Best Practice & Research Clinical Endocrinology & Metabolism 33 (2019) 101269

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

The risk/benefit ratio of radiotherapy in pituitary tumors

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ARTICLE INFO

Article history:
Available online 16 April 2019

Keywords:
radiosurgery
fractionated stereotactic radiotherapy
nonfunctioning and secreting pituitary adenomas
toxicity

Radiation therapy (RT) is an effective treatment for patients with either nonfunctioning or secreting pituitary adenomas unsuccessfully treated by surgery and/or medical therapy, resulting in local control of 90–95% at 5–10 years and variable normalization of hormonal hypersecretion for patients with GH-, ACTH-, and prolactin-secreting adenomas in the range of 40–80% at 5 years; however, its use has been limited because of concerns regarding potential late toxicity of radiation and delayed efficacy in normalization of hormone hypersecretion. In the last decades, there have been advances in all aspects of radiation treatment, including more accurate immobilization, imaging, treatment planning and dose delivery. RT has evolved with the development of highly conformal stereotactic techniques and new planning and dose delivery techniques, including intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). All these new techniques allow precise and sharply focused radiation delivery reducing the dose to surrounding critical neurovascular and brain structures, and potentially limiting the long-term consequences of radiation treatments. In this review, we present a critical analysis of the more recent available literature on the use of RT in patients with both nonfunctioning and secreting pituitary adenomas, focussing particularly on the risk/benefit ratio of modern radiation techniques.

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https://doi.org/10.1016/j.beem.2019.04.003
1521-690X/

Introduction

Surgery, radiation therapy (RT), and medical therapies, are available treatments for patients with both nonfunctioning or secreting pituitary pituitary adenomas. Historically, transsphenoidal surgery has been recommended in the initial management of pituitary tumors, with complete resection and biochemical normalization of hormone hypersecretion which is achieved in up to 80% of patients, depending on the size, location, and extension of the tumor, and with a low incidence of surgical complications [1–4]. In the last two decades, medical treatment of GH-secreting, ACTH-secreting and prolactin-secreting adenomas has improved and several medical therapies are now available, including dopamine agonists, somatostatin analogs, and the GH-receptor antagonist pegvisomant with a reported normalization of hormone hypersecretion in more than 70% of patients, especially those with prolactinoma and acromegaly [5–8].

Conventional RT has been generally employed in the past for patients with residual or recurrent non-functioning pituitary adenomas after surgery to prevent tumour growth, achieving local control in up to 90% of patients at 10–20 years [9,10]. Main complication of treatment is represented by the development or worsening of hypopituitarism occurring in 30–60% of patients 5–10 years after irradiation, while other toxicities, such as radiation-induced optic neuropathy, neurocognitive deterioration, cerebrovascular accidents, and secondary tumors that have been reported in less than 5% of patients [9–14]. For patients with secreting tumors, several retrospective series have shown similar local control rates of 90% at 10 years and remission of hormone hypersecretion in more than half irradiated tumors [15–19]; however, because of concerns regarding the safety and delayed normalization of hormonal excess that may take several years, the use of conventional RT in the management of these tumors has been limited.

In the last decades, implementation of imaging techniques and radiotherapeutic technology have enabled more precise and focal irradiation. For patients with a pituitary adenoma, radiation techniques have evolved from 3D conformal RT to the stereotactic techniques, either stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT), with the aim of delivering high radiation doses with a steeper dose gradient between the tumor and the surrounding critical neurovascular structures, potentially reducing long-term adverse effects of radiation treatments [21]. In patients with benign pituitary tumors, data from recently published series indicate that modern techniques, either SRS or fractionated RT, can achieve excellent long-term control with apparently low radiation-induced toxicity compared to old-fashioned radiation techniques [22].

In this review, we present an update of available literature on the use of RT in patients with pituitary adenomas, focussing particularly on the risk/benefit ratio of current radiation techniques for pituitary tumors in the era of modern RT.

Advances in radiotherapy technology

Fractionated radiotherapy

Radiation techniques have evolved from conventional RT to 3 dimensional (3-D) conformal and stereotactic techniques, with technical improvements seen in all aspects of radiation treatment, including better imaging and 3-D planning, patient immobilization, and sophisticated imaging systems for accurate patient repositioning in the treatment room which lead to a more precise dose delivery and reduction of normal brain structures irradiated to high radiation doses [22]. Typically, patients are immobilized in an individual shaped thermoplastic mask and doses of 45–54 Gy are usually delivered in 25–30 daily fractions. Tumor localization has improved with the use of computed tomography (CT) and magnetic resonance (MR) imaging which are co-registered to better define the tumor volume and its relationship to adjacent critical structures, such as optic chiasm and neurovascular structures in the cavernous sinus. A margin of 3–5 mm beyond the visible extent of tumor, named planning target volume, is added to allow for set-up variations and patient movement during the treatment.

Further improvements in RT planning are represented by 3-D tumor delineation, calculation and delivery of the prescribed dose. Better dose distribution is usually achieved by shaping the radiation

beams to conform to the shape of tumor with the use of multileaf collimators and increasing the number of beams, resulting in higher absolute dose differences between irradiated volumes and surrounding normal brain structures. Multileaf collimators can also be used to dynamically modulate the intensity of the radiation by altering the shape of beams, and this is described as intensity modulated radiotherapy (IMRT). For patients receiving FSRT, better immobilization is usually achieved with the use of more precise mask systems, with a reported repositioning accuracy of 1–2 mm [23]. Improvements in radiation delivery include improved patient's repositioning accuracy in the treatment room with the use of orthogonal x-rays (ExacTrac®) and cone beam CT (CBCT) in-room imaging systems that are able to correct translating and rotating positioning errors with an accuracy < 0.5–1 mm [24,25].

Particle radiation has been also applied successfully in the treatment of pituitary adenomas. The physical properties of proton irradiation can offer superior dose conformality when compared to 3D-conformal RT and IMRT, therefore offering the potential for better sparing of normal tissue particularly beyond the principal target. A few series report high local control and relatively low toxicity in patients with pituitary adenomas receiving proton radiation [26–29]. Currently, potential advantages of proton therapy for pituitary tumors over photon therapy in terms of efficacy and long-term toxicity remain to be proven.

Stereotactic radiosurgery

SRS for pituitary adenomas is typically delivered as single-fraction SRS or, less frequently, as multi-fraction SRS given in 2–5 fractions. The most commonly available radiosurgery technologies include the use of the Gamma Knife (GK), the CyberKnife (CK) or a modified linear accelerator (LINAC) [30–35].

GK uses an array of 192 cobalt sources that are arranged in a collimator helmet system concentrated towards a central point [30,31]. Each eight different sectors containing 24 cobalt-60 sources can generate radiation beams through 3 different collimators of 4 mm, 8 mm, and 16 mm of diameter at isocenter. For large not spherical tumors like the majority of large pituitary adenomas, optimal conformity can be achieved by combining the number, the position and the aperture of the collimators. Patients are immobilized in a fixed frame and radiation dose is typically delivered in a single session, with the dose prescribed to the 50% isodose to achieve rapid dose fall-off. In the last Icon GK unit, patients can be immobilized in a thermoplastic mask and the total dose delivered as fractionated SRS.

CyberKnife (Accuray, Sunnyvale, CA) is a relatively new technology for frameless SRS in which a mobile linear accelerator is mounted on a robotic arm with an image-guided robotic system. Patients are immobilized in a thermoplastic mask and radiation doses can be delivered in a single or few fractions with a target accuracy of 0.5–1 mm, similar to that achieved with frame-based SRS [32,33].

LINAC is frequently used for delivering SRS. The dose is precisely delivered through multiple fixed fields or arcs shaped using a multileaf collimator with *a* leaf width of between *2*.5 and 5 mm [34,35]. Dose conformity can be improved by the use of intensity modulation of the beams (IMRS) or volumetric modulated arc therapy (VMAT). Patients are usually immobilized in a high precision frameless fixation systems with a reported accuracy of 1–2 mm; however, submillimetric accuracy of patient repositioning is achieved by the use of on-board imaging ExacTrac and CBCT [24,25].

Overall, despite technical differences among GK, CK and LINAC, the clinical superiority of a technique over another remains unknown. Regardless of the technology used, a robust quality assurance program, encompassing all aspects of the treatment, is mandatory to ensure SRS accuracy and patient safety.

Risk/benefit ratio of fractionated RT

Large series assessing the long-term efficacy of conventional RT for patients with pituitary adenomas show local control rates in the region of 80%–94% and 75%–90% at 10 and 20 years, respectively, being similar for secreting and nonfunctioning pituitary adenomas [9,10,15,18,35–39] (Table 1). For patients with acromegaly, normalization of GH/IGF-I levels occurs in approximatively 40%–60% of patients 5–10 years after treatment [16,17], with a 50% decline of GH and IGF-1 pre-radiation levels in about 2 and 5 years, respectively [16,18]; this means that faster biochemical control of the disease in

less than 5 years is expected only in patients with pre-treatment IGF-1 levels increased up to 2–2.5 times the upper limit of normal, whereas patients with IGF-1 levels 3–4 times the upper limit of normal may require 10 years or more to achieve biochemical control of disease. For patients with persistent Cushing's disease, normalization of cortisol excess occurs in 50–80% of patients, with the majority of them achieving the biochemical control of disease within 3 years from radiation treatment [15,19]. Conventional RT has been usually reserved for prolactinomas resistant to medical therapy with dopamine agonists; few retrospective series reporting its efficacy in patients with prolactinoma have shown normalization of hyperprolactinemia in about one third of patients after 5–10 years [9,20,36].

Conventional RT for patients with pituitary adenomas is associated with potential risk of late complications [9–20,36–40,42–55]. The most common reported late toxicity of RT is hypopituitarism which can be triggered by direct effects on the pituitary gland or abnormalities in hypothalamic-pituitary stalk [41]; several series have observed new or worsening pituitary hormonal deficits in 30–50% of irradiated patients at 5 years following conventional RT at doses of 45–50 Gy in 1.8–2 Gy fractions [9,10,14–20,36–40], and this proportion is likely to increase with time from treatment. The reported incidence of radiation-induced optic neuropathy causing visual deficit is 0–6% [9,10,15–19,36–40] (Table 1). The risk is related to the total dose, the dose per fraction and the pre-existing visual deficits; for a total dose of 45 Gy given in daily doses of 1.8 Gy, the reported incidence of optic neuropathy is less than 2%.

An increased incidence of cerebrovascular accidents and excess cerebrovascular mortality has been reported in few retrospective series [13,43–45]. In 334 patients treated with conventional RT for a pituitary adenoma, Brada et al. [13] observed a 4-fold increase of cerebrovascular accidents, and a similar increased risk has been reported by others [43–45]. Another potential complication of RT is represented by the development of a second radiation-induced brain tumor [14,46]. In a cohort of 426 patients with pituitary adenomas who received conventional RT at the Royal Marsden Hospital (RMH) between 1962 and 1994, the cumulative risk of second brain tumors following the treatment was 2% and 2.4% at 10 and 20 years, respectively. Relatively high radiation doses to large brain volume or hippocampi are recognised to be associated with neuro-cognitive decline [47–49], although the consequences of small volume irradiation, surgery, and tumor itself on neurocognitive functions and quality of life for patients with pituitary tumors remain to be better defined, [50–53].

Recent series of FSRT report similar efficacy and less toxicity than conventional RT [56–66] (Table 2). Hypopituitarism has been reported in 10–40% of patients at 5 years, whereas the incidence of optic neuropathy is less than 3% of patients for radiation doses less than 50.4 Gy given in 1–8 Gy fractions. Other complications occur rarely, including nerves deficits, and neurocognitive and cerebrovascular complications [56–66]. Overall, published data suggest lower incidence of long-term toxicity with the

Table 1
Selected series of conventional and conformal RT for nonfunctioning and functioning pituitary adenomas.

Authors	Type of adenoma	Patients	Follow-up median (years)	Tumor control %	Hypopituitarism (%)	Visual deficits (%)
Brada et al., 1993 [9]	NFA, SA	411	10.8	88 at 20 years	30 at 10 years	1,5
Tsang et al., 1994 [10]	NFA, SA	160	8.7	87 at 10 years	23	0
Zierhut et al., 1995 [36]	NFA, SA	138	6.5	95 at 5 years	27	1,5
Estrada et al., 1997 [15]	SA (ATCH)	30	3.5	73 at 2 years[a]	48	0
Barrande et al., 2000 [16]	SA (GH)	128	11	53 at 10 years[a]	50 at 10 years	0
Biermasz et al., 2000 [17]	SA (GH)	36	10	60 at 10 years[a]	54 at 10 years	0
Minniti et al., 2005 [18]	SA (GH)	45	12	52 at 10 years[a]	45 at 10 years	0
Langsenlehner et al., 2007 [37]	NFA, SA	87	15	93 at 15 years	88 at 10 years	0
Minniti et al., 2007 [19]	SA (ATCH)	40	9	84 at 10 years[a]	62 at 10 years	0
Rim et al., 2011 [38]	NFA, SA	60	5.7	96 at 10 years	76 at 10 years	0
Sebastian et al., 2016 [39]	NFA, SA	94	6	97.9 at 5 years	5.3	6.4
Scheick et al., 2016 [40]	NFA, SA	116[a]	9	96 at 10 years	25	2

NFA, nonfunctioning adenoma; SA, secreting adenoma.
[a] hormone hypersecretion normalization.

use of modern radiation techniques compared to old-fashioned techniques; however, large series with minimum follow-up time of 15–20 years need to confirm these results.

In summary, "modern" fractionated RT is an effective treatment for patients with pituitary adenomas of any size which failed surgery or medical therapy. Even though the reported incidence of long-term complications is lower than that reported after conventional RT, the risk/benefit ratio of treatment needs to be carefully evaluated. Firstly, the development of new pituitary deficits is reduced but not eliminated, and this remains a serious clinical concern because hypopituitarism is associated with decreased quality of life [54,55] and increased mortality, mainly due to cardiovascular and cerebrovascular diseases [13,43–45]. In addition, compromised fertility due to hypogonadotropic hypogonadism represents a serious clinical condition in younger subjects. Finally, the risk of developing a second tumor may increase with time; this means, in clinical practice, that RT should always be considered carefully in young patients.

Risk/benefit ratio of SRS

The efficacy of SRS in patients with nonfunctioning adenomas has been reported in several retrospective series showing a median tumor control of 90–100% at 5 years [63,67–87]. Selected large series are shown in Table 3 [75,77,79,82,83,85]. In a large retrospective multicentre study, Sheehan et al. [85] observed no significantly differences in tumor control rates for patients treated with 12–20 Gy versus those receiving doses > 20 Gy; in contrast, a margin dose less than 12 Gy was associated with worse control rates. In clinical practice, doses of 13–14 Gy can be sufficient to achieve long-term tumor control with acceptable long-term neurological toxicity. Among factors predicting local control after SRS, large invasive tumors with suprasellar/parasellar extension have been associated with worse local control [78,82,83,85]. Most series report the use of GK SRS, although similar efficacy and toxicity have been observed with the use of Linac or CK.

Several retrospective series have reported the efficacy of SRS for GH-secreting adenomas [29,76,88–96] (Table 4). Using SRS doses of 16–25 Gy, tumor control has been observed in 90–100% of patients, with a variable normalization of GH/IGF-1 hypersecretion ranging from 30% to 80%, depending on the different follow-up time and criteria used to define the "cure" of disease. When the biochemical control of disease is defined by "stringent criteria" (glucose-suppressed plasma GH levels during OGTT and normal age-corrected IGF-I values), 5-year hormonal normalization rates is more than 40% in most published series [76,91–96]. Although faster declining of serum GH concentration after SRS over fractionated RT has been suggested in few series [97,98], recent reports show that

Table 2
Selected series of fractionated stereotactic radiotherapy for pituitary adenomas.

Authors	Type of adenoma	Patients (n)	Follow-up (months)	Tumor control (%)	Hypopituitarism (%)	Visual deficits (%)
Milker-Zabel et al., 2001 [56]	NFA, SA	68	38	93 at 5 years	5 at 5 years	7,5
Milker-Zabel et al., 2004 [57]	GH	20	26	100 (92[a])	3	0
Paek et al., 2005 [58]	NFA, SA	68	30	98 at 5 years	6 at 5 years	3
Colin et al., 2005 [59]	NFA, SA	110	48	99 at 5 years	29 at 4 years	1,8
Minniti et al., 2006 [60]	NFA, SA	92	32	98 at 5 years (50[a])	22 at 5 years	1
Kong et al., 2007 [61]	NFA, SA	66	36.7	97 at 5 years	27.3 at 5 years	0
Roug et al., 2010 [62]	GH	34	34	91 (30[a])	29 at 4 years	0
Wilson et al., 2012 [63]	NFA	67	60.1	93 at 5 years	7 at 5 years	1,5
Kim et al., 2013 [64]	NFA, SA	76	80	97,1 at 7 years	48 at 7 years	0
Barber et al., 2016 [65]	NFA, SA	75	72	97.9 at 6 years	6.4	5.3
Minniti et al., 2016 [66]	NFA	68	75	91 at 10 years	40 at 5 years	3

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

biochemical remission of disease is similar to that reported after conventional RT, depending on GH and/or IGF-1 pre-treatment levels [90,91,93,94].

In patients with Cushing's disease, biochemical remission of disease, as measured by normalization of 24 h urinary free cortisol and plasma cortisol levels, has been reported in 45–55% of patients 5 years following SRS using doses of 18–28 Gy [28,99–104] (Table 5). Notably, a recurrence rate up to 20% after an initial remission of disease has been reported in some series [101–103,105], indicating that a careful follow-up is mandatory also in patients who achieve normal hormone levels.

For patients with prolactinomas, SRS is usually reserved to medical resistant adenomas. Few retrospective series reporting the clinical outcomes following variable SRS doses of 16–30 Gy, show tumor control rates and normalization of prolactin levels of 85%–95% and 40–50% at 5 years, respectively [105–111] (Table 6).

Based on the available published series, the overall rate of serious complications after SRS is low. As for series of fractionated RT, the most common reported complication is the development of hypopituitarism, with 5-year incidence of new or worsening pituitary deficits ranging from 10 to 40% (Tables 3–6). Pre-existing anterior pituitary deficits, larger tumor volumes, and doses to pituitary gland and pituitary stalk higher than 15 Gy have been associated with significantly increased incidence of hypopituitarism [112–115]. Other toxicities, including radiation optic neuropathy and other cranial deficits, have been rarely reported. The reported incidence of radiation-induced optic neuropathy is less than 3% when doses less than 8–10 Gy are delivered to optic apparatus, although the risk is significantly increased for doses higher than 12 Gy [116–119]. Other cranial nerves deficits (third, fourth, and sixth) have been reported in less than 7% of patients. The risk to develop a second tumor and cardiovascular complications after SRS appears to be significantly less than that seen following conventional RT; however the relatively short length of follow-up of most published series (<10 years) does not allow for any definitive conclusion about the relative risk of developing such complications.

Few studies report the efficacy and safety of fractionated SRS delivered in 2–5 fractions in patients with pituitary tumors in close proximity to optic nerve and chiasm [120–124]. Using doses of 21 Gy in 3 fractions or 25 Gy in 5 fractions delivered with CK in 100 patients with nonfunctioning pituitary adenomas, Iwata et al. [122] reported local control rates of 98% at 3 years, with respective incidence rates of long-term toxicity of 5%, including visual disorders and hypopituitarism. Similar tumor control and low incidence of optic neuropathy have been reported in other few series using similar doses and fractionation [119,120,123]. Although these data suggest that multi-fraction SRS may represent an effective treatment option for relatively large tumors in close proximity to optic apparatus that are not suitable for single-fraction SRS, larger series with longer follow-up times need to confirm the efficacy and safety of fractionated schedules over other radiation techniques.

Summary

RT remains an effective treatment modality for patients with residual or progressive pituitary adenoma with an excellent long-term tumor control. The use of modern radiation techniques allows for lower radiation doses to normal surrounding brain structures compared to old conventional techniques, and this is likely to translate into reduced radiation-induced late complications. Nevertheless, minimizing the radiation dose to the normal brain tissue does not eliminate the risks of developing late

Table 3
Selected series of SRS for nonfunctioning pituitary adenomas.

Authors	Patients (n)	Follow-up (months)	Tumor control (%)	Hypopituitarism (%)	Visual deficits (%)
Mingione et al., 2006 [75]	100	44.9	92.2	19.7	0
Liscak et al., 2007 [77]	140	60	100	2	0
Kobayashi et al., 2009 [79]	71	50.2	96.7	8.2	2.8
Park et al., 2011 [82]	125	62	90 (94 at 5 years)	24	0,8
Starke et al., 2012 [83]	140	50	89.6 (97 at 5 years)	30.3	0
Sheehan et al., 2013 [85]	512	36	93.4 (95 at 5 years)	21	7.9

Table 4
Selected series of SRS for GH-secreting pituitary adenomas.

Authors	Patients (n)	Follow-up (months)	Tumor control (%)	Biochemical control (%)	Hypopituitarism (%)	Visual deficits (%)
Kobayashi et al., 2005 [88]	67	63.3	100	17	14.6	11.1
Jezkova et al., 2006 [89]	96	53.7	100	50 (44 at 5 years)	27.1	0
Voges et al., 2006 [76]	64	54.3	97	37.5 (33 at 5 years)	12.3 (18 at 5 years)	1,4
Pollock et al., 2007 [90]	46	63	100	50 (60 at 5 years)	36	2.2
Vik-Mo et al., 2007 [91]	61	66	100	38 (58 at 5 years)	23	0
Losa et al., 2008 [92]	83	69	97.6	60 (52 at 5 years)	8.5 (11.8 at 5 years)	0
Castinetti et al., 2009 [93]	43	96	100	42 at 5 years	23	0
Franzin et al., 2012 [94]	103	71	97.3	60.7 (57 at 5 years)	7.8	0
Wilson et al., 2013 [95]	86	66	96	18.6	19.8	1,2
Lee et al., 2014 [96]	136	61.5	98.5	65.4 (73.4 at 6 years)	31.6	3.7
Wattson et al., 2014 [29]	50	51.5	100	48 (49 at 5 years)	57 (62 at 5 years)	0

complications, and the decision of irradiating a pituitary adenoma should always be based on a careful evaluation of the risk/benefit ratio of treatment. In current clinical practice, single radiosurgical doses of 13–14 Gy for non-functioning adenomas and 16–22 Gy for functioning adenomas are sufficient to achieve tumor and biochemical control of irradiated tumors, since higher doses do not result in better clinical outcome. The most common complication is represented by the development of hypopituitarism which requires lifetime hormone replacement and is associated with excess cardiovascular mortality and decreased quality of life. Other complications, including the risk of optic neuropathy and other cranial deficits, occur in less than 5% of irradiated tumors. Although new techniques carries a lower risk of long-term toxicity as compared to old RT techniques, the potential benefits and risks of treatments need to be carefully assessed by an experienced multidisciplinary team including endocrinologists, neurosurgeons, radiation oncologists, medical oncologists, neuroradiologists, and neuropathologists. In current clinical practice, radiation treatments is not an alternative to surgery or medical therapy, but should be reserved for patients with progressive pituitary adenomas or at high risk of regrowth after uncomplete resection who do not respond or became resistant to medical therapies.

Both fractionated RT and SRS achieve similar long-term tumor control and hormone hypersecretion normalization. Currently, there is no data supporting the superiority of a technique over another in terms of tumor control and faster biochemical control. The choice of radiation technique should be based on size and site of the tumor. Large single radiation doses to normal brain structures carry higher risk of toxicity compared with similar doses given in conventional fractionation. The risk of radiation optic neuropathy following SRS is significantly increased after single doses exceeding 8–10 Gy to the optic chiasm; this means that SRS is usually offered to patients with pituitary adenomas less than 3 cm in size not in contact with the optic apparatus, in order to keep the dose below 8–10 Gy.

For patients not suitable for single-fraction SRS, few retrospective series suggest that SRS given in 3–5 fractions may be a safer alternative to single-fraction SRS; however, the advantages of SRS fractionated schedules over other stereotactic techniques need more evidences. For such patients, modern fractionated radiation techniques using 45–50.4 Gy in 25–28 daily fractions should be recommended, since the delivered total dose to the tumor is under the tolerance of normal brain structures.

Regarding the clinical outcomes of early versus delayed postoperative RT for a pituitary adenoma, there is no clear evidence that the timing of treatment can influence the balance between risks and benefit. Several retrospective series showed no difference in tumor control and toxicity for patients receiving immediate postoperative RT compared to those treated at the time of recurrence or progression [56,59,60]. In contrast, series reporting clinical outcomes after SRS suggest that early postoperative treatment may provide the best therapeutic option for patients with residual tumor, preventing the development of neurological deficits associated with tumor growth and reducing the risk of long-term toxicity [73,124]. Based on available literature, deferring RT for patients with small

Table 5
Selected series of SRS for ATCH-secreting pituitary adenomas.

Authors	Patients (n)	Follow-up (months)	Tumor control (%)	Biochemical control (%)	Hypopituitarism (%)	Visual deficits (%)
Sheehan et al., 2000 [99]	43	44	100	63	16	2
Devin et al., 2004 [100]	35	35	91	49	40	0
Castinetti et al., 2007 [101]	40	54.7	100	42.5	15	2.5
Jagannathan et al., 2007 [102]	90	45	96	54	22	5.5
Petit et al., 2007 [28]	33	62	94	52	52	0
Sheehan et al., 2013 [103]	96	48	98	70	36	5
Wattson et al., 2014 [29]	74	47	98.6	67 at 5 years	62 at 5 years	0
Wilson et al., 2014 [104]	36	66	97	25	13.9	0

Table 6
Selected series of SRS for prolactin-secreting pituitary adenomas.

Authors	Patients	Follow-up (months)	Tumor control (%)	Biochemical remission (%)	Hypopituitarism (%)	Visual deficits (%)
Pan L et al., 2000 [105]	128	41	99	41	NA	0
Pouratian et al., 2006 [106]	23	55	89	26	28	7
Jezkova et al., 2009 [107]	35	75.5	97	37.1	14.3	0
Wan et al., 2009 [108]	176	67.5	90.3	23.3	1.8	0
Tanaka et al., 2010 [109]	22	60	100	18	42 at 4 years	4
Liu et al., 2013 [110]	22	36	86	27.3	4.5	0
Cohen-Inbar et al., 2015 [111]	38	42.3	92	50	30.3	4.2

asymptomatic postoperative residual tumors may be a reasonable approach. In contrast, immediate postoperative RT should be recommended for patients with “high risk” tumors, as defined by high proliferative potential by mitotic count and Ki-67 index, and other clinical parameters such as tumor invasion [125].

Research continues in all fields of radiation oncology to develop more effective and less toxic treatments. With regard to the radiation treatment of pituitary adenomas, clinical studies need to better understand the relationship between radiation doses to pituitary gland and stalk and the development of pituitary deficits, as well to determine optimal dose and fractionation for different types of pituitary adenomas, and to identify the molecular markers predictive of better tumor response, either local control or hormone hypersecretion normalization. This will help to improve the risk/benefit ratio of radiation treatments for patients with pituitary tumors.

Practice points

- Radiation should be reserved for patients with progressive pituitary adenomas not otherwise controlled by surgery and/or medical therapy.
- The potential benefits and risks of radiation treatments need to be carefully assessed by an experienced multidisciplinary team.
- Stereotactic radiosurgery and fractionated radiotherapy are both effective treatments for pituitary adenomas. The choice of dose and fractionation depends on the site and volume of tumor; for large lesions involving the optic apparatus conventionally fractionated radiotherapy is recommended.
- The role of early postoperative radiation is unclear; there is little evidence that “high risk” postoperative residual tumors may benefit of early radiation treatments; however, patients can be offered postoperative surveillance, provided that they are monitored closely with MR imaging.

Research agenda

- Further studies need to investigate the relationship between doses to pituitary gland and stalk and the development of hypopituitarism, as well the impact of different doses on neurocognitive function and quality of life.
- Safety and efficacy of different dose fractionation radiation schedules should be explored in clinical trials.
- Identification of molecular markers predicting tumor aggressive behaviour and rapid recurrence, as well those predicting radiation sensitivity and resistance.
- Define the efficacy of different radiation techniques on the normalization of hormone hypersecretion for GH-, ATCH- and PRL-secreting tumors.
- Define the optimal timing of radiosurgery and fractionated radiotherapy for different types of pituitary adenomas.

Disclosure of interest

The authors have no conflicts of interest to declare.

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