Pituitary Adenoma

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Learning Objectives

- Learn the epidemiology, risk factors, genetics, presentation, and treatment paradigms associated with pituitary adenomas.
- Understand the diagnosis and appropriate workup for pituitary adenomas with imaging, pathology, and labs.
- Know the appropriate medical, surgical, and radiotherapeutic management for both nonfunctioning and functioning pituitary adenomas.
- Recognize indications for various radiotherapy approaches including fractionated radiation or stereotactic radiosurgery.
- Learn appropriate target volumes and doses for both stereotactic radiosurgery and stereotactic fractionated radiation therapy for nonfunctioning and functioning pituitary adenomas.
- Know the local control rates, hormone normalization rates, and side effects associated with treating pituitary adenomas with radiation therapy.

Epidemiology

Pituitary adenomas account for 16% of all brain tumors diagnosed in the United States (USA), making it the second most common brain tumor in adults. With an average of 11,733 new pituitary adenomas diagnosed annually, the incidence is estimated at 3.66 per 100,000 [1]. The incidence increases with age, peaking in the seventh and eighth decade, and is slightly more common in women than men and African-Americans than Caucasians [2]. Clinically nonfunctioning pituitary adenomas account for 25–30% of pituitary adenomas, of which 80–90% arise from gonadotropic cells. Functioning or secreting adenomas oversecrete a hormone normally produced by the pituitary gland and comprise the remaining 70–75%, with prolactinomas being the most common. Prolactinomas (PRL) account for approximately 32–51% of pituitary adenomas, followed by growth hormone (GH)-secreting adenomas (9–11%) and adrenocorticotropic hormone (ACTH)-secreting adenomas (3–6%.) Less than 1% of pituitary adenomas are thyroid-stimulating secreting or gonadotropin secreting [3].

The etiology of pituitary adenomas is largely unknown. Although studies have examined associations between pituitary adenoma and factors such as cigarette smoking, past diagnosis of head trauma, or prior brain neoplasms, no causal relationship has been identified [4]. There is no successful prevention of, or screening for, pituitary adenomas.

Approximately 60% of pituitary adenomas occur sporadically with no known genetic predisposition. Somatic mutations, including mutations in GNAS, USP8, PIK3CA, and complex I genes, account for almost 40% of pituitary adenomas. Germline mutations and mosaic mutations account for the rest of pituitary adenoma mutations. The most notable germline mutations include a mutation in the MEN1 gene causing multiple endocrine neoplasia type 1 (MEN1). This is associated with the classic triad of parathyroid tumors, pancreatic/gastrointestinal adenomas, and pituitary adenomas. The other mutation is the NF1 gene causing neurofibromatosis type 1 (NF1) which is associated with café-au-lait macules, neurofibromas, freckling, and other clinical features. Mosaic mutations include GNAS and GPR101 [5]. However, underlying genetic mutations do not affect management of pituitary adenomas.

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Diagnosis and Prognosis

Early detection and treatment of pituitary adenomas are important. A normal pituitary gland is typically 8 millimeter (mm) by 10 mm by 6–8 mm anterior-posterior, transverse, and cranial-caudal, respectively. Pituitary adenomas that are detected incidentally on imaging studies are often termed incidentalomas and can occur in upward of 20% of CT scans and 38% of MRI scans [6, 7]. If not caught incidentally, nonfunctioning pituitary adenomas often go undiagnosed until they are large enough to cause clinical symptoms due to mass effect. These patients will most commonly present with visual symptoms including loss of temporal fields due to compression of the optic chiasm, followed by headaches and hypopituitarism [8]. Patients with secreting pituitary adenomas present with clinical findings related to hypersecretion of hormones. Prolactin-secreting tumors can cause galactorrhea and hypogonadotropic hypogonadism manifesting as amenorrhea and infertility in females and decreased libido, impotence, infertility, and gynecomastia in men. Growth hormone-secreting adenomas cause acromegaly with clinical findings of coarse facial features including macrognathia, furrowing of the forehead, and enlargement of the nose and ears. In children, gigantism can occur [9]. Adrenocorticotropic hormone-secreting adenomas can cause Cushing's disease with clinical symptoms of central obesity, abdominal stria, buffalo hump, and moon facies. Thyrotropin adenomas can cause signs of hyperthyroidism including warm skin, onycholysis, weight loss, agitation, and urinary frequency [3].

The workup for a suspected pituitary adenoma should include a detailed history and physical examination, referral to an endocrinologist for hormone evaluation and a neuro-ophthalmologist for visual field testing, and pituitary imaging. Hormonal evaluation should include measurements of serum prolactin, insulin-like growth factor-1 (IGF-1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), alpha subunit, thyrotropin-releasing hormone (TRH) when available (currently not available in the US), and a 24-h urine free cortisol measurement.

Magnetic resonance imaging is the most sensitive imaging modality for pituitary adenomas. A dynamic MRI with fat suppression with and without contrast in axial, coronal, and sagittal views should be obtained to evaluate the extent of disease (Fig. 2.1). Thin slices less than 3 mm are recommended as false-negative rates as high as 45–62% have been associated with conventional T1 MR imaging [10]. Pituitary adenomas generally enhance more slowly than the adjacent pituitary and thus will be relatively hypointense compared to the intensely enhancing pituitary gland. Pituitary adenomas are difficult to diagnosis on CT as two-thirds are hypodense on contrast-enhanced images. It is important to try to distinguish pituitary adenomas from other sellar lesions including other tumors such as craniopharyngioma, meningioma, chordoma, primary lymphoma, germ cell tumor, and metastatic disease, as well as other findings in the sella-like Rathke's cleft cyst, infiltrative diseases such as granulomas, lymphocytic hypophysitis and tuberculosis, and inflammatory lesions [10].

The majority of pituitary adenomas are benign neoplasms of adenohypophysial cell origin that do not invade nearby structures or spread systemically. However, there is a spectrum of pituitary neoplasms from benign to malignant. Up to 25% of pituitary adenomas infiltrate and actively invade surrounding sellar structures and may clinically behave more aggressively. Pathologically these tumors show signs of increased proliferation and aggressiveness. Typical pituitary adenomas do not demonstrate mitoses on histology, have low ki-67 labeling indices, and show minimal p53 immunoreactivity and no invasion into other structures, although microscopic dural invasion is common and is not considered an atypical feature. Pituitary adenomas that show signs of increased proliferation rate, invasion, and aggressiveness are termed atypical pituitary adenomas. Distinguishing a typical pituitary adenoma from an atypical pituitary adenoma is not clearly defined. The WHO classification system designates atypical pituitary adenomas as having any of the following features: elevated mitotic count, ki-67 labeling indices >3%, extensive nuclear staining for p53, or invasion into other structures. However, the required degree of increased mitotic count or extensive p53 immunoreactivity is not clearly defined. If metastases are present or the pituitary neoplasm has spread to the cerebrospinal fluid (CSF), it is considered a pituitary carcinoma. Less than 1% of pituitary tumors are pituitary carcinomas [11].

The normal pituitary gland is composed of small acinic cells surrounded by intact reticulin. In cases of pituitary hyperplasia, the reticulin stays intact, while the acini are increased in size. Histologically the hallmark appearance of pituitary adenomas is the monotonous and monomorphous proliferation of neoplastic cells that replaces the normal acinar pattern of the pituitary and disrupts the reticulin fiber (WHO classification). Synaptophysin is consistently positive in pituitary adenomas with a lower percentage immunostaining positive for chromogranin A and low molecular weight keratins. Immunoreactivity for GH, PRL, β-TSH, β-FSH, β-LH, ACTH, and alpha subunit of the glycoproteins (α-SU) aids in pituitary adenoma classification [11].

Pituitary adenomas are now classified by looking at functional characteristics including histology, immunohistochemistry, and ultrastructural features as well as looking at biochemical hormone production, imaging, and surgical features [12]. Functioning pituitary adenomas include GH,

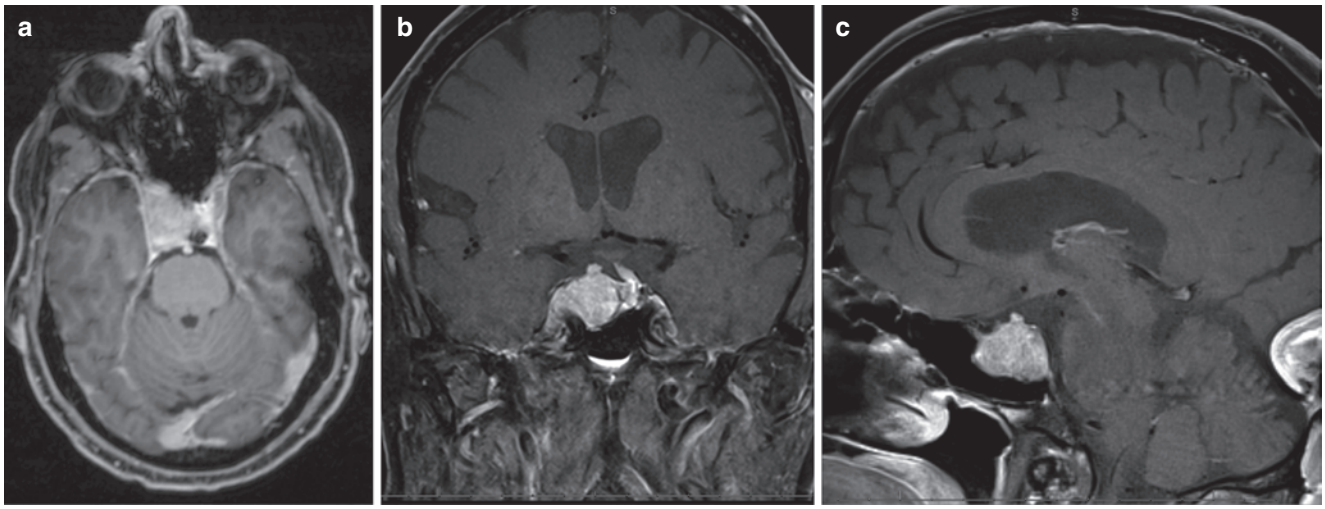

Fig. 2.1 A fine slice T1 MRI with fat suppression showing the pituitary adenoma within the right sella that extended into the right sphenoid sinuses and posterior clinoid process and displaced the pituitary stalk and pituitary tissue to the left. Views are obtained in the axial (**a**), coronal (**b**), and sagittal (**c**) plane prior to radiation therapy

PRL, thyroid-stimulating hormone (TSH), ACTH, and gonadotropin-producing adenomas; however, most gonadotropin-producing adenomas are classified as nonfunctioning pituitary adenomas. Pituitary adenomas do not always secrete just one hormone; mixed adenomas can occur as well. Plurihormonal adenomas have immunoreactivities for more than one pituitary hormone, and their cytophysiology and developmental mechanisms do not explain their immunoreactivities making them unusual. These do not include common combinations of mixed secreting adenomas like GH, PRL, and TSH or FHS and LH. Nonfunctioning pituitary adenomas are largely composed of gonadotropin adenomas but also include null cell adenomas where no hormone immunoreactivity and no other immunohistochemical or ultrastructural markers of specific adenohypophysial cell differentiation are detected [11].

Pituitary adenomas are often characterized by size with microadenomas being <1 cm and macroadenomas ≥1 cm. One of the most common classification systems initially established by Hardy and later updated by Wilson grades pituitary adenomas on extension and invasion into the sella and sphenoid sinus [13]. Grade 0 has no abnormality of the sphenoid bone, grade I is a normal or focally expanded sella with tumor ≤1 cm, grade II is an enlarged sella with tumor >1 cm, grade III is a localized perforation of the sellar floor, grade IV is a diffuse destruction of the sellar floor, and grade V is spread into the CSF or blood. The extension into the suprasellar region is type A, extension to the anterior recesses of the third ventricle is type B, extension into the whole anterior third ventricle is type C, extension into the intracranial extradural is type D, and extracranial extradural extension is type E [13]. Parasellar extension is also often assessed using a radiographic grading system that looks at the extension of the adenoma into the cavernous sinus in association with the internal carotid artery. These grading systems can assist in surgical planning and determination of the feasibility of resection [14]. The initial grading system proposed in 1993 has more recently been updated to further subdivide the grading system by surgical validation with an endoscopic transnasal transsphenoidal approach [15].

Histologically, pituitary adenomas have been considered benign tumors; however, there is an increased risk of mortality with pituitary adenomas due to mass effect on vascular structures and hormonal imbalances. In nonfunctioning adenomas an increase in mortality has been estimated to be as high as 1.7 (95% confidence interval (CI) 1.34–2.15) compared to the endemic rate, mainly due to hypopituitarism [16]. With secreting pituitary adenomas, if left undiagnosed, there is a significant reduction in life expectancy. Growth hormone-secreting tumors can cause acromegaly. A two- to threefold increased risk of mortality has been demonstrated in patients with acromegaly compared with age- and sex-matched controls [17]. An oversecretion of ACTH can lead to hypercortisolism causing Cushing's disease. If left untreated, Cushing's disease has a median survival of around 5 years [16].

Overall Treatment Strategy

The management of pituitary adenomas often involves a multimodality approach. An endocrinologist, neurosurgeon, otorhinolaryngologist, radiation oncologist, neuroradiologist, neuro-ophthalmologist, and neuropathologist should be

involved in each case. In general, the overall goals of treatment are to preserve or restore normal hormonal function and remove or control any mass effect from the tumor that may be causing neurological or hormonal symptoms. Management can range from observation to a multimodality approach with surgery, radiation therapy, and medical management. Specific treatment recommendations are largely based on the type of pituitary adenoma and extent of disease.

Nonfunctioning "incidentalomas" should undergo a complete workup that includes laboratory evaluation for hormonal hypersecretion or hypopituitarism, appropriate pituitary imaging, and a visual field examination if it is near or abutting the optic chiasm. If there are no signs of visual field deficits, other neurological sequelae, or hormonal imbalances, observation is the recommended management strategy. Those that are less than 1 cm are often managed with close observation. Repeat MRI scans and possible visual field and hormonal evaluation can be performed annually. Many slow-growing tumors may never need further treatment.

The advent of transsphenoidal surgery has provided a less invasive first-line surgical option for many pituitary adenomas that are not appropriate for observation. A transsphenoidal resection can be completed either endoscopically or microscopically through a transnasal, sublabial, transethmoidal, or transantral approach [18]. In cases where there is intracranial extension or a transsphenoidal surgery is not applicable, then a transcranial approach may be used.

In nonfunctioning pituitary adenomas, tumor recurrence/progression has been estimated to be between 10% and 20% after a gross total resection (GTR) and 50% and 60% after a subtotal resection (STR) [19]. With functional pituitary adenomas in the hands of experienced neurosurgeons, GH-secreting adenomas have been found to have normalization of IGF-1 levels in 80–90% of microadenomas and 50% of macroadenomas [20]. In Cushing's disease, surgery has been associated with a 69–98% remission rate but a 3–17% relapse rate. Many studies reporting surgical remission rates of TSH-secreting pituitary adenomas have been poor; however, more recently remission rates with surgical resection have been reported to be as high as 100% for microadenomas and 81% for macroadenomas [21]. Surgery can be a second-line treatment for prolactinomas in those that do not tolerate medical therapy, are unresponsive, and develop visual deficits or for women desiring pregnancy. Surgical resection of prolactinomas has been reported to have curative rates in 74% of microadenomas and 33.9% of macroadenomas [22]. General surgical complications may include bleeding, infection, and thrombosis. Other complications may include CSF leak; damage to surrounding structures including the internal carotid artery, chiasm, and optic nerve; and abnormal secretion of one or more pituitary hormones resulting in symptoms such as diabetes insipidus from decreased antidiuretic hormone (ADH) production and death.

Medical management is the first-line treatment for prolactinomas and often used as adjuvant treatment after surgical resection and radiation therapy for secreting pituitary adenomas if hormonal levels do not normalize. Dopamine is a neuroendocrine inhibitor for secretion of prolactin in the pituitary. A dopamine agonist like bromocriptine or cabergoline has been shown to rapidly normalize prolactin levels and reduce tumor size in 80–90% of patients with prolactinomas [23]. Octreotide and lanreotide are somatostatin analogs that can be used in GH-secreting tumors to lower elevated GH levels before surgery, normalize levels in the latency period after radiation therapy, or treat patients that are not candidates for surgery and/or radiation therapy due to medical comorbidities. Insulin-like growth factor type 1 levels have been shown to decrease in 50–79% of patients and lead to tumor shrinkage in 40–73% patients receiving somatostatin analogs [22]. Growth hormone receptor antagonists like pegvisomant and dopamine analogs, as mentioned above, can also be used to treat acromegaly and aid in normalizing IGF-1 levels. Dopamine agonist and somatostatin analogs have also been found to normalize TSH levels in 79% of patients with TSH hypersecretion [24]. Medical management of ACTH-secreting adenomas is only provided in those that do not have remission after surgical resection and radiation therapy. Medications that inhibit steroidogenesis such as ketoconazole, aminoglutethimide, metyrapone, mitotane, and etomidate can but used for the treatment of persistent ACTH-secreting adenomas [25].

Hypopituitarism resulting from surgical treatment, radiation therapy, or tumor is best managed by an endocrinologist. Treatment may include glucocorticoid replacement with hydrocortisone, thyroid replacement with L-thyroxine, GH replacement in those found to be deficient, and testosterone and estrogen replacement if needed [26].

Although the first-line treatment of pituitary adenomas is typically surgery or medical management, radiation therapy, both fractionated radiation and SRS, can be used in the management of pituitary adenomas. The next sections will discuss in detail the indications, treatment, complications, and outcomes for the treatment of pituitary adenomas with radiation therapy.

Indications for Radiotherapy

After maximal safe resection, indications for radiation therapy include subtotal surgical resection, recurrent or progressive tumors, hormone refractory disease, and atypical or carcinoma histologies. Hormone normalization and control of tumor growth are the main goals of radiation therapy for functioning adenomas, whereas in nonfunctioning adenomas the primary goal is tumor control. Due to high recurrence rates after a subtotal resection, postoperative radiation therapy is often recommended. However, the timing of postop-

erative radiation therapy is controversial with some advocating for treatment immediately after the surgery (within 6 months) and others favoring delayed radiotherapy (>6 month or at time of progression). Studies have shown mixed results on control rates and long-term toxicity [19, 27, 28]. Fractionated radiation therapy or SRS after a subtotal resection or debulking surgery can provide excellent local control rates. For atypical pituitary adenomas, there is little data on whether radiation therapy should be administered immediately after surgery or at the first signs of progression. In cases of atypical pituitary adenomas, it is best to assess all clinical data available and weigh the risks of toxicities associated with radiation therapy to the risks associated if the tumor progresses. A lower threshold for radiation therapy treatment should be applied for atypical pituitary adenomas compared to classic pituitary adenomas.

Treatment Field Design/Target Delineation

Advances in radiation therapy techniques have greatly improved the therapeutic ratio for treatment of pituitary adenomas. Historically, these were treated with opposed laterals or a 3-field technique that delivered large doses of radiation to the temporal and frontal lobes. Advances in radiation delivery systems and the development of stereotactic localization have greatly improved treatment of skull-based tumors. Creating an optimal target volume requires adequate visualization of the pituitary adenoma. This is best obtained with a T1 MRI sequence through the skull base with 1 mm slice thickness. A pre- and post-contrast T1 MRI as well as fat suppression can be helpful in distinguishing post-op changes from residual blood products and fat-packing from the residual tumor. Since the pituitary is located in the sella adjacent to the optic nerves and chiasm, stereotactic localization and image guidance are recommended to allow for precise treatment to the tumor.

When stereotactic localization is used, treatment margins around the tumor can be reduced. A thin slice T1 post-contrast MRI should be fused with the simulation CT scan and used to define the lesion to create the gross tumor volume (GTV) (Fig. 2.2). The CT simulation scan should have slices <3 mm. As pituitary adenomas are typically not infiltrative or invasive, no clinical target volume is needed; however, one may add a small 1–5 mm margin to encompass potential areas of microscopic spread in the cavernous sinus or other areas of concern. The stereotactic headframe originally developed for the Gamma Knife has long been known to

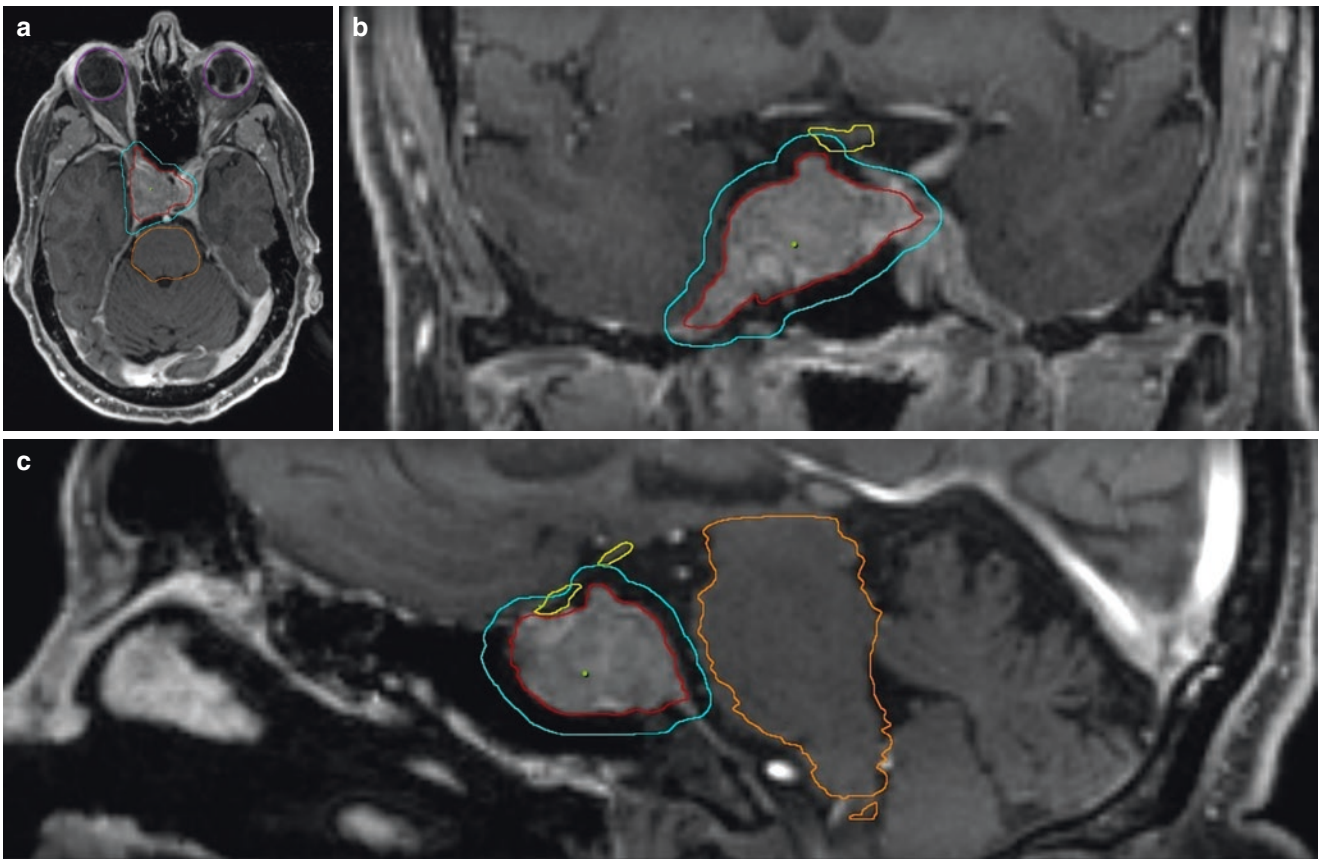

Fig. 2.2 Axial (**a**), coronal (**b**), and sagittal (**c**) views of the pituitary adenoma contoured to create the GTV followed by a 3 mm expansion to create the PTV. GTV, red; PTV, cyan; eyes, purple

have submillimeter accuracy [29]. A stereotactic frameless mask along with an image-guided system has been previously reported to obtain geometric accuracy of <0.5 mm [30]. Although up to a 2.8 mm displacement has been reported for fusions using soft tissue, the rigidity of the skull base allows for negligible deviations in position [31]. Due to the precision of setup, no planning treatment volume (PTV) is necessary for SRS. However, some centers may add a 1–3 mm expansion from GTV to PTV.

Due to the proximity of the pituitary to many critical structures, it is important to accurately contour organs at risk (OARs). In this region, OARs should include the optic nerves and chiasm, brainstem, pituitary stalk, and pituitary. Other OARs that could be contoured include the retina, lens, hypothalamus, cranial nerves (CN) within the cavernous sinus (CN III, IV, V1, V2, VI), retina, and hippocampus.

Radiation Dose Prescription and Organ at Risk Tolerances

For fractionated SRS, doses range from 45 to 50.4 Gy for nonfunctioning adenomas and 50.4 to 54 Gy for functioning adenomas delivered in 1.8 Gy daily fractions (Fig. 2.3). With SRS a dose of 15 Gy is commonly used for nonfunctioning adenomas and 20 Gy for functioning adenomas [32]. Higher doses of radiation therapy are required in secreting pituitary adenomas to obtain hormone normalization. A hypofractionated SRS course of 25 Gy in 5 fractions or 21 Gy in 3 fractions delivered over 5 and 3 days, respectively, is also an acceptable option for pituitary adenomas not meeting dose constraints for single-fraction treatment [33, 34].

Different treatment delivery systems may be used for SRS including Gamma Knife, LINAC-based, and CyberKnife™. Gamma Knife is a frame-based system that utilizes 192 radio-

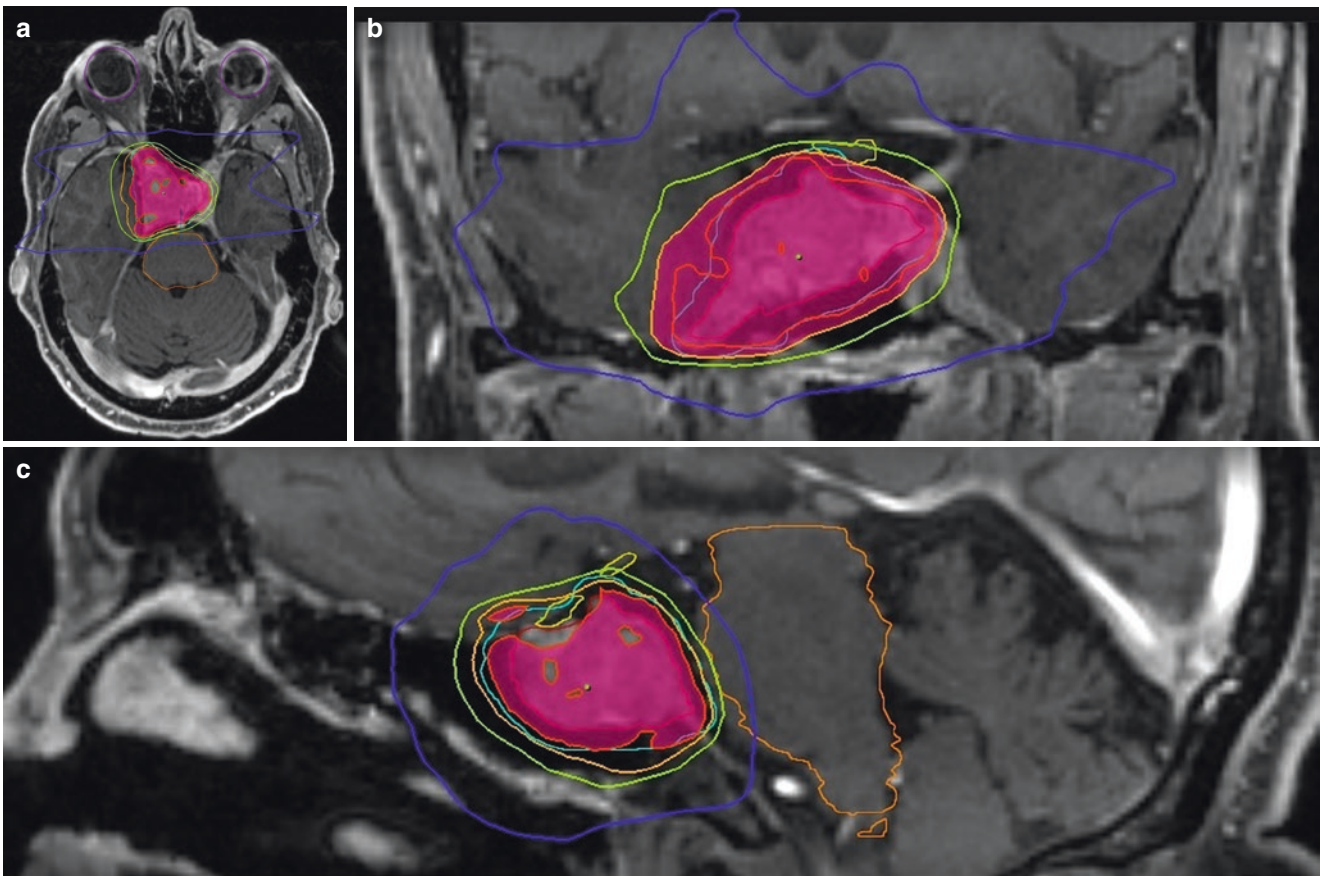

Fig. 2.3 Axial (**a**), coronal (**b**), and sagittal (**c**) views of a treatment plan with a dose of 50.4 Gy in 28 fractions prescribed to the 100% isodose line using an 11-field IMRT technique. Ninety-five percent of the dose is covering 99.4% of the PTV, and 95% of the PTV is covered by 99.2% of the dose (D95, 99.4%; V95, 99.2%). The GTV is covered by 97.7% of the dose, and 99.1% of the GTV is getting full dose (D100, 97.7%; V100, 99.1%). The isodose lines are as follows: 100% isodose line, orange; 95% isodose line line, light orange; 80% isodose line, lime green; 30% isodose line, purpur. The 100% coverage is represented by the pink fill

active cobalt-60 sources arranged in a conical shape to create multiple focal beam shots focused at the target. The dose is usually prescribed at the 50% isodose line to maximize the dose within the each pinpoint target and minimize dose at the target edge. A fixed frame or frameless mask can be used in a LINAC-based SRS system, and treatment is often delivered using multiple dynamic conformal arcs or intensity-modulated radiation therapy to focus the dose in the center of the target. CyberKnife™ is a robotic arm with a mobile linear accelerator that has a robotic image-guided system that allows for a frameless mask to be used with SRS. Each delivery method has its benefits and drawbacks with LINAC-based SRS being more homogeneous for large tumors and Gamma Knife providing better conformality with irregular lesions; yet, no one technique has been proven to be superior.

Complication Avoidance

In planning radiation therapy for pituitary adenomas, it is important to minimize dose to critical structures. Decreasing dose to the normal pituitary gland can avoid radiation-associated neuroendocrine deficits. Limiting the pituitary to a mean dose of ≤15 Gy has been found to decrease hypopituitarism when treating with SRS. It has also been suggested to decrease the infundibulum dose to a mean of ≤17 Gy [35]. It is also important to limit the dose to the optic apparatus. Classically, SRS has been not recommended for tumors within 3 mm of the optic apparatus as it is difficult to obtain enough dose to the tumor and meet the limitations of the optic apparatus. When dose constraints for perioptic tumors cannot be met, a fractionated or hypofractionated SRS course is recommended.

In general, for fractionated radiation therapy, OAR dose tolerances should include a maximum dose of 55 Gy to the optic nerve and chiasm, 54 Gy to the brainstem, 45 Gy to the retina, 7–8 Gy to the lenses, 50 Gy to the hypothalamus, a maximum of 50 Gy to the entire pituitary, and a mean of ≤45 Gy to the cochlea [36–38]. Tolerance doses of CN III, IV, V, VI, and VII are largely unknown but the recommended dose is ≤60 Gy. For SRS, the optic nerve should be limited to a maximum point dose of 10 Gy, the brainstem to a dose of 16 Gy, and the pituitary and distal infundibulum to a mean of ≤15 Gy, the cochlea to a mean dose of ≤3.7 Gy, CN VII ≤12.5–15 Gy, and CN V ≤12.5–13 Gy [35, 39]. Tolerance doses to CN III, IV, and VI are unknown but it is recommended these be kept as low as possible.

Radiation Toxicity: Acute and Late Effects

Fractionated radiation therapy and SRS are important treatment options for patients with pituitary adenomas; however, they are not without potential acute and long-term side effects. During fractionated radiation therapy, patients may experience temporary alopecia, skin erythema, fatigue, and headaches. It is uncommon to have more severe side effects like vision loss or other cranial nerve deficits. With frame-based SRS, acute side effects may include numbness, tenderness, and bleeding at the frame pin sites. Otherwise, there are minimal side effects associated with SRS, aside from a possible headache and fatigue.

Long-term toxicities include hypopituitarism, optic neuropathy and other cranial neuropathies of the cavernous sinus, radiation necrosis, neurocognitive effects, vascular complications, and secondary malignancies. Hypopituitarism is the most common long-term toxicity and estimated to occur in approximately half of patients undergoing radiation therapy [36]. Hypopituitarism prior to radiation therapy has not been found to be predictive for new or worsening endocrine deficits. The most common hormonal deficiencies after radiation therapy are thyroid and cortisol which can be supplemented with levothyroxine and hydrocortisone [40]. Whether the hypopituitarism is caused by damage to the pituitary, hypothalamus, or both is unknown [41]. As mentioned above minimizing dose to the normal pituitary gland with SRS to a mean of ≤15 Gy and the infundibulum to a mean of ≤17 Gy reduces rates of neuroendocrine deficits.

Another potential long-term toxicity with radiation therapy is optic neuropathy. Keeping the optic apparatus below a dose of 8 Gy has been regarded as extremely safe [42]; however, studies suggest point doses up to 10 Gy results in <2% risk of optic neuropathy [43]. Leber et al. reported no radiation-induced optic neuropathy in patients receiving SRS with a max point dose of <10 Gy and a 26.7% optic neuropathy rate for a point dose of 12–15 Gy [44]. Fractionated external beam radiation carries a very low risk of damage to the optic pathway with an estimated incidence of 0.8% at 10 years [45]. With a hypofractionated course of 5 Gy × 5 fractions, a median maximum chiasm dose of 23.3 Gy (range 18.3–25.1 Gy) was reported with no visual deficits [34]. Excellent results have also been reported for a course of 7 Gy × 3 fractions keeping the mean optic nerve dose to 16.7 Gy and the chiasm to 14.6 Gy [33].

Long-term cranial neuropathies of the cavernous sinus nerves are not common [35]. Newer series assessing SRS for pituitary adenomas have reported new cranial nerve deficits to be below 2% [46]. A dose association has not been found for cranial neuropathies in SRS [42]. Cranial neuropathies with fractionated radiation therapy rarely occur.

Other rare long-term toxicities with radiation therapy include radiation necrosis, vascular complications, and secondary malignancies. Radiation necrosis occurred in 13 of 1567 patients on a meta-analysis of SRS for pituitary adenomas, approximately a 0.8% risk [47]. A fourfold increase in stroke and cerebrovascular accidents has been reported in patients receiving treatment for pituitary adenomas compared to the endemic rate; however, the relative contribution of radiation therapy is debatable [48]. A report from the Netherlands comparing pituitary

adenomas treated with radiation therapy and those not irradiated did not show a difference in the incidence of stroke [45, 49]. Meta-analysis data showed a 0.25% rate of cerebrovascular accidents, of which, only 2 of 1567 patients were symptomatic [47]. Lastly, radiation-induced malignancies are always a concern with radiation, although the risk is low with fractionated radiation therapy and negligible with SRS. A review of 426 patients with pituitary adenomas treated at the Royal Marsden Hospital with surgery followed by fractionated radiotherapy found a cumulative risk of secondary brain tumors at 10 years to be 2% and 2.4% at 20 years [50]. The risk of secondary neoplasms at 15 years with SRS has been reported to be around 0.04% [44]. Overall, the risks of long-term side effects can be minimal if appropriate dose constraints are enforced and there appears to be no significant difference in long-term toxicities between SRS and fractionated radiation therapy.

Outcomes: Tumor Control and Survival

Excellent tumor control rates have been reported for both SRS and fractionated radiation therapy. Fractionated courses of radiation therapy for nonfunctioning and secreting pituitary adenomas have reported rates of tumor control >90% at 5-year follow-up (Table 2.1). A large study of 252 nonfunctioning pituitary adenomas treated with a 3-field conventional plan to doses of 45–50 Gy had 10-year local control rates of 97% and 20-year local control rates of 92% [60]. More recently a large study by Chang et al. found a local control rate of 91% at a median follow-up of 8.4 years in 340 patients with resected nonfunctioning pituitary adenomas [61]. Studies using fractionated SRS have also shown local control rates to be >90% at 10 years. Even in large invasive nonfunctioning pituitary adenomas, postoperative fractionated stereotactic radiotherapy (FSRT) has proven to be effective with local control rates of 97% and 91% at 5 and 10 years, respectively [51].

In secreting pituitary adenomas, control is measured both by tumor growth and secreting hormone normalization. Unfortunately, biochemical control rates are difficult to assess across studies as the interpretation of hormone normalization and biochemical remission values vary among studies. Biochemical normalization of GH-secreting tumors with conventional or stereotactic fractionated radiation therapy may take up to 5–10 years. In a study of 884 patients treated with conventional radiation therapy to a median dose of 45 Gy, normalization of GH levels below 2.5 ng/mL was

Table 2.1 Selected fractionated stereotactic radiosurgery and hypofractionated radiosurgery studies published since 2010 onward

Study	# of pts	Type of RT	Tumor volume (mean, cm^3)	Fun/ nonfun	Dose/fx (mean)	f/u (median)	LC (5 years)	Hormone control	Visual tox	Hypopitu
Minniti [51]	68	FSRT	22.6 (11.1–52.2)	NF	45 Gy/25fx	75	97%	–	0%	26.4%
Diallo [52]	34	FSRT	24.5	GH	50 Gy /27fx	152	97%	38.2%		39%
Puataweepong [53]	71 (NF) 11 (GH) 9 (PRL) 3 (ACTH)	FSRT	10 (0.8–45.5)	NF, GH, PRL, ACTH	45 Gy/25	62	95% at 6 years	– 26% (GH) 4.3% (PRL) 34.6% ACTH	3%	9.6%
Kopp [54]	29 (NF) 8 (F)	FSRT	22.8 (2.0–78.3)	NF, F	49.4 Gy/28	57	91.9%	–	5%	5%
Kim [55]	54 (NF) 22 (F)	FSRT	10.5` (1.5–37.8)	NF, F	50.4 Gy/28fx	80	97% at 7 years	63.6%	0%	48%
Wilson [56]	53 (CRT) 67 (FSRT)	CRT FSRT	6.8 (0.2–115.6)	NF	50.4 Gy/28fx	53 61	86.9% (CRT) 92.8% (FSRT)	–	11% (CRT) 1.5% (FSRT)	7% CRT) 32% (FSRT)
Sun [57]	13 (NF) 10 (F)	FSRT	2 cm (0.5–3.5)	NF, GH, ACTH, PRL	50.4 Gy/28fx	39	96% (NF)~ 100% (F)~	62.5% (F)	15% (NF) 0% (F)	0% (NF) 10% (F)
Schalin-Jantti [58]	20 (NF) 10 (F)	FSRT	8.48` (0.06–65)	NF, F	45 Gy/25fx	63	100%	All had ↓ in abnormal hormones	0%	40%
Liao [33]	21 (NF) 13 (F)	hSRS—3fx	5.06 (0.82–12.69)	NF, F	21 Gy/3fx	37	100%~	– 14%	0%	–
Iwata [59]	83 (3fx) 17 (5fx)	hSRS—3fx hSRS—5fx	5.01` (0.7–64.3)	NF	21 Gy/3fx 25 Gy/5fx	33	98%° (3fx) 96%° (5fx)	–	0.1% (3fx) 0% (5fx)	3.6% (3fx) 0% (5fx)

`is the median
%° is 3 year local control

Table 2.2 Select stereotactic radiosurgery studies published since 2010 onward with large patient population (>90 patients)

Study	# of pts	Type of RT	Tumor volume	Fun/ nonfun	Dose/fx (mean)	f/u	LC (5 years) (%)	Hormone control	Visual tox	Hypopitu (%)
Sheehan [69]	512	GK	4.6 ± 4.9	NF	16`	36	95	–	6.6%	21
Starke [70]	140	GK	5.6 (0.6–35)	NF	18	50	97	–	12.8%	30.3
Park [71]	125	GK	3.5` (0.4–28.1)	NF	13	62	94	–	0.8%	24
Franzin [72]	103	GK	1.8 (0.1–7.2)	GH	22.5	71	97.3	58.5% @5y	0	14
Sheehan [73]	130	GK	1.9 (0.1–27)	GH	24	31	93	53%	2.4%	24.4
Sheehan [40]	96	GK	1.8 (0.2–12.4)	ACTH	16	48	98	70%	5.2%	36

`median

22%, 63%, 74%, and 77% at 2-, 10-, 15-, and 20-year follow-up, respectively, with IGH-1 dose levels paralleling the GH levels [62]. Another study treating GH-secreting pituitary adenomas with FSRT to a median total dose of 52 Gy found biochemical normalization in 84% of the 25 patients at a median follow-up of 26 months [63]. More recently, a report of 34 patients treated with 50 Gy using FSRT found a 97% normalization rate of IGH-1 at a median follow-up of 12 years. All tumors were locally controlled as well [52].

For ACTH-secreting pituitary adenomas, normalization of cortisol levels usually occurs in the first 2 years. A study reported in the NEJM found a mean radiation dose of 50 Gy (range, 48–54 Gy) to yield biochemical control in 83% of patients at a median follow-up of 42 months [64]. Minniti et al. reported an overall remission rate in cortisol hypersecretion of 80% at median follow-up of 9 years with doses between 45 and 50 Gy. Local tumor control rate was 93% at 10 years. This study also found that biochemical normalization improved with time as 28%, 73%, 78%, and 84% of patients had normalization of cortisol secretion at 1, 3, 5, and 10 years, respectively [65].

Prolactinomas are less commonly treated with radiation therapy as it is a third-line treatment and only used in those resistant to medical management and surgery. Definitive radiation therapy for prolactinomas has been well studied but has historically yielded poor biochemical response in comparison to medical management and surgery [22]. However, more recent studies showed 100% prolactin normalization after FSRT with doses between 45 and 54 Gy [57, 58].

Due to the rarity of TSH-secreting tumors, local control and biochemical control rates after radiation therapy have not been well reported. In a large study of 25 TSH-secreting tumors, 12 received radiation therapy, 2 were treated definitively with radiation therapy. The patients receiving both surgery and radiation therapy with or without medical management had a 57% biochemical remission rate [66]. In another study, 8 of 43 TSH-secreting adenomas had radiation therapy due to uncontrollable tumor after surgery. The dose ranged between 42 and 45 Gy. With a median follow-up of 6.8 years, there were five that had biochemical control at a mean time of 3 years from treatment [67].

Traditionally, pituitary adenomas were treated with conventional radiation therapy. However, more recently conventional radiation therapy has been reserved for cases not amenable to SRS, typically due to the proximity to the optic nerve or large size of the adenoma. The efficacy and safety of SRS appear to be similar to FSRT [68]. Stereotactic radiosurgery in nonfunctioning pituitary adenomas has reported local control rates between 87 and 100% at 5 years assessed by tumor growth (Table 2.2) [74].

Pooling together 15 studies using SRS for 684 patients, the actuarial tumor control rate was 94% at 5 years [75]. In GH-secreting pituitary adenomas, a tumor control rate of 95–100% has been reported in 13 studies using SRS with a median follow-up of 5 years or more [59]. Biochemical remission rates with SRS for GH-secreting pituitary adenomas have been reported in 29 studies for a compiled total of 1215 patients to be 44% (range 15–60%) and 74% (range 46–86%) at 5 and 10 years, respectively [75]. Normalization of IGF-1 levels and biochemical response ranged from 1 to 5.6 years.

In ACTH-secreting pituitary adenomas in studies with a median follow-up of ≥5 years, a tumor control rate with SRS has been reported to be >95% [74]. At a median follow-up of 45 months in 12 studies, 48% of patients with Cushing's disease had biochemical response with a range from 3 months to 3 years for time to response [75].

When radiation is needed for prolactinomas, SRS is a well-utilized option. In studies with a median follow-up of greater than 5 years, the tumor control rate for prolactinomas with SRS was 97–100% but had a biochemical remission rate of 18–46.6% [74]. A pooled analysis of 11 studies utilizing SRS in prolactinomas resistant to medical management and surgery found normalization of PRL levels in 35% of the 338 and patients and the response rate to range between 12 and 66 months [74]. The tumor control rate in this pooled analysis was 99% at a weighted average follow-up of 42 months.

Although hypofractionated courses of SRS have been less studied, local tumor control and biochemical remission appear to be similar to SRS with one fraction [33, 34, 59]. It should be noted that medical therapy for secreting adenomas

should be stopped approximately 2 months before radiation therapy as the medications may alter the cell cycle making the tumor less radiosensitive.

Follow-up

Six to 12 months after the completion of radiation therapy, a baseline MRI of the pituitary and history and physical examination is recommended. Due to the slow-growing nature of most pituitary adenomas, subsequent follow-up imaging is usually on an annual basis. Atypical or carcinoma histology may require more frequent imaging, although the optimal schedule is not known. An MRI with and without contrast and fine slices through the pituitary in all three plans (axial, coronal, and sagittal) is important for assessing tumor recurrence. A history and physical examination should be obtained annually with special attention to visual deficits, cranial nerves that course through the cavernous sinus, panhypopituitarism, and any signs of long-term toxicity from radiation therapy. Follow-up management of treated pituitary adenomas often includes other providers including an endocrinologist, a neuro-ophthalmology, and a skull base/neurosurgeon. For secreting pituitary adenomas, careful attention to normalization of the secreting hormone as well as hypopituitarism of the other pituitary hormones is important. In nonfunctioning adenomas, lab work should be obtained at any concerning finding for hypopituitarism as this is the most common long-term side effect after radiation therapy [73].

Cases

Case 1

A 72-year-old male presented with visual symptoms, and an MRI was completed revealing a 3 cm pituitary adenoma that extended superiorly out of the diaphragmatic sella and compressed the optic chiasm as well as invaded the right cavernous sinus. He was seen by an endocrinologist for further workup of his new diagnosis of a pituitary adenoma. Labs were obtained revealing a slightly elevated prolactin level due to compression of the infundibulum. He underwent a transnasal transsphenoidal resection of the pituitary macroadenoma. The pituitary adenoma was markedly debulked, but residual disease remained due to extension into the right cavernous sinus. Pathology revealed a hypercellular, monotonous neoplasm composed of sheets of cells with eosinophilic cytoplasm and oval nuclei with stippled chromatin. There was moderate pleomorphism to the cells consistent with a pituitary adenoma. There were no mitoses or evidence of necrosis. A postoperative brain MRI revealed a debulking of the pituitary adenoma with fat-packing in the nasal cavity and sphenoid sinus. There was residual pituitary adenoma in the right cavernous sinus encasing the right carotid artery measuring 15 × 26 × 15 mm (CC × AP × transverse) in the right cavernous sinus. He developed panhypopituitarism after his surgery and was followed by his endocrinologist. Two years after his surgery, a pituitary protocol MRI revealed interval growth of the pituitary adenoma involving the right cavernous sinus that now measured 36 × 23 × 22 mm in size (Fig. 2.1). He refused any further surgery and therefore was referred to the radiation oncology department. Due to the location next to the right optic nerve, SRS was not possible. Thus, a stereotactic fractionated course of radiation therapy with 50.4 Gy in 28 fractions was recommended. He had a stereotactic fine slice T1 MRI through the pituitary with gadolinium as well as a stereotactic T1 fat suppression through the pituitary region. A CT simulation with a Brainlab mask was completed. The residual tumor was outlined on the T1 fat suppression MRI scan which allowed for better assessment of the disease extent near the orbit and the fat-packing. The GTV was then expanded 3 mm in all directions to create a PTV (Fig. 2.2). A plan was made using an 11-field intensity-modulated radiation therapy (IMRT) technique (Fig. 2.3). The dose-volume histogram illustrates all the normal structures are well below acceptable tolerance doses and the GTV is covered by 97.7% of the dose and 99.1% of the GTV is getting full dose (Fig. 2.4). The patient tolerated the treatment well without difficulty. He is now 3 years out from radiation therapy and has no evidence of disease progression or worsening visual symptoms (Fig. 2.5).

Case 2

A 21-year-old male presented to his ophthalmologist and was found to have bitemporal hemianopsia. An MRI scan was completed which showed a large enhancing mass expanding out of the sella turcica and into the suprasellar cistern causing compression of the optic chiasm. This was consistent with a pituitary tumor (Fig. 2.6). He was seen by an endocrinologist and on further workup was found to

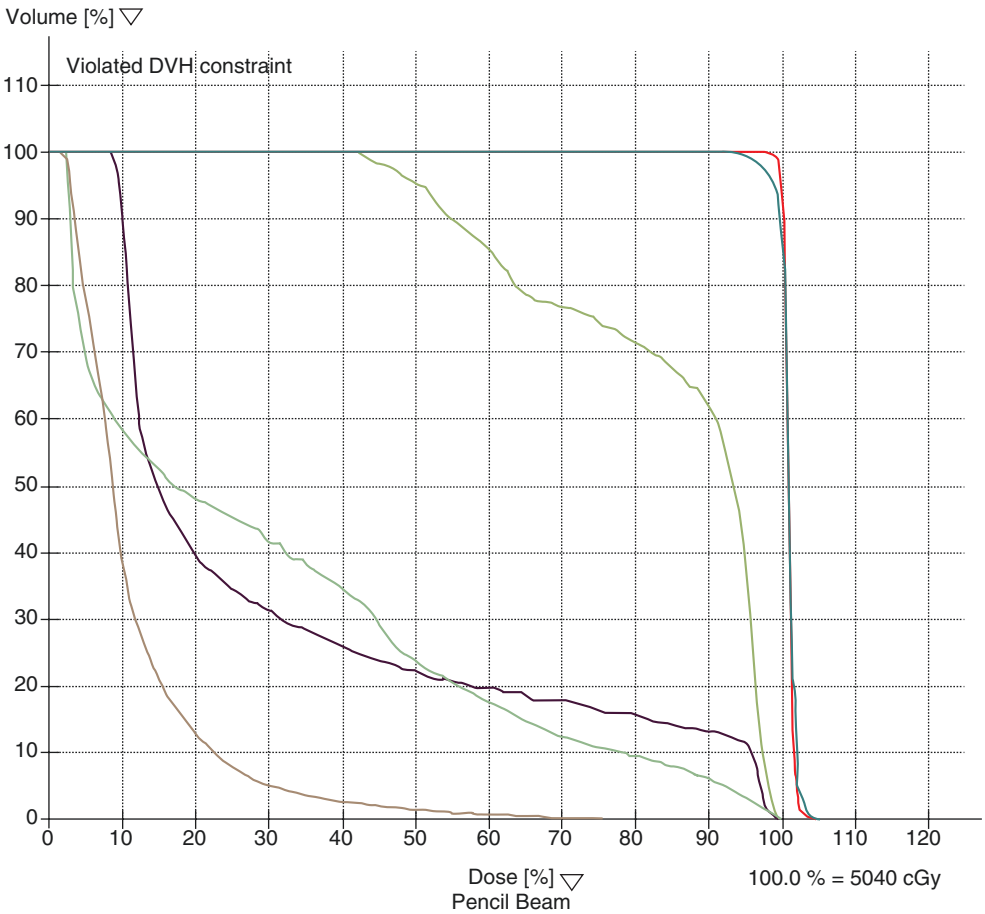

Fig. 2.4 Dose-volume histogram showing the brainstem, chiasm, and optic nerves all well below tolerance levels. This was easily achievable due to the prescribed dose being only 50.4 Gy. GTV, red; PTV, cyan; eyes, purple; left optic nerve, pink; right optic nerve, green

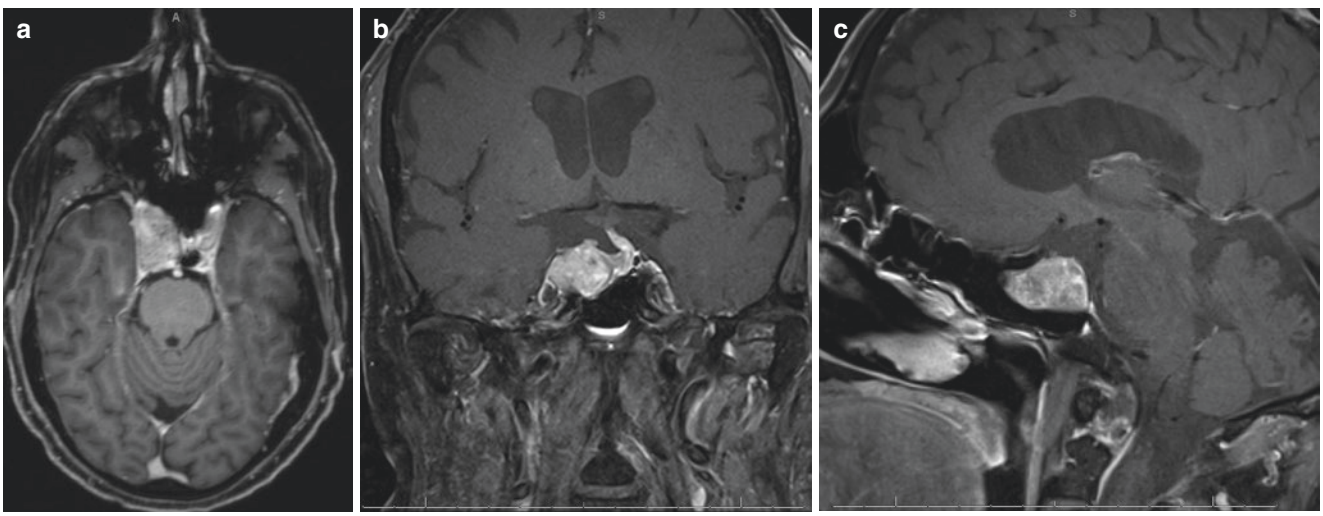

Fig. 2.5 Axial (**a**), coronal (**b**), and sagittal (**c**) views showing an unchanged pituitary adenoma in the right posterior aspect of the sella that extends into the right cavernous sinus and encases the internal carotid artery

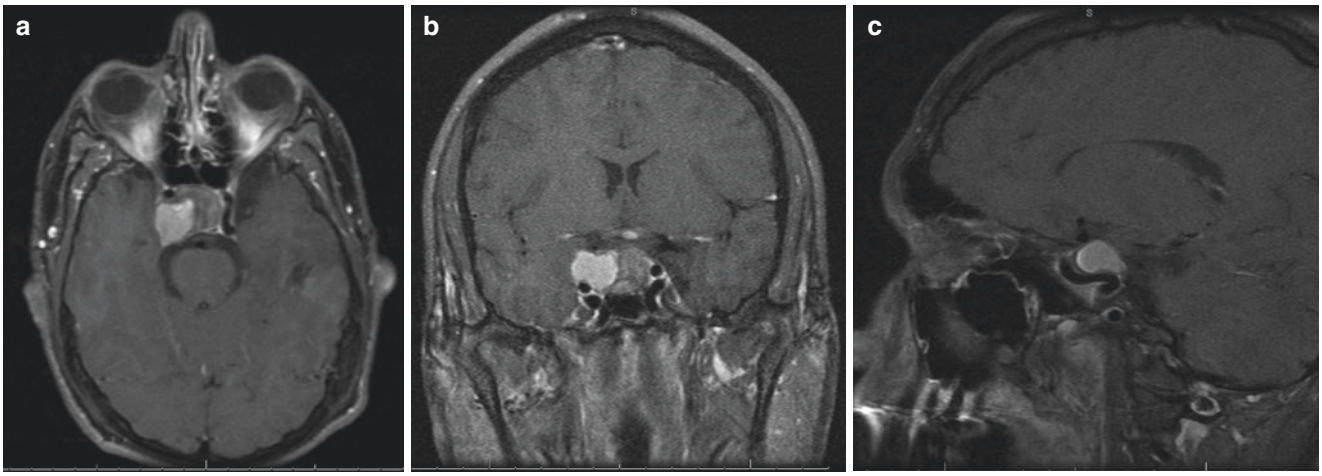

Fig. 2.6 Axial (**a**), coronal (**b**), and sagittal (**c**) views of the pituitary adenoma extending into the suprasellar cistern, displacing the pituitary stalk and compressing the optic chiasm

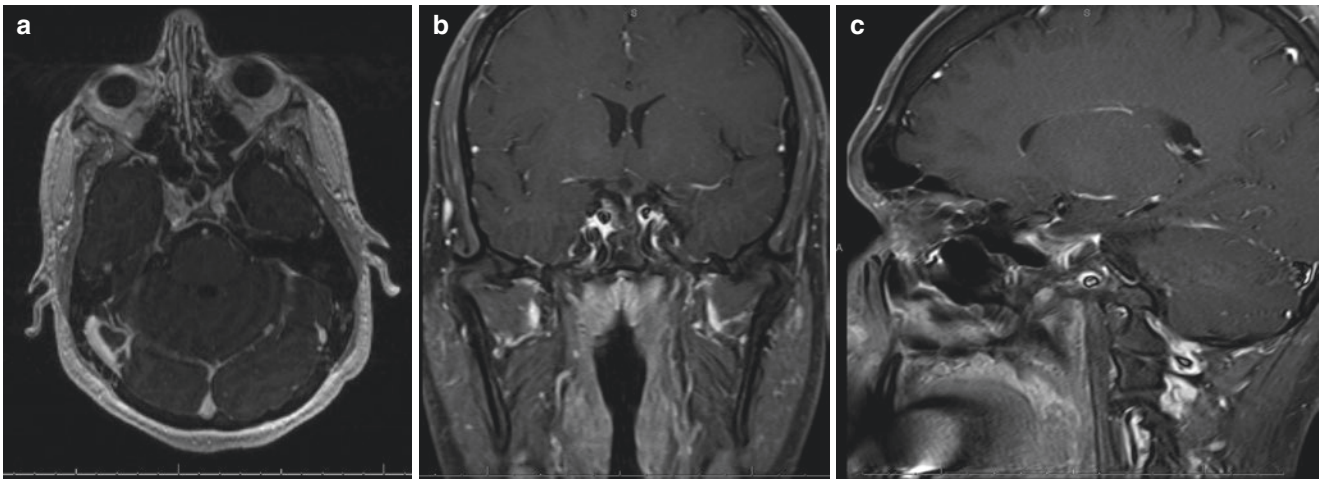

Fig. 2.7 Axial (**a**), coronal (**b**), and sagittal (**c**) views of the residual pituitary adenoma on the right lateral aspect of the sella turcica after surgical resection

have a GH level of 24 ng/mL and an insulin-like growth factor of 1100. He was taken to the operating room for a transnasal transsphenoidal surgical resection. Pathology revealed a pituitary adenoma with no mitoses. A postoperative MRI showed some residual enhancement within the sella representing either residual tumor or postoperative changes, and his GH and IGF-1 normalized. Unfortunately, over the course of the next year, he had a rise in his GH and IGF-1, and an MRI showed enlargement of an enhancing mass predominantly on the right side of the sella. He was taken back for a redo transsphenoidal resection where pituitary adenoma was resected from the right side of the pituitary gland. Unfortunately, there was adherent tissue along the right lateral aspect of the sella turcica that could not be fully resected. A postoperative MRI revealed residual disease along the right lateral sella turcica (Fig. 2.7). He was then started on Sandostatin by his endocrinologist. He was followed with stable MRIs and his GH and IGF-1 levels normalized to 0.7 ng/mL and 217 ng/mL, respectively. Unfortunately, 3 years later he was unable to continue Sandostatin. His case was discussed at a multidisciplinary tumor board and it was recommended he undergo SRS. He underwent SRS planning with the GTV encompassing the residual pituitary adenoma on the right lateral sella turcica and no PTV expansions (Fig. 2.8). An 8-field IMRT plan was constructed, prescribing 20 Gy to the GTV (Fig. 2.9). The optic nerves and chiasm were kept well below 8 Gy and the brainstem was limited to 12 Gy. The dose-volume histogram shows that the GTV is covered by 100% of the dose (Fig. 2.10). Prior to SRS, he had been off Sandostatin for over a year and his IGF-1 level rose to 383. He tolerated his SRS treatment well and was seen back in follow-up 6 months later. A brain MRI showed no evidence of progression (Fig. 2.11)

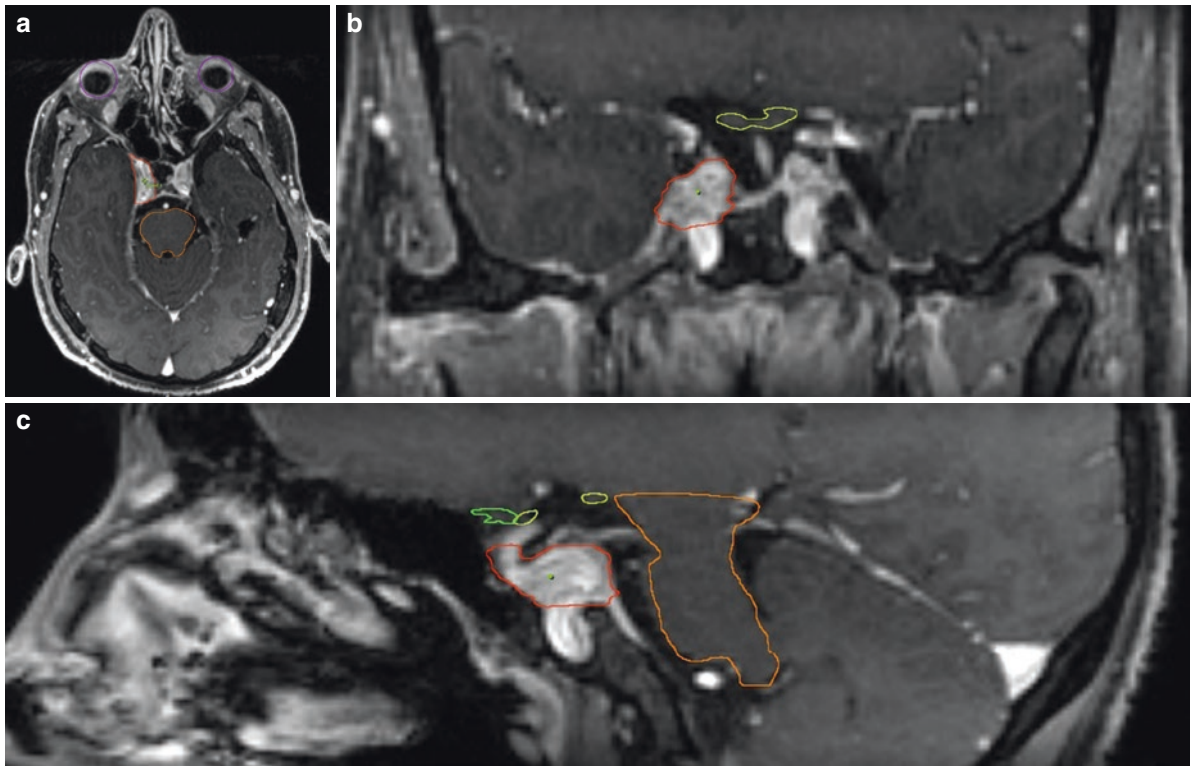

Fig. 2.8 Axial (**a**), coronal (**b**), and sagittal (**c**) views of the residual pituitary adenoma contoured to create the GTV with no PTV. GTV, red; eyes, purple; right optic nerve, green; chiasm, yellow

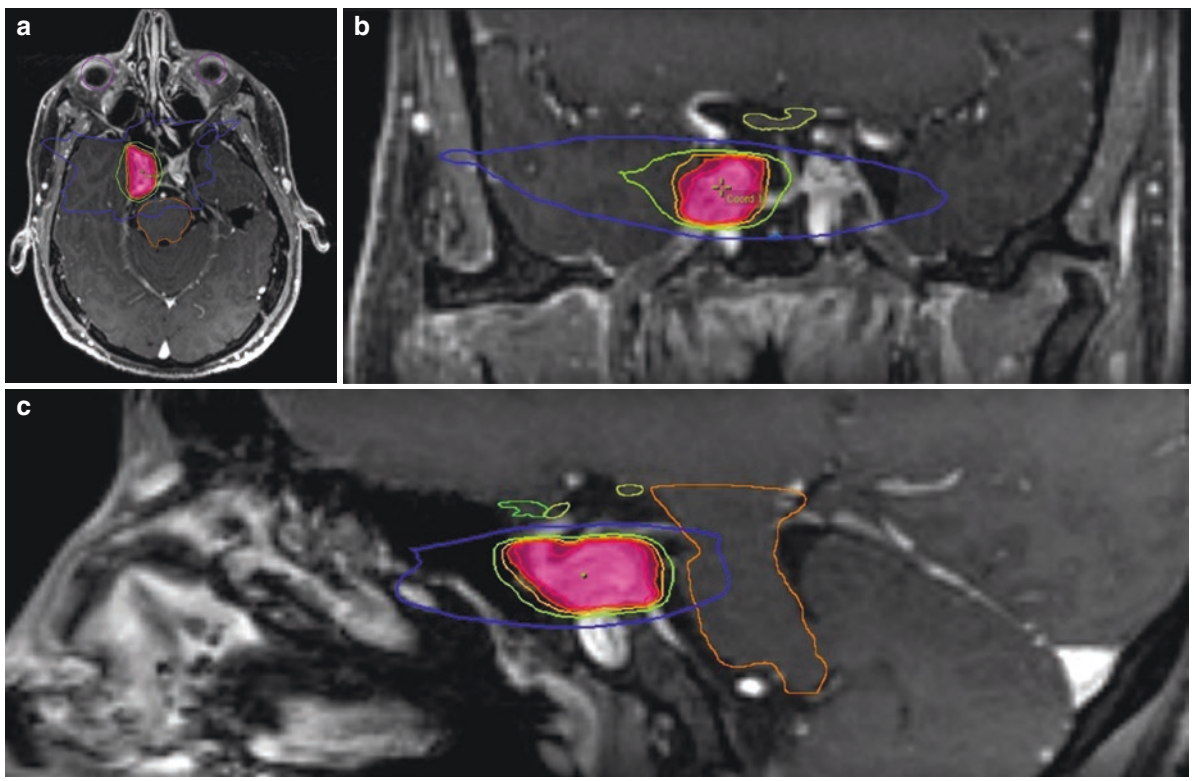

Fig. 2.9 Axial (**a**), coronal (**b**), and sagittal (**c**) views of the treatment plan. A dose of 20 Gy in a single fraction was prescribed to the 100% isodose line using an 8-field IMRT technique. A three-dimensional conformal arch or volumetric modulated radiation therapy (VMRT) technique may also be utilized. One hundred percent of the GTV covered 100% of the dose which is shown above. The isodose lines are as follows: 100% isodose line, orange; 95% isodose line line, light orange; 80% isodose line, lime green; 30% isodose line, purpur. The 100% coverage is represented by the pink fill

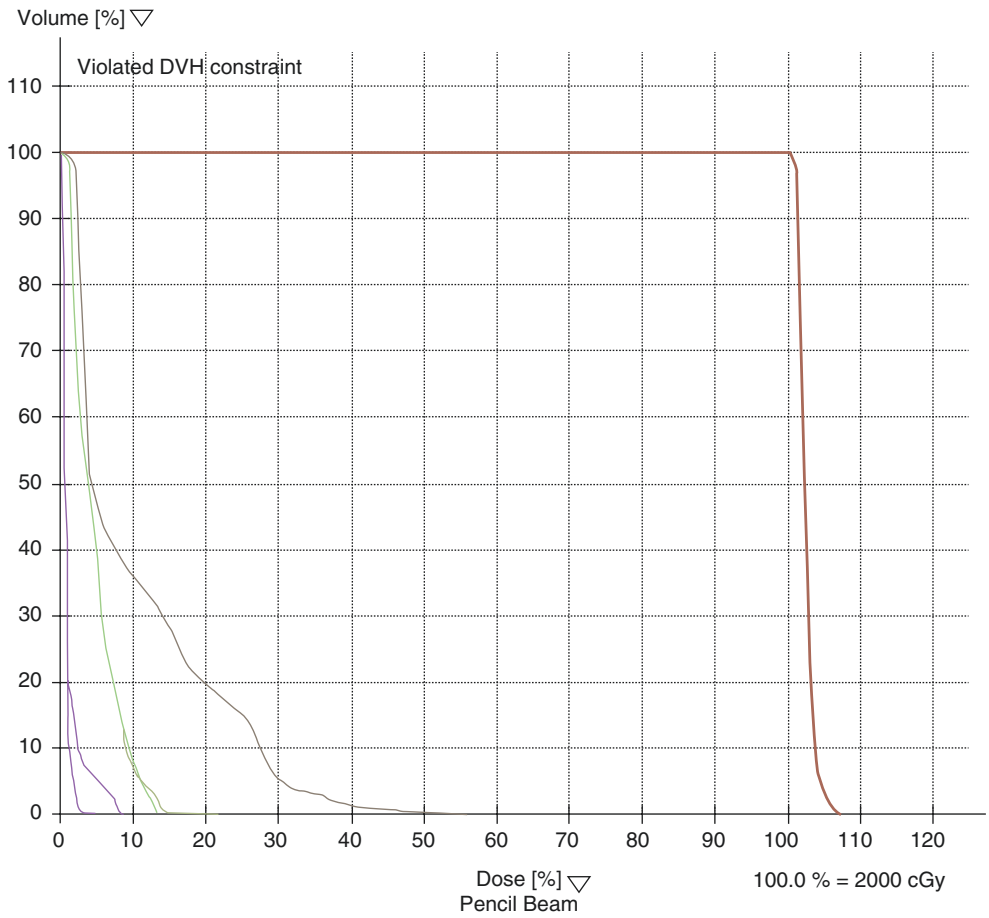

Fig. 2.10 Dose-volume histogram showing the brainstem, chiasm, and optic nerves all well below tolerance levels. GTV, red; eyes, purple; left optic nerve, pink; right optic nerve, green; pituitary, blue

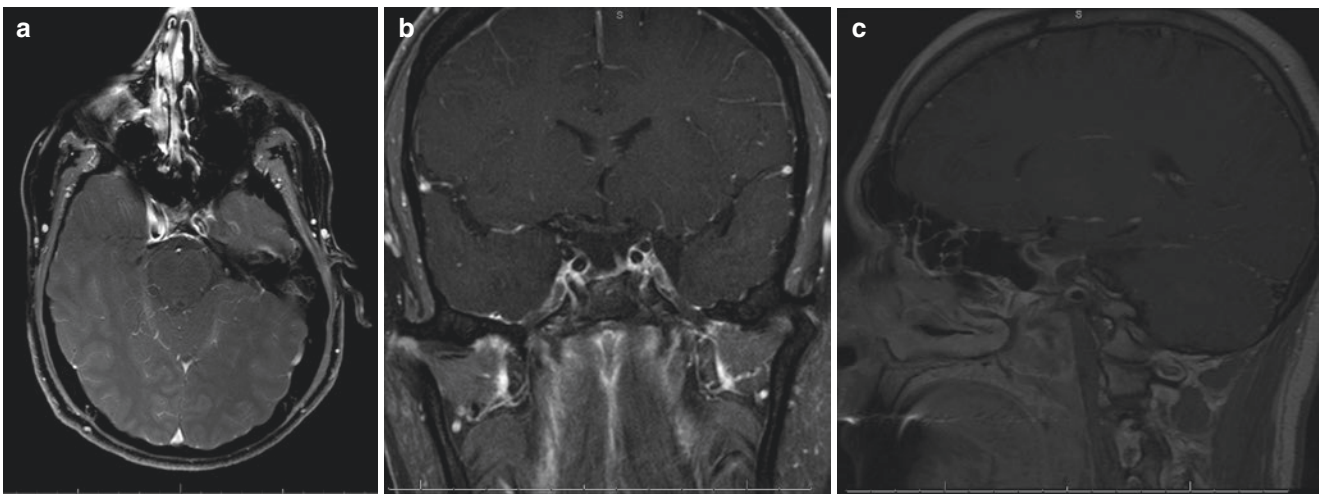

Fig. 2.11 Axial (**a**), coronal (**b**), and sagittal (**c**) views of the sella showing no evidence of pituitary adenoma

and his IGF-1 level had dropped to 103. He was then followed annually with repeat IGF-1 levels and MRIs. Seven years out from treatment, he is doing well with no evidence of any residual disease progression on MRI, an IGF-1 level of 19, and no radiation-induced toxicities.

Summary

- Pituitary adenomas are a common benign neoplasm of the brain estimated to represent approximately 15–20% of all intracranial neoplasms.

- Clinically nonfunctioning pituitary adenomas account for 25–30% of pituitary adenomas, while functioning or secreting adenomas oversecrete a hormone normally produced by the pituitary gland and comprise the remaining 70–75%.
- Patients with pituitary adenomas will commonly present with visual symptoms including loss of temporal fields due to compression of the optic chiasm, followed by headaches and hypopituitarism. Patients with secreting pituitary adenomas also present with clinical findings related to hypersecretion of hormones.
- The management of pituitary adenomas involves a multimodality approach with the goals of treatment to preserve or restore normal hormonal function and remove or control any mass effect from the tumor that may be causing neurological or hormonal symptoms.
- Indications for radiation therapy in the treatment of pituitary adenomas include a subtotal resection, recurrent or progressive tumors, hormone refractory disease, and atypical or carcinoma histologies.
- Radiosurgery can be used to treat pituitary adenomas if the optic structures are approximately 3 mm from the pituitary adenoma.
- Fractionated doses of 45–50.4 Gy and radiosurgery doses of 15 Gy are used to treat nonfunctioning pituitary adenomas.
- Secreting pituitary adenomas require slightly higher doses of radiation with fractionated doses of 50.4–54 Gy and radiosurgery doses of 20 Gy.
- Fractionated courses of radiation therapy for nonfunctioning and secreting pituitary adenomas have reported rates of tumor control >90% at 5-year follow-up.
- SRS in nonfunctioning pituitary adenomas have reported local control rates between 87% and 100% at 5 years assessed by tumor growth.
- For secreting pituitary adenomas, biochemical control rates with fractionated radiation and radiosurgery are difficult to assess across studies as the interpretation of hormone normalization and biochemical remission values vary among studies.
- Long-term toxicities with radiation therapy include hypopituitarism, optic neuropathy and other cranial neuropathies of the cavernous sinus, radiation necrosis, neurocognitive effects, vascular complications, and secondary malignancies.

Self-Assessment Questions

1. Pituitary adenomas are best visualized on which type of imaging scan?
   A. CT scan with and without contrast
   B. T2-weighted brain MRI
   C. T1-weighted brain MRI with gadolinium
   D. PET/CT scan

2. What is the fractionated radiation therapy dose for a secreting pituitary?
   A. 41.4–45 Gy
   B. 45–50.4 Gy
   C. 50.4–54 Gy
   D. 54–59.4 Gy

3. A nonfunctioning pituitary adenoma recurs along the right cavernous sinus and abuts the right optic nerve. The best management would be:
   A. SRS with 15 Gy
   B. SRS with 20 Gy
   C. Fractionated radiation with 45 Gy
   D. Fractionated radiation with 54 Gy

4. The most common side effect from radiation therapy for treatment of a pituitary adenoma is
   A. Visual deficit
   B. Hypopituitarism
   C. Stroke
   D. Secondary malignancies

5. After radiation therapy, repeat imaging should occur:
   A. Every month
   B. Every 3 months
   C. Six months after completing radiation, then annually
   D. Every 2 years

Answers

1. C
2. C
3. C
4. B
5. C

References

1. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. Neuro Oncol. 2015;17(Suppl 4):iv1–iv62.
2. Gittleman H, Ostrom QT, Farah PD, et al. Descriptive epidemiology of pituitary tumors in the United States, 2004–2009. J Neurosurg. 2014;121(3):527–35.
3. Mehta GU, Lonser RR. Management of hormone-secreting pituitary adenomas. Neuro Oncol. 2017;19(6):762–73.
4. Schoemaker MJ, Swerdlow AJ. Risk factors for pituitary tumors: a case-control study. Cancer Epidemiol Biomark Prev. 2009;18(5):1492–500.
5. Caimari F, Korbonits M. Novel genetic causes of pituitary adenomas. Clin Cancer Res. 2016;22(20):5030–42.
6. Vasilev V, Rostomyan L, Daly AF, et al. MANAGEMENT OF ENDOCRINE DISEASE: Pituitary 'incidentaloma': neuroradio-

logical assessment and differential diagnosis. Eur J Endocrinol. 2016;175(4):R171–84.
7. Paschou S, Vryonidou A, Goulis DG. Pituitary incidentalomas: a guide to assessment, treatment and follow-up. Maturitas. 2016;92:143–9.
8. Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. Endocrinol Metab Clin N Am. 2008;37(1):151–71, xi.
9. Vilar L, Naves LA, Azevedo MF, et al. Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. Pituitary. 2010;13(2):123–9.
10. Ouyang T, Rothfus WE, Ng JM, et al. Imaging of the pituitary. Radiol Clin N Am. 2011;49(3):549–71, vii.
11. DeLellis RA, Lloyd RV, Heitz PU, et al. World Health Organization Classification of Tumors. Pathology and genetics of tumours of endocrine organs. Lyon: IARC; 2004.
12. Kovacs K, Horvath E, Vidal S. Classification of pituitary adenomas. J Neurooncol. 2001;54(2):121–7.
13. Wilson CB. A decade of pituitary microsurgery. The Herbert Olivecrona lecture. J Neurosurg. 1984;61(5):814–33.
14. Knosp E, Steiner E, Kitz K, et al. Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery. 1993;33(4):610–7; discussion 7–8.
15. Micko AS, Wohrer A, Wolfsberger S, et al. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. J Neurosurg. 2015;122(4):803–11.
16. Sherlock M, Ayuk J, Tomlinson JW, et al. Mortality in patients with pituitary disease. Endocr Rev. 2010;31(3):301–42.
17. Melmed S, Colao A, Barkan A, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009;94(5):1509–17.
18. Chole RA, Lim C, Dunham B, et al. A novel transnasal transsphenoidal speculum: a design for both microscopic and endoscopic transsphenoidal pituitary surgery. J Neurosurg. 2011;114(5):1380–5.
19. Pomeraniec IJ, Dallapiazza RF, Xu Z, et al. Early versus late Gamma Knife radiosurgery following transsphenoidal resection for nonfunctioning pituitary macroadenomas: a matched cohort study. J Neurosurg. 2016;125(1):202–12.
20. Erturk E, Tuncel E, Kiyici S, et al. Outcome of surgery for acromegaly performed by different surgeons: importance of surgical experience. Pituitary. 2005;8(2):93–7.
21. Yamada S, Fukuhara N, Horiguchi K, et al. Clinicopathological characteristics and therapeutic outcomes in thyrotropin-secreting pituitary adenomas: a single-center study of 90 cases. J Neurosurg. 2014;121(6):1462–73.
22. Platta CS, Mackay C, Welsh JS. Pituitary adenoma: a radiotherapeutic perspective. Am J Clin Oncol. 2010;33(4):408–19.
23. Gillam MP, Molitch ME, Lombardi G, et al. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27(5):485–534.
24. Beck-Peccoz P, Brucker-Davis F, Persani L, et al. Thyrotropin-secreting pituitary tumors. Endocr Rev. 1996;17(6):610–38.
25. Schteingart DE. Drugs in the medical treatment of Cushing's syndrome. Expert Opin Emerg Drugs. 2009;14(4):661–71.
26. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016;101(11):3888–921.
27. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab. 2008;93(10):3717–26.
28. Sadik ZH, Voormolen EH, Depauw PR, et al. Treatment of non-functional pituitary adenoma post-operative remnants: adjuvant or delayed gamma knife radiosurgery? World Neurosurg. 2017;100:361.
29. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand. 1951;102(4):316–9.
30. Lamba M, Breneman JC, Warnick RE. Evaluation of image-guided positioning for frameless intracranial radiosurgery. Int J Radiat Oncol Biol Phys. 2009;74(3):913–9.
31. Guckenberger M, Baier K, Guenther I, et al. Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. Int J Radiat Oncol Biol Phys. 2007;69(1):294–301.
32. Loeffler JS, Shih HA. Radiation therapy in the management of pituitary adenomas. J Clin Endocrinol Metab. 2011;96(7):1992–2003.
33. Liao HI, Wang CC, Wei KC, et al. Fractionated stereotactic radiosurgery using the Novalis system for the management of pituitary adenomas close to the optic apparatus. J Clin Neurosci. 2014;21(1):111–5.
34. Killory BD, Kresl JJ, Wait SD, et al. Hypofractionated CyberKnife™ radiosurgery for perichiasmatic pituitary adenomas: early results. Neurosurgery. 2009;64(2 Suppl):A19.
35. Vladyka V, Liscak R, Novotny J Jr, et al. Radiation tolerance of functioning pituitary tissue in gamma knife surgery for pituitary adenomas. Neurosurgery. 2003;52(2):309–16; discussion 16–7.
36. Pai HH, Thornton A, Katznelson L, et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys. 2001;49(4):1079–92.
37. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109–22.
38. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S10–9.
39. Anker CJ, Shrieve DC. Basic principles of radiobiology applied to radiosurgery and radiotherapy of benign skull base tumors. Otolaryngol Clin N Am. 2009;42(4):601–21.
40. Sheehan JP, Xu Z, Salvetti DJ, et al. Results of gamma knife surgery for Cushing's disease. J Neurosurg. 2013;119(6):1486–92.
41. Darzy KH. Radiation-induced hypopituitarism after cancer therapy: who, how and when to test. Nat Clin Pract Endocrinol Metab. 2009;5(2):88–99.
42. Tishler RB, Loeffler JS, Lunsford LD, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. Int J Radiat Oncol Biol Phys. 1993;27(2):215–21.
43. Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumors. Radiat Oncol. 2016;11(1):135.
44. Patel TR, Chiang VL. Secondary neoplasms after stereotactic radiosurgery. World Neurosurg. 2014;81(3–4):594–9.
45. Erridge SC, Conkey DS, Stockton D, et al. Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. Radiother Oncol. 2009;93(3):597–601.
46. Bir SC, Murray RD, Ambekar S, et al. Clinical and radiologic outcome of gamma knife radiosurgery on nonfunctioning pituitary adenomas. J Neurol Surg B Skull Base. 2015;76(5):351–7.
47. Laws ER, Sheehan JP, Sheehan JM, et al. Stereotactic radiosurgery for pituitary adenomas: a review of the literature. J Neurooncol. 2004;69(1–3):257–72.
48. Brada M, Ashley S, Ford D, et al. Cerebrovascular mortality in patients with pituitary adenoma. Clin Endocrinol. 2002;57(6):713–7.
49. Sattler MG, Vroomen PC, Sluiter WJ, et al. Incidence, causative mechanisms, and anatomic localization of stroke in pituitary adenoma patients treated with postoperative radiation therapy versus surgery alone. Int J Radiat Oncol Biol Phys. 2013;87(1):53–9.
50. Minniti G, Traish D, Ashley S, et al. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. J Clin Endocrinol Metab. 2005;90(2):800–4.
51. Minniti G, Scaringi C, Poggi M, et al. Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response. Eur J Endocrinol. 2015;172(4):433–41.
52. Diallo AM, Colin P, Litre CF, et al. Long-term results of fractionated stereotactic radiotherapy as third-line treatment in acromegaly. Endocrine. 2015;50(3):741–8.

53. Puataweepong P, Dhanachai M, Hansasuta A, et al. Outcomes for pituitary adenoma patients treated with Linac-based stereotactic radiosurgery and radiotherapy: a long term experience in Thailand. Asian Pac J Cancer Prev. 2015;16(13):5279–84.
54. Kopp C, Theodorou M, Poullos N, et al. Fractionated stereotactic radiotherapy in the treatment of pituitary adenomas. Strahlenther Onkol. 2013;189(11):932–7.
55. Kim JO, Ma R, Akagami R, et al. Long-term outcomes of fractionated stereotactic radiation therapy for pituitary adenomas at the BC Cancer Agency. Int J Radiat Oncol Biol Phys. 2013;87(3):528–33.
56. Wilson PJ, De-Loyde KJ, Williams JR, et al. A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the Linear Accelerator (Linac). J Clin Neurosci. 2012;19(3):370–4.
57. Sun DQ, Cheng JJ, Frazier JL, et al. Treatment of pituitary adenomas using radiosurgery and radiotherapy: a single center experience and review of literature. Neurosurg Rev. 2010;34(2):181–9.
58. Schalin-Jantti C, Valanne L, Tenhunen M, et al. Outcome of fractionated stereotactic radiotherapy in patients with pituitary adenomas resistant to conventional treatments: a 5.25-year follow-up study. Clin Endocrinol. 2010;73(1):72–7.
59. Iwata H, Sato K, Tatewaki K, et al. Hypofractionated stereotactic radiotherapy with CyberKnife™ for nonfunctioning pituitary adenoma: high local control with low toxicity. Neuro Oncol. 2011;13(8):916–22.
60. Brada M, Rajan B, Traish D, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol. 1993;38(6):571–8.
61. Chang EF, Zada G, Kim S, et al. Long-term recurrence and mortality after surgery and adjuvant radiotherapy for nonfunctional pituitary adenomas. J Neurosurg. 2008;108(4):736–45.
62. Jenkins PJ, Bates P, Carson MN, et al. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol Metab. 2006;91(4):1239–45.
63. Milker-Zabel S, Zabel A, Huber P, et al. Stereotactic conformal radiotherapy in patients with growth hormone-secreting pituitary adenoma. Int J Radiat Oncol Biol Phys. 2004;59(4):1088–96.
64. Estrada J, Boronat M, Mielgo M, et al. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med. 1997;336(3):172–7.
65. Minniti G, Osti M, Jaffrain-Rea ML, et al. Long-term follow-up results of postoperative radiation therapy for Cushing's disease. J Neurooncol. 2007;84(1):79–84.
66. Brucker-Davis F, Oldfield EH, Skarulis MC, et al. Thyrotropin-secreting pituitary tumors: diagnostic criteria, thyroid hormone sensitivity, and treatment outcome in 25 patients followed at the National Institutes of Health. J Clin Endocrinol Metab. 1999;84(2):476–86.
67. Socin HV, Chanson P, Delemer B, et al. The changing spectrum of TSH-secreting pituitary adenomas: diagnosis and management in 43 patients. Eur J Endocrinol. 2003;148(4):433–42.
68. Li X, Li Y, Cao Y, et al. Safety and efficacy of fractionated stereotactic radiotherapy and stereotactic radiosurgery for treatment of pituitary adenomas: a systematic review and meta-analysis. J Neurol Sci. 2017;372:110–6.
69. Sheehan JP, Starke RM, Mathieu D, et al. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg. 2013;119(2):446–56.
70. Starke RM, Williams BJ, Jane JA Jr, et al. Gamma Knife surgery for patients with nonfunctioning pituitary macroadenomas: predictors of tumor control, neurological deficits, and hypopituitarism. J Neurosurg. 2012;117(1):129–35.
71. Park KJ, Kano H, Parry PV, et al. Long-term outcomes after gamma knife stereotactic radiosurgery for nonfunctional pituitary adenomas. Neurosurgery. 2011;69(6):1188–99.
72. Franzin A, Spatola G, Losa M, et al. Results of gamma knife radiosurgery in acromegaly. Int J Endocrinol. 2012;2012:342034.
73. Sheehan J, Pouratian N, Steiner L, et al. Gamma Knife surgery for pituitary adenomas: factors related to radiological and endocrine outcomes. J Neurosurg. 2011;114(2):303–9.
74. Minniti G, Clarke E, Scaringi C, et al. Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas. Rep Pract Oncol Radiother. 2016;21(4):370–8.
75. Amichetti M, Amelio D, Minniti G. Radiosurgery with photons or protons for benign and malignant tumours of the skull base: a review. Radiat Oncol. 2012;7:210.