevant target for immune-checkpoint inhibitors. Clinical trials are

being conducted to examine this strategy in patients with DTC [20].

Tumor-associated macrophages (TAMs) represent another potential target of therapeutic relevance in patients with advanced DTC. Increased TAM density in DTC samples was associated with greater invasiveness and decreased cancer-related OS [20].

Although advances in the molecular biology of thyroid cancer pathogenesis and the development of targeted therapies in this setting have been notable in recent years, no predictive biomarkers of clinical benefit for these agents are currently available. Nonetheless, genotyping for the main genetic events in refractory DTC (BRAF, RAS, RET/PTC, etc.) should be considered in patients with advanced RAI-refractory DTC, since it can contribute to better understanding the mechanisms underlying responsiveness and resistance to novel therapies such as MKIs.

### The role of chemotherapy and radiotherapy in RAI-refractory DTC

Classical chemotherapeutic agents have shown limited activity in DTC. Doxorubicin is the only chemotherapeutic agent approved for refractory DTC, as well as the most highly developed. Albero A. et al. evaluated the effectiveness of chemotherapy in RAI-refractory DTC in a systematic bibliographic review [21]. Sixteen publications were included: one randomized clinical trial (Shimaoka et al. 1985), 13 phase II studies/prospective case series, and two retrospective series. The drugs analyzed were: doxorubicin or cisplatin in monotherapy in 3 studies, doxorubicin combinations in 11, and another five studies examined other treatment schemes. The response rate was 25 % with 3.4 % showing complete response.

Because chemotherapy effectiveness and PFS and OS benefit have not been properly established, well-designed, randomized studies of patients with RAI-refractory DTC in progression are necessary, with homogenous imaging techniques to evaluate response and analyzing survival, quality of life, safety, and sequential therapy with MKIs.

EBRT has been used to improve locoregional disease control and palliate some distant metastases locations, such as CNS or bones. However, current recommendations for locoregional disease control are limited to macroscopic, unresectable tumors in older patients [22].

### The value of thyroglobulin determination in decision-making and follow-up of RAI-refractory DTC

Thyroglobulin serum levels have been one of the most important tools for monitoring patients with persistent or recurrent disease. Significantly increasing thyroglobulin levels tend to suggest disease progression and indicate successive sessions of RAI therapy until the tumor is cured or becomes RAI-resistant. In refractory situations, thyroglobulin levels can become less accurate in correlation with tumor burden and tumor response to systemic therapies in parallel with the dedifferentiation process of DTC.

Thus, no systemic therapies should be started based solely on thyroglobulin levels, just as no systemic therapies should be suspended based on thyroglobulin variations.

### TSH suppression is not recommended in RAI-refractory disease

Overall, TSH suppression is advised in patients with DTC following surgery to reduce the risk of recurrence [23]. Initial suppression to below 0.1 mU/L is recommended in thyroid cancer patients with high and intermediate-risk, while maintenance at below the lower limit of normal (<0.5 mU/L) is appropriate for low-risk patients. However, no clear recommendation regarding TSH suppression is available in RAI-refractory DTC. The progressive, undifferentiating process that DTC cells undergo during the disease process produces TSH-independent growth that calls TSH suppression into question. Furthermore, most new targeted agents cause some degree of refractoriness to levothyroxine (LT4) and increased TSH is often seen in thyroid cancer patients treated with MKIs. It is therefore necessary to increase levothyroxine doses to maintain TSH levels within the normal range and prevent the fatigue syndrome typically observed in these patients.

## Concluding remarks: future directions and research

Multidisciplinary management of thyroid cancer should be mandatory and concentrated in referral centers to maximize patients' chances for a cure. Future research will focus on identifying prognostic biomarkers and better patient molecular characterization, redifferentiation process of follicular thyroid cancer cells leading to NIS restoration and RAI reinduction, optimization, and innovation in systemic treatment. Thus, nuclear medicine targeted therapy, novel molecular targeted agents, and combinations are currently changing the natural history of RAI-refractory DTC.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Research involving human participants and/or animals** Not applicable.

**Informed consent** Not applicable.

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## References


1. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA. 2006;295(18):2164–7.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9–29.
3. Schlumberger MJ. Papillary and follicular thyroid carcinoma. N Engl J Med. 1998;338(5):297–306.
4. Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R. Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol. 2013;2013:965212.
5. Lope Carvajal V, Pollan Santamaria M, Pérez-Gómez B, Aragonés Sanz B, Suárez Rodríguez JM, Carrasco Gimeno J, et al. Incidencia y mortalidad por cáncer de tiroides en España. Boletín epidemiológico ISCIII Ministerio de Sanidad. 2004;12(15):161–72.
6. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892–9.
7. Dupuy DE, Monchik JM, Decrea C, Pisharodi L. Radiofrequency ablation of regional recurrence from well-differentiated thyroid malignancy. Surgery. 2001;130(6):971–7.
8. Lewis BD, Hay ID, Charboneau JW, McIver B, Reading CC, Goellner JR. Percutaneous ethanol injection for treatment of cervical lymph node metastases in patients with papillary thyroid carcinoma. AJR Am J Roentgenol. 2002;178(3):699–704.
9. Eustatia-Rutten CF, Romijn JA, Guijt MJ, Vielvoye GJ, van den Berg R, Corssmit EP, et al. Outcome of palliative embolization of bone metastases in differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2003;88(7):3184–9.
10. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014;384(9940):319–28.
11. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015;372(7):621–30.
12. Spitzweg C, Bible KC, Hofbauer LC, Morris JC. Advanced radioiodine-refractory differentiated thyroid cancer: the sodium iodide symporter and other emerging therapeutic targets. Lancet Diabetes Endocrinol. 2014;2(10):830–42.
13. Capdevila J, Trigo JM, Aller J, Manzano JL, Garcia Adrian S, Zafon C, et al. Axitinib treatment in advanced RAI-resistant differentiated thyroid cancer (DTC) and refractory medullary thyroid cancer (MTC). Proc Am Soc Clin Oncol. 2014;32:5s.
14. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013;368(7):623–32.
15. Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res. 2015;21(5):1028–35.
16. Grande E, Diez JJ, Zafon C, Capdevila J. Thyroid cancer: molecular aspects and new therapeutic strategies. J Thyroid Res. 2012;2012:847108.
17. Lim SM, Chang H, Yoon MJ, Hong YK, Kim H, Chung WY, et al. A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes. Ann Oncol. 2013;24(12):3089–94.
18. Brose MS, Troxel AB, Yarchoan M, Cohen AB, Harlacker K, Dyanick NA, et al. A phase II study of everolimus (E) and sorafenib (S) in patients (PTS) with metastatic differentiated thyroid cancer who have progressed on sorafenib alone. J Clin Oncol. 2015;33(Suppl; abstr 6072).
19. Jasim S. et al. Multi-cohort phase II trial of VB-111 in advanced radioactive iodine-refractory differentiated thyroid cancer [abstract 638]. Presented at the 15th international thyroid congress and 85th annual meeting of the American Thyroid Association (2015).
20. Bible KC, Ryder M. Evolving molecularly targeted therapies for advanced-stage thyroid cancers. Nat Rev Clin Oncol. 2016;13(7):403–16.
21. Albero A, Lopéz JE, Torres A, de la Cruz L, Martín T. Effectiveness of chemotherapy in advanced differentiated thyroid cancer: a systematic review. Endocr Relat Cancer. 2016;23(2):R71–84.
22. Terezakis SA, Lee KS, Ghossein RA, Rivera M, Tuttle RM, Wolden SL, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys. 2009;73(3):795–801.
23. McGriff NJ, Csako G, Gourgiotis L, Lori CG, Pucino F, Sarlis NJ. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. Ann Med. 2002;34(7–8):554–64.