target of rapamycin (mTOR) signaling pathway have been reported to be effective in treating pancreatic NETs and in doubling the progression-free survival time.

Other Pancreatic NETs NETs secreting growth hormone–releasing hormone (GHRH), GHRHomas, have been reported rarely in patients with MEN 1. It is estimated that ~33% of patients with GHRHomas have other MEN 1–related tumors. GHRHomas may be diagnosed by demonstrating elevated serum concentrations of growth hormone and GHRH. More than 50% of GHRHomas occur in the lung, 30% occur in the pancreas, and 10% are found in the small intestine. Somatostatinomas secrete somatostatin, a peptide that inhibits the secretion of a variety of hormones, resulting in hyperglycemia, cholelithiasis, low acid output, steatorrhea, diarrhea, abdominal pain, anemia, and weight loss. Although 7% of pancreatic NETs secrete somatostatin, the clinical features of somatostatinoma syndrome are unusual in patients with MEN 1.

Pituitary Tumors (See also Chap. 403) Pituitary tumors occur in 15–50% of patients with MEN 1 (Table 408-1). These occur as early as 5 years of age or as late as the ninth decade. MEN 1 pituitary adenomas are more frequent in women than men and significantly are macroadenomas (i.e., diameter >1 cm). Moreover, about one-third of these pituitary tumors show invasive features such as infiltration of tumor cells into surrounding normal juxtatumoral pituitary tissue. However, no specific histologic parameters differentiate between MEN 1 and non–MEN 1 pituitary tumors. Approximately 60% of MEN 1–associated pituitary tumors secrete prolactin, <25% secrete growth hormone, 5% secrete adrenocorticotropic hormone (ACTH), and the remainder appear to be nonfunctioning, with some secreting glycoprotein subunits (Table 408-1). However, pituitary tumors derived from MEN 1 patients may exhibit immunoreactivity to several hormones. In particular, there is a greater frequency of somatolactotrope tumors. Prolactinomas are the first manifestation of MEN 1 in ~15% of patients, whereas somatotrope tumors occur more often in patients older than 40 years of age. Fewer than 3% of patients with anterior pituitary tumors will have MEN 1. Clinical manifestations are similar to those in patients with sporadic pituitary tumors without MEN 1 and depend on the hormone secreted and the size of the pituitary tumor. Thus, patients may have symptoms of hyperprolactinemia (e.g., amenorrhea, infertility, and galactorrhea in women, or impotence and infertility in men) or have features of acromegaly or Cushing's disease. In addition, enlarging pituitary tumors may compress adjacent structures such as the optic chiasm or normal pituitary tissue, causing visual disturbances and/or hypopituitarism. In asymptomatic patients with MEN 1, periodic biochemical monitoring of serum prolactin and insulin-like growth factor I (IGF-I) levels, as well as MRI of the pituitary, can lead to early identification of pituitary tumors (Table 408-3). In patients with abnormal results, hypothalamic-pituitary testing should characterize the nature of the pituitary lesion and its effects on the secretion of other pituitary hormones.

TREATMENT PITUITARY TUMORS

Treatment of pituitary tumors in patients with MEN 1 consists of therapies similar to those used in patients without MEN 1 and includes appropriate medical therapy (e.g., bromocriptine or cabergoline for prolactinoma; or octreotide or lanreotide for somatotrope tumors) or selective transsphenoidal adenomectomy, if feasible, with radiotherapy reserved for residual unresectable tumor tissue. Pituitary tumors in MEN 1 patients may be more aggressive and less responsive to medical or surgical treatments.

Associated Tumors Patients with MEN 1 may also develop carcinoid tumors, adrenal cortical tumors, facial angiofibromas, collagenomas, thyroid tumors, and lipomatous tumors.

Carcinoid Tumors (See also Chap. 113) Carcinoid tumors occur in more than 3% of patients with MEN 1 (Table 408-1). The carcinoid tumor may be located in the bronchi, gastrointestinal tract, pancreas, or thymus. At the time of diagnosis, most patients are asymptomatic and do not have clinical features of the carcinoid syndrome. Importantly, no hormonal or biochemical abnormality (e.g., plasma chromogranin A) is consistently observed in individuals with thymic or bronchial carcinoid tumors. Thus, screening for these tumors is dependent on radiologic imaging. The optimum method for screening has not been established. CT and MRI are sensitive for detecting thymic and bronchial tumors (Table 408-3), although repeated CT scanning raises concern about exposure to repeated doses of ionizing radiation. Octreotide scintigraphy may also reveal some thymic and bronchial carcinoids, although there is insufficient evidence to recommend its routine use. Gastric carcinoids, of which the type II gastric enterochromaffin-like (ECL) cell carcinoids (ECLomas) are associated with MEN 1 and Zollinger-Ellison syndrome, may be detected incidentally at the time of gastric endoscopy for dyspeptic symptoms in MEN 1 patients. These tumors, which may be found in >10% of MEN 1 patients, are usually multiple and smaller than 1.5 cm. Bronchial carcinoids in patients with MEN 1 occur predominantly in women (male-to-female ratio, 1:4). In contrast, thymic carcinoids in European patients with MEN 1 occur predominantly in men (male-to-female ratio, 20:1), with cigarette smokers having a higher risk for these tumors; thymic carcinoids in Japanese patients with MEN 1 have a less marked sex difference (male-to-female ratio 2:1). The course of thymic carcinoids in MEN 1 appears to be particularly aggressive. The presence of thymic tumors in patients with MEN 1 is associated with a median survival after diagnosis of approximately 9.5 years, with 70% of patients dying as a direct result of the tumor.

TREATMENT CARCINOID TUMORS

If resectable, surgical removal of carcinoid tumors is the treatment of choice. For unresectable tumors and those with metastatic disease, treatment with radiotherapy or chemotherapeutic agents (e.g., cisplatin, etoposide) may be used. In addition, somatostatin analogues, such as octreotide or lanreotide, have resulted in symptom improvement and regression of some tumors. Little is known about the malignant potential of gastric type II ECLomas, but treatment with somatostatin analogues, such as octreotide or lanreotide, has resulted in regression of these ECLomas.

Adrenocortical Tumors (See also Chap. 406) Asymptomatic adrenocortical tumors occur in 20–70% of patients with MEN 1 depending on the radiologic screening methods used (Table 408-1). Most of these tumors, which include cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, and carcinomas, are nonfunctioning. Indeed, <10% of patients with enlarged adrenal glands have hormonal hypersecretion, with primary hyperaldosteronism and ACTH-independent Cushing's syndrome being encountered most commonly. Occasionally, hyperandrogenemia may occur in association with adrenocortical carcinoma. Pheochromocytoma in association with MEN 1 is rare. Biochemical investigation (e.g., plasma renin and aldosterone concentrations, low-dose dexamethasone suppression test, urinary catecholamines, and/or metanephrines) should be undertaken in those with symptoms or signs suggestive of functioning adrenal tumors or in those with tumors >1 cm. Adrenocortical carcinoma occurs in approximately 1% of MEN 1 patients but increases to >10% for adrenal tumors larger than 1 cm.

TREATMENT ADRENOCORTICAL TUMORS

Consensus has not been reached about the management of MEN 1–associated nonfunctioning adrenal tumors, because the majority are benign. However, the risk of malignancy increases with size, particularly for tumors with a diameter >4 cm. Indications for surgery for adrenal tumors include: size >4 cm in diameter; atypical or suspicious radiologic features (e.g., increased Hounsfield unit on unenhanced CT scan) and size of 1–4 cm in diameter; or significant