Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant inherited disorder that affects tumorigenesis in at least 8 endocrine and nonendocrine tissues. The true prevalence of MEN 1 is likely underestimated but varies from 0.2 to 2 per 100,000 population. The major clinical manifestations in MEN 1 include “the 3 Ps”: primary hyperparathyroidism (HPT), pancreatic and duodenal neuroendocrine tumors, and pituitary tumors (Figure 1). Expression of the disease rarely occurs before the age of 10 years, and most often the syndrome presents itself between the ages of 20 and 40 years. Two of the 3 major lesions must be present to confirm the clinical diagnosis in a proband. In the members of a known MEN 1 kindred, the presence of 1 major lesion is diagnostic. Genetic testing confirms the clinical diagnosis.

The gene responsible for MEN 1 was identified in 1997 and is located on chromosome 11q13. The MEN1 gene encodes a nuclear protein referred to as menin. Menin interacts with other proteins involved in transcription and cell growth. Therefore, MEN1 acts as a tumor suppressor gene. MEN1 gene testing, most often using direct DNA sequencing, is clinically available in at least 4 molecular genetics laboratories in North America.

The preferred surgical approach for the MEN 1 patient with primary hyperparathyroidism is subtotal parathyroidectomy with transcervical thymectomy.

Pancreatic and duodenal endocrine tumors remain the number 1 cause of tumor-related death in MEN 1 patients.

Morbidity may be reduced and survival prolonged with early detection of pancreatic and duodenal endocrine tumors in at-risk MEN 1 family members, hence the importance of presymptomatic testing.

Figure 1. Manifestations of MEN 1. GI, gastrointestinal; HPT, hyperparathyroidism; ZES, Zollinger-Ellison syndrome.
4 molecular genetics laboratories in North America. Germline mutations may be absent in up to 20% of indexed cases, and linkage analysis can be used to track the disease alleles through the family.

**Pituitary Tumors**

Pituitary tumors in MEN 1 family members occur less frequently than primary HPT or pancreatic and duodenal neuroendocrine tumors. Up to 60% of MEN 1 patients may develop pituitary neoplasms. Mean age at diagnosis of the pituitary tumor is 38 years, with a range of 12 to 83 years. In the majority of MEN 1 patients, the pituitary tumors are macroadenomas, most of which are prolactinomas (60%). Monitoring for pituitary tumor development in patients with MEN 1 should include yearly measurement of serum prolactin and insulin-like growth factor 1 and imaging the pituitary by MRI every 2 to 3 years.

**Primary Hyperparathyroidism**

Most MEN 1 patients develop hypercalcemia and primary HPT by the fourth decade of life. In screened patients, HPT has been detected in patients as young as 19 years. Primary HPT is the initial clinical manifestation of MEN 1 in 60% to 90% of patients, and the primary pathology is asymmetric hyperplasia or multiple adenomas involving all parathyroid glands.

The timing of parathyroidectomy is an important issue. Primary HPT in MEN 1 patients involves all parathyroid tissue; thus, any treatment we provide is considered palliative at best. Attempts at eradicating all parathyroid tissue can result in a treatment outcome far worse than the disease itself (permanent hypoparathyroidism). In patients with mild disease, it is appropriate to delay surgery until the serum calcium level is at least 1 mg/dL higher than the upper limit of normal.

The preferred surgical approach for an MEN 1 patient with primary HPT is subtotal parathyroidectomy with transcervical thymectomy. Although recurrence rates are somewhat higher with this approach compared with total parathyroidectomy with immediate autotransplantation, the risk of permanent hypoparathyroidism is markedly reduced (1%-2% vs 20%-30%).

**Pancreatic and Duodenal Neuroendocrine Tumors**

Pancreatic and duodenal neuroendocrine tumors represent the second most frequent classic manifestation in MEN 1 and remain the number 1 cause of tumor-related death. These neoplasms become clinically apparent in 50% to 75% of kindred members, and more than 80% of MEN 1 patients have histologic changes within the pancreas. All pancreatic and duodenal endocrine tumors are capable of malignant transformation, and this is especially true for nonfunctioning tumors. When discovered clinically, nearly 50% of these tumors have metastasized to regional lymph nodes, liver, or both at the time of exploration.

Insulinoma associated with endogenous hyperinsulinism is the most common functioning primary endocrine tumor in MEN 1 patients younger than 25 years. Although these patients often have multiple pancreatic tumors, typically only 1 or 2 of the tumors are the source of insulin excess. Although insulinomas are most often benign, there is no effective medical therapy, and without surgery, including an extended distal pancreatectomy and pancreatic head tumor enucleation, hormonal sequelae remain debilitating and life threatening.

In MEN 1 patients, glucagonomas, VIPomas, and obviously malignant nonfunctioning tumors warrant an aggressive surgical approach that includes an 80% distal pancreatectomy, splenectomy, and lymphadenectomy, along with enucleation of any residual tumors. Isolated liver metastases or a finite number of multiple metastases can be successfully managed with excellent control of hormonal sequelae using a combination of hepatic resection, radiofrequency thermoablation, and hepatic artery embolization. Intramuscular octreotide and systemic chemotherapy can also be used for palliation of advanced disease.

Gastrinomas are the most common functioning tumors in MEN 1 patients. Nearly one-third of Zollinger-Ellison syndrome patients are MEN 1 kindred members and more than 50% of MEN 1 patients have hypergastrinemia. Although medical therapy with proton pump inhibitors is quite effective for managing the hormonal effects of gastrin excess, it does not prevent malignant transformation and progression. More than 90% of gastrinomas in MEN 1 patients are duodenal in origin. The surgical approach involves a distal pancreatectomy, lymphadenectomy, enucleation of residual tumors in the head of the pancreas, and exploratory duodenotomy to excise all visible and palpable duodenal carcinoid tumors.

If you have questions about MEN 1 or if you have a patient who might benefit from consultation with an endocrinologist and an endocrine surgeon at Mayo Clinic, a facilitated appointment can be made by calling 800-313-5077.
Minimally Invasive Parathyroidectomy

Primary hyperparathyroidism (HPT) is the most common cause of hypercalcemia, affecting as many as 1 per 1,000 women over the age of 60 years. Cure of primary HPT reliably benefits patients with osteoporosis or osteopenia and those with subtle but clinically significant neuropsychiatric and muscular symptoms. These benefits may be expected regardless of the level of hypercalcemia, even when the serum calcium level is less than 11.0 mg/dL. Standard bilateral cervical exploration is a safe and effective procedure, with a cure rate higher than 95% and risk of recurrent laryngeal nerve damage or hypoparathyroidism of less than 1%. This high level of success in curing the disease and minimizing complications has led to patient-focused improvements and has prompted a shift from standard open surgical approaches to minimally invasive techniques. Minimally invasive parathyroidectomy (MIP) has emerged as a popular method in endocrine surgery (Figures 1-4). Several key advances have facilitated the development of MIP:
- High-quality parathyroid adenoma localization techniques
- High-quality, rapid intraoperative parathyroid hormone (PTH) measurement
- Small-incision outpatient procedure

High-Quality Localization Techniques

The sensitivity and specificity of high-resolution, real-time small parts ultrasonography are approximately 70% and 90%, respectively, in adenoma localization, provided that highly expert radiologists are performing the examination. It is noninvasive and the most inexpensive preoperative localization technique. It is anatomically precise and capable of identifying 95% of adenomas weighing more than 1,000 mg. However, ultrasonography identifies less than 50% of adenomas weighing less than 200 mg. The key limiting factor for ultrasonographic localization is its extreme dependence on the operator.

The introduction of technetium-sestamibi (MIBI) scanning in 1989 advanced preoperative localization. The 1990 National Institutes of Health Consensus Development Conference on Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism (http://consensus.nih.gov/cons/082/082_statement.htm) concluded that preoperative localization was not indicated in patients with asymptomatic HPT who had not undergone prior neck exploration. However, throughout the 1990s, preoperative localization was used in at least 75% of patients. With or without thyroid subtraction scan, often with the addition of SPECT imaging and oblique views, MIBI scanning has become the localization procedure of choice. It is minimally invasive and depends on physiologic hyperfunction of the

Points to Remember

- Minimally invasive parathyroidectomy may be appropriate for up to two-thirds of patients with primary hyperparathyroidism undergoing initial surgical treatment.
- With minimally invasive parathyroidectomy, an outpatient procedure with local anesthesia is an option.
- Minimally invasive parathyroidectomy is associated with a smaller incision, shorter hospitalization time, and faster postoperative recovery.
enlarged parathyroid gland rather than pure anatomic identification. Adenomas anywhere in the neck or mediastinum can be localized. MIBI scanning is somewhat less dependent than ultrasonography on the size of the parathyroid adenoma for imaging, but the cost is usually higher. A major advantage of MIBI over ultrasonography is its minimal dependence on operator experience to obtain a high-quality scan. The generally accepted overall sensitivity of MIBI scanning is 75% to 80%.

The Mayo Clinic Experience
In June 1998, we gradually introduced MIP at Mayo Clinic. Through March 2004, we performed 1,534 parathyroid operations. Excluding reoperative parathyroid surgery, the total of 1,365 included 738 conventional procedures (54%), 602 MIPs (44%), and 25 procedures (2%) that were converted from MIP to a conventional approach. The cure rate for both conventional open exploration and MIP was 97%. Localization was performed with MIBI scanning (1,250 patients) and ultrasonography (506 patients). The sensitivity and positive predictive value of MIBI were 86% and 93%, respectively, whereas comparable figures for ultrasonography were 61% and 87%. Important to these figures is the median weight of the largest resected parathyroid gland of 420 mg, and a mean calcium value of 10.9 mg/dL (reference range, 8.9-10.1 mg/dL).

Of the patients undergoing MIP, 339 (56%) received general anesthesia, and 263 (44%) had a combination of local anesthesia and intravenous sedation. Of these, 295 patients (49%) were dismissed from the hospital the day after the operation, whereas 278 (46%) had outpatient procedures. Intraoperative PTH monitoring was used in 682 patients, with sensitivity, positive predictive value, and accuracy rates of 98%, 99%, and 98%, respectively. The true-negative rate, defined as no decline in the PTH value when the patient still had an additional enlarged parathyroid gland, was 8% in this series.

Numerous factors precluded the use of MIP in the patients who underwent conventional surgery: 244 were reoperative cases (parathyroid related, 164; prior thyroidectomy and other neck procedures, 80); 38 were parathyroid related (multiple endocrine neoplasia, familial HPT, etc); 216 had localization problems; 51 had combined operations requiring general anesthesia; and 109 were combined with thyroidectomy.

The successful outcome of parathyroid surgery, specifically MIP, depends on a highly skilled and experienced multidisciplinary team. The endocrinologist, nuclear medicine specialist or ultrasonographer, clinical laboratory and intraoperative PTH technician, and surgeon as well as the nursing and paramedical staff all must function together smoothly and efficiently to achieve consistently successful outcomes. The general accuracy of intraoperative PTH has been widely verified and enthusiastically supported. Local anesthesia, a small incision, and brief outpatient recovery are further advantages of the unilateral MIP approach.

If you have questions about MIP, or if you have a patient who may benefit from this procedure, a facilitated appointment at Mayo Clinic can be made by calling 800-313-5077.

Percutaneous Ethanol Injection to Treat Recurrent Differentiated Thyroid Cancer

Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the endocrine system. In the United States, an estimated 19,500 new cases of thyroid cancer are diagnosed each year, and more than 80% are PTC. PTC typically has a benign course. Five-year survival is nearly 100% for patients with pTNM stage I and II disease, and the 10-year cause-specific survival for all stages is 93%. Near-total thyroidectomy with wide excision of affected regional nodes, often followed by remnant ablation with radioactive iodine, is the most common primary treatment. In a large Mayo Clinic study, 38% of patients had metastatically involved nodes at the time of operation. Despite the extent of initial neck node dissection, residual or recurrent metastatic adenopathy is common and is seen in 10% to 20% of PTC patients during clinical and ultrasonographic follow-up (Figure 1).

Several treatment options are typically
available for PTC patients with recurrent metastatic lymphadenopathy. One is radioiodine therapy, although the success of this technique has been variable in the treatment of metastatic adenopathy. Given the indolent nature of the disease, “watchful waiting” is an option for some patients, including elderly patients, those who are poor surgical candidates, or those who are considered to be at “low risk.” Many younger patients in whom radioiodine therapy has failed or who had pTNM stage III disease at initial operation are usually subjected to further neck exploration and metastatic lymph node resection. However, surgery may be an overaggressive treatment approach in some patients. Surgery is also more difficult in patients who have had previous neck dissection or external beam irradiation, and there may be a limit to how many surgical reexplorations can be safely attempted. These disadvantages highlight the need for a less invasive method for treating patients with limited nodal metastases.

Treatment Technique

The technique of percutaneous ethanol injection (PEI) for the treatment of metastatic neck lymph nodes is based on a procedure that has been used at Mayo Clinic since 1988 to treat selected patients with benign parathyroid adenomas. Before the procedure, each lymph node is measured in 3 dimensions and color Doppler ultrasonography is performed to document baseline size and nodal perfusion. A conventional 3-cm, 25-gauge needle is attached to a tuberculin syringe containing up to 1 mL of 95% ethanol. Patients receive local anesthesia with 1% lidocaine before the procedure.

The needle is placed into the lymph node under ultrasonographic guidance. A free-hand technique is used to allow fine-needle positioning, which is required for complete treatment. Each node is punctured and injected in multiple sites. As the ethanol is injected, the injected portion of the node becomes intensely echogenic from the formation of microbubbles of gas. The needle is then repositioned, and small amounts (0.05-0.1 mL) of ethanol are injected in multiple sites within the node (average total amount of ethanol injected into a single node is 0.4 mL) (Figure 2).

The number of treatment sessions varies between 1 and 4, with an average of 2. Patients with 1 or 2 small nodes can be treated in 1 session. Patients with larger nodes or with nodes in locations that are difficult to inject are treated with multiple sessions. Treated patients receive routine clinical and ultrasonographic follow-up, typically every 3 to 6 months. Patients who show evidence of residual nodal perfusion on color Doppler ultrasonography are retreated.

Patient Selection and Outcomes

Patient selection requires biopsy-proven metastatic PTC in cervical lymph nodes identified by ultrasonography, and the nodes must be technically amenable to PEI. Often these nodes are single or few in number and located in the lateral neck, but selected nodes in the central compartment can be treated as well. Most patients are either poor surgical candidates or prefer not to have further surgery and have not responded in the past to radioiodine therapy.

More than 90 patients have been treated with this technique at Mayo Clinic. Our initial results
Stereotactic Radiosurgery for Patients With Pituitary Adenomas

Although medical therapy and surgical resection are the primary treatments for the majority of patients with pituitary adenomas, some patients do not respond to medical therapy and sometimes complete tumor resection is not possible. Fractionated radiotherapy has been used for patients who have unsuccessful medical and surgical treatment of their pituitary adenoma. In recent years, stereotactic radiosurgery has been increasingly used as an alternative to surgery or radiotherapy to manage patients with pituitary adenomas.

Stereotactic radiosurgery is the precise delivery of a single fraction (dose) of radiation to an imaging-defined target. Radiosurgery combines stereotactic localization techniques developed in neurosurgery with radiation physics to distribute energy (x-rays, gamma rays, protons) to lesions both intracranially and extracranially. Although the types of energy used in radiosurgery are the same as in radiotherapy, fundamental differences exist between the techniques and need to be appreciated.

In radiosurgery, modern equipment permits highly conformal dose plans that result in little radiation exposure to the adjacent tissues. Conversely, external beam radiotherapy (EBRT) plans are generally not as conformal, and more radiation is delivered to nearby structures. To reduce the likelihood of radiation injury after EBRT, dose fractionation is used. Each patient should be evaluated with an appreciation of the advantages and drawbacks of both radiosurgery and EBRT to decide which modality is most appropriate for the clinical situation. As our understanding of this technique has grown, we have seen a steady increase in the number of patients with pituitary adenomas having...
radiosurgery at our center over the past 15 years (Figure 1).

Patient Selection
Proper patient selection is the most important factor associated with good outcomes after radiosurgery. As a rule, pituitary adenomas with considerable suprasellar extension are typically not considered good candidates for radiosurgery because patients with larger lesions often have visual loss related to mass effect. Although radiosurgery does result in growth control and size reduction in the majority of pituitary adenomas, these effects occur gradually over several years. Therefore, surgical resection is the preferred approach for patients with large pituitary adenomas. However, for many patients, it is recognized in advance that complete tumor removal is not possible because the tumor extends into the cavernous sinus. In these patients, radiosurgery can be part of a staged approach with microsurgery. Initially, the tumor is debulked to create a separation between the top surface of the tumor and the optic apparatus without an attempt at resection of the tumor involving the cranial nerves, major arteries, or dural venous sinuses. Radiosurgery can then be performed for the remaining tumor volume with little risk of cranial nerve deficits.

Such multimodality treatment should result in reduced patient morbidity, with long-term tumor control. Our center and others have also determined that the results of pituitary adenoma radiosurgery are adversely affected by the use of pituitary suppressive medications (bromocriptine, cabergoline, octreotide) at the time of radiosurgery. Consequently, we now have patients discontinue these medications 4 to 8 weeks before radiosurgery.

Radiosurgery With the Gamma Knife
Radiosurgery is performed at Mayo Clinic using the Leksell Gamma Knife (Elekta Instruments, Norcross, Georgia). The Gamma Knife has been used for 35 years to treat more than 75,000 patients worldwide. Radiosurgery is an outpatient procedure, performed with the patient under local anesthesia, and requires virtually no recovery time. After placement of a stereotactic headframe, the patient has an MRI performed for dose-planning purposes. A dose plan is then created and reviewed by a neurologic surgeon, a radiation oncologist, and a radiation physicist (Figure 2).

Since January 1990, 167 of more than 2,800 patients with pituitary adenomas have undergone stereotactic radiosurgery at Mayo Clinic. More than 90% of the 167 patients have undergone craniotomy, microsurgery, and radiosurgery with excellent results. Our center and others have determined that the results of pituitary adenoma radiosurgery are adversely affected by the use of pituitary suppressive medications (bromocriptine, cabergoline, octreotide) at the time of radiosurgery. Consequently, we now have patients discontinue these medications 4 to 8 weeks before radiosurgery.

Points to Remember
- Stereotactic radiosurgery is the precise, single-session delivery of radiation to an imaging-defined target.
- Biochemical remission is possible in approximately 80% of properly selected patients with hormone-producing pituitary adenomas.
- Tumor growth control is achieved in more than 95% of patients with nonfunctional pituitary adenomas.
- The majority of pituitary adenomas decrease in size after radiosurgery, although this typically occurs over months to years. For patients with symptomatic mass effect (visual decline), surgical resection is required.
prior surgery; approximately 75% had tumors with extension into the cavernous sinus. To minimize the incidence of visual deficits after radiosurgery, we limit the radiation dose to the optic nerves to less than 12 Gy. Such dose prescription has resulted in visual morbidity of less than 2%. The tumor growth control rate for pituitary adenomas exceeds 95% with follow-up that now extends beyond 10 years. Figure 3 shows the MRIs of a patient with a recurrent nonfunctional pituitary adenoma after prior transsphenoidal surgery and following radiosurgery.

Two factors appear to correlate with endocrine cure after radiosurgery: higher radiation doses and the absence of pituitary suppressive medications at the time of radiosurgery. Patients with hormone-producing tumors not taking pituitary suppressive medications and who receive more than 20 Gy to the tumor margin have a greater than 80% chance of biochemical cure. The average time to endocrine normalization is between 1 and 3 years (Figure 4). The incidence of new anterior pituitary deficits ranges from about 10% for small tumors to as much as 50% for large tumors that fill the entire sella. The incidence of diabetes insipidus after radiosurgery is exceedingly rare.

If you have questions about pituitary adenoma radiosurgery or if you have a patient who might benefit from consultation with an endocrinologist and a specialist in radiosurgery at Mayo Clinic, a facilitated appointment can be made by calling 800-313-5077.

Figure 3. MRIs of a patient with a recurrent nonfunctional pituitary adenoma after prior transsphenoidal surgery and following radiosurgery. A, MRI at the time of radiosurgery. B, MRI 6 years later showing much smaller tumor.

Figure 4. The serum concentrations of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) for a patient with acromegaly having radiosurgery. The age- and sex-adjusted normal range of IGF-1 for this patient was less than 290 ng/mL.