Medullary Thyroid Cancer

Our Current Understanding of Optimum Treatment

Amanda La Greca, MD*, Bryan Haugen, MD

KEYWORDS

• Medullary thyroid carcinoma • Calcitonin • RET mutation • Surgery
• Kinase inhibitors

KEY POINTS

- Medullary thyroid carcinoma (MTC) constitutes approximately 2% of all thyroid cancers, yet it is responsible for about 8% of deaths related to thyroid malignancies.
- 80% to 85% of patients with MTC survive for more than 10 years.
- Preoperative and postoperative calcitonin levels can help guide imaging modalities and surgical approach.
- Germline RET mutation testing is recommended for all new patients diagnoses of MTC.
- Tumor RET mutation testing is recommended for patients being considered for systemic therapy.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a primary neuroendocrine cancer in the thyroid gland that originates from the calcitonin-secreting parafollicular C cells.[1]

MTC constitutes approximately 2% of all thyroid cancers, yet it is responsible for about 8% of deaths related to thyroid malignancies.[2] The prevalence of occult MTC in a series of autopsies was found to be 0.14%.[3] No significant gender differences have been observed in the distribution of medullary thyroid cancer, and it typically presents in the fourth and fifth decades of life, although it can occur at a wide range of ages.[4]

The development of MTC is primarily associated with the activation of the RET proto-oncogene, which is typically caused by point mutations or small insertions/deletions.[5] The sporadic form of MTC accounts for approximately 75% of cases, while

Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado, 12801 East 17th Avenue, 7103 Research 1 South, Aurora, CO, USA
* Corresponding author.
E-mail address: Amanda.lagreca@cuanschutz.edu

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Abbreviations	
CEA	carcinoembryonic antigen
CT	computed tomography
EBRT	external beam radiation therapy
HPTH	primary hyperparathyroidism
HR	hazard ratio
MEN	multiple endocrine neoplasia
MTC	medullary thyroid carcinoma
PHEO	pheochromocytoma
PTC	papillary thyroid cancer

the hereditary or familial form makes up about 25%. RET activation is responsible for both sporadic and familial forms of MTC. RET activation is found in nearly all cases of familial MTC/multiple endocrine neoplasia (MEN), but it account of approximately 40% to 50% of sporadic MTC (others being RAS and other mutations). In sporadic cases, the RET mutation occurs only in the tumor tissue (somatic mutation), while in familial cases, the RET mutation is inherited in an autosomal dominant manner.[6]

In terms of prognosis, 80% to 85% of patients with MTC survive for more than 10 years. The most significant prognostic factors for these patients are age at diagnosis[7] and the stage of the disease at the time of diagnosis.[8]

CLINICAL PRESENTATION

Most patients with sporadic MTC present with a solitary thyroid nodule typically located in the upper portion of the thyroid lobe as C cells are more concentrated in this area.[8–10] Around 70% of patients with MTC show signs of cervical lymph node involvement at diagnosis. Up to 15% may experience symptoms related to compression or invasion of the upper aerodigestive tract, such as dysphagia or hoarseness. Lymph node metastases are more frequently seen in patients with multifocal disease.[11] About 5% to 10% of patients present with distant metastatic disease, more commonly seen in the liver, lung, bones, and, less often, in the brain and skin. In very advanced cases, symptoms such as diarrhea and/or flushing syndrome, caused by elevated levels of calcitonin, may be among the first signs of the disease.[12,13] In some cases, tumors may secrete corticotropin (adrenocorticotropic hormone [ACTH]), leading to ectopic Cushing syndrome.[14]

DIAGNOSIS

Biochemical Tests and Imaging

Basal serum calcitonin levels typically correlate with tumor size and also reflect the degree of tumor differentiation.[13] Serum calcitonin levels ranging from 20 to 100 pg/mL, may be associated with C-cell hyperplasia or other neuroendocrine tumors. While these levels can raise suspicion for MTC, they are not diagnostic.[15] Additional diagnostic tools should be employed to confirm or rule out the condition. Most MTCs also secrete carcinoembryonic antigen (CEA), which, similar to calcitonin, can serve as a tumor marker.[16]

Imaging

Thyroid ultrasound is generally the primary imaging method used to evaluate the characteristics of a thyroid nodule. The ultrasound features of MTC are not as distinctive as those of PTC, and MTC nodules may not be flagged as suspicious. While hypoechogenicity and macrocalcifications are common ultrasound features of MTC nodules,

MTC is less likely than PTC to demonstrate microcalcifications, irregular margins, and taller-than-wide shape (Figs. 1A–C). A study that evaluated both the ultrasound features of MTC and the performance of ultrasound risk stratification systems to identify MTC found that 45.4% to 47.4% MTCs were classified as high-risk based on ultrasound, and that fine-needle aspiration (FNA) was recommended in only 48.7% to 63.8% of all nodules that ultimately were diagnosed as MTC.[17] In a retrospective study that analyzed the ultrasound characteristics of nodules confirmed to be MTC and papillary thyroid cancer (PTC) through histology, it was found that 50% of MTC nodules were solid and hypoechoic, and 16% exhibited microcalcifications. In contrast, for PTC, 69.2% were solid and hypoechoic, and 69.2% showed microcalcifications.[18]

Diagnosis

MTC is often referred to as the *great masquerader* of the thyroid gland due to the challenges it presents in diagnosis, both in terms of thyroid nodule sonographic features and cytologic findings.

MTC is usually diagnosed following a FNA biopsy in patients with a solitary thyroid nodule or a sonographically concerning nodule in the presence of a multinodular goiter.

MTC can have a variety of appearances on cytology and may be misinterpreted as other tumors, especially oncocytic or follicular neoplasms. Common features include

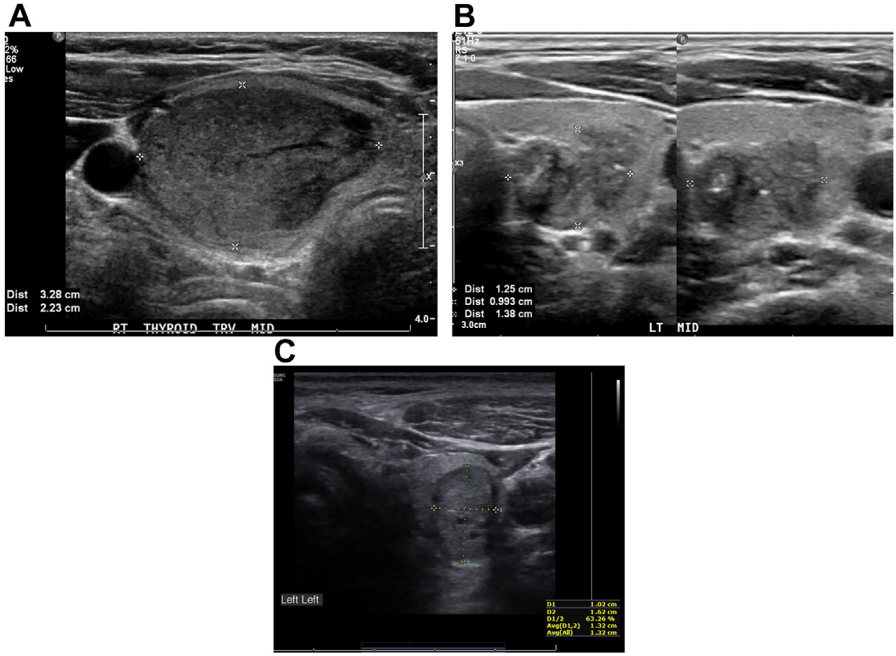

Fig. 1. Thyroid ultrasound images of nodules with cytologic and surgical results consistent with MTC. While hypoechogenicity and macrocalcifications are common sonographic features of MTC nodules, MTC is less likely than PTC to demonstrate microcalcifications, irregular margins, and taller-than-wide shape. (*A*) Right 3.28 cm MTC, hypo to isoechoic, with regular borders, no microcalcifications or macrocalcifications. (*B*) Left 1.38 cm MTC, hypoechoic, irregular borders, presence of microcalcifications (*C*). Left 1.62 MTC, isoechoic, solid with cystic spaces, taller than wide, no microcalcifications or macrocalcifications.

plasmacytoid/spindled cells, reduced cell cohesion, binucleation, *salt and pepper* chromatin, intranuclear pseudoinclusions, and extracellular amyloid deposition (Fig. 2). A meta-analysis by Trimboli and colleagues reported the sensitivity of cytology alone (with no calcitonin wash) for diagnosing MTC ranged from 12.5% to 88.2% (mean 56.4%).[19] With the addition of calcitonin needle rinse from the FNA specimen (*calcitonin washout*) the sensitivity increased to more than 95% for all studies. Although the sensitivity of serum calcitonin for MTC is also high, it is not routinely recommended in North America as part of the standard evaluation of a thyroid nodule due to the lack of pentagastrin stimulation testing in some countries. Calcitonin stimulation testing by calcium infusion is a reasonable alternative to pentagastrin stimulation when stimulating serum calcitonin is considered.[20] Lastly, a high sensitivity and specificity for the diagnosis of MTC has been documented for some of the commercially available molecular tests.[21]

Hereditary Medullary Thyroid Cancer

MTC is found in about 25% of individuals with multiple endocrine neoplasia type II (MEN II). There are 2 subtypes: MEN2A and MEN2B. Both are inherited in an autosomal dominant pattern with very high penetrance and are associated with the development of MTC. These syndromes result from mutations in the RET proto-oncogene on chromosome 10.[22,23]

A. MEN2A (accounts for 95% of MEN2 cases), 4 variants[13]:
   1. Classical MEN2A (MTC, pheochromocytoma [PHEO], primary hyperparathyroidism [HPTH], or both)
   2. MEN2A with cutaneous lichen amyloidosis.
   3. MEN2A with Hirschsprung disease
   4. FMTC with RET germline mutations who have MTC but neither PHEOs nor HPTH.

B. MEN2B—these tumors develop at an earlier age and are more aggressive than MEN2A. MTC occurs in almost all patients.
   1. MTC and PHEO but does not include HPTH
   2. Patients can have:
      - Marfanoid habitus (but not Marfan syndrome)
      - Mucosal neuromas
      - Intestinal ganglioneuromatosis

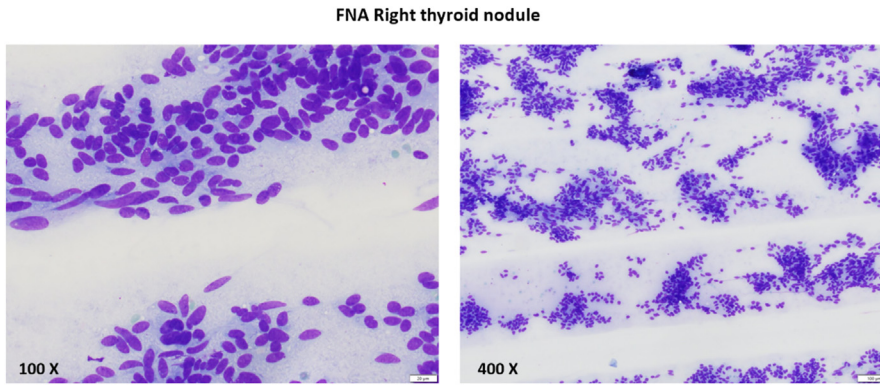

Fig. 2. MTC—findings on FNA biopsy. The aspirate is hypercellular with numerous noncohesive spindle-shaped cells. The nuclei are elongated with granular chromatin and inconspicuous nucleoli. (*Courtesy of* Von Samedi, MD)

The prognosis of MTC varies in the 2 syndromes. MEN2A has different degrees of aggressiveness depending on the RET gene mutation; the Revised American Thyroid Association Guidelines has subclassified the risk of aggressive MTC in MEN2A and MEN2B into moderate, high or highest.[13]

Evaluation

Once a patient is diagnosed with MTC, additional evaluation should include measuring serum calcitonin and CEA levels, performing neck ultrasound with thorough evaluation of lateral cervical lymph nodes, testing for germline RET mutations, and screening of PHEO.[13]

If a patient is found to have neck lymph node metastases or has a preoperative serum basal calcitonin level greater than 500 pg/mL, additional imaging should be considered as this could indicate the presence of distant metastatic disease.[14] The American Thyroid Association recommends neck and chest computed tomography (CT), 3-phase contrast-enhanced liver CT or contrast-enhanced liver MRI, and axial MRI or bone scintigraphy.[13] Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning is not recommended for diagnosis of distant metastatic disease due to its low sensitivity, but positron emission tomography scanning with alternative tracers (eg, 18F-dihydroxyphenylalanine and 68Ga-DOTA peptides) could potentially detect distant metastatic disease in patients with high serum calcitonin levels.[24]

Germline RET testing should be offered to all patients with newly diagnosed MTC. Approximately 6 to 7% of individuals have germline RET mutations.[25] The ATA recommends consulting with genetic counselors given both the ethical considerations and the legal requirements for informed consent in genetic testing.[13] Around 60% of patients with sporadic MTC have somatic (acquired) mutations in the RET gene within the tumor cells.[26]

Before thyroidectomy, most patients require biochemical evaluation to check for coexisting tumors, plasma fractionated metanephrines are indicated to rule out PHEO and serum calcium levels to rule out PHPT, since germline genetic testing results are usually not available in time before surgery.[13]

Staging

MTC is staged from I to IV according to the American Joint Committee on Cancer 8th Edition, based on tumor size and the presence or absence of extrathyroidal invasion, local and regional nodal metastases, and distant metastases.[27]

The International Medullary Thyroid Carcinoma Grading System incorporates a histologic grading system for mitotic count as an important prognostic variable in individual risk stratification. This includes Ki67 proliferative index, and assessment of tumor necrosis into a 2-tiered staging system: low grade tumors (<5 mitoses/2 mm2, Ki67 <5%, no tumor necrosis) and high grade tumors ($\geq$5 mitoses/2 mm2, Ki67 $\geq$5%, tumor necrosis).[28] A high tumor grade independently predicted a reduction in overall survival, disease-specific survival, distant metastasis-free survival, and locoregional recurrence-free survival.[29]

Initial treatment

Surgery. The initial treatment of MTC is surgical, typically involving a total thyroidectomy and a prophylactic central neck dissection.[13] The indication for total thyroidectomy is primarily driven by the occurrence of multicentricity and bilaterality in up to 10% of sporadic tumors and 100% of hereditary tumors.[25] In addition, patients with hereditary MTC often exhibit premalignant diffuse C-cell hyperplasia.[30] Lateral neck dissection in the absence of identifiable lymph node metastases in preoperative

imaging is typically not recommended, although some surgeons rely on presurgical calcitonin levels independently of the preoperative assessment of lymph node metastases.[31] The revised ATA guidelines proposed that prophylactic neck dissections might be considered based on preoperative serum calcitonin levels. Specifically, they recommended prophylactic ipsilateral central and ipsilateral lateral neck dissection for patients with basal serum calcitonin values greater than 20 pg/mL and prophylactic dissection of uninvolved contralateral lateral neck compartments for serum calcitonin values greater than 200 pg/mL.[13] For patients with locally advanced or metastatic MTC, total thyroidectomy with resection of affected lymph node compartments is recommended. A more conservative approach may be considered in these cases due to the palliative nature of the surgery, aiming to prevent additional comorbidities and surgical complications such as vocal cord paralysis and hypoparathyroidism.[13]

Neoadjuvant therapy. The purpose of neoadjuvant therapy is to reduce the size of a locally advanced tumor before surgery, making the surgical procedure more successful and minimizing potential complications. In patients with locally advanced or metastatic *RET*-mutated MTC, the potential use of RET-targeted kinase inhibitors before surgery, as neoadjuvant therapy, is currently being explored. A small case series of 4 patients with locally advanced MTC treated for 4 to 6 months with Selpercatinib preoperatively showed that using this selective RET inhibitor in the neoadjuvant setting may help achieve locoregional disease control.[32] Currently, a clinical trial is underway to further assess the effectiveness and safety of this novel treatment strategy in patients with RET-mutated MTC.[33]

Postoperative monitoring. Serum calcitonin and CEA are typically measured 3 months after surgery to detect the presence of persistent disease.[13] In some patients, the serum calcitonin concentration may decrease gradually after surgery (disappearance half-life of approximately 30 hours), with the nadir not occurring until several months later, particularly noticeable in patients who had high preoperative calcitonin concentrations.[34] The first postoperative neck ultrasound is recommended to be obtained 6 months after initially surgery.

If the postoperative calcitonin is undetectable or within normal range, the recommendation is to reevaluate the patient every 6 to 12 months. If the calcitonin is lesser than 150 pg/mL and no evidence of persistent or recurrent disease on physical examination or neck ultrasound, the recommendation is to measure calcitonin and CEA every 3 months to calculate doubling times, and physical examination with neck ultrasound every 6 months. If the postoperative calcitonin is more than 150 pg/mL, additional imaging is recommended including CT or MRI of neck, chest, and abdomen; bone scan or bone MRI in patients suspected of having skeletal metastases.[13]

Patients with persistent/recurrent disease

Biochemical incomplete response For patients with detectable calcitonin or abnormal CEA levels but no identifiable structural disease by imaging studies, disease monitoring is recommended. Calculation of calcitonin and CEA doubling time periodically (every 6–12 months) to assess the rate of progression of disease is advised. A doubling time less than 0.5 to 1 year is a poor prognostic factor, for both recurrence and death.[35] The initial imaging approach for localization of disease should be a thorough neck ultrasound due to the high likelihood of persistent disease in the cervical lymph nodes. If the postoperative serum calcitonin level rises above 150 pg/mL, patients should be evaluated by further imaging, including neck ultrasound or CT, chest CT, MRI with contrast or 3-phase contrast-enhanced CT of the liver, and bone scintigraphy and MRI of the pelvis and axial skeleton.[13]

Structural incomplete response In patients with locoregional persistent/recurrent disease that can be identified structurally, the primary treatment approach typically involves surgical resection. This could be followed by external beam radiation therapy (EBRT) for an R1 (positive microscopic margins postoperatively) or R2 resection (presence of gross residual tumor postoperatively).

Locally directed therapies. In patients with distant metastatic disease, the option of local treatments should always be considered for single, enlarging lesions or for multiple lesions when one is symptomatic, such as pain, potential invasion into nearby organs, or risk of fracture.

External beam radiotherapy. Postoperative adjuvant EBRT to the neck and mediastinum should be evaluated in patients at high-risk for local recurrence including those patients with residual microscopic or macroscopic MTC, extrathyroidal extension, or significant cervical lymph node involvement, as well as those who may be at risk for airway obstruction.[13] Adjuvant EBRT following thyroidectomy and node dissection for MTC is not advised as a prophylactic measure. EBRT may enhance locoregional control, but the impact on overall survival remains uncertain.[36]

Other local therapies for distant metastatic disease. EBRT and surgical decompression could be used for bone metastasis and spinal cord compression. Patients with fractures or are at risk of fractures may require surgery, thermoablation (radiofrequency or cryotherapy), cement injection, and EBRT. Denosumab or bisphosphonates are also recommended for patients with bone metastases. Surgical resection and/or radiofrequency ablation could be considered in patients with large solitary lung metastases. For large hepatic metastasis (3 cm or less), surgical resection or chemoembolization could be considered. Rarely, patients with MTC develop cutaneous metastases and these could be removed surgically, or treated with EBRT or ethanol injection.[13]

Systemic therapy. Systemic therapy is reserved for patients with progressive or symptomatic metastatic disease who are not candidates for local treatments. Patients with sporadic MTC should undergo molecular testing of the primary tumor (or metastatic lesion) to detect any somatic RET pathogenic variants, which would guide the use of a specific RET inhibitor. For patients with somatic or germline RET mutations, the selective RET kinase inhibitor selpercatinib is recommended. In the open-label LIBRETTO-001 study of selpercatinib in 143 patients with advanced RET-mutant MTC, either pretreated with cabozantinib and/or vandetanib, or receiving no prior systemic therapy, the overall response rates were 73% and 69%, respectively. Selpercatinib was generally well-tolerated by patients, with main side effects being hypertension, dry mouth, and diarrhea. Treatment-related adverse events grade 3 were seen in 28% of patients and grade 4 in only 2% of patients.[37]

For patients without a RET mutation, multikinase inhibitor, either vandetanib or cabozantinib are recommended.[13] Vandetanib is approved for managing symptomatic or progressive MTC in patients with locally advanced or metastatic disease that is unresectable.[38] An international, randomized phase III study of vandetanib with more than 300 patients with sporadic or hereditary MTC, demonstrated a significant improvement in progression-free survival compared to placebo (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.31 to 0.69).[39]

Cabozantinib is the other oral multikinase inhibitor FDA approved for the use of metastatic progressive MTC.[40] In a randomized trial where 330 patients with progressive

Table 1
Current therapeutic trials (new drugs) for patients with medullary thyroid cancer

NCT#	Drug	Action (Target)	Route	Study Type
04787328	HA121–28	MKI (EGFR, RET, VEGFR)	oral	Phase II, single-arm, open-label
05830500	anlotinib	MKI (VEGFR, FGFR, PDGFR, c-Kit)	oral	Retrospective/prospective observational study
04877613	GFRα4 CART	CART cell against GFRα4	IV	Phase I, open-label
05675605	TY-1091	RET kinase inhibitor	oral	Phase I/II, open-label
05278364	SY-5007	RET kinase inhibitor	oral	Phase I/II, open-label
06141369	mRNA-0523-L001	Individualized mRNA neoantigen vaccine	IM	Phase I, open-label

Abbreviations: c-KIT, receptor tyrosine kinase encoded by the KIT gene; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GFRalpha4, GDNF family receptor alpha-4; GDNF, glial cell line-derived neurotrophic factor; IM, intramuscular; IN, intravenous; MKI, multikinase inhibitor; mRNA, messenger riboNucleic acid; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; VEGFR, vascular endothelial growth Factor receptor

From clinicaltrials.gov, December 2024.

and metastatic MTC were assigned to receive either cabozantinib or placebo once daily, a prolongation in progression-free survival was observed for cabozantinib treatment compared with placebo (11.2 vs 4.0 months; HR 0.28, 95% CI 0.19–0.40).[40]

Both vandetanib and cabozantinib can have similar side effects. The most frequent adverse events common to all antiangiogenic multikinase inhibitors include hypertension, renal failure, bleeding, myelosuppression, hand-foot skin reaction, arterial thromboembolism, delayed wound healing, hepatotoxicity, and muscle wasting.

As treatment progresses, some patients start to develop drug resistance, and the discontinuation of the tyrosine kinase inhibitor is recommended. Second-line or third-line non-FDA approved agents for MTC could be considered (Lenvatinib, Sorafenib, or Sunitinib).

There are several ongoing clinical trials with new potential systemic therapies for patients with MTC requiring systemic therapy (**Table 1**).

SUMMARY

MTC is a rare form of thyroid cancer that is more aggressive and has different treatment approaches than differentiated thyroid cancer. MTC can be a challenge to diagnose by ultrasound imaging and FNA, so it should be considered in the differential diagnosis of any atypical thyroid nodules. Preoperative serum calcitonin levels can help guide the surgical approach in patients, and postoperative levels can help guide considerations for monitoring and additional imaging. Calcitonin and CEA doubling times are helpful in prognosis and imaging intervals in patients with MTC. RET-directed kinase inhibitors have significantly improved our therapeutic options for patients requiring systemic therapy and newer RET-inhibitors are being studied in clinical trials.

CLINICS CARE POINTS

- The sporadic form of medullary thyroid cancer (MTC) accounts for approximately 75% of cases, while the hereditary or familial form makes up about 25%

- MTC is often referred to as the *great masquerader* of the thyroid gland due to the challenges it presents in diagnosis, both in terms of thyroid nodule sonographic features and cytologic findings
- If a patient has a preoperative serum basal calcitonin level greater than 500 pg/mL, neck and chest computed tomography (CT), 3-phase contrast-enhanced liver CT or contrast-enhanced liver MRI, and axial MRI or bone scintigraphy should be considered to assess for metastatic disease
- Germline RET testing should be offered to all patients with newly diagnosed MTC
- The initial treatment of MTC is surgical, typically involving a total thyroidectomy and a prophylactic central neck dissection
- If the postoperative calcitonin is more than 150 pg/mL, additional imaging is recommended including CT or MRI of neck, chest, and abdomen; bone scan or bone MRI in patients suspected of having skeletal metastases
- Patients with somatic or germline RET mutations and distant metastatic disease requiring systemic therapy should be offered selpercatinib as first-line therapy
- For patients without a RET mutation, a multikinase inhibitor, either vandetanib or cabozantinib are recommended

DISCLOSURES

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