-Original Clinical Research-

Hypo-fractionated stereotactic radiotherapy for peri-optic pituitary adenomas – Early results of a novel experience

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Abstract

Background/Objective

To report our early experience with a novel Hypo-fractionated Stereotactic Radiotherapy (HF-SRT) regimen in the treatment of pituitary adenomas located in close proximity to the optic apparatus.

Methods

Twelve patients were treated using HF-SRT— total doses of 35-40 Gy in 7-10 fractions (4-5 Gy/fx). Sixty seven percent received 40 Gy in 10 fractions. Doses were prescribed to the 80-95% isodose line when the technique was cone-based, and to 85-95% of the Planning Target Volume (PTV) when IMRT-based. The end-points were visual function preservation, and local control as defined by follow-up MRI and/or biochemical control.

Results

Median age was 44.5 years. Sixty seven percent (8/12) had secretory adenomas. Median tumor volume as 5.8 cc. Median follow-up was 18.5 months. Mean marginal tumor dose was 42.7 Gy. Mean minimum distance from the optic chiasm was 2.3 mm. Mean maximum dose to the optic apparatus was 36 Gy. Visual improvement/stabilization rate was 87.5% (7/8). Radiological local control rate was 92% (11/12), CR in 25% (3/12), PR in 33% (4/12), SD in 33% (4/12), and PD in 8% (1/12). Endocrinological response was seen in all patients with abnormal hormone levels prior to therapy (8/8). Acute toxicity included headaches (42%) and nausea (8%). One patient with a previous history of pituitary hemorrhage suffered an episode of pituitary apoplexy 2 months after HF-SRT. Another patient with history of prior full dose conventional radiotherapy 2.5 years prior to HF-SRT, developed dissection and thrombosis of the right internal carotid artery.

Conclusions

Early results of HF-SRT (4-5 Gy/fx) in 7-10 fractions show comparable radiological and endocrinological tumor control to conventionally fractionated radiotherapy or single fraction SRS, with excellent visual preservation. Longer follow-up is needed to ascertain efficacy and long term toxicity of this technique.

Key words:

Hypo-fractionated Stereotactic Radiotherapy; Stereotactic Radiosurgery; Biologically Effective Dose; Pituitary Adenoma; Optic Apparatus

INTRODUCTION

Pituitary adenomas are the most common cause of sellar masses from the third decade on, accounting for up to 10% of all intracranial neoplasms. [1] They can arise from any type of cell in the anterior pituitary and may result in increased secretion of the hormone(s) produced by that cell and/or decreased secretion of other hormones due to compression of adjacent cell types. Sellar masses can present with neurologic or visual symptoms, abnormalities related to under or over secretion of pituitary hormones, or as an incidental finding on radiologic examination. Thirty percent of all pituitary adenomas are nonfunctional. In operable patients, initial treatment for both functional and nonfunctional pituitary adenomas, with the exception of prolactinomas, is usually surgery. [2, 3] The degree of resection is often limited by proximity to critical structures. Alternatively, radiotherapy is an established option in the treatment of pituitary adenomas, [4, 5] especially when tumor size or patient morbidity prohibits surgery. For large tumors and after incomplete resection, postoperative irradiation is generally recommended for functional and nonfunctional pituitary adenomas. In such cases local tumor control rates of approximately 90% after 10 years are achieved with the combination of surgery and postoperative radiotherapy. [3, 6, 7]

Stereotactic therapy defines the ability to localize objects in a three dimensional space, to enable sub-millimeter precision for treatment delivery. This strategy is of particular use in benign, slow growing neoplasms, like pituitary adenomas and meningiomas, which are considered to be relatively radio resistant. [8] Stereotactic Radiosurgery (SRS) generally implies a single high-dose treatment, while stereotactic radiotherapy (SRT) refers to the use of stereotactic localization for delivery of multiple smaller fractionated doses. Although less-convenient for patients who require multiple rather than single treatments, SRT possibly allows sensitive normal structures to repair and regenerate throughout the course of therapy. This is especially crucial for normal tissues such as the optic apparatus (optic chiasm and the optic nerves), where the potential for permanent injury depends mainly on dose per fraction. As a result, SRT is usually favored over SRS when these critical structures lie in close proximity (<5 mm) to the radiotherapy target.

Theoretically, there is no size or distance (from critical structures) limitation for SRT, but treatment schedules may vary widely from the "conventional fractionation" of 1.8-2.0 Gy (delivered over 5-6 weeks) to "hypo-fractionation" of daily doses >2.0 Gy (delivered over 2-3 weeks). The purpose of this study is to report on disease control endpoints and toxicity of a cohort of patients treated with a novel regimen of HF-SRT (4-5 Gy/fx). Our goal is to add to existing radiosurgical literature, a unique and safe regimen for stereotactic radiotherapy in the management of these critically located tumors.

RADIOBIOLOGIC RATIONALE

SRS has been shown (in theory and practice) to have numerous advantages over conventional fractionation. Radiobiological effect of dose and fractionation on tissue can be estimated using the linear quadratic cell survival curve model. In this model, the α/β ratio reflects cell response to changes in radiotherapy fraction size and a lower α/β ratio implies sensitivity to larger dose-per-fraction. Malignant tumors and other rapidly proliferating tissues (e.g., skin, mucosa, bone marrow) demonstrate high α/β ratio (8–12) and exhibit modest sparing through dose fractionation. Many normal tissues, including those of the CNS, have lower α/β ratio (2–4) and demonstrate marked sparing with dose fractionation. [9, 10] The exact α/β ratio for pituitary adenomas is not known. We assume a low α/β ratio of 2 for pituitary adenomas based on low α/β ratios (~2-3) of other benign CNS tumors like meningiomas and acoustic neuromas. [11] In general a low α/β ratio suggests a decreased benefit from conventional fractionation and more favored response to single-dose SRS or HF-SRT.

Using the linear-quadratic (LQ) model, it is possible to estimate the biologically equivalent doses between different fractionation schemes. The biologically equivalent dose for a pituitary tumor given an EBRT dose of 45 Gy in 25 fractions of 1.8 Gy per fraction is 85.5 Gy when $\alpha/\beta=2$. Using this formula, an equivalent SRS dose scheme for a biologically equivalent dose of 85.5 Gy could consist of 25 Gy delivered in five fractions or 12.3Gy in a single dose. [12] A comparison of BED calculations for 4 different RT fractionation regimens is shown in Table 1. It was found that the BED of our HF-SRT regimen was a suitable alternative to conventionally fractionated RT or single fraction radiosurgery. Row #4 shows that our hypo-fractionation regimen might have a marginally superior BED for tumor control (the higher the better). The last column shows the various local control rates (with the corresponding technique and studies in parentheses), suggesting that radiotherapy has a very high success rate in treating these tumors.

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Table 1 Comparison of BED values and outcomes for 4 different RT regimens

RT Fx	No. of Fractions	Total Dose	BED α/β = 2	BED α/β = 10	Local Control
Conventional RT [5, 13-16]	25-30	45-55 Gy	85-105	53-65	76-97%
SRS (Gamma Knife ®) [17-21]	1	12-15 Gy	84-105	26-33	92-97%
SRS (CyberKnife ®) [22, 23]	1-5	14-30 Gy	53-120	22-45	92%
HF-SRT (Linac-based) *	7-10	35-40 Gy	120-123	53-56	92%

*Our Series, SRS – Stereotactic Radiosurgery, HF-SRT – Hypo-fractionated Stereotactic Radiotherapy, BED – Biologic Equivalent Dose.

MATERIALS AND METHODS

We performed a retrospective review of a prospectively-maintained database of 12 patients with pituitary adenoma treated at our institution using HF-SRT. This study was approved by the institutional review board (IRB) of the University Of Louisville. Of the 12, 42% were male and 58% were female. Therapy was for a primary tumor (1/12), recurrent tumor status post prior gross total resection (5/12) and residual tumor post-surgical de-bulking or a subtotal resection (6/12). CT images (1.5 mm slices) were obtained for treatment planning. MRI fusion was performed for all patients to view the details of the optic nerves and chiasm without difficulty. Therapy was planned using either Varian (Z Med-Fastplan) or Radionics (X-Knife) systems. Treatments were delivered using 6 MV photons. A total dose of 35-40 Gy in 7-10 fractions (4-5 Gy/fx) was given either once (33%) or twice (67%) a week. Two-thirds of the patients (67%) were treated to 40 Gy in 10 fractions. Patient #12 had received prior conventional radiation therapy to 60 Gy at 2 Gy per fraction 2.5 years prior. Patient characteristics (Table 2) and treatment plan details (Table 3 & 4) are summarized.

Table 2 Patient Characteristics

Patient No.	Age/ Sex	Adenoma Type	Pre-RT Hormone Levels	Symptoms at Diagnosis	Recurrent Tumor	Prior Surgery	Time Since Surgery (mos)	Follow-up (mos)
1	39/F	Non-secretory	WNL	HA	Yes	GTR	12	6
2	67/F	Prolactinoma	↑ PL	VA	Yes	GTR	50	4
3	38/M	Non-secretory	WNL	HA, VA	No	STR	1	7
4	60/M	Pluri-hormonal	↑ACTH	VA	No	STR	3	12
5	36/F	GH secreting	↑ GH	HA, VA	Yes	GTR	24	6
6	33/F	Prolactinoma	↑ PL	Incidental	Yes	GTR	22	25
7	35/F	ACTH secreting	↑ Cortisol	HP	No	STR	2	34
8	51/F	Prolactinoma	↑ PL	Incidental	No	No	NA	39
9	66/M	Prolactinoma	↑ PL	VA, HP	Yes	GTR	132	71
10	63/M	Non-secretory	WNL	VA	No	STR	3	80
11	61/M	Non-secretory	LOW	VA	No	STR	4	52
12	53/F	Pluri-hormonal	↑ PL & Cortisol	VA, HP	Yes	STRx2	5	10

WNL – Within Normal Limits, ACTH – Adrenocorticotrophic Hormone, GH – Growth Hormone, PL – Prolactin, HA- Headaches, VA- Visual Abnormality, HP – Hypopituitarism, GTR – Gross Total Resection, STR – Sub-total Resection.

Table 3 Summary of Treatment Plans-1

Patient No.	Pre-RT Tumor Volume (cc)	Extra Sellar Extension	Distance from Chiasm (mm)	Collimator Size (mm)	No of Arcs	No of Iso-centers	PlanningSystem/ Software
1	3.78	Yes	2	22	6	1	Z Med/ Fast Plan
2	9.28	Yes	<1	30	5	1	Z Med/ Fast Plan
3	4.95	Yes	<1	30	8	1	Z Med/ Fast Plan
4	7.87	Yes	3	**A**	**B**	NA	Varian Eclipse
5	1.42	Yes	3	22	6	1	Z Med/ Fast Plan
6	5.2	Yes	4	24	5	1	Z Med/ Fast Plan
7	6	Yes	<1	35	7	1	Radionics/ X-knife
8	0.74	Yes	2	22.5	3	1	Radionics/ X-knife
9	27	Yes	<1	40	7	1	Radionics/ X-knife
10	5.6	No	7	27.5	7	1	Radionics/ X-knife
11	6.4	Yes	1.5	32.5	6	1	Radionics/ X-knife
12	9.7	Yes	<1	**C**	**D**	NA	Tomotherapy

A - MLC based Step & Shoot IMRT, B - 8 non-coplanar fields used, C - Tomotherapy based IMRT, D - Dynamic MLC's

Mean number of Cone-based arcs used were 6 (3-8). Treatments were delivered to a single isocenter when cone-based technique was used (83% cases). Cone sizes used ranged from 22-40 mm. Patients were immobilized using a frameless (42%) or a non-invasive head frame (42%) linac delivered Cone-based stereotactic technique. One patient was treated with step and shoot IMRT – multi leaf collimator (MLC) based technique (Varian Eclipse™), and another using dynamic co-planar IMRT (Tomotherapy®), with the treatments prescribed to 95% and 85% of the PTV respectively. Dose was prescribed to the 80-100% isodose line covering 100% of the target volume when cone based technique was used. IMRT (Figure 2) was used due to the irregular shape of the tumor and to better avoid the surrounding optic apparatus as compared to a cone-based technique (Figure 1).

Table 4 Summary of Treatment Plans-2

Patient No.	Dose (Gy)	No. of Fractions	Prescription Isodose line	Avg Tumor Marginal Dose (Gy) / (%)	Fractions (per week)	Max Dose to Optic Apparatus (Gy) / (% of Total dose)
1	40	10	80%	45(90%)	2	42.5 (85%)
2	40	10	80%	47.5(95%)	2	50 (100%)
3	40	10	80%	45(90%)	2	37.5 (75%)
4	40	10	95% vol *	41.6(104%)	2	40 (100%)
5	40	8	80%	47.5(95%)	2	15 (30%)
6	40	8	80%	47.5(95%)	2	25 (50%)
7	35	7	95%	35.3(92%)	1	25.8 (70%)
8	36	9	80%	37.9(84%)	2	32.9 (73%)
9	40	10	80%	37.6(75%)	1	44.8 (90%)
10	40	10	80%	41(82%)	1	40.5 (81%)
11	40	10	90%	40.1(90%)	1	36.2 (82%)
12	40	10	85% vol *	46(115%)	2	41.9 (105%)

* - Percent volume receiving 100% of the dose (IMRT)

The end-points were evaluation of visual function preservation as determined by clinical visual field testing and subjectively by the patient; and assessment of local control as defined by follow-up MRI and/or endocrinologic tumor control. Endocrinological tumor control was assessed based on return of elevated hormone levels to normal or near normal levels. Formal endocrinologic tests like blood glucose challenge or dexamethasone suppression tests were not performed as part of the follow-up. There is no formal grading to assess imaging response for pituitary tumors. We graded the MRI response as follows - No residual/complete response (CR), Decrease in size (PR), No change/stable size (SD), and Increase/progression in size (PD).

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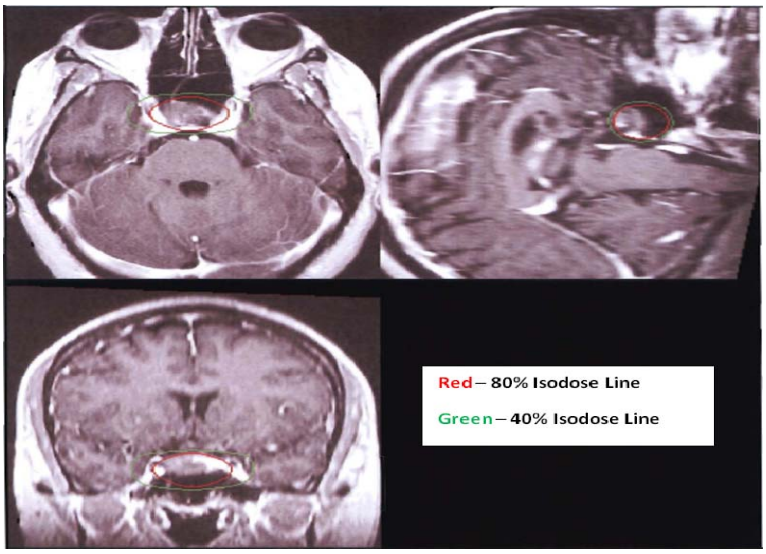

Figure 1 HF-SRT plan with a cone-based technique

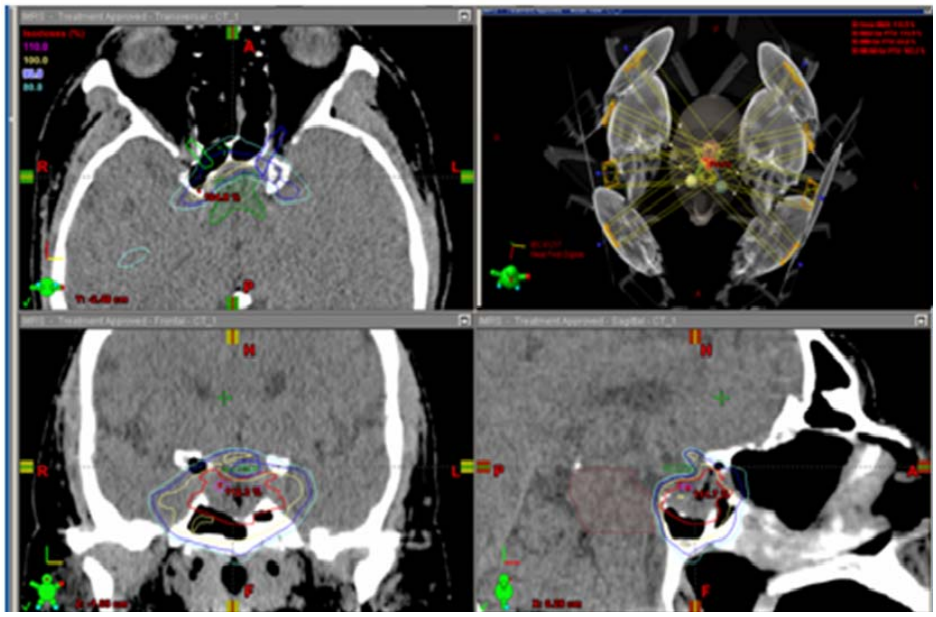

Figure 2 HF-SRT plan with Intensity Modulated Radiotherapy (IMRT) based technique, Eight non-coplanar field Intensity Modulated Radiotherapy plan with Isodose lines used for an irregular target. CT images of an 8 non-coplanar field Intensity Modulated Radiotherapy (IMRT) plan with Isodose lines used for an irregular target. Pituitary target (red), Optic Chiasm (dark green), and Yellow (100% isodose line [IDL]).

RESULTS

Mean age was 50, with a median of 44.5 (33-67 years). Median tumor volume was 5.8 cc (0.74-27 cc). The median follow-up was 18.5 months (4-80 months). Follow-up was greater than 10 months in 67% patients. The adenomas were secretory in 67%, and non-secretory in 33%. Of the secretory tumors, 63% were Prolactinomas, 25% ACTH secreting and 12% GH secreting. All patients with prolactinomas had failed prior medical therapy and 3 out of 4 had a failed prior total resection. All patients completed the planned full course of radiotherapy. Mean marginal tumor dose was 42.7 Gy (35.3-47.5 Gy). The optic apparatus and/or the cavernous sinus were in close proximity to the tumor margin in all patients in this series. The mean minimum distance from the optic chiasm was 2.3 mm (< 1-7 mm). Four patients had tumor within 1 mm or abutting the optic apparatus. Extra-sellar extension was seen in all but one patient. The mean maximum dose to the optic apparatus was 36 Gy, with a minimum of 30% to a maximum of 100% (15-50 Gy) of

prescription dose. However due to fractionation, the dose to the optic apparatus was kept to less than 5 Gy per fraction in all patients. Radiotherapy was delivered post-operative in 92% cases (GTR-42%, STR-50%). The median time from GTR to HF-SRT was 24 mos, and from STR to HF-SRT were 3 mos.

On follow-up MRI, CR was seen in 25%, PR in 33%, SD in 33%, and PD in 8 % cases. The patient with progressive disease had local control for 58 months prior to progression. Overall radiological local control rate was 92%. Of the 8 patients who initially presented with visual symptoms, 5 had complete clinical resolution and 2 had persistence of symptoms but no further deterioration. One patient had progressive decline in visual acuity. The visual improvement/stabilization rate was 87.5%. All 4 patients (33%) who had no visual symptoms prior to therapy continued to have intact vision on last follow-up. Of the 8 patients who had a secretory tumor with abnormally elevated hormone levels, post-RT levels obtained prior to last follow-up were noted to be within normal limits in 6 and were noted to be decreasing in the remaining 2 patients without the need for additional medications. Longer follow-up of at-least a few years would be needed to ascertain the exact endocrinologic tumor control. The optimal timing to measure post-RT hormone levels is unknown as there tends to be lag periods of several months to even few years before hormonal levels normalize. At last follow-up, 11/12 of patients were alive, for an overall survival of 92%. One patient had died secondary to lung cancer.

Acute toxicity included nausea (8%) and headaches (42%). Steroids were needed in 25% patients while on treatment and all completed the full planned course of radiation therapy without any interruptions. All patients had complete resolution of acute symptoms after completing therapy. One patient had an episode of pituitary apoplexy 2 months after completion of HF-SRT. Another patient developed dissection with thrombosis of the right ICA. Four of the twelve patients had evidence of hypopituitarism prior to HF-SRT and they continued to be hypo-pituitary on last follow-up. Two new cases of hypothyroidism were observed post-RT. Two patients had a transient decrease in their testosterone levels which however returned to normal on longer follow-up. We remain cautious as additional side effects might present with longer follow-up.

DISCUSSION

Trans-sphenoidal resection is currently the most widely used procedure for pituitary adenomas. The management of peri-optic tumors poses a major challenge and although microsurgical resection continues to be the initial treatment of choice, complete tumor resection may pose an unacceptable risk of damage to the visual apparatus. As a result, microsurgery alone provides long-term tumor control rates of approximately 50 to 80%,[24, 25] and adjuvant or salvage therapy is often required.

The role of radiotherapy in the management of pituitary adenomas is well established. Tumor control has been reported to be highly dose dependent.[4,5] McCollough, *et al.* [5] showed excellent long-term control rates with total doses > 45 Gy. Grigsby, *et al.* [26] demonstrated a decreased failure rate with total doses > 50 Gy after surgery. Zierhut, *et al.* [14] reported a tumor control rate of only 50% for a 35-Gy dose. Thus for conventionally fractionated radiotherapy, to obtain an approximate 90% recurrence-free survival rate, a dose of 45 Gy to 55 Gy is required. [15, 27] These total doses lie well within accepted TD5/5 for the optic chiasm of 50 Gy. [28]

Scientific literature supports the efficacy and safety of single-fraction radiosurgical ablation for the treatment of Pituitary adenomas.[29, 30] Tumor control rates following Gamma Knife SRS is about 92-97%.[20, 21] In a series from Stanford University, [23] Cyberknife SRS was delivered in 2-5 fractions to a cumulative average marginal dose of 20 Gy. They reported tumor control and visual preservation rates of greater than 90%. Despite these results reported by retrospective studies, close (i.e., 3 mm or less) proximity of a tumor to the visual apparatus poses a significant risk to performing SRS. Thus, the major challenge for safely delivering SRS is that single fraction tolerance dose of the chiasm is 8 Gy, while the therapeutic dose for the adenoma is 15 Gy.[29, 31]

There are limitations to the linear-quadratic model, which does not integrate many of the biological effects radiation present *in vivo*, such as tumor heterogeneity, hypoxia, and micro-vascular response to irradiation. [32] Even so, histopathological evaluation of pituitary adenoma specimens following either SRS or conventionally fractionated radiation therapy has shown a more potent radiobiological effect of SRS. In terms of endocrine symptoms, the improvement rate of endocrinopathies has been reported to be higher after SRS (78-93%)[20, 33] than for conventional radiotherapy (30-70%).[14,15] SRS appears to lead to faster normalization of hormone levels than conventionally fractionated radiotherapy, further supporting the notion of its greater radiobiological potency. [34]

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The most frequent complication is hypopituitarism. Several groups have reported a low incidence (0–36%) of pituitary dysfunction following radiosurgery. This incidence is higher when patients are followed long-term, with the Karolinska Institute reporting a 72% incidence of hypopituitarism when patients were followed longer than 10 years.[35] One patient (#2) who initially had presented with pituitary hemorrhage had an episode of pituitary apoplexy 2 months after completion of HF-SRT. Radiotherapy has been known to cause pituitary apoplexy[36-38] and it is possible that HF-SRT might have aggravated a second episode in this patient. Another (#12), with an extensive tumor encasing the bilateral internal carotid arteries (ICA), developed dissection with thrombosis of the right ICA. This patient had previously also received 60 Gy conventional radiotherapy apart from having undergone 2 attempted STR's, the last being 5 months prior to the HF-SRT. Endothelial damage post SRT by induction of an inflammatory response with fibroblastic proliferation, hyalinization and scarring of vessels is known to occur.[39,40] The incidence of side effects can tend to be higher in patients who have had prior surgical resection secondary to vascular and structural changes. Stenosis or occlusion of the ICA has also been observed after pituitary radiosurgery,[30, 41] and was observed in one patient in our series.

A median follow-up of 18.5 months provides some reassurance about the safety regarding this regimen of HF-SRT, as radiation-induced visual field deficits which tend to occur between 8-18 months after treatment.[31, 42] However, we remain cautious as longer follow-up may reveal additional toxicity that occurs beyond 2 years.[29]

Similarly longer follow-up of at-least several years would be needed to ascertain the exact endocrinologic response rate to radiotherapy.

CONCLUSIONS

HF-SRT represents a treatment strategy that incorporates the biologic advantages of large fraction size with critical inter-fraction repair of normal tissue. Our institutional regimen of 7-10 fraction of 4-5 Gy each was designed to treat adenomas too large or too close to the optic chiasm to safely administer SRS. Early results of HF-SRT (4-5 Gy/Fx) in 7-10 fractions given once or twice a week are encouraging, with satisfactory tumor control, excellent visual preservation and a low overall toxicity profile. Our results compare favorably with published series of both SRS and conventional radiotherapy. This approach appears especially suitable for patients with lesions that are in very close proximity to the optic chiasm and optic nerves. Additional follow-up time and corroborative studies of the use of HF-SRT schedules at other institutions will be needed to validate these results.

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Authors Contributions: ADB – Conceived study design, data collection, Manuscript draft;AED – Mentored & supervised study, manuscript drafting & proof-reading;GAB – Formatted Tables, Figures, Manuscript preparation;KL – Data collection, Manuscript draft;YG – Study design, Interpretation of data;CLS – Senior Author, Conceived RT fractionation, Manuscript draft.

REFERENCES

[1] Freda PU, Post KD. Differential diagnosis of sellar masses. Endocrinol Metab Clin North Am 1999; 28: 81-117, vi. http://dx.doi.org/10.1016/S0889-8529(05)70058-X

[2] Baskin DS, Boggan JE, Wilson CB. Transsphenoidal microsurgical removal of growth hormone-secreting pituitary adenomas. A review of 137 cases. J Neurosurg 1982; 56: 634-641. http://dx.doi.org/10.3171/jns.1982.56.5.0634 PMid:7069474

[3] Serri O, Rasio E, Beauregard H et al. Recurrence of hyperprolactinemia after selective transsphenoidal adenomectomy in women with prolactinoma. N Engl J Med 1983; 309: 280-283. http://dx.doi.org/10.1056/NEJM198308043090505 PMid:6866052

[4] Grigsby PW, Stokes S, Marks JE, Simpson JR. Prognostic factors and results of radiotherapy alone in the management of pituitary adenomas. Int J Radiat Oncol Biol Phys 1988; 15: 1103-1110. http://dx.doi.org/10.1016/0360-3016(88)90191-5

[5] McCollough WM, Marcus RB, Jr., Rhoton AL, Jr. et al. Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after greater than or equal to 4500 cGy. Int J Radiat Oncol Biol Phys 1991; 21: 607-614.
http://dx.doi.org/10.1016/0360-3016(91)90677-V
[6] Chun M, Masko GB, Hetelekidis S. Radiotherapy in the treatment of pituitary adenomas. Int J Radiat Oncol Biol Phys 1988; 15: 305-309.
http://dx.doi.org/10.1016/S0360-3016(98)90009-8
[7] Salinger DJ, Brady LW, Miyamoto CT. Radiation therapy in the treatment of pituitary adenomas. Am J Clin Oncol 1992; 15: 467-473.
http://dx.doi.org/10.1097/00000421-199212000-00003
PMid:1449108
[8] Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC. Stereotactic radiosurgery for meningiomas. Neurosurg Clin N Am 1999; 10: 317-325.
PMid:10099096
[9] Withers HR. Biologic basis for altered fractionation schemes. Cancer 1985; 55: 2086-2095.
http://dx.doi.org/10.1002/1097-0142(19850501)55:9+<2086::AID-CNCR2820551409>3.0.CO;2-1
[10] Thames HD, Jr., Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. International journal of radiation oncology, biology, physics 1982; 8: 219-226.
http://dx.doi.org/10.1016/0360-3016(82)90517-X
[11] Shrieve DC. Basic principles of radiobiology applied to radiotherapy of benign intracranial tumors. Neurosurgery clinics of North America 2006; 17: 67-78, v.
http://dx.doi.org/10.1016/j.nec.2006.02.003
PMid:16793500
[12] Hoban PW, Jones LC, Clark BG. Modeling late effects in hypofractionated stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 1999; 43: 199-210.
http://dx.doi.org/10.1016/S0360-3016(98)00369-1
[13] Grigsby PW, Simpson JR, Emami BN et al. Prognostic factors and results of surgery and postoperative irradiation in the management of pituitary adenomas. Int J Radiat Oncol Biol Phys 1989; 16: 1411-1417.
http://dx.doi.org/10.1016/0360-3016(89)90942-5
[14] Zierhut D, Flentje M, Adolph J et al. External radiotherapy of pituitary adenomas. Int J Radiat Oncol Biol Phys 1995; 33: 307-314.
http://dx.doi.org/10.1016/0360-3016(95)00071-6
[15] Rush S, Cooper PR. Symptom resolution, tumor control, and side effects following postoperative radiotherapy for pituitary macroadenomas. Int J Radiat Oncol Biol Phys 1997; 37: 1031-1034.
http://dx.doi.org/10.1016/S0360-3016(96)00586-X
[16] 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: 79-84.
http://dx.doi.org/10.1007/s11060-007-9344-0
PMid:17356896
[17] Mingione V, Yen CP, Vance ML et al. Gamma surgery in the treatment of nonsecretory pituitary macroadenoma. J Neurosurg 2006; 104: 876-883.
http://dx.doi.org/10.3171/jns.2006.104.6.876
PMid:16776330
[18] Pollock BE, Carpenter PC. Stereotactic radiosurgery as an alternative to fractionated radiotherapy for patients with recurrent or residual nonfunctioning pituitary adenomas. Neurosurgery 2003; 53: 1086-1091; discussion 1091-1084.
[19] Pollock BE, Cochran J, Natt N et al. Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. Int J Radiat Oncol Biol Phys 2008; 70: 1325-1329.
http://dx.doi.org/10.1016/j.ijrobp.2007.08.018
PMid:18029107
[20] Ganz JC, Backlund EO, Thorsen FA. The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies. Stereotact Funct Neurosurg 1993; 61 Suppl 1: 30-37.
http://dx.doi.org/10.1159/000100657
[21] Jagannathan J, Yen CP, Pouratian N et al. Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the Gamma Knife. J Neurooncol 2009; 92: 345-356.
http://dx.doi.org/10.1007/s11060-009-9832-5
PMid:19357961
[22] Cho CB, Park HK, Joo WI et al. Stereotactic Radiosurgery with the CyberKnife for Pituitary Adenomas. J Korean Neurosurg Soc 2009; 45: 157-163.
http://dx.doi.org/10.3340/jkns.2009.45.3.157
PMid:19352477 PMCid:2666117
[23] Adler JR, Jr., Gibbs IC, Puataweepong P, Chang SD. Visual field preservation after multisession cyberknife radiosurgery for perioptic lesions. Neurosurgery 2006; 59: 244-254; discussion 244-254.
http://dx.doi.org/10.1227/01.NEU.0000223512.09115.3E
PMid:16883165
[24] Chandler WF, Schteingart DE, Lloyd RV et al. Surgical treatment of Cushing's disease. J Neurosurg 1987; 66: 204-212.
http://dx.doi.org/10.3171/jns.1987.66.2.0204
PMid:3806203
[25] Mampalam TJ, Tyrrell JB, Wilson CB. Transsphenoidal microsurgery for Cushing disease. A report of 216 cases. Ann Intern Med 1988; 109: 487-493.
PMid:2843068
[26] Grigsby PW, Thomas PR, Simpson JR, Fineberg BB. Long-term results of radiotherapy in the treatment of pituitary adenomas in children and adolescents. Am J Clin Oncol 1988; 11: 607-611.
http://dx.doi.org/10.1097/00000421-198812000-00001
PMid:3189225
[27] Flickinger JC, Nelson PB, Martinez AJ et al. Radiotherapy of nonfunctional adenomas of the pituitary gland. Results with long-term follow-up. Cancer 1989; 63: 2409-2414.
http://dx.doi.org/10.1002/1097-0142(19890615)63:12<2409::AID-CNCR2820631206>3.0.CO;2-M

[28] Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 109-122. http://dx.doi.org/10.1016/0360-3016(91)90171-Y
[29] Ove R, Kelman S, Amin PP, Chin LS. Preservation of visual fields after peri-sellar gamma-knife radiosurgery. Int J Cancer 2000; 90: 343-350. http://dx.doi.org/10.1002/1097-0215(20001220)90:6<343::AID-IJC6>3.0.CO;2-H
[30] Pollock BE, Nippoldt TB, Stafford SL et al. Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization. J Neurosurg 2002; 97: 525-530. http://dx.doi.org/10.3171/jns.2002.97.3.0525 PMid:12296634
[31] Girkin CA, Comey CH, Lunsford LD et al. Radiation optic neuropathy after stereotactic radiosurgery. Ophthalmology 1997; 104: 1634-1643. PMid:9331204
[32] Flickinger JC, Kondziolka D, Lunsford LD. Dose selection in stereotactic radiosurgery. Neurosurg Clin N Am 1999; 10: 271-280. PMid:10099092
[33] Park YG, Chang JW, Kim EY, Chung SS. Gamma knife surgery in pituitary microadenomas. Yonsei Med J 1996; 37: 165-173. PMid:8826781
[34] Kong DS, Lee JI, Lim do H et al. The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas: long-term results of 125 consecutive patients treated in a single institution. Cancer 2007; 110: 854-860. http://dx.doi.org/10.1002/cncr.22860 PMid:17599761
[35] Hoybye C, Grenback E, Rahn T et al. Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. Neurosurgery 2001; 49: 284-291; discussion 291-282.
[36] Weisberg LA. Pituitary apoplexy. Association of degenerative change in pituitary ademona with radiotherapy and detection by cerebral computed tomography. Am J Med 1977; 63: 109-115. http://dx.doi.org/10.1016/0002-9343(77)90122-X
[37] Alatakis S, Malham GM, Fabinyi GC. Spontaneous haemorrhage into an empty sella turcica mimicking pituitary apoplexy. J Clin Neurosci 2000; 7: 557-560. http://dx.doi.org/10.1054/jocn.2000.0722 PMid:11029243
[38] Arafah BM, Harrington JF, Madhoun ZT, Selman WR. Improvement of pituitary function after surgical decompression for pituitary tumor apoplexy. J Clin Endocrinol Metab 1990; 71: 323-328. http://dx.doi.org/10.1210/jcem-71-2-323
[39] Andisheh B, Brahme A, Bitaraf MA et al. Clinical and radiobiological advantages of single-dose stereotactic light-ion radiation therapy for large intracranial arteriovenous malformations. Technical note. J Neurosurg 2009; 111: 919-926. http://dx.doi.org/10.3171/2007.10.17205 PMid:19392591
[40] Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. Cancer Cell 2005; 8: 89-91. http://dx.doi.org/10.1016/j.ccr.2005.07.014 PMid:16098459
[41] Lim YJ, Leem W, Park JT et al. Cerebral infarction with ICA occlusion after Gamma Knife radiosurgery for pituitary adenoma: A case report. Stereotact Funct Neurosurg 1999; 72 Suppl 1: 132-139. http://dx.doi.org/10.1159/000056449 PMid:10681701
[42] Kline LB, Kim JY, Ceballos R. Radiation optic neuropathy. Ophthalmology 1985; 92: 1118-1126. PMid:4047605