



Radiosurgery Practice Guideline Initiative

Stereotactic Radiosurgery for Patients with Pituitary Adenomas

Practice Guideline Report #3-04

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MOST RECENT LITERATURE SEARCH: April 2004

This practice guideline, together with a report on "Pituitary Tumors: Overview" is an original guideline approved by the IRSA[®] (International RadioSurgery Association) Board of Directors and issued in April 2004.

Preface

Summary

The IRSA[®] (International RadioSurgery Association) Radiosurgery Practice Guideline Initiative aims to improve outcomes for pituitary adenomas by assisting physicians in applying research and clinical evidence to clinical decisions while promoting the responsible use of health care resources.

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KEY WORDS • pituitary adenoma • acromegaly • Cushing's disease • prolactinomas
• stereotactic radiosurgery • Gamma Knife[®] • linear accelerator • proton beam
• Bragg peak proton therapy • irradiation

Consensus Statement

Objective

To develop a consensus-based radiosurgery practice guideline for treatment recommendations to be used by medical and public health professionals for patients with the diagnosis of pituitary adenoma.

Participants

The working group included neurosurgeons, radiation oncologists, endocrinologists and physicists, all of whom staff major medical centers that provide radiosurgery treatment.

Evidence

The first authors (LDL/AN) conducted a literature search in conjunction with the preparation of this document and the development of other clinical guidelines. The literature identified was reviewed and opinions were sought from experts in the diagnosis and management of pituitary adenomas, including members of the working group.

Consensus Process

The initial draft of the consensus statement was a synthesis of research information obtained in the evidence-gathering process. Members of the working group provided formal written comments that were incorporated into the

preliminary draft of the statement. No significant disagreements existed. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Group Composition

The Radiosurgery Guidelines Committee is comprised of neurological surgeons, radiation oncologists, physicians, endocrinologists and medical physicists. Community representatives did not participate in the development of this guideline but will in future updates.

Names of Group Members: L. Dade Lunsford, M.D., Neurosurgeon, Chair; Ajay Niranjani, M.B.B.S., M.Ch., Neurosurgeon; Tatsuya Kobayashi, M.D., Ph.D., Neurosurgeon; Mark Linskey, M.D., Neurosurgeon; Thomas Witt, M.D., Neurosurgeon; Alex Landolt, M.D., Neurosurgeon; Roman Liscak, M.D., Neurosurgeon; Edward R. Laws Jr., M.D., Neurosurgeon; Mary Lee Vance, M.D., Endocrinologist; John Buatti, M.D., Radiation Oncologist; Jonathan Knisely, M.D., Radiation Oncologist; Paul Sperduto, M.D., Radiation Oncologist; Sammie Coy, Ph.D., Medical Physicist; Tonya K. Ledbetter, M.S., M.F.S., Editor; Rebecca L. Emerick, M.S., M.B.A., C.P.A., ex officio.

Conclusions

Specific recommendations are made regarding target population, treatment alternatives, interventions and practices and additional research needs. Appropriate use of radiosurgery in those patients with pituitary adenoma following medical and/or surgical management may be beneficial.

This guideline is intended to provide the scientific foundation and initial framework for the person who has been diagnosed with a pituitary adenoma. The assessment and recommendations provided herein represent the best professional judgment of the working group at this time, based on research data and expertise currently available. The conclusions and recommendations will be regularly reassessed as new information becomes available.

Stereotactic Radiosurgery

Stereotactic radiosurgery involves the use of precisely directed single fraction (one session) radiation to create a desired radiobiologic response within the targeted tissue volume with minimal effects on surrounding structures or tissues. In the case of pituitary adenoma a single highly conformal dose of focused radiation is delivered precisely to the tumor under the direct supervision of a multidisciplinary radiosurgery team (neurosurgeon, radiation oncologist, physicist, and often a registered nurse).

Pituitary Radiosurgery: Overview

Pituitary tumors are relatively common neoplasms that represent between 10% and 15% of all intracranial tumors (2, 6, 8, 64, 65). Incidental pituitary tumors are found in approximately 10% of patients undergoing brain imaging for other reasons (7). The vast majority of these tumors are benign and grow slowly, but certain factors involved in the genesis of the tumor (G-protein abnormalities, ras gene mutations, p53 gene deletions, mutations) may determine its rate of growth and aggressiveness.

Classification of Pituitary Tumors

Based on size, pituitary adenomas can be divided into microadenomas (≤ 1 cm diameter) and macroadenomas (>1 cm diameter). They also can be classified on the basis of clinical presentation, serum hormone levels and immunohistochemical staining characteristics. The current prevalent classification (functional) method relies on immunohistochemistry performed on tissue samples obtained at surgery.

Presenting Symptoms

Clinical symptoms result from mass effect on surrounding structures, tumor invasion and symptoms related to elevated or reduced systemic hormone levels. With pituitary macroadenomas, symptoms related to mass effect and pressure on surrounding structures, and occasionally tumor invasion of those structures, tends to dominate the clinical presentation. Fifty to sixty percent of patients with macroadenomas present with visual field abnormalities due to compression of optic nerve structures. Nonspecific headache can be seen, or headache symptoms may be referred to the forehead in the distribution of cranial nerve V1. Compression of the normal pituitary can cause hypopituitarism. Invasion of the cavernous sinus may cause other visual symptoms (ophthalmoplegia, diplopia,

ptosis) or facial numbness or pain. Extension into the sphenoid sinuses can cause spontaneous cerebrospinal fluid (CSF) rhinorrhea. In addition to these symptoms resulting from tumor mass effect or invasion of surrounding structures, endocrine dysfunction can result from excess production of pituitary hormones from the tumor (functional or secretory adenoma), or from compression of the stalk or of the normal pituitary gland. The endocrinologic manifestations are dependent on the specific overproduction or underproduction of a hormone or hormones associated with the tumor. Rarely a patient with a pituitary adenoma will present with sudden onset headache, visual loss, and hormonal dysfunction resulting from sudden hemorrhage and/or infarction within the tumor leading to sudden, rapid expansion of tumor size (pituitary apoplexy).

Hormonal Overproduction—Clinical Effects

Prolactin

- Hypogonadism, if hyperprolactinemia is sustained, especially in males
- Women—Amenorrhea, galactorrhea and infertility
- Men—Decreased libido and impotence
- Osteoporosis

Growth Hormone

- Children and adolescents—May result in pituitary gigantism
- Adults—Acromegaly (changes in the size of hands and feet, coarseness of the face, frontal bossing, prognathism, changes in the voice, diabetes mellitus, hypertension, sleep apnea and cardiomyopathy)

ACTH

- Cushing's disease is characterized by weight gain, centripetal obesity, moon facies, hirsutism, violet striae, easy bruisability, proximal myopathy, mood disorder, diabetes mellitus, and secondary cardiac changes

Sex

Symptomatic prolactinomas are found more frequently in women. Cushing's disease also is more frequent in women (female-to-male ratio 3:1). The incidence of acromegaly is equal for men and women.

Age

Most pituitary adenomas occur in young adults, but they may be seen in adolescents and elderly persons. Acromegaly usually is diagnosed in the fourth and fifth decades of life.

Laboratory Studies

Prolactinomas

- Serum prolactin levels are elevated. Levels above 200 mg/L in a patient with a macroadenoma greater than 10 mm in size are diagnostic of a prolactinoma. Levels below that range in a macroadenoma suggest that hyperprolactinemia may be secondary to pituitary stalk or hypothalamic compression (stalk dysinhibition effect). Levels >2000 mg/L are highly suggestive of an invasive growth of a prolactinoma (23).

Growth Hormone Abnormalities

- Growth hormone (GH) levels are elevated in acromegaly but can fluctuate significantly. The oral glucose tolerance test (OGTT) is the definitive test for the diagnosis of acromegaly; a positive result is the failure of GH to decrease to $<1 \mu\text{g/L}$ after ingesting 50-100 g of glucose. A GH level $>5 \mu\text{g/L}$ suggests acromegaly.
- Serum insulin-like growth factor 1 (IGF-1) level is a more practical endocrinologic test for acromegaly. The IGF-1 level reflects GH concentration over the preceding 24 hours.

Cushing's Disease

- Twenty-four hour urine free cortisol is elevated. Usually two baseline values are obtained.
- Low-dose dexamethasone test: Two-day baseline serum and urine cortisol levels are determined. The patient is then given four doses of 0.5 mg dexamethasone at six hour intervals. Normal suppression is a serum cortisol level of $<138 \text{ nmol/L}$ or a urine level of $<55 \text{ nmol/L}$. If cortisol levels are increased abnormally, corticotrophin-releasing factor (CRF) in a dose of 1.0 mg can be given to differentiate between Cushing's disease and other causes of hypercortisolism (i.e., Cushing's syndrome). With pituitary adenomas, cortisol secretion is increased over the baseline.
- High-dose dexamethasone test: Cortisol suppression after high-dose dexamethasone (8 mg) confirms the diagnosis of a pituitary adenoma. It suppresses the pituitary gland even in the presence of an adenoma. If cortisol levels remain unchanged, the cause of increased cortisol is not a pituitary adenoma.
- Serum levels of ACTH: The serum concentration of ACTH is higher than normal ($>5.5 \text{ pmol/L}$ at 9 am and $>2.2 \text{ pmol/L}$ at midnight). At times, venous sampling of ACTH from the inferior petrosal sinuses by means of cerebral venography may be valuable in confirming the diagnosis. Inferior petrosal sinus sampling (IPSS) may be used in selected cases to suggest lateralization of the tumor.

Imaging Studies

Pre- and post-gadolinium MRI of the brain and sellar region with multiplanar thin sections (1 mm) is of critical importance, especially in the coronal plane.

Medical Management

The majority of prolactinomas respond to dopamine receptor agonists such as bromocriptine. Medical management can result in improvement in visual field abnormalities, resolution of symptoms associated with hyperprolactinemia (galactorrhea, amenorrhea) and tumor shrinkage. Somatostatin analogues (e.g. octreotide) and a growth hormone receptor antagonist, pegvisomant, can be helpful in the treatment of increased postoperative levels of GH in cases of acromegaly. Dopamine agonists also have been used. Pituitary hormone replacement therapy for decreased or absent hormones should be instituted as needed. For selected

patients with Cushing's disease, ketoconazole may be prescribed to reduce cortisol production. Medical management is extremely useful as either first line therapy for secretory adenomas or as an adjunct in a combined multimodal approach to overall patient management. Care must be used when employing these agents peri-operatively for either microsurgical resection or stereotactic radiosurgery. Accumulated clinical experience suggests that these agents can lead tumors to be denser and more fibrotic, thus technically more challenging to remove during microsurgery. Likewise, there are some data to suggest that both bromocriptine and octreotide may confer relative radioresistance to tumors undergoing stereotactic radiosurgery (25–27). As a result, many clinicians suggest stopping these agents four to six weeks prior to any contemplated surgical intervention. These agents can be restarted one week after radiosurgery.

Surgical Management

The primary aim of treatment for clinically hyperfunctioning or nonfunctioning pituitary macroadenomas is tumor removal and preservation of visual function. Transphenoidal surgery is the preferred approach for managing pituitary adenomas (8, 9, 64, 65, 69). For large lesions with lateral suprasellar extension, a craniotomy may be necessary to decompress the visual pathways as well as resect any non-midline suprasellar extension that may have occurred. Adequacy of treatment is assessed by radiological and visual evaluations. Because microadenomas ($\leq 10 \text{ mm}$ in diameter) are recognized due to endocrinopathy related to tumor hormonal secretion, the aim of treatment is to correct endocrine dysfunction. This usually requires radical tumor removal. The adequacy of treatment for hypersecreting adenomas is defined by correction of endocrinopathy and preservation of normal pituitary function. Transphenoidal resection is associated with an excellent outcome and successful decompression of the visual pathways. Surgical complications are relatively rare but can include incomplete resection of large adenomas, transient or permanent diabetes insipidus, CSF rhinorrhea, hormonal deficiencies and residual visual field defects. The main endocrine complication after transphenoidal surgery is hypopituitarism. All patients should be assessed for potential need for selective hormone replacement therapy following transphenoidal resection of an adenoma. Failure to achieve permanent remission occurs in at least 5–15% of cases (15), even in the hands of experienced surgeons. The success and complication rates are significantly less favorable with second surgical resection.

Fractionated Radiation Therapy

Fractionated radiation therapy has been used for the treatment of unresectable pituitary adenomas. Rates of tumor control have been reported to vary from 76% to 97%. Fractionated radiation therapy, however, has been less successful (38–70%) in reducing hypersecretion of hormones by hormonally active tumors. It may take years before the full therapeutic effect is exhibited. The delayed complications of fractionated radiation therapy (2–10 years) include a relatively high risk of hypopituitarism (12–100%) and a low but definite risk of optic neuropathy (1–2%) and secondary tumor formation. Some investigators have reported a higher likelihood of cerebrovascular disease in patients treated with radiation therapy for pituitary tumors. In patients with a benign

neoplasm and an otherwise normal expected life span, external beam fractionated radiotherapy (EBRT) leads to exposure of normal surrounding brain to potential long-term cognitive effects of radiotherapy. Newer fractionated radiotherapy techniques such as intensity modulated radiotherapy (IMRT) can minimize the amount of normal brain exposed to radiation compared with conventional or standard 3-D conformal techniques. However, the medial temporal lobes on either side, which are intimately involved in memory processing and learning, often remain exposed as the radiation distribution is shifted away from the optic nerves and chiasm. Minimal long-term outcome data exist for IMRT.

Stereotactic Radiosurgery

The endocrine control aims of radiosurgery are no different from those of surgical resection; namely, normalization of any hypersecretory syndrome without new onset hypopituitarism. Unlike surgical resection, which eliminates the tumor on subsequent neuroimaging, the neoplastic goal of stereotactic radiosurgery is permanent tumor control. This means that a tumor, which has been enlarging, is made incapable of further tumor growth, and this control is confirmed through long-term neuroimaging follow-up. While permanent stabilization of tumor size is the desired goal, the majority of tumors will demonstrate varying degrees of tumor shrinkage over time. Thus the goal of pituitary adenoma radiosurgery is to permanently control tumor growth, maintain pituitary function, normalize hormonal secretion in the case of functional adenomas, and preserve neurological function, especially vision. The small risks of late radiation-induced tumorigenesis and of late cerebrovascular accidents from radiation damage to the internal carotid arteries also exist for patients treated with radiosurgery. Delayed complications are less than that of stereotactic radiotherapy.

Radiosurgery Dose Planning

High-resolution stereotactic magnetic resonance imaging is mandatory for pituitary radiosurgery. Contrast enhanced stereotactic 3D volume acquisition (gradient recalled) is ideal. For patients with a history of trans-sphenoidal surgery a fat suppression sequence is performed. Pituitary radiosurgery planning is usually complex because a highly conformal dose plan is needed to spare the optic apparatus (optic nerves, chiasm and tracts) as well as any remaining normal pituitary gland. Dose selection is based on the tolerance of the adjacent structures. The optic pathway is the most sensitive structure to radiation exposure, and ideally the dose to this structure is kept less than 9 Gy (31, 60). If the goal is close to zero percent risk of permanent optic neuropathy, most radiosurgeons consider 8 Gy to be a safe dose, so long as the patient has not received a prior radiation dose to the area. There are occasions where it is appropriate to deliver higher doses to the optic apparatus, particularly in cases of secretory macroadenomas where higher tumor doses are required to normalize endocrine function. In these cases, a small risk of optic neuropathy is measured against the need for tumor control or hormonal normalization and these differential risks are shared and discussed with the patient pre-operatively. Current data suggest that the risk of permanent optic neuropathy is <2% for doses as high as 12 Gy/10Gy delivered with the Gamma Knife®, as long as the patient has not received prior radiotherapy (56). It is however the volume of optic apparatus receiving high dose that determines the rate of optic neuropathy. The optic

apparatus may be more vulnerable because of previous compression and prior surgery. Most centers limit the radiosurgical dose to the optic apparatus to < 8 Gy. With current technique a 1–5 mm distance between the tumor and the optic chiasm is enough to safely and effectively perform Gamma Knife® radiosurgery depending on margin dose and target volume. If necessary, selected radiation sources can be blocked to reduce dose fall off to the optic apparatus. A minimum margin dose of 12 Gy is generally considered a safe tumor control dose. Higher doses of at least 15 Gy to ensure reliable and early tumor growth control may be prescribed when distance from the tumor margin to the optic apparatus allows. Although tumor growth control is achieved in most patients, the rate of hormone normalization after radiosurgery is lower with lower doses. Some investigators suggest higher marginal dose (up to 30–35 Gy) whenever possible for treating small volume secretory pituitary adenomas (20, 21). Higher marginal doses are may be associated with a higher rate of hormone normalization.

Tumor Growth Control After Radiosurgery

Non-functioning pituitary adenomas are usually diagnosed late when patients complain of visual dysfunction. Trans-sphenoidal decompression is recommended as the first line of management for these patients. Radiosurgery is often indicated as an adjuvant management after partial resection or later recurrence of pituitary adenomas. However, radiosurgery can be performed as the primary management of non-functioning adenomas in carefully selected patients, including those who are high risk for surgery or consciously choose not to undergo resective surgery. Tumor growth control rates of 90–100% have now been confirmed by multiple centers following pituitary radiosurgery (13, 20, 21, 24, 26, 41). The anti-proliferative effect of radiosurgery has been reported in nearly all patients who underwent Gamma Knife radiosurgery (24, 41). Relatively few patients (who usually had received lower margin doses) eventually required additional treatment (12, 46).

Cavernous Sinus Invasion

Cavernous sinus invasion can occur de novo in patients with large pituitary macroadenomas, but is more commonly seen in patients who develop a recurrent tumor after an attempted microsurgical resection attempt. The cranial nerve complication and cerebrovascular risks of cavernous sinus microsurgery are significantly greater than these risks for routine trans-sphenoidal surgical approaches. As a result, cavernous sinus involvement of a pituitary adenoma is an excellent indication for stereotactic radiosurgery. In many cases, the cavernous sinus mass can be treated while selectively sparing not only the optic apparatus, but also the pituitary stalk and residual pituitary gland within the sella turcica. For secretory adenomas, initial first stage extracavernous microsurgery is often optimal in order to reduce the subsequent tumor volume and create space between the tumor and the optic apparatus, thus allowing safe delivery of the highest dose of radiosurgery possible. For nonsecretory adenomas, the desirability of performing first stage microsurgical extracavernous debulking often depends on overall tumor volume and the space already present between the tumor and the optic apparatus. Microsurgery and stereotactic radiosurgery are now often utilized in a coordinated and planned staged manner for patients with pituitary adenomas that exhibit cavernous sinus involvement at the time of presentation. Adenomas that have invaded the

cavernous sinus and require deliberate high-dose irradiation of tumor contiguous to the carotid may increase the risk for delayed cerebrovascular problems.

Functional Effect of Radiosurgery

Growth Hormone Secreting Adenomas (Acromegaly)

A biochemical remission is defined as GH level suppressed to below 1 µg/L on OGTT and normal age-related serum IGF-1 levels. OGTT remains the gold standard for defining a cure of acromegaly. IGF-1, however, is far more practical. Decrease of random GH to less than 2.5 µg/L is achieved more frequently than the normalization of IGF-1 but it is necessary to obtain the fulfilment of both criteria. Microsurgery results in biochemical remission in 31–80% of patients (1, 5, 19, 53, 59). The suppression of hormonal hyperactivity is more effective when higher doses of radiation are used. Hormonal normalization after radiosurgery was achieved in 29–82% of cases in the published series (3, 4, 11–14, 17, 19, 20, 22, 24, 25, 30, 32, 33, 35, 36, 41, 42, 45, 47–49, 57, 62, 68). Because hormone-suppressive medication during radiosurgery may act as a radioprotective agent, this medication should be discontinued at least six to eight weeks prior to radiosurgery (25, 49) and may be resumed after a week. In a study at the University of Pittsburgh, 38% of patients were cured (GH \leq 1 µg/L) and overall, 66% had growth hormone levels \leq 5 µg/L, 3–5 years after radiosurgery (44). An important goal of resective surgery is to achieve an immediate postoperative effect, while the results of radiosurgery have a latency of about 20–28 months (18, 28) that must be sometimes temporized through the temporary use of hormone suppressive medications.

ACTH Secreting Adenomas

Cushing's disease: The results to date achieved by radiosurgery (usually used after failed resective surgery) are slightly inferior to those reported after primary surgical resection in regard to secretory normalization. In addition there is a latency of approximately 14–18 months for maximal therapeutic response (18, 28). Patients with Cushing's disease respond to radiosurgery but more than one procedure may be needed. In various published series 63–98% hormone normalization after radiosurgery has been observed (10, 16, 29, 33, 36, 38, 40, 43, 46, 50, 51, 54, 55, 58, 63).

Nelson's syndrome: Maintenance of elevated ACTH levels indicates continued biochemical activity of a pituitary adenoma after prior adrenalectomy for Cushing's disease. Strict hormonal normalization is not as important for the treatment of pituitary adenomas associated with Nelson's syndrome as it is for other secretory pituitary adenomas. The most important task of radiosurgery in the case of Nelson's syndrome is to control the growth of the tumor, which has been achieved in the majority of cases (66).

Prolactin Secreting Adenomas

Most prolactinomas can be controlled successfully by medical treatment. Surgery is indicated for cases of intolerance to medical treatment, in cases where women desire to have children, or when patients are dopamine agonist resistant (5–10% of patients). Some patients prefer microsurgery or radiosurgery to the need for life long medical treatment. In published studies of patients treated with radiosurgery, 25–29% showed normalization (26, 49). The possible radioprotective effect of dopaminergic drugs should be taken into account. In one of the studies patients treated with dopamine agonist had lower remission rates. It is therefore recommended that

radiosurgery for prolactinoma be performed during a period of drug withdrawal (26).

Radiation Tolerance of Functioning Pituitary Tissue

The most important factor influencing post-irradiation hypopituitarism seems to be the mean dose to the hypophysis (pituitary stalk). Vladyka et al. observed some worsening of gonadotropic, corticotropic or thyrotropic functions 12–87 months after radiosurgery and usually 4–5 years after radiosurgery (61). There was no post radiation worsening of gonadotropic and thyrotropic functions when the mean dose to the hypophysis did not exceed 15 Gy. The limiting mean dose to the hypophysis for adrenocorticotrophic function was 18 Gy (61). In another study, deterioration in pituitary functions was observed when the pituitary stalk received higher doses (10). The risk for hypopituitarism after stereotactic radiosurgery thus becomes a primary function of the anatomy of the tumor and the dose prescribed. For recurrent tumors primarily involving the cavernous sinus, where the pituitary stalk (and even at times the residual pituitary gland) is separate from the tumor, easily visualized, and can be excluded from the treatment volume, the risk of hypopituitarism is extremely small, even when high doses are utilized for secretory adenomas. For adenomas that cannot be visually separated from the normal gland, particularly if they extend upward to involve or compress the pituitary stalk, the risk is predominantly related to the dose necessary to effectively achieve all treatment goals for the functional status of the tumor (higher for secretory than nonsecretory adenomas).

Complications of Pituitary Radiosurgery

Complications of pituitary radiosurgery fall into three categories: hypopituitarism, visual deterioration and hypothalamic damage. The following rates of hypopituitarism have been reported: Levy et al. (32), 33%; Thoren et al. (57), 24%; Rocher et al. (52), 33%; and Lunsford et al. (34), 0%. As discussed in the section above, hypopituitarism risks vary with tumor anatomy relative to the pituitary stalk and gland, and vary with whether the adenoma is secretory or non-secretory (higher dose needed in the former). Stereotactic radiosurgery for residual or recurrent nonsecretory adenomas solely involving the cavernous sinus carries the lowest risk of subsequent hypopituitarism, while secretory tumors close to the median eminence or requiring targeting of the whole pituitary gland carry the highest risk. Future studies must stratify for these variables in order to better predict hypopituitarism risk after stereotactic radiosurgery in an individual patient. Levy et al. (32) reported <1% increase in visual deficit in their large series. Lunsford et al. (34) reported one patient with visual compromise. Using LINAC radiosurgery, Rocher et al. reported a 39% incidence of some visual compromise (6% of patients were blinded) (52). The key to avoiding this complication lies in proper patient selection (adequate space between the optic apparatus and the superior edge of the tumor for the radiosurgery technique you are employing), insisting on strictly conformal planning at the critical structure interface, and accurate dose delivery. Lunsford et al. reported one death due to hypothalamic injury in a patient who had multiple operations, prior pituitary apoplexy and prior fractionated radiation therapy (34). Voges et al. reported one patient who developed a severe hypothalamic syndrome (62). Mitsumori et al., using LINAC radiosurgery for tumor invading the cavernous sinus, reported three cases of temporal lobe necrosis (39). As

discussed above, there is a theoretical risk of late radiation-induced tumorigenesis for patients receiving radiosurgical treatment. A small risk also exists of late cerebrovascular accidents from the effect of the ionizing radiation on the cerebral circulation passing adjacent to the pituitary gland. Fortunately, while the risk of major morbidity or mortality is not zero with radiosurgery, these occurrences appear to be extremely rare.

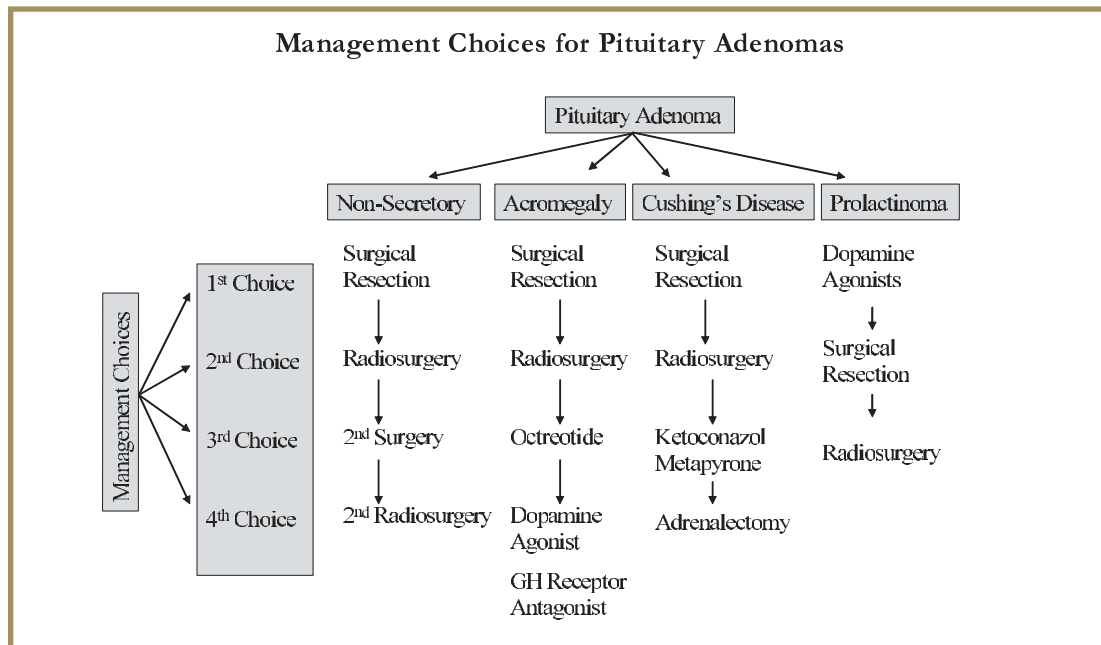
Conclusion

Patients with pituitary adenomas are best managed with a multidisciplinary team approach. Multimodal treatment is often necessary, and options include medical management, microsurgery, stereotactic radiosurgery and fractionated radiotherapy. Trans-sphenoidal tumor resection remains the primary recommendation for macroadenomas compressing the optic apparatus or when a rapid reduction in excessive hormone level is required. However about 30% of patients require adjuvant treatment after microsurgery. For residual or recurrent tumors fractionated radiation therapy has been the traditional treatment in the past (37, 67). Fractionated radiation therapy, however, has a prolonged latency up to one decade for its effects and is associated with more frequent side effects: hypopituitarism, visual damage, cerebral vasculopathy, radiation necrosis, potential cognitive effects and radiation induced tumors. While many of these risks have been reduced through improvement in fractionated radiotherapy techniques, the long latency of the effect, and the potential for cognitive effects from exposed normal brain continues to be a significant problem. For many residual or recurrent tumors single session radiosurgery provides growth control and long-term endocrine control that is superior to that of repeat resective surgery. The latency of the radiation response after radiosurgery is substantially shorter than that of fractionated radiotherapy. This short

latency can be managed by suppressive medical therapy as a temporizing measure in selected cases. The risk of hypopituitarism is significantly lower with single session radiosurgery as compared to fractionated radiation therapy. The absence of long-term adverse cognitive effects after stereotactic radiosurgery is consistent with technical differences between radiosurgery and fractionated techniques. Stereotactic radiosurgery better limits radiation exposure of the surrounding normal brain. At the present time the major role of pituitary adenoma radiosurgery is as an adjuvant to surgical resection, although it has a primary role for selected cases who are higher medical risk for general anesthesia or microsurgery, for patients with cavernous sinus tumor involvement, and for patients who consciously choose not to undergo microsurgery.

Clinical Algorithms

A broad outline of management choices is shown below; however, the final recommendation is usually influenced by the cumulative experience of the medical management team. The choices listed are not mutually exclusive. Combinations of different treatments may be necessary and/or desired under certain circumstances. Common examples include patients with cavernous sinus involvement present at diagnosis who undergo first stage microsurgery for the extracavernous portion of their tumor followed by second stage radiosurgery for the cavernous sinus component, and patients with secretory adenomas who undergo radiosurgery but are then maintained on their antisecretory medications during the latency period for hormonal normalization after radiosurgery. The common need for staged or tandem treatments with multiple modalities underscores the importance of the presence of a comprehensive and coordinated multidisciplinary team in the optimal management of pituitary adenoma patients.

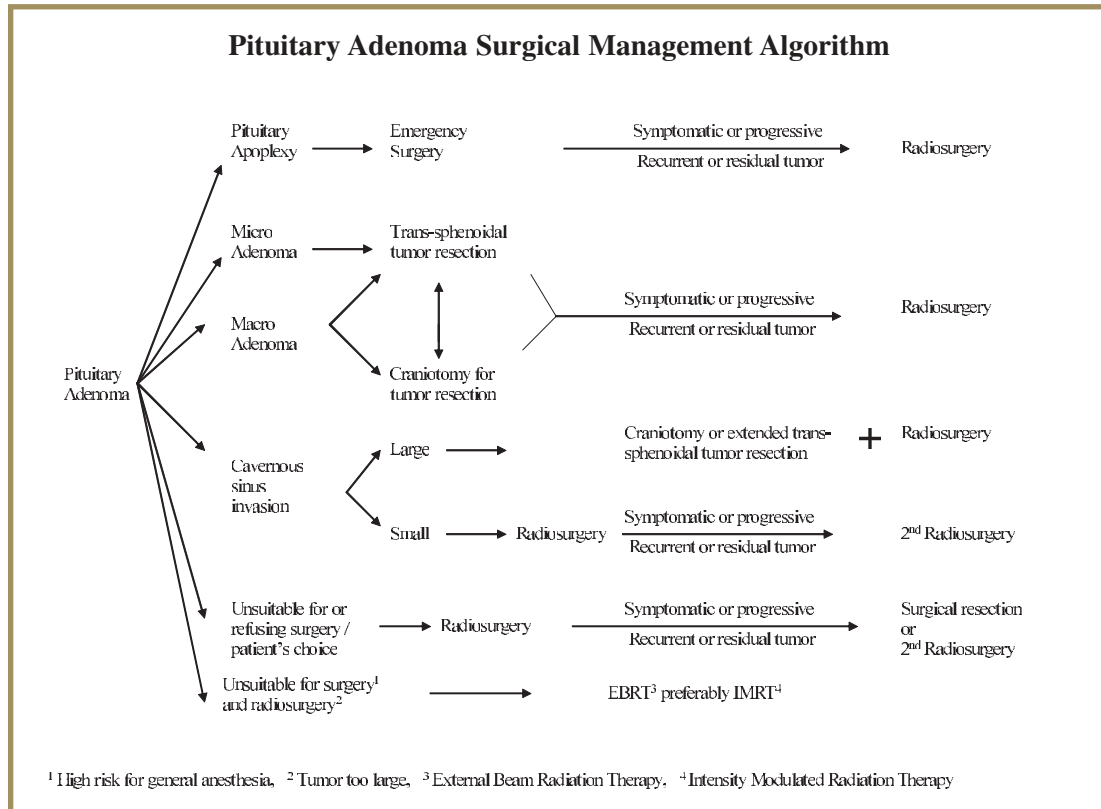


Surgical Management Considerations

A number of factors are considered in making a recommendation regarding surgical management. These factors include:

1. Patient's age
2. Hormonal status of the adenoma (secretory or non-secretory)

3. Presenting symptoms and neurological status (vision) of the patient
4. Patient's medical condition (comorbidities)
5. Previous tumor resection (via trans-sphenoidal approach or craniotomy) history
6. Prior radiation exposure
7. Volume of the tumor
8. Proximity to the optic apparatus
9. Response to medical management



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COMPLETE SUMMARY

TITLE:

Stereotactic Radiosurgery for Patients with Pituitary Adenomas.

RELEASE DATE:

April 2004

DEVELOPER AND FUNDING SOURCE:

IRSA (International RadioSurgery Association)

DEVELOPER COMMENT:

IRSA (International RadioSurgery Association) is a non-profit entity dedicated to promoting the development of scientifically relevant practice guidelines for stereotactic radiosurgery. IRSA is a professional association that works to educate and provide support for physicians, hospitals, insurers and patients.

COMMITTEE:

The IRSA Medical Advisory Board Guidelines Committee and representatives in the industry

GROUP COMPOSITION:

The Radiosurgery Guidelines Committee is comprised of neurological surgeons, endocrinologists, radiation oncologists, and medical physicists.

Names of Group Members: L. Dade Lunsford, M.D., Neurosurgeon, Chair; Ajay Niranjani, M.B.B.S., M.Ch., Neurosurgeon; Tatsuya Kobayashi, M.D., Ph.D., Neurosurgeon; Mark Linskey, M.D., Neurosurgeon; Thomas Witt, M.D., Neurosurgeon; Alex Landolt, M.D., Neurosurgeon; Roman Liscak, M.D., Neurosurgeon; Edward R. Laws Jr., M.D., Neurosurgeon; Mary Lee Vance, M.D., Endocrinologist; John Buatti, M.D., Radiation Oncologist; Jonathan Knisely, M.D., Radiation Oncologist; Paul Sperduto, M.D., Radiation Oncologist; Sammie Coy, Ph.D., Medical Physicist; Tonya K. Ledbetter, M.S., M.F.S., Editor; Rebecca L. Emerick, M.S., M.B.A., C.P.A., "ex officio."

DISEASE/CONDITION:

Pituitary adenomas, acromegaly, Cushing's disease, Nelson's syndrome, prolactinoma.

NUMBER OF REFERENCES:

70

CATEGORY:

Treatment, proposed surgical management

CLINICAL SPECIALTY:

Neurological surgery
Radiation oncology
Neurology
Medical Physics
Endocrinology
Gynecology

INTENDED USERS:

Physicians
Health Care Providers
Hospitals
Managed Care Organizations
Nurses
Utilization Management

OBJECTIVES:

To provide guidelines about the use of stereotactic radiosurgery in symptomatic patients with imaging identified pituitary adenomas with treatment recommendations to be used by medical and public

health professionals. Such patients may or may not be candidates for alternative management strategies that include observation, medical management, surgical resection via trans-sphenoidal approach or craniotomy and fractionated radiation therapy.

TARGET POPULATION:

Men and women >2 years old with imaging identified functional or nonfunctional pituitary adenomas.

INTERVENTIONS AND PRACTICES:

Stereotactic radiosurgery of pituitary adenomas is performed using a single procedure or occasionally staged procedure (volume staging) techniques based on intraoperative stereotactic guidance and digitally acquired images (CT or preferably MRI). Minimal tumor margin doses in a single radiosurgical procedure vary from 11 to 16 Gy for non-functional (non-secretory) adenomas. Higher marginal doses (25–35 Gy) are necessary for hormone normalization in cases of functional (secretory) pituitary adenomas. The dose prescription for volumetric conformal pituitary radiosurgery in an individual case is designed to provide maximal dose sparing to surrounding critical structures, especially optic apparatus.

OUTCOMES CONSIDERED:

Long-term growth control (stabilization or regression) of non-functional pituitary adenomas and pituitary hormone normalization in cases of functional pituitary adenomas are the primary end points of interest. Maintenance of quality of life, employability, and prevention of adverse radiation effects are also considered.

METHODS TO COLLECT EVIDENCE:

Hand Searches of Published Literature (Primary Sources); Hand Searches of Published Literature (Secondary Sources); Searches of Electronic Databases

DESCRIPTION OF METHODS TO COLLECT EVIDENCE:

MEDLINE and PUBMED searches were completed for the years 1971 to April 2004. Search terms included pituitary adenomas, acromegaly, Cushing's disease, prolactinoma, stereotactic radiosurgery, Gamma Knife, irradiation, Linac radiosurgery, proton beam radiosurgery, Bragg peak proton therapy, clinical trials, research design, practice guidelines and meta-analysis. Bibliographies from recently published reviews were reviewed and relevant articles were retrieved.

METHODS TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE:

Expert consensus (committee)

METHODS TO ANALYZE EVIDENCE:

Review of published meta-analysis

REVIEW METHODS:

External peer review; internal peer review

DESCRIPTION OF REVIEW METHODS:

The recommendations were originally suggested by a core group of two members (LDL/AN). These recommendations were electronically mailed to all committee members. Feedback was obtained in order to revise the proposed guidelines. Committee members

were asked whether the recommendations should serve as a practice guideline. No significant disagreements existed. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with the final consensus recommendations supported by all working group members.

MAJOR RECOMMENDATIONS:

- Patients with pituitary adenomas, defined by modern neurodiagnostic imaging (CT, MRI scan) constitute the study group. Such patients typically present with symptoms related to pituitary hormone imbalance (acromegaly, Cushing's disease, prolactinoma, etc.) in cases of functional adenomas and symptoms of mass effect (headache, visual changes and progressive neurological deficits) in cases of non-functional adenomas. Pituitary adenomas are considered suitable for multimodal management including observation, surgical excision, fractionated radiation therapy and stereotactic radiosurgery. Stereotactic radiosurgery is typically employed in combination with prior surgery but may be employed alone in particular circumstances. The selection of patients suitable for radiosurgery is dependent on the prior treatment history, the age of the patient, existing co-morbidities, anatomic location of the tumor and clinical history. Single session radiosurgery, a minimally invasive, single high-dose, closed skull treatment strategy, may be especially suitable for patients in advanced age groups, those with excessive medical co-morbidity risk factors for surgical excision, and those with adenoma involving the cavernous sinus.
- The optimal dose range for volumetric conformal stereotactic pituitary radiosurgery has been largely established based on tumor anatomy (proximity to visual apparatus), hormonal secretory status, volume, estimated adverse radiation risks, pre-existing neurological conditions and prior history of radiation therapy. Minimum doses to the margin of the non-functional pituitary adenomas typically range from 12–16 Gy in a single fraction. For secretory adenomas, minimal margin doses as high as 30–35 Gy are optimal if they can be administered safely given the anatomic relationship of the tumor edge to surrounding radiosensitive structures. Stereotactic volumetric imaging (high resolution) is usually necessary for precise conformal dose planning. MRI target imaging is preferred. Depending upon the technology used, the margin of the radiosurgery dose is usually 50–90% of the central target dose within the tumor. Sharp fall-off of the radiation dose outside of the target volume is required. Current radiation delivery technologies for volumetric stereotactic conformal single session radiosurgery include Gamma Knife®, proton beam using Bragg peak effect, and specially modified linear accelerators.
- Patients may receive a single stress dose of corticosteroids at the conclusion of the radiosurgery procedure. It is recommended that hormone suppression therapy (dopaminergic drugs for prolactinomas and octreotide for acromegaly) be discontinued at least 1–2 months prior to radiosurgery. Currently used long acting drugs (e.g. slow release octreotide) should be discontinued 3–4

months prior to radiosurgery. These medications can be restarted one week after the radiosurgery procedure. Patients can continue to take other medications as recommended by their physicians.

- Postradiosurgical clinical examinations and MR studies are requested by referring physicians at six month intervals for the first year and then annually to assess the effect of radiosurgery for 4–5 years. Visual field and acuity testing along with serum and urinary hormone screening are recommended at intervals coinciding with clinical and neuroimaging re-evaluations. Tumors proven to be stable over five years can then be subsequently reassessed at 2–4 year intervals.
- For non-functional adenomas estimated tumor control rates vary from 90–100%. Stereotactic radiosurgery should not be considered as the panacea for large volume pituitary adenomas, which are better managed initially by surgery. This is particularly true for patients who present with sudden symptomatic mass effect from pituitary apoplexy.
- Causes for failure of stereotactic radiosurgery include inadequate visualization of the tumor, lack of intraoperative stereotactic 3-D (volumetric) imaging, and insufficient dose (due to proximity with optic apparatus) to achieve the growth control response.
- Stereotactic radiosurgery is defined as a relatively high dose of focused radiation delivered precisely to the pituitary adenoma, under the direct supervision of a medical team (neurosurgeon, radiation oncologist, registered nurse, and medical physicist), in one surgical treatment session.

TYPE OF EVIDENCE:

Type I, II and III evidence (Bandolier) exists in support of stereotactic radiosurgery for pituitary adenomas.

POTENTIAL BENEFITS:

All the published studies have shown a significant tumor control response of stereotactic radiosurgery for non-functioning pituitary adenomas with a low (satisfactory) rate of adverse radiation effect. For functional adenomas normalization of hormone levels is considered necessary in order to define success. Successful outcomes include complete tumor control (stabilization or regression), symptomatic relief, no new neurological deficits, no long-term complications and normalization of pituitary hormone levels.

Literature has documented the cost savings benefit of stereotactic radiosurgery versus invasive surgical procedures and the lower risk potential of bleeding, anesthesia problems, infections and side effects which may include transient or permanent disabilities from open surgery.

SUBGROUP(S) MOST LIKELY TO BENEFIT:

Patients with residual or recurrent pituitary adenoma after resection. Patients with small pituitary adenoma without any previous surgery.

POTENTIAL HARMS:

Major adverse effects of radiosurgery are based on location, volume, and dose, and these risks can be estimated based on published data and experience. Individual risks are related to the anatomic proximity of pituitary adenoma with the optic apparatus and structures of cavernous sinus. Risk of delayed hypopituitarism after single session radiosurgery is low.

SUBGROUP(S) LIKELY TO BE HARMED:

Patients with large volume adenomas causing symptomatic mass effect on optic apparatus who are treated with large doses in a single session radiosurgery as primary management. Patients with functional adenomas treated with low dose will benefit least from radiosurgery.

GUIDELINE STATUS:

This is the full current release of the guideline.

GUIDELINE AVAILABILITY:

Electronic copies: Available in Portable Document Format (PDF) from www.IRSA.org

Print copies: Available from IRSA, 3005 Hoffman Street, Harrisburg, PA 17110

PATIENT RESOURCES:

Patient resources are available on line at www.IRSA.org, by email at intouch@IRSA.org or by calling +717-260-9808.

See "publications" for patient resources for pituitary tumors: www.IRSA.org/publications.html/

Brain Talk® Volume 8, No. 3:

Another Perspective® Volume 4, No. 2; Volume 2, No. 4

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