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STEREOTACTIC RADIATION THERAPY IN PITUITARY ADENOMAS, IS IT BETTER THAN CONVENTIONAL RADIATION THERAPY?

M.L. Gheorghiu[1,*], M. Fleseriu[2]

[1]"Carol Davila" University of Medicine and Pharmacy, "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania, [2]Oregon Health & Science University, Departments of Medicine (Endocrinology) and Neurological Surgery, and Northwest Pituitary Center, Portland, USA

Abstract

Pituitary radiotherapy (RT) has undergone important progress in the last decades due to the development of new stereotactic techniques which provide more precise tumour targeting with less overall radiation received by the adjacent brain structures. Pituitary surgery is usually first-line therapy in most patients with nonfunctioning (NFPA) and functioning adenomas (except for prolactinomas and large growth hormone (GH) secreting adenomas), while RT is used as second or third-line therapy. The benefits of RT (tumour volume control and, in functional tumours, decreased hormonal secretion) are hampered by the long latency of the effect and the potential side effects. This review presents the updates in the efficacy and safety of the new stereotactic radiation techniques in patients with NFPA, GH-, ACTH- or PRL-secreting pituitary adenomas.

Methods. A systematic review was performed using PubMed and articles/abstracts and reviews detailing RT in pituitary adenomas from 2000 to 2017 were included.

Results. Stereotactic radiosurgery (SRS) and fractionated stereotactic RT (FSRT) provide high rates of tumour control i.e. stable or decrease in tumour size, in all types of pituitary adenomas (median 92 - 98%) at 5 years. Endocrinological remission is however significantly lower: 44-52% in acromegaly, 54-64% in Cushing's disease and around 30% in prolactinomas at 5 years. The rate of new hypopituitarism varies from 10% to 50% at 5 years in all tumour types and as expected increases with the duration of follow-up (FU). The risk for other radiation-induced complications is usually low (0-5% for new visual deficits, cranial nerves damage or brain radionecrosis and extremely low for secondary brain tumours), however longer FU is needed to determine rates of secondary tumours. Notably, in acromegaly, there may be a higher risk for stroke with FSRT.

Conclusion. Stereotactic radiotherapy can be an effective treatment option for patients with persistent or recurrent pituitary adenomas after unsuccessful surgery (especially if residual tumour is enlarging) and/or resistance or unavailability of medical therapy. Comparison with conventional radiation therapy (CRT) is rather difficult, due to the substantial heterogeneity of the studies. In order to evaluate the potential brain-sparing effect of the new stereotactic techniques, suggested by the current data, long-term studies evaluating secondary morbidity and mortality are needed.

Key words: pituitary adenoma, stereotactic radiotherapy, fractionated radiotherapy, hypopituitarism.

INTRODUCTION

Pituitary adenomas represent 10 - 20% of all intracranial tumours and are classified into functional (about 70% of the pituitary adenomas) and nonfunctional (about 30%) (1). Surgery is usually recommended as first-line therapy in most patients with nonfunctioning, GH - secreting or ACTH-secreting pituitary adenomas, while medical therapy with dopamine agonists (DA) is indicated in patients with prolactin-secreting adenomas. External pituitary radiation (RT) has traditionally been used in the treatment of pituitary adenomas, usually as an adjuvant to neurosurgery. Currently, RT is indicated for patients with large residual or recurrent pituitary adenomas after surgery, when medical therapy is unavailable, unsuccessful, or not tolerated (2-5).

Radiation techniques

CRT, the method with the largest experience, is administered by a linear accelerator (4–8 MeV) in a total dose of 40–54 Gy, fractionated in at least 20 sessions (usually 1.8-2 Gy per day). Single beams of high-energy radiation are focused onto a small treatment area using either a single rotational field or 2-5 fields (6). CRT achieves tumour growth control (i.e. stabilization or decrease in size) at 10 years in 80 – 98% of patients with either functioning or non-functioning pituitary adenomas (7-9). CRT eventually induces GH/IGF1 normalization in 60-80% of patients

*Correspondence to: Monica Livia Gheorghiu, "Carol Davila" University of Medicine and Pharmacy, "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania, E-mail: monicagheorghiu@yahoo.com

with acromegaly (10), cortisol normalization in 40-80% of patients with Cushing's disease (CD) (11) and prolactin (PRL) normalization in 20 – 60% of patients with prolactinomas (12). The benefits, especially in hormonal hypersecretion, are hampered by the very slow onset of effects (5–15 years until maximal benefit) and the high risk of late toxicity, attributed to the radiation of healthy surrounding brain tissues: hypopituitarism in 30 - 80% of patients at 5 – 10 years (7, 8, 12-14), radiation-induced optic neuropathy in 0-5%, cranial nerve deficit and brain necrosis in 0 – 3%, secondary brain tumours in up to 2% at 10 – 20 years (15-17), neuropsychological alterations (18). The significant rate of cerebrovascular accidents (CVA) and mortality after CRT have been of great concern: CVA 4% at 5 years and up to 21% at 20 years was noted in 334 patients with various pituitary tumours irradiated with 3-field CRT in 1962 - 1986 (19). More recently, other studies showed lower rates, varying between 0 – 11.6% (20, 21). Increased mortality has been also reported in patients with acromegaly or NFPAs treated with CRT: 1.6 – 4.1 times higher compared to general population (22-27), mainly due to cerebrovascular disease. The causal link between pituitary radiation and mortality still remains a subject of debate, other factors being also associated with increased mortality in patients with pituitary adenomas (hypopituitarism or vascular trauma after surgery) (28-32). The quality of life (QoL) in patients with pituitary adenomas is low, mostly related to hypopituitarism, but can be directly related to radiation (33-35).

Stereotactic techniques including stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) have been devised to ensure better immobilization, imaging, planning and treatment than CRT. They accurately deliver a high radiation dose to a precisely defined target with a steep dose gradient at the tumour margin, thus limiting the radiation and the damage to the surrounding brain structures.

Stereotactic radiosurgery is applied using photons (gamma knife (GK), cyberknife (CK) and linear accelerator (LINAC) or using proton-beam radiotherapy.

Gamma knife (GK) delivers the radiation in a single session from a hemispherical array of 192 or 201 sources of radioactive isotope cobalt-60 which focus on single or multiple central points (isocenters) with the aid of a collimator metal helmet fixed on the patient's skull. Radiation is usually prescribed at the 50% isodose to obtain the maximum dose at the center of each pinpointed target and the prescribed dose at tumour margins(36).

Linear accelerator (LINAC) uses X-rays obtained by colliding accelerated electrons with a target metal. The treatment is delivered using multiple arcs or beams shaped with a multileaf collimator, allowing intensity modulation or volumetric arc therapy, to conform to the shape of the tumour and shield the normal structures. Two radiosurgical techniques use LINAC, delivering radiation usually in a single-fraction or in 3-5 fractions (hypofractionated SRS):

Modified LINAC machines have an improved frameless stereotactic fixation system with sub-millimeter accuracy (using orthogonal X-ray imaging or cone-beam CT with infrared tracking or vacuum detection for patient movement)(37, 38);

Cyberknife (CK) consists of a linear accelerator mounted on a mobile robotic arm combined with an image-guided robotic system, while the patient is fixed in a more confortable thermoplastic mask (39, 40).

Fractionated stereotactic radiotherapy (FSRT) is an improved conventional RT in which a total dose of 45-54 Gy is delivered by a LINAC in 25 - 33 daily fractions. Patient's immobilization in a frameless stereotactic mask and a SRS-like planning system allow better accuracy compared to CRT (6).

Selection of the RT method should be individualized; it depends on both tumour volume and distance from the optic structures (nerves, optic chiasm). The risk of visual complications is proportional with the radiation dose that reaches the optic nerves; this dose is larger when RT is delivered in a single session, compared to fractionated sessions. Therefore, single - session SRS is usually recommended for tumours smaller than 3 cm, located more than 3-5 mm away from the optic structures (2, 41). Fractionated RT methods are indicated in large pituitary tumours or in those that abut or invade the optic nerves.

Hypofractionated SRS (by CK or LINAC) has been successfully used in perioptic tumors(38, 42).

The purpose of this review is to present updates in the efficacy and safety of stereotactic radiation techniques in patients with pituitary adenomas.

METHODS

An online search for journal articles relevant to the topic was conducted using the PubMed Database from 2000 up to 2017 by entering combinations of the MeSH terms "pituitary", "radiosurgery", "radiation", "radiotherapy", "fractionated", "Gamma Knife", "Cyberknife", "proton beam", "acromegaly",

"prolactinoma", "Cushing's disease", Nelson syndrome', "nonfunctioning adenoma". Articles were limited to the English language. Cited references within articles were also searched for relevancy to the topic. Combined data from multiple studies are calculated as weighted means of the reported medians, but for concision in text are presented as medians.

DISCUSSION

Nonfunctioning pituitary adenomas

Transsphenoidal surgery (TSS) is the treatment of choice in NFPA. However, even after complete or near complete surgical resection, NFPAs recur in 12% to 58% of patients within 5 years (43, 44). According to the latest neurosurgical guidelines published in 2016, RT is indicated in residual or recurrent NFPA when the risk of a repeat resection is high, however, neuroimaging surveillance is recommended for patients with no or small intrasellar remnant (5). Adjuvant RT for residual/recurrent NFPA, regardless of type of administration, induces a lower rate of recurrence than observation alone (5, 45)

Stereotactic radiosurgery (SRS) in NFPA

Efficacy

SRS in NFPA was evaluated in a recent review of 1965 patients, most of them previously operated, included in 23 studies from 2002 to 2016: 19 with GK, 3 with LINAC and 1 with CK (36).

Local tumour control has been achieved in 83 – 100% of patients (median 94%), at a median follow-up (mFU) of 47.3 months (21.7 – 95) using a median marginal dose of 16 Gy. Notably, doses delivered to the tumour margin are lower for NFPA (10 – 20 Gy) than for secreting adenomas (18 – 35 Gy)(36). In a large study (512 patients), progression-free survival was 95% and 85% at 5, respectively 10 years FU (46).

Tumour shrinkage is seen in 20 – 60% of GK-treated patients (36) and tumour control was better in GK-treated patients compared to not RT-treated patients (5-year progression-free survival 89.8% *versus* 51.1%) (47).

Unfavourable prognostic factors for RT efficacy are larger tumour volume (eg. > 4 mL (48)), suprasellar extension, radiosurgical marginal doses below 12 Gy (49-51) and silent corticotroph tumours (SCA), which are more aggressive and regrow more frequently after surgery (52, 53). In a multicenter study comparing 50 confirmed SCA with 307 matched patients with non SCA NFPA, tumour control rate after SRS was lower in the SCA group (82% *versus* 94.1%, $p < 0.01$). A margin dose ≥ 17 Gy significantly influenced the adenoma progression rate in the entire cohort (52).

Interestingly, an early transient increase of the tumour volume post RT (> 15%) has been shown in 62.5% of 34 patients treated with CK (93% having NFPA), mainly in the first 4 months. Fortunately, this was not predictive of the eventual tumour regression or progression (54). The median time for a tumour that initially progressed to tumour volume stability was 9.2 months (54). Transient swelling has also been reported in 9% of 45 patients with NFPA treated with GK (55).

Early GK radiosurgery (≤ 6 months after TSS) for NFPA macroadenomas was associated in a multicenter cohort of 222 patients with mFU of 68.5 months with a lower risk of radiological tumour progression compared with late GK in subtotally resected adenomas ($p < 0.05$) (56). Though similar results have been also shown in some studies using CRT (53, 57), there is no consensus yet regarding the optimal timing for postoperative RT.

There is limited data on use of GK as primary treatment for NFPA. In a group of 41 NFPA patients, median age 69 years and 48 months FU, the actuarial tumour control rate was 94% and 85% at 5 and 10 years postradiosurgery, respectively, using a median margin dose of 12 Gy (6.2-25.0 Gy) (58). In another group of 16 NFPA patients with tumour in the suprasellar region and slightly compressing or very close to the optic apparatus, treated with median margin dose of 15 Gy, tumour control was achieved in all patients, with tumour regression in 15 /16, after a mFU of 98 months (59).

SRS side effects in NFPA

Radiation-induced hypopituitarism is the main side-effect, occurring in 0-40% of patients with NFPA (median 18%) at mFU of 47 months (6). In 2 studies with GK as first-line therapy, hypopituitarism occurred in 6 – 24.4% (58, 59). Since hypopituitarism can appear up to 10-15 years after RT, yearly assessment of pituitary function is recommended in all RT treated patients (5).

Radiation-induced optic neuropathy and other cranial nerve deficit (nerves III, IV, VI) occurred in average in 2.4% (0 – 7.9%) (36). Maximum point doses < 8-10 Gy to the optic nerves and chiasm are recommended for single-fraction SRS in order to avoid radiation-induced neuropathy (60). It has been shown that 75% of patients post GK in which ophthalmological complications were observed had received prior fractionated radiation therapy (61).

Radiation-induced neoplasia or cerebral ischemia were not noted in the SRS studies on NFPA (5, 6).

Secondary brain tumours after SRS have not been observed in the large majority of studies, after a mFU of 60 months (62). A recent review identified 137 secondary intracranial tumours that occurred following RT to pituitary adenomas (48 neuroepithelial tumours, 37 meningiomas and 52 sarcomas), published in 1959–2017 (63). Only 4.3% of the tumours have been associated with SRS, which is reassuring. Most of the published tumours were described in patients with NFPA (41.6% of cases) or acromegaly (27.7%), more rarely in prolactinoma (7.2%) and CD (2.9%). Longer latency between RT and diagnosis of the secondary tumour was recorded in NFPA (14 years), than in acromegaly (11 years, $p < 0.05$ compared to NFPA), PRL- secreting tumours and CD (9 and 7 years, respectively)(63).

Mortality rate and neurocognitive dysfunction were not systematically studied in SRS-treated NFPA. Long-term studies are needed in order to better evaluate SRS potential late toxicity.

Types of SRS in NFPA

Gamma knife, cyberknife and LINAC seem to have similar efficacy and safety in NFPA patients (Table 1).

Fractionated stereotactic radiotherapy (FSRT) in NFPA

Few reports studied the outcome of FSRT specifically for NFPA: 6 studies including 320 patients, using median total doses of 45-54 Gy for mFU of 54 months (30 – 75 months)(64-69).

Efficacy. Local tumour control was reported in 90.4 – 100% of patients (median 95.4%), with 5-year control rate of 90.4 – 98%. Tumour shrinkage was shown in 65 – 72%.

Safety. New hypopituitarism was recorded in 5 – 40% of patients (median 15.5%) at median 54 months FU. Visual deficits were noted in 0 – 5% (median 1.7%) (64-69).

In a study including 68 patients with large residual or recurrent NFPA treated with FSRT (median dose of 45 Gy), the 5 and 10-year actuarial local control after a mFU of 75 months were 97% and 91%, respectively. However, the actuarial incidence of new hypopituitarism was 40% and 72%, respectively (67).

Visual toxicity was shown in 0 – 5% of cases (64-69). No stroke or brain necroses were recorded, and a single tumour (glioblastoma) was described 2 years after FSRT in a 77 years old patient. A 2 -year interval was considered too short to define this tumour as clearly radiation-induced (70). Mortality rate was not systematically studied in FSRT-treated NFPA.

Comparison SRS vs. FSRT in NFPA. A recent meta-analysis (71) compared the safety and efficacy of FSRT and SRS in 8 eligible studies of patients with various pituitary adenomas (30 – 65% NFPA).

There were no significant differences in the disease control rate, endocrine cure rate, new-onset hypopituitarism rate, and rate of occurrence of visual disturbances between SRS and FSRT.

Comparison FSRT vs. CRT in NFPA. In 3 studies with 406 patients (NFPA only) (72-74), treated with CRT (median doses 45 – 46.7 Gy) with a mFU of 8.4 years (7.5 – 9 years), local tumour control was obtained in 89% (87 – 93%) at 10 years.

Data on new hypopituitarism were reported only in 1 study, 23% (72); visual deficits in 0 – 1%.

Cerebrovascular accidents. There is an increased risk of CVA in NFPA patients compared to the general population, in non-radiated (20) as well as in radiated patients (majority treated with CRT) (32). A study including 806 patients with NFPA from the Dutch national registry for GH treatment in adults

Table 1. Summary of efficacy and side effects of RT in patients with NFPA

RT Type	No of studies	Patients	Dose (Gy), median	Follow-up (median, months)	Tumor control (%)	New Hypopituitarism (%)	Visual defects (%)	Brain radionecrosis (%)	Second brain tumor (%)
SRS type: *GK*	19	1716	16	46.6	95 (88-97)	22	2.9 (0-7.9)	0-<1	0
CK	1	100	7x3 fr/5x5 fr	36	98 at 3 y	4	1	0	0
LINAC	3	149	45	48-84	98-100	10.1	0-1.4	0-2.8	0
CRT	3	406	45.5	101	89 at 10y (87 – 93)	23	0-1	0-1	0-2 at 10-20y*
FSRT	6	320	45-54	54	95.4	15.5	1.7 (0-5)	0	0.3

Legend. The results are expressed in weighted means calculated from the published studies; SRS = stereotactic radiosurgery; CRT = conventional fractionated radiotherapy; FSRT = fractionated stereotactic radiotherapy; GK = gamma knife radiosurgery; LINAC = linear accelerator radiosurgery; CK = Cyberknife radiosurgery; y = years; fr = fractions; * actuarial rates in 331 various pituitary adenomas (17).

revealed a three times higher (95%-CI 1.31–6.79) risk of stroke in radiated, compared to non-radiated men (32). A Swedish nationwide study reported an increased incidence of ischemic stroke in patients with NFPA compared to the general population, higher in women than men, but no significant difference was identified in patients treated with RT (20).

Mortality after RT in a Swedish population of 2473 NFPA patients was increased to 2 – 3 fold over general population, mainly due to cerebrovascular disease: SMR 4.57 (1.24 –11.7) in RT treated and 1.55 (1.13–2.08) in patients not treated with RT (26). However, other studies including 546 NFPA patients from UK and 806 from the Dutch national registry for GH treatment have shown that RT did not influence the mortality rate (30, 32, 75). The frequency of secondary intracranial tumours did not differ between radiated and non-radiated patients in one NFPA study(32).

Neurocognitive impairments have been attributed to CRT - induced dysfunction on hippocampus and temporal lobes (18). Other studies did not find neuropsychological impairments, nor alterations in the hippocampus or differences in white matter lesions or brain atrophy in radiated NFPA patients compared to non-radiated ones (76, 77).

Overall, current data suggest a brain-sparring effect of SRS compared to CRT, but the duration of FU is shorter in SRS than in CRT - treated patients (median 4 years compared to over 10 – 20 years).

GH-secreting pituitary adenomas

A recent review summarized outcomes of radiation in patients with acromegaly (62).

Stereotactic radiosurgery (SRS)

Efficacy. SRS was evaluated in 35 studies in acromegaly (1876 patients): 26 studies using GK, 4 with LINAC SRS, 3 with CK and 2 with proton SRS (cited in (62)). The median doses delivered to the tumour margin ranged from 15 to 35 Gy.

Local tumour control was recorded in 93 – 100% of patients (median 98%) at a mFU of 59 months, similar to CRT-induced tumour control (95 – 100% at mFU 129 months)(62); tumour shrinkage occurred in about 50–75% of cases (78-81).

Biochemical control. In SRS, the remission rate ranges from 44-52% at 5 years, at a median dose of 23.5 Gy (36, 62). Notably, patients with acromegaly seem to have longer latency before achieving hormonal remission than patients with CD: 41.5 months (12 - 144 months), *versus* 12 - 25 months (80, 82). However, the greatest effect of SRS in acromegaly occurs within the first 2 years from RT (83, 84). Overall, biochemical control does not seem significantly higher in SRS than in CRT (52% versus 36%, at 5 years), but might be different at a longer FU (85).

Higher margin radiation dose (> 25 Gy), higher maximum dose and lower initial GH/IGF-1 level are all favourable prognostic factors for GH/IGF-1 remission after SRS (79, 80). Interestingly, in contrast to their response to medical therapy, both densely and sparsely granulated GH-secreting tumours seem to have a similar response to SRS (86).

Treatment with somatostatin analogs at the time of GK may decrease efficacy, as suggested by some authors (84, 87, 88), but not all (80, 83, 89, 90). Therefore temporary withdrawal of medical treatment before and during RT was suggested (2); medication should be resumed after RT and RT efficacy evaluated annually.

SRS Side effects

Radiation-induced hypopituitarism occurred in median 22% of patients with acromegaly (0-66%) at mFU of 60.5 months. The risk is apparently lower than in CRT treated patients (33%) (85), but increases over time as in patients treated with CRT (91).

Radiation-induced optic neuropathy occurs in 0–4.2% of patients usually during the first 3 years after SRS (81, 88).

Cranial neuropathies and brain radionecrosis have been reported in 0–5% of patients (92, 93).

CVA and mortality after SRS have not been systematically studied in acromegaly. CVA have been described in only 2 out of 23 studies (median 0.3% of patients)(62): 2 transient ischemic attacks at 72 and 132 months(94) and one coronary artery stenosis (84).

In older studies using CRT, the mortality rate was higher in irradiated patients (who usually did not receive medical therapy afterwards) as compared to the general population (95) or to non-irradiated patients (24). In more recent studies, the mortality rate was similar in irradiated and not irradiated patients with acromegaly (31, 96, 97), although the overall mortality rate in acromegaly is still increased compared to general population (HR: 1.3 in a Danish population)(97).

The current data support the expected brain-sparring effect of SRS, compared to CRT, but longer FU prospective studies are still needed.

Quality of life in patients with acromegaly treated with stereotactic RT has not been studied. Recently, RT (of unknown type) was a predictor of poor mental QoL and depression, described in about

one-third of 165 patients with acromegaly operated in a single center in Germany from 2000 to 2012 (98). An association of CRT with reduced QoL, even after disease remission, was also found in previous studies in acromegaly (33-35). More aggressive tumours and higher incidence of hypopituitarism in patients postRT could also contribute to this effect.

Neuropsychological performance after SRS was not studied. A dose and field-size related impairment on verbal memory and executive function was associated with postoperative pituitary CRT in patients with acromegaly (most affected were patients with CD, then acromegaly, followed by NFPA) (18).

Types of SRS in acromegaly

The current data suggest that all the SRS techniques (GK, CK, LINAC, proton beam) achieve similar results (Table 2).

Fractionated stereotactic radiotherapy (FSRT)

Efficacy was evaluated in a review including 261 patients irradiated with median total dose of 49 Gy (range 45-54 Gy) (62).

Local tumour control was achieved in 97% (92 – 100%) of patients after mFU of 71 months, similar to SRS or CRT. Tumour shrinkage occurred in 48 -53 % (99, 100). Biochemical control rate: median 35% (18 to 75%) at mFU of 71 months.

Side effects: new hypopituitarism in 29.4% of patients, visual defects in 0 – 5%, secondary brain tumour (meningioma) in 1 patient (1.3%), no cranial neuropathies or brain necrosis were reported at mFU of 71 months (62). In 2 FSRT studies the rate of stroke was 8.2 – 9% (100, 101), while in other study was 0% at more than 10 years of FU (99).

Overall, FSRT seems to have a similar efficacy with SRS and risk rate for hypopituitarism and neuropathies, but the risk of stroke may be higher and should be further evaluated.

Comparison between SRS and fractionated RT in acromegaly

In a systematic review of 30 heterogeneous studies including 2464 patients with acromegaly (FU between 12 – 240 months, different remission criteria), SRS was associated with a nonsignificant trend of higher IGF-I-based remission rate (52% *vs*. 37%, P = .14) or GH-based remission (49% *vs*. 36%) at the latest FU period, compared to fractionated RT (including FSRT and CRT) (85). Interestingly, the length of FU did not significantly affect remission rate.

SRS had a lower incidence of hypopituitarism than RT with borderline statistical significance (32% *vs*. 51%, p = 0.05), the difference being largely due to hypogonadism. The authors concluded that SRS may be more efficient than fractionated RT, but the strength of evidence was very low, mainly due to the substantial heterogeneity among studies (85).

A faster decline in serum GH concentration after GK SRS compared with fractionated CRT was observed by some authors (83, 92, 102); others did not confirm this finding (78, 89, 103-105).

Overall, current data suggest a slightly increased benefit of SRS in acromegaly compared mainly to CRT, regarding biochemical remission and side effects (radiation-induced hypopituitarism, secondary tumour formation, perhaps also for cerebrovascular disease, as the latter seems more frequent in FSRT treated patients than in SRS). Longer FU studies are needed in order to elucidate these effects.

Cushing's disease

TSS is the recommended first-line therapy in patients with CD, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess. Medical therapy, repeat surgery, radiotherapy or bilateral adrenalectomy are possible second-line therapies after failed surgery or in recurrent CD (4). Pituitary RT is

Table 2. Summary of efficacy and side-effects of radiation therapy methods in patients with acromegaly

RT Type	No of studies	Patients	Dose (Gy), median	Follow-up (median, months)	Tumor control (%)	Hormonal remission (%)	New Hypopituitarism (%)	Visual defects (%)	Brain radionecrosis (%)	Second brain tumor (%)
SRS type: *GK*	26	1536	23	58	98 (93-100)	46 (17-65) 52 at 5y	22 (2-58)	1.5 (0-4)	0.5	0
CK	3	67	22.5	33	99	22.5 (17-44)	6.5 (0-33)	0	0	0
LINAC	4	193	19	69	96	39 (23-68)	20.5 (12 – 46)	1.8 (0 – 3)	3.3	0-1
Proton	2	72	20	58	98.5	51 (50-67)	51 (62 at 5y)	0	1.4	0
CRT	9	1383	46.5	99	98	56 (36 at 5y)	33 (35 at 5y)	0.8 (0-5)	2.5 (0-3)	0-2 in 20 years*
FSRT	8	261	49	71	97 (92-100)	35 (25 at 5y)	29 (22-39)	1.8 (0-5)	0	0.3 (0-1)

Legend. The results are expressed in weighted means calculated from the published studies; SRS = stereotactic radiosurgery; CRT = conventional fractionated radiotherapy; FSRT = fractionated stereotactic radiotherapy; GK = gamma knife radiosurgery; LINAC = linear accelerator radiosurgery; CK = Cyberknife radiosurgery; y = years; * actuarial rates in 331 various pituitary adenomas (17).

also recommended in aggressive tumours. There is an increasing role for medical therapy to control cortisol excess (4, 106, 107), thus radiation use in CD is diminishing overall. Notably, medical therapy is needed while awaiting radiation effects on cortisol levels.

SRS Efficacy

Local tumour control. A review of 21 studies (from 2000 – 2015) included 706 patients with CD (15 studies with GK, 4 with LINAC and 2 with protons, cited in (36)), with a mFU of 56 months (range 2 – 17 years) and a margin dose of 18 – 29.5 Gy (median 22.8). Median tumour control rate was 95% (83.3 - 100%) at a mFU of 56 months (36). In a study of 49 patients with visible tumours, shrinkage occurred in 80% of them after GK (108) but no correlation between change in tumour volume and hormone response to GK has been described (14).

Biochemical remission. With SRS, the remission rate is most probably 54% - 68% at 5 - 10 years at a mean dose of 23.6 Gy (36,109,110). There is a large heterogeneity in the methodological criteria and cutoff points used to define biochemical remission and recurrence in these studies. The most commonly used diagnostic tests included morning serum cortisol level, urinary free cortisol (UFC), or a combination of tests. In one review, weighted median cortisol control rate was 54% (range 17 – 80.7%) with a median time to hormone normalization from 12 to 25 months (36).

In a meta-analysis including 571 patients with SRS in CD, 65% of them previously operated (109), biochemical remission was 68% (95% CI, 61 to 77%) at the longest FU. Most likely biochemical control is higher at short-term FU (≤1-2 years) than later, due to recurrences in some patients. Another review of 35 studies published from 1986 (including 5 with LINAC, 3 with protons), totalizing 850 patients, showed median remission rate of 57.2% (0 - 100%) during a mFU of 47.2 months (2–264) (110).

Interestingly, similar to TSS, disease recurrence in CD is also high after RT and may occur in up to 20-32% after an initial remission after SRS (95% CI, 16 to 60%). The median time to recurrence was 25.5-37 months (range 6-60) (49, 108).

Although late-night cortisol levels (LNSC) seem to be the best early predictor of recurrence after TSS (111), a normal diurnal rhythm is rarely achieved after RT, so increased LNSC may persist in patients with normalized UFC. It is currently unknown if this represents persistence of mild residual hypercortisolism (4). Long-term monitoring with cortisol or UFC off-medication at 6- to 12-month intervals after RT is recommended; adrenal insufficiency symptoms while on stable medical therapy should prompt immediate work-up (4).

Prognostic factors for RT outcome in CD are not clearly defined. There is no correlation between SRS margin dose and remission rate (36), however, higher radiation doses (> 45 Gy) were associated with better remission and lower recurrence rates than lower doses (< 40-45 Gy)(14,109). Postoperative GK seems more effective than primary GK, with a remission rate 57.2% (16.7 - 100%) compared to 50% (10 - 83.3%) (110). Although it has been suggested in some GK studies, the role of anticortisolemic medication use in the outcome of SRS or RT is not well-defined (108, 112, 113).

No study is available on the utility of SRS in the treatment of patients with tumours not visible on imaging, although SRS has been used by targeting the whole sella turcica in such cases, albeit with lower-dose radiation (4).

Repeated SRS irradiation after CRT or FSRT is possible in selected cases of pituitary adenomas of all types (salvage therapy), improving rates of hormonal normalization or tumour control, but with a higher rate of neurological complications, visual defects and hypopituitarism (114, 115). It was suggested that 50% of the original radiation dose, recalculated as a single-fraction dose, remains active in occulomotor nerve (115) and 40% in the optic nerve (116).

SRS side effects in CD

Radiation-induced hypopituitarism rate, evaluated in 706 CD patients with a mFU of 56 months, varied from 0 to 66% (median 26.7%)(36). In 9 studies with mFU around 5 years, hypopituitarism ranged from 12.3 to 52% (median 22.6%).

Radiation-induced visual toxicity occurred in 0 – 3.9%. Cranial nerves neuropathy was reported in 0 – 5.5% (exception: 15.4%, i.e. 2 patients in a study with 13 patients (117). As expected, incidence was increased in patients previously irradiated before SRS (108,117). No secondary brain tumour was reported after SRS in CD yet and brain toxicity was very rare, 0 - 2% (108,118). CVA, mortality and neurocognitive side effects after SRS have not been systematically evaluated. A small study on 14 patients (9 with CD and 5 NFPA,) found no evidence that GK impairs the neurocognitive functioning of patients with pituitary disease above any impairment caused by the disease itself (119).

SRS types in CD

The SRS methods used in patients with CD

(GK, LINAC and proton beam) show similar efficacy and safety (Table 3).

GK efficiency in CD was recently evaluated in a multicenter retrospective study including 278 patients (92% previously operated) with a mean FU of 5.6 years (0.5 – 20.5) and a mean margin dose of 23.7 Gy (120). The rate of durable UFC normalization was 64% at 10 years (68% in those with primary SRS). Recurrences occurred in 18% of patients. The reported side effects were hypopituitarism in 25% and cranial neuropathy in 3% (120).

FSRT in CD

Data is limited. One study in 12 previously operated patients with CD, mFU of 29 months, reported complete hormonal remission in 9/ 12 patients (75%), with an actuarial remission rate of 56% at 3-5 years. No new hypopituitarism or neurologic or optic injuries were noted, but FU was short (124).

Another study with modern conformal LINAC fractionated RT in 20 patients with persistent CD after TSS, treated with 45 Gy in 25 fractions, mFU 37.5 months (range 12–144), reported tumour control in 95% of patients. Remission (based on suppressed cortisol level after 2 mg LDDST) was noted in 75% after 20 months mFU (125). No recurrences were seen, but 1 tumour progressed. Post RT, new pituitary deficiencies were seen in 40% of patients, but no other side effects were noted (125).

Comparison between SRS and fractionated RT in CD

No direct comparison can be made between SRS and CRT, due to large heterogeneity of studies.
Local tumour control after CRT in CD patients at mFU of 8 years was 97% (93 – 100%) (14).

Biochemical remission. A recent meta-analysis evaluated 21 studies with SRS and 29 studies with fractionated RT. CRT studies, all but one published after 1975, enrolled 721 CD patients (109). Overall biochemical remission rate after SRS was 68% and recurrence rate of 32% at the last FU, while for fractionated RT were 66% (95% CI, 58 to 75%), and 26% (95% CI, 14 to 48%) respectively. Higher remission rates were observed in patients who received TSS prior to RT. However, the authors state that the quality of the evidence for recurrence and remission outcomes was low due to high risk of bias, heterogeneity, and imprecision (109).

A review including 15 CRT studies published between 1971 and 2007 (110), with 341 CD patients treated with median dose 45 Gy (range 20 – 54) showed a median biochemical remission rate of 60% (19.6 to 100%) after mFU of 86.2 months (1 – 300) (110). The rate was 60.8% in first-line RT and higher, 80.8% in adjuvant RT. Median time to remission was 6.5 – 16 months. Recurrences were described in 16% of cases (0 – 62.5%) and seemed higher after primary CRT than adjuvant CRT (but no statistical comparison was done).

Side effects. Radiation-induced hypopituitarism in CRT studies occurred in median 30% of patients (FU 1 - 300 months), increasing to 48.3% (range 0 – 100%) in series with at least 5 years FU (110). Visual deficits were usually 0%. Secondary tumours: a fibroblastic meningioma developed 25 years after CRT (121) and an optochiasmatic glioblastoma developed 6 years after CRT (122). Mortality in patients with CD is increased, compared with patients treated for NFPA macroadenomas and compared to the general population, but there was no difference in RT treated *vs.* not treated patients in a study (126).

Overall, SRS appears to have similar efficacy to CRT in CD, with no clear difference in the time-line of

Table 3. Summary of efficacy and side-effects of stereotactic radiation therapy methods in patients with Cushing's disease

RT Type	No of studies	Patients	Dose (Gy), median	Follow-up (median, months)	Tumor control (%)	Biochemical control (%)	Recurrence (%)	New Hypopituitarism (%)	Visual defects (%)	Brain radionecrosis (%)	Second brain tumor (%)
Cushing's disease											
SRS type: *GK*	15	494	24.6	57.4	96.5	55 (64^)	0-18	22 (25^)	3.3 (0-5.5)	0-3	0
LINAC	4	105	17.3	47.5	92	43	0-23.5	22	1.4	0-2	0
Protons	2	107	20	51.6	97	62	0-15	59 (52-62 at 5y)	0.7	0-2	0
CRT	15	341	45	86	92.5-100	60	15.9* (0-62.5)	30	0-1.4	NA	2 tumours #
FSRT	2	32	45	29-37.5	95	75 (56 at 3-5y)	NA	0-40	0	0	0
Nelson's syndrome											
GK	3	51	25-28	116.8	92.5-100	10-30	NA	7-40	0-7.1	NA	1 tumour ##

Legend. The results are expressed in weighted means calculated from the published studies; SRS = stereotactic radiosurgery; CRT = conventional fractionated radiotherapy; FSRT = fractionated stereotactic radiotherapy; GK = gamma knife radiosurgery; LINAC = linear accelerator radiosurgery; y = years; ^ in a multicenter study with 278 patients, at 67 months mFU (120); * mean; # a fibroblastic meningioma at 25 years after CRT (121) and an optochiasmatic glioblastoma multiforme at 6 years after CRT (122); ## a glioblastoma at 14 years after GK (123).

cortisol levels decline compared to CRT. The incidence of second brain tumours appears to be lower in SRS than CRT, but longer FU is needed to evaluate this potential benefit.

Cushing's disease in children

Data on SRS efficacy in children is scarce. Higher remission rates were recorded in children (100% in 5 children) compared to adults (84.7% in 59 adult patients) in a study using protons or helium ions (marginal doses of 30 – 150 Gy, divided in 3-4 daily fractions in most of the patients, with FU of more than 10 years) (127).

In a review of CRT studies in children with CD, biochemical remission rate after RT was 82% (95% CI, 68 to 99%), and recurrence was 55% (95% CI, 28 to 100%) at the longest FU, while in adults the remission rate was 70% (95% CI, 60 to 83%), and recurrence 31% (95% CI, 13 to 77%) at the longest FU (109).

Four studies including 43 children with CD (usual RT dose 45 Gy in 25 fractions) show biochemical remission in 50 – 100% of cases (79% of all cases), usually during the first 1-2 years after RT (128-131). Interestingly, remission after RT in children may occur earlier than in adults (130). New pituitary deficits, mainly GH and gonadotropin deficiency, were seen in up to 83% of patients, but GH deficiency was transient in 3 of 4 children retested 9.3 years later (129).

Nelson syndrome (NS)

NS, i.e. corticotroph tumour progression, may occur after bilateral adrenalectomy (BLA) for CD in 0 to 34.6% of patients (up to 47% if evaluated by pituitary MRI) and may be diagnosed at 0.5–24 years after BLA, but usually within the first 3 years (132). RT could be indicated in cases with significant pituitary tumour progression, especially after incomplete surgical excision. In selected cases, RT can be used prophylactically before BLA.

SRS efficacy was evaluated in 3 studies with GK, including 51 patients with NS, treated with median doses of 25 – 28 Gy and with a mFU of 116.8 months (84 – 144) (123, 133, 134).

Local tumour control was achieved in 92.5 – 100% (median 94.1%), but in one study 2 patients underwent repeated GK during FU (133). Tumour shrinkage was recorded in 63.6% (at 5-10 years in (133) - 90% (123).

Effect on ACTH secretion: reduction was reported in 67 – 100%, with normalization in 10 – 30% of cases. A shorter time to remission was associated with a shorter duration between TSS and RT (123, 134), but not with the margin dose or prior ACTH level (134).

In a small LINAC study applying SRS in 5 patients and FSRT in 2 patients, tumour control was recorded in 3 / 5 patients with SRS and in 1 / 2 with FSRT (total 57%) (135). In a study using protons in 17 NS patients, tumour control was achieved in 94%, but ACTH normalization in none (127).

SRS side effects. In GK studies, RT-induced hypopituitarism occurred in 7.1 - 40% of cases (123, 133, 134, 136). Permanent cranial nerve toxicity occurred in 0% up to 4.5 – 7.1% of patients (133, 136). A glioblastoma was noted in a patient 14 years after GK (123). CRT has been demonstrated to decrease plasma ACTH levels and induce tumour shrinkage in 93.3% of 15 patients with NS at 9.6 years mFU (137).

Prophylactic pituitary RT in patients with CD immediately after BLA or prior to BLA is controversial. Some studies show a reduction in the risk of developing corticotroph tumour progression and NS after prophylactic RT. None of the radiated patients developed NS, compared with 50% of those who did not receive prophylactic RT in a relatively large study (39 patients followed over 15 years after BLA) (138). In another study of 56 patients, 25% of the patients receiving prophylactic pituitary RT developed NS, compared with 50% of those who did not receive RT (139). Furthermore, RT prior to BLA might have prevented corticotroph tumour progression in another study on 20 patients, too; during mFU of 5.4 years (0.6 – 12 years), only 5% developed progression (140). Despite these suggestions, use of prophylactic RT is not recommended in every patient, and the potential benefits should be carefully weighed against the high probability of hypopituitarism and other possible side effects of RT (110,141).

Prolactinomas

Radiotherapy is usually reserved for prolactinomas with DA resistance or intolerance (10-18%) or in patients with invasive or malignant prolactinomas, typically as an adjuvant to surgery (3, 142).

SRS efficacy

Eighteen studies including 623 patients, from 2000 – 2015, treated with GK in 15 studies, LINAC in 2 studies and with protons in 1 study at median dose 24.7 Gy (15 – 34 Gy) were reviewed (36).

Local tumour control was reported in 94% (83 – 100%) after mFU of 53 months (25 – 75.5)(36).

Biochemical remission. Normalization of serum PRL after mFU of 50 months has been seen in 31.4% of patients (range 0 – 60%, frequently around 20 - 30%).

Latency to PRL normalization ranged from 1 - 2 years, apparently shorter than after CRT, where it requires several years (143). In primary GK therapy, 20.8% of 77 patients were cured after more than 2 years FU (144).

Landolt *et al.* and Pouratian *et al.* (145,146) reported lower remission rates in patients who were on DA at the time of GK, therefore DA withdrawal at the time of RT is recommended.

SRS Side effects in prolactinomas

New hypopituitarism developed in median 14.8% (0 – 57% of patients) after mFU of 50 months - 42% at 4 years (36, 147). Visual damage occurred only in 6 / 16 studies, in median 1% (0 to 4.2%, except in 1 GK study of 11 patients (followed for 48 months) where rates were much higher, 9.1%). Cranial nerve deficit was noted in 0 – 5% of patients. There were no reported cases of secondary intracranial malignancies (12) or brain lesions. Mortality, cerebrovascular disease and neurocognitive impairments were not studied in these patients.

SRS types in prolactinomas

Overall, the 3 SRS methods (GK, LINAC and proton beam RT) show relatively equal efficacy and safety, but there is a large heterogeneity among studies (Table 4).

FSRT in prolactinomas

Efficacy. Two series including 34 patients after unsuccessful TSS achieved PRL normalization rates of 36.3% and 25% (148, 149). This was comparable to those obtained by CRT: 34.1% success in a series of approximately 250 patients who have undergone treatment with CRT alone or after failure of medical and/ or surgical therapy, mean FU 3 - 13 years (143); or 28% in a Romanian series of 7 DA-resistant prolactinomas (150).

Side effects. New hypopituitarism was recorded in 20 – 28.5% of FSRT treated patients (in series with various pituitary tumours) and no central nervous system adverse effects or visual deficits were recorded at 3-4 years FU (148, 149).

Overall, RT seem to induce a lower biochemical remission in prolactinomas than in other functional tumours (61,151), with perhaps just a slightly better efficacy in SRS compared to fractionated RT. RT is indicated just in resistant or invasive prolactinomas, where it can control tumour growth, reduce PRL and thus DA dosage, increase the PRL normalization rate on medical treatment and allow pregnancy in some cases (142, 146, 152, 153). However, an individualized approach should evaluate the benefit risk ratio, especially hypopituitarism for each patient.

Trends in radiotherapy use for pituitary adenomas

In patients with NFPA, a recent analysis in Swedish population shows a stable use of RT since 1997 until 2014 (in 4.6% - 5.9% - 3.6% of the patients, evaluated at 5 year intervals) (154). In contrast, the advances in medical therapy in acromegaly for the last 20 years (new drugs acting at tumour level or growth hormone receptor) were followed by a progressive decline in the use of RT: from 62.8% of patients treated prior to 1980, to 11.9 % in 2000 ($p < 0.001$) in an analysis of the Spanish national registry (155); a similar decrease was shown in a Greek center, from 57.8% of patients with acromegaly treated with RT before 1990 to 16.8% after 1990, $p < 0.001$)(156).

In CD, the increasing medical armamentarium addressing the ACTH-secreting adenoma as well as the adrenal cortisol secretion and glucocorticoid receptor blockers will potentially reduce use of RT over time. Notably, with RT use restricted for aggressive or drug resistant tumours, biochemical cure for secreting adenomas could be even lower in future studies.

CONCLUSION

Stereotactic radiotherapy remains an effective treatment option for patients with persistent or recurrent

Table 4. Summary of efficacy and side effects of radiation therapy methods in patients with prolactinomas

RT Type	No of studies	Patients	Margin dose (Gy), median	Follow-up (median, months)	Tumor control (%)	Biochemical control (%)	New Hypopituitarism (%)	Visual defects (%)	Brain radionecrosis (%)	Second brain tumor (%)
SRS type: *GK*	15	588	25.4	52.4	93.7	32.6 (18-83)	13.8 (0-42)	1 (0-9.1)	0	0
LINAC	2	26	20	64	100	7.7 (0-15.4)	18.3 at 5y	0	2.8#	0
Protons	2	29	20*	60**	98	48.2 (22-60)	30 – 57	1*	1*	NA
CRT	11	250	45-50	3 – 13 y	96^	34.1 (40 at 10y)	35^ at 10y	NA	NA	NA
FSRT	2	34	45	3-4	NA	25 - 36	20-28.5^	0	0	0

Legend. The results are expressed in weighted means calculated from the published studies; SRS = stereotactic radiosurgery; CRT = conventional fractionated radiotherapy; FSRT = fractionated stereotactic radiotherapy; GK = gamma knife radiosurgery; LINAC = linear accelerator radiosurgery; y = years, # in a series with 175 various tumors; * in 20 patients the reported dose was 50 – 150 Gy in 4 fractions, in a cohort of 475 patients with various tumors (127); ** 20 patients had ≥ 1 year follow-up (127);^ in series with various pituitary tumors.

pituitary adenomas after unsuccessful surgery and resistance, intolerance or unavailability of medical therapy in some countries. Comparison of SRS with fractionated RT (either conventional or stereotactic) is rather difficult, due to the substantial heterogeneity among studies, risk of bias and imprecision. Systematic reviews have suggested that SRS may potentially be more effective than conventional RT regarding biochemical remission in acromegaly, but not in Cushing's disease. Long-term studies evaluating cerebrovascular disease and mortality rate after the new stereotactic techniques are needed, in order to evaluate their brain-sparing effects.

Conflict of interest

The authors declare no conflict of interest regarding this manuscript. This article does not contain any direct studies with human participants or animals performed by the author.

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The list of bibliographic references of the studies included in this analysis is provided as a supplementary material and may be consulted with authorization.

References

1. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. Cancer 2004; 101(3):613-619.
2. Katznelson L, Laws ER, Jr., Melmed S, Molitch ME, Murad MH, Utz A, Wass JA. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99(11):3933-3951.
3. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96(2):273-288.
4. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015; 100(8):2807-2831.
5. Sheehan J, Lee CC, Bodach ME, Tumialan LM, Oyesiku NM, Patil CG, Litvack Z, Zada G, Aghi MK. Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline for the Management of Patients With Residual or Recurrent Nonfunctioning Pituitary Adenomas. Neurosurgery 2016; 79(4):E539-E540.
6. Minniti G, Clarke E, Scaringi C, Enrici RM. Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas. Rep Pract Oncol Radiother 2016; 21(4):370-378.
7. Becker G, Kocher M, Kortmann RD, Paulsen F, Jeremic B, Muller RP, Bamberg M. Radiation therapy in the multimodal treatment approach of pituitary adenoma. Strahlenther Onkol 2002; 178(4):173-186.
8. Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, Uttley D. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. Clin Endocrinol (Oxf) 1993; 38(6):571-578.
9. Minniti G, Jaffrain-Rea ML, Osti M, Cantore G, Enrici RM. Radiotherapy for nonfunctioning pituitary adenomas: from conventional to modern stereotactic radiation techniques. Neurosurg Rev 2007; 30(3):167-175.
10. Minniti G, Jaffrain-Rea ML, Osti M, Esposito V, Santoro A, Solda F, Gargiulo P, Tamburrano G, Enrici RM. The long-term efficacy of conventional radiotherapy in patients with GH-secreting pituitary adenomas. Clin Endocrinol (Oxf) 2005; 62(2):210-216.
11. Losa M, Picozzi P, Redaelli MG, Laurenzi A, Mortini P. Pituitary radiotherapy for Cushing's disease. Neuroendocrinology 2010; 92 Suppl 1:107-110.
12. Olsen LJS, Irizarry LR, Chao ST, Weil RJ, Hamrahian AH, Hatipoglu B, Suh JH. Radiotherapy for prolactin-secreting tumours. Pituitary 2012; 15:135-145.
13. Jenkins PJ, Bates P, Carson MN, Stewart PM, Wass JA. Conventional pituitary irradiation is effective in lowering serum growth hormone and insulin-like growth factor-I in patients with acromegaly. J Clin Endocrinol Metab 2006; 91(4):1239-1245.
14. Minniti G, Osti M, Jaffrain-Rea ML, Esposito V, Cantore G, Maurizi ER. Long-term follow-up results of postoperative radiation therapy for Cushing's disease. J Neurooncol 2007; 84(1):79-84.
15. Ecemis GC, Atmaca A, Meydan D. Radiation-associated secondary brain tumours after conventional radiotherapy and radiosurgery. Expert Rev Neurother 2013; 13(5):557-565.
16. Erridge SC, Conkey DS, Stockton D, Strachan MW, Statham PF, Whittle IR, Grant R, Kerr GR, Gregor A. Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. Radiother Oncol 2009; 93(3):597-601.
17. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. J Clin Endocrinol Metab 2005; 90(2):800-804.
18. Lecumberri B, Estrada J, Garcia-Uria J, Millan I, Pallardo LF, Caballero L, Lucas T. Neurocognitive long-term impact of two-field conventional radiotherapy in adult patients with operated pituitary adenomas. Pituitary 2015; 18(6):782-795.
19. Brada M, Burchell L, Ashley S, Traish D. The incidence of cerebrovascular accidents in patients with pituitary adenoma. Int J Radiat Oncol Biol Phys 1999; 45(3):693-698.
20. Olsson DS, Bryngelsson IL, Ragnarsson O. Higher incidence of morbidity in women than men with non-functioning pituitary adenoma: a Swedish nationwide study. Eur J Endocrinol 2016; 175(1):55-61.
21. van Westrhenen A., Muskens IS, Verhoeff JJC, Smith TRS, Broekman MLD. Ischemic stroke after radiation therapy for pituitary adenomas: a systematic review. J Neurooncol 2017; 135(1):1-11.
22. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-I concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab 2004; 89(4):1613-1617.
23. Bex M, Abs R, T'Sjoen G, Mockel J, Velkeniers B, Muermans K, Maiter D. AcroBel--the Belgian registry on acromegaly: a survey of the 'real-life' outcome in 418 acromegalic subjects. Eur J Endocrinol 2007; 157(4):399-409.
24. Colao A, Vandeva S, Pivonello R, Grasso LF, Nachev E, Auriemma RS, Kalinov K, Zacharieva S. Could different treatment approaches in acromegaly influence life expectancy? A comparative study between Bulgaria and Campania (Italy). Eur J Endocrinol 2014; 171(2):263-273.
25. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, Gomez JM, Halperin I, Lucas-Morante T, Moreno B, Obiols G, de PP, Paramo C, Pico A, Torres E, Varela C, Vazquez JA, Zamora J, Albareda M, Gilabert M. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol 2004; 151(4):439-446.
26. Olsson DS, Nilsson AG, Bryngelsson IL, Trimpou P, Johannsson G, Andersson E. Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study. J Clin Endocrinol Metab 2015; 100(7):2651-2658.

27. Sherlock M, Reulen RC, Alonso AA, Ayuk J, Clayton RN, Sheppard MC, Hawkins MM, Bates AS, Stewart PM. ACTH deficiency, higher doses of hydrocortisone replacement, and radiotherapy are independent predictors of mortality in patients with acromegaly. J Clin Endocrinol Metab 2009; 94(11):4216-4223.
28. Brown PD, Blanchard M, Jethwa K, Flemming KD, Brown CA, Kline RW, Jacobson DJ, St SJ, Pollock BE, Garces YI, Stafford SL, Link MJ, Erickson D, Foote RL, Laack NN. The incidence of cerebrovascular accidents and second brain tumours in patients with pituitary adenoma: a population-based study. Neurooncol Pract 2014; 1(1):22-28.
29. Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH. Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016; 101(11):3888-3921.
30. Ntali G, Capatina C, Fazal-Sanderson V, Byrne JV, Cudlip S, Grossman AB, Wass JA, Karavitaki N. Mortality in patients with non-functioning pituitary adenoma is increased: systematic analysis of 546 cases with long follow-up. Eur J Endocrinol 2016; 174(2):137-145.
31. Sattler MG, van Beek AP, Wolffenbuttel BH, van den Berg G, Sluiter WJ, Langendijk JA, van den Bergh AC. The incidence of second tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone. Radiother Oncol 2012; 104(1):125-130.
32. van Varsseveld NC, van Bunderen CC, Ubachs DH, Franken AA, Koppeschaar HP, van der Lely AJ, Drent ML. Cerebrovascular events, secondary intracranial tumours, and mortality after radiotherapy for nonfunctioning pituitary adenomas: a subanalysis from the Dutch National Registry of Growth Hormone Treatment in Adults. J Clin Endocrinol Metab 2015; 100(3):1104-1112.
33. Vandeva S, Yaneva M, Natchev E, Elenkova A, Kalinov K, Zacharieva S. Disease control and treatment modalities have impact on quality of life in acromegaly evaluated by Acromegaly Quality of Life (AcroQoL) Questionnaire. Endocrine 2015; 49(3):774-782.
34. van der Klaauw AA, Biermasz NR, Hoftijzer HC, Pereira AM, Romijn JA. Previous radiotherapy negatively influences quality of life during 4 years of follow-up in patients cured from acromegaly. Clin Endocrinol (Oxf) 2008; 69(1):123-128.
35. Biermasz NR, van Thiel SW, Pereira AM, Hoftijzer HC, van Hemert AM, Smit JW, Romijn JA, Roelfsema F. Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. J Clin Endocrinol Metab 2004; 89(11):5369-5376.
36. Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumours. Radiat Oncol 2016; 11(1):135.
37. Gevaert T, Boussaer M, Engels B, Litre CF, Prieur A, Wdowczyk D, Verellen D, Storme G, D'Haens J, Colin P, De RM. Evaluation of the clinical usefulness for using verification images during frameless radiosurgery. Radiother Oncol 2013; 108(1):114-117.
38. Liao HI, Wang CC, Wei KC, Chang CN, Hsu YH, Lee ST, Huang YC, Chen HC, Hsu PW. Fractionated stereotactic radiosurgery using the Novalis system for the management of pituitary adenomas close to the optic apparatus. J Clin Neurosci 2014; 21(1):111-115.
39. Roberts BK, Ouyang DL, Lad SP, Chang SD, Harsh GR, Adler JR, Jr., Soltys SG, Gibbs IC, Remedios L, Katznelson L. Efficacy and safety of CyberKnife radiosurgery for acromegaly. Pituitary 2007; 10(1):19-25.
40. Iwata H, Sato K, Nomura R, Tabei Y, Suzuki I, Yokota N, Inoue M, Ohta S, Yamada S, Shibamoto Y. Long-term results of hypofractionated stereotactic radiotherapy with CyberKnife for growth hormone-secreting pituitary adenoma: evaluation by the Cortina consensus. J Neurooncol 2016; 128(2):267-275.
41. Petrovich Z, Jozsef G, Yu C, Apuzzo ML. Radiotherapy and stereotactic radiosurgery for pituitary tumours. Neurosurg Clin N Am 2003; 14(1):147-166.
42. Puataweepong P, Dhanachai M, Hansasuta A, Dangprasert S, Swangsilpa T, Sitathanee C, Jiarpinitnun C, Vitoonpanich P, Yongvithisatid P. The Clinical Outcome of Hypofractionated Stereotactic Radiotherapy With CyberKnife Robotic Radiosurgery for Perioptic Pituitary Adenoma. Technol Cancer Res Treat 2016; 15(6):NP10-NP15.
43. Ferrante E, Ferraroni M, Castrignano T, Menicatti L, Anagni M, Reimondo G, Del MP, Bernasconi D, Loli P, Faustini-Fustini M, Borretta G, Terzolo M, Losa M, Morabito A, Spada A, Beck-Peccoz P, Lania AG. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumours. Eur J Endocrinol 2006; 155(6):823-829.
44. Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, Stern N. Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. Clin Endocrinol (Oxf) 2003; 58(6):763-769.
45. Gheorghiu ML, Anghel R, Chicos P, Hortopan D, Dumitrascu A, Alexandrescu D, Coculescu M. Effect of Postoperative Radiotherapy on Tumour Growth of Nonfunctioning Pituitary Adenomas. Acta Endocrinologica-Bucharest 2008; 4(4):401-414.
46. Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, Lee JY, Kano H, Park KJ, Niranjan A, Kondziolka D, Barnett GH, Rush S, Golfinos JG, Lunsford LD. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg 2013; 119(2):446-456.
47. Picozzi P, Losa M, Mortini P, Valle MA, Franzin A, Attuati L, Ferrari da PC, Giovanelli M. Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas. J Neurosurg 2005; 102 Suppl:71-74.
48. Chen Y, Li ZF, Zhang FX, Li JX, Cai L, Zhuge QC, Wu ZB. Gamma knife surgery for patients with volumetric classification of nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Eur J Endocrinol 2013; 169(4):487-495.
49. Sheehan JP, Xu Z, Salvetti DJ, Schmitt PJ, Vance ML. Results of gamma knife surgery for Cushing's disease. J Neurosurg 2013; 119(6):1486-1492.
50. Pollock BE, Cochran J, Natt N, Brown PD, Erickson D, Link MJ, Garces YI, Foote RL, Stafford SL, Schomberg PJ. Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. Int J Radiat Oncol Biol Phys 2008; 70(5):1325-1329.
51. Park KJ, Kano H, Parry PV, Niranjan A, Flickinger JC, Lunsford LD, Kondziolka D. Long-term outcomes after gamma knife stereotactic radiosurgery for nonfunctional pituitary adenomas. Neurosurgery 2011; 69(6):1188-1199.
52. Cohen-Inbar O, Xu Z, Lee CC, Wu CC, Chytka T, Silva D, Sharma M, Radwan H, Grills IS, Nguyen B, Siddiqui Z, Mathieu D, Iorio-Morin C, Wolf A, Cifarelli CP, Cifarelli DT, Lunsford LD, Kondziolka D, Sheehan JP. Prognostic significance of corticotroph staining in radiosurgery for non-functioning pituitary adenomas: a multicenter study. J Neurooncol 2017; 135(1):67-74.
53. Stancu C, Cimpean AM, Gheorghiu ML, Galoiu S, Dumitrascu A, Hortopan D, Anghel RM, Ciubotaru V, Badiu C, Raica M, Coculescu M. The Efficacy of Early Postoperative Radiotherapy for Non-Functioning Pituitary Macro Adenomas, with Tumour Cells Expressing or not Expressing Pituitary Hormones. Acta Endo (Buc) 2014; 10(4):605-620.
54. Yu YL, Yang YJ, Lin C, Hsieh CC, Li CZ, Feng SW, Tang CT, Chung TT, Ma HI, Chen YH, Ju DT, Hueng DY. Analysis of volumetric response of pituitary adenomas receiving adjuvant CyberKnife stereotactic radiosurgery with the application of an exponential fitting model. Medicine (Baltimore) 2017; 96(4):e4662.
55. Wowra B, Stummer W. Efficacy of gamma knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow up with magnetic resonance imaging-based volumetric analysis. J Neurosurg 2002; 97(5 Suppl):429-432.
56. Pomeraniec IJ, Kano H, Xu Z, Nguyen B, Siddiqui ZA, Silva D, Sharma M, Radwan H, Cohen JA, Dallapiazza RF, Iorio-Morin C, Wolf A, Jane JA, Jr., Grills IS, Mathieu D, Kondziolka D, Lee

CC, Wu CC, Cifarelli CP, Chytka T, Barnett GH, Lunsford LD, Sheehan JP. Early versus late Gamma Knife radiosurgery following transsphenoidal surgery for nonfunctioning pituitary macroadenomas: a multicenter matched-cohort study. J Neurosurg 2017;1-10.
57. van den Bergh AC, van den Berg G, Schoorl MA, Sluiter WJ, van der Vliet AM, Hoving EW, Szabo BG, Langendijk JA, Wolffenbuttel BH, Dullaart RP. Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy. Int J Radiat Oncol Biol Phys 2007; 67(3):863-869.
58. Lee CC, Kano H, Yang HC, Xu Z, Yen CP, Chung WY, Pan DH, Lunsford LD, Sheehan JP. Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas. J Neurosurg 2014; 120(3): 647-654.
59. Hasegawa T, Shintai K, Kato T, Iizuka H. Stereotactic Radiosurgery as the Initial Treatment for Patients with Nonfunctioning Pituitary Adenomas. World Neurosurg 2015; 83(6):1173-1179.
60. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. Int J Radiat Oncol Biol Phys 2010; 76(3 Suppl):S28-S35.
61. Sheehan JP, Pouratian N, Steiner L, Laws ER, Vance ML. Gamma Knife surgery for pituitary adenomas: factors related to radiological and endocrine outcomes. J Neurosurg 2011; 114(2):303-309.
62. Gheorghiu ML. Updates in outcomes of stereotactic radiation therapy in acromegaly. Pituitary 2017; 20(1):154-168.
63. Yamanaka R, Abe E, Sato T, Hayano A, Takashima Y. Secondary Intracranial Tumours Following Radiotherapy for Pituitary Adenomas: A Systematic Review. Cancers (Basel) 2017; 9(8).
64. Wilson PJ, De-Loyde KJ, Williams JR, Smee RI. A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the Linear Accelerator (Linac). J Clin Neurosci 2012; 19(3):370-374.
65. Selch MT, Gorgulho A, Lee SP, Mattozo C, Solberg TD, Agazaryan N, Desalles AA. Stereotactic radiotherapy for the treatment of pituitary adenomas. Minim Invasive Neurosurg 2006; 49(3):150-155.
66. Paek SH, Downes MB, Bednarz G, Keane WM, Werner-Wasik M, Curran WJ, Jr., Andrews DW. Integration of surgery with fractionated stereotactic radiotherapy for treatment of nonfunctioning pituitary macroadenomas. Int J Radiat Oncol Biol Phys 2005; 61(3):795-808.
67. Minniti G, Scaringi C, Poggi M, Jaffrain Rea ML, Trillo G, Esposito V, Bozzao A, Enrici MM, Toscano V, Enrici RM. Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumour response. Eur J Endocrinol 2015; 172(4):433-441.
68. Kopp C, Theodorou M, Poullos N, Jacob V, Astner ST, Molls M, Grosu AL. Tumour shrinkage assessed by volumetric MRI in long-term follow-up after fractionated stereotactic radiotherapy of nonfunctioning pituitary adenoma. Int J Radiat Oncol Biol Phys 2012; 82(3):1262-1267.
69. Bostrom JP, Meyer A, Pintea B, Gerlach R, Surber G, Lammering G, Hamm K. Risk-adapted single or fractionated stereotactic high-precision radiotherapy in a pooled series of nonfunctioning pituitary adenomas: high local control and low toxicity. Strahlenther Onkol 2014; 190(12):1095-1103.
70. Kopp C, Theodorou M, Poullos N, Astner ST, Geinitz H, Stalla GK, Meyer B, Molls M, Nieder C, Grosu AL. Fractionated stereotactic radiotherapy in the treatment of pituitary adenomas. Strahlenther Onkol 2013; 189(11):932-937.
71. Li X, Li Y, Cao Y, Li P, Liang B, Sun J, Feng E. Safety and efficacy of fractionated stereotactic radiotherapy and stereotactic radiosurgery for treatment of pituitary adenomas: A systematic review and meta-analysis. J Neurol Sci 2017; 372:110-116.
72. Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. Int J Radiat Oncol Biol Phys 1994; 30(3):557-565.
73. Gittoes NJ, Bates AS, Tse W, Bullivant B, Sheppard MC, Clayton RN, Stewart PM. Radiotherapy for non-function pituitary tumours. Clin Endocrinol (Oxf) 1998; 48(3):331-337.
74. Breen P, Flickinger JC, Kondziolka D, Martinez AJ. Radiotherapy for nonfunctional pituitary adenoma: analysis of long-term tumour control. J Neurosurg 1998; 89(6):933-938.
75. Nielsen EH, Lindholm J, Laurberg P, Bjerre P, Christiansen JS, Hagen C, Juul S, Jorgensen J, Kruse A, Stochholm K. Nonfunctioning pituitary adenoma: incidence, causes of death and quality of life in relation to pituitary function. Pituitary 2007; 10(1):67-73.
76. Brummelman P, Sattler MG, Meiners LC, Elderson MF, Dullaart RP, van den Berg G, Koerts J, Tucha O, Wolffenbuttel BH, van den Bergh AC, van Beek AP. Cognitive performance after postoperative pituitary radiotherapy: a dosimetric study of the hippocampus and the prefrontal cortex. Eur J Endocrinol 2012; 166(2):171-179.
77. Sattler MG, Meiners LC, Sluiter WJ, van den Berg G, Langendijk JA, Wolffenbuttel BH, van den Bergh AC, van Beek AP. Brain abnormalities on MRI in non-functioning pituitary adenoma patients treated with or without postoperative radiotherapy. Radiother Oncol 2015; 114(2):239-244.
78. Jezkova J, Marek J, Hana V, Krsek M, Weiss V, Vladyka V, Lisak R, Vymazal J, Pecen L. Gamma knife radiosurgery for acromegaly--long-term experience. Clin Endocrinol (Oxf) 2006; 64(5):588-595.
79. Lee CC, Vance ML, Xu Z, Yen CP, Schlesinger D, Dodson B, Sheehan J. Stereotactic radiosurgery for acromegaly. J Clin Endocrinol Metab 2014; 99(4):1273-1281.
80. Losa M, Gioia L, Picozzi P, Franzin A, Valle M, Giovanelli M, Mortini P. The role of stereotactic radiotherapy in patients with growth hormone-secreting pituitary adenoma. J Clin Endocrinol Metab 2008; 93(7):2546-2552.
81. Vik-Mo EO, Oksnes M, Pedersen PH, Wentzel-Larsen T, Rodahl E, Thorsen F, Schreiner T, Aanderud S, Lund-Johansen M. Gamma knife stereotactic radiosurgery for acromegaly. Eur J Endocrinol 2007; 157(3):255-263.
82. Jagannathan J, Yen CP, Pouratian N, Laws ER, Sheehan JP. Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the Gamma Knife. J Neurooncol 2009; 92(3):345-356.
83. Yan JL, Chang CN, Chuang CC, Hsu PW, Lin JD, Wei KC, Lee ST, Tseng JK, Pai PC, Chen YL. Long-term follow-up of patients with surgical intractable acromegaly after linear accelerator radiosurgery. J Formos Med Assoc 2013; 112(7):416-420.
84. Pollock BE, Jacob JT, Brown PD, Nippoldt TB. Radiosurgery of growth hormone-producing pituitary adenomas: factors associated with biochemical remission. J Neurosurg 2007; 106(5):833-838.
85. Abu Dabrh AM, Asi N, Farah WH, Mohammed K, Wang Z, Farah MH, Prokop LJ, Katznelson L, Murad MH. Radiotherapy *versus* radiosurgery in treating patients with acromegaly: a systematic review and metaanalysis. Endocr Pract 2015; 21(8):943-956.
86. Lee CC, Vance ML, Lopes MB, Xu Z, Chen CJ, Sheehan J. Stereotactic radiosurgery for acromegaly: outcomes by adenoma subtype. Pituitary 2015; 18(3):326-334.
87. Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J, Wellis G. Octreotide may act as a radioprotective agent in acromegaly. J Clin Endocrinol Metab 2000; 85(3):1287-1289.
88. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Jr., Steiner L, Vance ML. Gamma knife radiosurgery for acromegaly: outcomes after failed transsphenoidal surgery. Neurosurgery 2008; 62(6): 1262-1269.
89. Castinetti F, Taieb D, Kuhn JM, Chanson P, Tamura M, Jaquet P, Conte-Devolx B, Regis J, Dufour H, Brue T. Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion. J Clin Endocrinol Metab 2005; 90(8):4483-4488.
90. Liu X, Kano H, Kondziolka D, Park KJ, Iyer A, Niranjan A, Flickinger JC, Lunsford LD. Gamma knife radiosurgery for clinically persistent acromegaly. J Neurooncol 2012; 109(1):71-79.

91. Cohen-Inbar O, Ramesh A, Xu Z, Vance ML, Schlesinger D, Sheehan JP. Gamma knife radiosurgery in patients with persistent acromegaly or Cushing's disease: long-term risk of hypopituitarism. Clin Endocrinol (Oxf) 2016; 84(4):524-531.
92. Wilson PJ, De-Loyde KJ, Williams JR, Smee RI. Acromegaly: a single centre's experience of stereotactic radiosurgery and radiotherapy for growth hormone secreting pituitary tumours with the linear accelerator. J Clin Neurosci 2013; 20(11):1506-1513.
93. Castinetti F, Morange I, Dufour H, Regis J, Brue T. Radiotherapy and radiosurgery in acromegaly. Pituitary 2009; 12(1):3-10.
94. Ronchi CL, Attanasio R, Verrua E, Cozzi R, Ferrante E, Loli P, Montefusco L, Motti E, Ferrari DI, Giugni E, Beck-Peccoz P, Arosio M. Efficacy and tolerability of gamma knife radiosurgery in acromegaly: a 10-year follow-up study. Clin Endocrinol (Oxf) 2009; 71(6):846-852.
95. Brada M, Ashley S, Ford D, Traish D, Burchell L, Rajan B. Cerebrovascular mortality in patients with pituitary adenoma. Clin Endocrinol (Oxf) 2002; 57(6):713-717.
96. Mercado M, Gonzalez B, Vargas G, Ramirez C, de los Monteros AL, Sosa E, Jervis P, Roldan P, Mendoza V, Lopez-Felix B, Guinto G. Successful mortality reduction and control of comorbidities in patients with acromegaly followed at a highly specialized multidisciplinary clinic. J Clin Endocrinol Metab 2014; 99(12):4438-4446.
97. Dal J, Feldt-Rasmussen U, Andersen M, Kristensen LO, Laurberg P, Pedersen L, Dekkers OM, Sorensen HT, Jorgensen JO. Acromegaly incidence, prevalence, complications and long-term prognosis: a nationwide cohort study. Eur J Endocrinol 2016; 175(3):181-190.
98. Kreitschmann-Andermahr I, Buchfelder M, Kleist B, Kohlmann J, Menzel C, Buslei R, Koltowska-Haggstram M, Strasburger C, Siegel S. Predictors of quality of life in 165 patients with acromegaly: results from a single-center study. Endocr Pract 2017; 23(1):79-88.
99. Diallo AM, Colin P, Litre CF, Diallo MM, Decoudier B, Bertoin F, Higel B, Patey M, Rousseaux P, Delemer B. Long-term results of fractionated stereotactic radiotherapy as third-line treatment in acromegaly. Endocrine 2015; 50(3):741-748.
100. Gheorghiu ML, Purice M, Poiana C, Coculescu M. Efficacy of pituitary radiotherapy on growth hormone (GH) secretion in patients with acromegaly. Abstract book for the American Association of Clinical Endocrinologists' 21st Annual Meeting and Clinical Congress, May 23-27, Philadelphia, 2012 , A152. 2012.
101. Kim MY, Kim JH, Oh YK, Kim E. Long-term outcomes of surgery and radiotherapy for secreting and non-secreting pituitary adenoma. Radiat Oncol J 2016; 34(2):121-127.
102. Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J, Wellis G. Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy. J Neurosurg 1998; 88(6):1002-1008.
103. Gutt B, Wowra B, Alexandrov R, Uhl E, Schaaf L, Stalla GK, Schopohl J. Gamma-knife surgery is effective in normalising plasma insulin-like growth factor I in patients with acromegaly. Exp Clin Endocrinol Diabetes 2005; 113(4):219-224.
104. Kobayashi T, Mori Y, Uchiyama Y, Kida Y, Fujitani S. Long-term results of gamma knife surgery for growth hormone-producing pituitary adenoma: is the disease difficult to cure? J Neurosurg 2005; 102 Suppl:119-123.
105. Voges J, Kocher M, Runge M, Poggenborg J, Lehrke R, Lenartz D, Maarouf M, Gouni-Berthold I, Krone W, Muller RP, Sturm V. Linear accelerator radiosurgery for pituitary macroadenomas: a 7-year follow-up study. Cancer 2006; 107(6):1355-1364.
106. Fleseriu M, Castinetti F. Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies. Pituitary 2016; 19(6):643-653.
107. McCartney S, Fleseriu M. A New Era of Cushing Disease Therapeutics. Acta Endocrinologica-Bucharest 2013; 9(1):89-96.
108. Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML. Gamma Knife surgery for Cushing's disease. J Neurosurg 2007; 106(6):980-987.
109. Abu Dabrh AM, Singh Ospina NM, Al NA, Farah WH, Barrionuevo P, Sarigianni M, Mohabbat AB, Benkhadra K, Carranza Leon BG, Gionfriddo MR, Wang Z, Mohammed K, Ahmed AT, Elraiyah TA, Haydour Q, Alahdab F, Prokop LJ, Murad MH. Predictors of biochemical remission and recurrence after surgical and radiation treatments of Cushing disease: a systematic review and meta-analysis. Endocr Pract 2016; 22(4):466-475.
110. Pivonello R, De LM, Cozzolino A, Colao A. The Treatment of Cushing's Disease. Endocr Rev 2015; 36(4):385-486.
111. Fleseriu M, Hamrahian AH, Hoffman AR, Kelly DF, Katznelson L. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: diagnosis of recurrence in Cushing disease. Endocr Pract 2016; 22(12):1436-1448.
112. Castinetti F, Nagai M, Morange I, Dufour H, Caron P, Chanson P, Cortet-Rudelli C, Kuhn JM, Conte-Devolx B, Regis J, Brue T. Long-term results of stereotactic radiosurgery in secretory pituitary adenomas. J Clin Endocrinol Metab 2009; 94(9):3400-3407.
113. Sheehan JM, Vance ML, Sheehan JP, Ellegala DB, Laws ER, Jr. Radiosurgery for Cushing's disease after failed transsphenoidal surgery. J Neurosurg 2000; 93(5):738-742.
114. Swords FM, Monson JP, Besser GM, Chew SL, Drake WM, Grossman AB, Plowman PN. Gamma knife radiosurgery: a safe and effective salvage treatment for pituitary tumours not controlled despite conventional radiotherapy. Eur J Endocrinol 2009; 161(6):819-828.
115. Landolt AM, Lomax N, Scheib SG, Girard J. Gamma Knife surgery after fractionated radiotherapy for acromegaly. J Neurosurg 2006; 105 Suppl:31-36.
116. Flickinger JC, Deutsch M, Lunsford LD. Repeat megavoltage irradiation of pituitary and suprasellar tumours. Int J Radiat Oncol Biol Phys 1989; 17(1):171-175.
117. Hayashi M, Chernov M, Tamura N, Nagai M, Yomo S, Ochiai T, Amano K, Izawa M, Hori T, Muragaki Y, Iseki H, Okada Y, Takakura K. Gamma Knife robotic microradiosurgery of pituitary adenomas invading the cavernous sinus: treatment concept and results in 89 cases. J Neurooncol 2010; 98(2):185-194.
118. Wattson DA, Tanguturi SK, Spiegel DY, Niemierko A, Biller BM, Nachtigall LB, Bussiere MR, Swearingen B, Chapman PH, Loeffler JS, Shih HA. Outcomes of proton therapy for patients with functional pituitary adenomas. Int J Radiat Oncol Biol Phys 2014; 90(3):532-539.
119. Tooze A, Hiles CL, Sheehan JP. Neurocognitive changes in pituitary adenoma patients after gamma knife radiosurgery: a preliminary study. World Neurosurg 2012; 78(1-2):122-128.
120. Mehta GU, Ding D, Patibandla MR, Kano H, Sisterson N, Su YH, Krsek M, Nabeel AM, El-Shehaby A, Kareem KA, Martinez-Moreno N, Mathieu D, McShane B, Blas K, Kondziolka D, Grills I, Lee JY, Martinez-Alvarez R, Reda WA, Liscak R, Lee CC, Lunsford LD, Vance ML, Sheehan JP. Stereotactic Radiosurgery for Cushing Disease: Results of an International, Multicenter Study. J Clin Endocrinol Metab 2017; 102(11):4284-4291.
121. Tsukamoto H, Yoshinari M, Okamura K, Ishitsuka T, Fujishima M. Meningioma developed 25 years after radiation therapy for Cushing's disease. Intern Med 1992; 31(5):629-632.
122. Sarkar S, Rajaratnam S, Backianathan S, Chacko G, Chacko AG. Radiation-induced opticochiasmatic glioblastoma multiforme following conventional radiotherapy for Cushing's disease. Br J Neurosurg 2014; 28(4):510-512.
123. Vik-Mo EO, Oksnes M, Pedersen PH, Wentzel-Larsen T, Rodahl E, Thorsen F, Schreiner T, Aanderud S, Lund-Johansen M. Gamma knife stereotactic radiosurgery of Nelson syndrome. Eur J Endocrinol 2009; 160(2):143-148.
124. Colin P, Delemer B, Nakib I, Caron J, Bazin A, Bernard MH, Peruzzi P, Scavarda D, Scherpereel B, Longuebray A, Redon C, Petel F, Rousseaux P. [Unsuccessful surgery of Cushing's disease. Role and efficacy of fractionated stereotactic radiotherapy]. Neurochirurgie 2002; 48(2-3 Pt 2):285-293.
125. Budyal S, Lila AR, Jalali R, Gupta T, Kasliwal R, Jagtap VS, Bandgar T, Menon P, Shah NS. Encouraging efficacy of modern conformal fractionated radiotherapy in patients with uncured

Cushing's disease. Pituitary 2014; 17(1):60-67.
126. Dekkers OM, Biermasz NR, Pereira AM, Roelfsema F, van Aken MO, Voormolen JH, Romijn JA. Mortality in patients treated for Cushing's disease is increased, compared with patients treated for nonfunctioning pituitary macroadenoma. J Clin Endocrinol Metab 2007; 92(3):976-981.
127. Levy RP, Fabrikant JI, Frankel KA, Phillips MH, Lyman JT, Lawrence JH, Tobias CA. Heavy-charged-particle radiosurgery of the pituitary gland: clinical results of 840 patients. Stereotact Funct Neurosurg 1991; 57(1-2):22-35.
128. Acharya SV, Gopal RA, Goerge J, Menon PS, Bandgar TR, Shah NS. Radiotherapy in paediatric Cushing's disease: efficacy and long term follow up of pituitary function. Pituitary 2010; 13(4):293-297.
129. Chan LF, Storr HL, Plowman PN, Perry LA, Besser GM, Grossman AB, Savage MO. Long-term anterior pituitary function in patients with paediatric Cushing's disease treated with pituitary radiotherapy. Eur J Endocrinol 2007; 156(4):477-482.
130. Jennings AS, Liddle GW, Orth DN. Results of treating childhood Cushing's disease with pituitary irradiation. N Engl J Med 1977; 297(18):957-962.
131. Thoren M, Rahn T, Hallengren B, Kaad PH, Nilsson KO, Ravn H, Ritzen M, Petersen KE, Aarskog D. Treatment of Cushing's disease in childhood and adolescence by stereotactic pituitary irradiation. Acta Paediatr Scand 1986; 75(3):388-395.
132. Assie G, Bahurel H, Coste J, Silvera S, Kujas M, Dugue MA, Karray F, Dousset B, Bertherat J, Legmann P, Bertagna X. Corticotroph tumour progression after adrenalectomy in Cushing's Disease: A reappraisal of Nelson's Syndrome. J Clin Endocrinol Metab 2007; 92(1):172-179.
133. Marek J, Jezkova J, Hana V, Krsek M, Liscak R, Vladyka V, Pecen L. Gamma knife radiosurgery for Cushing's disease and Nelson's syndrome. Pituitary 2015; 18(3):376-384.
134. Caruso JP, Patibandla MR, Xu Z, Vance ML, Sheehan JP. A Long-Term Study of the Treatment of Nelson's Syndrome With Gamma Knife Radiosurgery. Neurosurgery 2017.
135. Wilson PJ, Williams JR, Smee RI. Nelson's syndrome: single centre experience using the linear accelerator (LINAC) for stereotactic radiosurgery and fractionated stereotactic radiotherapy. J Clin Neurosci 2014; 21(9):1520-1524.
136. Mauermann WJ, Sheehan JP, Chernavvsky DR, Laws ER, Steiner L, Vance ML. Gamma Knife surgery for adrenocorticotropic hormone-producing pituitary adenomas after bilateral adrenalectomy. J Neurosurg 2007; 106(6):988-993.
137. Howlett TA, Plowman PN, Wass JA, Rees LH, Jones AE, Besser GM. Megavoltage pituitary irradiation in the management of Cushing's disease and Nelson's syndrome: long-term follow-up. Clin Endocrinol (Oxf) 1989; 31(3):309-323.
138. Gil-Cardenas A, Herrera MF, Diaz-Polanco A, Rios JM, Pantoja JP. Nelson's syndrome after bilateral adrenalectomy for Cushing's disease. Surgery 2007; 141(2):147-151.
139. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM. The long-term outcome after adrenalectomy and prophylactic pituitary radiotherapy in adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 1995; 80(1):165-171.
140. Mehta GU, Sheehan JP, Vance ML. Effect of stereotactic radiosurgery before bilateral adrenalectomy for Cushing's disease on the incidence of Nelson's syndrome. J Neurosurg 2013; 119(6):1493-1497.
141. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M. Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab 1996; 81(7):2647-2652.
142. Coculescu M, Anghel R, Badiu C, Caragheorgheopol A, Hortopan D, Dumitrascu A, Virtej I, Trifanescu RA, Capatina C, Voicu D. Additional effects of radiotherapy to dopamine agonists in the treatment of macroprolactinomas. Acta Endocrinologica-Bucharest 2005; 1(1):43-59.
143. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev 2006; 27(5):485-534.
144. Pan L, Zhang N, Wang EM, Wang BJ, Dai JZ, Cai PW. Gamma knife radiosurgery as a primary treatment for prolactinomas. J Neurosurg 2000; 93 Suppl 3:10-13.
145. Pouratian N, Sheehan J, Jagannathan J, Laws ER, Jr., Steiner L, Vance ML. Gamma knife radiosurgery for medically and surgically refractory prolactinomas. Neurosurgery 2006; 59(2):255-266.
146. Landolt AM, Lomax N. Gamma knife radiosurgery for prolactinomas. J Neurosurg 2000; 93 Suppl 3:14-18.
147. Tanaka S, Link MJ, Brown PD, Stafford SL, Young WF, Jr., Pollock BE. Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas. World Neurosurg 2010; 74(1):147-152.
148. Colin P, Jovenin N, Delemer B, Caron J, Grulet H, Hecart AC, Lukas C, Bazin A, Bernard MH, Scherpereel B, Peruzzi P, Nakib I, Redon C, Rousseaux P. Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. Int J Radiat Oncol Biol Phys 2005; 62(2):333-341.
149. Mitsumori M, Shrieve DC, Alexander E, III, Kaiser UB, Richardson GE, Black PM, Loeffler JS. Initial clinical results of LINAC-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. Int J Radiat Oncol Biol Phys 1998; 42(3):573-580.
150. Coculescu M, Anghel R, Trifanescu RA, Voicu D, Karavitaki N, Wass JA. The outcome of macroprolactinomas resistant to dopamine agonists. Acta Endocrinologica Bucharest 2005; 1(4):423-440.
151. Pollock BE, Brown PD, Nippoldt TB, Young WF, Jr. Pituitary tumour type affects the chance of biochemical remission after radiosurgery of hormone-secreting pituitary adenomas. Neurosurgery 2008; 62(6):1271-1276.
152. Cohen-Inbar O, Xu Z, Schlesinger D, Vance ML, Sheehan JP. Gamma Knife radiosurgery for medically and surgically refractory prolactinomas: long-term results. Pituitary 2015; 18(6):820-830.
153. Gheorghiu ML, Gussi I, Lutescu I, Galoiu S, Hortopan D, Caragheorgheopol A, Coculescu M. Maintaining physiological levels of serum prolactin in prolactinomas treated with dopamine agonists throughout pregnancy prevents tumour growth. Acta Endocrinologica-Bucharest 2005; 1(3):281-298.
154. Olsson DS, Bryngelsson IL, Ragnarsson O. Time trends of mortality in patients with non-functioning pituitary adenoma: a Swedish nationwide study. Pituitary 2017; 20(2):218-224.
155. Sesmilo G, Gaztambide S, Venegas E, Pico A, Del PC, Blanco C, Torres E, Alvarez-Escola C, Fajardo C, Garcia R, Camara R, Bernabeu I, Soto A, Villabona C, Serraclara A, Halperin I, Alcazar V, Palomera E, Webb SM. Changes in acromegaly treatment over four decades in Spain: analysis of the Spanish Acromegaly Registry (REA). Pituitary 2013; 16(1):115-121.
156. Karapanou O, Tzanela M, Christoforaki M, Papastathopoulou L, Moutsatsou P, Botoula E, Tsagarakis S. Therapeutic trends and outcome of acromegaly: a single center experience over a 40-year period. Hormones (Athens) 2016; 15(3):368-376.