REVIEW

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Oligometastatic disease from differentiated thyroid cancer: best treatment schemes

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Purpose of review
Patients with slowly progressive and/or symptomatic oligometastatic radioactive iodine refractory (RAIR) differentiated thyroid carcinomas (DTCs) are candidates to receive locoregional treatment to delay the start of systemic therapy with multikinase inhibitors. Information provided by the recent literature has not been extensively reviewed in previous published works, thus we aim to bridge this gap.

Recent findings
We present for each metastatic site the different locoregional treatment options, contraindications and potential adverse events. Some techniques can be combined together, whereas others are discouraged in certain situations, requiring a high level of expertise and multidisciplinarity in the treatment algorithm.

Summary
Different techniques of radiation therapy and interventional radiology allow to control the metastatic spread. However, as no clinical trials are available to compare the treatment schemes in terms of safety and potential impact on the prognosis, the most appropriate option for each patient should be selected within a multidisciplinary decision making, taking into account the clinical conditions and the pattern/rapidity of metastatic disease.

Keywords
interventional radiology, metastasectomy, oligometastases, radiation therapy, radioiodine-refractory thyroid cancer

INTRODUCTION

In the setting of metastatic radioactive iodine refractory (RAIR) differentiated thyroid carcinoma (DTC), few systemic therapies are available [1▪]. The pattern of metastasization frequently implies a slow evolution involving a limited number of organs. Metastasectomy, radiation therapy, radiofrequency ablation (RFA) and chemoembolization are frequently employed in the real-world practice, as locoregional treatments can prevent the onset of mass-related symptoms, potentially delaying the initiation of antiangiogenic systemic therapy, associated with a broad spectrum of adverse events. At present, no clinical trials have compared the different treatment schemes in terms of safety and potential impact on the prognosis in DTC. Specific recommendations on locoregional techniques for oligometastatic DTC are lacking, and indications are based mainly on studies of other solid tumors. This review aims at examining the treatment options for these patients, based on international guidelines and the available literature.

EPIDEMIOLOGY AND PATHOLOGICAL FEATURES

Thyroid carcinomas (TCs) are the most frequent endocrine neoplasms, with a global incidence of 10/100 000 women and 3/100 000 men, variable across Countries [2]. The 2022 WHO Classification [3] divides malignant follicular cell-derived

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Curr Opin Oncol 2023, 35:15–21

DOI:10.1097/CCO.0000000000000921

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KEY POINTS

- Radioiodine-refractory metastatic differentiated thyroid carcinomas (DTCs) have dismal prognosis.
- DTC variants have different metastasization patterns, but the treatment strategy depends on site and size of the lesions.
- Selective treatment of oligometastases can prolong the disease control, provide pain relief and delay the initiation of systemic therapy.
- The choice of the most suitable treatment strategy for DTC oligometastases should involve surgeons, radiotherapists and interventional radiologists in a multidisciplinary setting.

differentiated neoplasms into five categories based on morphological and molecular features:

(1) Follicular thyroid carcinoma (FTC);
(2) Follicular variant papillary carcinoma (FVPTC);
(3) Papillary thyroid carcinoma (PTC);
(4) Oncocytic carcinoma (OCA), formerly known as Hürthle cell carcinoma;
(5) Follicular-derived carcinomas, high-grade, including:
    (a) Differentiated high-grade thyroid carcinoma (DHGTC) with papillary/follicular/oncocytic features;
    (b) Poorly differentiated thyroid carcinoma (PDTC).

DTCs represent 90% of all TCs and harbor a variety of molecular drivers and clinical behaviors (Fig. 1). The majority is cured with surgery, with a 5 year-overall survival (OS) rate exceeding 90%. Age $\geq$60 years is the most relevant prognostic factor for recurrence and mortality. Almost 10% of DTCs develop metastases (mDTC), 5% are found at diagnosis and 5% after months/years from the primary treatment. Risk factors for recurrent/metastatic disease are highlighted in the last American Thyroid Association (ATA) and European Society of Medical Oncology (ESMO) guidelines [4,5]. Patients with mDTCs have 5- and 10-year mortality rates of 65% and 75%, respectively [5]. Central nervous system (CNS) and multiorgan metastases are associated with worse prognosis [6]. A recent study performed on the Surveillance, Epidemiology, and End Results (SEER) database on 530 patients with mDTC at diagnosis assessed that synchronous bone and lung or liver/brain metastases (BMs) predicted unfavorable short-term outcomes, independently from surgical and radioactive iodine (RAI) primary treatment [7]. In the metastatic setting of RAI-avid DTCs, the repetition of RAI therapy is recommended up to a cumulative dose of 600 mCi, in absence of RAIR disease. Thyroid stimulating hormone (TSH) suppression with levothyroxine targeted to a TSH serum level below 0.1 lU/ml is recommended for all patients with persistent DTC in the absence of specific contraindications, as it reduces the risk of recurrence/progression [8].

In the RAIR DTCs metastatic setting, the initiation of systemic therapy is suggested in case of symptomatic and/or progressive disease, defined as 20% increase in sum of longest diameters of target lesions or the appearance of new lesions [5]. Selective treatment of metastases can be evaluated in case of oligometastatic disease, defined as 1–5 metastatic lesions in safely treatable metastatic sites [9]. International guidelines support the treatment of individual distant metastases of RAIR DTCs [4,5,10]. In comparison with active surveillance, local therapies aim to prevent local complications, improve symptoms such as pain/mass effect, delay the initiation of systemic treatments and improve disease control in patients with few metastases. ATA guidelines recommend stereotactic radiation or thermal ablation to be considered prior to initiation of systemic treatment when distant metastases are symptomatic or at high risk of local complications. Local therapies can be also considered for oligoprogressions during systemic treatment [4].

DTC histotypes have distinct genetic landscapes and specific metastatic patterns [11] related to different prognoses [12▪▪]. Currently, in the oligometastatic setting, indications and feasibility of each treatment modality vary on the site and size of the lesions, independently from the histotype and molecular features. Here we present the current options to treat RAIR DTC oligometastases according to the sites most frequently involved (Fig. 2).

LUNG OLIGOMETASTASES

Lung is the most frequent metastatic site in DTC. In a recent SEER-based study on 1608 patients treated with RAI therapy, 61.9% had pulmonary metastases; the onset was associated with advanced age, poor differentiation, FTC, lymphatic metastasis, tumor size >10 mm, and extracapsular invasion [13]. In another SEER-based study, isolated lung metastases implied better OS and disease-specific survival than lung–liver, lung–brain, and lung–other multiple metastases; better survival outcomes were related to age <55 years, surgery to the primary site and to the distant sites [14].

	PTC	FVPTC	FTC	OCA	DHGTC	PDTC
Oncogenic drivers	-BRAFV600E mutation -RET fusion -NTRK fusion	-Encapsulated variant: RAS gene family mutations (NRAS > HRAS > KRAS) -Infiltrative variant: BRAF V600E mutation	-RAS gene family mutations (most prevalent NRAS > HRAS > KRAS) -AKT pathway (PTEN, PIK3CA) -PAX8-PPARG fusion	Mitochondrial DNA (mtDNA) mutations, Chromosome 7-12-17 amplification, RAS, EIF1AX, TERT, TP53, NF1, and CDKN1A mutations	The majority develop from PTC: BRAF V600E mutation + additional genetic changes (TP53, TERT promoter mutations)	The majority develop from FTC: RAS mutations + additional genetic changes (TP53, TERT promoter mutations)
Differentiation	Good	Good	Good	Good	Good	Poor
Grade	Low	Low	Low	Low	High	High
Prevalence	80-90%	25% of PTCs*	10%	4%	-	5%
% with single-organ metastases at presentation [Ref. (12)]	53.9%	ND	11.9%	2.8%	ND	1.6%
% with multi-organ metastases at presentation [Ref. (12)]	38.3%	ND	14.9%	3.1%	ND	1.7%
Prevalent pathway of metastasization	Lymph nodes	Blood Lymph nodes	Blood	Blood	Lymph nodes	Blood
Prevalent metastatic patterns [Ref. (12)]	Distal nodes (30.5%) Lung (53.4%) Bone (28.1%) Liver (8.3%) Brain (4.7%) [Ref. (6)]	Distal nodes 7% encapsulated 65% infiltrative	Bone (> 60%) Lung (> 40%) Liver (< 5%) Brain (> 5%)	Lung (> 60%) Bone (>40%) Liver (10%) Brain (< 5%)	ND	Lung (70%) Bone (40%) Brain (10%)

FIGURE 1. Molecular and clinical features of differentiated thyroid cancers categorized according to the last WHO Classification of Thyroid Neoplasms (5th Edition, 2022). DHGTC, differentiated high-grade thyroid carcinoma (with papillary/follicular/oncocytic features); FTC, follicular thyroid carcinoma; FVPTC, follicular variant papillary carcinoma; ND, no data available*; OCA, oncocytic carcinoma of the thyroid (formerly known as Hürthle cell carcinoma); PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma. *FVPTC and DHGTC are recently introduced categories.

Lesions are usually multiple, bilateral, ranging from few millimeters (micronodular) to ≥1 cm (macronodular). Three main patterns of progression have been identified in a population with DTC macronodular lung lesions: slow (≥3 years), moderate (1–3 years), and rapid (<1 year), with an estimated doubling time of tumor burden of 19.3, 5.9, and 1.8 years, respectively. Disease progression within the first year was an independent predictor of cancer-specific survival (hazard ratio [HR] = 8.6; $P = 0.003$) [15]. The identification of growth pattern can help the clinician to select the best approach for each patient, opting for active surveillance, local treatment, or systemic pharmacotherapy. For slow-moderate growing lesions, the treatment of oligometastases can be evaluated to achieve disease control and delay the need for systemic treatment. ATA guidelines support the use of SBRT delivered at cumulative doses of 20–75 Gy in 5–15 fractions, reporting a high local control rate (63–98%) and complete response rates of 70–90% at 2–3 years, whereas G3–G4 toxicities (pneumonitis, pleural effusion) were reported in less of 3% of cases. ESMO Guidelines suggest considering metastasectomy in patients with oligometastases and good PS, whereas RFA is an alternative for solitary, small (<3 cm) and/or symptomatic lesions not amenable to surgery [5]. ATA guidelines highlight the possibility of using RFA on small lesions without soft tissue or mediastinum invasion and without contact with large vessels; the procedure can be repeated on the same lesion. Pneumothorax/pleural effusions were observed in up to 50% of RFA procedures, but they rarely required further treatments [4].

A retrospective study on 47 patients from 10 centers (TUTHYREF network) with lung lesions treated by thermal ablation (TA) techniques over 10 years showed that OS after TA was 93% at 2 years (95% confidence interval [CI]: 86–94) and 79% at 3 years (95% CI: 66–91) overall [16▪▪]. Histology played a relevant role on the survival outcomes: OS at 3 years was 94% for follicular, oncocytic, or

	SURGERY	RADIATION THERAPY	INTERVENTIONAL RADIOLOGY
Lung	**Metastasectomy** if slow-progressing lesion (doubling time < 3 years) and good PS	**SBRT** (e.g. 20-75 Gy in 5-15 fractions) If slow-moderate progressing lesion	**RFA** If solitary, small (< 3 cm) and/or symptomatic lesions not amenable to surgery, without soft tissue/mediastinum invasion and without contact with large vessels
Bones	**Metastasectomy** young patients having solitary spinal lesion without non-spinal BMs or other organ metastases **Spinal stabilization + SBRT** If pathological or impending fracture risk and spinal cord compression with or without vertebral fracture	**SABR/SBRT** Inoperable bone lesions associated with pain or high fracture risk	**Embolization** Prior to surgical resection of bone metastases to reduce the intraoperative bleeding risk; it can be combined with SBRT **Cementoplasty/vertebroplasty** If symptomatic osteolytic spinal metastases at risk of SRE. Vertebroplasty can be combined with RFA **RFA/CA** to achieve rapid (1 – 7 days) and long-lasting pain control. CA can treat larger lesions than RFA and can be associated with cementoplasty
Liver	**Metastasectomy** can be considered for solitary and slow-progressing lesions (few data available)	**SBRT** if RFA/TACE not feasible	**RFA*** If lesion < 30 mm, distant at least 3 mm from surrounding vessels, well visible on ultrasonography (avoid RFA if lesion at the hilum) **TACE*** if multiple liver metastases with bilobar liver involvement and adequate arterial vascularization *Techniques can be repeated and combined in case of large and highly vascularized lesions
CNS	**Neurosurgery + SRS/SRT** If solitary lesion suitable to surgery	**SRS (e.g. Gamma Knife)** If solitary lesion **SRS/SBRT +/- systemic therapy** if multiple lesions (n < 10) and good prognostic profile (favorable PS, controlled extra-CNS disease and expected survival > 3 months) **WBRT** If multiple lesions (n > 10) and uncontrolled extra-CNS disease	ND

FIGURE 2. Current options for the treatment of oligometastases from RAIR DTCs according to the sites most frequently involved. CA, cryoablation; CNS, central nervous system; ND, no data available; PS, performance status; RFA, radiofrequency ablation; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; SRE, skeletal related event; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; TACE, transartherial chemoembolization; WBRT, whole brain radiation therapy.

papillary follicular variant carcinomas, compared to 59% for papillary and insular carcinomas ($P = 0.0001$). No major (G4–G5) CTCAE complications were observed.

BONE OLIGOMETASTASES

Bone metastases (BoM) are found in 2–13% of DTCs and in 50% of mDTCs, usually presenting as osteolytic lesions with soft tissue involvement in the axial skeleton. Compared with PTC, FTC has threefold higher rate of BoM. In 43% of FTCs and 26.5% of OCAs bone is the only metastatic site. Metastases to bone alone correlate with improved outcome compared to liver, lung, and brain alone [12▪▪]. Overall, the 10-year OS of patients with BoM ranges from 13% to 21% [17]. Almost 78% of patients with DTC BoM experience skeletal-related events (SREs) as pathologic factures, spinal cord compression and malignant hypercalcemia; 65% of them experience a second SRE after a median of 10.7 months [18].

Compared with active surveillance, locoregional treatments provide a longer progression-free survival (PFS) and may be curative [5]. Surgical approaches are recommended for persistent pain, spinal instability with/without spinal compression, neurologic injury and impending fracture risk [17]. A score of 13–18 at the Spinal Instability Neoplastic Score (SINS) indicates the need of surgical stabilization [19].

Bone surgery for mDTCs includes [20]:

(1) *Metastasectomy*. Complete resection of the bone metastases is appropriate for young patients with solitary spinal lesion without nonspinal BMs or other organ metastases, and it can prolong survival.
(2) *Palliative surgery*. Bone stabilization, with or without partial tumor resection, is indicated in the presence of impending fracture risk and spinal cord compression with or without vertebral fracture. For limb lesions, EBRT after surgery

gives the best outcomes, reducing progression and preventing prosthesis displacement [21].

SBRT is a highly conformational technique [22]. NCCN guidelines recommend surgical palliation and/or SBRT for symptomatic or asymptomatic lesions in weight-bearing sites [10]. As reported in ATA guidelines, SBRT achieve high local tumor control rate (88–100%), especially in sites of previously surgically resected BoMs, with a pain relief rate of 30–83% [4]. The major limitation of SBRT in spine lesions is the cumulative dose potentially leading to neural injury. SBRT may increase number of SRE in patients with risk factors such as elderly, preexisting fracture, osteolytic lesions, high tumor burden, high radiation dose and baseline BoM-related pain. These cases require evaluation for prophylactic vertebral stabilization prior to SBRT [23].

Inoperable bone lesions associated with pain or high fracture risk can be treated with hypofractioned SBRT (20 Gy/5 fx, 30 Gy/10 fx) or a single-fraction external SBRT (8 Gy) and/or interventional radiology techniques [5]. The latter provide minimally invasive alternatives to surgery for of patients with poor performance status (PS), small BoM and/or a local recurrence at a site of previous surgery [17]. Percutaneous techniques can be:

(1) *Vascular*. Embolization induces rapid tumor shrinkage and pain relief. It can be considered prior to surgical resection of BoMs to reduce the intraoperative bleeding risk [10]. Embolization followed by EBRT allows to achieve a longer symptoms control compared with embolization alone (15 vs. 6.5 months) [24].
(2) *Consolidative* (cementoplasty, vertebroplasty). The injection of polymethylmethacrylate in unstable bone segments is indicated for patients affected by symptomatic osteolytic spinal metastases at risk of SRE. Vertebroplasty can be combined also with RFA.
(3) *Ablative*. ATA guidelines support the use of RFA and cryoablation (CA) to achieve rapid (1–7 days) and long-lasting pain control. CA can treat larger lesions than RFA and it is frequently associated with cementoplasty to consolidate the bone.

In case of spinal cord compression, the preferred treatment approach correlates with life expectancy. If prognosis exceeds 6 months, surgery and long RT fractionations are recommended (e.g. 30 Gy in 10 fractions); below a 6-months prognosis, either a single fraction of 8 Gy or 20 Gy in 5 fractions EBRT can be used to alleviate pain and neurological complications [5,25].

LIVER OLIGOMETASTASES

Liver is involved in 10% of mDTCs, but single-organ dissemination to the liver is found in <5% of cases [12▪▪]. Lesions are usually multiple, but locoregional therapies can be proposed in selected cases. The prognostic advantage of metastasectomy is still debated, and few cases of liver metastasectomy in DTCs have been reported in the literature so far [26]. The most frequently employed techniques are trans-arterial chemoembolization (TACE) and RFA (both laparoscopic and percutaneous). Other possible strategies are also available and explored in a recent review [27].

The best outcome of RFA is associated to lesions with maximum diameter below 30 mm, distant at least 3 mm from surrounding vessels, and clearly visible on ultrasonography. RFA should be avoided if the metastatic lesion is located at the hepatic hilum, due to the possible damage of biliary ducts and vessels [5]. Ablation is performed by radiofrequency needles introduced into the lesion under ultrasound guidance, inducing thermal tumor cell necrosis. Adverse events from ablation of liver lesions include intestinal perforation, abdominal pain or intraperitoneal bleeding [4]. If both surgery and RFA are contraindicated, hepatic TACE can be evaluated [5]. TACE is suitable in case of multiple liver metastases with bilobar liver involvement and adequate arterial vascularization. It is performed under fluoroscopic guidance and requires the selective catheterization of the hepatic artery followed by the superselective catheterization of the target lesion in the liver with drug-eluting beads usually loaded with anthracyclines. Possible adverse events include liver function test abnormalities, nausea, abdominal pain and fatigue.

In case of large and highly vascularized lesions, both RFA and TACE can be combined. The response to locoregional treatments can be evaluated by abdominal CT scan performed 3–4 weeks after the procedure.

CENTRAL NERVOUS SYSTEM OLIGOMETASTASES

Less than 1.5% of patients with DTC – mostly PTCs – present with BMs at diagnosis, but almost 4.5–18% of patients with metastatic TC can develop BMs. Therefore, a CNS study is required in the imaging of RAIR mDTC. The diagnostic work-up of patients with suspected BM includes cranial MRI with pre and postcontrast T1-weighted, T2-weighted and/or T2-FLAIR and diffusion-weighted sequences. The prognosis is dismal (7–33 months), but it can be improved with a comprehensive treatment. The optimal strategy should be defined in a multidisciplinary setting involving oncologists, radiologists, radiation oncologists and neurosurgeons.

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Solitary CNS lesions can be treated with resection and/or stereotactic radiosurgery (SRS), that allows spatially precise high-dose irradiation of intracranial tumors in a single fraction [10]. A retrospective study reported that both SRS and neurosurgery had an impact on PFS, but only neurosurgery improved also OS [28]. For multiple CNS lesions, the EANO–ESMO Guidelines recommend that the individuals with favorable prognostic factors (less than 10 BMs, controlled extra-CNS disease, good PS and expected survival > 3 months) should receive surgery followed by SRS/SRT, or SRS/SRT, or surgery followed by systemic pharmacotherapy, or directly systemic pharmacotherapy [29]. Since NTRK- and RET-inhibitors penetrate through the blood-brain barrier, a molecular profiling of the primary DTC should be obtained. In patients undergoing surgery, treatment-relevant predictive biomarkers detected in the primary tumor should be reconfirmed in the resected BM [29].

A multicenter study evaluated the efficacy of Gamma Knife SRS on the BMs of 42 patients, divided between PTC (83%) and FTC (17%) histologies [30▪▪]. Median number of BMs per patient was 2 (range 1–10), median SRS dose 20 Gy (range 8–24). At a median follow-up of 25.2 months, complete response, partial response and stable disease were documented in 26%, 24% and 33% of patients, respectively. Local failure (progression and/or radiation necrosis) was found in 4% of treated BMs. Median survival after SRS was 14 months (range 3–58). OS was inversely correlated with the number of BMs (1 vs. ≥2) and directly correlated with the performance status at the time of SRS. Radiation necrosis and other adverse radiation events can occur in 10% of cases treated with SRS.

Whole brain radiotherapy can be considered in cases with >10 BMs and uncontrolled extra-CNS disease, but it is not recommended in the oligometastatic setting [29]. For progressive and/or symptomatic disease not amenable to RT or selective targeted therapy, the initiation of systemic treatment can be considered, balancing the bleeding risk given by BMs with the same risk given by antiangiogenic therapy. In a retrospective study on 35 patients with DTC BMs, 60% had hemorrhagic lesions, and the risk was directly related to size of the lesion (>1 cm) [31].

CONCLUSION

The clinical management of patients with metastatic RAIR DTC is challenging, as this condition does not require *per se* the immediate initiation of systemic therapy. International guidelines agree on treating oligometastatic cases with locoregional approaches. Future research should address the issue of whether selective targeted therapy (e.g. RET-/NTRK-inhibitors) may be combined with these treatments, aiming to increase the rate of patients with potentially curable oligometastatic disease.

Acknowledgements

None.

Financial support and sponsorship

The authors declare that no external assistance nor financial support/sponsorship were provided for the purposes of this review.

Conflicts of interest

L.L. received occasional conference honoraria/Advisory Board fees from Astrazeneca, Bayer, MSD, Merck-Serono, AccMed, Neutron Therapeutics, Inc. E.C. and A.O. have not potential conflicts of interest to disclose.

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