Overview

There are 3 main histologic types of thyroid carcinoma: differentiated (including papillary, follicular, and Hürthle), medullary, and anaplastic (aggressive undifferentiated tumor). Of 53,856 patients treated for thyroid carcinoma between 1985 and 1995, 80% had papillary, 11% had follicular, 3% had Hürthle cell, 4% had medullary, and 2% had anaplastic thyroid carcinoma. These NCCN guidelines focus on medullary thyroid carcinoma (MTC). Another NCCN guideline addresses papillary, follicular, Hürthle cell, and anaplastic thyroid carcinomas (see NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma [to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org]).

MTC derives from the neuroendocrine parafol-
licular calcitonin-producing (C) cells of the thyroid.\textsuperscript{2–4} Sporadic MTC accounts for approximately 80\% of all cases of the disease. The remaining cases consist of inherited tumor syndromes, such as multiple endocrine neoplasia type 2A (MEN 2A), which is the most common type; MEN 2B; or familial MTC.\textsuperscript{5,6} Sporadic disease typically presents in the fifth or sixth decade. Familial forms of the disease tend to present at earlier ages.\textsuperscript{2}

Because the C cells are predominantly located in the upper portion of each thyroid lobe, patients with sporadic disease typically present with upper pole thyroid nodules. Metastatic cervical adenopathy appears in approximately 50\% of patients at initial presentation. Symptoms of upper aerodigestive tract compression or invasion are reported by up to 15\% of patients with sporadic disease.\textsuperscript{7}

Symptoms from distant metastases in the lungs or bones occur in 5\% to 10\% of patients. The ability of the tumor to secrete measurable quantities of calcitonin, occasionally along with other hormonally active peptides (i.e., adrenocorticotropic hormone [ACTH] or calcitonin-gene related peptide [CGRP]), can contribute to the development of diarrhea, Cushing’s syndrome, or facial flushing in many patients with advanced disease. The risk for concomitant or subsequent development of pheochromocytoma and hyperparathyroidism must always be considered.\textsuperscript{2}

**Epidemiology**

Thyroid nodules are approximately 4 times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a

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Specialties: ðEndocrinology; ¶Surgery/Surgical Oncology;
#Pathology; †Medical Oncology; φNuclear Medicine; ÙInternal Medicine; ζOtolaryngology
**CLINICAL PRESENTATION**

- Solitary nodule > 1-1.5 cm in diameter
- Increased suspicion if any of the following are present:
  - Age < 15 y
  - Male sex
  - Nodule > 4 cm in diameter
  - History of radiation exposure
  - History of diseases associated with thyroid cancer:
    - Pheochromocytoma
    - MEN2
    - Familial adenomatous polyposis
    - Carney complex
    - Cowden's syndrome
  - Suspicious criteria by ultrasound
  - Incidentally identified focal PET positive lesion in the thyroid

- Nodules < 1 cm in diameter without suspicious findings and without suspicious lymph nodes by ultrasound, or simple cyst

**WORKUP**

- Highly suspicious:
  - Rapid nodule growth
  - Very firm nodule
  - Fixation to adjacent structures
  - Family history of thyroid cancer
  - Vocal cord paralysis
  - Enlarged regional lymph nodes
  - Symptoms of invasion into neck structures

- Follow-up as clinically indicated
- Consider lateral neck ultrasound
- If findings consistent with criteria of increased suspicion - see pathway above

Thyroid nodule with unknown TSH

- Thyroid nodule with low TSH
  - Radiodine imaging
  - Cold
  - FNA
  - Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)

Papillary carcinoma, finding postlobectomy for benign disease

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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In selected cases, it may be reasonable to follow with serial ultrasounds.

Patients with elevated thyroid stimulating hormone (TSH) levels may have an increased risk for malignancy.

Consider surgery after fine needle aspiration (FNA).
**NODULE EVALUATION**

**FNA RESULTS**

- **Carcinoma**
  - Papillary or suspicious for papillary
  - Medullary or suspicious for medullary
  - Anaplastic or suspicious for anaplastic

- **Follicular or Hürthle cell neoplasm**
  - TSH high or normal
  - TSH low

- **Follicular lesion of undetermined significance**
  - TSH high or normal
  - TSH low

**TREATMENT**

- **See guidelines for Papillary Carcinoma in the NCCN Thyroid Carcinoma Guidelines**
- **See Primary Treatment (page 516)**
- **See guidelines for Anaplastic Carcinoma in the NCCN Thyroid Carcinoma Guidelines**
- **See guidelines for Follicular or Hürthle Cell Carcinoma in the NCCN Thyroid Carcinoma Guidelines**
- **Surgery**
  - Cold
  - Hot
  - Evaluation and treat for thyrotoxicosis as indicated (malignancy is rare)
- **Repeat FNA, consider surgery based on clinical grounds, concerning growth, or suspicious sonographic findings**
- **Evaluate and treat for thyrotoxicosis as indicated (malignancy is rare)**
- **See NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin’s Lymphomas**
- **Correlate with ultrasound, re-aspirate suspicious areas**
- **Repeat FNA, consider ultrasound guidance and immediate cytologic review or consider surgery**
- *** Observe**
- **If nodule growth, repeat FNA or consider surgery**

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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\*Alternative term: suspicious for follicular or Hürthle cell neoplasm. Estimated risk for malignancy is 20%-30%.

\* Alternative terms include: atypia of undetermined significance, rule out neoplasm, atypical follicular lesion, and cellular follicular lesion. Estimated risk for malignancy is 5%-10%.

\* Includes nodular goiter, colloid nodule, hyperplastic adenomatoid nodule, and Hashimoto’s thyroiditis. Estimated risk for malignancy is < 1%.

\* Surgery usually means a diagnostic lobectomy for these follicular lesions. Consider total thyroidectomy for bilateral disease, unilateral disease > 4 cm (especially in men), or patient preference.

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*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.*

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Diagnostic categories for FNA results reflect NCI state of the science conference, available at http://www.cytojournal.com/content/5/1/6. Cytology reports should be interpreted in light of terminology used by local cytopathologists.
Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step in the pathway.

Germline mutation of RET proto-oncogene should prompt family testing of first-degree relatives and genetic counseling. (See NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.)

In view of the risks associated with thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
## Medullary Carcinoma Version 1:2010

### CLINICAL PRESENTATION

**MEN 2B**
- (codon 918, 883, or compound heterozygous [V804M + E805K, Y806C or S904C] RET mutations)

**MEN 2A**
- (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations)

- Familial medullary thyroid carcinoma (See MEN 2A for RET mutations)

- Germline mutation of RET proto-oncogene

### ADDITIONAL WORKUP

<table>
<thead>
<tr>
<th>Addl</th>
<th>MEN 2B</th>
<th>MEN 2A</th>
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<tbody>
<tr>
<td>Basal calcitonin level</td>
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<tr>
<td>CEA</td>
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<tr>
<td>Pheochromocytoma screening</td>
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<td>•</td>
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<tr>
<td>Neck ultrasound</td>
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### PRIMARY TREATMENT

- Total thyroidectomy during the first year of life or at diagnosis
- Consider bilateral central neck dissection (level VI)
- Consider more extensive node dissection (levels II–V) if tumor(s) > 0.5 cm in diameter
- Consider adjuvant RT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and following resection of moderate to high volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension (rarely recommended in children)
- Postoperative administration of levothyroxine to normalize TSH

### MANAGEMENT

- See Management 2-3 Months Postoperative (page 519)

- See Primary Treatment (page 518)

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*a* In view of the risks associated with thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.

*b* Lethality of medullary thyroid carcinoma associated with a single codon 768, 790, 804, and 891 RET mutation is lower than with other RET mutations. Prophylactic thyroidectomy may be delayed in patients with less high-risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)

*c* Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.

*d* Screening for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A) should be performed annually. For some RET mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.
**MEDULLARY CARCINOMA**

### Primary Treatment

- **Total thyroidectomy by age 5 yrs** or when mutation identified\(^a\) (if mutation identified at older age)
- Therapeutic ipsilateral or bilateral central neck dissection (level VI) if elevated calcitonin or CEA test or ultrasound identified thyroid or nodal abnormality
- Consider prophylactic ipsilateral modified neck dissection if high-volume or gross disease is present in the adjacent central neck
- Consider more extensive lymph node dissection (levels II–V) if tumors > 1.0 cm or central nodes positive
- Consider adjuvant RT for gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and of moderate- to high-volume disease in the central or lateral neck lymph nodes with extra-nodal soft tissue extension (rarely recommended in children)
- Postoperative administration of levothyroxine to normalize TSH

**CLINICAL PRESENTATION**

- No primary hyperparathyroidism
- Measure serum intact parathyroid hormone + calcium
- Primary hyperparathyroidism

**MANAGEMENT**

- **2-3 MONTHS POSTOPERATIVE**
  - Observe
  - Imaging positive or symptomatic disease
  - Imaging negative and asymptomatic disease

**SURVEILLANCE**

- Annual serum calcitonin, CEA
- Consider neck ultrasound
- Additional studies or more frequent testing if significantly rising calcitonin or CEA
- No additional imaging required if calcitonin and CEA stable

**MEN 2A** (codon 609, 611, 618, 620, 630, 634, 768, 790, 791, 804, or 891 RET mutations)\(^a,d\)

\(^a\)In view of the risks associated with thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.

\(^d\)Lethality of medullary thyroid carcinoma associated with a single codon 768, 790, 791, 804, and 891 RET mutation is lower than with other RET mutations. Prophylactic thyroidectomy may be delayed in patients with less-high-risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658-5671 and American Thyroid Association Guidelines Task Force. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.)

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**Clinical trials:** The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
Lethality of medullary thyroid carcinoma associated with a single codon 768, 790, 791, 804, and 891 RET mutation is lower than with other RET mutations.

In view of the risks associated with thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.


Prophylactic thyroidectomy may be delayed in patients with less-high-risk RET mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement.

(See Primary Treatment as outlined above)

**MANAGEMENT**

**2-3 MONTHS**

**POSTOPERATIVE**

- Neck imaging
  - Consider additional imaging if calcitonin > 150 pg/mL
  - Contrast-enhanced CT or MRI of the neck, chest, abdomen with liver protocol

**BASED ON POSTOPERATIVE SERUM BLOODWORK**

- Basal calcitonin
- CEA

- Detectable basal calcitonin or elevated CEA
  - Serum calcitonin, CEA every 6-12 mo
  - Additional studies or more frequent testing if significantly rising calcitonin or CEA
  - No additional imaging required if calcitonin and CEA stable
  - Imaging positive
  - Imaging negative and asymptomatic
  - Observe

- Basal calcitonin undetectable or CEA within reference range
  - Annual serum calcitonin, CEA
  - Consider neck ultrasound
  - Additional studies or more frequent testing if significantly rising calcitonin or CEA
  - No additional imaging required if calcitonin and CEA stable
  - For MEN 2B or 2A, annual screenings for pheochromocytoma and hyperparathyroidism (MEN 2A)

**SURVEILLANCE**

- Imaging positive or symptomatic disease
  - Additional studies or more frequent testing if significantly rising calcitonin or CEA
  - No additional imaging required if calcitonin and CEA stable
  - Imaging negative and asymptomatic
  - Observe

- Imaging negative and asymptomatic
  - Annual serum calcitonin, CEA
  - Consider neck ultrasound
  - Additional studies or more frequent testing if significantly rising calcitonin or CEA
  - No additional imaging required if calcitonin and CEA stable
  - For MEN 2B or 2A, annual screenings for pheochromocytoma and hyperparathyroidism (MEN 2A)

- Imaging negative
  - Continue observation

- Imaging positive
  - See Recurrent or Persistent Disease (page 520)
  - Continue observation
  - Consider cervical reoperation, if primary surgery incomplete

- Imaging negative
  - See Recurrent or Persistent Disease (page 520)
  - Continue observation

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9 The likelihood of significant residual disease with an undetectable basal calcitonin is very low.

Bone scan, FDG-PET scan, and MRI of axial skeleton should be considered in patients with very elevated calcitonin levels.
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

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prevalence of approximately 5% in the United States population aged 50 years and older. New nodules are even more prevalent when the thyroid gland is examined at autopsy or surgery, or when using ultrasonography; 50% of the thyroids so studied have nodules, which are almost always benign. New nodules develop at a rate of approximately 0.1% per year, beginning in early life, but develop at a much higher rate (~2% per year) after exposure to head and neck irradiation.

By contrast, thyroid carcinoma is uncommon. For the United States population, the lifetime risk for being diagnosed with thyroid carcinoma is less than 1% (0.83% for women, 0.33% for men). Approximately 37,200 new cases of thyroid carcinoma were estimated to be diagnosed in the United States in 2009. The 10-year disease-specific survival rate for patients with MTC is approximately 75%.

In 2009, approximately 1630 cancer deaths will occur among persons with thyroid carcinoma in the United States. Anaplastic thyroid carcinoma is almost uniformly lethal; however, most thyroid carcinoma deaths are from papillary, follicular, and Hürthle cell carcinomas, which account for nearly 95% of all thyroid carcinoma cases. Although thyroid carcinoma occurs more often in women, mortality rates are higher for men, probably because men are usually older at diagnosis.

Thyroid Nodule Evaluation

Patients with MTC can be identified using pathologic diagnosis or prospective genetic screening. Separate paths are included in the guidelines algorithm (see page 516) depending on the method of identification used. MTC must be distinguished from the other types of thyroid carcinoma (see page 515). The American Thyroid Association (ATA) recently published a guideline on MTC.

Fine-needle aspiration (FNA) is the preferred procedure for evaluating suspicious thyroid nodules. The Society of Radiologists in Ultrasound wrote a consensus statement on managing thyroid nodules identified at thyroid ultrasonography. Their recommendations describe which nodules should undergo FNA based on nodule size and ultrasound characteristics, and on clinical features that might predict risk for morbidity from an undiagnosed malignancy. Suspicious criteria by ultrasound include central hyper-vascularity, microcalcifications, and irregular borders.

Although more than 50% of all malignant nodules are asymptomatic, the pretest probability of malignancy in a nodule increases considerably when signs or symptoms are present (see page 514). For example, the likelihood that a nodule is malignant increases approximately 7-fold if it is very firm, fixed to adjacent structures, rapidly growing, associated with enlarged regional lymph nodes, and causing vocal cord paralysis, or if symptoms of invasion into neck structures are present. Family history of thyroid cancer is also indicative of malignancy. If 2 or more of these features are present, the likelihood of thyroid cancer is virtually assured; however, this is a rare situation.

A patient’s age and gender also affect the probability of malignancy. The risk for malignancy is higher in patients younger than 15 years and in men. Other factors that increase the suspicion of malignancy include: 1) a history of head and neck irradiation; 2) a history of diseases associated with thyroid carcinoma, such as familial adenomatous polyposis (formerly called Gardner’s syndrome), Carney complex, Cowden’s syndrome, and MEN 2A or 2B; 3) evidence of other thyroid cancer–associated diseases or syndromes, such as hyperparathyroidism, pheochromocytoma, marfanoid habitus, and mucosal neuromas (MEN2B), which make the presence of MTC more likely; or 4) the presence of suspicious findings detected with imaging, such as focal 18-fluorodeoxyglucose (FDG) uptake on PET, or central hypervascularity, irregular border, and/or microcalcifications on ultrasound.

Initial Workup of Thyroid Nodule

In patients who are clinically euthyroid, FNA of the nodule and clinically suspicious lymph nodes is recommended as the first diagnostic test before any imaging studies are performed. Ultrasound of the thyroid and central neck is also recommended. Ultrasound of the lateral neck can also be performed (category 2B). Ideally, the serum thyrotropin (thyroid-stimulating hormone [TSH]) results should be known before FNA is performed. This is often impractical, however, and FNA may be performed during the initial office visit. Recent data show that higher TSH levels are associated with risk for differentiated thyroid cancer.

Some clinicians, especially in Europe, recommend obtaining serum calcitonin levels from all patients with thyroid nodules. However, controversy
Medullary Carcinoma

exists surrounding the cost-effectiveness of this practice in the United States, especially in the absence of confirmatory pentagastrin stimulation testing and the assumptions used in cost-effective analyses. The ATA is equivocal about measuring serum calcitonin. A recent study showed that calcitonin screening may be cost effective in the United States. However, false-positive calcitonin readings that can result from minimal calcitonin elevations can only be ruled out with pentagastrin testing, and pentagastrin is not available in the United States.

Cytologic examination of an FNA specimen is typically categorized as 1) carcinoma (papillary, medullary, or anaplastic) or suspicious for malignancy; 2) follicular or Hurthle cell neoplasm; 3) follicular lesion of undetermined significance; 4) thyroid lymphoma; 5) benign (i.e., nodular goiter, colloid goiter, hyperplastic/adenomatoid nodule, Hashimoto’s thyroiditis); or 6) insufficient biopsy (nondiagnostic; see page 515). These diagnostic categories for FNA results reflect the National Cancer Institute’s State of the Science conference held in 2007 (http://www.cytojournal.com/content/5/1/6).

Pathology and cytopathology slides should be reviewed at the treating institution by a pathologist with expertise in diagnosing thyroid disorders. Although FNA is a very sensitive test, particularly for papillary, false-negative results are sometimes obtained; therefore, a reassuring FNA should not override concerns in the presence of worrisome clinical findings. Medullary carcinoma may occasionally require additional immunohistochemical studies (e.g., calcitonin) to confirm the diagnosis (http://www.cytojournal.com/content/5/1/6).

Hurthle cell neoplasms can sometimes mimic medullary carcinoma cytologically and on frozen section, and sometimes anaplastic thyroid cancer can be difficult to discriminate from other primary thyroid malignancies (i.e., MTC, thyroid lymphoma) or poorly differentiated cancer metastatic to the thyroid. Metastatic renal carcinoma can mimic a follicular neoplasm, melanoma can mimic medullary carcinoma, and metastatic lung cancer can mimic anaplastic carcinoma of the thyroid (http://thyroidfna.cancer.gov/pages/conclusions/).

Sporadic MTC

Sporadic MTC is usually suspected after FNA of a solitary nodule (see page 515). Reports suggest that approximately 3% of patients with nodular thyroid disease will have an increased serum calcitonin level when measured with a sensitive immunometric assay; 40% of these patients will have MTC at thyroidectomy. However, the NCCN does not recommend routine measurement of the basal serum calcitonin concentration for evaluating patients with nodular thyroid disease because of the expense incurred by screening all thyroid nodules to find only a few cases of MTC, the lack of confirmatory pentagastrin stimulation testing, and the resulting need for thyroidectomy in some patients who actually have benign thyroid disease.

Inherited MTC

In kindreds known to have inherited MTC, prospective family screening with testing for mutant RET (rearranged during transfection) genes can identify disease carriers long before clinical symptoms or signs are noted. The traditional approach of stimulating secretion of calcitonin with either pentagastrin or calcium infusion is no longer recommended, because elevated calcitonin is not a specific or adequately sensitive marker for MTC and pentagastrin is no longer available in the United States. Serum intact parathyroid hormone levels and calcium levels are measured when MEN 2A is suspected (see page 518). Compared with sporadic disease, the typical age of presentation for familial disease is the third or fourth decade, without gender preference. In MEN 2A, signs or symptoms of hyperparathyroidism or pheochromocytoma rarely present before those of MTC, even in the absence of screening.

All familial forms of MTC and MEN 2 are inherited in an autosomal dominant fashion. Mutations in the RET proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of familial MTC. Familial MTC is now viewed as a variant of MEN 2A. The RET proto-oncogene codes for a cell membrane–associated tyrosine kinase receptor for a glial, cell line–derived neurotrophic factor. Mutations associated with MEN 2A and familial MTC have been primarily identified in several codons of the cysteine-rich extracellular domains of exons 10, 11, and 13, whereas MEN 2B and some familial MTC mutations are found within the intracellular exons 14 through 16. Somatic mutations in exons 11, 13, and 16 have also been found in at least 25% of spo-
radic MTC tumors, particularly the codon 918 mutation that activates the tyrosine kinase function of the receptor and is associated with poorer prognosis.

Approximately 6% of patients with what appears to be clinically sporadic MTC carry a germline mutation in RET, allowing new kindreds to be identified among many previously undiagnosed affected individuals. Genetic testing for RET proto-oncogene mutations should be encouraged for all patients with newly diagnosed clinically apparent sporadic MTC, and for screening children in adults known kindreds with inherited forms of MTC. Genetic counseling should be considered.

Generally accepted approaches to preoperative workup include measurement of serum markers (basal calcitonin and serum carcinoembryonic antigen [CEA]) and screening patients with germline RET proto-oncogene mutations for pheochromocytoma (MEN 2A and 2B) and hyperparathyroidism (MEN 2A). Before undertaking surgical therapy for MTC, coexisting pheochromocytoma must be diagnosed and prospectively treated to avoid hypertensive crisis during surgery. Pheochromocytoma can be removed through laparoscopic adrenalectomy.

Preoperative neck ultrasound is recommended. Contrast-enhanced CT of the chest and mediastinum or MRI can be considered if the patient has N1 disease or calcitonin greater than 400 pg/mL. Vocal cord mobility can also be evaluated.

Staging
The TNM criteria for clinicopathologic tumor staging are based on tumor size, the presence or absence of extrathyroidal invasion, locoregional nodal metastases, and distant metastases (see the staging table, available online, in these guidelines, at www.NCCN.org [ST-1]; 6th edition AJCC staging manual). An MTC tumor 2 cm or less in diameter without evidence of disease outside the thyroid gland is classified as stage I. Any larger tumor (> 2 ≤ 4 cm) limited to the thyroid without nodal or distant metastases is classified as stage II. The presence of level 6 nodal metastases, minimal extrathyroidal invasion, or tumor size greater than 4 cm is classified as stage III. A tumor extending beyond the perithyroid soft tissues, involving lymph nodes beyond level 6, or spreading to distant metastatic sites is classified as stage IV. Note that staging for MTC has slightly changed in the recent AJCC update (i.e., 7th edition AJCC staging manual), which was effective January 1, 2010. In the 7th edition, T3,N0,M0 has been downstaged from stage III to stage II.

Note that all follow-up studies reporting on AJCC-TNM staging have referred to the 5th edition and not the 6th or 7th editions. In one study with a median follow-up period of only 4 years, mortality from MTC was 0% for stage I, 13% for stage II, 56% for stage III, and 100% for stage IV disease.

However, the TNM staging classification lacks other important prognostic factors. Notably absent is the age at diagnosis. Patients younger than 40 years at diagnosis have 5- and 10-year diseasespecific survival rates of approximately 95% and 75%, respectively, compared with 65% and 50% for those older than 40 years. Controlling for the effect of age at diagnosis, the prognosis of patients with inherited disease (who typically are diagnosed at an earlier age) is probably similar to those with sporadic disease. Despite an even younger typical age at diagnosis, however, patients with MEN 2B who have MTC are more likely than those with either MEN 2A or familial MTC to have locally aggressive disease.

Other factors that may be important for predicting a worse prognosis include 1) the heterogeneity and paucity of calcitonin immunostaining of the tumor; 2) a rapidly increasing CEA level, particularly in the setting of a stable calcitonin level; and 3) postoperative residual hypercalcitoninemia. A study comparing different staging systems found that the EORTC system incorporating age, gender, and distant metastases had the greatest predictive value; however, the AJCC staging system was deemed to be the most appropriate. Codon analysis is useful for predicting prognosis. Presence of an exon 16 mutation, either within a sporadic tumor or associated with MEN 2B, is associated with more aggressive disease. More than 95% of patients with MEN 2B have a mutation in exon 16 (codon 918), whereas 2% to 3% have a mutation in exon 15 (codon 883).

Surgical Management
Surgery is the main treatment for MTC, because no known curative systemic therapy exists. MTC cells do not concentrate radioactive iodine, and MTC does not respond well to conventional cytotoxic chemotherapy. Therefore, radioiodine imaging can-
not be used, and radioiodine treatment is not effective in these patients. Postoperative levothyroxine is indicated for all patients; however, TSH suppression is not appropriate, because C cells lack TSH receptors. Thus, TSH should be kept in the normal range through adjusting the levothyroxine dose.\textsuperscript{2}

Even with patients who have apparently sporadic disease, the possibility of MEN 2 should dictate that a \textit{RET} proto-oncogene mutation is absent or that hyperparathyroidism and pheochromocytoma should be excluded preoperatively. Pheochromocytomas should be removed (e.g., laparoscopic adrenalectomy) with \(\alpha\)-adrenergic blockade (phenoxybenzamine) or \(\alpha\)-methyltyrosine before surgery on the thyroid to avoid hypertensive crisis during surgery. Forced hydration and \(\alpha\)-blockade are necessary to prevent hypotension after the tumor is removed. After institution of \(\alpha\)-blockade and hydration, \(\beta\)-adrenergic blockade may be necessary to treat tachyarrhythmia.

For all patients with MTC whose tumor is 1 cm or larger or who have bilateral thyroid disease, total thyroidectomy and bilateral central neck dissection (level VI) are indicated. For those who have a tumor smaller than 1 cm and have unilateral thyroid disease, total thyroidectomy is recommended and neck dissection can be considered (see page 516).\textsuperscript{7} Given the risks associated with thyroidectomy in very young children, referral is advised to a surgeon and team experienced in pediatric thyroid surgery.

If a patient with inherited disease is diagnosed early enough, the recommendation is to perform a prophylactic total thyroidectomy by age 5 years or when the mutation is identified (in older patients), especially in patients with codon 609, 611, 618, 620, 630, or 634 \textit{RET} (risk level B) mutations.\textsuperscript{2,51} Note that C634 mutations are the most common mutation.\textsuperscript{2} Total thyroidectomy is recommended in the first year of life or at diagnosis for patients with MEN 2B or carriers of codon 883 \textit{RET}, 918 \textit{RET}, or compound heterozygous (V804M + E805K, V804M + Y806C, or V804M + S904C) \textit{RET} mutations (see page 517), because these mutations are associated with the highest risk for MTC (i.e., level D).\textsuperscript{2}

However, for patients with codon 768, 790, 791, 804, and 891 \textit{RET} (risk level A) mutations, the lethality of MTC may be lower than with other \textit{RET} mutations.\textsuperscript{52} In patients with these level A \textit{RET} mutations, annual basal calcitonin testing and ultrasound are recommended; total thyroidectomy and central node dissection may be deferred if these tests are normal, there is no family history of aggressive MTC, and the family agrees (see page 517).\textsuperscript{2,53}

Delaying thyroidectomy may also be appropriate for children with risk level A mutations because of the late onset of MTC development.\textsuperscript{2,54} A study found no evidence of persistent or recurrent MTC 5 years or more after prophylactic total thyroidectomy in young patients with \textit{RET} mutations for MEN 2A; longer follow-up is necessary to determine if these patients are cured.\textsuperscript{55}

Variations in surgical strategy depend on the risk for locoregional node metastases and whether simultaneous parathyroid resection for hyperparathyroidism is necessary. A bilateral central neck dissection (level VI) can be considered for all patients with MEN 2B. For those with MEN 2A who undergo prophylactic thyroidectomy, therapeutic ipsilateral or bilateral central neck dissection (level VI) is recommended if they have an increased calcitonin or CEA test or if ultrasound shows a thyroid or nodal abnormality. Similarly, more extensive lymph node dissection (levels II–V) is considered for patients with primary tumors 1 cm or larger in diameter (\(>0.5\) cm for patients with MEN 2B) or central compartment lymph node metastases (see page 518).

For patients with a concurrent diagnosis of hyperparathyroidism in MEN 2A or familial MTC, surgeons should leave or autotransplant the equivalent mass of 1 normal parathyroid gland if multiglandular hyperplasia is present. Cryopreservation of resected parathyroid tissue should be considered to allow future implantation in the event of iatrogenic hypoparathyroidism. Disfiguring radical node dissections do not improve prognosis and are not indicated. In the presence of grossly invasive disease, more extended procedures with resection of involved neck structures may be appropriate. Function-preserving approaches are preferred.

\textbf{Surgical Complications:} The most common significant complications of thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve injury, which occur with higher frequency after total thyroidectomy. Transient clinical hypoparathyroidism after surgery is common in adults\textsuperscript{56} and children\textsuperscript{57,58} undergoing total thyroidectomy.

However, the rates of persistent hypocalcemia are reported to be much lower in the hands of expe-
rienced thyroid surgeons. In a review of 7 published surgical series, the average rates of long-term recurrent laryngeal nerve injury and hypoparathyroidism, respectively, were 3% and 2.6% after total thyroidectomy, and 1.9% and 0.2% after subtotal thyroidectomy. One study reported hypocalcemia in 5.4% of patients immediately after total thyroidectomy, persisting in only 0.5% of patients 1 year later.

When experienced surgeons perform thyroidectomies, complications occur at a lower rate. A study of 5860 patients treated in the state of Maryland found that surgeons who performed more than 100 thyroidectomies per year had the lowest overall complication rate (4.3%), whereas those who performed fewer than 10 thyroidectomies a year had 4 times as many complications.

### Adjuvant Radiation Therapy

External-beam radiation therapy (RT) has not been adequately studied as adjuvant therapy in medullary carcinoma. Although slight improvements have been reported in local disease-free survival after external-beam RT for selected patients, such as those with extrathyroidal invasion or extensive locoregional node involvement, most centers do not have extensive experience with adjuvant RT for this disease. When external-beam RT is used, 40 Gy is typically administered in 20 fractions to the cervical, supraclavicular, and upper mediastinal lymph nodes over 4 weeks, with subsequent booster doses of 10 Gy in 5 fractions to the thyroid bed. Postoperative adjuvant RT to the neck and mediastinum may be considered for patients with gross extrathyroidal extension (T4a or T4b) with positive margins after resection of all gross disease and moderate- to high-volume disease in the central or lateral neck lymph nodes with extranodal soft tissue extension. However, this practice is rarely recommended in children (see pages 517 and 518). External-beam RT can also be given to palliate painful or progressing bone metastases.

### Persistently Increased Calcitonin

Basal serum concentrations of calcitonin and CEA should be measured 2 or 3 months postoperatively. Approximately 80% of patients with palpable MTC and 50% of those with nonpalpable but macroscopic MTC who undergo supposedly curative resection have serum calcitonin values indicative of residual disease. Patients with residual disease may benefit from further evaluation to detect either residual resectable disease in the neck or the presence of distant metastases. Patients with detectable basal calcitonin or elevated CEA who have negative imaging and are asymptomatic may be followed up (see page 519).

Patients with a basal serum calcitonin value greater than 1000 pg/mL and with no obvious MTC in the neck and upper mediastinum probably have distant metastases, most likely in the liver. However, occasionally patients have relatively low serum CEA and calcitonin levels but have extensive metastatic disease; initial postoperative staging imaging is therefore not unreasonable despite the absence of very high serum markers.

The prognosis for patients with postoperative hypercalcitoninemia depends primarily on the extent of disease at initial surgery. In a study of 31 patients (10 patients with apparently sporadic disease, 15 with MEN 2A, and 6 with MEN 2B), the 5- and 10-year survival rates were 90% and 86%, respectively.

Two studies have reported higher mortality rates for patients with high postoperative serum calcitonin values, with more than 50% of patients experiencing a recurrence during a mean follow-up of 10 years. Routine lymphadenectomy or excision of palpable tumor generally fails to normalize the serum calcitonin concentrations in these patients; therefore, some clinicians have focused on detecting and eradicating microscopic tumor deposits with a curative intent in patients without distant metastases. Extensive dissection to remove all nodal and perinodal tissue from the neck and upper mediastinum was first reported to normalize the serum calcitonin levels in 4 of 11 patients at least 2 years postoperatively. In subsequent larger studies, 20% to 40% of patients undergoing microdissection of the central and bilateral neck compartments were biochemically cured, with minimal perioperative morbidity.

When repeat surgery is planned for curative intent, preoperative assessment should include locoregional imaging (e.g., ultrasonography of the neck and upper mediastinum) and attempts to exclude patients with distant metastases, which may involve contrast-enhanced CT or MRI of the neck, chest, and abdomen.
**Medullary Carcinoma**

**Postoperative Management and Surveillance**

Calcitonin is very useful for surveillance, because it is produced in the parafollicular cells. Therefore, measurements of serum calcitonin and CEA levels are the cornerstone of postoperative assessment for residual disease (see page 519). For patients with a detectable basal calcitonin or elevated CEA level, neck imaging is recommended. Patients with undetectable calcitonin levels can be followed up with annual measurements of serum markers, reserving additional studies or more frequent testing for significantly rising calcitonin or CEA. Nonetheless, the likelihood of significant residual disease is very low in patients with an undetectable basal calcitonin level using a sensitive assay. If the patient has MEN 2, annual screening for pheochromocytoma (MEN 2B or 2A) and hyperparathyroidism (MEN 2A) should be performed. For some low-risk RET mutations (e.g., codons 768, 790, 804, or 891), less frequent screening may be appropriate.

Patients with detectable serum markers should undergo contrast-enhanced CT or MRI of the neck, chest, and abdomen with a liver protocol. Bone scan, FDG-PET scan, or MRI of axial skeleton should be considered in patients with very elevated calcitonin levels. The panel recognizes that many different imaging modalities may be used to examine for residual or metastatic tumor, but evidence is insufficient to recommend any particular choice or combination of tests.²

For asymptomatic patients with detectable markers in whom imaging fails to identify foci of disease, the panel recommends conservative surveillance with repeat measurement of the serum markers every 6 to 12 months. For asymptomatic patients with abnormal markers and repeated negative imaging, continued observation or consideration of cervical reoperation is recommended if primary surgery was incomplete. For patients with increasing serum markers, more frequent imaging may be considered. Outside of clinical trials, no therapeutic intervention based on abnormal markers alone is recommended.

**Recurrent or Persistent Disease**

When locoregional disease is identified in the absence of distant metastases, surgical resection is recommended with or without postoperative RT. If symptomatic progressive or unresectable locoregional disease is present, then RT can be considered. Distant metastases that are causing symptoms (e.g., those in bone) could be considered for palliative resection, ablation (e.g., radiofrequency, embolization), or other regional treatment (see page 520). These interventions may be considered for asymptomatic distant metastases (especially for progressive disease), but observation is acceptable given the lack of data on alteration in outcome. In the setting of disseminated symptomatic metastases, the guidelines recommend 1) a clinical trial (preferred); 2) RT for focal symptoms; 3) consideration of small molecule kinase inhibitors (i.e., sorafenib or sunitinib) if clinical trials are not available or appropriate;⁶⁹–⁷¹ 4) systemic chemotherapy, using dacarbazine or combinations including dacarbazine;⑦² ⑦³ ⑦⁴ consideration of bisphosphonate therapy for bone metastases; and 5) best supportive care.

In patients with metastatic MTC, sorafenib reduces symptoms caused by hypercalcitonemia and metastases.⁶⁹ Recently, stable disease rates of approximately 50% and clinical benefit rates of approximately 70% have been seen with motesanib diphosphate (AMG-706) in sporadic, metastatic MTC, and with vandetanib in hereditary metastatic MTC.⁷⁴,⁷⁵ In addition, clinical response was seen in 6 of 8 patients treated with a combination of sorafenib and the farnesyltransferase inhibitor tipifarnib.⁷⁶ Sunitinib was associated with clinical response in 2 patients published as case reports.⁷⁰,⁷⁷

Ongoing clinical trials are studying the effectiveness of novel multitargeted therapies, including sunitinib,⁷⁰,⁷⁸ sorafenib,⁷⁶,⁷⁹ XL 184,⁸⁰,⁸¹ and pazopanib (GW786034). Several recent published reviews have examined novel therapies and the therapeutic approach to the management of aggressive MTC.⁸²–⁸⁴ Of interest, calcitonin levels decreased dramatically after vandetanib therapy, which did not correlate directly with changes in tumor volume; thus, calcitonin may not be a reliable marker of tumor response in patients undergoing RET inhibitor therapy.⁷⁷ A study in patients with progressive metastatic MTC assessed treatment using pretargeted anti-CEA radioimmunotherapy with ⁱ³¹ I; overall survival was improved in the subset of patients with calcitonin doubling times of less than 2 years.
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References


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NCCN Clinical Practice Guidelines in Oncology
Medullary Carcinoma


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Dr. Hughes has disclosed that she has a patent, equity, or royalty in Myriad Genetic Laboratories, Inc.; Affymetrix; and Qiagen NV. The remaining guidelines staff have disclosed that they have no conflicts of interest.