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Review

Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas

Giuseppe Minniti[a,b,*], *Enrico Clarke*[a], *Claudia Scaringi*[a], *Riccardo Maurizi Enrici*[a]

[a] *Department of Radiation Oncology, Sant' Andrea Hospital, University of Rome Sapienza, Rome, Italy*
[b] *IRCCS Neuromed, Pozzilli, IS, Italy*

ARTICLE INFO

Article history:
Received 21 April 2014
Received in revised form
28 July 2014
Accepted 16 September 2014
Available online 14 October 2014

Keywords:
Fractionated stereotactic radiotherapy
Radiosurgery
Pituitary adenoma
Acromegaly
Cushing's disease

ABSTRACT

Radiotherapy (RT) is frequently employed in patients with residual or recurrent pituitary adenoma with excellent rates of tumor control and remission of hormonal hypersecretion. Advances in RT have improved with the use of stereotactic techniques either as fractionated stereotactic radiotherapy (FSRT) or stereotactic radiosurgery (SRS), all aiming to improve the dose distribution to the tumor while reducing the amount of normal brain receiving significant doses of radiation. We provide an overview of the recent published literature on the long-term efficacy and adverse effects of stereotactic irradiation in nonfunctioning and secreting pituitary adenomas. Both techniques are associated with excellent clinical outcomes; however, advantages and drawbacks of each of these techniques in terms of local control, hormonal excess normalization, and radiation-induced toxicity remain a matter of debate. In clinical practice, single-fraction SRS may represent a convenient approach to patients with small and medium-sized pituitary adenoma away at least 2 mm from the optic chiasm, whereas FSRT is preferred over SRS for lesions >2.5–3 cm in size and/or involving the anterior optic pathway.

1. Background

Radiotherapy (RT) has traditionally been used in patients with residual or recurrent secreting and nonfunctioning pituitary adenomas after surgery, resulting in a variable long-term tumor control of 80–97%[1–5] and normalization of elevated hormone levels in 40–70% of patients.[6–10] Hypopituitarism occurs in 30–60% of patients 5–10 years after irradiation, while other toxicities, including radiation-induced optic neuropathy, cerebrovascular accidents, and second tumors have been reported in 0–3%.[10–13]

Stereotactic techniques have been developed with the aim to deliver more localized irradiation and minimize the long-term consequences of treatment. The techniques used for treatment of pituitary adenomas involve either photon energy

* *Corresponding author at*: Unit of Radiation Oncology, Sant' Andrea Hospital, University of Rome Sapienza, Via di Grottarossa 1035, 00189 Rome, Italy. Tel.: +39 06 33776034; fax: +39 06 33776608.
E-mail addresses: gminniti@ospedalesantandrea.it, giuseppeminniti@libero.it (G. Minniti).
http://dx.doi.org/10.1016/j.rpor.2014.09.004

with cobalt-60 radiation-emitting sources (Gamma Knife, GK) or a modified linear accelerator (LINAC), and are given as a single-fraction stereotactic radiosurgery (SRS) or as fractionated stereotactic radiotherapy (FSRT).[14] Data from published literature indicate that either SRS or FSRT may achieve excellent long-term tumor control and hormone hypersecretion normalization; however, advantages and disadvantages of the different stereotactic techniques in the management of patients with pituitary adenomas and their optimal indications are still a matter of debate.

In this review, we present an update of the recent available literature on the use of stereotactic techniques in patients with pituitary adenoma. The efficacy, safety, and optimal indications for SRS and FSRT in nonfunctioning and secreting adenomas, including GH-secreting adenomas, ACTH-secreting adenomas and prolactinomas are discussed.

2. Stereotactic techniques

Stereotactic techniques are a refinement of high conformal RT with further improvement in immobilization, imaging and treatment delivery. The principal advances of stereotactic techniques are improved immobilization with either a frame-based or a frameless mask stereotactic system that act as a fiducial reference system, leading to a submillimetric accuracy in terms of patient movement. Stereotactic irradiation can be delivered as single-fraction SRS, multi-fraction SRS (2–5 fractions), and as FSRT when a conventional fractionation of 1.8–2.0 Gy per fraction is used.

In the multiheaded cobalt unit Gamma Knife (GK), 201 small Cobalt sources of gamma rays are arrayed in a hemisphere. A primary collimator aims the radiation emitted by these sources to a common focal point. A second external collimator helmet, which fits within the primary collimator, has an array of removable tungsten collimators (one per source) with circular apertures from 4 to 18 mm in size that are used to create different diameter fields at the focus point. In the new version of the machine (Gamma Knife Perfexion), the external helmet collimators have been replaced by a single internal collimation system: the cobatl-60 sources move along the collimator body to locations, where 4 mm, 8 mm, and 16 mm apertures have been created. High degree of conformity for larger non-spherical pituitary adenomas can be achieved through complex multi-isocenter computer planning that defines the optimum combinations of number, aperture and position of the collimators. The dose is typically prescribed at 50% isodose to obtain the maximum dose at the center of each pinpointed target and the prescribed dose at the target edge. Instead of using an array of cobalt sources, LINAC SRS utilizes X-rays which are derived from colliding accelerated electrons with a target metal. Linac FSRT uses multiple fixed fields or arcs at each daily session, shaped with a multileaf collimator (MLC). All fields and arcs conform to the shape of the tumor allowing a sharp dose gradient between the target and normal brain tissue. Dose conformity can be improved by the use of intensity modulation of the beams, lengths and dynamic collimator optimization of arcs, use of micro-multileaf collimator, and multiple isocenter.

CyberKnife (Accuray, Sunnyvale, CA) is a relatively new technological device that combines a mobile linear accelerator mounted on a robotic arm with an image-guided robotic system.[15] The treatment couch also has movements in six degrees of freedom. It has got 3 translation movements (longitudinal, lateral and vertical) and 3 rotational movements (pitch, roll and yaw). Patients are fixed in a thermoplastic mask and the treatment can be delivered as single-fraction or multi-fraction SRS. Single isocenters are used for spherical lesions, whereas irregularly shaped lesions are usually treated with a non-isocentric technique. A variable number of overlapping beams (up to 200) are delivered non-isocentrically to the target, resulting in excellent dose coverage to the target and conformity. The set of beam directions and analysis of dose distribution are chosen through an inverse planning process.

The superiority in terms of dose delivery and distribution for each of these techniques remains a matter of debate. Dose distribution to the target delivered by LINAC-based SRS is usually more homogeneous as compared to CyberKnife and GK SRS, and this may represent an advantage when treating larger tumors that include radiation-sensitive brain structures. By contrast, GK and CyberKnife may achieve a better conformity when irradiating irregularly shaped targets as compared to LINAC-based SRS. Regardless of the advantages claimed for each of these radiosurgical techniques, the reported clinical efficacy and toxicity are similar.

In FSRT, the delivered total dose is the same as in conventional RT (45–55 Gy in 25–33 daily fractions over a period of 5–6 weeks). Patients are usually immobilized in a high precision frameless stereotactic mask fixation system with a reported accuracy of 1–3 mm.[16] The principal aim of FSRT is to deliver more localized irradiation as compared with conventional RT, leading to a reduction of the volume of normal brain tissue irradiated to high radiation doses, possibly minimizing the long-term consequences of treatment.

The principal difference between SRS and FSRT is in the number of fractions. Large single doses of radiation as used in SRS are more toxic to normal brain structures than similar doses given in a fractionated manner, as used in FSRT. A dose-dependent risk of radiation optic neuropathy exists following single doses of irradiation. A few retrospective studies have indicated that the incidence of radiation-induced optic neuropathy is about 2% for single doses of 8–12 Gy, and becomes >10% for doses of 12–15 Gy to the optic apparatus.[17–20] Leavitt et al.[20] have recently reviewed 222 patients treated with GK SRS for a benign tumor adjacent to the anterior visual pathway. The risk of optic neuropathy was 0% for patients receiving a maximum dose of 8–12 Gy and 10% for those receiving >12 Gy, respectively, suggesting that small portions of anterior visual pathway in the range of 0.02–0.04 cm^3 may receive doses up to 12 Gy. The reported tolerance of cranial nerves in the cavernous sinus after single-fraction SRS is 16–18 Gy,[17,18] whereas a maximum dose of 12–13 Gy in a single fraction to the brainstem is recommended. By contrast, there is no restriction to the size of pituitary adenoma suitable for FSRT, since the delivered doses of 45–55 Gy using a conventional fractionation are within the tolerance of normal brain structures, including the optic nerves and chiasm.

3. Efficacy and toxicity of SRS

SRS is frequently used in patients with residual or recurrent nonfunctioning pituitary adenoma with a reported tumor control ranging from 87% to 100% at a variable median follow-up of 36–90 months (Table 1).[21–36] In a large retrospective multicenter study of 512 patients with nonfunctioning pituitary adenomas treated with SRS at a median dose of 16 Gy to the tumor margin, Sheehan et al.[35] reported an actuarial tumor control of 95% and 85% at 5 and 10 years, respectively. New or worsened hypopituitarism after SRS occurred in 21% of patients, and progressive or new onset optic neuropathy occurred in 6.6% of patients. A similar 5-year and 10-year tumor control of 97% and 87% has been reported in a series of 140 patients with nonfunctioning pituitary adenoma treated at the University of Virginia with GK SRS using a median marginal dose of 18 Gy.[32] At a median time of 50 months, hypopituitarism was observed in 30.3% of patients and new or worsening cranial nerve deficits in 13.7% of patients. Overall, a weighted average tumor control of 95% at 5 years has been observed in 9 studies including 1054 patients with a nonfunctioning pituitary adenoma, with an incidence of hypopituitarism of 23% and a new or worsened neurological deficit of 6.5%.[24–26,29,31,32,34–36] The dose used for achieving tumor control is 14–16 Gy, which is lower than that usually employed for controlling tumor growth in patients with secreting pituitary adenomas.

SRS is commonly used in patients with a GH-secreting pituitary adenoma failing surgery and/or resistant to medical therapy. Data from 28 studies of SRS using a variable marginal dose of 18–32 Gy (with a mean of 25 Gy) show a tumor control and biochemical control of disease in 88–97% and 35–100% of patients, respectively (Table 2).[37,21,38–63] However, the different criteria used to define GH/IFG1 plasma levels normalization, the variable follow-up period, the preirradiation GH/IGF-I levels and concomitant medical therapies make difficult the interpretation of published results and the real efficacy of SRS. Nevertheless, using stringent criteria of cure, as defined by suppressed GH levels <1 ng/ml during an oral glucose tolerance test (OGTT) and normal age-corrected IGF-I levels, the weighted average biochemical remission rate reported in 8 studies (including 515 patients) was 48% at 5 years,[44–47,49,50,53,59] and normalization of GH/IGF-I levels continued throughout the follow-up period.

Using similar criteria for defining the cure, Jezkova et al.[44] reported biochemical remission rates of 45%, 58%, and 57% at 3, 5, and 8 years, respectively, in 96 acromegalic patients with a median time to normalization of 66 months. In another series of 108 patients with acromegaly treated with GK SRS at University of Milan San Raffaele, Franzin et al.[59] reported an actuarial biochemical remission rate of 58.3% at 5 years, with an incidence of hypopituitarism of 7.8%. Similar biochemical remission rates in the range of 45–60% at 5 years have been observed in the majority of series,[44–47,49,50,59] although lower rates have been reported in a few studies.[39,41,43,45,53] Early reports suggest that the declining of serum GH concentration after GK SRS is faster compared with fractionated RT[62,63]; however, the rate of serum GH/IGF-I decline observed in other series is similar to that reported following fractionated RT.[41,45,49,50]

SRS data for 465 patients with Cushing's disease included in 15 studies are shown in Table 3.[21,58,61,66–77] At a weighted average follow-up of 46 months, the median tumor control was 98% and biochemical remission of disease, as measured by normalization of 24 h urinary free cortisol (UFC) and/or plasma cortisol concentration, was 64%. In a retrospective series of 96 patients with Cushing's disease treated by GK SRS at the University of Virginia, Sheehan et al.[76] reported a tumor control and biochemical remission rates of 98% and 70%, respectively, with a time to normalization of 16.6 months. New or worsened hypopituitarism occurred in 36% of patients, and progressive or new onset optic neuropathy occurred in 4.5% of patients. In a series of 40 patients with Cushing's disease treated by GK SRS, at a mean follow-up of 54 months, Castinetti et al.[70] reported the biochemical remission of disease in 42.5% of

Table 1 – Summary of recent published results (2000–2014) on SRS for nonfunctioning pituitary adenomas.

Authors	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Late toxicity (%)	
					Visual	Hypopituitarism
Izawa et al., 2000	23	19.5	>6	NA	1	NA
Wowra and Stummer, 2002	45	16	55	93 at 3 years	0	14
Petrovich et al., 2003	56	15	36	94 at 3 years	4	NA
Pollock and Carpenter, 2003	33	16	43	97 at 5 years	0	41 at 5 years
Losa et al., 2004	56	16.6	41	88 at 5 years	0	24
Iwai et al., 2005	34	12.3	60	93 at 5 years	0	6.5
Mingione et al., 2006	100	18.5	45	92.2	0	25
Liscak et al., 2007	140	20	60	100	0	2
Pollock et al., 2008	62	16	64	95 at 5 years	0	27
Gopalan et al., 2011	48	18.4	95	83	0	39
Park et al., 2011	125	13	62	94 at 5 years	0.8	24
Starke et al., 2012	140	18	50	97 at 5 years	12.8	30.3
Runge et al., 2012	61	13	83	98	0	9.8
Wilson et al., 2012	51	14	50	100 at 5 years	0	NA
Sheehan et al., 2013	512	16	36	95 at 5 years	6.6	21
Lee et al., 2014	41	12	48	85 at 10 years	2.4	24.4

NA, not assessed.

Table 2 – Summary of recent published results (2000–2014) on SRS for GH-secreting pituitary adenomas.

Authors	Patients	Dose (Gy)	Follow-up (months)	Tumor control (%)	Biochemical remission (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Zhang et al., 2000	68	31	>12	100	40	NA	NA
Izawa et al., 2000	29	22.5	>6	93	41	0	0
Pollock et al., 2002	26	20	36	100	47	4	16%
Attanasio et al., 2003	30	20	46	100	23	0	6.3%
Jane et al., 2003	64	15	>18	NA	36	0	28
Castinetti et al., 2005	82	26	49.5*	NA	17	1.2	17
Gutt et al., 2005	44	23	22	100	48	NA	NA
Kobayashi et al., 2005	67	18.9	63	100	17	11	15
Jezkova et al., 2006	96	35	53.7	100	44 at 5 years	0	27.1
Voges et al., 2006	64	16.5	54.3	97	14 and 33 at 3 and 5 years	1.4	13 and 18 at 3 and 5 years
Pollock et al., 2007	46	20	63	100	11 and 60 at 2 and 5 years	0	33 at 5 years
Vik-Mo et al., 2007	53	26.5	67	100	58 and 86 at 5 and 10 years	3.8	10 at 5 years
Jagannathan et al., 2008	95	22	57	98	53	4	34
Losa et al., 2008	83	21.5	69	97	52 and 85 at 5 and 10 years	0	10 at 10 years
Ronchi et al., 2009	35	20	114	100	46 at 10 years	0	50
Wan et al., 2009	103	28	67	95	37	0	6
Hayashi et al., 2010	25	25	36	100	40	0	0
Iwai et al., 2010	26	20	84	96	17 and 47 at 5 and 10 years	0	8
Castinetti et al., 2009	43	28	96	100	42.0	0	23
Leenstra et al., 2010	31	20	32	100	NA	NA	45 at 5 years
Erdur et al., 2011	22	23.8	60	95.2	54.5	0	28.6
Sheehan et al., 2011	130	24	31	93.0	53	2.4	24.4
Sicignano et al., 2012	39	25	60	97.7	54	NA	12.3
Franzin et al., 2012	103	22.5	71	97.3	58.3 at 5 years	0	14
Liu et al., 2012	40	21	72	97.5	47.5	0	40
Zeiler et al., 2013	21	14.2	33*	100	30	3.9	13.2
Yan et al., 2013	22	23	98	95	68.2	0	22.7
Wilson et al., 2013	86	20	66	96	18.6	1.2	19.8

NA, not assessed.

Table 3 – Summary of recent published results (2000–2014) on SRS for ACTH-secreting pituitary adenomas.

Authors	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Biochemical remission (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Izawa et al., 2000	12	23	>6	100	17	NA	0
Sheehan et al., 2000	43	16.5	44	100	63	2.5	16
Hoybye et al., 2001	18	NA	180	100	83	0	66
Kobayashi et al., 2002	20	28.7	60	100	35	NA	NA
Devin et al., 2004	35	14.7	35	91	49	0	40
Castinetti et al., 2007	40	29.5	54	100	42.5	2.5	15
Jagannathan et al., 2007	90	23	45	96	54	5.5[a]	22
Pollock et al., 2008	8	20	73	100	87 at 4 years	0	26 at 4 years
Tinnel et al., 2008	12	25	37	83.3	50	0	50
Sicignano et al., 2012	15	23.8	60	97.7	64	NA	12.3
Wein et al., 2012	17	18	23	94.1	58.8	0	11.8
Zeiler et al., 2013	8	24.7	35	100	50	3.9	13.2
Grant et al., 2013	15	35	40.2	100	73	3.2	32
Sheehan et al., 2013	96	16	48	98	70	5	36
Wilson et al., 2014	36	20	66	97	25	0	13.9

NA, not assessed.
[a] In 5 patients who underwent reirradiation.

patients, with a mean time to hormone normalization of 22 months. Similar remission rates have been shown by others, with a variable time to hormonal normalization of 14–26 months (Table 3). A higher margin radiation dose of 25–30 Gy is significantly associated with better control of adenoma growth and biochemical remission.[64,65,74] A recurrence rate of up to 20% after an initial remission of disease has been reported in some series,[40,66,76] indicating that a careful follow-up is mandatory also in patients who achieve hormonal normalization.

SRS is usually reserved for prolactinomas resistant to medical therapy with dopamine agonists. In a large retrospective series of 112 patients with a prolactinoma treated with GK using a median dose of 31 Gy, at a median follow-up of 33 months Pan et al.[79] reported hormonal normalization rate of 52%. In another series of 26 patients treated with GK SRS, Pouratian et al.[80] observed a tumor control in 89% and remission of the disease in 26% of patients, respectively, with an average time to normalization of 24.5 months. Complications included new pituitary hormone deficiencies in 28% of patients and cranial nerve palsy in 7% of patients. Overall, data for 338 patients reported in 11 studies show tumor control and normalization of serum prolactin concentration in 99% and 35% of patients at a weighted average follow-up of 42 months, respectively (Table 4).[21,54,55,57,72,78–83] Using a variable dose of 18–34 Gy (with a median of 28 Gy), the reported time to hormonal response ranges from 12 months to 66 months, with better tumor control and biochemical remission rates after single doses >25–30 Gy.[79,80]

There are only a few reports on the use of LINAC SRS in patients with either nonfunctioning or secretary pituitary adenomas.[33,34,45,62,63,69,77] The tumor control, biochemical remission of disease, and toxicity reported so far are broadly equivalent to those reported for GK SRS.

The overall rate of serious complications after SRS is low. The main complication is hypopituitarism, which is reported in 0–66% of patients, with higher rates in those series with a longer median follow-up. A lower incidence of hypopituitarism has been observed when normal pituitary gland receives a single dose <7.5 Gy.[55,57] At doses lower than 10 Gy to the optic apparatus, the reported rate of radiation-induced optic neuropathy is 0–4%. Cranial neuropathies and brain radio necrosis have been reported in 2–6% of patients when marginal doses >20 Gy are used. The risk to develop a new tumor after SRS appears to be significantly lower than that seen following fractionated RT,[13] however, the relatively short length of follow-up of most published series does not allow any definitive conclusion.

Multi-fraction SRS (2–5 fractions) has been employed in patients with tumors involving the optic apparatus who are considered not suitable for SRS.[84–87] Using doses of 18–24 Gy delivered in two to five sessions with CyberKnife, Adler et al.[84] reported high rates of tumor control and preservation of visual function in a small group of patients with pituitary adenomas within 2 mm of the optic apparatus. In a small study of nine patients with acromegaly treated to doses of 18–24 Gy in one to three fractions, at a mean follow up of 25.4 months, biochemical remission was observed in 4 patients.[85] Iwata et al.[86] reported a local control rate of 98% at 3 years in 100 patients with nonfunctioning pituitary adenomas treated with hypofractionated SRS with CyberKnife using 21–25 Gy in 3–5 fractions. Complications were represented by a grade 2 visual disorders in one patient and new onset of hypopituitarism in 4 patients. However, the evaluation of radiation tolerance of the optic chiasm and nerves using hypofractionated schedules was not performed. Thus, the efficacy of hypofractionated treatment schedules in terms of tumor control and reduced risk of radiation-related adverse effects as compared to single-fraction SRS needs to be better elucidated in future studies.

4. Efficacy and toxicity of FSRT

FSRT data for 668 patients with nonfunctioning and secreting pituitary adenomas reported in 11 studies are showed in Table 5.[88–95,34,96,97] In a series of 110 patients with either nonfunctioning or secreting pituitary adenomas treated with FSRT at a dose of 50.4 Gy delivered in 28 fractions, after a minimum follow-up of 48 months, the 5-year tumor control was 99%; hormone hypersecretion normalization occurred in 42% (20/47) of patients with a secreting tumor.[91] Kong et al.[93] reported the clinical outcomes in 125 patients with pituitary adenomas (54 secreting adenomas and 71 nonfunctioning adenomas) who received FSRT at a mean dose of 50.4 Gy in 28 fractions or single-fraction GK SRS with a mean marginal dose of 25.1 Gy. At a mean follow up of 36.7 months, 2-year and 4-year overall actuarial progression-free survival rates and hormone complete remission rates were 99% and 97%, and 26.2% and 76.3%, respectively. No difference was observed between the FSRT group and the SRS group, although the median time to complete biochemical remission was shorter after SRS. Hypopituitarism developed in 5.7% of patients at 3 years and 27.3% of patients at 5 years. A similar high tumor control for either nonfunctioning or secreting pituitary adenomas has been observed in most series (Table 5).

Only few data are available on the efficacy of FSRT in secreting adenomas.[89,91,92,94,34] In a series of 25 patients with acromegaly treated by FSRT with a median total dose of 52 Gy, Milker-Zabel et al.[89] reported normalization of elevated GH levels in 21 (84%) out of 25 patients at a median follow-up of 26 months. In another series of 34 acromegalic patients treated by FSRT with a total dose of 54 Gy, at a median follow-up of 30 months, 34% of patients had biochemical normalization of disease, with 29% of patients who developed a deficit of one or more pituitary hormones.[94] In a small series of 12 patients with Cushing disease, Colin et al.[91] observed hormone normalization in 9 (75%) out of 12 patients after a median time of 29 months.

Hypopituitarism has been observed in 6–48% (median 15%) of patients at a weighted average follow-up of 37.6 months (Table 5). Incidence of permanent optic neuropathy occurred in 1–5% of patients; however, it has been reported in less than 2% with total doses <50 Gy delivered in fractions of 1.8 Gy. No other complications, such as brain necrosis, second tumors, and cerebrovascular disease have been reported; however, the short follow-up does not allow definitive conclusions about the potential less toxicity of treatment.

In summary, FSRT is a safe and effective treatment in controlling tumor growth and normalizing hormone hypersecretion in patients with a residual or progressive pituitary

Table 4 – Summary of recent published results (2000–2014) on SRS for prolactin-secreting pituitary adenomas.

Authors	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Biochemical remission (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Landolt et al., 2000	20	25	29	85	25	0	NA
Pan et al., 2000	128	31.2	33	99	41	0	NA
Izawa et al., 2000	15	23.8	>6	100	16	0	NA
Pouratian et al., 2006	23	18.6	48	89	26	7	28
Pollock et al., 2008	11	18	48	100	18 at 4 years	9.1	26 at 4 years
Castinetti et al., 2009	15	28	96	100	46.6	0	21
Jezkova et al., 2009	35	34	75.5	97	37.1	NA	NA
Tanaka et al., 2010	22	25	60	100	18	4	42 at 4 years
Leenstra et al., 2010	15	20	63	100	NA	NA	41
Sheehan et al., 2011	32	24	31	93	26	2.4	24.4
Liu et al., 2013	22	15	36	86	27.3	13.6	4.5

NA, not assessed.

Table 5 – Summary of recent published results (2000–2014) on FSRT for pituitary adenomas.

Authors	Type of adenoma	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Milker-Zabel et al., 2001	NFA, SA	68	50.4	38	93 at 5 years	7.5	5
Milker-Zabel et al., 2004	GH	20	52.2	26	100 (92[a])	0	3
Paek et al., 2005	NFA, SA	68	50	30	98 at 5 years	3	6
Colin et al., 2005	NFA, SA	110	50.4	48	99 at 5 years	1.8	29 at 4 years
Minniti et al., 2006	NFA, SA	92	45	32	98 at 5 years	1	22
Kong et al., 2007	NFA, SA	66	50.4	36.7	97	0	27.3 at 5 years
Roug et al., 2010	GH	34	54	34	91 (30[a])	0	29 at 4 years
Schalin-Jantti et al., 2010	NFA, SA	30	45	64	100	0	40
Wilson et al., 2012	NFA	67	50	60.1	93 at 5 years	1.5	7
Kopp et al., 2013	NFA, SA	37	49.4	57	91.9	5	5
Kim et al., 2013	NFA, SA	76	50.4	80	97.1 at 7 years	0	48

NFA, nonfunctioning adenoma; SA, secreting adenoma.
[a] Biochemical remission of disease.

adenoma; the advantage of reducing the volume of normal brain irradiated in terms of the reduction in long-term morbidity requires longer follow-up.

5. Conclusions

Stereotactic irradiation remains an effective treatment modality for patients with both nonfunctioning and secreting pituitary adenomas after unsuccessful surgery and/or resistant to medical therapy. Both SRS and FSRT provide excellent tumor control in the range of 85–95% at 5–10 years, with normalization of hormone hypersecretion in more than 50% of patients. Hypopituitarism represents the most commonly reported late complication of treatment, whereas the reported incidence of other late effect radiation complications are low. A few series suggest that multi-fraction SRS may be an appropriate treatment in patients with tumors in a close proximity to the optic apparatus; however, the advantages of hypofractionated schedules in terms of local control and risk of radiation-induced toxicity as compared to other stereotactic techniques need to be better evaluated in future studies.

On the evidence available, no data support the superiority of SRS over FSRT for the treatment of patients with pituitary tumors. Dose and fractionation are usually chosen on the basis of the size and position of the pituitary adenoma. In current clinical practice, single-fraction SRS at doses of 16–25 Gy may represent a convenient approach to patients with a relatively small pituitary adenoma away from the optic chiasm, whereas FSRT is preferred over SRS for lesions >2.5–3 cm in size and/or involving the anterior optic pathway.

Authors' contributions

GM participated in article preparation and wrote the manuscript. EC participated in article preparation and data analysis. RME helped to revise the manuscript. All authors have approved the final article.

Conflict of interest

None declared.

Financial disclosure

None declared.

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