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# Radiotherapy Techniques for Pituitary Gland Adenomas: A Practical View for Clinicians

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Author CFB designed the study and wrote the first draft of the manuscript. Author DCR managed a careful analysis of the study. Author SRP managed the literature searches. Authors FFV and AFL added figures and tables. All authors read and approved the final manuscript.*

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## ABSTRACT

**Aim:** To give physicians in the field of Endocrinology and Internal Medicine a glance about the current treatment of secretory (SPA) and nonfunctioning pituitary adenomas (NFA) focusing on the role of radiotherapy (RT), its principles and indications, and the perspectives of novel irradiation techniques.

**Background:** Pituitary gland adenomas are the most common intracranial tumors. Due to the variety of clinical sequelae they produce, treatment options range from observation, medical therapy or surgical resection depending on the biochemical profile and clinical status of the patient.

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In case of incomplete surgical resection, tumor recurrence or unresponsiveness to medical treatment, radiotherapy and radiosurgery are commonly offered as adjuvant therapies.

**Materials and Methods:** The latest systematic reviews, primary studies and new diagnostic and treatment guidelines on pituitary gland adenomas were analyzed. Clinical outcomes together with the technical aspects and the role of RT were also evaluated.

**Results:** New data are available about local therapies with radiotherapy. Radiosurgery and fractionated stereotactic radiotherapy play an important role in the management of patients with pituitary adenomas.

**Conclusions:** This article provides an exhaustive review of the current literature about treatment with different radiotherapy techniques.

*Keywords: Pituitary gland; adenoma; radiotherapy; radiosurgery.*

## 1. BACKGROUND

Pituitary adenomas are common among general population. There are several anatomical and histopathological classifications for these tumors, but for treatment purposes it seems appropriate to classify them by size into microadenomas (<1 cm) and macroadenomas (≥ 1 cm). They are also classified by its hormone secretory ability in hormone-producing and non- hormone producing tumors [1].

The first line treatment for symptomatic pituitary adenomas is surgical resection except for prolactinomas, which respond well using medical treatment. However, a large proportion of patients will require additional course of action with further treatment and adjuvant radiation therapy to achieve disease control [2].

In spite of years of clinical experience there remains a scarcity of randomized clinical trials to enable a robust evidence based approach to the optimal use of radiotherapy techniques. This is to some extent offset by the large number of single institution non-randomized retrospective case series which provide evidence on clinical outcomes and toxicities associated with pituitary radiotherapy. Nevertheless, given the nature of the available data, there continue to be areas of controversy regarding the use of particular radiotherapy modalities. We review the available published data on modern radiotherapy techniques for pituitary adenomas treatment, to provide the rationale for radiotherapy technique selection that are available in almost all hospitals.

## 2. RADIOBIOLOGY OF CENTRAL NERVOUS SYSTEM

The aim of radiotherapy techniques for pituitary adenomas is to avoid tumor growth, normalize hormone hypersecretion and preserve neurological functioning of important structures surrounding the sella turcica, especially the optic nerve (See Table 1).

The optical pathway is the most sensitive structure in the brain and the irradiation dose should not exceed 8Gy per fraction [3,4]. Because of the high radiation dose used in each fraction of stereotactic radiosurgery (SRS) total dose to the brainstem should be kept <14Gy, the mean dose to preserve normal pituitary function should be <15Gy, total dose to distal infundibulum should be kept <17Gy, bilateral cochlea should be kept <14Gy, and optic chiasm should be kept less than 12Gy [5-6]. Other surrounding areas of the brain tolerate higher doses of radiation (ie, the ocular motor nerve that passes through the cavernous sinus tolerate total radiation doses of 40Gy) [7].

## 3. PRACTICAL ISSUES OF RADIOTHERAPY TECHNIQUES FOR PITUITARY GLAND ADENOMAS

Radiotherapy aims to deliver effective treatment dose to the target tumor volume minimizing the radiation dose delivered to surrounding normal tissues, thereby reducing the risk of normal tissue injury. This aim has been reached with the modern high precision techniques described below. Improved precision of radiotherapy treatment relies on the increased accuracy in tumor volume delineation achieved by using modern magnetic resonance imaging (MRI).

### 3.1 Fractionated Stereotactic Radiotherapy (FSRT)

It refers to radiation with a daily dose of 1.8-2Gy per fraction to accumulate 50 Gy for NFA and

54-55 Gy for SPA given within 5-6 weeks. The technique used for stereotactic radiotherapy include a linear accelerator with energy >6MV and a highly conformal technique to the target volume. For treatment planning a 1.5-mm-slice-thickness T1 contrast-enhanced fat saturation MRI study of the brain is obtained and coregistered to a 1.5-mm contrast-enhanced computed tomography scan (CT) performed with an individualized thermoplastic head mask for immobilization. The CT and 3D MRI is co-registered and the extent of the tumor, described as the gross tumor volume (GTV), is delineated on the MRI scan, while radiotherapy dosimetry is calculated using the CT scan data. The GTV is expanded isotropically in all three dimensions by a margin of 5-10 mm to account for the uncertainties of immobilization, treatment planning, and delivery. The resulting expanded volume is defined as the planning target volume (PTV). The actual GTV to PTV margin should be based on measurements of uncertainty in treatment delivery that are specific to each hospital immobilization systems. Normal tissue structures adjacent to the pituitary, such as the optic chiasm and optic nerves, the brain stem and the hypothalamus are also outlined to enable the calculation and recording of normal tissue dosimetry. Multiple radiation beams are directed at target and each beam is shaped by a multi-leaf collimator (MLC) to conform closely to the shape of the target volume (See Fig. 1).

**Table 1. QUANTEC, dose constraints for radiotherapy of pituitary adenomas**

| Organ | Volume segment | Endpoint | Dose (Gy), or dose/ volume parameters | Rate (%) |
|---|---|---|---|---|
| **Fractionated External Beam Radiotherapy (FSRT)** | | | | |
| Brain | Whole Organ | Symptomatic necrosis | Dmax <60 | <3 |
| | Whole Organ | Symptomatic necrosis | Dmax= 72 | 5 |
| | Whole Organ | Symptomatic necrosis | Dmax= 90 | 10 |
| | Whole Organ | Symptomatic necrosis | V12 <5-10cc | <20 |
| Brain Stem | Whole Organ | Permanent Cranial Neuropathy or necrosis | Dmax <54 | <5 |
| | Whole Organ | Permanent Cranial Neuropathy or necrosis | D1-D10 <59 | <5 |
| Optic Nerve/ Chiasm | Whole Organ | Optic Neuropathy | Dmax <55 | <3 |
| | Whole Organ | Optic Neuropathy | Dmax 55-60 | 3-7 |
| | Whole Organ | Optic Neuropathy | Dmax>60 | >7-20 |
| Cochlea | Whole Organ | Sensory neural hearing loss | Mean Dose <45 | <30 |
| **Single Dose Stereotactic Radiosurgery (SRS)** | | | | |
| Brain | Whole Organ | Symptomatic necrosis | V12 <5-12cc | <20 |
| Brain Stem | Whole Organ | Permanent Cranial Neuropathy or necrosis | Dmax <12.5 | <5 |
| | <0.5cc | Neuropathy | 10Gy | - |
| Optic Nerve/ Chiasm | Whole Organ | Optic Neuropathy | Dmax <12 | 10 |
| Cochlea | Whole Organ | Sensory neural hearing loss | Prescription Dose <14 | <25 |
| | | Hearing loss | 10 | |
| **Three Fraction Stereotactic Radiosurgery (SRS)** | | | | |
| Brain Stem | <0.5cc | Neuropathy | 18 (6Gy/fx) | |
| Optic Nerve | 0.2cc | Neuropathy | 15 | |
| Cochlea | | Hearing Loss | 17 | |
| **Five Fraction Stereotactic Radiosurgery (SRS)** | | | | |
| Brain | 100% | Necrosis | 20 | |
| Brain Stem | <0.5cc | Neuropathy | 23 (4.6 Gy/fx) | |
| Optic Nerve | 0.2cc | Neuropathy | 20 | |
| Cochlea | | Hearing Loss | 23 | |

*Modified from Marks et al. [7], Benedict et al. [8], Grimm et al. [9]. QUANTEC: Quantitative Analysis of Normal Tissue Radiation Effects in the Clinic*

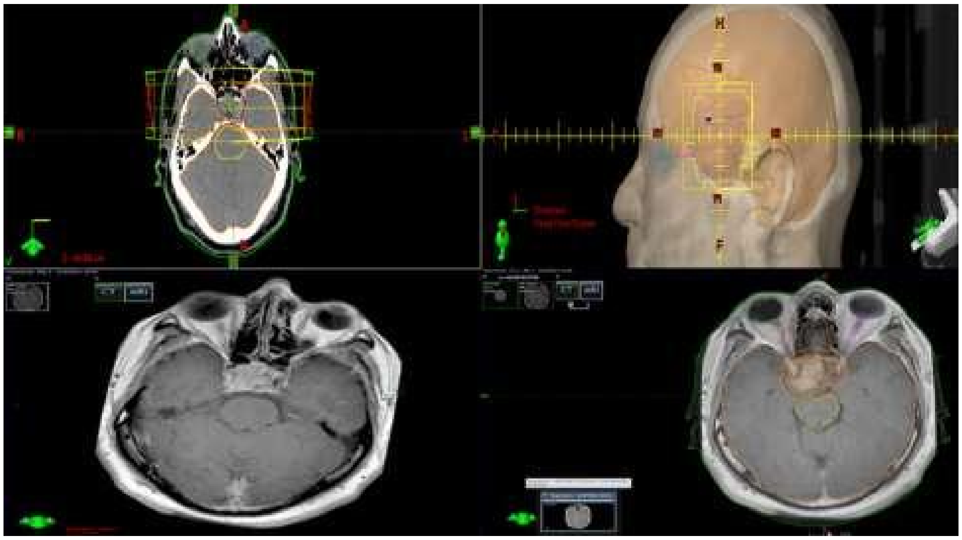

**Fig. 1. CT images from virtual simulation coregistered with MRI images for FSRT planning of a recurrent non-functioning pituitary adenoma**

Even though fractionated radiotherapy has been widely replaced by radiosurgery, current indications for treatment with this technique are:

a) Suboptimal resection of macroadenomas where the optic chiasm is less than 2 mm away from the irradiation field,
b) Persistent hormone production despite complete surgical resection and absence of macroscopic disease by imaging methods,
c) Tumor recurrence surrounding the optic chiasm,
d) Unresectable tumors,
e) Facilities where modern techniques (ie, Gamma Knife®, CyberKnife®, Novalis system) are not available.

Long-term biochemical control is achieved in 93% of cases and it prevents tumor progression in 75-90% of patients. Highly conformal radiotherapy techniques like intensity modulated radiation therapy (IMRT) are now used for the majority of patients with sellar and suprasellar tumors [10]. However, a recent technique of arc IMRT called volumetric modulated arc therapy (VMAT) is used to irradiate pituitary adenomas while preserving healthy surrounding tissues [11]. The advantage of using these techniques relies in their ability of preserving both temporal lobes with a total dose <30Gy thereby significantly reducing the risk of long-term neurocognitive side effects and is increasingly used as an alternative to fixed field 3D FEBRT technique (Fig. 2) [12,13].

### 3.2 Stereotactic Radiosurgery (SRS)

The term “stereotactic” is derived from neurosurgical techniques, and refers to a method of determining the position of a lesion within the brain using an external 3D co-ordinate system based on a method of immobilization, usually an invasive head frame or frameless method with a thermoplastic mask. The term radiosurgery is used for radiation treatment given as a single large ablative dose (a single fraction), and the term radiotherapy is used for treatment that is given as multiple, usually daily, small doses over a week (three to five fractions). The fractionation of radiation treatment is a mechanism for protecting normal tissues, and permits the delivery of higher total doses of radiation [14].

**Single Dose SRS:** The use of single fraction SRS is based on a belief that there is greater clinical benefit from single fraction for pituitary adenomas. This was based on radiobiological modelling which defines equivalent radiation doses and fractionation schemes through biologically derived parameters based on the radiobiology of malignant tumors. As benign tumors are rarely grown in culture, the precise mechanism of the observed clinical benefit of irradiation is not elucidated and remains largely theoretical [15-17].

Initially developed by Lars Leksell in 1951, radiosurgery delivers a single high dose of radiation to the target volume. Gamma Knife® was first used in 1968 to irradiate pituitary adenomas. Since then several technologies have been developed and commercialized (Cyberknife®, Novalis®, Edge®, proton therapy). This technique is characterized by administering a punctual dose allowing lower radiation doses into healthy tissues (See Fig. 3). Dose usually ranges between 12-18Gy for nonfunctioning adenomas and 15-30Gy for secretory adenomas [18].

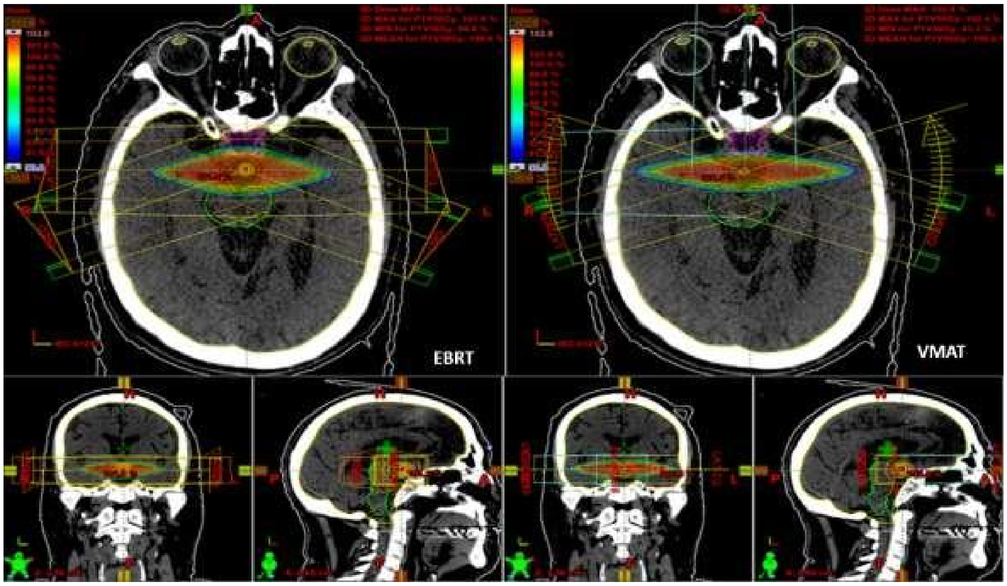


**Fig. 2. Comparison of EBRT and VMAT treatment planning for a patient with secretory adenoma after surgical resection**

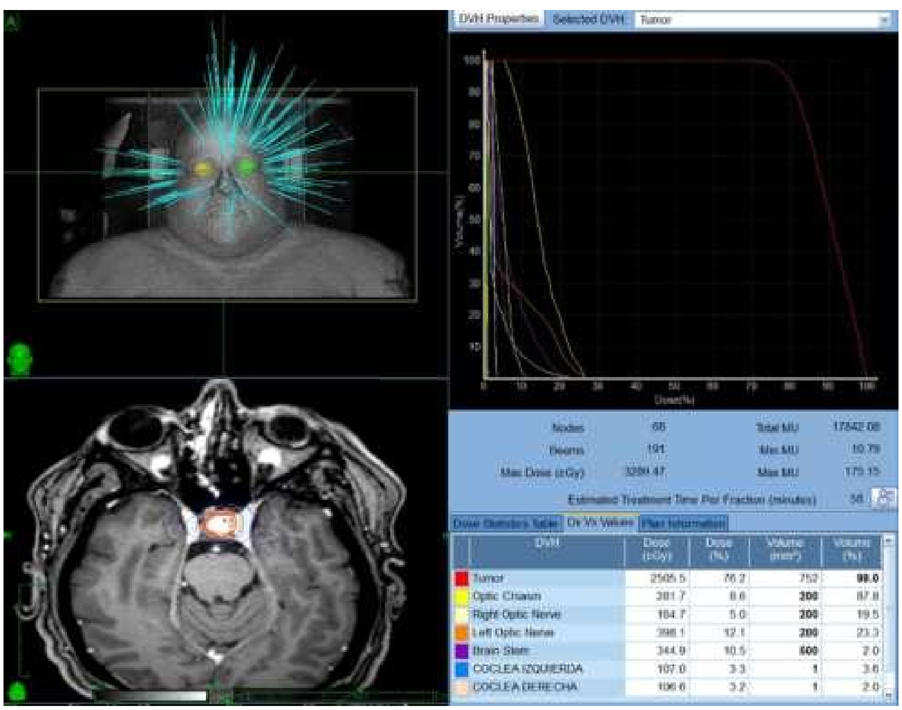


**Fig. 3. Treatment planning of a patient with secretory microadenoma of the pituitary gland treated with CyberKnife® technology**

**Fractionated SRS:** It combines the precision of stereotactic patient positioning and treatment delivery with standard radiotherapy fractionation, which preferentially spares normal tissue. Complete avoidance of surrounding normal tissue structures, such as the optic apparatus, is not generally practiced as the dose fractionation schemes used are below the radiation tolerance doses of the CNS [18]. The fractionated SRS technique is therefore, suitable for pituitary adenomas of all sizes, regardless of their relationship to adjacent critical normal tissue structures. This technique allows up to 5 fractions of very conformal and high radiation dose but lower than a single dose SRS [19]. The dose administered for NFA is 20Gy, while for SPA is 35Gy divided into 2-5 fractions.

**Contraindications for SRS:** Symptomatic compression of the optic pathway is a contraindication for radiosurgery for two reasons. First, size reduction and decompression of the optic pathway may take several years to happen and is not guaranteed in all patients. Second, vision loss due to compression of the optical pathway is an emergency and must be treated quickly [20].

## 4. LONG-TERM OUTCOMES

The clinical efficacy of radiotherapy for pituitary adenomas should be assessed in terms of overall survival (OS), actuarial tumor control, progression-free survival (PFS) and quality of life (QoL). Commonly reported endpoints for retrospective studies of radiation treatment for non- functioning pituitary adenomas are local tumor control and long term morbidity. In patients with functioning pituitary adenomas, the principal endpoint in addition to PFS and morbidity, is the rate of normalization of elevated pituitary hormone levels. The rate of pituitary hormone decline after irradiation varies with the type of functioning tumor, and the time to reach normal hormone levels is dependent on the initial pre-treatment hormone levels. The appropriate comparative measure for each pituitary hormone is the time to reach 50% of the pre-treatment hormone level, and this should be corrected for the confounding effect of medical treatment.

**Nonfunctioning Pituitary Adenomas (NFPA):** Fractionated external beam radiotherapy is highly effective in the treatment of NFPA. Tumor control rates achieve 87.5%, 77.6% and 64.7% at 10, 20 and 30 years respectively [21]. A systematic review of 22 studies found a 10-year PFS of 84% in patients who received definitive radiation therapy. While for patients who received adjuvant radiotherapy, PFS was 92%, 89% and 79% at 5, 10 and 20 years respectively. Stereotactic radiosurgery is an excellent option to treat patients with residual disease, tumor progression or recurrence after initial surgical resection, with control rates of 50-80% [22]. Single dose SRS with doses up to 20Gy provides excellent tumor growth control ranging from 83-100%, with secondary hypopituitarism occurring in 40% of the patients. Tumor growth control rates in NFPA are 93% with secondary hypopituitarism risk of 21% using gamma Knife® [23].

**Cushing´s Disease:** SRS is used for patients with active disease after surgery. Doses range between 15-35Gy. The time needed to achieve biochemical remission after SRS may take 12 months [24]. A published report of patients treated with gamma Knife® showed that normalization of 24h urinary cortisol was 46.2%, 65.4% and 84.6% at 2, 3, and 5 years, respectively, with an average time of normalization of two years [25-26]. After SRS for Cushing's disease, urinary free cortisol (UFC) is reduced to 50% of the pre-treatment levels after an interval of 6-12 months, and plasma cortisol after *ca*. 12 months. The median time to cortisol level normalization is around 24 months after treatment. The overall tumor and hormone control rates in the reported studies are 97% and 74% respectively, after a median follow up of 8 years [27].

**Acromegaly:** After surgery, SRS is the most commonly used radiation technique with doses ranging from 14-35Gy. Biochemical remission is achieved in 82% of the patients. Adenomas with volumes smaller than 3cc are more likely to achieve endocrine remission compared with those with a larger volume [28]. For patients with growth-hormone (GH) pituitary adenomas, endocrine remission is usually reached after 24 months [29]. FEBRT achieves normalization of GH/IGF-1 levels in 30-50% of patients at 5-10 years, and in 75% of patients at 15 years after treatment [30]. Time to normalize GH levels is related to the pre-treatment GH serum level. The time to achieve a 50% reduction in GH levels which takes into account the starting GH level, is 2 years, with IGF-1 reaching half of pre-treatment levels somewhat after the GH [31].

**Nelson´s Syndrome:** There is little information available on this entity. A review published in

2004 identified a cure rate up to 36% and tumor growth control rates of 82-100% [32]. Other series showed tumor control rates of 91-100% [33]. A recent study showed tumor control rates of 60% in patients treated with radiosurgery and 50% in those with fractionated stereotactic radiosurgery [34].

**Prolactinoma:** Radiosurgery is used in cases of resistance to pharmacological treatment, intolerance to dopamine agonists or in an attempt to reduce the dose needed. It is also used to decrease the size of macroadenomas in those cases were dopamine agonists showed little or no effect in reducing tumor size. In a recently published series with a follow up of 36 months, 27.3% of patients achieved endocrine normalization and 54.5% showed endocrine improvement with decreased levels of prolactin [35].

## 5. RADIATION-INDUCED LATE COMPLICATIONS

The most common adverse effect is late hypopituitarism, developed by up to 40% of patients with NFA and up to 70% of patients with SPA. Factors affecting the occurrence of this complication include gland function before radiosurgery treatment, therapeutic modalities used, and radiation dose to no-adenomatous pituitary gland [2]. Loss of pituitary hormones secretion follows a characteristic sequence, starting with GH deficiency, followed by gonadotrophins, ACTH, and finishing with TSH. Long term follow-up after pituitary irradiation, measuring all pituitary axes, is therefore warranted as an essential part of the post-treatment management of these patients. Fertility issues should be discussed with every young patient before starting radiotherapy because of the risk for late hypogonadism present for all radiotherapy techniques available. For stereotactic techniques, deterioration in pituitary function is mostly reported after a mean radiation dose to the hypophysis exceeding 15Gy for gonadotropic and thyrotropic axes and 18Gy for adrenocorticotropic axis [19,36] (See Table 2). There are other complications traditionally attributed to FSRT but increasingly questioned in recent years. Brummelman et al. suggested that patients with irradiated nonfunctioning macroadenomas have a higher risk of cognitive impairment when they were compared to general population [37]. Instead, Sattler et al. showed that patients with nonfunctioning adenomas treated with adjuvant FEBRT have a risk of brain tumors similar to patients treated with surgery alone. The authors also noticed that long-term mortality is increased but no statistical difference between irradiated and non-irradiated subjects [38]. Secondary hypopituitarism and use of high doses of glucocorticoids replacement could have contributed to increased mortality observed in patients with nonfunctioning pituitary adenomas [39].

The second most common complication includes damage to multiple cranial nerves: II, III, IV, V and VI are at risk of radiation neuropathy due to the short distance from the pituitary. Most radiosurgery series reported neurological deficit rates under 5%, optic neuropathy being the most common [41]. Other rare complications include radiation necrosis of brain parenchyma and stenosis of the internal carotid artery [42]. Intracranial radiotherapy is associated with the development of second, radiation-induced, brain tumors. In retrospective case series, the cumulative incidence of gliomas and meningiomas following radiotherapy for pituitary adenomas is 2% at 20 years [43]. To date, there are no cases of radiosurgery-induced pituitary tumors reported [44].

**Table 2. Neuro-endocrine consequences following conventional stereotactic cranial radiotherapy for Pituitary Adenomas (up to 54Gy)**

| Hormone deficiency | Incidence of dysfunction |
|---|---|
| Growth Hormone | 100% at 5 years |
| Gonadotropin Hormone | 60% at 10 years |
| Thyroid Stimulating Hormone | 30% at 10 years |
| Adrenocorticotropic Hormone | 60% at 10 years |
| Hypoprolactinemia | 20-50% but mostly in women and usually subclinical |

*Modified from Darzy et al. [40]*

## 6. COMPARISON BETWEEN FRACTIONATED RADIOTHERAPY AND RADIOSURGERY FOR PITUITARY ADENOMAS

On the available evidence, no data support the superiority of SRS over FSRT. Single fraction radiosurgery, while possibly more convenient, is less effective in achieving long term disease control of pituitary adenoma tumor growth, and does not achieve faster decline in hormone levels in secretory tumors. In addition, single fraction treatment of larger adenomas close to critical structures carries a significant risk of radiation induced damage. Additionally, pituitary cells have better radiobiological response to higher doses of radiation. It has been shown that the achievement of endocrine remission is faster in patients treated with SRS than those treated with FSRT but fractionated stereotactic techniques have the ability to spare healthy tissues and neural structures better than single dose radiosurgery [41].

## 7. CONCLUSION

Radiosurgery and fractionated stereotactic radiotherapy play an important role in the management of patients with pituitary adenomas. Both modalities are used in patients with residual or recurrent tumor in case of non-functioning adenomas, and in patients that fail to achieve disease remission after surgery in secretory adenomas. Hypopituitarism is the most common complication, however, hormone replacement is usually available. Neuroimaging and biochemical monitoring are recommended for those patients treated with SRS or FSRT.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab. 2008;93(10):3717–3726.
2. Ding D, Starke M, Jason P. Sheehan JP. Treatment paradigms for pituitary adenomas: Defining the roles of radiosurgery and radiation therapy. J Neurooncol. 2014;117:445–457.
3. Leber KA, Bergloff J, Pendl G. Dose response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. J Neurosurg. 1998;88:43–50.
4. 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;27:215–21.
5. Lisca´k R, Vladyka V. Radiosurgical hypophysectomy in painful bone metastasis from breast cancer. Cas Le´k Cesk. 1998;137:154–7.
6. Marek J, Je_zkova´ J, Ha´na V, et al. Is it posible to avoid hypopituitarism after irradiation of pituitary adenomas by the Leksell gamma knife? Eur J Endocrinol. 2011;164:169–78.
7. Marks LB, Ten Haken RK, Martel MK. Guest Editor´s Introduction to Quantec: A users guide. Int J Radiat Oncol Bio Phys. 2010;76 (Suppl 3):S1-S2.
8. Benedict SH, Yenice KM, Followill D, et al. Stereotactic Body Radiation Therapy: The report of AAPM Task Group 101, Med Phys. 2010;37:4078-4101.
9. Grimm J, LaCouture T, Croce R, et al. Dose Tolerance Limits and dose volumen histogram evaluation for stereotactic body radiotherapy. J Applied Clin Med Phys. 2011;12:267-292.
10. Mackley HB, Reddy CA, Lee SY, Harnish GA, Mayberg MR, Hamrahiam AH, Suh JH. Intensity-modulated radiotherapy for pituitary adenomas: The preliminary report of the cleveland clinic experience. Int J Radiat Oncol Biol Phys. 2007;67(1):232-9.
11. Fogliata A, Clivio A, Nicolini G, Vanetti E, Cossi L. Intensity modulation with photons for benign intracranial tumors: A planning comparison of volumetric single Arc, helical arc and fixed gantry techniques. Radiother Oncol. 2008;89(3):254-62.
12. Ajithkumar T, Brada M. Stereotactic linear accelerator radiotherapy for pituitary tumors. Treat Endocrinol. 2004;3(4):211-6.
13. Parhar P, Duckworth T, Shah P, De Wyngaert J, Narayana A, Formenti S, Shah. Decreasing temporal lobe dose with

five-field intensity-modulated radiotherapy for treatment of pituitary macroadenomas. Int J Radiat Oncol Biol Phys. 2010;78(2).
14. Saberian F, Ghate A, Kim M. Optimal fractionation in radiotherapy with multiple normal tissues. Math Med Biol; 2015. DOI: 10.1093/imammb/dqv015
15. Larson DA, Flickinger JC, Loeffler JS. The radiobiology of radiosurgery. Int J Radiat Oncol Biol Phys. 1993;25(3):557-61.
16. Park C, et al. Universal survival curve and single fraction equivalent dose: Useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys. 2008;70(3):847-52.
17. Vladyka V, Li_s_ca´k R, Novotny´ J Jr., et al. Radiation tolerance of functioning pituitary tissue in gamma knife surgery for pituitary adenomas. Neurosurgery. 2003; 52:309–16.
18. Barnett GH, Linskey ME, Adler JR, Cozzens JW, Friedman WA, Heilbrun MP, Lunsford LD, Schulder M, Sloan AE. Stereotactic radiosurgery–an organized neurosurgery- sanctioned definition. J Neurosurg. 2007;106(1):1–5.
19. Breen P, Flickenger JC, Kondziolka D et al. Radiotherapy for nonfunctional pituitary adenomas: Analysis of long-term tumour control. J Neurosurg. 1998;89:933-938.
20. Becker G, Kocher M, Kortmann RD, et al. Radiation therapy in the multimodal treatment approach of pituitary adenoma. Strahlenther Onkol. 2002;178:173-186.
21. Hoybye C, Rahn T. Adjuvant Gamma Knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients. Pituitary. 2009;12(3):211–216.
22. Starke RM, Williams BJ, Jane JA Jr, Sheehan JP. Gamma Knife surgery for patients with nonfunctioning pituitary macroadenomas: Predictors of tumor control, neurological deficits, and hypopituitarism. J Neurosurg. 2012; 117(1):129–135.
23. Izawa M, Hayashi M, Nakaya K, Satoh H, Ochiai T, Hori T, Takakura K. Gamma Knife radiosurgery for pituitary adenomas. J Neurosurg. 2000;93(Suppl 3):19–22.
24. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML. Gamma Knife surgery for Cushing’s disease. J Neurosurg. 2007;106(6):980–987.
25. Minniti G, et al. Long-term follow-up results of postoperative radiation therapy for Cushing's disease. J Neurooncol. 2007; 84(1):79-84.
26. Wann H, Chihiro O, Yuan S. MASEP gamma radiosurgery for secretory pituitary adenomas: Experience in 347 consecutive cases. J Exp Clin Cancer Res. 2009; 11:28–36.
27. Sheehan JP, Pouratian N, Steiner L, Laws ER, Vance ML. Gamma Knife surgery for pituitary adenomas: Factors related to radiological and endocrine outcomes. J Neurosurg. 2011;114(2):303–309.
28. Jezkova´ J, Marek J, Ha´na V, et al. Gamma knife radiosurgery for acromegaly – long-term experience. Clin Endocrinol. 2006;64:588–95.
29. Biermasz NR, Dulken HV, Roelfsema F. Postoperative radiotherapy in acromegaly is effective in reducing GH concentration to safe levels. Clin Endocrinol (Oxf). 2000; 53(3):321-7.
30. Minniti G, et al. The long-term efficacy of conventional radiotherapy in patients with GH-secreting pituitary adenomas. Clin Endocrinol (Oxf). 2005;62(2):210-6.
31. Laws ER, Sheehan JP, Sheehan JM, et al. Stereotactic radiosurgery for pituitary adenomas: A review of the literature. J Neurooncol. 2004;69:257–72.
32. Vik-Mo EO, Øksnes M, Pedersen PH, et al. Gamma knife stereotactic radiosurgery of Nelson syndrome. Eur J Endocrinol. 2008; 160:143–8.
33. Mauermann WJ, Sheehan JP, Chernavvsky DR, et al. Gamma Knife surgery for adrenocorticotropic hormone-producing pituitary adenomas after bilateral adrenalectomy. J Neurosurg. 2007;106:988–93.
34. Wilson P, Williams J, Smee R. Nelson’s syndrome: Single centre experience using the linear accelerator (LINAC) for stereotactic radiosurgery and fractionated stereotactic Radiotherapy. Journal of Clinical Neuroscience. 2014;21:1520–1524.
35. Liu X, Kano H, Kondziolka D, Park KJ, Iyer A, Shin S, Niranjan A, Flickinger JC, Lunsford LD. Gamma Knife stereotactic radiosurgery for drug resistant or intolerant invasive prolactinomas. Pituitary. 2013; 16(1):68–75.
36. Sheehan JP, Starke RM, Mathieu D, Young B, Sneed P, Chiang V, Lee JYK, Kano H, Park KJ, Niranjan A, Kondziolka D, Barnett GH, Rush S, Golfinos J, Lunsford LD. Gamma Knife radiosurgery

for the management of nonfunctioning pituitary adenomas: A multicenter study. J Neurosurg. 2013;119((2):446–456.
37. Brummelman P, Elderson MF, Dullaart R, van den Bergh A, Timmer CA, van den Berg G, et al. Cognitive functioning inpatients treated for nonfunctioning pituitary macroadenomaand the effects of pituitary radiotherapy. Clin Endocrinol. 2011;74:481-7.
38. Sattler MGA, van Beek AP, Wolffenbuttel BHR, van denBerg G, Sluiter WJ, Langendijk JA, et al. The incidence of second tumours and mortality in pituitaryadenoma patients treated with postoperative radiotherapyversus surgery alone. Radiother Oncol. 2012;104: 125-30.
39. Zueger T, Kirchner P, Herren C, Fischli S, Zwahlen M,Christ E, et al. Glucocorticoid replacement andmortality in patients with nonfunctioning pituitaryadenoma. J Clin Endocrinol Metab. 2012;97:e1938-42.
40. Darzy Ken H. Radiation-induced hypopituitarism. Curr Opin Endocrinol Diabetes Obes. 2013;20:342–353.
41. Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J, Wellis G. Stereotactic radiosurgery for recurrent surgically treated acromegaly: Comparison with fractionated radiotherapy. J Neurosurg. 1998;88(6):1002–1008.
42. Lim YJ, Leem W, Park JT, Kim TS, Rhee BA, Kim GK. Cerebral infarction with ICA occlusion after Gamma Knife radiosurgery for pituitary adenoma: a case report. Stereotact Funct Neurosurg. 1999; 72(Suppl 1):132–139.
43. Brada M, et al. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. BMJ. 1992;304(6838):1343-6.
44. Loeffler JS, Niemierko A, Chapman PH. Second tumor after radiosurgery: Tip of the iceberg or a bump in the road? Neurosurgery. 2003;52(6):1436–1440.



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