In the Name of God

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Management of Advanced Thyroid Cancer: Overview, Advances, and Opportunities

American Society of Clinical Oncology. 2023 .

- ***Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 30: 1856–1883, 2019***
- ***Differentiated thyroid cancer refractory to standard treatment: Systemic therapy; Uptodate 2023***
- ***Medullary thyroid cancer: Systemic therapy and immunotherapy; Uptodate 2023***
- ***Anaplastic thyroid cancer ; Uptodate 2023***
- ***The Evolving Treatment Landscape of Medullary Thyroid Cancer. Current Treatment Options in Oncology (2023) 24:1815–1832***

Thyroid cancer is the **most common** endocrine malignancy with the prevalence in the United States currently exceeding 900,000 cases. Rates vary widely from country to country, with the highest figures (per 100 000 person-years) reported in Lithuania (15.5), Italy (13.5), Austria (12.4), Croatia (11.4) and Luxembourg (11.1).

Estimated incidence rates among females were approximately threefold higher than those for males (9.3 and 3.1 cases per 100 000 person-years).

The ***rising incidence*** rates are almost entirely due to the increased diagnosis of papillary thyroid cancers (PTCs) in particular. Incidence rates for follicular (FTC), anaplastic (ATC) and medullary (MTC) thyroid cancers have remained relatively stable over the past 30 years.

Overall, the majority of thyroid cancers detected are early-stage well-differentiated thyroid cancers (DTCs) that have an excellent prognosis; some evidence shows that the incidence of advanced thyroid cancers has increased in recent years. In 2022, 2,230 patients died of thyroid cancer in the United States.

Follicular-derived thyroid cancers include papillary thyroid cancer, follicular thyroid cancer, Hurthle cell cancer, poorly DTC, and undifferentiated (anaplastic) thyroid cancer (ATC).

Although surgery and radioactive iodine (RAI) are the **standard** of care for DTCs often leading to cure, patients with radioactive-iodine refractory (RAIR) disease DTCs, and ATCs confer poorer prognosis and pose significant challenges for treating clinicians.

Medullary thyroid cancer (MTC) arises from parafollicular or C cells and accounts for fewer than **5%** of thyroid cancer diagnoses but approximately **13%** of thyroid cancer deaths.

They can secrete calcitonin and carcinoembryonic antigen (CEA), both of which can serve as tumor markers, along with other humoral substances that may contribute to **paraneoplastic syndromes.**

MTCs occur either as sporadic tumors or as inherited components of multiple endocrine neoplasia (MEN) type 2.

Approximately 20% of cases are familial secondary to a germline rearranged during transfection **(RET) mutation** while the remaining cases are sporadic.

Patients with MTC who present with regional lymph node metastases and/or distant metastases are less likely to be cured of their disease.

The presence or absence and the type of RET mutations have an impact on the choice of first-line therapy, RET inhibitor drugs, or multikinase inhibitors (MKIs).

The primary treatment for MTC is extensive and meticulous surgical resection. External beam radiation therapy (EBRT) has a limited role. For patients with progressive or symptomatic metastatic disease who cannot be treated with surgery, radiotherapy, or other focal ablative interventions, targeted systemic therapies are effective interventions.

Radiation therapy is efficacious in the management of **bone metastasis** to alleviate pain and to prevent skeletal-related complications (i.e., spinal cord compression, or a pathological fracture) or in the management of a single growing metastatic **liver lesion**. Bone metastases should also be treated with bisphosphonates or the RANK-L inhibitor denosumab.

This review focuses on the current status of advanced thyroid cancer treatment options, summarizing the role of surgery in advanced thyroid cancer management, challenges in the management of RAIR thyroid cancer, and advances in systemic therapies, particularly progress pertaining to targeted therapies.

DEFINITION OF ADVANCED THYROID CANCER:

Advanced thyroid cancer is a term used to describe aggressive tumors; however, there is significant variability among specialties.

Surgeons refer to unresectable tumors as advanced thyroid cancers,

Endocrinologists to describe RAIR tumors,

and oncologists when there are distant metastases.

A recent consensus statement by the American Head and Neck Society (AHNS) Endocrine Surgery Section and International Thyroid Oncology Group defined advanced thyroid cancer according to four categories.

The **structural/surgical category** encompasses the following:

(1) bulky, invasive, or inoperative locoregional disease;
(2) recurrence;
(3) distant metastases;
(4) gross residual neck disease without option for reoperation;
(5) rapid progression on imaging;
(6) imminent threat posed by tumor burden.

Tumors refractory to RAI, unresponsive to thyroid-stimulating hormone (TSH) suppression, and rapid calcitonin, carcinoembryonic antigen, or thyroglobulin doubling times constitute the **biochemical category**.

The **histologic/ molecular category** includes findings such as poorly differentiated or other aggressive histology components, high Ki67 index, high mitotic count or tumor necrosis, and all anaplastic thyroid carcinoma.

Finally, tumors can be categorized as advanced thyroid cancer at the discretion of the treating physician if there are features that portend aggressive tumor behavior (**clinician prerogative**).

PRACTICAL APPLICATIONS

• Surgical management of advanced thyroid cancer is challenging and should evolve multidisciplinary discussion integrating individual disease characteristics, expected surgical morbidity, and patient preferences.

• Common clinical scenarios suggestive of **RAI refractory thyroid cancer** include a negative diagnostic RAI uptake whole body scan, loss of RAI uptake on post-therapy RAI scan, presence of RAI in some tissues but not others, and metastatic disease progression despite ability to concentrate RAI, including a cumulative activity of >600 mCi.

• An improved understanding of thyroid cancer pathogenesis has led to a remarkable change in the landscape of available **systemic targeted therapies** for patients with advanced and refractory disease in the past several years.

• Treatment decisions regarding use of targeted therapies for advanced thyroid cancer should be made judiciously by a multidisciplinary team while weighing risks versus benefits and undertaking close surveillance for disease progression and adverse events.

Preoperative workup in patients with thyroid cancer includes imaging and thyroid function tests. Ultrasound is the recommended initial imaging modality and should include the thyroid, central compartment, and bilateral lateral neck nodes.

Additional imaging, CT and MRI with IV contrast for suspicion for local invasion, and multiple or bulky lymphadenopathy. Chest CT for low mediastinal nodes or pulmonary metastasis.

PET may be used in recurrent cases or for surveillance.

When invasion is suspected, additional preoperative workup including **larynx evaluation**, **swallow function**, and dedicated imaging with CT of the chest (trachea) and MRI (esophagus) is recommended.

ROLE OF SURGERY IN ADVANCED THYROID CANCER DTC

According to the ATA guidelines, patients with DTC are subdivided into three categories with treatment implications:

1. Thyroid cancer >4 cm, gross extrathyroidal extension (ETE; clinical T4), nodal disease (clinical N1), or distant metastasis

2. Thyroid cancer >1 cm and <4 cm without ETE and without nodal disease or metastasis

3. Thyroid cancer <1 cm without ETE and without nodal disease

For group 1, total thyroidectomy is the recommended treatment. For patients in group 2, either option of lobectomy or total thyroidectomy is acceptable. The decision making process involves a cohesive discussion between the treatment team and the patient. If RAI is planned or likely to be recommended, total thyroidectomy would be indicated.

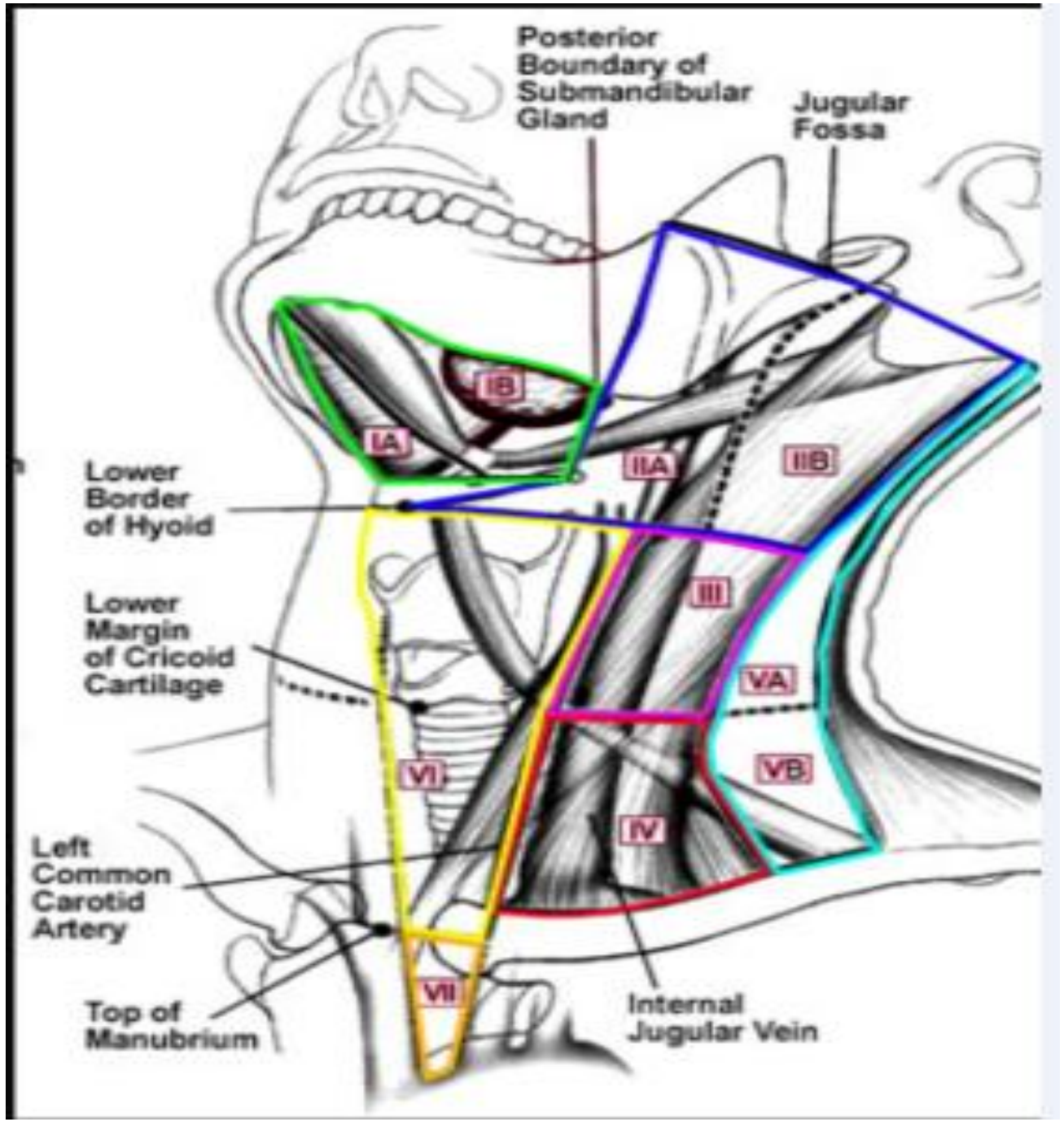
Finally, for patients in group 3, watchful waiting with surveillance may be an option in cases of low-risk differentiated tumors; if surgery is preferred, thyroid lobectomy is recommended unless there is an **indication to remove the contralateral lobe** or a history of **previous head and neck radiation** or **familial thyroid carcinoma**.

The ATA guidelines incorporate indications for nodal dissection.

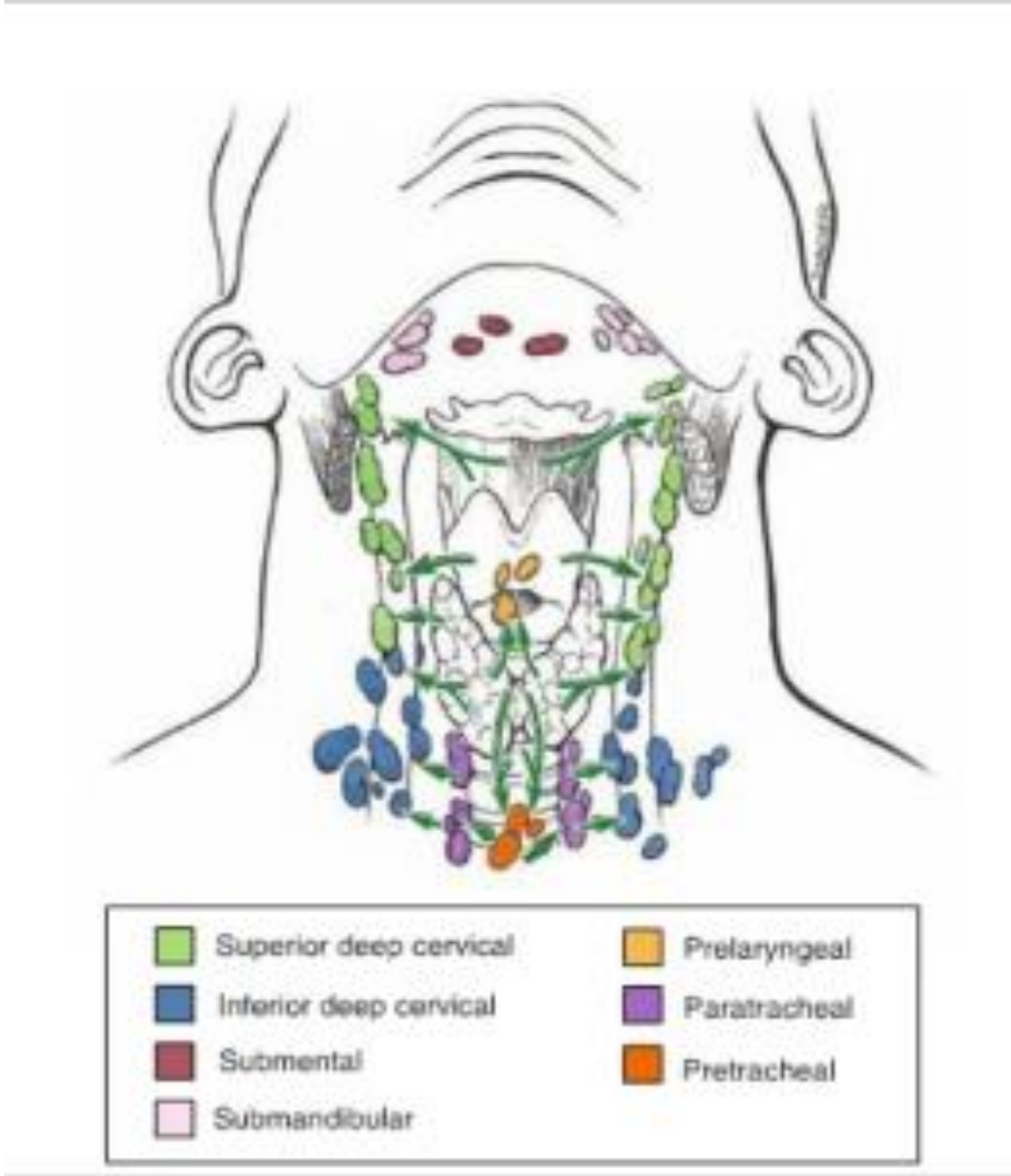
.With clinically evident central compartment and/ or lateral neck disease, dissection is recommended at the time of initial surgery. Central compartment lymph node dissection, or level VI, includes pretracheal and paratracheal nodes. Lateral neck dissection typically incorporates level II-IV nodal levels.

Nodal dissection of an additional level may be incorporated if there is clinically evident nodal disease.

.Prophylactic central compartment dissection can be considered in patients with papillary carcinoma (T3 or T4), clinically involved lateral nodes, or if the nodal tissue may guide adjuvant treatment.



lateral neck extending from the skull base superiorly to the clavicle inferiorly and from the strap muscles medially to the posterior border of the sternocleidomastoid muscle laterally


Superior deep cervical
Inferior deep cervical
Submental
Submandibular
Prelaryngeal
Paratracheal
Pretracheal

Invasive DTC occurs in up to 15% of patients, the AHNS published a series of consensus statements in 2014.

The recurrent laryngeal nerve (RLN) is involved in 33%-61% of patients with invasive cancer. **Fiberoptic laryngoscopy** is the preferred method of laryngeal evaluation, particularly when voice is abnormal, if history of thyroid surgery, or if ETE is suspected.

Management of the RLN during surgery varies according to preoperative function, degree of invasion, and status of the contralateral nerve and has important functional implications for voice, breathing, and swallow. Although intraoperative RLN monitoring is commonly used for evaluation of nerve status.

Postoperative unilateral dysfunction is often evident if voice changes occur and may lead to aspiration, whereas bilateral dysfunction typically presents with shortness of breath and stridor.

Preservation of the **parathyroid glands** should be attempted with dissection along the thyroid capsule to avoid inadvertent injury to their vascular supply. Intraoperatively, the thyroid specimen should be carefully examined after removal for any parathyroid tissue. If identified, the parathyroid should be reimplanted into nearby muscle, and postoperative calcium and parathyroid hormone levels should be monitored.

Trachea and larynx may be abutted or directly invaded in patients with advanced DTC. If invasion is suspected, **direct laryngoscopy** and **bronchoscopy** are performed. Because esophageal invasion usually involves only the muscularis layer, extent of **invasion may not be seen on esophagoscopy**. Similar to the larynx and trachea, esophageal resection may be limited to the outer layers or involve composite resection if intraluminal tumor is present.

Although rare, in cases of suspected major vascular invasion by tumor, CT or magnetic resonance angiogram is performed preoperatively.

It is important to note that nearly **one-quarter** of patients with invasive cancer die from **airway obstruction** secondary to tracheal invasion and **28%** from respiratory failure secondary to **lung involvement**.

Patients with locally invasive cancer who are candidates for surgical resection and achieve gross total resection have good outcomes, with one study reporting >90% 5-year disease-free survival.

Tumors invading the prevertebral fascia or encasing the carotid artery are classified as unresectable; there are instances when near total gross resection may be indicated for palliation in well-differentiated tumors with overall good outcome. palliation with **tracheostomy** may be recommended in patients where airway obstruction from tumor is imminent or when planned for nonsurgical therapy.

Finally, some patients who would not have been good candidates for surgery may now be considered for surgical treatment either for **local disease control or for palliation**. The nuances stemming from having received neoadjuvant treatment and the implications on surgery remain to be studied.

In 2016, the AHNS published a consensus statement recommending revision surgery for tumor and nodal recurrence, if feasible. In revision surgery, the primary goal is to **remove recurrent cancer** in the thyroid or nodal tissue, remove remaining thyroid tissue, and perform nodal dissection in regions suspected to have microscopic disease.

Medullary Thyroid Carcinoma

Total thyroidectomy and central neck dissection (level VI), with dissection of lymph nodes in the lateral compartments (levels II-V) depending on calcitonin levels and ultrasound findings, is a standard treatment for patients with sporadic or hereditary MTC.

When preoperative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, **contralateral neck dissection** should be considered if the **basal serum calcitonin level is >200 pg/mL.**

Anaplastic Thyroid Carcinoma

Surgical options must be carefully evaluated in patients with ATC while balancing risks and benefits with goals of care. The primary goal for resectable tumors (stages **IVA** and **IVB**) is an aggressive approach with **complete resection**, followed by definitive **chemoradiation**.

In stage IVC ATC, the limited benefit from surgery must be carefully weighed against other palliative approaches, such as radiation and systemic therapy.

RAIR-DTC

After thyroidectomy, RAI remains the most frequently used adjuvant therapy for follicular-derived thyroid cancers, with the main goals to improve disease-specific **survival**, reduce **recurrence** rates, and improve progression-free survival (**PFS**). Several patients with advanced DTC are radioactive-iodine resistant/refractory.

According to the 2015 ATA guidelines, DTCs are considered refractory to RAI when (1) they do not concentrate RAI at the time of initial treatment, such as in patients with structurally evident disease and a negative RAI uptake whole-body scan; (2) they lose their ability to concentrate RAI in the setting of previous RAI uptake, often occurring in patients with multiple large metastases; (3) concentrate RAI in some tissues but not others, evident by comparing findings from a RAI whole-body scan with those from a 18FDG-PET scan; or (4) there is metastatic disease progression despite ability to concentrate RAI.

The exact definition of RAIR-DTC is still controversial, and different definitions have been proposed by different societies. A recent consortium of experts from the ATA, the European Association of Nuclear Medicine, … noted that **no current definition**, classification, criterion, or clinical scenario is an absolute indicator that a patient has RAIR DTC. The common clinical scenarios suggesting that
a patient may have RAIR-DTC derived from this consortium are outlined in Table 1 and provide a framework addressing important management issues in patients with RAIR-DTC.

TABLE 1. Common Clinical Scenarios Suggestive of RAIR-DTC

Clinical Scenario	Considerations
No RAI uptake on diagnostic ^{131}I scan	Adequate low-iodine diet and TSH stimulation before scan High-resolution imaging with SPECT/CT scan provides more functional detail than planar imaging
No RAI uptake on a post-therapy ^{131}I scan (performed several days after therapy)	Post-therapy ^{131}I scans may miss up to 12% of DTC metastases that have RAI uptake
RAI uptake is only present in some but not other tumor tissues	Can treat RAI-avid tumor tissues with ^{131}I and use local treatment modalities for non–RAI-avid tissues
Progression of DTC metastases despite ^{131}I uptake	Metric used for successful response to previous ^{131}I therapy, duration of response, metric used to determine progression of disease post-^{131}I therapy, amount of ^{131}I activity previously administered, potential for administering higher ^{131}I activity, side effects, and patient preferences should be considered when deciding to pursue additional ^{131}I administrations
Progression of DTC metastases despite cumulative ^{131}I activity of >600 mCi	Increased likelihood of DTC becoming RAIR with increased cumulative ^{131}I activity and number of doses Response to previous treatments, duration of response, individual ^{131}I activity administered in each previous treatment, side effects, and patient preferences should be considered when deciding to pursue additional ^{131}I administrations

Abbreviations: DTC, differentiated thyroid cancer; mCi, millicuries; RAI, radioactive iodine; RAIR, radioactive-iodine refractory; SPECT/CT, single-photon emission computed tomography with computed tomography; TSH, thyroid-stimulating hormone.

Importantly, factors such as the amount of RAI uptake on post-therapy whole-body scans compared with the total RAI dose the patient received, tolerability of side effects, and tumor response to previous RAI treatments should be considered to optimize therapy in these patients.

Patients with inoperable and/or metastatic RAIR-DTC have a worse overall prognosis than those who have RAI sensitive follicular derived thyroid cancers.
Before the routine availability of targeted therapies, studies showed that patients with RAIR-DTC had median 5-year survival rates of 60%-70%, and those with **metastatic RAIR-DTC had the worse outcomes** with a median 10-year survival rate of 10%.

The significance of **identifying** patients who may **harbor RAIR** disease lies with the need for early intervention in these patients to improve disease-free progression and survival, with **molecular testing** and **mutational mapping** having emerged as adjuncts to imaging and pathology of identification of more aggressive disease.

Many patients with RAIR-DTC have **slow-growing**, low volume disease. For patients with **asymptomatic RAIR DTC** which may persist for years, low tumor burden or minimal progression over time, **watchful waiting with TSH suppression**, and periodic imaging can be used.

In patients with **locoregional recurrence**, surgical intervention is usually used as the therapeutic approach of choice, with external-beam radiation therapy used in combination with surgery in select cases. Typically, **symptomatic patients with distant metastases** to the lungs and/or bone are often offered local therapies before consideration of systemic treatments.

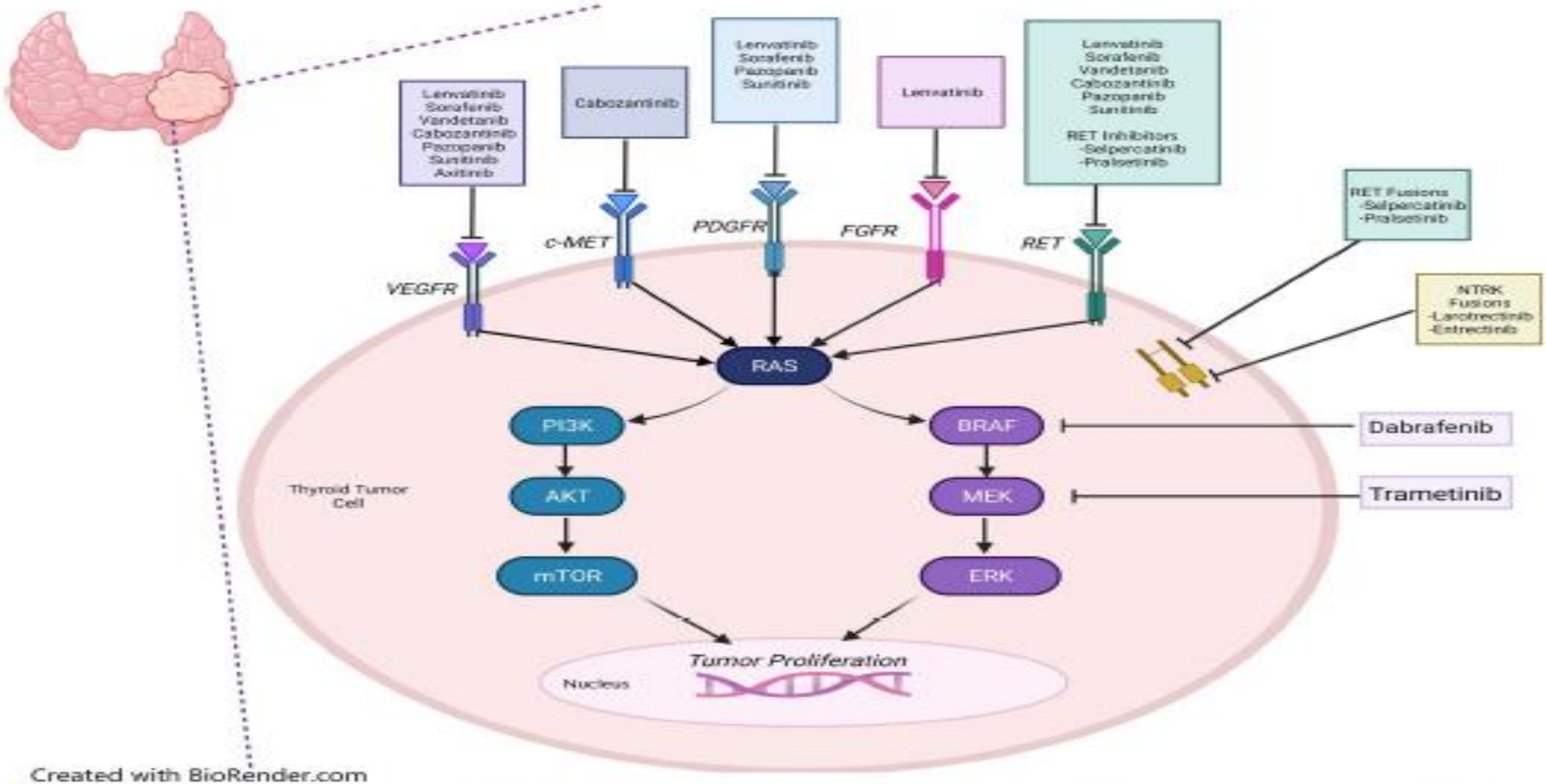
SYSTEMIC THERAPY IN ADVANCED THYROID CANCER

The decision to initiate systemic therapy in thyroid cancer is an area in endocrine oncology where significant clinical practice **variability** exists. The specific histopathological variables play a role in the timing of antineoplastic treatment.

In general, the sole increase of tumor markers is not decisive in starting systemic therapy for thyroid cancer. Patients with metastatic RAIR-DTC and MTC with asymptomatic disease and small tumors with slow indolent progression are amenable to close active surveillance with serial imaging. Specifically, for RAIR-DTC and MTC, **targeted therapy** is recommended for (1) **rapidly progressive** tumors not amenable or failure to alternative localized therapies, (2) **symptomatic** disease, or (3) tumors in a **threatening location**.

The evolving availability of different molecular testing modalities has allowed the incorporation of precision oncology for prognostic and therapeutic purposes in advanced thyroid cancer and is consistent with current National Comprehensive Cancer Network guidelines. Given the potential for druggable targets, the preferred somatic testing approach is next-generation sequencing (NGS) in contrast to single-gene tests. **All ATC** tumors should undergo **molecular testing**.

However, immunohistochemistry (IHC) evaluation for **BRAF V600E** should also be incorporated into the initial assessment of ATC while awaiting NGS results; rapid BRAF V600E IHC–positive results can lead to early therapeutic interventions with dabrafenib and trametinib.



RG 1. Available systemic targeted therapies for advanced thyroid cancer and mechanisms of action. ERK, extracellular-regulated kinase; FGFR, fibroblast growth factor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor α; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; VEGFR, vascular epithelial growth factor receptor.

DTC

Distant metastases occur in fewer than 10% of patients with DTC. Half are present when the tumor is first discovered; the others are found later, sometimes decades after initial treatment.

Metastases are observed most frequently in patients with **aggressive histological** subtypes (e.g. tall-cell, hobnail, diffuse sclerosing and columnar-cell variants): vascular invasion, large primary tumors, macroscopic extrathyroidal extension, bulky locoregional nodal disease.

The most common sites are lungs and bones. Bone metastases are more common in FTC than in PTC. Distant metastases are usually diagnosed because of clinical symptoms or suspicious imaging/laboratory findings (abnormal uptake on a post-ablation WBS, or a positive finding on an FDG– PET-CT scan or a cross-sectional study prompted by elevated Tg levels in patients whose post-ablation WBS is negative).

Our approach to identifying patients for systemic therapy is as follows:

- Patients treated with systemic agents should have a baseline performance status sufficiently functional to tolerate these interventions, such as being ambulatory at least 50 percent of the day (Eastern Cooperative Oncology Group [ECOG] **performance status 2 or better**).
- Patients should be evaluated with comprehensive (CT) and/or (MRI) to establish the extent of disease and disease progression. Prior to therapy or in any patient with suspicious central nervous system symptoms, imaging of the brain should be performed to rule out **intracranial metastases** that might require other forms of intervention first, such as surgery or radiation.

● Patients with **asymptomatic metastatic** tumors generally **less than 1 to 2 cm** in diameter and growing in diameter **less than 20 percent per year** can usually be **monitored** for disease progression (active surveillance). known sites of metastatic disease should be imaged by CT or MRI every six months, and potential new sites of disease should be imaged every 12 to 24 months. We continue treatment with TSH suppression.

● Patients with **unresponsive metastatic** tumors of at least 1 to 2 cm in diameter and growing by at least 20 percent per year, or patients with **symptoms related to multiple metastatic foci** that cannot be alleviated with localized treatment such as surgery or external beam radiotherapy (EBRT) are candidates for **systemic therapy**.

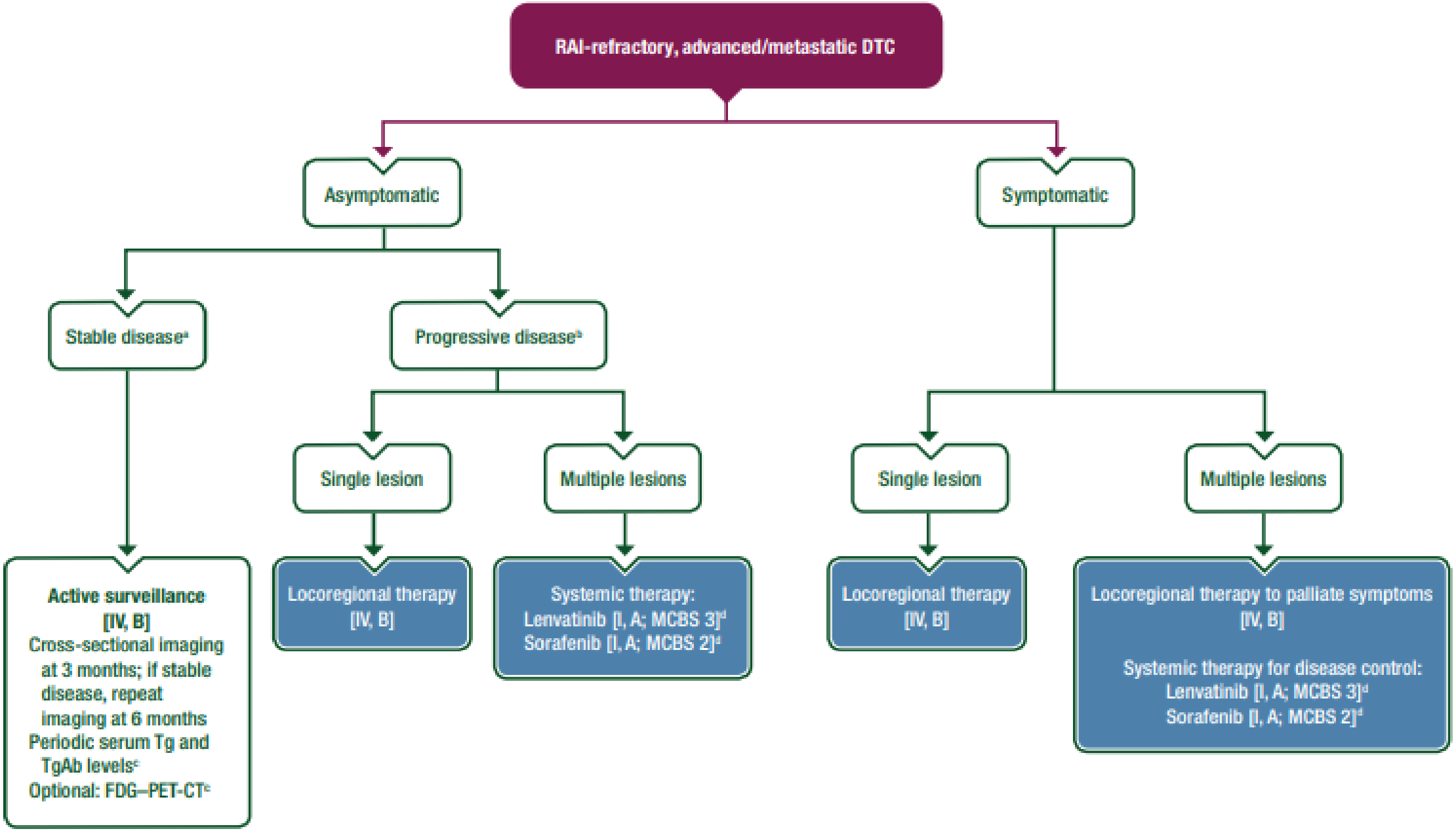


Figure 4. Recommendations for management of RAI-refractory, advanced/metastatic DTC patients.

Initial oral antineoplastic regimens for advanced thyroid cancers consisted of multikinase inhibitors (MKIs). The DECISION study, evaluated the utilization of **sorafenib** 400 mg twice daily versus placebo. Study treatment in this trial continued until radiographically documented disease progression, unacceptable toxicity, noncompliance or withdrawal of consent.

Sorafenib resulted in a meaningful improvement in PFS of 10.8 versus 5.8 months in the placebo cohort (hazard ratio [HR], 0.59; 95% CI, 0.45 to 0.76; P,.0001). The overall response rate (ORR) was 12.2% versus 0.5% in favor of sorafenib.

Adverse events occurred in most patients (98.6%) treated with this MKI, classified predominantly as grade 1-2. Common noted side effects included hand-foot skin reaction (76.3%), diarrhea (68.6%), alopecia (67.1%), rash (50.2%), fatigue (49.8%), weight loss (46.9%), hypertension (40.6%), anorexia .9%), and mucositis (23.2%).

lenvatinib, an MKI aiming at vascular epithelial growth factor receptor (VEGFR), fibroblast growth factor receptors, RET, KIT, and platelet-derived growth factor receptor α, has shown substantial responses in advanced thyroid cancer.

In the SELECT trial, the lenvatinib (24 mg orally once daily) treated cohort attained a PFS of 18.3 months compared with 3.6 months in the placebo group (HR, 0.21; 99% CI, 0.14 to 0.31; P , .001). In patients pretreated with another MKI, lenvatinib, the PFS was 15.1 months. The ORR is 64.8% in the oral antineoplastic cohort; the majority were partial responses (63.2%) by RECIST 1.1.

lenvatinib has demonstrated a benefit in the overall survival of patients older than 65 years.

Adverse events included hypertension (67.8%), diarrhea (59.4%), fatigue (59%), decreased appetite (50.2%), weight loss (46.4%), nausea (41%), stomatitis (35.6%), palmar-plantar erythrodysesthesia syndrome (31.8%), proteinuria (31%), vomiting (28.4%), headache (27.6%), and dysphonia (24.1%).

Both sorafenib and lenvatinib are Food and Drug Administration (FDA)–approved therapies in the United States for advanced RAIR-DTC. Given the development of resistance mechanisms resulting in progression, many patients with advanced thyroid cancer require an **eventual change** in treatment.

In 2021, **cabozantinib** has received FDA approval as second-line therapy for RAIR-DTC on the basis of COSMIC-311 study results. In this trial, which enrolled patients after progression on anti-VEGFR therapy, cabozantinib resulted in a PFS of 11 months over 1.9 months in placebo with an ORR of 11%. The best overall responses included 11% partial responses, 69% stable disease, and a confirmed complete response (1%).

Adverse event profile was similar to previous discussed antiangiogenic MKIs, including any-grade diarrhea (62%), palmar-plantar erythrodysesthesia (47%), and hypertension (32%). Smaller studies have explored the utilization of additional MKIs in RAIR-DTC, including **pazopanib, sunitinib, vandetanib, and axitinib.**

- **Contraindications to aaMKI** — Relative contraindications to antiangiogenic multikinase inhibitors (aaMKIs) may include major surgery within 28 days, active bleeding, untreated hemorrhagic brain metastases, encasement by tumor of major arteries such as the carotid, or arterial thromboembolic event within the last 6 to 12 months. We also try to minimize use of potent antiangiogenic agents in patients with prior external beam radiotherapy (EBRT) to the neck due to reports of tracheoesophageal fistulas.
- As MKIs may cause fatal harm when administered to a pregnant woman and may result in reduced fertility in both sexes, fertility preservation approaches should be discussed before treatment starts

MKIs described are used without any biomarker selection, For patients with contraindications to aaMKIs, a BRAF inhibitor (eg, vemurafenib, dabrafenib) with or without an MEK inhibitor is an alternative, but these inhibitors **approved only in presence of specific gene alterations**.

For BRAF V600E–altered RAIR-DTC, the utilization of BRAF and MEK inhibitors has been studied, given the success of these therapies in other solid tumors. Recently, a phase II open-label multicenter clinical study explored the implementation of BRAF inhibitor **dabrafenib** (150 mg twice daily) alone or in combination with a MEK inhibitor (**Trametinib** 2mg daily). Using a modified RECIST including minor responses (decreased tumor by 20%-29%), partial and complete responses, the ORR modified RECIST was 42% for dabrafenib monotherapy versus 48% dabrafenib with trametinib (P = .67).

Periodic dermatological assessments are recommended as **skin toxicities** can occur, especially if treated with dabrafenib monotherapy (65%). **Pyrexia** was present in both cohorts in more than 50% of patients. In addition, BRAF inhibitor alone was commonly associated with **hyperglycemia**, whereas the BRAF/MEK inhibitor had a frequency of 52% for fatigue, nausea, and chills.

RET inhibitors

Highly selective RET inhibitors, including **selpercatinib** and **pralsetinib**, have been approved for **metastatic RET-mutant MTC** and **RET fusion–positive progressive RAIR-DTC**. In previously treated RET fusion–positive thyroid cancer, the objective response was 79% with a PFS of 20.1 months. Best response distribution by RECIST 1.1 was 5% complete responses, 74% partial responses, and 21% stable disease.

In this group of patients with thyroid cancer, who were on pralsetinib, the ORR was 85.7% with a PFS of 19.4 months. Both antineoplastic agents had dose reduction (eg, reduce both the morning and evening dose by 40 mg) requirements in <45% of patients, which is a reflection that the majority of adverse events were minor in severity (grade1-2).

Dosing and monitoring

.Selpercatinib For patients ≥50 kg, the initial dose is 160 mg twice daily (with or without food), whereas for patients <50 kg, it is 120 mg twice daily. It is important to **avoid concomitant use of gastric acid-reducing medications**, which can reduce plasma concentrations of selpercatinib. If not possible and the patient is taking a proton pump inhibitor, selpercatinib should be taken with food. If patients are taking a locally acting antacid or an H2 receptor antagonist, selpercatinib should be taken two hours before the acid-reducing medication, or 2 or 10 hours after the locally acting antacid or H2 receptor antagonist, respectively.

pralsetinib In adults, initial dose is 400 mg once daily, on an empty stomach.

Common **adverse events** of RET inhibitors include dry mouth, gastrointestinal side effects, elevated transaminases, and QT prolongation.

With selpercatinib, grade 3 events occurred in a minority of patients including hypertension (12%) and high liver enzymes (17%), and in <5% headache, diarrhea, QT prolongation, and weight gain.

Cytopenias are more frequently developed with pralsetinib; grade 3 side effects noted (>10%) included hypertension, neutropenia, lymphopenia, and anemia. Severe rare side effects may happen, including pneumonitis in a minority of patients (4%) or hypersensitivity reactions. Liver biochemical tests should be measured prior to initiating pralsetinib and every two weeks after initiation. If liver tests remain stable after the first three months, monitor monthly thereafter.

TRK inhibitor

NTRK (neurotrophic tropomyosin receptor kinase) genes rearrangements have been reported in up to 6.7% of papillary thyroid cancers; in pediatric patients, the frequency of NTRK fusions is higher. Grouped data from several phase I/II trials revealed a 71% ORR for **larotrectinib**, a NTRK inhibitor.

Common **side effects** included myalgia, fatigue, nausea, transaminitis, edema, and gastrointestinal symptoms; nevertheless, toxicities were low grade and ,10% dose reductions.

The profound responses and toxicity profile of the gene alteration–specific antineoplastic agents highlight the importance of ensuring that patients with advanced thyroid cancer undergo comprehensive molecular testing, including comprehensive evaluation of mutations and gene rearrangements.

Several clinical trials and case reports demonstrate restoration of iodine uptake in tumors, an approach known as **redifferentiation**, after a course of the gene alteration–specific inhibitors targeting BRAF, MEK, RET, or NTRK.

The advantages include the possibility of discontinuation of targeted therapy after an additional RAI treatment, resulting in tumor control. Further studies are warranted to identify the best responders to ensure the appropriate selection of candidates and ideal implementation time on the disease course.

Immunotherapy

The use of agents that accentuate the capacity of a patient's own immune system to attack a malignant tumor has rapidly expanded in the past few years with the introduction of "checkpoint inhibitors." Drugs that block key cell-surface components on tumor cells or T lymphocytes, regulating the interaction between these two cell types, permit the immune system to recognize tumor-specific epitopes or neoantigens presented on the surface and thus allow immune targeting of these abnormal cells.

In DTC, one trial evaluated the programmed cell death receptor 1 (PD-1) inhibitor **pembrolizumab**, 10 mg/kg given intravenously every two weeks for 24 months or until progression or intolerable toxicity. Of 22 patients, only two (9.1 percent) experienced a partial response and 54.5 percent had stable disease as their best overall response. The median PFS rate was seven months. Adverse events were typical of those seen in other tumor types, including diarrhea, fatigue, and colitis.

Cytotoxic agents:

the availability of MKI that induce durable responses or stability has changed the standard approach of progressive metastatic disease, further limiting the role of cytotoxic agents.

Doxorubicin (60 mg/m^2 every three weeks) is the only cytotoxic agent approved by (FDA) for metastatic thyroid cancer. Other chemotherapeutic agents, including: **Bleomycin, cisplatin, carboplatin, methotrexate, melphalan, mitoxantrone, etoposide**,… have not been shown to improve response rates.

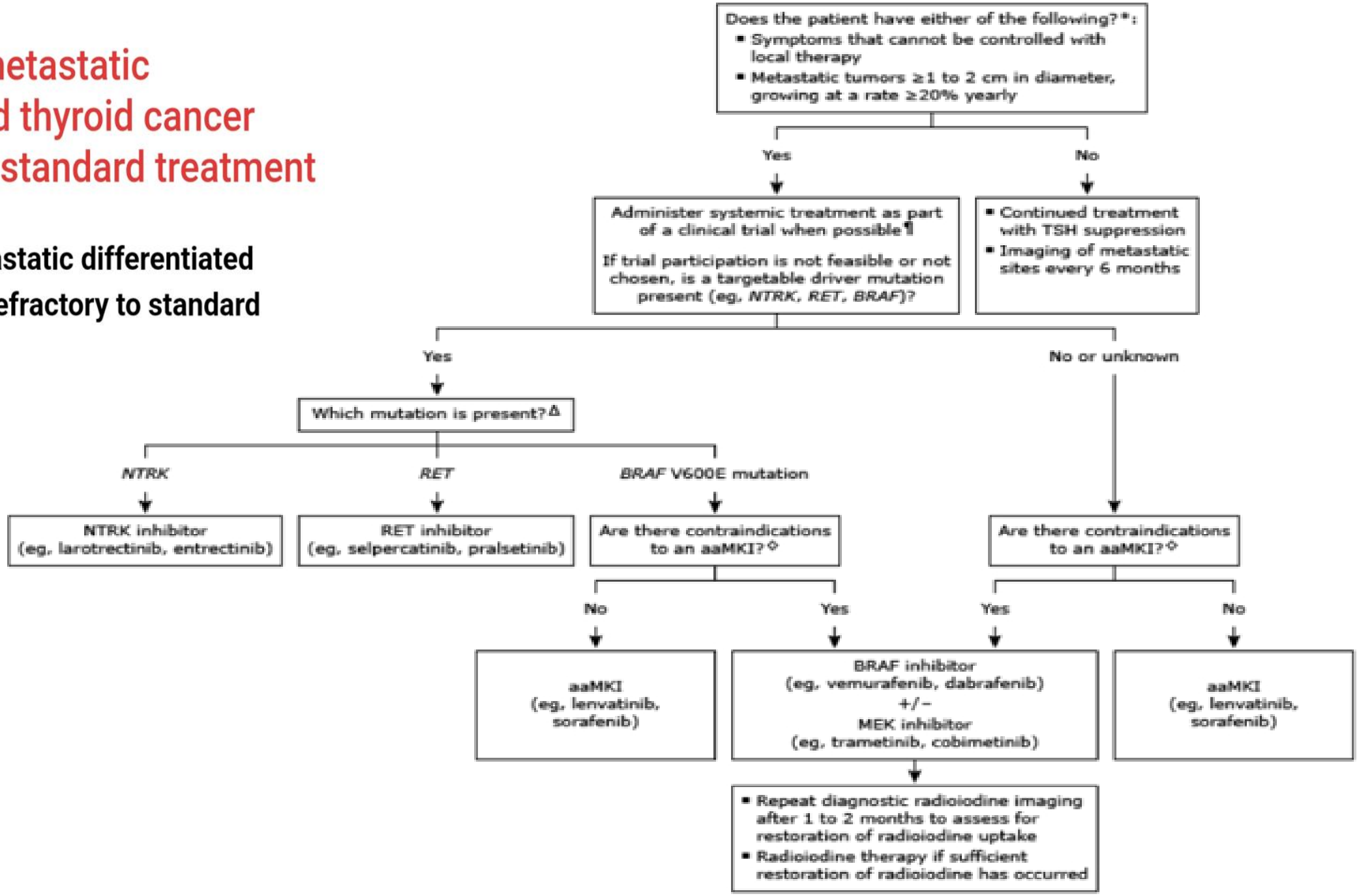
Typically reserve conventional cytotoxic agents (eg, doxorubicin) for patients with metastatic refractory DTC who are unable to participate in clinical trials or who either cannot tolerate or fail antiangiogenic multikinase inhibitors (aaMKIs).

Cisplatin or other agents may be considered in whom doxorubicin is inappropriate (eg, those with pre-existing impaired cardiac function or myelosuppression).

Common **adverse events** can include granulocytopenia with accompanying infections, nausea, vomiting, and alopecia.

Therapy of metastatic differentiated thyroid cancer refractory to standard treatment

Therapy of metastatic differentiated thyroid cancer refractory to standard treatment



Medullary Thyroid Carcinoma:

●**Progressive metastatic disease** – These patients are monitored with serum calcitonin and (CEA) levels **every three to six months** as well as (CT) and/or (MRI) of the neck, chest, and abdomen. Known sites of metastatic disease should be imaged by CT or MRI every 6 to 12 months, and screening for potential new sites should be performed every 12 to 24 months. Scanning frequency can be guided by CEA and calcitonin serial measurements measured every three to six months.

Radionuclide bone imaging can be helpful when cross-sectional imaging fails to identify the source of the persistent hypercalcitoninemia. (FDG-PET) and gallium-68 (Ga-68) DOTATATE) can both be used when biochemical and anatomic progression do not correlate, to detect small soft tissue lesions, bone lesions, or lesions outside the field of view of cross-sectional scans; some studies favor GA-DOTATATE over FDG-PET.

Patients with adequate performance status to tolerate systemic therapy [ECOG scale 2 or better] and any of the following are candidates for systemic therapy:

• symptomatic disease not amenable to any localized or symptom-specifc therapies,

• progressive (by RECIST) within 12–14 months or Metastatic tumors ≥1 to 2 cm in diameter, growing by ≥20 percent per year,

•Calcitonin doubling times ≤2 years (particularly those with calcitonin doubling times <6 months),

• tumor invasion to vital structures not amenable to localized therapies,

•severe, intractable MTC-related diarrhea or paraneoplastic Cushing's syndrome with lack of an alternative efficacious treatment,

Patients without any of these features can usually be monitored, treating symptoms like diarrhea with symptomatic support.

Vandetanib, an MKI-targeting RET, VEGFR, and epidermal growth factor receptor, was the **first** FDA approved targeted therapy for MTC. After safety and tolerability data from phase II trials, the phase III ZETA trial demonstrated improvement in the PFS compared with placebo.

Cabozantinib-treated patients had an improvement in PFS of 11 months versus 4 months in placebo.

RET inhibitors, selpercatinib and pralsetinib, induced sustained responses in RET-mutant MTC..

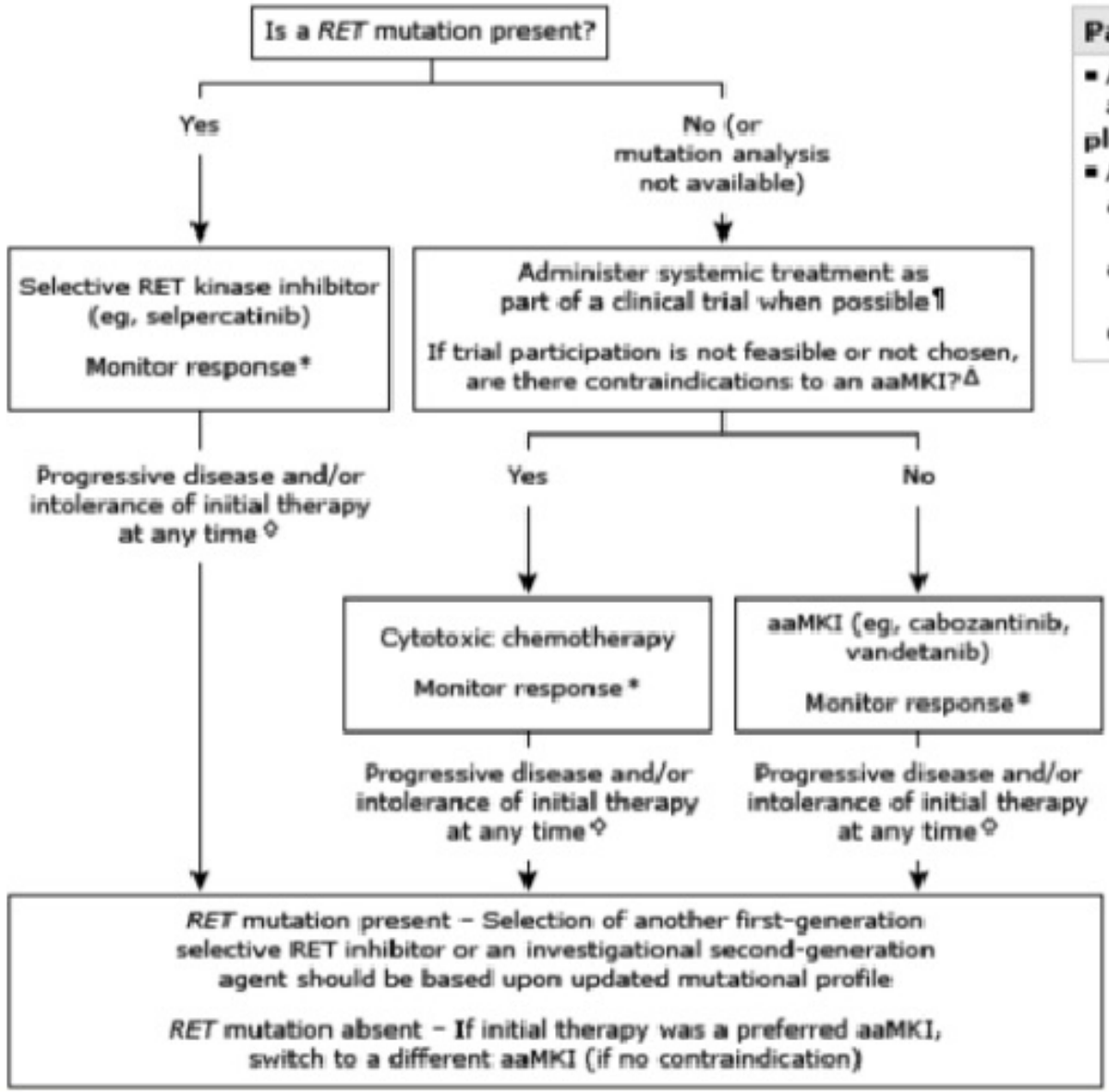
RET-mutant MTC cases without previous targeted therapies treated with selpercatinib had an objective response of 73% and 69% for pretreated patients. Pralsetinib resulted in an ORR of 71% for RET-mutant, treatment-naıve MTC versus 60% in the cohort previously treated by vandetanib, cabozantinib, or both TKIs.

Neoadjuvant RET inhibitor treatment has shown promise to facilitate **successful resection** of thyroid cancers; this novel utilization of targeted therapy is currently studied in clinical trials.

Tumor vaccines: A novel approach to targeted immunotherapy is the use of tumor vaccines. Dendritic cells, which are derived from bone marrow antigen-presenting cells, are capable of presenting tumor-associated antigens, thereby generating cytotoxic T-cells targeting tumor cells.

Toxicities are minor, including low-grade fever and asymptomatic transient autoantibody development.

Systemic targeted therapy for metastatic or advanced medullary thyroid cancer



Patient selection for systemic targeted therapy

- Adequate performance status (eg, ECOG PS ≥2; ambulatory ≥50% of day)

plus

- Any of the following:
  - Symptoms that cannot be controlled with local therapy
  - Metastatic tumors ≥1 to 2 cm in diameter and growing at a rate ≥20% yearly
  - Calcitonin doubling time ≤2 years

Anaplastic Thyroid Carcinoma

ATC, as a stage IV highly lethal malignancy, benefits from expedited comprehensive evaluation, airway assessment, and molecular testing (BRAF V600E and NGS). For resectable tumors **(stage IVA-IVB), surgical resection is followed by definitive chemoradiation**.
Between 20% and 50% of ATC tumors are driven by BRAF V600E mutation, allowing for combination dabrafenib and trametinib therapy in a neoadjuvant approach for stage IVB unresectable tumors or as up-front long-term therapy for stage IVC disease. Combination BRAF/MEK inhibitor in BRAF-altered ATC has demonstrated an ORR of 61%, including complete responses. Targeted therapies have improved overall survival in ATC.

RET or NTRK inhibitors may be used in the management of ATC tumors with the respective identified fusion drivers.

●**Cytotoxic chemotherapy**: There are some data to support the use of cytotoxic chemotherapy. In a randomized trial comparing **combination cisplatin and doxorubicin** versus doxorubicin alone, the complete response rate was higher in the combination group (3 of 18 patients [17 percent] compared with none of 21 patients in the doxorubicin group

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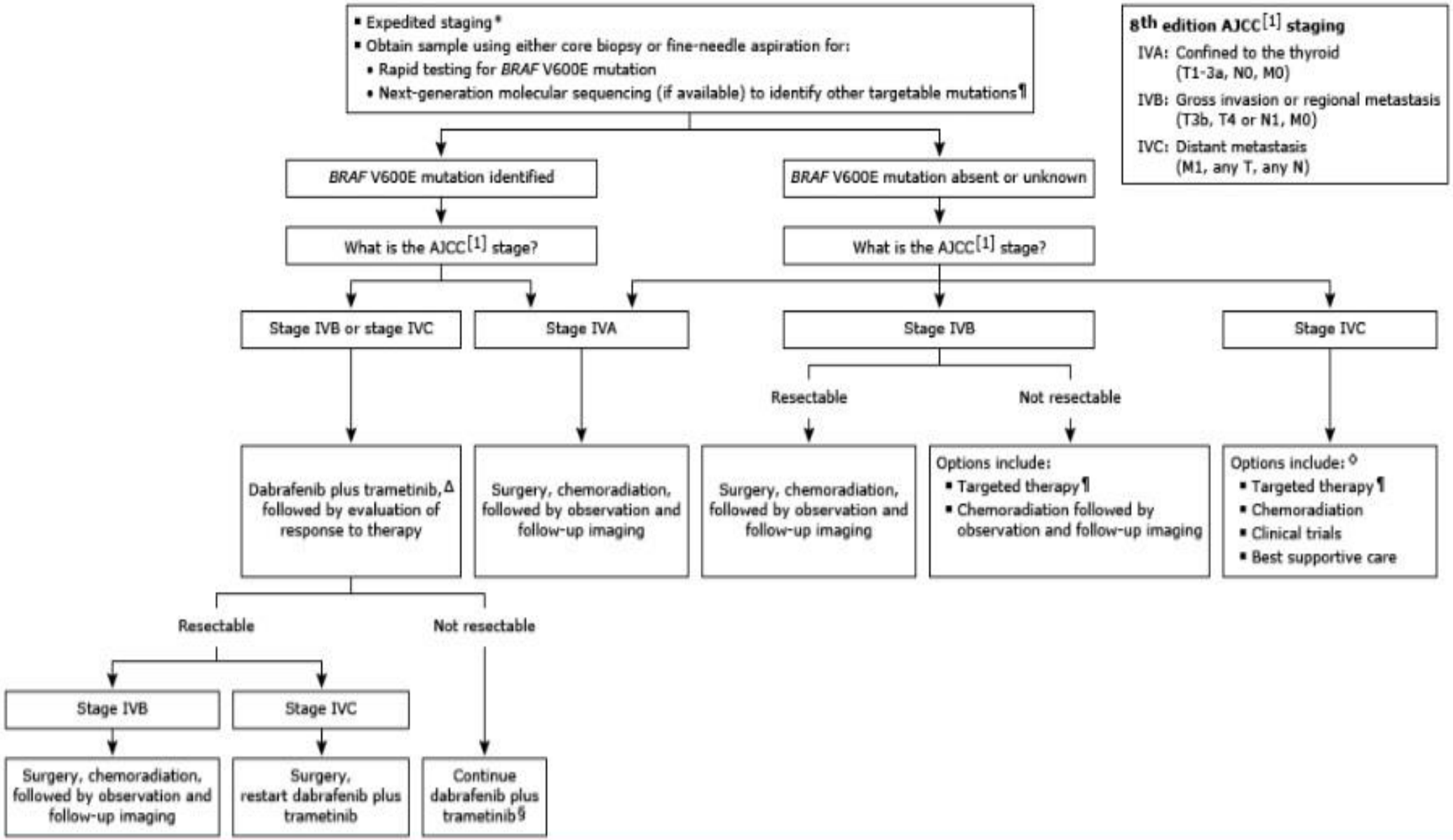
●**Immunotherapy**: Immunotherapy, particularly in combination therapies, whether along **BRAF/MEK inhibitor** or **antiangiogenics**, has provided further therapeutic pathways for patients with ATC. (ATLEP) study evaluated the combination of lenvatinib and pembrolizumab in both anaplastic and poorly differentiated thyroid cancer . In 27 patients with anaplastic thyroid cancer, 51.9 percent of patients had a partial response. The median PFS was reported to be 9.5 months and median overall survival was 10.25 months.

Consideration for enrollment in ongoing clinical trials is recommended given the rarity and aggressiveness of this tumor.

In patients with advanced disease who do not desire or who are not eligible for systemic therapy, **palliation of symptoms** is a high priority. Treatment should be directed toward securing the airway and ensuring access for nutritional support. Locoregional resection may be necessary for palliation of airway or esophageal obstruction. However, death is usually attributable to upper airway obstruction and suffocation (often despite tracheostomy) in 50 to 60 percent of patients and to a combination of complications of local and distant disease in the remainder.

For patients with bone metastases, palliative radiotherapy may be beneficial in improving pain.


▪ Expedited staging*
▪ Obtain sample using either core biopsy or fine-needle aspiration for:
• Rapid testing for *BRAF* V600E mutation
• Next-generation molecular sequencing (if available) to identify other targetable mutations¶
8th edition AJCC[1] staging
IVA: Confined to the thyroid (T1-3a, N0, M0)
IVB: Gross invasion or regional metastasis (T3b, T4 or N1, M0)
IVC: Distant metastasis (M1, any T, any N)
BRAF V600E mutation identified
BRAF V600E mutation absent or unknown
What is the AJCC[1] stage?
What is the AJCC[1] stage?
Stage IVB or stage IVC
Stage IVA
Stage IVB
Stage IVC
Resectable
Not resectable
Dabrafenib plus trametinib,Δ followed by evaluation of response to therapy
Surgery, chemoradiation, followed by observation and follow-up imaging
Surgery, chemoradiation, followed by observation and follow-up imaging
Options include:
▪ Targeted therapy¶
▪ Chemoradiation followed by observation and follow-up imaging
Options include:◊
▪ Targeted therapy¶
▪ Chemoradiation
▪ Clinical trials
▪ Best supportive care
Resectable
Not resectable
Stage IVB
Stage IVC
Surgery, chemoradiation, followed by observation and follow-up imaging
Surgery, restart dabrafenib plus trametinib
Continue dabrafenib plus trametinib§

CONCLUSION

Management of advanced thyroid cancer requires a multidisciplinary approach to optimize patient outcomes and provide access to the latest cutting-edge therapies.

There has been significant progress in understanding the genetic landscape and molecular basis of thyroid cancer, leading to the development of novel targeted therapies for advanced disease, leading to improved PFS;

however, questions still remain in regard to optimal timing of systemic treatment initiation for advanced thyroid cancer and relevant variables that inform decision making. Future studies on redifferentiation and neoadjuvant therapy in the presence of bulky neck disease, immunotherapy, and development of other gene alteration–specific therapies will hopefully lead to thyroid cancer cure.

THANKS FOR YOUR ATTENTION