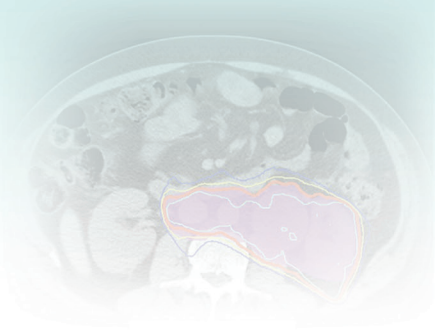
CHAPTER

29 Pituitary Tumors and Craniopharyngiomas



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INCIDENCE

Pituitary tumors represent roughly 10% to 15% of primary intracranial tumors. Based on a meta-analysis, the overall estimated prevalence of pituitary adenoma is 16.7% (14.4% in autopsy series and 22.5% in radiographic series of all patients).

BIOLOGIC CHARACTERISTICS

Most pituitary tumors are benign. They may express or secrete excess hormones and are monoclonal in origin. MAPK and PI3K/Akt signaling pathways appear to have putative roles in pituitary tumorigenesis or continued growth. Genetic predisposition for the development of pituitary adenomas has been described in multiple endocrine neoplasia (MEN) syndromes, Carney syndrome, and isolated familial somatotropinomas. Pituitary carcinomas are extremely rare.

STAGING EVALUATION

Evaluation for patients with pituitary tumors includes a complete history and physical examination, neuroophthalmic assessment, laboratory tests with emphasis on the endocrine profile, and magnetic resonance imaging (MRI) of the brain with emphasis on the sellar and parasellar regions. Although no formal staging exists, these tumors are broadly classified by endocrine dysfunction, anatomic size, and secretory status.

PRIMARY THERAPY AND RESULTS

Primary therapy is optimized by a multidisciplinary approach, including endocrinology, neurosurgery, neuropathology, neuroradiology, neuroophthalmology, otorhinolaryngology, and radiation oncology. Depending on the endocrine abnormality, tumor size, location, and clinical presentation, management strategies can range from observation to surgery, medical management, radiation therapy, or a combination of these options. The primary goals of treatment include preservation or restoration of normal hormonal function, reversal of hypersecretory endocrine abnormalities, and improvement or stabilization of visual changes or neurologic symptoms. The standard surgical approach is transsphenoidal microsurgery.

ADJUVANT THERAPY

Adjuvant medical and radiation therapy options may be used to manage pituitary adenomas. Radiation options include fractionated radiation therapy and stereotactic radiosurgery (SRS), which are both generally used as adjuvant therapies rather than as primary therapies.

LOCALLY ADVANCED DISEASE

Large nonfunctional and some functional pituitary adenomas may require a combination of approaches, such as surgery, medical therapy, and radiation therapy to optimize long-term tumor control.

PALLIATION

Metastases to the pituitary are uncommon and occur most frequently from breast and lung cancer. The majority of metastases involve the posterior pituitary lobe. A short course of radiation therapy is usually effective in controlling these tumors.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are uncommon tumors that are postulated to arise from the embryologic remnants of Rathke's pouch. They are typically slow growing and encapsulated. Although benign in nature, tumor growth and treatment can result in endocrinopathies and visual deficits. Gross total resection (GTR) results in excellent local control but can cause morbidity including hypothalamic dysfunction and visual deficits. Subtotal resection followed by external beam radiation therapy may yield equivalent control with less morbidity. Other options include SRS, intracystic bleomycin, and intracystic phosphorous 32. The 5-year progression free survival is approximately 85%.

INTRODUCTION

This chapter focuses on the etiology, epidemiology, detection, biology, anatomy, pathology, evaluation, and management (specifically the irradiation techniques and associated treatment side effects) of pituitary tumors. Given the diverse presentations of these tumors along with their complex anatomic location and proximity to critical structures such as the optic apparatus, cranial nerves, and internal carotid arteries, a multidisciplinary approach is needed for optimal patient care. Involvement of the endocrinologist, neurosurgeon, otorhinolaryngologist, radiation oncologist, neuroradiologist, neuroophthalmologist, and neuropathologist optimizes management of patients with pituitary tumors. At the end of this chapter, the evaluation and management of craniopharyngiomas will be briefly discussed.

ETIOLOGY AND EPIDEMIOLOGY

Etiology

The etiology of most pituitary tumors is not known. Based on rodent models, two primary modes of pituitary oncogenesis have been suggested.[1] The first model, known as the hyperplasia-adenoma sequence, suggests a hormone-dependent pathway. In this model, dysregulation of hormone or growth factor signaling leads to hyperplasia and tumor formation. For example, there is evidence that implicates overexpression of

transforming growth factor–alpha (TGF–α), fibroblast growth factor (FGF), and fibroblast growth factor receptors (FGFRs) in tumor formation.[2] In the second model, adenomas are believed to arise de novo, without the development of hyperplasia, likely as a result of one or a sequence of genetic alterations, a mechanism supported by some transgenic and knockout animal models.[2] In humans four genes known to be associated with familial pituitary tumor syndromes: multiple endocrine neoplasia (MEN) 1; cyclin dependent kinase inhibitor (CDKN) 1B; protein kinase, cAMP-dependent, regulatory (PRKAR) 1A; and aryl hydrocarbon receptor-interacting protein (AIP).[3]

For patients with MEN1, which is an autosomal dominant disease characterized by tumors of the pancreatic islet cells, parathyroid glands, and pituitary gland, 40% will develop pituitary adenomas, most commonly prolactinomas. Pituitary tumors associated with the MEN1 syndrome demonstrate loss of heterozygosity of chromosome 11q13 (location of the *MEN1* gene), which has also been implicated in malignant progression of some pituitary adenomas.[4] Alterations of *MEN1* do not appear to increase the risk for sporadic pituitary adenomas.[5]

In Carney's complex, a rare inherited condition characterized by endocrine overactivity, schwannomas, abnormal skin pigmentation, and myxomas, the implicated genetic defect is loss of function of PRKAR1A, whose gene is located on chromosome 17q23-24.[6] Additional genetic alterations are found in the McCune-Albright syndrome, a genetic disorder of bones, skin pigmentation, and hormones associated with premature puberty. Activating or gain-of-function *GNAS1* mutations (of the guanine nucleotide-binding protein [G protein], alpha-stimulating activity polypeptide 1 gene on chromosome 20q13.1) are seen in this condition. Patients with McCune-Albright syndrome demonstrate mosaicism, resulting from a postzygotic somatic mutation appearing early in the course of development that yields a monoclonal population of mutated cells within variously affected tissues.

In isolated familial somatotropinomas (i.e., the occurrence of two or more cases of acromegaly in a family without a history of MEN or Carney's complex), germline alterations in the aryl hydrocarbon receptor interacting gene (*AIP* gene) have been identified.[7,8] The syndrome of familial isolated pituitary adenomas (FIPA) accounts for 2% of pituitary adenomas and is associated with mutations in *AIP*, the gene that encodes aryl hydrocarbon receptor interacting protein.[9] The FIPA syndrome is also liked to mutations in *AIP* in 15% to 25% of families, and those affected are typically younger patients with more aggressive tumors[10] *AIP* mutations are usually associated with growth hormone secretion, but prolactinomas, nonfunctional adenomas, Cushing's disease, and other adenoma types can occur.

Finally, heterozygous mutations of *CDNK1B*, which encodes a 196 amino acid protein, the cyclin-dependent kinase CDK1 p27Kip1, can lead in humans to a multiple endocrine syndrome of familial pituitary adenomas and primary hyperparathyroidism, like MEN1, but also including testicular cancer and renal angiomyolipoma. The alterations in *CDNK1B*, located at 12p13, are rare, and lead to the multiple endocrine syndrome known as MEN4.[11]

Epidemiology

Although 10% of normal adults have a pituitary abnormality detectable on MRI, pituitary tumors account for only 10% to 15% of all primary intracranial tumors. The frequency of pituitary adenomas varies greatly, although recent community-based studies from Belgium and the United Kingdom suggest that the prevalence is higher than has been historically noted.[12,13]

Based on a meta-analysis, the overall estimated prevalence of pituitary adenomas was 16.7%, with 14.4% observed in autopsy series and 22.5% in radiographic series of volunteers or patients imaged for other diseases.[14] Over time, different criteria have been used for distinguishing hyperplasia from pituitary adenomas. The broader application of immunohistochemical staining for pituitary hormones and the differences in slice thicknesses for MRI may account for the wide variation in incidence reported in the literature.

The frequency of the various types of pituitary adenomas differs widely according to age and gender. Prolactinomas are the most common, followed by nonfunctioning adenomas, growth hormone (GH)–secreting adenomas, and adrenocorticotropic hormone (ACTH)–secreting adenomas. Nelson's syndrome (growth of an ACTH-secreting pituitary adenoma after bilateral adrenalectomy resulting from loss of adrenal suppression of pituitary inhibition) and thyroid-stimulating hormone (TSH)–secreting adenomas are rare.

PREVENTION AND EARLY DETECTION

No successful strategy has been described or is known to exist that prevents the development of these tumors. Given the prevalence of pituitary abnormalities on MRI scans in normal adult patients, the routine use of screening MRI or endocrine workup is not feasible and is not recommended. When imaging is performed not specifically for a pituitary lesion, an incidental finding of a pituitary lesion, the so-called "incidentaloma," may be diagnosed.[15] Most incidentalomas are <1 cm, nonfunctional, and may be associated with pituitary hormonal deficiencies, excess hormone secretion, or visual field defects.[16] The majority of incidentalomas in reality are pituitary adenomas with incomplete or limited biochemical work-up. Patients with macroincidentalomas (≥1 cm) should be evaluated for hypopituitarism and undergo visual field testing if the sellar mass abuts or compresses the optic chiasm. Based on autopsy series, pituitary incidentaloma occurs in 1.5% of children and adolescents.[17]

A patient with signs or symptoms suggestive of an endocrine abnormality should be referred to an endocrinologist for appropriate evaluation. Consultation with an endocrinologist and a medical geneticist is appropriate for patients if MEN1 or another familial syndrome associated with pituitary adenoma is suspected. For these patients, a baseline MRI of the pituitary can be considered, although routine imaging of the pituitary in a patient without clinical symptoms is not uniformly practiced. The management of inherited pituitary tumors is usually similar to that of sporadic adenomas.[18] Because pituitary tumors that arise as a part of MEN 1 and FIPA are more aggressive, occur at a younger age, and often respond poorly to treatment, earlier identification may be useful. To help identify carriers in whom regular clinical and biochemical monitoring would be useful, genetic screening for mutations in the relevant genes is recommended in patients with MEN 1 and Carney complex.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Despite the screening of common oncogenes and tumor suppressor genes in pituitary adenomas, the molecular and cellular pathogenesis of pituitary tumors is largely unknown.[19] Based on *X* chromosome inactivation analysis, it appears that most pituitary adenomas derive from a monoclonal expansion, which suggests that general principles of tumorigenesis may apply to pituitary adenoma formation.[20] The MAPK (mainly Ras/extracellular signal-regulated protein kinase

[ERK]) and the PI3K/Akt signaling pathways appear to have putative roles in pituitary tumorigenesis or continued growth because the activity of these pathways are often activated in pituitary tumors. Because the Raf/MEK (mitogen-activated protein kinase/ERK kinase)/ERK signaling is a major pathway in the regulation of cell growth, proliferation and survival, it is likely that these genetic alterations could contribute to several aspects of pituitary tumor growth and survival.[21] Although its role is not fully understood, a docking protein in the endothelial growth factor receptor (EGFR) pathway, EGF pathway substrate number 8 (Eps8), is overexpressed (almost sixfold higher) in pituitary tumors compared with normal anterior pituitary tissue.[22] Because pituitary tumors are mostly benign, a protective mechanism to restrict uninhibited growth of tumor cells is probably active. The concept of oncogene-induced senescence is one possible mechanism. High pituitary $p21^{Cip1/WAF1}$ levels appear to promote senescence and restrict tumor growth.[23] One study proposed the possible presence of pituitary adenoma stemlike cells,[24] which has encouraged the investigative development of newer pharmacologic agents.[25] HMGA1B and HMGA2 overexpression in mice induces the development of GH and prolactin (PRL) pituitary adenomas mainly by increasing E2F1transcriptional activity.[26] Upregulation of PIT1, a transcriptional factor that regulates the gene expression of GH, Prl, Ghrhr, and Pit1 itself, also has a role in pituitary tumorigenesis.[27]

For somatotroph (growth hormone) adenomas, an activating mutation of the alpha subunit of the guanine nucleotide stimulatory protein (Gs-alpha) gene is found in about 40% of patients, which results in activation of adenylyl cyclase.[28] Overexpression of the pituitary tumor transforming gene (*PTTG*) is also seen in most human somatotroph adenomas.[29] Mutations of fibroblast growth factor-4 (FGF-4) have led to development of lactotroph adenomas in transgenic mice.[30]

ANATOMY, PATHWAYS OF SPREAD, AND PATHOLOGY

Anatomy and Pathways of Spread

The pituitary gland is a midline intracranial organ that measures approximately 8 mm in the anteroposterior axis, 10 mm in the transverse axis, and 6 to 8 mm in the supero-inferior axis. It occupies the cavity in the sphenoid bone known as the sella turcica. The pituitary gland is separated from the structures above it (i.e., the optic chiasm, hypothalamus, anterior cerebral arteries, and floor of the third ventricle) by the sellar diaphragm, which is formed by a circular fold of dura. Immediately anterosuperior to the diaphragm sella lies the optic chiasm. The pituitary stalk (infundibulum) crosses the sellar diaphragm and connects the hypothalamus to the pituitary gland. Anteriorly, the tuberculum sellae lies in the floor of the sella and extends supero-laterally to form the anterior clinoid processes. The posterior aspect of the sella forms the dorsum sellae and extends supero-laterally to form the posterior clinoid processes. Laterally, the cavernous sinuses contain cranial nerves III, IV, V_1 (ophthalmic nerve), V_2 (maxillary nerve), and VI and the internal carotid artery. Given the proximity of the pituitary to these various structures, parasellar tumors can affect cranial nerves III, IV, V, and VI, and suprasellar tumor extension can lead to bitemporal hemianopsia via compression of the optic chiasm. Figure 29-1 demonstrates the complex anatomy of the parasellar region.

The pituitary has two distinct embryologic origins; the first gives rise to the anterior and intermediate pituitary lobes, and the second gives rise to the posterior pituitary lobe. The anterior (adenohypophysis) and intermediate lobes are derived from Rathke's pouch, which is an evagination of ectodermal tissue from the primitive oral cavity (pharyngeal pouches). The

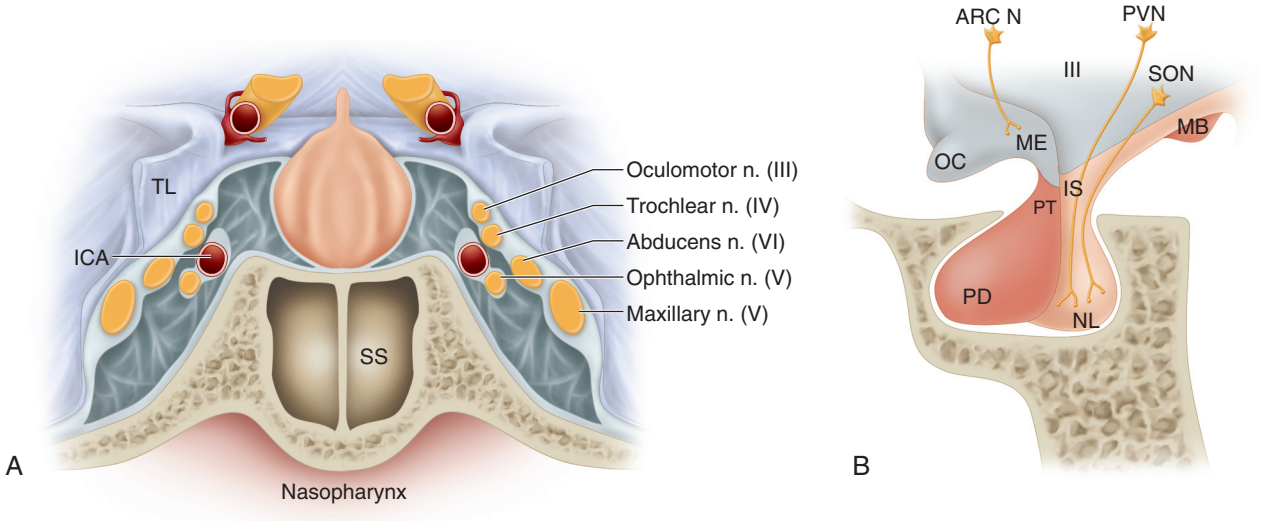

Figure 29-1 **A,** Anatomy of the sellar and parasellar regions. This coronal-view diagram illustrates the proximity of the pituitary gland to several important neural and vascular structures. The gland is laterally bordered by the cavernous sinuses *(black)*, which contain within their confines or their walls the carotid artery and the oculomotor, trochlear, maxillary, and abducens nerves and the first two divisions of the trigeminal nerves. The optic chiasm lies immediately superior to the gland. *ICA,* Internal carotid artery; *SS,* sphenoid sinus; *TL,* temporal lobe; *III,* third ventricle. **B,** Anatomy of the pituitary gland. This sagittal-view diagram of the pituitary gland shows the hypothalamus, pituitary stalk, and pituitary gland located in the sella turcica. The anterior gland, or adenohypophysis, is composed of the pars distalis (PD), rudimentary pars intermedia, and pars tuberalis (PT). The posterior gland, or neurohypophysis, is composed of the median eminence (ME), located in the hypothalamus, the infundibular stem (IS), and the neural lobe (NL). The large neurons located in the supraoptic (SON) and paraventricular (PVN) nuclei project to the neural lobe, where they store and release oxytocin and vasopressin into the systemic circulation under the appropriate stimulus. *ARC N,* Arcuate nucleus; *MB,* mammillary bodies; *OC,* optic chiasm.
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posterior lobe (neurohypophysis) and stalk are derived from the diencephalon and, therefore, have a neuroectodermal origin. The anterior pituitary lobe accounts for most of the pituitary gland and produces at least six hormones: prolactin (PRL), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH), and thyroid-stimulating hormone (TSH). The intermediate lobe produces melanocyte-stimulating hormone (MSH). The posterior lobe stores and releases two hormones, vasopressin (antidiuretic hormone [ADH]) and oxytocin, which are produced by the hypothalamus.

The hypothalamic-hypophyseal portal system, a vascular network that surrounds the infundibulum and connects the anterior lobe of the pituitary with the hypothalamus, has an important role in the regulation of the anterior pituitary hormones mediated by stimulating or inhibiting hormones derived from the hypothalamus. These hormones include GH-releasing hormone, GH-inhibiting hormone (somatostatin), prolactin-secreting hormone, prolactin-inhibiting hormone, corticotrophin-releasing hormone, thyrotropin-releasing hormone, FSH-releasing hormone, and LH-releasing hormone. The anterior pituitary hormones are also regulated by a hormonal feedback mechanism from the target glands such as the adrenals.

Pituitary tumors are generally classified as microadenomas or macroadenomas depending on the diameter of the tumor as described by Hardy.[31] A microadenoma is less than 1 cm in diameter, whereas a macroadenoma has a diameter of 1 cm or greater. Incidental microadenomas have been observed with a frequency of 3% to 25% in large, unselected autopsy series.[32] Microadenomas are more frequently seen in females, whereas macroadenomas occur with equal frequency in males and females. Macroadenomas are more common than microadenomas. For lesions less than 3 mm in diameter, the term *pico-adenoma* has been used.[33]

Pathology

Before the introduction of electron microscopy, modern immunohistochemical procedures, and modern staining and fixation techniques, pituitary tumors were classified according to Mallory's trichrome histologic staining technique as chromophobic, acidophilic (or eosinophilic), or basophilic tumors. Based on classic fixation and staining, Cushing's disease was associated with basophilic adenoma, acromegaly with eosinophilic adenoma, and nonfunctioning adenoma with chromophobic adenoma. With newer methods of immunostaining, it has become possible to identify cells as prolactin, ACTH, GH, LH FSH, alpha subunit, or TSH. It is important to note that the functional status of a pituitary adenoma is defined by clinical symptoms and not by immunohistochemical staining patterns.[34]

According to the World Health Organization (WHO) classification of pituitary tumors, they are defined as neoplasms located in the sella turcica. This classification is based on structural similarities of the normal parenchymal cells and the immunohistochemical demonstration of hormone secretion. Based on this definition, pituitary adenomas may express more than one or two hormones, based on immunohistochemical patterns. The classification includes a new entity designating a borderline adenoma or adenoma of uncertain behavior.[35] The atypical adenoma is defined as an invasive tumor with an elevated mitotic index (MIB-1-labeling index greater than 3%) and extensive nuclear immunostaining for TP53.[35] The German Registry of Pituitary Tumors reported the frequency of atypical pituitary adenomas as 2.7%.[36]

Most lesions are easily identified on routine histopathologic testing, but metastatic well-differentiated neuroendocrine carcinoma can present a diagnostic challenge.[37] For patients with acromegaly or Cushing's disease, hyperplasia may be clinically indistinguishable from an adenoma. Differentiation of hyperplasia from adenoma can be made using a reticulin stain. Normal pituitary tissue is composed of small acini of pituitary cells surrounded by an intact reticulin network. In hyperplasia, the architecture of the acini is maintained, but the acini are increased in size, and the reticulin stain demonstrates an intact network. Pituitary adenomas are characterized by a complete disruption of the reticulin fiber network.

The pathologic hallmark of pituitary adenomas is the monotonous and monomorphous proliferation of neoplastic cells that replaces the normal acinar pattern in the pituitary lobe. GH-producing cells are seen with greater frequency anteriorly in the lateral aspects of the pituitary. Prolactin-producing cells are distributed throughout the pituitary but have a greater density in the posterior lateral aspect of the gland. ACTH-producing cells are present in the median wedge. TSH-producing cells are seen in the anterior aspect of the median wedge. Gonadotropin-producing cells are distributed throughout the anterior pituitary. Nonfunctioning adenomas typically have solid sheets, nests, and sinusoidal patterns and are interrupted by pseudo-papillae and striking pseudo-rosettes around vascular channels. Overlap of the distribution of these functional hormonal secretory cells does exist, and they do not reside in well-demarcated zones of the pituitary. Mitoses are seen in 3.9% of noninvasive adenomas, 21.4% of invasive adenomas, and 66.7% of carcinomas.[38]

The usefulness of labeling-index and TP53 immunostaining is not clear because these assessments may not correlate with tumor behavior. Invasive pituitary adenomas usually exhibit a higher Ki-67 proliferation index.[39] Markers such as proliferating cell nuclear antigen (PCNA), Ki-67/MIB-1, and antiapoptotic Bcl-2 have not demonstrated consistent correlation with tumor invasiveness or recurrence.[40] Galectin-3, a β-galactoside-binding protein, may play a role in pituitary tumor progression, and immunostaining for this is also available.[41]

The pituitary is composed of at least six distinct cell types, which are responsible for the production of at least one hormone. Advances in molecular biology have identified three major pathways of cytodifferentiation of adenohypophyseal cells, T pit; Pit-1; and SF-1, GATA-2, ER.[42,43] These pathways are determined by a complex pattern of transcription expression, which help classify various adenomas.[44] In situations in which histologic and immunohistochemical profiles are atypical, electron microscopy can be helpful in achieving accurate classification.

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Clinical Manifestations

Patients with pituitary tumors can have a number of different symptoms and presentations, depending on the size and mass effect of the tumor and hormonal abnormalities. Headaches can occur with a lesion of any size. When the tumor extends superiorly into the suprasellar region, visual loss can occur, including bitemporal or homonymous hemianopsia, superior or inferior field cut deficits, and central scotoma. Extension into the cavernous sinus can lead to cranial nerve dysfunction (commonly III and IV cranial nerve palsies). Cranial nerves V and VI are less commonly affected. Lateral extension into the temporal lobe may cause seizures. The clinical presentations and endocrine abnormalities can vary, depending on the age and sex of the patient. Patients with large adenomas may have compromised pituitary function, which can lead to

hypogonadism, secondary hypothyroidism, and adrenal insufficiency.[45] Diabetes insipidus is extremely rare and most commonly is a manifestation of an invasive and infiltrative tumor (such as a metastasis), an inflammatory condition (such as neurosarcoidosis), or a lesion that arises from or is attached to the infundibulum or hypothalamus (such as a craniopharyngioma).[46] If the gland acutely infarcts or hemorrhages, pituitary apoplexy may result, which may require urgent surgical decompression.

Patient Evaluation

General Approach

For all patients, a detailed history should be obtained and a thorough physical examination performed. This will allow assessment of the possible manifestations of the underlying endocrine disorder and any neurologic deficits, such as bitemporal hemianopsia from superior compression of the optic apparatus by the tumor. Neurologic sequelae may include headache from pressure effects on the dura, cranial nerve (III, IV, V, and VI) abnormalities from extension into the cavernous sinus, visual symptoms from suprasellar extension to the optic chiasm or nerves, and behavioral changes.

Ophthalmologic evaluation with formal visual field testing should be done in patients with visual symptoms and those with extension of the tumor outside the sella. Bitemporal hemianopsia is classically associated with suprasellar extension of the pituitary tumor, causing compression of the anterior aspect of the optic chiasm. Other visual field deficits can also occur. Changes in ophthalmologic assessment can be used to monitor the response to therapy.

Laboratory Assessment

Initial tests help determine if a pituitary deficiency exists and diagnose the secretory status of the adenoma. Screening studies should include TSH, free thyroxine (T_4), ACTH, cortisol, prolactin, somatomedin C (insulin-like growth factor-1 [IGF-1]; this is the primary molecule mediating the effects of growth hormone at the cellular level, and its secretion, primarily from the liver, is directly regulated by growth hormone), LH, FSH, alpha subunit, and, in men, testosterone. The alpha subunit is common among the three glycoprotein pituitary hormones, FSH, LH, and TSH and is also found in placental chorionic gonadotropin; rarely pure alpha-subunit secreting tumors are identified, and these are generally otherwise "nonsecreting chromophobe adenomas." These patients often have visual field abnormalities and partial hypopituitarism. The elevated serum alpha subunit shows a variable response to stimulation by thyrotropin-releasing hormone and is generally not suppressed by thyroid hormone administration. Tumor immunocytochemical studies demonstrate the presence of only the alpha subunit. Following resection or radiotherapy, serum alpha level subunit levels decrease. These patients therefore represent a new subset of functioning pituitary tumors. Determination of alpha subunit concentration is useful in managing some patients with pituitary tumors previously thought to have nonfunctioning chromophobe adenomas.

In addition to endocrine evaluation, a complete blood count, blood chemistry assessment, and urinalysis should be obtained. Because physiologic hormonal variations in the blood and urine levels can occur, the interpretation of these results should be considered based on diurnal variations, age and gender of the patient, and pregnancy and menopausal status. The conditions and timing under which these samples are obtained also influence interpretations of the results. Because the diagnosis of Cushing's disease can be difficult, multiple tests are performed over time and at different times during the day to help make a conclusive diagnosis.[47]

For patients with suspected Cushing's disease, 24-hour urinary free cortisol (UFC), midnight salivary cortisol, and 1-mg overnight dexamethasone suppression tests have similar sensitivity and specificity. The most precise method of measurement for 24-hour urinary free cortisol is tandem mass spectrometry. Salivary cortisol levels can have a wide range of normal nighttime values, which can raise questions about accuracy. The overnight dexamethasone suppression test may be influenced by several medications and requires specific time constraints (i.e., the tablet needs to be taken at 11 pm and blood test performed at 8 am the next day). As a result, this test should not be used as the sole test for diagnosing Cushing's syndrome. The definitive test for Cushing's disease and exclusion of ectopic ACTH syndrome is inferior petrosal sinus sampling, which requires measurement of ACTH from the right and left petrosal sinuses and peripheral site before and after corticotropin-releasing hormone (CRH) administration.

For patients with prolactinoma who also have macroadenoma, the prolactin level is usually greater than 200 ng/mL. Other common conditions that have been associated with hyperprolactinemia include end-stage renal disease, renal insufficiency, depression, primary hypothyroidism, acquired immunodeficiency syndrome, sarcoidosis, and nonalcoholic cirrhosis.[48] On the other hand, pituitary stalk compression from tumor may also cause elevated prolactin levels in the range of 150 ng/mL or less. Because antidepressants, protease inhibitors, verapamil, and phenothiazines may elevate prolactin levels, careful review of the medications that the patient is taking is necessary. A pregnancy test is mandatory for women with amenorrhea or hyperprolactinemia. Elevated serum prolactin levels greater than 300 ng/mL are usually diagnostic of pituitary adenoma, and levels greater than 100 ng/mL in nonpregnant patients often are associated with pituitary adenoma.

For patients with acromegaly, most cases result from excess secretion of growth hormone by a pituitary tumor.[49] The definitive test is measurement of growth hormone response to 75 g or 100 g of oral glucose (oral glucose tolerance test). This glucose load should normally cause marked suppression of the GH release to a level under 2 ng/mL. To ensure accuracy, these measurements of serum glucose and GH must be performed every 30 minutes for 2 hours. IGF-1 is also elevated after adjusting for gender and age variation. IGF-1 levels provide the best intermittent method for monitoring response to treatment, although dynamic testing of GH kinetics with the oral glucose tolerance test (OGTT) is also frequently used.

Mild hyperprolactinemia (<200 ng/mL) may be seen in some patients with nonfunctional adenomas as this is a common finding when any sellar mass causes stalk compression, interrupts blood flow and leads to interference with the prolactin-inhibiting dopamine transport.[50,51] Because these patients do not have hormone-related symptoms, nonfunctioning adenomas can be quite large at the time of diagnosis.

Imaging

Dynamic MRI of the brain with gadolinium is the imaging test of choice[52] given its superior resolution compared with computed tomography (CT), which evaluates calcifications and bony changes better than MRI (Figure 29-2). Dynamic coronal imaging techniques after contrast administration enhance normal pituitary tissue earlier and more intensely and help delineate adenoma tissue, which tends to enhance later. Because pituitary adenomas are less vascular than the normal pituitary gland, they usually appear hypointense following gadolinium administration, in the early, or immediate postgadolinium phase, and later may either remain hypointense, hyperintense, or isointense to the rest of the gland, emphasizing the need for dynamic MR imaging. On noncontrast T1-weighted MR images

Regardless of the presentation, accurate diagnosis and implementation of appropriate therapy or therapies is desired. A multidisciplinary approach optimizes patient care.

Figure 29-2 Axial T1-weighted, contrast-enhanced MRI of a pituitary adenoma demonstrating a large macroadenoma extending beyond the sella.

they may appear hypointense or isointense to the normal pituitary gland.[53] The posterior lobe of the pituitary has a high signal intensity on T1-weighted images (posterior pituitary bright spot) that distinguishes it from the anterior lobe, which has signal intensity similar to that of white matter. Thin slices (at 2-mm to 3-mm intervals) obtained before and after gadolinium contrast administration with images in the coronal, axial, and sagittal planes provide detailed information for the initial diagnosis and allow detection of small lesions. For patients who have undergone previous surgery, fat suppression techniques can help differentiate surgical fat grafts from tumor tissue. For patients undergoing SRS, thin-slice (1-mm) imaging with contrast medium is obtained to define the tumor and optic apparatus. For hypersecretory adenomas, positron emission tomography (PET) imaging with coregistration may be valuable.[54]

For patients with suspected Cushing's disease, thin-slice images of 1-mm thickness have greater sensitivity; even so, the tumor may not be detected in about 50% of patients.[55] Spoiled gradient recalled acquisition sequences may have superior sensitivity (80%) compared with conventional spin echo images following contrast enhancement.[56] The degree of contrast enhancement does not differentiate one sellar mass from another. A clear distinction between an intrasellar mass and normal pituitary tissue is not consistent with a pituitary adenoma.

Macroadenomas can compress the adjacent pituitary and may distort the pituitary stalk. When larger lesions demonstrate extrasellar extension, MRI scans can help delineate the relationship of the cavernous sinus laterally and the optic chiasm superiorly. If a plane of normal pituitary tissue can be observed on coronal-view, T1-enhanced images, the likelihood of cavernous sinus involvement is extraordinarily low. When there is significant suprasellar extension, the optic chiasm can be difficult to identify and may be best seen on coronal-view, fast spin-echo T2-weighted images. Pituitary apoplexy is caused by intratumoral hemorrhage and can be seen on T1-weighted images as an area of high signal intensity.

Imaging studies other than MRI may be needed. High-resolution CT may be used when MRI is contraindicated (i.e., because the patient has a pacemaker). CT scans can be useful when planning for transsphenoidal surgery. Pneumatization of the sphenoid sinus and cortical thinning of the sellar floor can be determined by bone windows. Angiograms are useful when aneurysms are considered within the radiographic differential diagnosis.

Differential diagnosis for a sellar lesion includes pituitary adenoma, congenital lesions (craniopharyngioma and Rathke's cleft cyst), infiltrative disease (granuloma, lymphocytic hypophysitis, and tuberculosis), primary lymphoma, chordoma, germ cell tumor, metastases, arachnoid cysts, aneurysm, inflammatory lesions, and meningiomas.

Serial MRI should be performed on a regular basis to detect tumor recurrence. Following SRS or radiation therapy, the initial scan should be obtained 6 months after treatment and then yearly.

Staging

Classification of detectable or symptomatic pituitary tumors can be based on endocrine dysfunction, clinical presentation, and anatomic extent of disease. These tumors can also be broadly classified as functional or nonfunctional based on their secretory activity. As adenomas enlarge, they can extend into suprasellar, parasellar, or infrasellar structures. To aid with surgical and imaging assessment, Hardy and Verzina[57] developed a classification system. Wilson's[58] modification of this classification system incorporates imaging and intraoperative findings of sellar destruction (grade) and extrasellar extension (stage). Others have defined giant adenoma as a lesion with extension beyond the sella and suprasellar space or size greater than 4 cm.[59,60] No universally accepted staging system exists for pituitary tumors.

PRIMARY THERAPY

General Strategies

The primary objectives of therapy include preservation or restoration of normal hormonal function, reversal of endocrine dysfunction, removal or control of the tumor mass effect, and reversal of neurologic symptoms while minimizing potential morbidity such as hypopituitarism. Modern surgical approaches, medical management, and innovative radiation techniques have improved the likelihood of accomplishing these goals.

Surgery

Advances in transsphenoidal approaches with microsurgical techniques have made this procedure the initial treatment of choice for patients with nonfunctioning pituitary adenomas, acromegaly, Cushing's disease, and TSH-secreting adenomas. Surgery provides immediate decompression for patients with progressive visual loss, symptomatic pituitary hemorrhage (apoplexy), or other signs or symptoms of neurological mass effect such as cranial neuropathy or hydrocephalus. For patients with prolactinoma who do not tolerate or respond to medical therapy, surgery can be considered. Surgery has also been useful in reducing the tumor bulk for combined management with radiation therapy or medical therapy. For patients undergoing SRS, surgery may play an important role because

a distance of 2 mm to 5 mm is needed between the tumor and the optic apparatus to deliver a sufficient dose to the tumor and to minimize the risk for optic neuropathy. Reoperation results in lower rates of success compared with the initial surgery.[61]

Four different transsphenoidal approaches (transnasal, sublabial/transseptal, transethmoidal, or transantral) can be considered. The transsphenoidal technique is the preferred approach for microadenomas, for pituitary tumors with extension toward the sphenoid sinus, and for some macroadenomas with suprasellar extension. This technique provides decompression of the optic chiasm and removal of intrasellar and suprasellar tumor tissue.

Transcranial surgery is generally reserved for large intracranial extensions and for cases in which transsphenoidal surgery has technical limitations (e.g., small sella and inadequate pneumatization of the sphenoid sinus).

A wholly endoscopic approach, for which nasal septal or oral incisions are not needed, may be used, and appears to have results that are similar to minimally invasive transnasal or sublabial approaches, although no true randomized, head-to-head comparisons have been conducted to determine whether complications or length of hospitalization are altered.[62,63] For patients undergoing endoscopic endonasal approaches, nasal crusting (98%) and discharge (46%) were the most common postoperative symptoms based on a prospective cohort study.[64] It may also be used to complement microsurgical approaches.

Finally, a supraorbital approach (the Lynch or modified Lynch procedure) has also been used for recurrent and residual suprasellar tumors. This approach allows one to avoid scar tissue from previous approaches and provides access for optic apparatus decompression.[65]

The various approaches for giant pituitary tumors (>4 cm) have recently been compared in a systematic review by Komotar et al.[66] Endoscopic endonasal approach resulted in a higher rate of gross total resection (GTR) (47.2% versus 9.6%; $p < 0.003$) and improved visual outcomes (91.1% versus 45.7%; $p < 0.003$) than either the microscopic transsphenoidal or the open transcranial approach for these tumors. It is important to note that the open transcranial approach may remain the treatment of choice for certain tumors and factors such as suprasellar extension (particularly lateral extension) and the location of the optic chiasm should be accounted for during selection of the operative technique. Berkmann[67] described the use of intraoperative MRI in 32 patients with tumors exhibiting suprasellar extension and causing visual impairment. The authors used a 0.15 T MRI to perform intraoperative pituitary imaging after safe resection was thought to be complete. Following the intraoperative MRI, additional tumor was removed in 8 patients (25% of cases).

Based on a questionnaire study of 958 neurosurgeons reporting on their own experience with transsphenoidal surgery, the risk for complications was inversely proportional to the surgeon's level of experience.[68] Reported complication rates among experienced surgeons include perioperative mortality (<1%), central diabetes insipidus (2%), cerebrospinal fluid (CSF) rhinorrhea (2%), and meningitis (2%). Transient central diabetes insipidus is reported to occur in up to 22% of patients at an active pituitary surgery center.[69] These complications are more common in patients with macroadenomas. The experience of the surgeon may influence the rate of this and other complications.[63,70]

The incidence of postoperative CSF rhinorrhea after transsphenoidal surgery ranges from 0.5% to 15% with the majority reporting 0.5% to 6%.[71] Use of a synthetic collagen fleece may decrease CSF leak and can help avoid the use of a lumbar drain.[71]

Medical Therapy

Because management of hormonal dysfunction as a result of oversecretion or undersecretion can have significant effects on quality of life and longevity, medical therapies play an important role in the management of patients with pituitary tumors as either primary or adjuvant therapy. Primary goals include correction of hormonal dysfunction and reduction of the mass effect from a secretory adenoma.

The initial treatment of choice for most prolactinomas includes dopamine agonists such as bromocriptine or cabergoline because they are highly effective in controlling hyperprolactinemia. Dopamine is the primary neuroendocrine inhibitor for the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus is secreted into the hypothalamo-hypophyseal blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin secrete prolactin continuously in the absence of dopamine; dopamine inhibits this secretion. Thus, in the context of regulating prolactin secretion, dopamine was historically referred to as prolactin-inhibiting factor and is sometimes still referred to as prolactin-inhibiting hormone, or prolactostatin. Therefore, dopamine-agonists would be expected to and have been shown to be clinically effective at reducing prolactin secretion. In addition, partial tumor regression and improvement in mass effect from an enlarged adenoma are frequently observed with medical treatment alone. Long-term maintenance treatment is generally necessary to control hyperprolactinemia and growth of a prolactinoma.

Medical therapy can be used in several situations for patients with GH-secreting tumors as well. Somatostatin analogs such as octreotide or lanreotide can be used to lower elevated GH levels before surgery, for patients with persistent GH and IGF-1 elevation after surgery and for patients who continue to receive medical therapy until radiation therapy or radiosurgery has taken full effect. Pegvisomant is a modified version of human GH designed to bind to and block the GH receptor. It blocks the action of GH at the GH receptor level, especially in the liver, to reduce the production of IGF-1, which is responsible for most of the symptoms of acromegaly, thus normalizing its levels is effective in controlling the symptoms of acromegaly.[72] A number of concerns remain regarding its use, including high cost, a number of side effects such as reactions at the injection site, swelling of the limbs, chest pain, hypoglycemia, nausea, and hepatitis, but more importantly the fact that blocking of the GH receptor reduces feedback control of the GH regulation leading to increase in GH levels, the long-term effects of which remain ill-defined.

Medical management of Cushing's disease is generally reserved for patients who have failed surgery or radiation therapy, although this is controversial. Agents that modulate pituitary ACTH release (cyproheptadine), glucocorticoid antagonists (RU486), or agents that inhibit steroidogenesis (ketoconazole) must be taken for the rest of the patient's life and are associated with a number of side effects.

Medical treatment of hormonal deficiencies resulting from the pituitary tumor may be optimally managed by an endocrinologist, at least at those times when rapid or significant replacement or medication adjustment is needed. Hypopituitarism can have variable clinical manifestations, and management should be individualized to minimize the impact of this condition. Depending on the deficiency, glucocorticoids, gonadal steroids, and thyroid hormones may be needed. Commonly used medicines include hydrocortisone and cortisone acetate for glucocorticoid replacement and L-thyroxine for hypothyroidism. Gonadal steroids used include estrogen and progestin for women and testosterone for men. Careful

optimization of medication supplementation, especially to avoid supraphysiologic doses of steroids, appears to be important in minimizing the effect of hypopituitarism.[73]

Radiation Therapy and Stereotactic Radiosurgery

Radiation therapy and SRS are important and useful treatment options for select patients with pituitary tumors. They can be considered as postoperative treatment after subtotal removal of a pituitary adenoma, as treatment for recurrent or progressive tumors after surgical or medical treatment, and as primary treatment when surgery or medical therapy is contraindicated or ineffective. Unlike medical therapy, radiation options offer the potential for definitive control of the tumor and permanent reduction of hormone hypersecretion. Radiographic control of the tumor occurs in the vast majority of patients. Normalization of excess hormone production is, however, relatively slow, and quite variable, and depends on a number of factors. Because the effect of radiation on tumor control or hormone suppression may take years, the use of radiation therapy and SRS is variable among institutions. The type of radiation used depends on a number of factors, including tumor size, proximity of the tumor to the optic apparatus, technology availability and expertise, and physician preference.

The lack of prospective, randomized data comparing different radiation delivery methods has resulted in strong proponents for fractionated versus radiosurgical approaches.[74-76] Most of the literature is based on single-institutional results. Fractionated radiation therapy has the benefit of limiting radiation damage to nearby radiation-sensitive structures such as the optic apparatus, whereas SRS can be conveniently performed in a single session and results in more rapid biochemical remission.[77]

Advances in radiation therapy have led to techniques that allow more focused delivery of radiation to the tumor and decreased dose to the normal brain. Sophisticated treatment planning systems, incorporation of CT and MRI studies, stereotactic guidance, radiation therapy approaches such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT), micro-multileaf collimators, and relocatable frames or masks have improved precision.[76,78,79] Results with radiation therapy, including specifics regarding dose and margin selection, will be discussed in greater detail later in the chapter.

SRS delivers a highly focused, single, large fraction of ionizing radiation to a small intracranial target volume (Figure 29-3). Frame-based systems (e.g., proton beam, helium ion, Gamma Knife, and linear accelerator SRS techniques) and frameless systems (e.g., CyberKnife and linear accelerator-based units) have been used to treat pituitary tumors. Given the sharper dose gradient of SRS versus fractionated approaches, the potential for radiation injury to normal brain and vessels and secondary tumor formation may be less with SRS.

Because the results with SRS vary widely, the comparison of SRS with other treatments is difficult. Many of the published studies have used a wide range of tumor delineation approaches, doses, different prescription isodose line selection, different definitions for response or cure, and short follow-up times, and of course there is selection bias because larger tumors are often not selected for SRS. A wide spectrum of peripheral doses, ranging from 12 Gy to 35 Gy prescribed to the 30% to 100% isodose line have been used, although higher doses are typically reserved for secretory tumors. It is generally believed that lower doses (14 Gy to 18 Gy) are sufficient for nonfunctioning adenomas where the primary goal is radiographic tumor control, whereas higher doses (18 Gy to 35 Gy) are needed for functioning pituitary tumors, where the primary goal is ablation of endocrine oversecretion. Because the efficacy of SRS for functioning pituitary adenomas may be compromised by the concomitant use of cytostatic hormone-suppressing medical therapies, these drugs are typically stopped 6 to 8 weeks before and after SRS.

Given the proximity of the pituitary tumor to adjacent critical structures, particularly the optic nerves and chiasm, appropriate selection of patients for SRS is needed. The optic apparatus (optic chiasm and nerves) is the major dose-limiting critical structure in SRS and fractionated treatment planning. A single-fraction dose to the optic chiasm should be limited to 8 Gy to 9 Gy to minimize damage to the visual pathways. A retrospective review to evaluate the risk of clinically significant radiation optic neuropathy (RON) for patients having undergone SRS for tumors adjacent to the optic apparatus showed that 1.9% developed RON with a median maximum radiation dose to the optic nerve of 10 Gy.[80] RON developed at a median of 48 months after SRS. The authors suggested a clinically significant risk of RON of 1.1% for those who receive 12 Gy or less to a small segment of the optic apparatus. Accurate localization of the target volume and the optic chiasm using MRI is essential. For patients undergoing fractionated treatment, the dose to the chiasm should not exceed 54 Gy and the dose per fraction should be

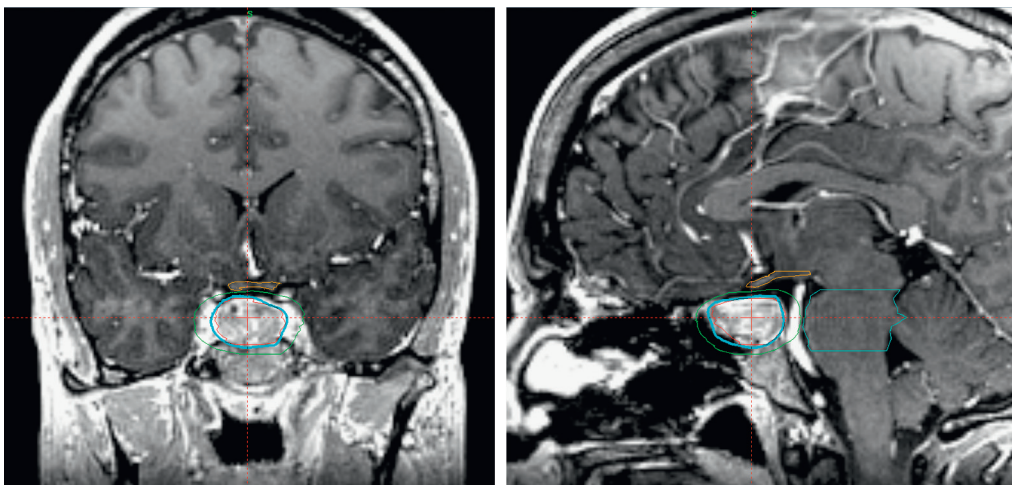

Figure 29-3 Stereotactic radiosurgery plan (coronal and sagittal) for a patient with a nonsecretory pituitary adenoma. A dose of 16 Gy was prescribed to the 50% isodose line *(blue)*. The 8-Gy isodose line is shown in green. The maximum dose to the optic chiasm *(outlined in orange)* was 6.4 Gy.

1.8 Gy/day. It is important to minimize the hot spot around the optic nerves and chiasm.

Unlike the optic nerves, the cranial nerves in the cavernous sinus are more resistant to radiation effects.[81] This may be a result of the increased sensitivity of sensory nerves such as the optic and acoustic nerves compared with the nonsensory nerves of the parasellar region. After repeat SRS, nonsensory cranial neuropathy, however, has been reported.[82]

TREATMENT STRATEGIES FOR SPECIFIC TUMORS

Nonfunctioning Adenoma

Nonfunctioning adenomas are the most frequent type of macroadenoma and typically present with decrease in visual acuity and constriction of the visual field defects, and in some cases, varying degrees of hypopituitarism.[83,84] Nonfunctioning adenomas account for approximately 30% of all pituitary adenomas and often extend beyond the sella turcica. Other presenting symptoms may include headaches from local mass effect or obstruction of the third ventricle causing hydrocephalus, cranial nerve deficits from cavernous sinus involvement, and hypopituitarism resulting from compression of the pituitary gland. Evaluation should include visual field testing, MRI scanning, and an endocrine workup. Generalized, schematic treatment algorithms for a nonfunctioning pituitary microadenoma and macroadenoma are outlined in Figures 29-4 and 29-5, respectively.

Surgery

Management of a nonfunctioning pituitary adenoma is influenced by the size of the tumor, symptoms, physical examination findings, and associated endocrine disorders. For a microadenoma or asymptomatic nonfunctioning adenoma, observation is generally recommended. For a symptomatic tumor or one with mass effect causing progressive symptoms or measurable visual impairment, surgery is the best option because it provides pathologic tissue confirmation, immediate debulking of the tumor, and amelioration of the mass effect, especially relative to the optic chiasm, in 90% to 95% of patients. The results with surgery are variable and depend on the extent of resection possible because of location of invasion (within the subarachnoid spaces intracranially, the cavernous sinuses, or the nose/paranasal sinuses). Recurrence rates range from 10% to 18% at 5 to 6 years and 20% to 80% at 10 years.[85-87]

Medical Therapy

No medical treatment has consistently reduced the size of nonfunctional pituitary adenomas. The use of a dopamine agonist is not recommended because response is uncommon.

Radiation Therapy Options

If the tumor cannot be completely removed, surgical decompression followed by radiation therapy or SRS can provide excellent results. For patients with recurrent tumors or those who are not good surgical candidates, fractionated radiation therapy or SRS can be considered, depending on the proximity of the tumor to the optic apparatus, as well as growth rate on

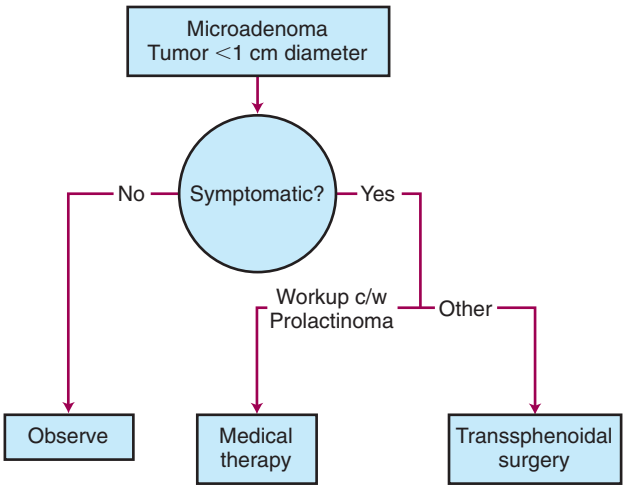

Figure 29-4 Generalized treatment algorithm for pituitary microadenoma.

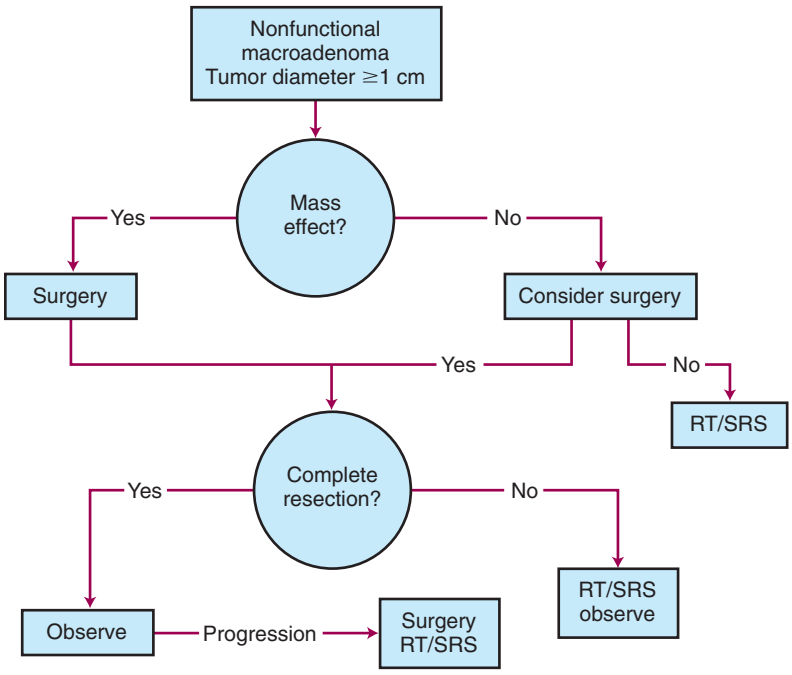

Figure 29-5 Generalized treatment algorithm for nonfunctional pituitary macroadenoma. *RT*, Radiation therapy; *SRS*, stereotactic radiosurgery.

sequential MRI scans. Table 29-1 summarizes some of the recent larger studies of SRS using doses ranging from 13 Gy to 20 Gy.[88-95] Using these doses, the local radiographic control rates are excellent (90% to 100%). The tumor volume in more than half of these patients decreases on follow-up MRIs. Hypopituitarism occurs in up to 39% of patients. More recent series have not reported visual complications, especially when the maximum dose to the optic apparatus is kept below 8 Gy to 9 Gy.

Numerous retrospective studies have demonstrated excellent local control rates with conventional fractionated radiation therapy (45 Gy in 25 fractions). The largest series from Brada et al[96] of 252 patients reported local control rates of 97% and 92% at 10 and 20 years, respectively. Another large study from Sasaki et al[97] demonstrated a 98% local control rate at 10 years. No prospective trials have compared fractionated radiation therapy to SRS.

Prolactinoma

Prolactinomas are the most common functioning pituitary tumors, with the vast majority occurring as microadenomas in women. Symptoms may include amenorrhea, galactorrhea, and infertility in women and decrease in libido, infertility, and visual disturbances in men. Diagnosis is typically made from sustained elevation of serum prolactin levels above the normal range. MRI of the brain can help confirm the diagnosis, although a negative MRI can be seen in women with microadenomas.[98]

Goals of treatment include restoration of sexual and reproductive function, normalization of prolactin levels, control of galactorrhea, and improvement of neurologic symptoms. It is important that other causes of increased prolactin levels such as effects of medicines, pregnancy, and renal insufficiency are considered in the differential diagnosis. Treatment options include observation, medical therapy, surgery, and irradiation.[48] A generalized schematic treatment algorithm for a prolactinoma is outlined in Figure 29-6.

Surgery

Surgery is standard second-line therapy and is reserved for patients who cannot tolerate medical therapy or are not responsive to maximally tolerated dose of dopamine agonists,[99] have rapid progressive vision loss, or women who wish

TABLE 29-1 Summary of Recently Published Larger Studies of SRS for Nonfunctioning Pituitary Adenomas

Author	Year	No. Pts	Follow-up (mo)	Peripheral Dose (Gy)	Local Control Rate (%)	Visual Complication Rate (%)	Hypopituitarism Rate (%)
Mingione[88]	2006	100	46.4*	18.5	92.2	0	25
Liscak[89]	2007	140	60	20	100	0	1.4
Pollock[90]	2008	62	64	16	96.8	0	27
Park[91]	2011	125	62	13	90	0.8	24
Gopalan[92]	2011	48	95	18.4	83	0	39
Iwata[93]	2011	100	33	21/3 fractions 25/5 fractions	98	1.7	4
Starke[94]	2012	140	50.4	18	90	0†	30.3
Sheehan[95]	2013	512	36	16	93	NA	21

Gy, *Gray;* mo, *months; NA, not available; SRS, stereotactic radiosurgery.*
**Mean follow-up.*
†15 patients (12.8%) had visual decline secondary to tumor progression.

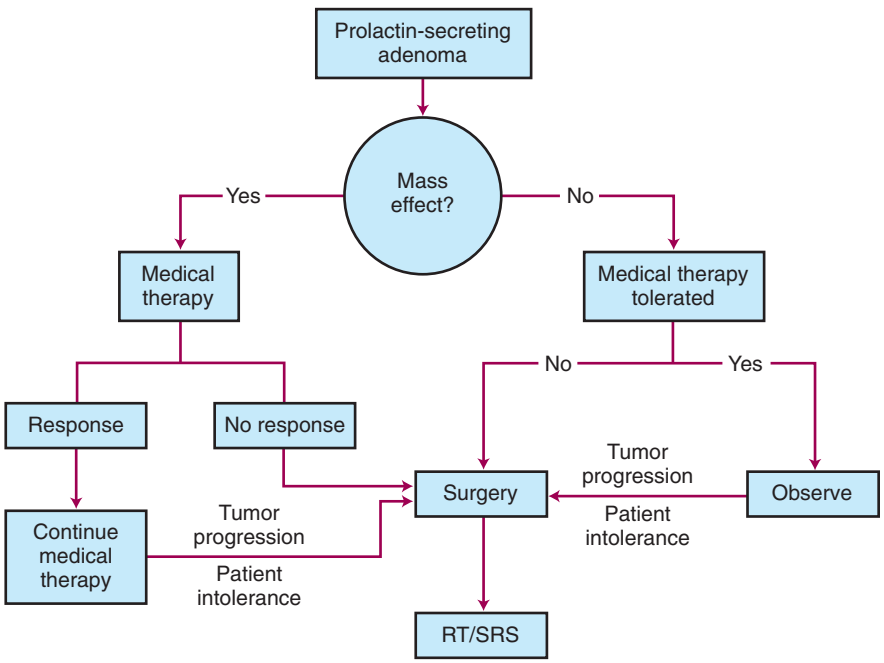

Figure 29-6 **Generalized treatment algorithm for prolactin-secreting adenoma. Note: some patients may elect to have surgery as definitive therapy.** *RT,* Radiation therapy; *SRS,* stereotactic radiosurgery.

to conceive. Based on a review of 50 surgical series of more than 4000 patients, the curative surgical resection rates for microprolactinomas and macroprolactinomas was 74.7% and 33.9%, respectively, using a normalization of prolactin levels before 12-week follow-up as the definition of remission.[100] Biochemical recurrence, however, occurs in 20% of patients within the first year. The best predictor for persistent cure is a prolactin level less than or equal to 5 ng/mL on postoperative day 1. The long-term surgical cure rates for microprolactinomas and macroprolactinomas are 50% to 60% and 25%, respectively, where a cure is considered normal prolactin levels. Surgery is also sometimes used in women with a large adenoma who want to become pregnant.

Medical Therapy

The initial treatment of choice for patients with prolactinoma is medical therapy with a dopamine agonist such as bromocriptine or cabergoline because these drugs decrease secretion and tumor size in most patients. Medical therapy can rapidly normalize prolactin levels and reduce tumor size in 80% to 90% of patients.[100] Bromocriptine, which is taken two or three times per day with meals, is associated with a greater number of side effects (e.g., nausea, vomiting, fatigue, and orthostatic hypotension) compared with cabergoline, which is taken once or twice a week. In a double-blinded study of 459 female patients comparing bromocriptine with cabergoline over 8 weeks, normal prolactin levels were achieved in 59% and 83% of patients, respectively.[101] Cabergoline was better tolerated, with 3% discontinuing its use versus 12% who stopped taking bromocriptine. Because cabergoline has been associated with an increased risk for cardiac valve thickening in patients with Parkinson's disease, who take much higher doses compared with patients with prolactinoma, this potential risk needs to be reviewed and carefully monitored.[102] For some patients, medical therapy may be gradually withdrawn every 2 years to 3 years to assess remission. This strategy is most effective for patients with low prolactin levels and small tumors. Approximately 8% of patients with prolactinoma are intolerant to or unresponsive to medical treatment.

Because the risk of symptomatic tumor enlargement during pregnancy is low for microprolactinomas (3% to 5%), it is recommended to stop medical treatment as soon as diagnosis of pregnancy is established[103,104]

Radiation Therapy Options

Based on the success of dopamine agonists and because of the risk for hypopituitarism in young female patients, radiation therapy or SRS is usually reserved as third-line therapy. For patients who do not respond to or are intolerant of medical therapy and are not candidates for surgical salvage, radiation options may be considered.

The results with conventional radiotherapy from the late 1970s to the early 1990s have been modest. One of the earliest studies from Sheline et al[105] of 28 patients demonstrated a prolactin normalization rate of 29%. Littley et al[106] found a decrease in serum prolactin levels in all 58 patients treated with external beam radiation therapy (EBRT) and a 50% probability of prolactin level reduction to 500 mU/L in 10 years. Patients more likely to achieve normalization of serum prolactin levels after EBRT had smaller tumors, pretreatment prolactin levels higher than 6000 mU/L, and tumors with positive immunostaining for prolactin. Tsagarakis[107] reported normal serum prolactin levels at a mean of 8.5 years after EBRT in 18 of 36 patients. Pituitary irradiation can lead to hypothalamic dysfunction and impairment of dopamine secretion, which causes hyperprolactinemia. This may explain the mildly elevated prolactin levels (usually, <50 mU/L) in some patients after radiotherapy of pituitary adenomas.

SRS has also been used after failure of medical therapy or surgical treatment. Table 29-2 summarizes recent larger publications on the results of SRS for prolactinomas with normalization rates for prolactin ranging from 17% to 43.5%.[108-113] A multidisciplinary approach is important to optimize treatment.[114]

Because it may take some time for normalization of prolactin levels to occur after EBRT or SRS, the use of dopamine agonists may be required. Landolt[115] reported worse outcomes for patients receiving dopamine agonists at the time of SRS. Pouratian[116] also reported worse outcomes in patients receiving antisecretory medication at the time of SRS. Antisecretory medications may alter the cell cycle, which makes the tumor cells less radiosensitive. As a result, a 2-month break between medical therapy and SRS has been suggested.[115]

Acromegaly

Acromegaly is a rare condition, with a prevalence of approximately 60 per million. GH hypersecretion leads to metabolic and functional disturbances of multiple organs (i.e., cardiovascular, musculoskeletal, and respiratory dysfunction) and an increased incidence of colonic polyps, although whether this increases the incidence of colorectal cancer is not fully determined.[49] The overall life span of patients with acromegaly is shorter than their normal counterparts, implying a significant risk of disease-associated mortality in the long term. In addition, characteristic bony and soft-tissue enlargement occurs in the frontal bones, hands, feet, spine, nose, and mandible. As a result, early diagnosis and treatment are essential to minimize the impact on life expectancy and morbidity. Unfortunately, the gradual onset of symptoms and changes as a result of excessive GH secretion delays diagnosis in many patients.

Although surgery is the initial treatment of choice for most patients, a multidisciplinary approach is often needed given

TABLE 29-2 Summary of Recently Published Larger Studies of SRS for Prolactinomas

Author	Year	No. Pts	FU (mo)	Peripheral Dose (Gy)	Hormone Remission Rate (%)	Local control rate (%)	Visual complication rate (%)	Hypopituitarism Rate (%)
Wan[108]	2009	176	67.3	35	23.3	90.3	0	1.7*
Kobayashi[109]	2009	27	37.4	18.4	17.4	100	0	0
Jezkova[110]	2009	35	75.5	49	37.1	97.1	0	14.3
Tanaka[111]	2010	22	60	25	17	100	0	42
Sheehan[112]	2011	32	31	24	26	93†	NA	38
Liu[113]	2013	22	36	15	27.3	86.4	0	4.5

FU, *Follow-up;* Gy, *Gray;* mo, *months;* NA, *not available;* No. Pts, *number of patients; SRS, stereotactic radiosurgery.*
**Included all 347 secretory adenomas treated with SRS.*
†*Included patients with acromegaly treated with SRS.*

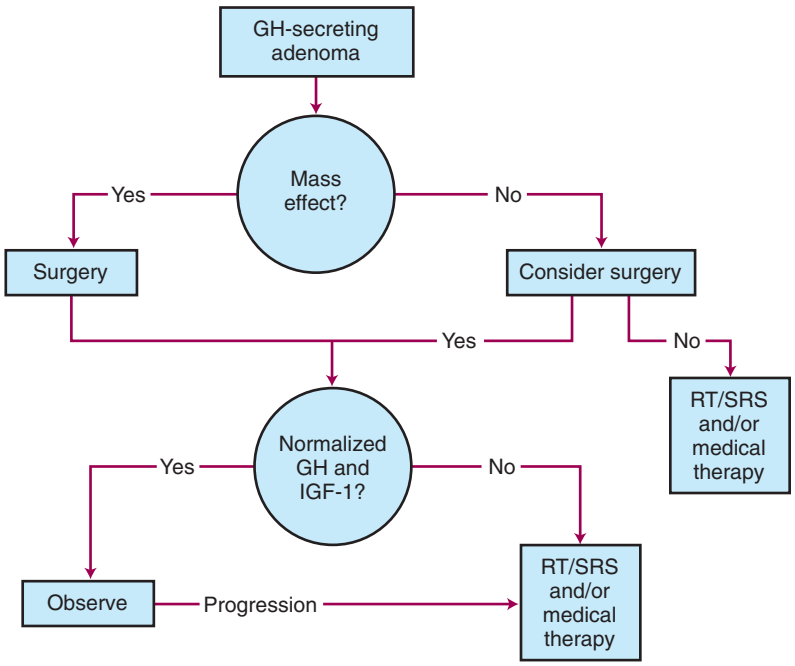

Figure 29-7 Generalized treatment algorithm for growth hormone–secreting adenoma. *GH*, Growth hormone; *RT*, radiation therapy; *SRS*, stereotactic radiosurgery.

the complexity of this disease.[117] Because liver-derived IGF-1 mediates the effects of GH at the tissue level, the primary goal of therapy is to normalize IGF-1 levels to within the reference range for the patient's age and gender; additional therapeutic goals are to preserve pituitary function and to prevent tumor growth. Normalization of age- and sex-matched IGF-1 levels and the suppression of serum GH levels to less than 0.4 mg/L in response to a 75-g oral glucose load are generally used to define biochemical cure for acromegaly.[118] Normalization of IGF-1 levels is a better criterion for cure than GH levels because some patients with acromegaly can have normal GH levels.[118,119] Untreated or incompletely treated acromegaly is associated with significant morbidity and excess mortality, which may be as high as three times that of the general population.[73,117] The treatment options for acromegaly include surgery, irradiation, medical therapy, or a combination of treatment approaches. A generalized treatment algorithm for acromegaly is outlined in Figure 29-7.

Surgery

The initial treatment of choice for acromegaly is surgery.[117,120] Goals of surgery include alleviation of mass effect from suprasellar extension and complete removal of the GH-secreting adenoma. Because the criteria used for biochemical cure have changed with time and the duration of follow-up varies, surgical series are not directly comparable. When surgery is performed by experienced pituitary neurosurgeons, the GH levels fall to normal in 80% to 90% of patients with microadenomas.[121,122] The success rate is lower in patients with higher preoperative GH concentrations or macroadenomas (<50%).[123] Recurrence rates after surgery are estimated to be approximately 20%.[124] Using modern criteria for cure (i.e., normal serum IGF-1 and glucose-suppressed GH concentrations of less than 1 ng/mL), the surgical remission rates are 70% and 61%, respectively.[125] The largest series evaluated 506 patients who underwent transsphenoidal surgery. Overall remission was 57.3% as defined by normalization of IGF-1 levels.[126] The normalization results for microadenomas and macroadenomas were 75% and 50%, respectively. A recent retrospective study of 46 patients with acromegaly with no residual tumor on postoperative MRI and nadir GH of less than 0.4 mg/L on a postoperative oral glucose tolerance test reported that the mean duration from surgery to IGF-1 normalization was 10 months (range, 3 days to 57 months).[127] Longer remission times were required for patients with higher postoperative IGF-1 levels.

Medical Therapy

Three different types of medicines (somatostatin analogs, dopamine agonists, and a GH receptor antagonist) are used to treat patients with acromegaly who have failed surgery, are not surgical candidates, or are refractory to radiation options. Given the latency for normalization of IGF-1 and GH levels after irradiation, medical therapy is also used as an adjunct after radiation treatments. The most commonly used medicines are the somatostatin analogs (octreotide and lanreotide) rather than somatostatin, given the much higher potency and half-life of the analogs. These analogs bind to somatostatin receptors subtypes 2 and 5, reduce IGF-1 levels in 38% to 66% of patients and lead to tumor shrinkage in 30% to 45% of patients.[128-130] Response is best predicted by determining whether the subtype of somatotroph adenoma is sparsely or densely granulated.[131] The most common side effects of somatostatin analogs include nausea, abdominal cramping, diarrhea, and gallstones. A disadvantage of these agents is the lifelong dependence. Dopamine agonists such as cabergoline are generally not effective and are not used frequently unless a patient is unable to tolerate somatostatin analogs.

Pegvisomant, a GH receptor antagonist that is administered daily via the subcutaneous route, has been tested in a placebo-controlled randomized trial and shown to normalize IGF-1 levels in 90% to 97% of patients.[132-134] Side effects include flu-like symptoms, nausea, diarrhea, and abnormal liver function tests. Because pegvisomant does not inhibit GH secretion or tumor growth, it is not used as first-line therapy. Pegvisomant requires lifelong treatment, may cause elevated aminotransaminases in 20% of patients, and may carry a small risk for increase in tumor size. In addition, pegvisomant is extraordinarily expensive compared with other medical therapies.

Radiation Therapy Options

Irradiation can be used in the definitive or adjuvant setting for patients with acromegaly. Given the relatively long lag time for normalization of the IGF-1 and GH levels after radiation treatment, it is important that these patients be followed closely with blood work every 3 to 6 months and yearly MRIs. If patients are taking a short-acting (daily) somatostatin analog (SSA), they may need to be off medication for about 1 month, or longer, to assess the efficacy of radiation; the interval for a patient on a long-active SSA, given once monthly, may need to be on a medication holiday up to 3 months, which means that perhaps only once yearly IGF-1 level will be measured. The published reports on radiation therapy and SRS have typically used varying definitions of cure relative to GH levels. Earlier publications, which defined remission as growth hormone levels below 5 ng/mL to 10 ng/mL, reported remission rates of 80% to 100%.[135,136] Using modern definitions for normalization of both GH levels (<2 ng/mL) and IGF-1 levels, the results for radiation therapy and SRS are less impressive. Table 29-3 summarizes the recent radiation therapy results.[137-141]

The rate of hormone remission and hypopituitarism at 10 years is approximately 50% to 60% and 60% to 80%, respectively. The largest study, a retrospective review of 884 patients with acromegaly undergoing radiotherapy, demonstrated that 63% of patients had normalization of IGF-1 levels by 10 years.[139] In this series, new hormone deficiencies included 18% for LH and FSH, 15% for ACTH, and 27% for TSH. Variability in the success rates in normalization of IGF-1 levels for patients undergoing radiation therapy may be a result of differences in pretreatment serum GH concentrations. Within the first 2 years mean GH values drop to 50% to 70% of their maximal values, followed by a slow decrease over years.[142] Higher doses of EBRT may be considered when treating patients with acromegaly (50.4 Gy to 54 Gy versus 45 Gy for nonfunctional tumors).

Table 29-4 summarizes the recent SRS results that have used IGF-1 level normalization as the definition for cure.[108,112,143-147] Using peripheral doses of 20 Gy to 26.5 Gy, IGF-1 level normalization rates range from 17% to 60%. The local control rates are excellent, suggesting that SRS could possibly also have a definitive role in this condition. Mean time to remission ranges from 24 to 36 months for patients undergoing SRS. Although the time to remission appears to be faster with SRS compared with radiation therapy, the ideal SRS candidate should have a well-defined target volume that is far enough away from the optic chiasm, and this limits the use of SRS.[146]

It is important to note that the latency period to achieve the hormonal control is directly related to hormone level and therefore the tumor volume before treatment.[148] Medication may be used as an adjuvant treatment after radiation therapy to help lower the growth hormone and IGF-1 levels. Given the concern for the potential suppressive effects of somatostatin analogs, which may compromise the effectiveness of radiation therapy, some centers do not recommend using these medications for, typically, 6 to 8 weeks before and after radiation.[143,149]

TABLE 29-3 Summary of Recently Published Studies of Radiation Therapy for Acromegaly

Author	Year	No. Pts	Follow-up (yr)	Hormone Remission Rate (%)
Barrande[137]	2000	128	2	7
			5	35
			10	53
			15	66
Minniti[138]	2005	74	2	9
			5	29
			10	52
			15	77
Jenkins[139]	2006	884	2	22
			10	63
			20	77
Jallad[140]	2007	89	5.9	54
Mullan[141]	2009	63	5	66
			10	71

FU, *Follow-up;* No. Pts, *number of patients;* yr, *years.*

Cushing's Disease

Cushing's disease results from an ACTH-secreting adenoma of the anterior pituitary, which is responsible for 70% to 80% of ACTH-dependent Cushing's syndrome cases in adults. Given the many nonspecific symptoms and signs, the diagnosis is often delayed. This syndrome, which is associated with increased morbidity and age-corrected mortality, occurs more commonly in women and is a heterogeneous disorder. Clinical findings include truncal obesity, hirsutism, acne, easy bruisability, muscle weakness, and moon facies. These patients can have menstrual irregularities, gonadal dysfunction, hypertension, diabetes mellitus, and osteoporosis. Tests used to diagnose Cushing's disease include a 24-hour urine collection to

TABLE 29-4 Summary of Recently Published Larger Studies of Stereotactic Radiosurgery for Acromegaly

Author	Year	No. Pts	FU (mo)	Peripheral Dose (Gy)	IGF-1 Normalization Rate (%)	Local Control Rate (%)	Visual Complication Rate (%)	Hypopituitarism Rate (%)
Pollock[143]	2007	46	63	20	50	100†	0	33
Vik-Mo[144]	2007	53	66	26.5	17	100	4	13.1
Losa[145]	2008	83	69	21.5	60	97.6	0*	8.5
Castinetti[146]	2009	43	102	24	42	NA	NA	21
Wan[108]	2009	103	67.3	21.4	36.9	95.1	NA	1.7
Sheehan[112]	2011	130	31	24	53	93‡	0	34.0
Franzin[147]	2012	103	71	22.5	60.7	97.3	0	7.8

FU, *Follow-up;* Gy, *Gray;* mo, *months;* NA, *not available;* No. Pts, *number of patients.*

**Included other types of adenomas.*

†Six patients did not have measurement on follow-up scans.

‡Included patients with prolactinomas.

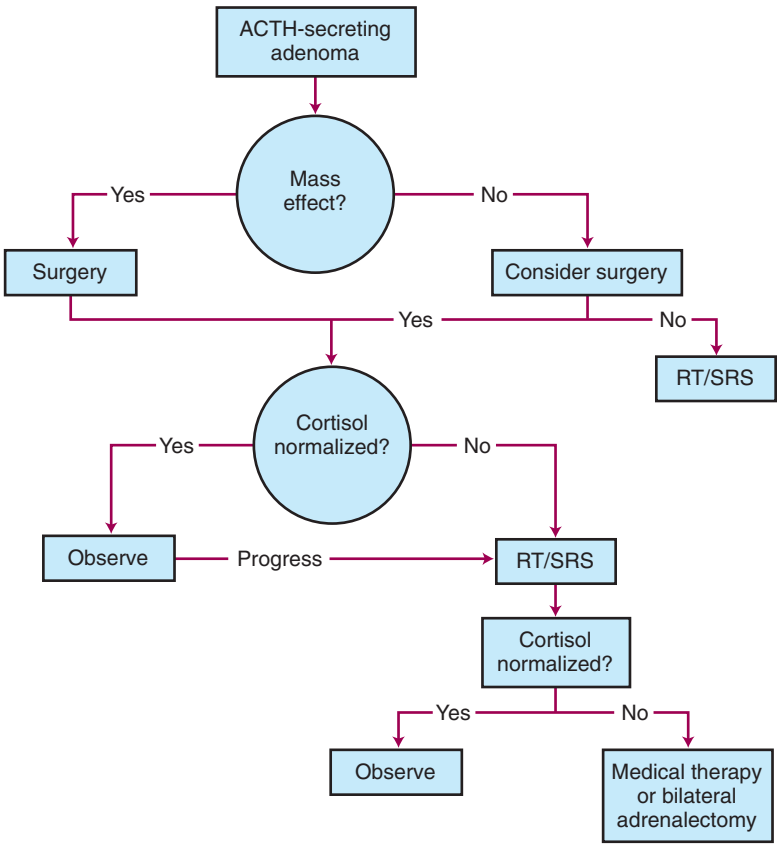

Figure 29-8 Generalized treatment algorithm for adrenocorticotropic hormone–secreting adenoma. *RT*, Radiation therapy; *SRS*, stereotactic radiosurgery.

measure urinary-free cortisol levels, midnight testing of ACTH levels, and dexamethasone suppression test among others.[47] Untreated or incompletely treated hypercortisolism is associated with significant morbidity and excess mortality, which may be as high as two to three times, or more, the rates of the general population.[73]

The treatment options for Cushing's disease include surgery, irradiation, medical therapy, total bilateral adrenalectomy, or a combination of treatment approaches.[150,151] Most centers define remission as urinary-free cortisol levels in the normal range with resolution of clinical findings or a series of normal serum cortisol levels obtained throughout the day.[152] A generalized, schematic treatment algorithm for Cushing's disease is outlined in Figure 29-8.

Surgery

Surgical removal of the pituitary adenoma is the best initial treatment for Cushing's disease because it can rapidly correct the hypersecretion of ACTH. Most patients have a microadenoma; 25% to 50% of patients with Cushing's disease will have no discernible lesion on MRI of the brain. Although a tumor is identified in 70% to 90% of cases, it is more likely that no tumor may be identified at the time of surgical exploration in patients with MRI-negative Cushing's disease.[153,154] For patients with no discernible lesion in whom surgery is being contemplated, bilateral inferior petrosal sinus sampling (BIPSS) may help improve the outcome, through better localization and lateralization. The inferior petrosal sinuses receive drainage from the pituitary without blood from other sources. Therefore, if the patient has pituitary Cushing's, the ACTH levels in the IPS are high compared to an ACTH level drawn in the periphery. In contrast, in ectopic Cushing's, the ACTH in the IPS and the periphery should be equivalent because the tumor is located elsewhere.

Ideally, an experienced neurosurgeon should remove the tumor in its entirety, leaving the normal pituitary intact. Although an abnormality may not always be seen on MRI of the brain, surgery leads to hormonal control in 80% to 90% of patients with microadenomas and in up to 50% with macroadenomas.[122] If a microadenoma cannot be identified in an adult patient in whom fertility is not an issue, one may perform either a hemihypophysectomy related to the potential side of localization suggested by BIPSS, although there remains concern about the localization capability of BIPSS. Total hypophysectomy is usually reserved for patients who undergo reoperation without visual identification at the second (or later) surgery of an adenoma, with remission rates of 50% to 70% even with this strategy.[155-158] Because dural invasion by ACTH-producing adenomas usually occurs laterally into the wall of the cavernous sinus, identification and removal of the invaded dura including the medial cavernous sinus wall allows for better biochemical cure.[159]

For most patients, the surgical approach is transsphenoidal. A series from Cavagnini of 300 patients with a follow-up time of 10 years demonstrated a remission rate of 70% and a recurrence rate of 15%.[160] In another study, low ACTH levels (<10 ng/mL) during the early postoperative period correlated with remission in 97.9% of cases, whereas an ACTH level of more than 30 ng/mL correlated with a remission rate of only 18%.[161] A more recent series from Patil et al[162] noted a 25% recurrence rate at 5 years for patients who achieved initial remission after transsphenoidal surgery. Given the varied results, experience with transsphenoidal surgery for Cushing's disease appears to be an important factor in terms of remission and recurrence.

If a patient does not achieve remission after surgery, a bilateral adrenalectomy can be considered. Patients undergoing bilateral adrenalectomy can develop Nelson's syndrome with

Under local anesthesia, femoral catheters are advanced bilaterally up to the IPS. After fluoroscopic confirmation of catheter position, multiple blood samples are drawn simultaneously from the right and left IPS and from a peripheral vein for ACTH level assessment, and the pituitary-to-peripheral ACTH ratios are calculated. If the ratio is greater than 2 the patient has Cushing's disease. If the pituitary-to-peripheral ratio is less than 1.5 to 1 the patient has ectopic Cushing's, and pituitary surgery should not be performed. Because each half of the pituitary drains into the ipsilateral IPS, BIPSS may also help lateralize the tumor.

a risk of 8% to 43% in adults[163] and 25% to 66% in children.[164,165] Bilateral adrenalectomy removes the peripheral source of cortisol, and hence the negative feedback suppression of ACTH production at the level of the pituitary is impaired; this can result in oversecretion of both ACTH and MSH (which is structurally similar to ACTH, and the loss of negative feedback results in oversynthesis of proopiomelanocortin, a precursor for both ACTH and MSH synthesis). This results in skin and mucosal hyperpigmentation, muscle weakness, and growth of the pituitary adenoma. For some patients, the growth of the adenoma can be quite rapid, leading to visual complications. Invasion of the cavernous sinus may cause cranial nerve palsies. In addition, the adenoma may be less responsive to radiation options, which is used in 20% to 30% of patients. Given its rarity and complexity and the controversies regarding diagnosis and treatment, it is one of the most challenging endocrine conditions.[166]

Medical Therapy

Medical management is reserved for patients who do not respond to surgery or irradiation options; lifelong therapy is needed. Medicines used to inhibit steroidogenesis include ketoconazole, aminoglutethimide, metyrapone, mitotane, and etomidate.[167] Ketoconazole is the best tolerated drug and is effective as monotherapy in up to 70% of patients. Because this drug can be hepatotoxic, it is important to monitor liver function tests. Metyrapone, an 11 alpha-hydroxylase inhibitor, is often used as an adjuvant to ketoconazole or radiation therapy.

Pasireotide, approved by the Food and Drug Administration (FDA) in December 2012, is a multireceptor-targeted somatostatin analog with high binding affinity to four of the five known somatostatin receptor subtypes (sst1, sst2, sst3, sst5)[168] and regulates anterior pituitary hormone secretion. Unlike other somatostatin analogs, pasireotide binds with the highest affinity to sst5, with 40-fold increased affinity to sst5 compared to other somatostatin analogs. Sst5 is the most prevalent somatostatin receptor expressed on ACTH-secreting pituitary adenomas.[169] In a double-blind Phase III, randomized, multicenter study (PASSPORT-CUSHINGS B2305) in 162 patients with de novo (if not surgical candidates), persistent or recurrent Cushing's disease, pasireotide demonstrated a rapid (approximately 50% decrease by 2 months) and sustained reduction in urinary-free cortisol levels, with significantly improved clinical signs and symptoms of Cushing's disease. Among those with a measurable pituitary tumor on MRI at baseline and month 12, mean percentage decrease in tumor volume was 43.8% in patients receiving pasireotide 900 µg bid.[170]

Radiation Therapy Options

Irradiation is typically used as an adjuvant for patients who are not cured after surgery. It can also be used definitively for patients unable to undergo surgery. For children, some consider this as the initial therapy because the cure rates are similar to those of surgery.[171,172] Both fractionated radiation therapy and SRS have been used to treat patients with Cushing's disease. For patients who are treated with EBRT, doses of 50 Gy to 54 Gy may be considered. One study from Estrada used postoperative irradiation (mean dose, 50 Gy) and reported an 83% remission rate at 5 years.[173] Minniti et al[174] reported on 40 patients with Cushing's disease who received 45 Gy of EBRT. The normalization rate of cortisol levels was 78% at 5 years and 84% at 10 years. Other EBRT series have yielded remission rates ranging from 46% to 56%.[175,176]

Most of the SRS series are small and report endocrine cure rates that are similar to the EBRT results. Recent series have reported remission rates of 28% to 53%,[82,108,109,112,177] which are listed in Table 29-5. As with other secretory tumors, the peripheral dose used is higher (>20 Gy). The largest series from Jagannathan[82] reported on 90 patients with a median follow-up of 45 months. In this series, a 54% remission rate was achieved. The timing of hormone normalization can be quite variable (2 months to 8 years), although most patients will achieve remission within the first 2 years. Patients with persistent disease should be considered for adrenalectomy or repeat SRS, which has been associated with higher rates of cranial nerve damage.[82] No trials have compared SRS with fractionated EBRT.

Nelson's Syndrome

Some Cushing's disease patients do not achieve remission after surgery or irradiation and may require bilateral adrenalectomy as salvage treatment. As a result, some patients may develop Nelson's syndrome, which is characterized by hyperpigmentation, rapid growth of the adenoma, and invasion of the tumor into the parasellar regions.[178] The few reports of SRS for Nelson's syndrome have resulted in endocrine remission rates of 36% or less.[179,180]

Thyroid-Stimulating Hormone–Secreting Adenomas

TSH-secreting adenomas are rare (0.5% to 1.5% of all pituitary tumors) and typically present as macroadenomas with mass effect and features of thyrotoxicosis.[181] Surgical removal of the TSH-secreting adenoma is the best treatment option after the hyperthyroidism has been controlled with medications. Because these tumors are usually large at diagnosis and can invade the sella or extend beyond it, complete removal can be difficult; for this reason, remission rates may be only 50% after surgery.[182] When the tumor cannot be completely removed or the patient is not a surgical candidate, irradiation can be considered. Somatostatin analogs or dopamine agonists have been used to decrease TSH hypersecretion. The use of octreotide results in normalization of TSH levels in 79% of patients.[183]

TABLE 29-5 Summary of Recently Published Larger Studies of Stereotactic Radiosurgery for Cushing's Disease

Author	Year	No. Pts	FU (mo)	Peripheral Dose (Gy)	Cortisol Normalization (%)†	Local Control Rate (%)	Visual Complication Rate (%)	Hypopituitarism Rate (%)
Jagannathan[82]	2007	90	45	25	53	95	5.6*	22
Petit[177]	2008	33	62	20	52	NA	0	52
Wan[108]	2009	68	67.3	23	27.9	NA	0	1.7
Kobayashi[109]	2009	30	64.1	28.7	35	100	NA*	NA
Sheehan[112]	2011	82	31	24	54	NA	NA	22

FU, *Follow-up;* Gy, *Gray;* mo, *months;* NA, *not available*; No. Pts, *number of patients.*

**Several patients had undergone previous stereotactic radiosurgery.*

†24-hour urinary-free normalization rate.

Etomidate can reduce cortisol levels within hours and is used for acute control of elevated cortisol levels. Etomidate, developed as an anesthetic induction agent, suppresses corticosteroid synthesis in the adrenal cortex by reversibly inhibiting 11-beta-hydroxylase; it leads to primary adrenal suppression and is associated with increased risk of pneumonia, sepsis, and death. In a retrospective review of almost 32,000 patients, etomidate, when used for the induction of anesthesia, was associated with a 2.5-fold increase in the risk of dying than those given propofol. Patients given etomidate also had significantly greater odds of having cardiovascular morbidity and significantly longer hospital stay. These results strongly suggest that clinicians should use etomidate judiciously.

Mitotane causes adrenal suppression of cortisol secretion and is cytotoxic to adrenocortical cells. It is typically used for patients who have failed multiple medical therapies. Until the effects of irradiation have normalized ACTH levels, hypercortisolism can be decreased by use of the aforementioned medications.

Gonadotropin-Secreting Adenomas

Gonadotropin-secreting adenomas usually present as macroadenomas with mass effect and hypogonadism. They secrete LH or FSH, alpha subunit, or a combination of these hormones. The results with irradiation are limited.

Pituitary Carcinomas and Aggressive Pituitary Tumors

Pituitary carcinomas are very rare (0.2% of all pituitary tumors).[184] They have clinical features of pituitary adenomas, with most secreting prolactin or ACTH. Because the malignant nature of these tumors cannot be clearly determined by pathologic testing, the diagnosis is a clinical one based on findings of subarachnoid spread, brain involvement, or systemic metastases from a pituitary tumor.[141] The overall prognosis for these tumors is poor despite aggressive treatments that have included radiation therapy with mean survival of 1.9 years.[185] Rare examples of persistent response to chemotherapy (temozolomide) have been reported.[186]

For patients with aggressive pituitary tumors, a significant number of the published cases have demonstrated a response to temozolomide. Overall, 24/40 (60%) of the published cases demonstrated a response to temozolomide. The highest response rates were seen among prolactinomas (73%) and ACTH-secreting tumors (60%), whereas nonfunctioning pituitary tumors exhibited lower response rates (40%). Responsivity became typically evident in the first 3 months of therapy and low MGMT expression, as determined by immunohistochemistry, was associated with a high response rate (76%), whereas high MGMT expression was not associated with responses. MGMT promoter methylation, however did not correlate with temozolomide response. Temozolomide is therefore the first chemotherapeutic agent to show substantial response rates in aggressive pituitary tumors. MGMT immunohistochemistry, but not MGMT methylation analysis, shows promise as a predictive tool.[187]

LOCALLY ADVANCED DISEASE AND PALLIATION

Repeated Course of Irradiation

If tumors recur after fractionated radiation therapy, a repeat course of fractionated treatments may be considered after careful consideration of alternative treatment options, the interval that has elapsed since the first course of radiation therapy, and the details of the prior radiation treatment (e.g., technique used, dose given, and fractionation schedule used). Schoenthaler reported on 15 patients who were reirradiated with a median dose of 42 Gy in 1.8-Gy to 2-Gy fractions.[188] Local control was achieved in 12 patients. All patients developed hypopituitarism from the initial or repeat course of radiation therapy. Two patients later developed pituitary carcinoma and temporal lobe radionecrosis. Flickinger et al[189] reported on 10 patients with suprasellar or pituitary tumors who were reirradiated with doses ranging from 35 Gy to 49.6 Gy in 1.8-Gy to 2-Gy fractions. Six patients had pituitary tumors. One patient developed optic neuropathy a little more than 1 year after completing the therapy. The study authors suggest that a 40% estimation of the original radiation dose effect is a reasonable guideline to account for prior radiation therapy.

Palliation of Metastases

Metastases to the pituitary occur infrequently and most commonly arise from breast and lung cancers.[190] The reported rates of breast cancer metastasizing to the pituitary range from 6% to 8%. The most commonly reported symptoms include diabetes insipidus, anterior pituitary dysfunction, visual field defects, and headaches. Most metastases occur in the neurohypophyseal region, although breast cancer metastases have a predilection for the adenohypophyseal region. Because these are invasive tumors, surgery is difficult. SRS (median dose, 13 Gy) has been used for select patients with a progression-free survival (PFS) rate of 66.7%, a 12-month survival rate of 18%, and a median survival time of 5.2 months.[191]

IRRADIATION TECHNIQUES AND TOLERANCE

Techniques of Irradiation

Before the advent of sophisticated radiation delivery techniques, imaging techniques, and treatment planning efforts, the field arrangement for pituitary tumors included a two-field, opposed lateral field technique, a three-field technique of two opposed lateral, and an anterior vertex field. Bilateral 110-degree coronal arcs with a 30-degree wedge and 330-degree rotational arcs were also used. Comparison of these various techniques demonstrated that the three-field technique delivered less dose to the temporal lobes than the two-field technique, the rotational techniques were superior to the stationary field techniques in terms of sparing the temporal lobes, and the four-field noncoplanar arc technique delivered less dose to the frontal lobe.[192] When comparing the three-field coplanar technique to the four-field noncoplanar arrangement, the mean volume of normal brain receiving dose was higher with the coplanar techniques.[193]

Modern techniques of fractionated radiation therapy and SRS have capitalized on improvements in immobilization, imaging, planning, and treatment delivery. Using a fixed head frame, SRS is delivered in one fraction using a linear accelerator (see Figure 29-3), cobalt unit (Gamma Knife), or protons. The use of SRS is limited to smaller tumors (<4 cm in diameter) that are 2 mm to 5 mm away from the optic apparatus.

Given the success of SRS in treating pituitary tumors, fractionated irradiation with highly conformal fields is being used more frequently for patients who are not ideal candidates for SRS or in centers that do not have access to SRS. The use of relocatable frames and precision thermoplastic masks and the daily verification of proper positioning before treatment have replaced conventional fractionated approaches at most centers. This precision allows for sparing of more normal brain tissue. As a result, the treatment margin around the tumor can be decreased to 3 mm to 5 mm. Minniti et al[76] reviewed the results of eight studies with 490 patients with functioning or nonfunctioning pituitary adenomas treated with stereotactic conformal radiotherapy. With a median follow-up of 39 months, tumor control was 98%. More recently, Kim reported 7-year PFS and disease-specific survivals (DSS) of 97.1% and 100%, respectively, for patients undergoing fractionated stereotactic radiation therapy.[194] The preliminary results suggest that conformal radiation techniques are equivalent to those of conventional radiation therapy, with significantly smaller brain volumes being irradiated, and in particular, with much lower doses to the temporal lobes. The potential difference in biologic effectiveness of SRS versus fractionated courses has not been tested in a prospective manner.

Treatment Morbidity

Both SRS and fractionated radiation therapy are well tolerated during and shortly following the course of treatment. Some patients undergoing fractionated irradiation may experience

temporary alopecia, fatigue, skin erythema, and headaches. Worsening of vision or other cranial nerve deficits during radiation therapy is uncommon. Patients undergoing frame-based SRS may notice headache, temporary tenderness and numbness of the pin sites, and fatigue. Because the treatment volumes with SRS are generally smaller compared with those of EBRT, the side effects are generally less for patients undergoing SRS. Unfortunately, no prospective trials have compared SRS with radiation therapy with regard to acute and long-term side effects. Unlike patients with some brain tumors, patients with pituitary tumors need to be followed for long periods of time because these tumors can recur 20 years or longer after primary treatment has been completed.

The most commonly reported long-term side effect from SRS and fractionated EBRT is hypopituitarism, and in particular hypothyroidism, which occurs in 30% to 80% of patients within 10 years after treatment. The cause for hypopituitarism (damage to the hypothalamus versus damage to the pituitary) is an area of debate.[195] Dosimetric data suggest that minimizing radiation dose to the pituitary and to the hypothalamus may reduce the incidence of radiation-associated hypopituitarism.[196] The risk of developing hypopituitarism following radiosurgery is lowered when the mean radiation dose to pituitary is kept below 15 Gy and the dose to the distal infundibulum is kept below 17 Gy.[197]

For patients undergoing conventional EBRT with older irradiation techniques, the incidence of optic neuropathy is 1% to 3% and the risk of radiation necrosis is 0% to 2%.[198,199] Fractionated radiation is associated with a low risk for optic pathway injury with estimate incidence of 0.8% to 1.3% at 10 years and 1.5% at 20 years.[96,200] A review of 34 studies of SRS for pituitary adenomas reported a 1% risk of decrease in visual acuity and a 1.3% risk for other cranial nerve neuropathies (trigeminal, oculomotor, trochlear, or abducens nerve) after SRS.[75] The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) report recommends optic chiasm dose tolerance ranges from 8 Gy to 10 Gy for single fraction and 55 Gy to 60 Gy for conventional fractionation.[201] If radiation-induced optic neuropathy occurs, it usually presents as painless vision loss within the first 3 years of treatment. Using modern radiation approaches and MRI-based planning, the risk for radiation necrosis and optic neuropathy should be 1% or less when using doses of 45 Gy in 25 fractions.

Vascular complications can also occur following EBRT and SRS although the risk of stroke is an area of debate. An increased incidence for cerebrovascular accidents has been reported for patients undergoing radiation therapy, although the relative contribution from irradiation remained to be determined.[202,203] The risk of injury to the cavernous portion of the carotid artery is low, with only a few case reports published.[204] Recently, 462 pituitary adenoma patients (236 of whom received radiotherapy) treated with surgery as primary therapy between 1959 and 2008 at the University Medical Center Groningen in The Netherlands were studied regarding the incidence of stroke.[205] The comparison of events was therefore between the two groups of patients with pituitary adenoma, treated with or without radiotherapy. Postoperative radiotherapy, mostly 45 Gy in 25 fractions, was not associated with an increased incidence of stroke (5.5% versus 5.3%, $p = 0.23$) or differences in causative mechanism or anatomic localization of stroke compared with surgery alone even though the follow-up was more than twice as long for the patients who had been irradiated. Preexisting coronary or peripheral artery disease was the primary stroke risk factors.

The effect of irradiation on neurocognitive status is not clear given the effects of other therapies, such as medications and surgery, and of the tumor.[206] It appears that patients who underwent surgery before radiation therapy may be at a higher risk for cognitive deficits.[207,208] A large study investigating radiotherapy effects on cognition,[209] noted a significant worsening in anterograde memory performance when comparing healthy controls to those with pituitary tumors treated with surgery or radiotherapy. This study showed that although treated pituitary tumors in general were associated with worsening memory, there was no significant difference when comparing the surgery and radiotherapy treatment groups.

Patients undergoing radiation therapy or SRS are at higher risk for secondary brain tumors. Brada reported that the cumulative risk for developing meningiomas and gliomas after the treatment of pituitary adenoma at 20 years is 2%.[210] An update from the Royal Marsden Hospital reviewed 426 pituitary adenoma patients treated with radiotherapy after resection and found a cumulative risk of second brain tumors of 2% at 10 years and 2.4% at 20 years with 12 years median follow-up.[211] Because the risk of second brain tumors may also be higher in patients with pituitary adenomas than the general population, estimating the relative risk of second brain tumors compared to general population may be flawed. Loeffler et al[212] reported on two patients with pituitary adenomas who developed new tumors following SRS. He concluded that the risk for new tumors after SRS appears to be significantly less than that after fractionated EBRT. Another study of 5000 Gamma Knife SRS patients followed for more than 10 years reported no increased risk of malignant disease.[213]

TREATMENT ALGORITHMS, CHALLENGES, CONTROVERSIES, FUTURE POSSIBILITIES, AND CLINICAL TRIALS

The optimal management of pituitary neoplasms requires a multidisciplinary and individualized approach because these tumors are diverse, are associated with morbidity and mortality, and present a challenge regarding the best treatment approach. Because the treatment management strategy varies depending on a number of factors, including the type of tumor (secreting tumor versus nonsecreting tumor), the imaging characteristics, and the clinical presentation and symptoms, a multidisciplinary approach ensures that the most effective therapy is being considered for each patient (see treatment algorithm by the five specific tumor types within prior section). Because surgical treatment, medical therapy, and radiation treatment options can be effective options, choosing the optimal treatment for an individual patient may be controversial and challenging. The patient's age, medical condition, compliance with medicine, treatment tolerance, and preference should also influence the decision, as should an assessment of the potential long-term effects of hypopituitarism on excess morbidity and mortality.[50] Close collaboration among the various disciplines is necessary for comprehensive long-term care. Clinical findings, endocrine evaluation, and MRI findings can establish the diagnosis of pituitary tumors in most patients and help define the initial treatment decisions.

Laboratory investigations and pituitary imaging provide detailed information concerning endocrine dysfunctions and anatomic relationships of pituitary tumors. Sophisticated surgical approaches and irradiation techniques provide safe and successful treatment of patients with pituitary adenomas. Pathobiologic assessments of pituitary tumors are yielding new insights into the genetic and molecular biologic makeup of these tumors and may help to predict which tumors are at higher risk for recurrence.

Because proponents exist for both SRS and fractionated EBRT, prospective, randomized controlled trials are needed to help answer questions. In the future, radiation sensitizers or combinations of medicines with radiation therapy may help

to improve the therapeutic ratio and decrease the latency of response, which would allow irradiation to become a more valuable treatment option.

CRANIOPHARYNGIOMA

Craniopharyngiomas are histologically benign neuroepithelial tumors that are postulated to arise from the hypophyseal duct or Rathke's pouch, or its remnants in the adult. They comprise 5% to 10% of pediatric and 1% to 4% of adult brain tumors and have a bimodal distribution with peak rates at childhood (5 year to 14 years) and older adulthood (50 year to 74 years).[214] Although these tumors are generally slow growing, circumscribed, and encapsulated, the frequent involvement of structures such as the pituitary stalk, hypothalamus, adjacent basal vasculature, and optic apparatus complicates their management.[215]

A large number of treatment modalities are used including GTR, limited surgery followed by radiation therapy, SRS, and intracystic radiotherapy and chemotherapy. In 1997, the 5-year survival rate was estimated at 80% and decreased with older age at diagnosis.[216] From more modern series, for adults treated with surgery and radiotherapy, the 5- and 10-year PFS rates were 85% and 69%, and cause-specific survival (CSS) rates were 88 and 88%, respectively.[217] In the pediatric population, a review of modern studies demonstrates a 5-year disease control of at least 90%.[218]

Treatment

Typical upfront management consists of either GTR or limited surgery followed by adjuvant radiotherapy. The timing of radiotherapy remains controversial and some series have demonstrated good salvage with radiotherapy at the time of progression.[227,228] Aggressive surgical resection can result in excellent long-term control and survival but can also be associated with significant morbidity including hypothalamic dysfunction, optic pathway damage, frontal lobe executive function damage, and rarely, mortality.[217] Surgical series demonstrate 10-year overall survival (OS) ranging from 85% to 92% and 10-year local control ranging from 42% to 81% depending on extent of tumor removed and whether radiotherapy was given.[227,228]

Radiotherapy

The group at Princess Margaret Hospital (PMH) reported their long-term follow-up results in 53 adult patients treated with surgery and radiotherapy (median dose 50 Gy in 25 fractions).[217] The 5- and 10-year PFS rates were 85% and 69%, OS rates were 76% and 70%, and CSS rates were 88% and 88%, respectively.

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The long-term morbidity associated with this disease and its treatments includes hypopituitarism, increased cardiovascular risk, hypothalamic damage, visual and neurological deficits, reduction in quality of life, cognitive and behavioral function, vasculopathies, and secondary malignancies.

Biologic Characteristics and Pathology

The two major histopathologic subtypes of craniopharyngioma are adamantinomatous and papillary. The papillary subtype is also referred to as squamous papillary and comprises 11% to 14% of all craniopharyngiomas and is only seen in adults.[219,220] Papillary craniopharyngiomas appear similar to Rathke cleft cysts that have undergone squamous differentiation and consist of mature squamous epithelium and pseudopapillae.[221] Macroscopically, they can have a combination of solid and cystic components. The cysts tend to contain a yellowish fluid. There is no evidence for a distinct mutation in this subtype.[222]

Adamantinomatous tumors are a more frequently observed subtype and are most commonly associated with childhood disease, although they can be seen across the age spectrum.[223] These tumors likely arise from the transformation of embryonic rests during the development and involution of the Rathke's pouch.[222] They also have solid and cystic components. A distinct feature includes dark brown to black fluid within the cysts related to cholesterol crystal deposition; it is often described as having an appearance and consistency similar to motor oil (or "crank-case oil"). More often than the papillary subtype, these tumors also contain calcification and tend to be more adherent to neighboring structures. Microscopically, they demonstrate Rosenthal fiber formation, nodules of wet keratin, a palisading basal layer of cells and intense surrounding gliosis.[223] Animal models have demonstrated a distinct relationship between aberrant Wnt/β-catenin pathway signaling in the pathogenesis of adamantinomatous craniopharyngioma.[224] In humans, some patients with adamantinomatous craniopharyngiomas also present with alterations of the β-catenin gene, CTNNB1, which alters intracellular levels of β-catenin, leading to accumulation of its unphosphorylated form, which is subsequently translocated to the nucleus, where it binds with transcription factors such as c-myc and cyclin D1, leading to oncogenesis.[222] This knowledge may lead to targeted therapies for adamantinomatous histology.

Anatomy and Pathways of Spread

Craniopharyngiomas are typically suprasellar in location although other rare presentations have been documented. They can be divided into prechiasmal and retrochiasmal because these locations may dictate the presenting symptoms. They can appear well encapsulated on gross examination but can be locally aggressive causing an intense glial reaction on adjacent brain. As these tumor grow they can compress adjacent structures including the pituitary and hypothalamic region, chiasm, and third ventricle, and if large the surrounding cerebral hemispheres and posterior fossa. The formation of multiple cysts is characteristic of these tumors.

Clinical Manifestations, Patient Evaluation, and Staging

Patients present with symptoms related to the surrounding structures mentioned previously. These include headaches, visual field cuts, decline in visual acuity, and hormonal abnormalities (including antidiuretic and GH insufficiency, amenorrhea, impotence, and galactorrhea).

Imaging

Craniopharyngiomas are common tumors located in the suprasellar region. Contrast enhancement, cyst formation, and calcification are the three characteristic features of craniopharyngiomas on CT. More than 90% of suprasellar craniopharyngiomas exhibit at least two of these three features, thus providing easy radiologic detection.[225] Of note the squamous papillary subtype is less likely to demonstrate calcifications on imaging. MRI typically demonstrates a hyperintense abnormality on T1-weighted images, which differentiates craniopharyngioma from Rathke's cleft and tumor cysts. Upon contrast administration, both the solid and cystic components typically enhance. CT and MRI have complementary roles in achieving the diagnosis and understanding the extent of the craniopharyngioma.[226] In addition to obtaining baseline CT and MRI with and without contrast, patients should also undergo baseline endocrine and ophthalmologic evaluations.

In the PMH series, age (<53 or ≥53) was found to be prognostic factor for OS and CSS and multiple surgeries were associated with worse PFS. The timing of radiotherapy had no prognostic significance. New endocrinopathies and visual dysfunction were observed in 53% and 17% of patients after surgery, and in 11% and 6% after radiotherapy, respectively. Unfortunately, no prospective data evaluating the role of radiotherapy in adult patients with craniopharyngioma exists.

Prospective data from 28 pediatric patients treated with three-dimensional (3D) conformal radiotherapy using a 1-cm clinical tumor volume (CTV) margin at St Jude demonstrated a 3-year PFS rate of 90.3%.[229] Review of the available outcomes for pediatric patients treated with surgery and radiotherapy demonstrates poorer cognitive outcome for patients younger than 7.4 years, long duration of prediagnosis symptoms, more extensive surgery, multiple surgical procedures, and diabetes insipidus. The percentage of total brain, supratentorial brain, or left temporal lobe volumes receiving a dose in excess of 45 Gy had a significant impact on longitudinal IQ.

Irradiation Techniques and Tolerance

Surgical decompression should be considered before radiotherapy. Fractionated radiotherapy typically consists of doses of 54 Gy given at 1.8 Gy per fraction. Conformal radiotherapy including 3D-CRT or IMRT should be considered given the proximity of these tumors to critical normal structures. A range of CTV margins from 2 cm down to 5 mm have been used. Cyst expansion can occur during radiotherapy, and therefore the smaller CTV margin should be used in the setting of surveillance MRIs throughout therapy to ensure target coverage.[230]

SRS can be considered for these tumors. A retrospective report from Pakistan used SRS to treat 35 patients (17 children and 18 adults) with craniopharyngioma.[231] The prescription dose ranged from 8 Gy to 14 Gy resulting in 88.5% tumor control rate at a mean follow-up of 22 months. A multimodality treatment approach including stereotactic drainage and intracystic bleomycin followed by SRS with a mean dose of 10.8 Gy ± 8.7 Gy demonstrated good response for patients with monocystic and small tumors, but progression occurred in most patients with large multicystic targets.[232] A retrospective review of 222 benign skull-based tumors (including 7 with craniopharyngioma) treated with Gamma Knife SRS estimated the long-term risk (mean clinical follow-up of 83 months) of radiation-induced optic neuropathy (RION): the chance of RION according to the maximum radiation dose received by the anterior visual pathway was 0% for patients receiving ≤8 Gy, 8.1 Gy to 10.0 Gy, 10.1 Gy to 12.0 Gy, and 10% for those receiving >12 Gy.[233]

Proton therapy has been used for these tumors both as the only treatment and as an adjunct to photon therapy.[234-237] Dosimetric comparative studies demonstrate the possibility of reduced whole-brain and whole-body radiotherapy doses when compared to modern photon-IMRT.[238] When considering proton therapy, monitoring for changes in tumor, and especially cyst anatomy during treatment remains important with one report describing intervention needed in 6 out of 17 children because of changes in the tumor.[235] A retrospective evaluation of quality of life and executive function following surgery and proton therapy demonstrates a high incidence of depression and decline in executive function in this population.[234]

Cystic craniopharyngiomas may be treated with intracystic phosphorus-32 (^{32}P), which has been used for many decades.[239-241] To deliver ^{32}P, the cyst volume is estimated to determine the amount of P32 necessary to deliver 200 Gy to 250 Gy to the cyst wall. A cannula is placed into the cyst stereotactically and 1 cc of fluid is removed. ^{32}P is instilled thorough the cannula with 0.2 cc of saline to flush the cannula. Patients are typically admitted overnight for observation. This technique results in good control of the treated cyst with a reported 5-year freedom from progression of 86%.[242] However, the 5-year freedom from progression outside of the treated cyst was only 54.5%. Overall freedom from progression was 45.6% at 5 years. Ten percent of these patients developed permanent deterioration of vision, attributed to tumor progression. Hasegawa et al reported that 23% patients experienced worsened visual function after intracystic ^{32}P. Although some vision loss was felt to be as a result of tumor progression, a few of these patients were felt to be related to radiation.[241] Because ^{32}P only treats the cyst and not the entire tumor, the use of ^{32}P has been described in combination with EBRT and SRS.[243,244]

Conclusions

Craniopharyngioma, although histologically benign, can be difficult to treat because of location, which makes a GTR difficult without morbidities. Radiation can help control disease that is not completely resected, with outcomes that may be favorable to a GTR by limiting the toxicities of treatment. These toxicities have implications on vision, growth, and cognitive development and need to be factored when choosing primary treatment. SRS can be considered in select cases when there is good separation of the optic pathway and the tumor. Recurrence is difficult to treat because many of these patients have already received radiation. SRS, intracystic bleomycin, and intracystic ^{32}P may be considered for recurrence. Future directions include targeted therapies, particularly for lesions where specific targetable alterations can be identified.

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