Reports of Practical Oncology and Radiotherapy 25 (2020) 586–593

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Radiotherapy for the treatment of pituitary adenomas: A dosimetric comparison of three planning techniques☆

Rubi Ramos-Prudencio[a,*], Sandra Ileana Pérez-Álvarez[a], Christian Haydée Flores-Balcazar[a], Mayra Angélica de León-Alfaro[a], José Alfredo Herrera-González[b], Jonathan Elizalde-Cabrera[b], Johnatan Rubalcava-Ortega[c], Lissett Espinoza-Alvarado[c], Ricardo Iván Balderrama-Ibarra[d]

[a] Department of Radiotherapy, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Belisario Domínguez, Sección XVI, Tlalpan, México City 14080, Mexico
[b] Division of Radiotherapy, Instituto Nacional de Cancerología, 22 San Fernando Ave, Sección XVI, Tlalpan, México City 14080, Mexico
[c] Department of Neuroimaging, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Salvador Zubirán, Vasco de Quiroga 15, Belisario Domínguez, Sección XVI, Tlalpan, México City 14080, Mexico
[d] Department of Radiotherapy, Instituto Mexicano Del Seguro Social (IMSS), Centro Médico Nacional de Occidente, Universidad de Guadalajara, Independencia Oriente, Guadalajara 44340, Mexico

ARTICLE INFO

Article history:
Received 22 August 2019
Received in revised form 14 April 2020
Accepted 28 April 2020
Available online 19 May 2020

Keywords:
Pituitary adenomas
Conformal radiotherapy
IMRT
VMAT

ABSTRACT

Aim: Our goal was to compare conformal 3D (C3D) radiotherapy (RT), modulated intensity RT (IMRT), and volumetric modulated arc therapy (VMAT) planning techniques in treating pituitary adenomas.
Background: RT is important for managing pituitary adenomas. Treatment planning advances allow for higher radiation dosing with less risk of affecting organs at risk (OAR).
Materials and methods: We conducted a 5-year retrospective review of patients with pituitary adenoma treated with external beam radiation therapy (C3D with flattening filter, flattening filter-free [FFF], IMRT, and VMAT). We compared dose-volume histogram data. For OARs, we recorded D2%, maximum, and mean doses. For planning target volume (PTV), we registered V95%, V107%, D95%, D98%, D50%, D2%, minimum dose, conformity index (CI), and homogeneity index (HI).
Results: Fifty-eight patients with pituitary adenoma were included. Target-volume coverage was acceptable for all techniques. The HI values were 0.06, IMRT; 0.07, VMAT; 0.08, C3D; and 0.09, C3D FFF ($p < 0.0001$). VMAT and IMRT provided the best target volume conformity (CI, 0.64 and 0.74, respectively; $p < 0.0001$). VMAT yielded the lowest doses to the optic pathway, lens, and cochlea. The position of the neck in extreme flexion showed that it helps in planning mainly with VMAT by allowing only one arc to be used and achieving the desired conformity, decreasing the treatment time, while allowing greater protection to the organs of risk using C3D, C3DFFF.
Conclusions: Our results confirmed that EBRT in pituitary adenomas using IMRT, VMAT, C3D, C3FFF provide adequate coverage to the target. VMAT with a single arc or incomplete arc had a better compliance with desired dosimetric goals, such as target coverage and normal structures dose constraints, as well as shorter treatment time. Neck extreme flexion may have benefits in treatment planning for better preservation of organs at risk. C3D with extreme neck flexion is an appropriate treatment option when other treatment techniques are not available.

Abbreviations: C3D, conformal three-dimensional radiotherapy; CI, conformity index; CT, computed tomography; CTV, clinical target volume; DVH, dose-volume histogram; EBRT, external beam radiation therapy; ESAPI, Eclipse Scripting Application Programming Interface; FF, flattening filter; FFF, flattening filter free; CFRT, conventional fractionated radiotherapy; GTV, gross tumor volume; HI, homogeneity index; IMRT, modulated intensity radiotherapy; MRI, magnetic resonance imaging; OAR, organs at risk; PTV, planning target volume; RION, radiation-induced neuropathy; RT, radiotherapy; SRS, stereotactic radiosurgery; VMAT, volumetric modulated arc therapy .

☆ Article from the Special Issue on Advanced Techniques in Radiation Oncology in Mexico.

* Corresponding author.
E-mail addresses: rub18_ramos@hotmail.com (R. Ramos-Prudencio), chrishaydee@hotmail.com (C.H. Flores-Balcazar).

https://doi.org/10.1016/j.rpor.2020.04.020
1507-1367/

1. Introduction

Pituitary adenomas are benign tumors that arise from the adenohypophysis. They are the second most frequent intracranial tumor after meningiomas and represent 16.2% of all primary intracranial neoplasms in adults.[1,2] Therapies for pituitary adenomas include transphenoidal surgery, medical treatment, and/or external beam radiation therapy (EBRT). Radiotherapy (RT) is crucial in the management of pituitary adenomas with incomplete resection, biochemical or radiographic recurrence or persistence, and those with high risk of recurrence despite surgical resection.[2–4] In previous reports, RT achieved a 10-year local control of up to 90%.[5] Less commonly, RT has also been used in medically inoperable patients or irresectable adenoma.[2–4]

Despite the efficacy of RT, the high risk of long-term radiation-induced pituitary deficit and risks of neurological deficit have limited its use in the past. More recently, advances in radiological imaging, software systems applied to treatment planning, and radiation dose delivery have led to more precise planning treatments. Radiation techniques have evolved from conformal three-dimensional RT (C3D) through modulated intensity RT (IMRT), volumetric modulated arc therapy (VMAT), and stereotactic radiosurgery (SRS). Techniques such as C3D with flattening filter (FF) and flattening filter-free (FFF) are used in small fields to achieve high compliance and, on the other hand, allow us to reduce the treatment time.[5] Currently, VMAT and modulated intensity RT (IMRT) are used to decrease higher radiation doses to the target and reduce doses to the surrounding healthy brain structures while maintaining effective therapeutic dose for the tumor, and reducing long-term toxicity.[5,6]

2. Objective

The primary objective of this review was to perform a dosimetric comparison of 3 planning techniques for EBRT (C3D, IMRT, and VMAT) in patients with pituitary adenomas with incomplete resection, with biochemical or radiographic recurrence or persistence and in inoperable patients.

3. Materials and methods

3.1. Study population

We conducted a retrospective review of 58 patients diagnosed with pituitary adenoma treated with EBRT at our institution between December 2013 and June 2018. We evaluated clinical, pathological, and biochemical data and treatment and follow-up characteristics. For magnetic resonance image (MRI) response Peer-review of all magnetic resonance imaging (MRI) available in our PACS (Carestream Vue PACS) before EBRT, 3–6 months after EBRT, and final follow-up were conducted by brain MRI radiologists. The formula used for residual volume calculation [transverse * antero-posterior * craniocaudal diameters * (π/6)] is suggested mainly for measurements of ellipsoid targets. Despite its limitations for measurement of residuals, it was used instead of accurate GTV volume in cubic centimeters since initial evaluation and further follow-up measurements were done with the radiology department system.

3.2. Simulation and volume delineation

Computed tomography (CT) simulation was done with a thermoplastic mask with the patient's neck in neutral position or extreme flexion. Extreme flexion was achieved by directing the base of jaw toward the sternal manubrium using a neck support. This position helped to avoid healthy structures, such as the optic pathway, retina and brain tissue, through the beam path. CT planning with 1.25 mm slice thickness was previously acquired and co-registered with the MRI sequences of interest using rigid fusion in the Eclipse Treatment Planning System (Version 11; Varian Medical Systems, Inc., Palo Alto, CA). All treatment volumes and organs at risk (OAR) contouring were reviewed. The gross tumor volume (GTV) was defined using MRI and CT. The clinical target volume (CTV) for non-operated patients was generated by a 3-mm to 5-mm isotropic margin (planning target volume [PTV] was the same as CTV). For operated patients, the CTV included the GTV with or without the tumor bed, and it was then expanded symmetrically by 3–5 mm to create the PTV to account for setup errors.[7,8] The following OARs were included: lenses, cochlea, eyeballs, optic nerves, chiasm, brainstem, and spinal cord.[9,10]

3.3. Treatment planning technique

Four treatment plans were created for each case: C3D with flattening filter and flattening filter-free (C3D FFF), VMAT, and IMRT. The plans were optimized with the different treatment techniques using the Varian Millenium 120-leaf multileaf collimators, with a spatial resolution of 0.5 cm in the isocenter for the central 20 cm and 1 cm in the outer region. In the first step of the planning process, the objective was to achieve at least 95% of the PTV receiving 100% of the prescribed dose (54 Gy in 27 fractions). Next, we needed to optimize OAR sparing without compromising PTV coverage. Therefore, the following dose constraints were used: for optic pathway (chiasm and optic nerves) and brainstem, maximum dose lower than 54 Gy; for lenses, Dmax <2 Gy; for cochlea, mean dose <30 Gy and Dmax <40 Gy; and, for spinal cord, Dmax <45 Gy.[9–14]

All conformal plans were created with the four-field technique positioned at 0°, 90°, 180° and 270°, using 10-MV photons and with collimator set to 0° for all plans. Using the same beam arrangement and field size, the C3D FFF was calculated with 10 MV FFF and a dose rate of 2400 MU/min.

For the IMRT technique, 5 fields were created with 6 MV FFF photons positioned to 0°, 72°, 144°, 216°, and 288° for patient's CT with neck flexion; for those with neutral neck position, in CT the fields were arranged at 180°, 230°, 280°, 80°, and 130°. For both scenarios, the collimator was placed at 0°, 20°, 40°, 60°, and 80°. The maximum dose rate was set at 1400 MU/min.

All VMAT plans were created with a full arc for 6 MV FFF photons; this arc was planned in a clockwise direction and with the collimator at 30°. In patients simulated with extreme neck flexion, a single complete arc was sufficient to achieve compliance with desired dosimetric goals, such as target coverage and normal structures dose constraints. For patient's CT with no neck flexion, a restriction of 315°–45° was placed and the arc was incomplete to sparing OAR. The maximum dose rate was set at 1400 MU/min. Final calculations were performed using the AAA algorithm in Eclipse Version 11.

3.4. Plan analysis

With a previously generated structure template that included treatment volumes (GTV, CTV, PTV) and OARs and using the Eclipse Scripting Application Programming Interface (ESAPI), our medical physicists have developed a script (c# code program) enabling easier, faster, and more precise dose-volume histogram (DVH) evaluation of each of the 4 plans of the 58 patients. This script enables automatic export of the analyzed information to a database (Table 1).

The plans analyses were based on DVH data reported and exported through ESAPI code. For OARs, we recorded D2%, maximum (Dmax), and mean (Dmean) dose. And for PTV we additionally registered V95% and V107% (represent the volume receiving 95% and 107% or more of the prescribe dose, respectively), D95%, D98%,

Table 1
Median size of residual tissue and pituitary gland on MRI.

	Residual size on MRI				Pituitary size on MRI			
	T (W)	AP (H)	CC (L)	V[a]	T (W)	AP (H)	CC (L)	V[a]
MRI before RT	11.6 (0–46.6)	5 (0–3.7)	8.16 (0–4.6)	0.272 (0–37.43)	16.0 (0–46.6)	6.2 (0–37)	10.7 (0–46)	0.63 (0–37.43)
MRI 3–6 months after EBRT	7.5 (0–30)	3 (0–20)	5 (0–28)	0.0591 (0–8.356)	13 (0–30)	5 (0–50)	9 (0–28)	0.3391 (0–8.35)
Last MRI	10.39 (0–30.7)	4 (0–22)	7.43 (0–28.4)	0.1088 (0–7.64)	13 (0–30.7)	4.55 (0–22)	8.78 (0–28.4)	0.2707 (0–7.64)
P-value	<0.0001			<0.0001	<0.0001			<0.0001

All diameters are in millimeters.
Abbreviations: MRI, magnetic resonance imaging; RT, radiotherapy; AP, anteroposterior diameter; EBRT, external beam radiation therapy; T, transverse diameter; W, width; H, height; L, length; CC, craniocaudal diameter; V, volume.
[a] Volume was calculated by multiplying T × AP × CC × (π/6), expressed in centimeters.

Table 2
Median dose in cGy (range) to PTV for C3D, C3D FFF, IMRT, and VMAT plans.

PTV		C3D	C3D FFF	IMRT	VMAT	Friedman
Maximum[a]		5784 (5602–5952)	**5842 (5633–6046)**	5725 (5613–5841)	**5835 (5765–5946)**	**<0.0001**
Minimum[a]		5145 (4312–5302)	5134 (4575–5293)	5111 (4282–5252)	**5033 (4420–5227)**	**<0.0001**
Mean[a]		5612 (5502–5729)	5633 (5512–5755)	**5556 (5513–5629)**	**5565 (5456–5633)**	**<0.001**
D95%	cGy	5400 (5318–5494)	5400 (5319–5488)	5400 (5381–5430)	5400 (5121–5429)	0.958
	%	100 (98.5–101.7)	100 (98.5–101.6)	100 (99.7–100.6)	100 (94.8–100.5)	0.985
D98%	cGy	5340 (5213–5414)	5338 (5203–5410)	**5346 (5302–5380)**	5341 (5038–5359)	**<0.0001**
	%	98.9 (96.5–100.3)	98.9 (96.4–100.2)	**99 (98.2–99.6)**	98.9 (93.3–99.2)	**0.001**
D50%	cGy	5633 (5507–5777)	5653 (5517–5786)	**5576 (5519–5667)**	**5577 (5492–5673)**	**<0.0001**
	%	104.3 (102–107)	104.7 (102.2–107.1)	**103.3 (102.2–105)**	**103.3 (101.7–105.1)**	**<0.0001**
D2%	cGy	5765 (5591–5963)	5813 (5616–6012)	**5666 (5593–5747)**	5728 (5646–5863)	**<0.0001**
	%	106.8 (103.5–109.9)	107.6 (104–111.3)	**104.9 (103.6–106.4)**	106.1 (104.6–108.6)	**<0.0001**
V95%		99.91 (99.46–100)	100 (99.38–100)	100 (99.5–100)	**99.98 (94.64–100)**	**0.011**
V107%		0.27 (0–49.66)	10.07 (0–51.81)	**0 (0–0.35)**	0.23 (0–14.56)	**<0.0001**
HI[1]		**1.07 (1.04–1.10)**	1.08 (1.04–1.12)	**1.06 (1.04–1.08)**	1.08 (1.07–1.10)	**<0.0001**
HI[2]		0.08 (0.04–0.12)	0.09 (0.05–0.13)	**0.06 (0.04–0.08)**	0.07 (0.05–0.14)	**<0.0001**
CI[1]		1.56 (1.13–2.15)	1.52 (1.14–2.1)	**1.06 (0.95–1.34)**	**1.01 (0.25–1.12)**	**<0.0001**
CI[2]		0.41 (0.29–0.53)	0.42 (0–0.56)	**0.64 (0–0.77)**	**0.74 (0.59–0.82)**	**<0.0001**

D95%, **D98%**, **D50%** and **D2%:** dose received by 95%, 98%, 50% and 2% of PTV in cGy or percentage. V95% and V107%: volume of PTV receiving or within the 95% and 107% isodose.
HI[1]: homogeneity index calculated as maximum dose divided by prescribed dose.
HI[2]: homogeneity index calculated as (D2%–D98%)/prescribed dose.
CI[1]: conformity index calculated as treatment volume divided by PTV volume (VPTV).
CI[2]: conformity index calculated as $(V95\% \cap VPTV)^2/(V95\% * VPTV)$.
Abbreviations: PTV, planning target volume; C3D, conformal 3D radiotherapy; C3D FFF, conformal 3D radiotherapy flattening filter-free; IMRT, modulated intensity radiotherapy; VMAT, volumetric modulated arc therapy; HI homogeneity index; CI, conformity index.
[a] Median dose (range) in cGy.

D50% and D2% (represent the dose received by 95%, 98%, 50%, and 2% of the structure, respectively), and minimum dose (Dmin). We also calculated the conformity index (CI) and the homogeneity index (HI) for the PTV (Table 2) using the following formulas:

- **HI** (formula 1): calculated as maximum dose divided by prescribed dose
- **HI** (formula 2): calculated as (D2%–D98%)/prescribed dose
- **CI** (formula 1): calculated as treatment volume divided by PTV volume (VPTV)
- **CI** (formula 2): calculated as (V95% ∩ VPTV)2/(V95% * VPTV)

The higher values of CI indicated better PTV conformity. The closer to 1 of HI with formula 1 and the lower values of HI with formula 2 indicate more homogeneous irradiation of PTV.[15],[16]

3.5. Statistical methods

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY). Kolmogorov-Smirnov Test was used to test for normality. Non-parametric statistical tests were used since data from PTV coverage and constraints to OARs had no normal distribution. To compare the PTV coverage and dose to OARs within the 4 different modalities (C3D, C3D FFF, IMRT and VMAT), non-parametric Friedman rank test for paired samples were used. Statistically significant difference was considered with p-value less than the significance level ($\alpha = 0.05$). To specifically identify which RT technique differ from which other, in each value measured and statistically significant after Friedman test, we further used pairwise comparisons using the Nemenyi multiple comparison test (Friedman post-hoc test using RStudio version 1.2.5033).

4. Results

4.1. Patient characteristics

A total of 58 patients with pituitary adenoma diagnosis were treated with conventional fractionated RT (CFRT): 41 women (70.7%), and 17 men (29.3%). The mean age at recurrence and the radiation therapy beginning was 46 years (range, 22–90 years). The majority (39 patients) had macroadenomas (67.2%), and 19 patients had microadenomas (32.8%). With regard to the endocrine status, 15 patients (25.9%) had nonfunctioning adenomas, and 43 patients (74.1%) had hormone-secreting functioning adenomas; 23 (39.7%) had corticotrophin/adrenocorticotropic hormone-secreting tumors, 15 (25.9%) had growth hormone-secreting tumors, and 8 (13.8%) had prolactin-secreting tumors.

Among all, 51 patients (87.9%) received adjuvant radiation after surgical resection (47 transsphenoidal surgery, 3 hypophy-

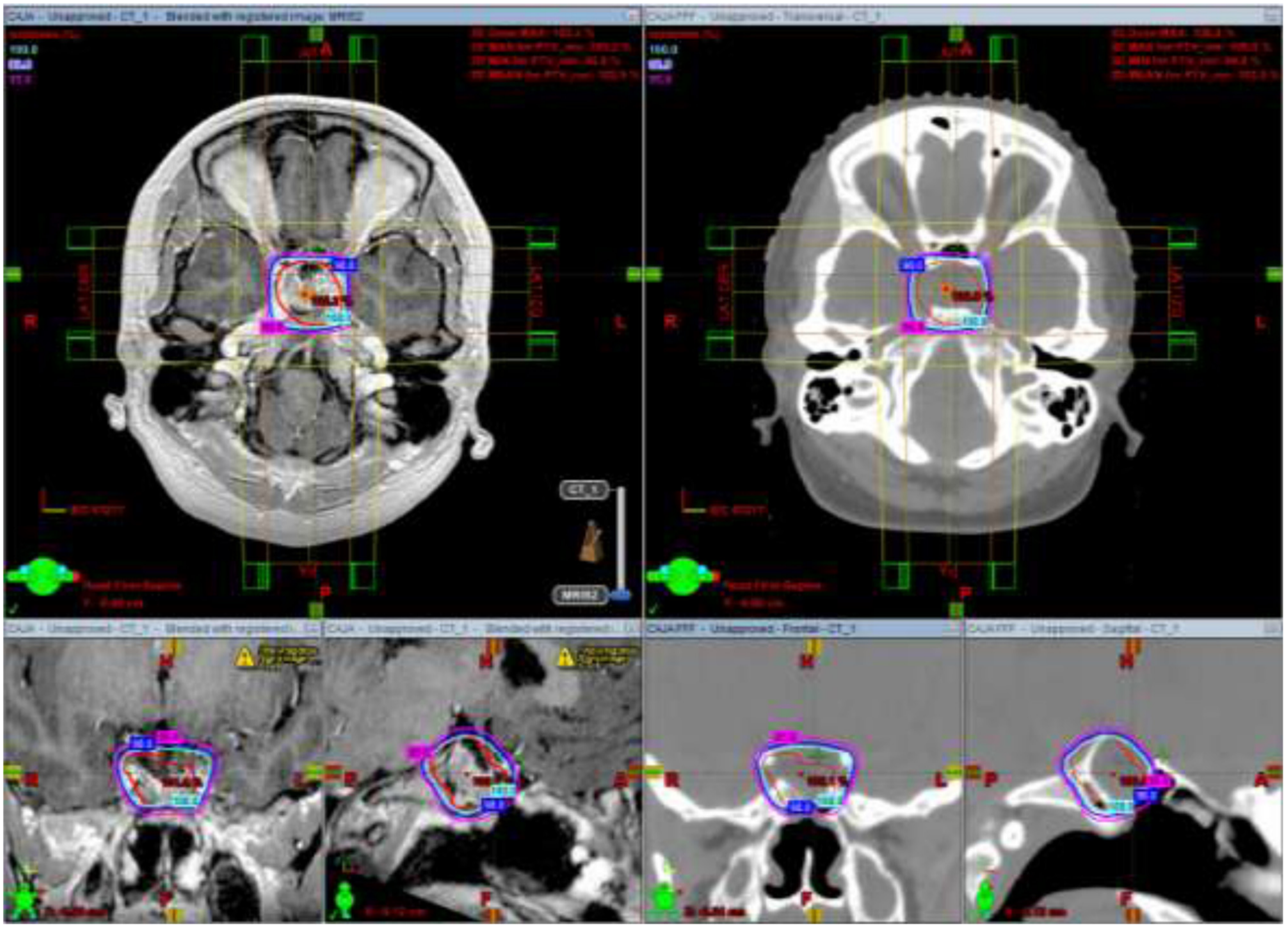

Fig. 1. Isodose curves of D100% (cyan), D98% (blue) and D95% (magenta) with C3D (left) and C3D FFF (right) with axial, coronal, and sagittal views of MRI and CT, respectively. Abbreviations: C3D, conformal 3D radiotherapy; C3D FFF, conformal 3D radiotherapy flattening filter-free; MRI, magnetic resonance imaging; CT, computed tomography. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

sectomies, 1 right subfrontal approach) with a median number of surgeries of 1 (range, 1–3); 4 patients (6.9%) received medical treatment before definitive RT (1 bromocriptine and 3 cabergoline); and, in 3 patients (5.2%), surgery was not feasible for medical reasons, and they received definitive RT. In 24 patients (41.4%), RT was indicated for recurrence (as the most frequent cause, biochemical recurrence in 15 patients [25.8%]), and in 32 patients (55.2%) due to persistence (the most common cause being residual identified by imaging in 22 patients [37.9%]).

4.2. Radiation therapy

RT was mainly administered to treat pituitary adenoma if surgical and medical treatments failed to remove the tumor or normalize hormone secretion. All patients received CFRT with a median overall treatment time of 39 days (range, 32–68 days), it was delivered with 3D-CRT in 45 patients (77.6%), VMAT in 10 patients (17.2%) with a median number of 5 fields (range, 5–7) and IMRT in 3 patients (5.2%) with a median number of 1 arc (range, 1–3). Median PTV volume was 5.32 cm3 (range, 1.04–34.74 cm^3), with 45 patients with volume $\leq 10\,cm^3$.

All patients were treated with once-daily megavoltage RT, 5 fractions per week. The median total dose delivered by TrueBeam linear accelerator (Varian Medial Systems, Palo Alto, CA, USA) was 54 Gy (range, 46–54 Gy) with a median daily dose of 2 Gy (1.8–2.16 Gy). Nearly equal doses were applied regardless of the functional type of adenoma. With a median number of 27 sessions (range, 23–30), 1 patient received 46 Gy and suspended the treatment.

4.3. Biochemical, clinical and image control

With a median follow-up of 43 months (range, 6–103 months) since recurrence or persistence treated with radiation therapy, 54 patients were alive (96.4%), 2 died for other medical causes. At last follow-up, 51 patients (87.9%) had no signs or symptoms of clinical activity, and 39 patients (67.2%) had normal biochemical hormone evaluation. Median residual and pituitary diameter size (width, height, and length) and volume on MRI at 3–6 months, and last follow-up MRI was significantly smaller than MRI before RT. Tumor control at 5 years was 91.1%.

4.4. PTV: variations in dosimetric distribution with 4 plans

In Table 2 and Figs. 1 and 2, we show differences between the 4 plans (C3D, C3D FFF, IMRT, and VMAT) and PTV dose distribution. Since a comparison was made with Friedman test ranks, rows with p value <0.05 identified values of PTV coverage (Table 2) or OAR constraint (Table 3) in which at least one of the planning techniques differs from the others. To further identify which RT technique differs from which other, pairwise comparisons using the Nemenyi multiple comparison test was used. The following results were obtained from these comparisons.

PTV maximum dose was significantly higher in conformal 3D FFF and VMAT. PTV minimum dose was significantly lower with VMAT.

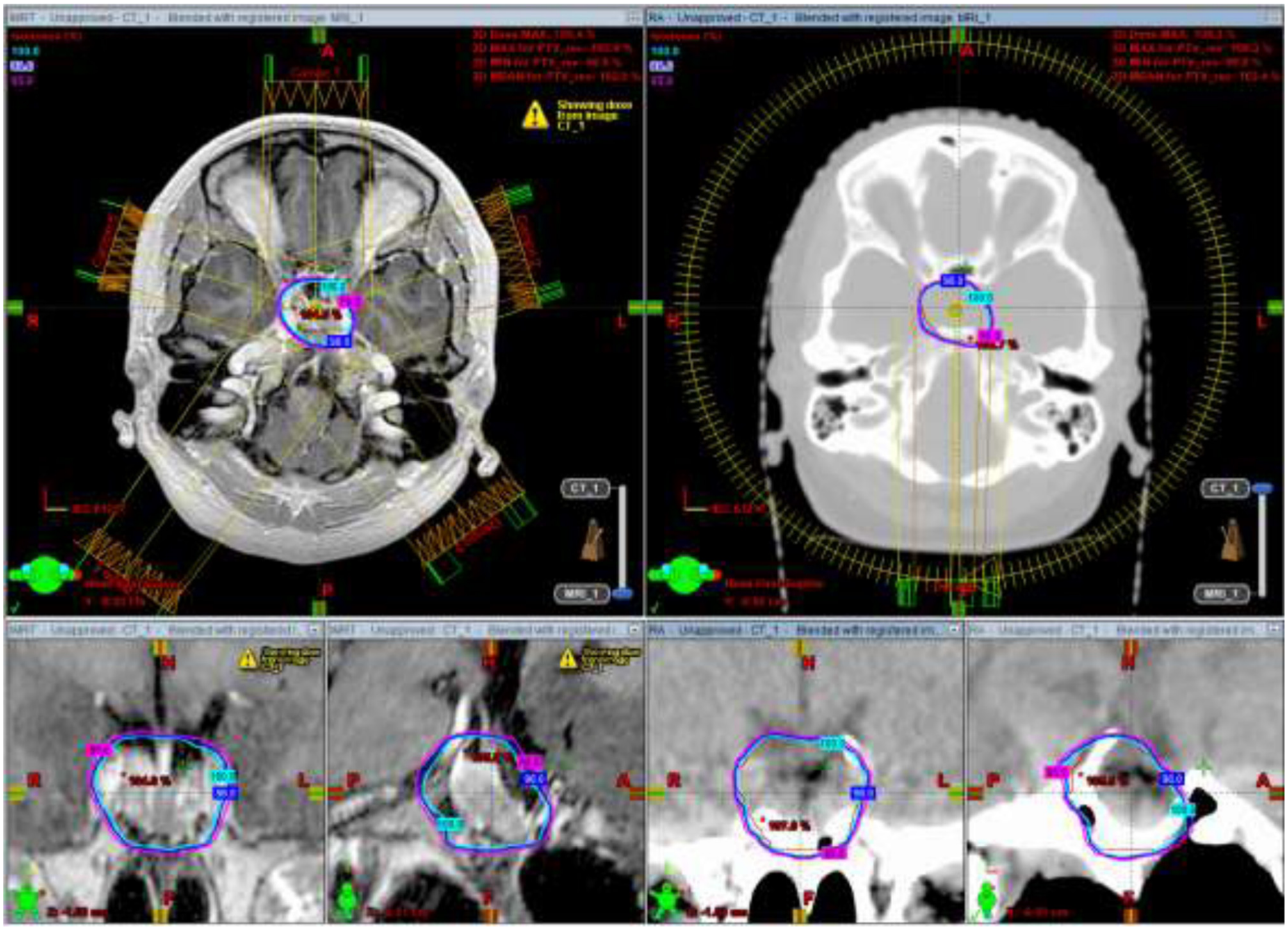

Fig. 2. Isodose curves of D100% (cyan), D98% (blue) and D95% (magenta) with IMRT (left) and VMAT (right) with axial, coronal and sagittal views of MRI and CT, respectively. Abbreviations: IMRT, modulated intensity radiotherapy; VMAT, volumetric modulated arc therapy; MRI, magnetic resonance imaging; CT, computed tomography. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Median PTV dose was lower with IMRT and VMAT. PTV D98% (in cGy and %) was significantly higher with IMRT compared to C3D FFF and VMAT. Median PTV D50% (in cGy and %) is significantly lower for VMAT and IMRT versus C3D and C3D FFF. Median PTV D2% (in cGy and %) was significantly lower with IMRT than C3D and VMAT, and all were lower than C3D FFF. Median V95% was lower with VMAT versus IMRT. Median PTV V107% was significantly lower with IMRT and higher with C3D FFF. However, these differences, although significant, are subtle differences limited to 1–2 Gy. A significantly better HI was achieved with IMRT considering both formulas, and a better CI was achieved with IMRT than VMAT, and both showed a better conformity than C3D and C3D FFF.

4.5. OARs: variations in dose and constraint compliance with 4 plans

Table 3 shows significantly lower maximum doses and D2% (within constraints) to optic nerves achieved with VMAT, with higher mean doses with VMAT and IMRT compared to C3D FFF and C3D plans. Chiasm received significantly lower maximum, mean dose and D2% with VMAT compared to IMRT, and higher dose with C3D and C3D FFF. Significantly lower maximum and median doses and D2% (within constraints) were delivered to the lens with IMRT and VMAT, and to the brainstem with VMAT. The dose was significantly lower (within constraints) to the cochlea with IMRT in those in which PTV extended to involve it and lower with VMAT when PTV did not extend to the temporal bone. The maximum, mean, and D2% to the eyes was significantly lower with IMRT and VMAT.

In the analysis of patients according to neck position, significantly ($p < 0.0001$) median lower doses were achieved with neck extreme flexion to the optic nerves with C3D (mean 496 vs. 1158 cGy) and C3D FFF (mean, 455 vs. 1058 cGy); to the lens, the mean, maximum, and D2% with C3D (D2% 64 vs. 133 cGy), C3D FFF (D2% 54 vs. 109 cGy), and VMAT (D2% 121 vs. 190 cGy, $p < 0.0001$); to the brainstem mean and D2% with C3D (D2% 3332 vs. 4320 cGy), and C3D FFF (D2% 3272 vs. 4259 cGy); and to the eye maximum, mean, and D2% with C3D (D2% 143 vs. 472 cGy) and C3D FFF (D2% 129 vs. 403 cGy). There were no differences in the OAR doses received with IMRT independently of neck position.

When the analysis was limited to patients with PTV ≤ 10 cm3, neck extreme flexion showed significantly reduced dose to the lenses with C3D (D2% 83 vs. 53 cGy; $p = 0.047$) and C3D FFF (D2% 46 vs. 69 cGy; $p = 0.035$); and, to the eyes with C3D (D2% 139 vs. 339 cGy; $p = 0.019$) and C3D FFF (D2% 120 vs. 294 cGy; $p = 0.017$). For VMAT with neck extreme flexion, significantly lower mean dose to the chiasm (2882 vs. 3698 cGy; $p = 0.023$), D2% to the lens (118 vs. 181 cGy; $p = 0.001$) but significantly higher mean dose to the cochlea (1149 vs. 803 cGy; $p = 0.022$). For IMRT, a treatment plan with CT simulation with neck extreme flexion was associated with lower D2% (5171 vs. 5306 cGy; $p = 0.032$)

The position of the neck in extreme flexion showed that it helps in planning mainly with VMAT by allowing the use of only one arc while achieving the desired conformity, decreasing the treatment time, while allowing greater protection to the organs of risk using C3D, C3DFFF.

Table 3
Median maximum and mean dose (in cGy) and median D2% to each organ at risk.

PTV		C3D	C3D FFF	IMRT	VMAT	
Left optic nerve	Max	2938	2883	2604	2309	<0.0001
		233–5603	204–5576	399–5595	423–5399	
	Mean	455	398	992	1023	<0.0001
		99–3495	90k3383	173–3366	190–3095	
	D2%	1788	1674	2031	1934	<0.0001
		194–5540	171–5483	335–5489	369–5184	
Right optic nerve	Max	3130	3037	2766	2372	<0.0001
		258–5652	227–5805	459–5582	342–5457	
	Mean	706	648	1033	1037	<0.0001
		92–5074	84–5143	214–4124	163–4248	
	D2%	2570	2455	2271	1974	<0.0001
		182–5624	162k5770	389–5509	291–5333	
Chiasm	Max	5384	5381	5325	5338	<0.0001
		2982–5785	2923–6008	2994–5640	2633–5471	
	Mean	3712	3622	3233	2975	<0.0001
		1488–5733	1374k5982	1105–5504	953–5400	
	D2%	5279	5264	5210	5131	<0.0001
		2740–55,756	2646–6006	2786–5520	2275–5407	
Left lens	Max	73	63	145	156	<0.0001
		28–1262	25–675	39–209	28–340	
	Mean	55.6	48	88	96	<0.0001
		25.9–325.7	22–262	37–169	26–215	
	D2%	70.5	58	126	140	<0.0001
		27.5–954.1	24–479	39–197	27–289	
Right lens	Max	77.0	62	133	165	<0.0001
		27.2–1400.2	25–1393	38–241	27–282	
	Mean	55.2	47	82	99	<0.0001
		24.3–556.5	21–494	32–199	26–225	
	D2%	72.6	59	117	153	<0.0001
		26.5–1187.2	24–1155	37–222	27–264	
Brainstem	Max	4942	4891	4504	3851	<0.0001
		3072–5606	49–5661	1799–5452	1586–5604	
	Mean	1772	1758	1158	906	<0.0001
		978–2893	44–2908	514–2411	412–2255	
	D2%	3425	3311	3271	2632	<0.0001
		2894–5357	47–5321	1265–4910	1309–4783	
Left cochlea	Max	498	533	1896	1559	<0.001
		73–5065	68–4866	151–3614	129–4697	
	Mean	227	212	1248	1559	<0.001
		54–3764	51–3551	101–2897	129–4697	
	D2%	424	427	1809	1513	<0.001
		70–4952	65–4743	134–3531	119–4426	
Right cochlea	Max	631	608	1944	1678	<0.001
		85–4957	101–4805	156–4800	145–4505	
	Mean	230	201	1383	1219	<0.001
		58–3206	55–3164	100–3363	97–3216	
	D2%	484	447	1831	1574	<0.001
		78–4712	95–4564	140–4552	134–4027	
Left eye	Max	353	303	832	882	<0.001
		68–2809	63–2744	119–2354	91–1879	
	Mean	82	72.4	261	265	<0.001
		31–835	29–843	54–486	39–705	
	D2%	224	193	724	686	<0.001
		51–2653	48–2604	95–1442	71–1624	
Right eye	Max	345	293	841	893	<0.001
		70–3321	62–3273	137–1934	95–2356	
	Mean	73	62	248	281	<0.001
		25–1198	23k1170	53k531	39–794	
	D2%	212	178	731	745	<0.001
		49–2848	43–2879	95–1377	74k1918	

Abbreviations: C3D, conformal 3D radiotherapy; C3D FFF, conformal 3D radiotherapy flattening filter-free; IMRT, modulated intensity radiotherapy; VMAT, volumetric modulated arc therapy.

5. Discussion

CFRT has traditionally been used in patients with residual or recurrent secreting and nonfunctioning pituitary adenomas that did not respond to prior medical management and/or surgery, resulting in variable long-term tumor control. Recurrence rates are 80%–90% at 10 years and 75%–90% at 20 years.[17–20] The RT may reduce recurrence rates to 6% after 10 years and 12% after 20 years.[19,21,23] Despite notably improved tumor growth control, there are concerns about potential late RT-induced toxicity and a delay to achieve adequate hormone control in secreting adenomas.[20,21] Our patients' clinical outcomes showed that the median residual and pituitary diameter (width, height, and length) and volume on MRI at 3–6 months and last follow-up MRI were significantly smaller than those visible on MRI before RT ($p < 0.0001$), with a tumor control at 5 years of 91.1%.

Delivering highly conformal doses to target volumes and reducing dose to surrounding healthy tissues could potentially increase tumor control and reduce adverse effects. These can be achieved with newer RT techniques such as SRS, VMAT, and IMRT; however, limited evidence has been published regarding different RT treatment modalities.[22] In our study, 4 treatment techniques for pituitary adenoma were compared, and all provided acceptable dosimetric results with adequate coverage to PTV. In FF and FFF C3D plans, using the same field setup, we confirmed no relevant differences in target coverage and OAR dose constraints. FF offer uniform and homogeneous dose distribution which has justified its use in C3D planning, however, it has also been demonstrated that the use of FFF mode is feasible in C3D and that it could even reduce peripheral doses.[24] The advantages of using FFF for modern planning techniques (such as IMRT and VMAT) are the inhomogeneous dose distribution, the MLC leakage reduction and the increased dose rate. This increase in dose rate is especially beneficial in IMRT due to the decrease in treatment time.

Significantly (albeit slight) better homogeneity index was achieved with IMRT, and better conformity was gained with VMAT compared with IMRT. Overall, VMAT was more conformal and offered better sparing of OARs. VMAT also had a faster treatment time. PTV maximum dose was higher in C3D FFF and VMAT. PTV minimum dose was lower with VMAT. Target-volume coverage was acceptable for all the techniques, with the 98% isodose covering a higher volume for IMRT with 99% (range, 98.2%–99.6%; $p < 0.001$). We found that VMAT and IMRT provided the best target volume conformity (CI of 1.01 and 1.06, respectively; $p < 0.0001$). As a result of this better conformity, a smaller volume of healthy brain tissue received high-dose radiation.

The quality of planning relies heavily on dose homogeneity, especially when treating pituitary adenomas where OARs are partially inside the PTV. Intra- and interfraction uncertainties can cause serious adverse events when dosing near these OARs. In our study, the IMRT and C3D plans, regardless of FFF, gave the best homogeneity (HI of 0.06 with IMRT vs. 0.07 with VMAT vs. 0.08 with 3D vs. 0.09 with 3D FFF; $p < 0.0001$). However, these differences, although significant, are subtle.

Another important aspect for RT for pituitary adenoma is to spare critical OARs.[14] Dosimetric constraints were maintained for all OARs using IMRT and VMAT. The dose was significantly lower (within constraints) to the cochlea with IMRT in those in whom PTV extended to areas near it, and lower with VMAT when PTV did not extend to the temporal bone. In our study, although the average dose received by the cochlea was lower with C3D and C3D FFF, the restriction dose was respected only in patients treated with VMAT. Several studies have attempted to correlate mean cochlear dose to hearing loss, reporting a significant increase in hearing loss when the cochlear dose exceeds 45–50 Gy.[22,23]

VMAT allows for the administration of significantly lower doses to the optical pathway, which carries a lower risk of radiation-induced neuropathy (RION). In CFRT, the incidence of RION primarily depends on the total radiation dose.[25,26] Certain baseline factors, such as diabetes mellitus, gender, tumor compression, or previous chemotherapy, have been reported to be associated with an increased risk. Typically, a maximum point dose (Dmax) of up to 54–55 Gy in 1.8- to 2-Gy fractions is recommended based on the observation that the incidence of RION increases markedly at doses >60 Gy, although instances of presumed RION have also been reported at lower doses.[27] In a review of optic pathway radiation induced toxicity by Mayo et al.,[28] complications were reported with maximum doses as low as 46 Gy with conventional fractionation according to previously reported studies.[29–31] In our study, significantly lower maximum dose fulfilling constraints were achieved with VMAT and IMRT.

Lower doses with IMRT or VMAT techniques (to normal tissue surrounding PTV) are associated with an increase in the incidence of solid cancers in long-term survivors.[32,33] We did not compare low dose volumes between the four treatment plans. However, low dose effects should still be considered. In a retrospective case series, the cumulative incidence of gliomas and meningiomas following RT for pituitary adenomas is 2% at 20 years.[34,35] Wiggenraad et al.[36] found similar results; however, they noted that more monitor units were needed with IMRT, even though they found no statistically significant difference between IMRT and VMAT with respect to the volume of irradiated brain tissue.

Neck extreme flexion during CT simulation significantly reduced the RT dose to the lens when planning with C3D, C3D FFF, and VMAT. Also, the doses to the optic nerves, brainstem, and eyes were significantly reduced when planning with C3D and C3D FFF. Therefore, when using conventional planning techniques (C3D and C3D FFF), it is desirable to do a simulation with neck extreme flexion. However, for IMRT planning, there were no dose differences between neck position in extreme or neutral flexion. Therefore, with IMRT a neutral neck position would be ideal as the neutral position carries a lower risk for set-up errors.

6. Conclusions

Our results confirmed that EBRT in pituitary adenomas using IMRT, VMAT, C3D, C3FFF provide adequate coverage to the target. VMAT with a single arc (in patients with neck flexion at CT simulation) or in complete arc (in those without neck flexion) had a better compliance with desired dosimetric goals, such as target coverage and normal structures dose constraints, as well as shorter treatment time. Neck extreme flexion may have benefits in treatment planning for better preservation of organs at risk. C3D with extreme neck flexion is an appropriate treatment option when other treatment techniques are not available.

Conflict of interest

None declared.

Financial disclosure

None declared.

References

1. Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro Oncol*. 2017;19(Suppl. 5):v1–v88, http://dx.doi.org/10.1093/neuonc/nox158.
2. Varlamov EV, McCartney S, Fleseriu M. Functioning pituitary adenomas — current treatment options and emerging medical therapies. *Neuroendocrinol Lett*. 2019;15(1):30–40, http://dx.doi.org/10.17925/EE.2019.15.1.30.
3. Scheick S, Amdur RJ, Kirwan JM, et al. Long-term outcome after fractionated radiotherapy for pituitary adenoma: the curse of the secretory tumor. *Am J Clin Oncol*. 2016;39:49–54, http://dx.doi.org/10.1097/COC.0000000000000014.
4. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100:2807–2831, http://dx.doi.org/10.1210/jc.2015-1818.
5. Minniti G, Flickinger J, Tolu B, Paolini S. Management of nonfunctioning pituitary tumors: radiotherapy. *Pituitary*. 2018;21(2):154–161, http://dx.doi.org/10.1007/s11102-018-0868-4.
6. Pashtan I, Oh K, Loeffler JS. Radiation therapy in the management of pituitary adenomas. In: Fliers E, Korbonits M, Rominj JA, eds. *Handbook of clinical neurology, vol. 124 (3rd series) clinical neuroendocrinology*. London: Elsevier; 2014:317–324.
7. Morana G, Maghnie M, Rossi A. Pituitary tumors: advances in neuroimaging. *Endocr Dev*. 2010;17:160–174, http://dx.doi.org/10.1159/000262537.
8. Guckenberger M, Baier K, Guenther I, et al. Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. *Int J Radiat Oncol Biol Phys*. 2007;69:294–301, http://dx.doi.org/10.1016/j.ijrobp.2007.05.030.
9. Scoccianti S, Detti B, Gadda D, et al. Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. *Radiother Oncol*. 2015;114:230–238, http://dx.doi.org/10.1016/j.radonc.2015.01.016.

10. Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumors. *Radiat Oncol*. 2016;11(1):135, http://dx.doi.org/10.1186/s13014-016-0710-y.
11. Kim H, Potrebko P, Rivera A, et al. Tumor volume threshold for achieving improved conformity in VMAT and gamma knife stereotactic radiosurgery for vestibular schwannoma. *Radiother Oncol*. 2015;115(2):229–234, http://dx.doi.org/10.1016/j.radonc.2015.03.031.
12. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991;21:109–122, http://dx.doi.org/10.1016/0360-3016(91)90171-y.
13. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Boil Phys*. 2010;76:S3–S9, http://dx.doi.org/10.1016/j.ijrobp.2009.09.040.
14. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014;32:3810–3816, http://dx.doi.org/10.1200/JCO.2014.57.2909.
15. Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT): contents. *J ICRU*. 2010;10(1), http://dx.doi.org/10.1093/jicru/ndq002. NP.
16. Feuvret L, Noël G, Mazeron J-J, Bey P. Conformity index: a review. *Int J Radiat Oncol Biol Phys*. 2006;64(2):333–342, http://dx.doi.org/10.1016/j.ijrobp.2005.09.028.
17. McCollough WM, Marcus Jr RB, Rhoton Jr AL, Ballinger WE, Million RR. Long-term follow-up of radiotherapy for pituitary adenoma: the absence of late recurrence after greater than or equal to 4500 cGy. *Int J Radiat Oncol Biol Phys*. 1991;21:607–614, http://dx.doi.org/10.1016/0360-3016(91)90677-V.
18. Brada M, Rajan B, Traish D, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol (Oxf)*. 1993;38:571–578, http://dx.doi.org/10.1111/j.1365-2265.1993.tb02137.x.
19. Tsang RW, Brierly 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;30:557–565, http://dx.doi.org/10.1016/0360-3016(92)90941-A.
20. Zierhut D, Flentje M, Adolph J, Erdmann J, Raue F, Wannenmacher M. External radiotherapy of pituitary adenomas. *Int J Radiat Oncol Biol Phys*. 1995;33:307–314, http://dx.doi.org/10.1016/0360-3016(95)00071-6.
21. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. *Clin Endocrinol (Oxf)*. 2006;64:542–548, http://dx.doi.org/10.1111/j.1365-2265.2006.02506.x.
22. Kong DS, Lee JI, Lim DH, et al. The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas (long-term results of 125 consecutive patients treated in a single institution). *Cancer*. 2007;110(4):854–860, http://dx.doi.org/10.1002/cncr.22860.
23. Pan CC, Eisbruch A, Lee JS, et al. Prospective study of inner ear radiation dose and hearing loss in head and neck cancer patients. *Int J Radiat Oncol Biol Phys*. 2005;61:1393–1402, http://dx.doi.org/10.1016/j.ijrobp.2004.08.019.
24. Kretschmer M, Sabatino M, Blechschmidt A, et al. The impact of flattening-filter-free beam technology on 3D conformal RT. *Radiat Oncol*. 2013;8(133), http://dx.doi.org/10.1186/1748-717X-8-133.
25. Deng X, Yang Z, Liu R, et al. The maximum tolerated dose of gamma radiation to the optic nerve during gamma knife radiosurgery in an animal study. *Stereotact Funct Neurosurg*. 2013;91:79–91, http://dx.doi.org/10.1159/000343212.
26. Brecht S, Boda-Heggemann J, Budjan J. Radiation-induced optic neuropathy after stereotactic and image guided intensity-modulated radiation therapy (IMRT). *Radiother Oncol*. 2019;134:166–177, http://dx.doi.org/10.1016/j.radonc.2019.02.003.
27. Doroslovacki P, Tamhankar MA, Liu GT, et al. Factors associated with occurrence of radiation-induced optic neuropathy at "safe" radiation dosage. *Semin Ophthalmol*. 2018;33(4):581–588, http://dx.doi.org/10.1080/08820538.2017.1346133.
28. 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):S28–5, http://dx.doi.org/10.1016/j.ijrobp.2009.07.1753.
29. van den Bergh AC, Dullaart RP, Hoving MA, et al. Radiation optic neuropathy after external beam radiation therapy for acromegaly. *Radiother Oncol*. 2003;68:95–100, http://dx.doi.org/10.1016/S0167-8140(03)00202-0.
30. Mackley HB, Reddy CA, Lee SY, et al. Intensity-modulated radiotherapy for pituitary adenomas: the preliminary report of the Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys*. 2007;67:232–239, http://dx.doi.org/10.1016/j.ijrobp.2006.08.039.
31. Aristizabal S, Caldwell WL, Avila J. The relationship of time-dose fractionation factors to complications in the treatment of pituitary tumors by irradiation. *Int J Radiat Oncol Biol Phys*. 1977;2:667–673, http://dx.doi.org/10.1016/0360-3016(77)90046-3.
32. Gondi V, Tomé WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol*. 2010;97:370–376, http://dx.doi.org/10.1016/j.radonc.2010.09.013.
33. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys*. 2006;65:1–7, http://dx.doi.org/10.1016/j.ijrobp.2006.01.027.
34. Brada M, Ford D, Ashley S, et al. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ*. 1992;304(6838):1343–1346, http://dx.doi.org/10.1136/bmj.304.6838.1343.
35. Loeffler JS, Niemierko A, Chapman PH. Second tumor after radiosurgery: tip of the iceberg or a bump in the road? *Neurosurgery*. 2003;52(6):1436–1440, http://dx.doi.org/10.1227/01.neu.0000064809.59806.e8.
36. Wiggenraad RGJ, Petoukhova AL, Versluis L, van Santvoort JPC. Stereotactic radiotherapy of intracranial tumors: a comparison of intensity-modulated radiotherapy and dynamic conformal arc. *Int J Radiat Oncol Biol Phys*. 2009;74:1018–1026, http://dx.doi.org/10.1016/j.ijrobp.2008.09.057.