Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response

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Abstract

Objective: We describe the use of fractionated stereotactic radiotherapy (FSRT) for the treatment of large, invasive, nonfunctioning pituitary adenomas (NFPAs). FSRT is frequently employed for the treatment of residual or recurrent pituitary adenomas.

Patients and methods: Sixty-eight patients with a large residual or recurrent NFPAs were treated between April 2004 and December 2012, including 39 males and 29 females (median age 51 years). Visual defects were present in 34 patients, consisting of visual field defects ($n=31$) and/or reduced visual acuity ($n=12$). Forty-five patients had evidence of partial or total hypopituitarism before FSRT. For most of the patients, the treatment was delivered through 5–10 noncoplanar conformal fixed fields using a 6-MV linear accelerator to a dose of 45 Gy in 25 fractions.

Results: At a median follow-up of 75 months (range 12–120 months), the 5- and 10-year actuarial local control were 97 and 91%, respectively, and overall survival 97 and 93%, respectively. Forty-nine patients had a tumor reduction, 16 remained stable, and three progressed. The relative tumor volume reduction measured using three-dimensional (3D) magnetic resonance imaging (MRI) was 47%. The treatment was well tolerated with minimal acute toxicity. Eighteen patients developed partial or complete hypopituitarism. The actuarial incidence of new anterior pituitary deficits was 40% at 5 years and 72% at 10 years. No other radiation-induced complications occurred.

Conclusions: Our results suggest that FSRT is an effective treatment for large or giant pituitary adenomas with low toxicity.

European Journal of
Endocrinology
(2015) 172, 433–441

Introduction

Surgery is the treatment of choice in the management of nonfunctioning pituitary adenomas (NFPAs) (1); however, in case of large and/or invasive pituitary adenomas, their removal by using either transsphenoidal or transcranial approaches is technically challenging, and a significant proportion of NFPAs will regrow, requiring further treatments (2, 3).

Stereotactic techniques have been employed in patients with incomplete resected benign skull base tumors, with the aim of delivering more accurate and focused irradiation with a steeper dose gradient between the tumor and the surrounding normal tissue, possibly reducing the long-term toxicity of radiation. Both stereotactic radiosurgery (SRS) and fractionated stereotactic

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radiotherapy (FSRT) at doses of 45–54 Gy delivered in 25–30 daily fractions are effective treatment options for patients with a residual or progressive pituitary adenoma with a reported 5-year local control in the region of 80–95% (4).

SRS is a convenient treatment for patients with either secreting or nonfunctioning pituitary tumors. However, caution should be used in treating patients with moderate- or large-sized lesions (>3 cm in size) of the skull base in close proximity to critical structures, such as the optic chiasm and brainstem for the risk of long-term radiation-induced toxicity (5). For such patients, FSRT may be a safer treatment option because of the radiobiological advantages of dose fractionation in reducing the risk of long-term toxicity. Studies of FSRT including either nonfunctioning or secreting pituitary adenomas of any size have shown tumor local control of more than 90% at 5 years (4), although most published work includes only a few patients with lesions larger than 3–4 cm.

We report our experience with postoperative FSRT in patients with large and invasive NFPA. Long-term clinical outcomes and volumetric magnetic resonance imaging (MRI) analysis of tumor response were evaluated.

Patients and methods

Patients

Between April 2004 and December 2012, 156 patients with a diagnosis of a pituitary adenoma were treated in the Unit of Radiation Oncology at Sant' Andrea Hospital, University of Rome Sapienza. Ninety-five patients had an NFPA and 61 patients a secreting adenoma. Among patients with an NFPA, 27 were excluded because of tumor size (≤ 3 cm) or a different type of radiation treatment (single-fraction or multi-fraction SRS). Finally, we have analyzed 68 patients with an NFPA > 3 cm in size as determined by MRI at the time of FSRT. All patients underwent physical examination, formal assessment of visual fields, and measurement of visual acuity. The diagnosis of pituitary hormone deficiency before FSRT and during the subsequent follow-up was based on the measurement of basal hormone levels and dynamic testing performed in different hospital laboratories using commercial immune assays for analysis. Central hypothyroidism was defined as a low free-thyroxine value with a normal level of thyroid-stimulating hormone (TSH). Corticotrophic deficiency was defined as baseline cortisol <100 nmol/l or cortisol <500 nmol/l following a standard dose adrenocorticotrophic hormone (ACTH) stimulation testing (250 μ g Synacthen i.v.). Gonadotrophin deficiency

in males was defined as low testosterone serum concentration (<10 nmol/l) in combination with inadequate low gonadotropins (luteinizing hormone (LH), follicle-stimulating hormone (FSH)). In females, gonadotrophin deficiency was defined as amenorrhea with a low estradiol level and gonadotropins within the normal range, or a low estradiol with premenopausal gonadotropins in post-menopausal women. Growth hormone (GH) deficiency was defined as low age-adjusted insulin-like growth factor 1 (IGF1) level and/or GH peak following the GH-releasing hormone (GHRH)/arginine test adjusted for BMI. Patients' data were obtained from a prospectively maintained database of patients with brain tumors treated with brain stereotactic irradiation at our institution.

FSRT treatment

All tumors were treated with FSRT using a dose of 45–50.4 Gy in 25–28 daily fractions of 1.8 Gy. The characteristics of the system and the technique has been previously described (6). Patient immobilization was achieved by using a commercially available head mask fixation system (Brainlab AG, Feldkirchen, Germany), together with a mouth bite positioned against the upper dentition and attached to the stereotactic frame. The target volumes were identified using fused computerized tomography (CT) and MRI scans performed at the time of FSRT. The gross tumor volume (GTV) was delineated as a contrast-enhancing tumor demonstrated on three-dimensional (3D) postcontrast T1-weighted magnetization-prepared rapid gradient-echo images (MP-RAGE) or postcontrast T1-weighted fat-suppressed images with 1 mm slice reconstruction and 0.5 mm axial pixel resolution. The clinical target volume (CTV) was equal to the GTV. The planning target volume (PTV) was generated by the geometric expansion of GTV plus 2 ($n=43$) or 3 ($n=25$) mm. Lenses, eyes, optic nerves, optic chiasm, brainstem, temporal lobes, hippocampi, and cochleae were contoured. An example of treatment planning is represented in Fig. 1. Treatment volumes were achieved with 5–10 noncoplanar conformal beams by using a BrainLab m3 micromultileaf collimator attached to a Varian Clinac 600 DBX. Doses were prescribed to the 85–95% isodose line normalized to the maximum dose to ensure coverage of at least 95% of the PTV with the prescription dose.

Follow-up and data analysis

A complete basal hormonal assessment and dynamic testing, as appropriate, were performed every 6 months to evaluate the pituitary function. The effect of treatment on

Figure 1

An example of the dose distribution in axial (A), sagittal (B), and coronal (C) views of a large nonfunctioning pituitary adenoma treated with fractionated stereotactic radiotherapy (FSRT). Multiple noncoplanar beams were used in order to achieve the best dose homogeneity and conformity for the target while reducing doses to the adjacent organs at risk. Isodose lines (range 15.0–47.2 Gy) covering the planning target volume (PTV) and surrounding brain structures are shown. The left and right hippocampi were encompassed by the 15–22.5 Gy isodose line (E, F, and G). Figure 1H shows a 3D cranial view of the PTV (red), the organs at risk (brainstem, yellow; right hippocampus, purple; left hippocampus, green), and beam entrance positions.

vision was assessed through serial ophthalmological examinations with visual field testing. An MRI scan was performed 3 months after the end of FSRT and thereafter annually. Tumor control was defined by the absence of radiological progression of the adenoma. Complete response was defined as ‘complete disappearance’ of the adenoma, ‘partial response’ was defined as any tumor shrinkage, ‘stable disease’ was defined as no tumor shrinkage, and ‘progression’ was defined as any tumor growth. Changes in tumor volume over time were calculated using 3D volumetric assessment with a BrainLab Brainscan (version 3.2) or iPlan (version 4.1) treatment planning system workstation and were evaluated after fusion of pre-treatment and posttreatment MRI scans.

Tumor control and overall survival were estimated using the Kaplan–Meier method calculated from the start of FSRT. Changes in tumor volume over time were assessed by the nonparametric Wilcoxon signed-rank test.

Results

Patients and tumor characteristics are summarized in Table 1. Based on pre-FSRT MRI scan, 51 patients had an

NFPA of 3–4 cm in size, and 17 patients had an adenoma >4 cm. The lesions were extended to one or both cavernous sinuses in 19 and 49 cases respectively. Forty-nine patients received FSRT after surgery, and the other 19 patients had FSRT for tumor progression. Forty-two patients had more than one surgical intervention. Vision was impaired in 34 patients, consisting of visual field defects ($n=31$) and/or reduced visual acuity ($n=12$). A partial or complete hypopituitarism before FSRT was present in 18 and 27 patients respectively. The median GTV was 22.6 cm³ (range 11.1–52.2 cm³), and the median PTV was 33.2 cm³ (range 20.3–82.7 cm³). All tumors had the pituitary gland and the optic chiasm, at least in part, included in the PTV. The mean hippocampus volume was 3.1±0.65 cm³. The average mean doses to the left hippocampus, right hippocampus, and bilateral hippocampi were 10.1±4.8 Gy (range 1.4–52.8 Gy), 10.6±5.0 Gy (range 1.8–53.3 Gy), and 10.2±4.9 Gy (range 2.9–53.3 Gy) respectively. Sixty-four patients were given a dose of 45 Gy and four patients with a silent corticotroph pituitary adenoma were given a dose of 50.4 Gy in daily fractions of 1.8 Gy.

Table 1 Patient and treatment characteristics.

Sex (M/F)	39/29
Median age (years) (range)	51 (22–74)
KPS	
70–80	15
90–100	53
Number of surgeries	
1/2/3	31/26/11
Pituitary function	
Normal	23
Hypopituitarism	45
Vision	
All	34
Visual field deficit	31
Reduced visual acuity	12
Tumor extension	
Size 3–4 cm	51
Size >4 cm	17
Suprasellar	68
Cavernous sinus	68
Gross tumor volume (GTV) (cm ³)	
Median	22.6
Range	11.1–52.2
Planning target volume (PTV) (cm ³)	
Median	33.2
Range	20.3–82.7
Radiation dose/fractions	
45 Gy/25 fractions	64
50.4 Gy/28 fractions	4

Figure 2

Local control (LC, dotted line) and overall survival (OS, continuous line) of 68 patients with nonfunctioning pituitary adenomas after FSRT.

Tumor control and survival

From April 2004 to December 2012, 68 patients with residual or recurrent NFPA > 3 cm in size were treated with FSRT. With a median follow-up of 75 months (range from 12 to 120 months), the 5- and 10-year local control rates were 97 and 91% respectively (Fig. 2). Three patients had an increase in tumor size after FSRT. One patient with a silent corticotroph adenoma progressed 72 months after FSRT and received six cycles of chemotherapy with the alkylating agent temozolomide; the tumor was stable at the last follow-up (May 2014). The other two patients had salvage transcranial surgery 36 and 84 months, respectively, after FSRT. One patient had no further progression, and one patient died a few days postoperatively. One additional patient died during follow-up for causes considered unrelated to their pituitary tumor or the radiation treatment (lung cancer). The 5- and 10-year overall survival rates were 97 and 93%, respectively, and disease-specific survival was 97%.

Volumetric assessment

The median tumor volume of all the adenomas before FSRT was 22.6 cm³ (range 11.1–52.2 cm³). With a median radiological follow-up of 72 months, the median absolute and relative volume reductions were 10.8 ml (range 0–21.5 ml) and 47% (range 0–100%) respectively. Volume changes over time are shown in Fig. 3. Compared with pre-treatment volumes, the median relative tumor shrinkages were 0.8 ml ($P=0.04$), 3.1 ml ($P=0.01$), 6.6 ml ($P=0.0001$), and 9.7 ml ($P=0.0001$) at 1, 3, 5, and

7 years after FSRT respectively. The largest volume reduction, as compared with the pre-treatment volume, was observed between 60 and 84 months after FSRT. Fourteen patients had a transient enlargement of their tumor at 3 months. Subsequent follow-up revealed a tumor volume reduction in all of these patients (median reduction 44%). An example of transient tumor enlargement is shown in Fig. 4. Overall, there was a reduction in the size of the tumors of 49 patients, no change in 16 patients, and progression in three patients. In two patients who had tumor progression, the tumor volume increased after an initial shrinkage (Fig. 5). No factors correlated with tumor response, including tumor volume, sex, timing of FSRT, or age.

Vision

Thirty-four patients had impaired vision before FSRT. After radiation treatment, visual fields and visual acuity improved in 11 and two patients respectively. Visual improvement occurred in seven patients who received postoperative FSRT (median time to FSRT 3 months, range 1–4 months) and in six patients who were treated for recurrent tumors presenting with visual impairment. Two patients had mild 6th nerve palsy and two patients had mild visual field deterioration during or immediately after FSRT, which were promptly resolved with corticosteroids. Two patients developed visual defects as a result of tumor

Figure 3

Volumetric magnetic resonance imaging (MRI) assessment of tumor response after fractionated stereotactic radiotherapy (FSRT). There was a progressive reduction in tumor volume over time. The median relative tumor shrinkage was 0.8 ml ($P=0.4$), 3.1 ml ($P=0.01$), 6.6 ml ($P=0.0001$), and 9.7 ml ($P=0.0001$) at 1, 3, 5, and 7 years respectively.

Figure 4

Coronal and axial T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) scan of a nonfunctioning pituitary adenoma before (A) and after (B, C, D, and E) FSRT. After a transient tumor enlargement 3 months after FSRT (B), the tumor volume decreased over time (3 (C), 5 (D), and 7 (E) years after FSRT).

regrowth 36 and 84 months, respectively, after treatment. Cranial deficits (IV and VI palsy) were present in four patients and did not improve after FSRT. No new cases of cranial nerve deficit occurred as a result of FSRT.

Toxicity

The most common transient effect of FSRT was the development of localized alopecia at the beam entrance, occurring in about 90% of patients. Fatigue occurred in 16 (24%) patients, lasting for up to 6–8 weeks after FSRT. Headache, nausea, and alteration of taste occurred in five, three, and four patients respectively.

Hypopituitarism was the most common long-term side effect of pituitary irradiation. Before FSRT, pituitary function was normal in 23 patients and impaired in 45 patients, as result of a complete ($n=27$) or a partial hypopituitarism ($n=18$). Specific abnormalities consisted of GH deficiency ($n=45$), TSH deficiency ($n=29$), ACTH deficiency ($n=24$), and hypogonadotropic hypogonadism ($n=36$). A worsening of a pre-existing partial hypopituitarism or the development of new hormonal deficits occurred in eight and ten patients, respectively, requiring new hormone replacement therapy with GH ($n=10$), gonadal steroids ($n=9$), thyroxine ($n=11$), and hydrocortisone ($n=9$). The actuarial incidence of new anterior pituitary deficits was 40% at 5 years and 72% at 10 years. No correlation was found between the treated volume and the development of hypopituitarism. No clinically apparent neurocognitive dysfunctions or other possible radiation-induced toxicities (i.e., cerebrovascular accidents or second tumors) have been observed during the follow-up. Posttreatment follow-up demonstrated no detectable MRI

signal-intensity abnormalities of the hippocampal and parahippocampal cortex, amygdala, or uncus.

Discussion

Despite improvements in neurosurgical techniques, the treatment of large invasive pituitary adenomas remains challenging. A transsphenoidal approach using either endoscopic or microsurgical techniques results in a gross total resection in more than 50% of patients with large pituitary adenomas, with a relatively low rate of postoperative complications and no mortality (7, 8, 9). A transcranial approach may represent an effective treatment for large tumors with extensive suprasellar extension that is associated with a subtotal removal in up to 75% of tumors and an improvement of vision in more than half patients (10, 11, 12); however, major morbidity (e.g., cranial nerves deficits, hypothalamic and vascular injuries, and CSF leakages) and mortality have been reported in 18–25 and 2.7–4.4% of patients respectively.

SRS and FSRT are frequently employed in patients with progressive disease or residual tumors after incomplete resection. In our series, all patients who received FSRT had an invasive residual or progressive tumor > 3 cm. At a median follow-up of 75 months, the 5- and 10-year local control were 97 and 91%, respectively, and overall survival

Figure 5

Coronal T1-weighted gadolinium-enhanced magnetic resonance imaging (MRI) scan before (baseline) and after fractionated stereotactic radiotherapy (FSRT) showing tumor progression in two patients with large nonfunctioning pituitary adenomas. (Patient 1: A, B, and C) After an initial tumor volume reduction 12 months after FSRT (B) compared with baseline (A), MRI scan documents tumor progression 18 months later (C). (Patient 2: D, E, F, and G) Compared with baseline, MRI scan obtained 36 (E) and 60 months (F) after FSRT shows a relative reduction of 6 and 90% in tumor volume, followed by a tumor regrowth in the right cavernous sinus 12 months later (G).

was 97 and 93% respectively. In a series of 74 patients with pituitary macroadenomas >2 cm in size and who received fractionated conventional radiotherapy, Yildiz *et al.* (13) reported 5-year local control values of 91% in 44 patients with pituitary macroadenomas 2–4 cm in size and 73% in 30 patients with pituitary macroadenomas >4 cm. Fisher *et al.* (14) reported local control values of 80% at 10 years in 31 patients treated with surgical debulking followed by radiotherapy for giant adenomas of >4 cm. In another series of 67 patients treated at Royal Marsden Hospital with FSRT for NFPAs, most with suprasellar extension (median volume 12.2 cm³), the actuarial local control was 98% at 5 years (15), and similar results have been observed by others (16, 17, 18, 19, 20). Our results from this study confirm that FSRT is an effective treatment for patients with large or giant NFPAs, with a tumor control comparable with that reported after conventional external beam radiotherapy.

Most patients in our study were treated using microscopic or endoscopic transsphenoidal surgery followed by postoperative FSRT. The goal of combining less invasive surgical approaches and irradiation for large and invasive skull base tumors is to provide high long-term tumor control, possibly reducing the risk related to more aggressive surgical approaches. The 3% tumor recurrence rate observed at 5 years in the current study is consistent with or even better than that reported after complete excision of pituitary tumors (21, 22, 23) and supports a multimodal treatment strategy for patients with large and invasive pituitary tumors, especially in patients for whom attempting to achieve a gross total resection of their tumors carries significant risk of morbidity and mortality.

SRS at doses of 13–16 Gy is an effective treatment for NFPAs with a tumor control >90% at 5 years (24). It is an advantageous treatment option for patients with a pituitary adenoma in terms of convenience and comfort; however, single large doses may be associated with an increased risk for neurologic morbidity from radiation necrosis. The reported incidence of radiation-induced optic neuropathy after SRS is ~2% for doses of 8–12 Gy and increases to >10% for doses of 12–15 Gy (25, 26, 27, 28, 29, 30). In a recent study of 133 patients with pituitary adenomas having SRS, Pollock *et al.* (30) have observed no radiation-induced optic neuropathy when doses of 10- and 12-Gy were given to median volumes of optic chiasm of 1.6 (0.5–5.3) mm³ and 0.1 (0.1–0.6) mm³, respectively, estimating a chance of developing a radiation-induced optic neuropathy of 0–4.7 and 0–13.9%, respectively. In contrast, FSRT doses ≤50 Gy administered to the chiasm carry a ‘near

zero’ risk of optic neuropathy, and the risk remains ‘rare’ for doses ≤55 Gy (5). These results indicate that FSRT should be considered preferentially over SRS for patients with large tumors abutting or compressing the optic pathway, as was the case for the patients treated in this study.

SRS delivered in 2–5 fractions for tumors involving the optic apparatus has been advocated as an alternative treatment for tumors that are not suitable for single-fraction SRS (31, 32). Using doses of 18–24 Gy delivered in 2–5 sessions with Cyberknife, Adler *et al.* (31) reported high rates of tumor control and preservation of visual function in a small group of patients with pituitary adenomas within 2 mm of the optic apparatus, and similar results have been shown by others (32, 33). Interestingly, in a series of 30 patients with brain metastases treated with 5×5 Gy SRS, no radiation-induced optic neuropathy was reported when doses of 25 Gy or higher were administered to less than one-third of the optic chiasm (34). Although these data are of some reassurance, a larger series with a longer follow-up period is needed to confirm the efficacy of these hypofractionated treatment schedules in terms of tumor control and the risk of radiation-related adverse effects as compared with single-fraction SRS and FSRT.

Using a dose of 45 Gy in 1.8 daily fractions, 16 tumors remained stable, 49 decreased, and three progressed. Volumetric assessment using 3D-MRI showed a significant relative reduction of tumor volume 3 years after FSRT, and the reduction continued over time. Kopp *et al.* (35) assessed changes in tumor volume using 3D-MRI in 16 patients with a NFPAs treated with FSRT at doses of 45.0–50.4 Gy delivered in 28–28 daily fractions. With a median follow-up of 63 months, they found that all patients presented tumor shrinkage; the mean relative tumor volumes were 26, 47, and 62% at ≤36, 36–72, and >72 months after FSRT, respectively. In a series of 42 patients with NFPAs who received FSRT with a median dose of 50.4 Gy given in 28 fractions, Milker-Zabel *et al.* (16) reported no changes in the tumors in 28 patients and tumor reduction in 14 patients, based on CT or MRI analyses, after an average of 13 months. In another series of 68 patients with NFPAs treated with FSRT using 50.4 Gy in 28 fractions, Paek *et al.* (18) found that tumors were reduced in size in 26 patients and were unchanged in 41 patients. These data suggest that FSRT doses of 45–50.4 Gy may be administered to NFPAs achieving tumor control similar to that reported following higher doses (13, 16), possibly decreasing the incidence of late-stage complications.

The major concern regarding the use of fractionated radiotherapy is the development of late-stage effects. Hypopituitarism represents the most commonly reported

late-stage complication of RT, occurring in 30–60% of irradiated patients (36, 37, 38). In addition, lower but significant incidences of visual defects, cerebrovascular accidents, and second tumors have been reported (39, 40, 41). In the present series, the new development or worsening of hypopituitarism occurred in 40% of patients with normal pituitary function or partial hypopituitarism previously. No other complications, such as the development of second tumors, radionecrosis, cranial nerve deficits, and optic neuropathy, or cognitive decline have been observed during follow-up. Minimizing the radiation dose to the normal brain tissue through FSRT has the potential of reducing, but not eliminating, the risks of developing such complications.

There is still a considerable debate about the effect of radiation on neurocognitive function. Several authors have reported a correlation between cognitive decline and doses to the temporal lobe (42, 43, 44, 45), and these changes are thought to be related to hippocampal damage (46). Gondi *et al.* (47) demonstrated that biologically equivalent doses in 2-Gy fractions (EQD2) delivered to 40% of the bilateral hippocampi (D40%) > 7.3 Gy (assuming an α/β ratio of 2 Gy) were associated with long-term impairment in list-learning delayed verbal recall in 18 patients receiving FSRT for benign brain tumors. In contrast, Brummelman *et al.* (48) found no significant differences in cognitive performance among 30 patients who received radiotherapy for NFPA when mean doses up to 15.2 Gy were given to 50% of the hippocampal volume. Delivering a mean dose of 10 Gy to the bilateral hippocampi, we observed no clinically apparent neurocognitive deterioration over time; however, the lack of formal neurocognitive testing and the relatively short follow-up do not allow a definitive conclusion to be drawn. While a significant reduction in dose to the hippocampi is feasible with FSRT and may represent an effective therapeutic strategy to prevent radiation-induced neurocognitive decline, the exact dose-response relationship for neurocognitive impairment remains to be elucidated.

In conclusion, FSRT achieves effective control of tumor growth in large and invasive NFPA. Postoperative tumor shrinkage assessed by 3D volumetric MRI indicated that the majority of tumors shrink after FSRT, with tumor reduction that continues with time. Hypopituitarism represents the most common late morbidity, whereas other late complications rarely occur. Advantages of reducing the volume of normal brain irradiated at high doses with the use of stereotactic techniques with regard to neurocognitive function and other radiation-induced toxicities need to be assessed in future studies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- 1 Dekkers OM, Pereira AM & Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 3717–3726. (doi:10.1210/jc.2008-0643)
- 2 Murad MH, Fernández-Balsells MM, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, Lampropoulos JF, Natividad I, Perestelo-Pérez L, Ponce de León-Lovatón PG *et al.* Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. *Clinical Endocrinology* 2010 **73** 777–791. (doi:10.1111/j.1365-2265.2010.03875.x)
- 3 Mortini P, Losa M, Barzaghi R, Boari N & Giovannelli M. Results of transphenoidal surgery in a large series of patients with pituitary adenoma. *Neurosurgery* 2005 **56** 1222–1233. (doi:10.1227/01.NEU.0000159647.64275.9D)
- 4 Minniti G, Gilbert DC & Brada M. Modern techniques for pituitary radiotherapy. *Reviews in Endocrine & Metabolic Disorders* 2009 **10** 135–144. (doi:10.1007/s11154-008-9106-0)
- 5 Lawrence YR, Li XA, el Naqa I, Hahn CA, Marks LB, Merchant TE & Dicker AP. Radiation dose-volume effects in the brain. *International Journal of Radiation Oncology, Biology, Physics* 2010 **76** S20–S27. (doi:10.1016/j.ijrobp.2009.02.091)
- 6 Minniti G, Valeriani M, Clarke E, D'Arienzo M, Ciotti M, Montagnoli R, Saporetti F & Enrici RM. Fractionated stereotactic radiotherapy for skull base tumors: analysis of treatment accuracy using a stereotactic mask fixation system. *Radiation Oncology* 2010 **13** 5. (doi:10.1186/1748-717X-5-1)
- 7 Koutourousiou M, Gardner PA, Fernandez-Miranda JC, Paluzzi A, Wang EW & Snyderman CH. Endoscopic endonasal surgery for giant pituitary adenomas: advantages and limitations. *Journal of Neurosurgery* 2013 **118** 621–631. (doi:10.3171/2012.11.JNS121190)
- 8 Cavallo LM, Solari D, Tasiou A, Esposito F, de Angelis M, D'Enza AI & Cappabianca P. Endoscopic endonasal transsphenoidal removal of recurrent and regrowing pituitary adenomas: experience on a 59-patient series. *World Neurosurgery* 2013 **80** 342–350. (doi:10.1016/j.wneu.2012.10.008)
- 9 Nakao N & Itakura T. Surgical outcome of the endoscopic endonasal approach for non-functioning giant pituitary adenoma. *Journal of Clinical Neuroscience* 2011 **18** 71–75. (doi:10.1016/j.jocn.2010.04.049)
- 10 Sinha S & Sharma BS. Giant pituitary adenomas – an enigma revisited. Microsurgical treatment strategies and outcome in a series of 250 patients. *British Journal of Neurosurgery* 2010 **24** 31–39. (doi:10.3109/02688690903370305)
- 11 Mortini P, Barzaghi R, Losa M, Boari N & Giovannelli M. Surgical treatment of giant pituitary adenomas: strategies and results in a series of 95 consecutive patients. *Neurosurgery* 2007 **60** 993–1002. (doi:10.1227/01.NEU.0000255459.14764.BA)
- 12 Juraschka K, Khan OH, Godoy BL, Monsalves E, Kilian A, Krischek B, Ghare A, Vescan A, Gentili F & Zadeh G. Endoscopic endonasal transsphenoidal approach to large and giant pituitary adenomas: institutional experience and predictors of extent of resection. *Journal of Neurosurgery* 2014 **121** 75–83. (doi:10.3171/2014.3.JNS131679)

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- 13 Yildiz F, Zorlu F, Erbaş T & Atahan L. Radiotherapy in the management of giant pituitary adenomas. *Radiotherapy and Oncology* 1999 **52** 233–237. (doi:10.1016/S0167-8140(99)00098-5)
- 14 Fisher BJ, Gaspar LE & Noone B. Giant pituitary adenomas: role of radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 1993 **25** 677–681. (doi:10.1016/0360-3016(93)90015-N)
- 15 Minniti G, Traish D, Ashley S, Gonsalves A & Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. *Clinical Endocrinology* 2006 **64** 542–548. (doi:10.1111/j.1365-2265.2006.02506.x)
- 16 Milker-Zabel S, Debus J, Thilmann C, Schegel W & Wannenmacher M. Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and non-functional adenomas of the pituitary gland. *International Journal of Radiation Oncology, Biology, Physics* 2001 **50** 1279–1286. (doi:10.1016/S0360-3016(01)01535-8)
- 17 Colin P, Jovenin N, Delemer B, Caron J, Grulet H, Hecart AC, Lukas C, Bazin A, Bernard MH, Scherpereel B *et al.* Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. *International Journal of Radiation Oncology, Biology, Physics* 2005 **62** 333–341. (doi:10.1016/j.ijrobp.2004.09.058)
- 18 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. *International Journal of Radiation Oncology, Biology, Physics* 2005 **61** 795–808. (doi:10.1016/j.ijrobp.2004.07.688)
- 19 Kim JO, Ma R, Akagami R, McKenzie M, Johnson M, Gete E & Nichol A. Long-term outcomes of fractionated stereotactic radiation therapy for pituitary adenomas at the BC Cancer Agency. *International Journal of Radiation Oncology, Biology, Physics* 2013 **87** 528–533. (doi:10.1016/j.ijrobp.2013.06.2057)
- 20 Kopp C, Theodorou M, Poulos N, Astner ST, Geinitz H, Stalla GK, Meyer B, Molls M, Nieder C & Grosu AL. Fractionated stereotactic radiotherapy in the treatment of pituitary adenomas. *Strahlentherapie und Onkologie* 2013 **189** 932–937. (doi:10.1007/s00066-013-0433-z)
- 21 Lillehei KO, Kirschman DL, Kleinschmidt-DeMasters BK & Ridgway EC. Reassessment of the role of radiation therapy in the treatment of endocrine-inactive pituitary macroadenomas. *Neurosurgery* 1998 **43** 432–438. (doi:10.1097/00006123-199809000-00020)
- 22 Zhang X, Fei Z, Zhang J, Fu L, Zhang Z, Liu W & Chen Y. Management of nonfunctioning pituitary adenomas with suprasellar extensions by transsphenoidal microsurgery. *Surgical Neurology* 1999 **52** 380–385. (doi:10.1016/S0090-3019(99)00120-2)
- 23 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. *Clinical Endocrinology* 2003 **58** 763–769. (doi:10.1046/j.1365-2265.2003.01784.x)
- 24 Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, Lee JY, Kano H, Park KJ, Niranjan A *et al.* Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *Journal of Neurosurgery* 2013 **119** 446–456. (doi:10.3171/2013.3.JNS12766)
- 25 Leber KA, Berglöff J & Pendl G. Dose–response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. *Journal of Neurosurgery* 1998 **88** 43–50. (doi:10.3171/jns.1998.88.1.0043)
- 26 Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E III, Kooy HM & Flickinger JC. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *International Journal of Radiation Oncology, Biology, Physics* 1993 **27** 215–221. (doi:10.1016/0360-3016(93)90230-S)
- 27 Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, Gorman DA & Schomberg PJ. A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. *International Journal of Radiation Oncology, Biology, Physics* 2003 **55** 1177–1181. (doi:10.1016/S0360-3016(02)04380-8)
- 28 Hasegawa T, Kobayashi T & Kida Y. Tolerance of the optic apparatus in single-fraction irradiation using stereotactic radiosurgery: evaluation in 100 patients with craniopharyngioma. *Neurosurgery* 2010 **66** 688–694. (doi:10.1227/01.NEU.0000367554.96981.26)
- 29 Leavitt JA, Stafford SL, Link MJ & Pollock BE. Long-term evaluation of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. *International Journal of Radiation Oncology, Biology, Physics* 2013 **87** 524–527. (doi:10.1016/j.ijrobp.2013.06.2047)
- 30 Pollock BE, Link MJ, Leavitt JA & Stafford SL. Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. *Neurosurgery* 2014 **75** 456–460. (doi:10.1227/NEU.0000000000000457)
- 31 Adler JR Jr, Gibbs IC, Puataweepong P & Chang SD. Visual field preservation after multisection cyberknife radiosurgery for perioptic lesions. *Neurosurgery* 2006 **59** 244–254. (doi:10.1227/01.NEU.0000223512.09115.3E)
- 32 Iwata H, Sato K, Tatewaki K, Yokota N, Inoue M, Baba Y & Shibamoto Y. Hypofractionated stereotactic radiotherapy with CyberKnife for non-functioning pituitary adenoma: high local control with low toxicity. *Neuro-Oncology* 2011 **13** 916–922. (doi:10.1093/neuonc/nor055)
- 33 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. *Journal of Clinical Neuroscience* 2014 **21** 111–115. (doi:10.1016/j.jocn.2013.03.024)
- 34 Minniti G, Esposito V, Clarke E, Scaringi C, Bozzao A, Falco T, De Sanctis V, Enrici MM, Valeriani M, Osti MF *et al.* Fractionated stereotactic radiosurgery for patients with skull base metastases from systemic cancer involving the anterior visual pathway. *Radiation Oncology* 2014 **9** 110. (doi:10.1186/1748-717X-9-110)
- 35 Kopp C, Theodorou M, Poulos N, Jacob V, Astner ST, Molls M & Grosu AL. Tumor shrinkage assessed by volumetric MRI in long-term follow-up after fractionated stereotactic radiotherapy of nonfunctioning pituitary adenoma. *International Journal of Radiation Oncology, Biology, Physics* 2012 **82** 1262–1267. (doi:10.1016/j.ijrobp.2011.02.053)
- 36 Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellers PJ, Nussey S & Uttley D. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clinical Endocrinology* 1993 **38** 571–578. (doi:10.1111/j.1365-2265.1993.tb02137.x)
- 37 Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB & Simpson WJ. Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. *International Journal of Radiation Oncology, Biology, Physics* 1994 **30** 557–565. (doi:10.1016/0360-3016(92)90941-A)
- 38 McCord MW, Buatti JM, Fennell EM, Mendenhall WM, Marcus RB Jr, Rhoton AL, Grant MB & Friedman WA. Radiotherapy for pituitary adenoma: long-term outcome and sequelae. *International Journal of Radiation Oncology, Biology, Physics* 1997 **39** 437–444. (doi:10.1016/S0360-3016(97)00335-0)
- 39 Kline LB, Kim JY & Ceballos R. Radiation optic neuropathy. *Ophthalmology* 1985 **92** 1118–1126. (doi:10.1016/S0161-6420(85)33898-8)
- 40 Brada M, Asley S, Ford D, Traish D, Burchell I & Rahan B. Cerebrovascular mortality in patients with pituitary adenoma. *Clinical Endocrinology* 2002 **57** 713–717. (doi:10.1046/j.1365-2265.2002.01570.x)
- 41 Minniti G, Traish D, Ashley S, Gonsalves A & Brada M. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 800–804. (doi:10.1210/jc.2004-1152)
- 42 Noad R, Narayanan KR, Howlett T, Lincoln NB & Page RC. Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clinical Oncology* 2004 **16** 233–237. (doi:10.1016/j.clon.2004.01.012)
- 43 Hsiao KY, Yeh SA, Chang CC, Tsai PC, Wu JM & Gau JS. Cognitive function before and after intensity-modulated radiation therapy in patients with nasopharyngeal carcinoma: a prospective study.

- International Journal of Radiation Oncology, Biology, Physics* 2010 **77** 722–726. (doi:10.1016/j.ijrobp.2009.06.080)
- 44 Jalali R, Mallick I, Dutta D, Goswami S, Gupta T, Munshi A, Deshpande D & Sarin R. Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 2010 **77** 974–979. (doi:10.1016/j.ijrobp.2009.06.025)
- 45 Armstrong GT, Conklin HM, Huang S, Srivastava D, Sanford R, Ellison DW, Merchant TE, Hudson MM, Hoehn ME, Robison LL *et al.* Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro-Oncology* 2011 **13** 223–234. (doi:10.1093/neuonc/noq178)
- 46 Gondi V, Tomé WA & Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiotherapy and Oncology* 2010 **97** 370–376. (doi:10.1016/j.radonc.2010.09.013)
- 47 Gondi V, Hermann BP, Mehta MP & Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *International Journal of Radiation Oncology, Biology, Physics* 2012 **83** e487–e493. (doi:10.1016/j.ijrobp.2011.10.021)
- 48 Brummelman P, Sattler MG, Meiners LC, Elderson MF, Dullaart RP, van den Berg G, Koerts J, Tucha O, Wolffenbuttel BH, van den Bergh AC *et al.* Cognitive performance after postoperative pituitary radiotherapy: a dosimetric study of the hippocampus and the prefrontal cortex. *European Journal of Endocrinology* 2012 **166** 171–179. (doi:10.1530/EJE-11-0749)

Received 14 October 2014

Revised version received 8 January 2015

Accepted 27 January 2015