TABLE 408-4 RECOMMENDATIONS FOR TESTS AND SURGERY IN MEN 2 AND MEN 3[a]

RET Mutation, Exon (Ex) Location, and Codon Involved	Risk[b]	Recommended Age (years) for Test/Intervention				
		RET Mutational Analysis	First Serum Calcitonin and Neck Ultrasound	Prophylactic Thyroidectomy	Screening for Pheochromocytoma	Screening for PHPT
Ex13 (768, 790)[c] Ex14 (804)[c]; Ex15 (891)[c]	+	<3–5	<3–5	5[d]	20	20
Ex10 (609, 611, 618, 620)[c]; Ex11 (630)[c]	++	<3–5	<3–5	<5[e]	20	20
Ex11 (634)[c]	+++	<3–5	<3–5	<5	8	20
Ex15 (883)[f]; Ex16 (918)[f]	++++	ASAP and by <1	ASAP and by <0.5–1	ASAP and by <1	8	—[g]

[a]Adapted from American Thyroid Association Guidelines, RT Kloos et al: Thyroid 6:565, 2009. [b]Risk for early development of metastasis and aggressive growth of medullary thyroid cancer: ++++, highest; +++, high; ++, intermediate; and +, lowest. [c]Mutations associated with MEN 2A (or medullary thyroid carcinoma only). [d]Consider surgery at 5 years or later if serum calcitonin is normal, neck ultrasound is normal, and there is a less aggressive family history and family preference. [e]Consider surgery before 5 years or later if serum calcitonin is normal, neck ultrasound is normal, and there is a less aggressive family history and family preference. [f]Mutations associated with MEN 2B (MEN 3). [g]Not required because PHPT is not a feature of MEN 2B (MEN 3).

Abbreviations: ASAP, as soon as possible; MEN, multiple endocrine neoplasia; PHPT, primary hyperparathyroidism.

FMTC and MEN 2A is difficult and should only be considered if there are at least four family members above the age of 50 years who are affected by MTC but not pheochromocytomas or primary hyperparathyroidism. All of the MEN 2 variants are due to mutations of the rearranged during transfection (*RET*) protooncogene, which encodes a TKR. Moreover, there is a correlation between the locations of *RET* mutations and MEN 2 variants. Thus, ~95% of MEN 2A patients have mutations involving the cysteine-rich extracellular domain, with mutations of codon 634 accounting for ~85% of MEN 2A mutations; FMTC patients also have mutations of the cysteine-rich extracellular domain, with most mutations occurring in codon 618. In contrast, ~95% of MEN 2B/MEN 3 patients have mutations of codon 918 of the intracellular tyrosine kinase domain (Table 408-1 and Table 408-4).

Medullary Thyroid Carcinoma MTC is the most common feature of MEN 2A and MEN 2B and occurs in almost all affected individuals. MTC represents 5–10% of all thyroid gland carcinomas, and 20% of MTC patients have a family history of the disorder. The use of *RET* mutational analysis to identify family members at risk for hereditary forms of MTC has altered the presentation of MTC from that of symptomatic tumors to a preclinical disease for which prophylactic thyroidectomy (Table 408-4) is undertaken to improve the prognosis and ideally result in cure. However, in patients who do not have a known family history of MEN 2A, FMTC, or MEN 2B, and therefore have not had *RET* mutational analysis, MTC may present as a palpable mass in the neck, which may be asymptomatic or associated with symptoms of pressure or dysphagia in >15% of patients. Diarrhea occurs in 30% of patients and is associated either with elevated circulating concentrations of calcitonin or tumor-related secretion of serotonin and prostaglandins. Some patients may also experience flushing. In addition, ectopic ACTH production by MTC may cause Cushing's syndrome. The diagnosis of MTC relies on the demonstration of hypercalcitoninemia (>90 pg/mL in the basal state); stimulation tests using IV pentagastrin (0.5 mg/kg) and or calcium infusion (2 mg/kg) are rarely used now, reflecting improvements in the assay for calcitonin. Neck ultrasonography with fine-needle aspiration of the nodules can confirm the diagnosis. Radionucleotide thyroid scans may reveal MTC tumors as "cold" nodules. Radiography may reveal dense irregular calcification within the involved portions of the thyroid gland and in lymph nodes involved with metastases. Positron emission tomography (PET) may help to identify the MTC and metastases (Fig. 408-2). Metastases of MTC usually occur to the cervical lymph nodes in the early stages and to the mediastinal nodes, lung, liver, trachea, adrenal, esophagus, and bone in later stages. Elevations in serum calcitonin concentrations are often the first sign of recurrence or persistent disease, and the serum calcitonin doubling time is useful for determining prognosis. MTC can have an aggressive clinical course, with early metastases and death in approximately 10% of patients. A family history of aggressive MTC or MEN 2B may be elicited.

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Individuals with *RET* mutations who do not have clinical manifestations of MTC should be offered prophylactic surgery between the ages of <1 and 5 years. The timing of surgery will depend on the type of *RET* mutation and its associated risk for early development, metastasis, and aggressive growth of MTC (Table 408-4). Such patients should have a total thyroidectomy with a systematic central neck dissection to remove occult nodal metastasis, although

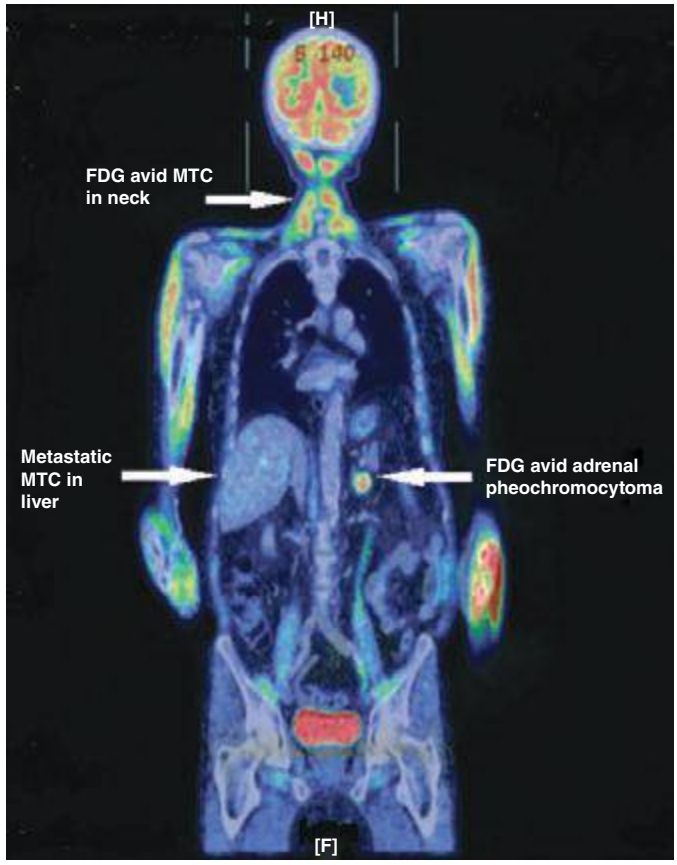

FIGURE 408-2 Fluorodeoxyglucose (FDG) positron emission tomography scan in a patient with multiple endocrine neoplasia type 2A, showing medullary thyroid cancer (MTC) with hepatic and skeletal (left arm) metastasis and a left adrenal pheochromocytoma. Note the presence of excreted FDG compound in the bladder. *(Reproduced with permission from A Naziat et al: Clin Endocrinol [Oxf] 78:966, 2013.)*