Fractionated Stereotactic Radiation Therapy for Pituitary Adenomas: an alternative escalating protocol of hypofractionated stereotactic radiotherapy delivering 35 Gy in 5 fractions

La radiothérapie stéréotaxique pour les adénomes hypophysaires : escalade de dose délivrant 35 Gy en 5 fractions

Shakeel Sumodhee[a]; Vincent Atallah[a]; Rémy Kinj[a]; Jérôme Doyen[a]; Baptiste L'Homel[a]; Pauline Gillon[a]; Philippe Paquis[b]; Fabien Almairac[b]; Sylvie Hieronimus[c]; Renaud Schiappa[d]; Jean-Louis Sadoul[c]; Dayyanah Sumodhee[e]; Nikolas Pontikos[f]; Quentin Richier[g]; Jean-Michel Hannoun-Levi[a]; Cyrielle Scouarnec[a]; Nicolas Chevalier[b]; Pierre-Yves Bondiau[a]

[a] Department of Radiation Oncology, Centre Antoine-Lacassagne, University Côte d'Azur, Nice, France
[b] Department of Neurosurgery, Centre Hospitalier Universitaire de Nice, Nice, France
[c] Department of Endocrinology, Centre Hospitalier Universitaire de Nice, Nice, France
[d] Department of Biostatistics, Centre Antoine-Lacassagne, Nice, France
[e] Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, King's College London, UK
[f] UCL Institute of Ophthalmology, University College London, London, UK
[g] Department of Internal Medicine, CHU de La Réunion, 97400 Saint Denis, France.

*Corresponding author: Shakeel SUMODHEE, MD
shakeel.sumodhee@nice.unicancer.fr
Centre Antoine-Lacassagne,
33 avenue de Valombrose France
Université Côte d'Azur France
06189 Nice - France
Tel: (+33) 4 92 03 12 60
Fax: (+33) 4 92 03 15 70

ABSTRACT

Background: Evaluate efficacy and toxicity of hypofractionated stereotactic radiotherapy (HSRT) for patients treated for pituitary adenoma (PA) with an alternative HSRT escalating protocol delivering 35Gy in 5 fractions.

Methods: From June 2007 to March 2017, 29 patients with pituitary adenoma were treated in Antoine Lacassagne Cancer Centre with an alternative HSRT protocol. Prescribed dose was 35Gy in 5 fractions of 7Gy. Radiographic responses were assessed by annual MRI. Hormone blood samples were evaluated each year after HSRT.

Results: A total of 29 patients aged between 23 and 86 years (median 54 years) were included. Twelve patients received HSRT for recurrent cases and 12 received postoperative adjuvant HSRT, 5 patients did not have surgery. After a median follow-up period of 47 months local control rate was 96%. One patient presented an out-field tumor regrowth 73 months after HSRT. The majority of PA were endocrine-active (18 patients, 62%). After HSRT, 8 patients (44%) presented complete response on initial secretion, 4 patients (23%) presented partial response on initial secretion. Four patients (14%) presented grade 2 or more acute radiation toxicities. One grade 4 visual disorder was observed for one patient.

Conclusions: HSRT delivering 35Gy in 5 fractions represents a feasible treatment and shows promising results to reduce hormonal overproduction and to improve local control in PA.

Keywords: pituitary adenoma; stereotactic radiotherapy; endocrine-active; escalating dose

Running title: Escalating protocol of stereotactic radiotherapy for pituitary adenomas

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RESUME

Objectif de l'étude : Évaluer l'efficacité et la toxicité de la radiothérapie stéréotaxique hypofractionnée (HSRT) pour les patients traités pour un adénome hypophysaire (AH) avec un protocole d'escalade de dose délivrant 35Gy en 5 fractions.

Matériel et méthodes : De juin 2007 à mars 2017, 29 patients présentant un AH ont été traités, avec un protocole d'escalade de dose, à la dose de 35Gy en 5 fractions de 7Gy. Les réponses radiologiques ont été évaluées par IRM annuelle. Des bilans sanguins hormonaux ont été évalués chaque année après la HSRT.

Résultats : Au total, 29 patients âgés de 23 à 86 ans (médiane 54 ans) ont été inclus. Douze patients ont reçu une HSRT pour des récidives et 12 ont reçu une HSRT adjuvante, 5 patients n'ont pas eu de chirurgie. Après un suivi médian de 47 mois, le contrôle local était de 96 %. Un patient a présenté une récidive tumorale hors-champ 73 mois après HSRT. La majorité des AH étaient endocriniens sécrétants (18 patients, 62 %). Après HSRT, 8 patients (44 %) ont présenté une réponse complète à la sécrétion initiale et 4 patients (23 %) ont présenté une réponse partielle. Quatre patients (14 %) ont présenté des toxicités aiguës de grade 2 ou plus. Un trouble visuel de grade 4 a été observé chez un patient.

Conclusions : La HSRT délivrant 35Gy en 5 fractions est un traitement réalisable et montre des résultats prometteurs pour réduire la surproduction hormonale et améliorer le contrôle local de l'AH.

Mots-clés : adénome hypophysaire ; radiothérapie stéréotaxique ; escalade de dose ; sécrétant

Fractionated Stereotactic Radiation Therapy for Pituitary Adenomas: an alternative escalating protocol of hypofractionated stereotactic radiotherapy delivering 35 Gy in 5 fractions.

S. Sumodhee

Background

Pituitary adenomas (PA) are divided into endocrine-active (functioning) and nonfunctioning PA and treatment goals differ between the two entities. Treatment of nonfunctioning PA is intended to control tumor growth and prevent or reverse visual disorders and endocrine deficiencies. One of the main goals of the treatment for functioning PA is hormonal remission and normalization [1,2]. Surgery is the standard treatment, which can often be curative. However, recurrence after surgery has been reported in 24% to 80% of cases according to previous studies, with higher recurrence rates in endocrine-active tumors and more aggressive subtypes [3,4].

Radiotherapy represents an option for inoperable or recurrent PA. Stereotactic radiation technique including single fraction radiosurgery (SRS) or conventional fractionated stereotactic radiotherapy (FSRT) is widely reported as an effective treatment of PA [4–14]. Stereotactic radiation techniques mainly involved Gamma Knife® system or the CyberKnife® system [3,9–13,15–19]. Until now, the majority of published studies used the Gamma Knife® system as the technique for SRS and dose was mainly delivered in one fraction. Hypofractionated stereotactic radiotherapy (HSRT) has been described as an attractive alternative treatment option for lesions near to optic tracts by some authors [14,16,17]. Dose per fraction used in these reports varied from 5 Gy (marginal total dose 25 Gy) to 7 Gy (total marginal dose 21 Gy).

Despite good results on control growth varying from 87% to 100%, hormonal control still remains a problem for endocrine-active PA [8]. Endocrine remission varies from 14% to 66.9% after SRS [15,20–22]. Results after HSRT appear similar with hormonal normalization rates varying from 17% to 54% although data are limited [14,16,17].

It has been reported that using prescription doses lower than the standard dose may increase the recurrence rate of non-functioning PA [3]. Studies evaluating SRS with Gamma Knife® system suggested that higher margin radiation dose is significantly associated with better control of adenoma growth and biochemical remission [3,20].

We hypothesized that an escalating dose of 35 Gy in 5 fractions of 7 Gy, using an advanced precision delivery platform, yields better efficacy without increased toxicity.

The aim of our study was to evaluate this hypothesis for patients treated for PA with an alternative HSRT escalating protocol delivering 35 Gy in 5 fractions.

Methods

After obtaining approval from the Institutional Review Board, clinical and radiation data were retrospectively collected from all consecutive patients treated in Antoine Lacassagne Cancer Centre between June 2007 and March 2017, with an alternative HSRT protocol delivering 35 Gy in 5 fractions using CyberKnife® irradiation system. Individual informed consent was obtained from all participants included in the study.

All patients received routine preoperative endocrine studies before surgery or radiotherapy delivery. Based on the decision of a multidisciplinary team, HSRT was proposed as primary (in case of non-operable PA), adjuvant or delivered after recurrence or failure to achieve satisfactory hormonal control. The multidisciplinary team included neurosurgeons, radiation oncologists, endocrinologists and radiologists.

Of the 32 patients selected for this study, three were excluded due to attrition. This brought the total sample size to 29 patients.

Radiation Parameters

The CyberKnife® system (Accuray, Sunnyvale, CA, USA) is equipped with a 6-MV photon beam linear accelerator mounted on a robotic arm which allows 6 degrees of freedom. A specific Target Locating System allows to perform intra-fraction corrections with high precision and a geometrical accuracy of up to 0.5 mm. Radiation treatment was planned using the Computed Tomography (CT)- based 3D treatment planning system Multiplan® (Accuray, Sunnyvale, CA, USA) with a ray-tracing algorithm for dose calculation.

CT images of 1.25 mm-thickness in supine position were acquired. Custom thermoplastic face masks (Qfix, Aquaplast-RT) were used for immobilization. For each patient, a Magnetic Resonance Imaging (MRI) was performed and T1-weighted contrast-enhanced images were obtained and then fused with CT images. Gross Tumor Volume (GTV), Clinical Target Volume (CTV) and organs at risks (OAR) were contoured using MRI and/or CT on Multiplan®. GTV is represented by the lesion visible on MRI/CT. The CTV includes microscopic disease. In general, additional margin expansion from GTV to CTV is unnecessary in pituitary adenomas; however, a small margin may be added in the intracavernous portion of aggressive adenomas to encompass potential areas of microscopic tumor infiltration. [23]. Planning Target Volume (PTV) was considered as equal to the Clinical Target Volume, except for small volume (inferior 1cc) where a margin was adopted for the physic optimization, in order to improve precision for planning optimization and dose calculation. For all cases, an inverse planning algorithm was used in order to design a conformal treatment plan. Dose objectives and constraints were set in order to achieve PTV

coverage with prescription dose and to spare critical structures in particular optic tracts and brainstem.

The planned dose was 35 Gy delivered in 5 fractions and radiation dose was prescribed on an isodose encompassing the PTV. Planification parameters were fixed so that the prescribed isodose covered more than 95% of the PTV. The selected isodose was generally 80%, but physician or physicist could choose to adjust the prescribed dose (from 78% to 82%) in order to improve coverage or to protect OAR. The constraint for optics tracts was $D_{max} < 25$ Gy. Constraints for brainstem was $D_{max} < 31$ Gy and $D_{0.5cc} < 21$ Gy. For some challenging cases, the dose delivered to critical structures (in particularly for optics tracts) exceeded tolerances. In these cases, physicians and physicists discussed to find a compromise between coverage and dose to OAR.

Follow-up

Clinical and radiographic follow-up was performed annually, and included both the radiation oncologist and the referring neurosurgeon after radiotherapy. Post-radiotherapy endocrine status was monitored by an endocrinologist or by the radiation oncologist every year. The following hormones were tested: follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), free thyroxin (fT4), cortisol, testosterone, prolactin, adrenocorticotropic hormone (ACTH), and insulin-like growth factor 1 (IGF-1). A complete hormonal response was defined by normalization of the hormonal level dosage without the need for antihormonal treatment. A partial hormonal response was defined either by a minimal 50% decrease of the initial level or normalization with the need for antihormonal treatment. Endocrine progression was defined as an increase of at least 20% of the hormonal secretion level and/or the subsequent need for antihormonal treatment. Pituitary deficiency was defined by a decrease in one or more hormones below normal and the need to

receive hormonal treatment to substitute for the TSH, FSH-LH, or ACTH axis. Ophthalmology examination was performed every 3 months for symptomatic patients with refraction test, visual field examination, ophthalmoscopy, slit lamp examination and tonometry. MRI was performed before each clinical examination. T1-weighted images after application of Gadolinium and T2-weighted images with slice thickness of 3–5 mm were included. Radiographic complete response was defined as complete disappearance of residual tumor. Radiographic partial response was defined as a decrease of at least 20% of the initial tumor volume.

Data Analysis

Frequency distributions and summary statistics were calculated for all clinical and radiographic variables. Fisher exact tests were used to compare distributions for categorical variables, and t-tests were used to investigate differences in the distributions of continuous variables between subsets of patients classified by dichotomous data. Tumor control and overall survival were estimated using the Kaplan–Meier method calculated from the start of the radiotherapy.

Results

Patients Demographics and Clinical Presentations

A total of 29 patients were included in this study including 16 women and 13 men. Median age was 54 years [range, 23-86]. Twenty-four patients had surgery before radiotherapy. Four patients did not have surgery before primary radiotherapy because of their health status and one because the patient refused surgery. After surgery, radiotherapy was adjuvant for 9 patients (37%) and delivered for recurrence to 15 patients (73%). The main clinical

presentation was acromegaly for 7 patients (24%), pituitary deficiency for 5 patients (17%) and Cushing syndrome for 4 patients (14%). According to Wilson-Hardy classification [24], 18 patients (48%) presented Grade IV PA at the time of initial intervention. The majority of PA were endocrine-active (18 patients, 62%). All clinical data are summarized in Table 1.

Radiation data

All patients were treated by a total dose of 35 Gy in 5 fractions. The mean prescribed isodose was 80.46% [range, 78-90]. The mean chiasma maximum dose was 20.8 Gy [range, 9.6-32.6] and chiasma maximum dose was superior to 25 Gy for 3 patients. All radiation data are summarized in Table 2.

Clinical outcomes

After a median follow-up period of 47 months [range, 12–121], overall survival and local control rates were 96% and 96%, respectively (Figures 1 and 2). Only one patient presented an out-field tumor regrowth 73 months after HSRT. Two patients (7%) presented complete radiographic response. Twelve (41%) patients presented partial objective response after HSRT. For these patients the mean reduction of volume was 45% [range, 14-78%]. Fourteen patients (48%) presented radiologic stabilization (Table 3).

Functional Outcomes

Eighteen patients (62%) presented an endocrine-active adenoma before HSRT. After HSRT, 8/18 patients (44%) presented complete response on initial secretion, 4/18 patients (23%) presented partial response on initial secretion (normalization with the need for antihormonal treatment in each case) and 6/18 patients (33%) presented no change (stabilization) on initial secretion. None of the patients presented worsening on initial secretion.

Toxicity profile

Four patients (14%) presented grade 2 or more acute radiation toxicities including headache (3 patients, grade 2) and nerve injury (neuropathic pain of V_1 and V_2 nerves) (1 patient, grade 3 treated by analgesia and short course of steroids.). All acute toxicities disappeared during the months following radiotherapy.

One grade 4 visual disorder was observed for one patient (unilateral cecity). For this particular patient, optic chiasma maximum dose was 32.6 Gy and chiasma volume receiving more than 25 Gy was 0.07 ml. No other visual disorder was observed for other patients.

Seven patients (24%) presented pituitary deficiencies before radiotherapy. After radiotherapy, 1/7 patients (14%) presented worsening of hormonal deficiencies. For the 22 other patients without pituitary deficiencies, 4 patients (18%) presented new post-radiotherapy hormonal deficiencies linked to HSRT (1 patient presented central hypothyroidism, 1 patient presented secondary adrenal deficiency, 2 patients presented mixed deficiency).

Discussion

This study presents the outcomes of 29 patients treated for PA with an alternative HSRT protocol using the CyberKnife® system to deliver 35 Gy in 5 fractions. We report a local tumor control rate of 96% and tumor volume shrinkage in 48% of cases with a median follow-up of 47 months. Our results are similar to previous studies with comparable follow-up evaluating local tumor control rate after SRS (87% -100%) [9–13] or FSRT (91%-100%) [4–8,25] as summarized in Table 4.

Endocrine-active PA are notoriously difficult to treat with radiotherapy when the goal is hormone control. In a review of five clinical studies with a total of 115 patients, Minniti et al.

report a biochemical cure rate of 36-80% after FSRT with a total dose between 45 and 52.5 Gy [26]. Endocrine remission varies from 14% to 66.9% after SRS according to the previous main studies [15,19–22]. Puataweepong et al. [19] described a local control of 97.5% and an endocrine remission of 54% with 13 endocrine-active PA and with a margin dose of 25 Gy. It is a little bit better than in our study but Killory et al. [16] find poorer endocrine control (20%) than Puataweepong et al. with the same fractionation.

Only a few previous studies described endocrinal remission rates after HSRT (maximal marginal dose 25 Gy in 5 fractions) showing endocrinal remission varying from 17 to 54% [14,16,17]. Comparing hormonal normalization between studies is difficult because of differences in baseline characteristics such as endocrinal-secretion type, pretreatment hormone levels, and difference in the definition of hormonal normalization [18].

Nevertheless, our study has demonstrated a relatively high hormone control rate for endocrine-active PA showing 44% of hormonal remission rate (without medication) and 23% hormonal normalization with the need for antihormonal treatment. Hormonal control after radiotherapy for endocrine-active PA remains challenging and the higher delivered dose in our study could be an opportunity to increase hormonal control. Lee et al. showed patients treated with a margin dose > 25 Gy and a maximum dose > 50 Gy with Gamma Knife® (SRS protocol) had better hormonal control and faster remission than other patients [20].

Higher dose efficacy on hormonal control still remains unclear after HSRT. However, using higher doses increases risk of side effects.

Hypothalamic-pituitary dysfunction is the most common complication of treatment for PA after FSRT or SRS. In our series, four patients developed a new hormone deficiency and one patient presented worsening on hormonal deficiencies, representing 5/29 patients (17%) with hypopituitarism directly linked to radiotherapy. According to a review by Minniti et al. [27],

3-40% of patients developed a radiation hypopituitarism after SRS or HSRT and 4-40% after FSRT, which is largely in line with our results.

Radiation-induced visual side-effect is also a major complication, especially for tumors close to optic tracts. In our study, one patient experienced grade 4 visual deficit. For this particular patient, constraints on optic tracts were largely exceeded (optic chiasma maximum dose was 32.6 Gy). No other patient experienced visual side-effect. For the other patients, optic chiasma maximum dose varied from 9.6 Gy to 25.2 Gy. Our results for incidence of visual deficits were similar to other studies of patients treated by HSRT for PA close to optic tracts [14,19,28]. These outcomes corroborate previous studies using SRS or FSRT which ranged between 0% and 7.5% [27].

Limitations of this study include its retrospective nature and the limited length of the follow-up (47 months). According to literature, patients usually develop a delayed onset of hypopituitarism 3 years after SRS. However, some cases has been described more than 10 years after radiotherapy [29] and our length of follow-up might be too short to conclude to the exact rate of new hypopituitarism.

Nonetheless, our length of follow-up seems sufficient to detect visual side-effects. Indeed, Adler et al. described that all decline in vision had occurred within the first 24 months after treatment for patients who had undergone radiotherapy for peri-optic masses [28].

Furthermore, other side-effects as neurocognitive degradation or vascular side-effects were optimally evaluated, although there were no reports of memory or cognitive difficulties on the clinical database.

Our escalating-dose design protocol showed low side-effects compared to other studies. Hormonal control after radiotherapy for endocrine-active PA remains challenging especially for tumors with low-prognostic outcomes. The high doses used in our protocol could be a solution to increase hormonal remission as suggested by our promising results on secretion.

Extended follow-up and prospective studies comparing fractionation are thus needed to confirm the results suggested by our study.

Conclusions

HSRT delivering 35 Gy in 5 fractions represents a feasible treatment and shows promising results to reduce hormonal overproduction and to improve local control in PA. However, the dose to the optic tract must be controlled with caution and no compromise to the optic tract constraints should be made. Extended follow-up and prospective studies are needed to confirm this strategy.

Declarations:

- Ethics approval and consent to participate: institutional review board approval (retrospective analysis)
- Competing interests: The authors declare that they have no competing interests
- Funding: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

- **List of abbreviations:**

  ACTH: adrenocorticotropic hormone
  CT: computed tomography
  CTV: clinical target volume
  FSH: follicle stimulating hormone
  FSRT: conventional fractionated stereotactic radiotherapy
  fT4: free thyroxin
  GTV: gross tumor volume
  HSRT: hypofractionated stereotactic radiotherapy
  IGF1: insulin-like growth factor 1
  LH: luteinizing hormone

MRI: magnetic resonance imaging
OAR: organ at risk
PA: pituitary adenoma
PTV: planning target volume
SRS: single fraction radiosurgery
TSH: thyroid stimulating hormone

References

[1] Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab 2009;94:1509–17. https://doi.org/10.1210/jc.2008-2421.

[2] Laws ER, Thapar K. Pituitary surgery. Endocrinol Metab Clin North Am 1999;28:119–31. https://doi.org/10.1016/s0889-8529(05)70059-1.

[3] 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;114:303–9. https://doi.org/10.3171/2010.5.JNS091635.

[4] Campbell PG, Kenning E, Andrews DW, Yadla S, Rosen M, Evans JJ. Outcomes after a purely endoscopic transsphenoidal resection of growth hormone-secreting pituitary adenomas. Neurosurg Focus 2010;29:E5. https://doi.org/10.3171/2010.7.FOCUS10153.

[5] Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. Clin Endocrinol (Oxf) 2006;64:542–8. https://doi.org/10.1111/j.1365-2265.2006.02506.x.

[6] Roug S, Rasmussen AK, Juhler M, Kosteljanetz M, Poulsgaard L, Heebøll H, et al. Fractionated stereotactic radiotherapy in patients with acromegaly: an interim single-centre audit. Eur J Endocrinol 2010;162:685–94. https://doi.org/10.1530/EJE-09-1045.

[7] Colin P, Jovenin N, Delemer B, Caron J, Grulet H, Hecart A-C, et al. Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. Int J Radiat Oncol Biol Phys 2005;62:333–41. https://doi.org/10.1016/j.ijrobp.2004.09.058.

[8] Barber SM, Teh BS, Baskin DS. Fractionated Stereotactic Radiotherapy for Pituitary Adenomas: Single-Center Experience in 75 Consecutive Patients. Neurosurgery 2016;79:406–17. https://doi.org/10.1227/NEU.0000000000001155.

[9] Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, et al. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. J Neurosurg 2013;119:446–56. https://doi.org/10.3171/2013.3.JNS12766.

[10] Liscák R, Vladyka V, Marek J, Simonová G, Vymazal J. Gamma knife radiosurgery for endocrine-inactive pituitary adenomas. Acta Neurochir (Wien) 2007;149:999–1006; discussion 1006. https://doi.org/10.1007/s00701-007-1253-7.

[11] Park K-J, Kano H, Parry PV, Niranjan A, Flickinger JC, Lunsford LD, et al. Long-term outcomes after gamma knife stereotactic radiosurgery for nonfunctional pituitary adenomas. Neurosurgery 2011;69:1188–99. https://doi.org/10.1227/NEU.0b013e318222afed.

[12] Starke RM, Williams BJ, Jane JA, Sheehan JP. Gamma Knife surgery for patients with nonfunctioning pituitary macroadenomas: predictors of tumor control, neurological

deficits, and hypopituitarism. J Neurosurg 2012;117:129–35. https://doi.org/10.3171/2012.4.JNS112250.
[13] Mingione V, Yen CP, Vance ML, Steiner M, Sheehan J, Laws ER, et al. Gamma surgery in the treatment of nonsecretory pituitary macroadenoma. J Neurosurg 2006;104:876–83. https://doi.org/10.3171/jns.2006.104.6.876.
[14] Liao H-I, Wang C-C, Wei K-C, Chang C-N, Hsu Y-H, Lee S-T, et al. Fractionated stereotactic radiosurgery using the Novalis system for the management of pituitary adenomas close to the optic apparatus. J Clin Neurosci 2014;21:111–5. https://doi.org/10.1016/j.jocn.2013.03.024.
[15] Tanaka S, Link MJ, Brown PD, Stafford SL, Young WF, Pollock BE. Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas. World Neurosurg 2010;74:147–52. https://doi.org/10.1016/j.wneu.2010.05.007.
[16] Killory BD, Kresl JJ, Wait SD, Ponce FA, Porter R, White WL. Hypofractionated CyberKnife radiosurgery for perichiasmatic pituitary adenomas: early results. Neurosurgery 2009;64:A19-25. https://doi.org/10.1227/01.NEU.0000341630.42160.18.
[17] Iwata H, Sato K, Tatewaki K, Yokota N, Inoue M, Baba Y, et al. Hypofractionated stereotactic radiotherapy with CyberKnife for nonfunctioning pituitary adenoma: high local control with low toxicity. Neuro-Oncology 2011;13:916–22. https://doi.org/10.1093/neuonc/nor055.
[18] Iwata H, Sato K, Nomura R, Tabei Y, Suzuki I, Yokota N, et al. Long-term results of hypofractionated stereotactic radiotherapy with CyberKnife for growth hormone-secreting pituitary adenoma: evaluation by the Cortina consensus. J Neurooncol 2016;128:267–75. https://doi.org/10.1007/s11060-016-2105-1.
[19] Puataweepong P, Dhanachai M, Hansasuta A, Dangprasert S, Swangsilpa T, Sitathanee C, et al. The Clinical Outcome of Hypofractionated Stereotactic Radiotherapy With CyberKnife Robotic Radiosurgery for Perioptic Pituitary Adenoma. Technol Cancer Res Treat 2016;15:NP10–5. https://doi.org/10.1177/1533034615607113.
[20] Lee C-C, Vance ML, Xu Z, Yen C-P, Schlesinger D, Dodson B, et al. Stereotactic radiosurgery for acromegaly. J Clin Endocrinol Metab 2014;99:1273–81. https://doi.org/10.1210/jc.2013-3743.
[21] Grant RA, Whicker M, Lleva R, Knisely JPS, Inzucchi SE, Chiang VL. Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report. World Neurosurg 2014;82:195–201. https://doi.org/10.1016/j.wneu.2013.01.127.
[22] Boström JP, Kinfe T, Meyer A, Pintea B, Gerlach R, Surber G, et al. Treatment of acromegaly patients with risk-adapted single or fractionated stereotactic high-precision radiotherapy: High local control and low toxicity in a pooled series. Strahlenther Onkol 2015;191:477–85. https://doi.org/10.1007/s00066-014-0802-2.
[23] Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumors. Radiat Oncol 2016;11:135. https://doi.org/10.1186/s13014-016-0710-y.
[24] Wilson CB. A decade of pituitary microsurgery. The Herbert Olivecrona lecture. J Neurosurg 1984;61:814–33. https://doi.org/10.3171/jns.1984.61.5.0814.
[25] Kim JO, Ma R, Akagami R, McKenzie M, Johnson M, Gete E, et al. Long-term outcomes of fractionated stereotactic radiation therapy for pituitary adenomas at the BC Cancer Agency. Int J Radiat Oncol Biol Phys 2013;87:528–33. https://doi.org/10.1016/j.ijrobp.2013.06.2057.
[26] Minniti G, Scaringi C, Amelio D, Maurizi Enrici R. Stereotactic Irradiation of GH-Secreting Pituitary Adenomas. Int J Endocrinol 2012;2012:482861. https://doi.org/10.1155/2012/482861.

[27] Minniti G, Flickinger J, Tolu B, Paolini S. Management of nonfunctioning pituitary tumors: radiotherapy. Pituitary 2018;21:154–61. https://doi.org/10.1007/s11102-018-0868-4.
[28] Adler JR, Gibbs IC, Puataweepong P, Chang SD. Visual field preservation after multisession cyberknife radiosurgery for perioptic lesions. Neurosurgery 2006;59:244–54; discussion 244-254. https://doi.org/10.1227/01.NEU.0000223512.09115.3E.
[29] Höybye C, Grenbäck E, Rähn T, Degerblad M, Thorén M, Hulting AL. Adrenocorticotropic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. Neurosurgery 2001;49:284–91; discussion 291-292. https://doi.org/10.1097/00006123-200108000-00008.