Cerebrovascular Events, Secondary Intracranial Tumors, and Mortality After Radiotherapy for Nonfunctioning Pituitary Adenomas: A Subanalysis From the Dutch National Registry of Growth Hormone Treatment in Adults

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Context: Radiotherapy is frequently administered as adjuvant treatment in patients with clinically nonfunctioning pituitary adenomas (NFPAs). However, concerns have been raised about potential long-term side effects, including cerebrovascular events (CVEs) and secondary intracranial tumors.

Objective: The aim of this study was to analyze the risk of CVEs, secondary intracranial tumors, and mortality in irradiated (IRR) NFPA patients, compared with NFPA patients who were not irradiated (non-IRR).

Design, Setting, and Patients: The study cohort included 806 patients with a NFPA from the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide long-term surveillance study in severe GH-deficient adult patients. IRR patients (n = 456) were compared with non-IRR patients (n = 350).

Main Outcome Measures: CVEs, secondary intracranial tumors, and mortality were measured.

Results: Sixty-nine subjects developed a CVE. In men, but not in women, the incidence of a CVE was significantly higher in IRR patients than in non-IRR patients (hazard ratio 2.99, 95% confidence interval 1.31–6.79). A secondary intracranial tumor developed in five IRR patients and two non-IRR patients. After adjustment for age, radiotherapy was not associated with mortality.

Conclusions: The incidence of secondary intracranial tumors and mortality did not differ between IRR and non-IRR patients. However, a CVE was found significantly more frequently in IRR men but not in women. Further research into the long-term effects of cranial radiotherapy seems mandatory. The potential risks of radiotherapy have to be taken into account when radiotherapy is considered in NFPA patients, and long-term follow-up is recommended. (***J Clin Endocrinol Metab*** **100: 1104–1112, 2015)**

Pituitary adenomas (PAs) are benign neoplasms of the pituitary gland, comprising approximately 8% of all primary brain and central nervous system tumors (1). In a recent Finnish study, approximately 36% of all PAs were clinically nonfunctioning pituitary adenomas (NFPAs), of which 82% were macroadenomas (2). In contrast to hor-

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Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; CVE, cerebrovascular event; GHD, GH deficiency; GHT, GH treatment; IRR, irradiated; NFPA, nonfunctioning PA; non-IRR, not irradiated; PA, pituitary adenoma.

mone-secreting PAs, NFPAs are not characterized by hormonal overproduction but usually present with symptoms and signs of tumor mass effects, such as visual field defects and hypopituitarism, often including GH deficiency (GHD) (3).

The primary treatment of choice for NFPAs is pituitary surgery, which aims at complete tumor removal or debulking and relieve of tumoral mass effects on adjacent structures, especially the optic chiasm. Losa et al (4) described that complete surgical removal may be achieved in more than 50% of the cases, although tumors may recur afterward. In case of substantial residual tumor or tumor progression, adjuvant radiotherapy is often advocated (5). Although beneficial effects of radiotherapy in terms of local tumor control have been described, its use in the management of NFPAs, especially prophylactically, is still a subject of debate because concerns remain about potential long-term side effects (3, 6–11). The most common observed side effect is the gradual development of hypopituitarism (12, 13). However, concerns have also been raised about other side effects, such as cerebrovascular disease and the development of secondary intracranial tumors, and their possible effects on mortality. In a cohort of 331 patients treated with pituitary surgery and radiotherapy, Brada et al observed a relative risk of cerebrovascular accident (CVA) of 4.1 compared with the general population, thereby suggesting a possible role for radiotherapy (14). Although some studies confirm this potential relationship between pituitary irradiation and cerebrovascular events (CVEs) and CVE-related deaths (8, 14, 15), other studies found no or less clear associations (16, 17).

Conflicting results have also been reported with regard to the development of secondary intracranial tumors after pituitary irradiation. Although some studies showed increased risks of secondary intracranial tumors (18, 19), other investigators found no firm indications for an increased risk (20–22).

Because most of these previous studies included patients with various types of PAs, interpretation of the results for NFPA patients specifically is complicated. Also, findings in PA patients were usually, although not in all cases, compared with those in a normal reference population, in whom other potentially contributing factors related to the PAs and their treatments are not applicable.

Therefore, we aimed to investigate the risk of CVEs, secondary intracranial tumors, and mortality in a large cohort of patients with a NFPA, using data from the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide long-term surveillance study in severe GHD adult patients, thereby comparing NFPA patients who received radiotherapy with those who did not receive radiotherapy.

Materials and Methods

Study population

The Dutch National Registry of Growth Hormone Treatment in Adults was initiated in 1998 by the Dutch Ministry of Health to gain more insight into the long-term efficacy, safety, and costs of GH treatment (GHT) in GHD adults. From that time on, reimbursement of GHT costs was linked to approval of the indication, severe GHD, by an independent board of endocrinologists as well as entry of anonymous patient data into the registry. All patients were informed by their attending physician. Severe GHD was diagnosed according to the Growth Hormone Research Society consensus guidelines (23). Data collection, patient characteristics, and test procedures have previously been described in more detail (24). The registry contains not only the follow-up data of most GHD patients who were treated with GHT but also the GHD patients in whom GHT was not commenced or (temporarily) discontinued for various reasons. Reasons for not commencing with or discontinuation of GHT have been described previously (25). Until data closure in 2009, a total of 2891 severe GHD adults were entered into the nationwide database.

For the present study, severe GHD patients with a NFPA were selected (n = 887). Patients from whom data could not be collected by a trained monitor due to application shortly before closure of the database in 2009, leading to insufficient follow-up, were excluded (n = 75). In addition, patients with inconclusive data on whether they had received pituitary radiotherapy (n = 6) were also excluded. Compared with those included in the study, excluded patients had a similar age at the diagnosis of the NFPA, gender, and onset of GHD.

Measurements

The data of all registered patients were collected (bi-)annually from medical records by specially trained monitors from the start of enrollment in the registry. When GHT had already been started before the first monitor visit, data were retrospectively retrieved. Collected data were checked for accuracy both before and after entry into the database. Also, in approximately 10% of the patients, data were collected twice by different monitors as an internal quality control.

The diagnosis of NFPA, made at the discretion of the attending physician, was verified at entry into the database, according to the collected data.

Relevant medical history and adverse events were searched and recorded thoroughly and coded for, among others, CVEs and secondary intracranial brain tumors. CVEs included CVAs and transient ischemic attacks. The date of the CVE or secondary intracranial tumor was that of the first recorded event. Cause and date of death were retrieved from medical records and death certificates from the Dutch Central Bureau of Statistics, as described previously (25).

Data concerning the treatment of the NFPAs, such as number, type, and timing of surgical procedures and radiotherapy, were also collected.

The GH dose was titrated on an individual basis by the attending physician with the purpose of achieving and maintaining age- and gender-specific normalized IGF-1 SD scores. Changes in GH dosage were recorded and the mean dose per patient was calculated as the cumulative dosage divided by the sum of GHT days. Other pituitary hormone deficiencies in addition to GHD were identified through recorded deficiencies and hormonal re-

placement therapies, based on diagnostic test performed by the attending physicians, at the start of registration and during follow-up. These deficiencies were adequately substituted at the discretion of the attending endocrinologist. The use of antiplatelet and anticoagulant medication, smoking status, and alcohol use were also recorded from the start of entry into the registry.

Statistical analysis

Continuous variables were expressed as either mean (SD) or median (range), whereas categorical variables were expressed as number (percentage). Parametric or nonparametric tests were used when appropriate. Kaplan-Meier survival curves were obtained to estimate the cumulative incidence of CVE in irradiated (IRR) and nonirradiated (non-IRR) patients, starting from the date of radiotherapy or diagnosis, respectively.

Cox proportional hazard analyses were used to study the association between radiotherapy and mortality risk and the risk of developing a CVE, respectively. Time was measured from the first date of radiotherapy for the IRR group and from the date of diagnosis of the NFPA for the non-IRR group, until the date of death or last follow-up in the mortality analyses. In the CVE analyses, time ended at the date of the first CVE, death, or last follow-up, whichever occurred first. Assumptions of proportional hazards were tested by log minus log plots and interaction terms. To examine relevant confounding, potentially influencing variables were added separately to the age and gender adjusted models. Variables that gave a change in the regression coefficient of greater than 10% were included in the model. Potentially confounding variables that were evaluated were GHT (yes or no), extension of pituitary deficiency (isolated GHD or multiple pituitary hormone deficiencies), and pituitary surgery (yes or no). In addition, ACTH insufficiency was also evaluated in the mortality analyses, whereas a history of CVE (unknown in eight subjects) was also considered in the CVE analyses. All continuous variables were individually checked for linearity with the outcome variables and in case of nonlinearity divided in categories. Potential effect modification by gender was examined by adding an interaction term to the fully adjusted model. In case of a value of $P < .10$, analyses were presented in stratified groups.

Sensitivity analyses were performed in the fully adjusted model for the risk of developing a CVE by excluding users (current or former) of anticoagulant or antiplatelet medication separately.

Due to the low number of events, the occurrence of secondary intracranial tumors is presented descriptively.

All statistical analyses were performed using the statistical software package IBM SPSS Statistics version 20. Two-sided values of $P \leq .05$ were considered significant.

Results

Patient characteristics

A total of 806 patients, 313 females (38.8%), with a mean age at the time of NFPA diagnosis of 48.3 (13.3 standard deviation) years, were included in the study. Almost all patients (95.5%) were treated with GHT, for a median period of 5.2 (0.03–20.2 range) years. The characteristics of IRR and non-IRR patients are shown in Table 1. Most IRR patients (63.8%) were treated with conventional radiotherapy, whereas a minority (5.9%) received stereotactic radiotherapy. In the remaining patients, data on radiotherapy modality were not available. The mean radiation dose, which was unknown in 104 patients, was 46.2 (6.1 standard deviation) Gy. Six patients (1.3%) were treated twice with radiotherapy.

The median follow-up time for the entire cohort was 10.0 (0.1–54.5 range) years. Median follow-up was 6.6 (0.5–48.8 range) years for non-IRR patients and 12.7 (0.1–54.5 range) years for IRR patients ($P < .001$).

Cerebrovascular events

Of the 806 patients, 69 (8.6%) had a CVE during follow-up (Table 2). In 15 of these cases (21.7%), two or more CVEs occurred. Mean age at the time of first CVE was 62.8 (10.3 standard deviation) years.

A CVA was observed in 37 cases (53.6%) and a transient ischemic attack in 25 cases (36.2%), whereas in the remaining cases, the first CVE was not further specified. Median time between NFPA diagnosis and the first CVE was 10.8 (0.4–51.0 range) years.

To analyze the association between radiotherapy and the risk of developing CVE, Cox proportional hazard analysis was used (Table 3). The analyses were stratified for gender because a significant interaction between radiotherapy and gender was observed ($P = .02$). Although several potential confounders were tested (GHT, extension of pituitary deficiency, pituitary surgery, and history of CVE), age was found to be the only relevant confounder. In both the crude and the adjusted model, the risk of developing a CVE was approximately 3 times higher in IRR men than in non-IRR men. In women, no significant associations were found. Separate exclusion of anticoagulant or antiplatelet medication users from the analyses did not substantially influence the results.

In Figure 1, the Kaplan-Meier curves describing the cumulative incidence of CVEs in IRR and non-IRR patients, according to gender, are shown. Median duration of GHT in men who developed a CVE was 6.2 (0.4–15.2 range) years, compared with 5.0 (0.03–15.6 range) years in men who did not develop a CVE ($P = .06$). In women, the median duration of GHT in those who did or did not develop a CVE was 3.5 (0.7–12.2 range) and 5.7 (0.07–20.2 range) years, respectively ($P = .22$). Median radiation dose, which was unknown in 31 patients, did not differ significantly between men and women with a CVE [46.0 (5–60 range) vs. 46.0 (42–45 range) Gy, $P = .87$].

Secondary intracranial tumors

Seven patients (0.9%) developed a secondary intracranial tumor, at a mean age of 60 (12.7 standard deviation) years (Table 4). None of the patients had a history of prior

Table 1. Characteristics of IRR and Non-IRR Patients With a NFPA

	No Radiotherapy	Radiotherapy	*P* Value[a]
Patients, n	350 (43.3)	456 (56.6)	
Gender			.15
Males	224 (64.0)	269 (59.0)	
Females	126 (36.0)	187 (41.0)	
Age at NFPA diagnosis, y [mean (SD)]	51.6 (13.8)	45.7 (12.2)	<.001
Extension of pituitary insufficiency, IGHD	13 (10.4)	11 (13.6)	.28
ACTH insufficiency	267 (76.3)	404 (88.6)	<.001
TSH insufficiency	275 (78.6%)	420 (92.1)	<.001
LH/FSH insufficiency	283 (80.9)	390 (85.5)	.08
ADH insufficiency	64 (18.3)	60 (13.2)	.05
PRL insufficiency	4 (1.1)	3 (0.7)	.46
Three or more other pituitary hormone deficits	210 (60.0)	352 (77.2)	<.001
Onset of GHD, childhood onset	2 (0.6)	3 (0.7)	.88
Pituitary surgery	302 (86.3)	452 (99.1)	<.001
Time between treatment NFPA and start GHT, y [median (range)][b]	1.7 (−1.6 to 34.9)	5.6 (−1.5 to 46.0)	<.001
Duration of follow-up, y [median (range)]	6.6 (0.5–48.8)	12.7 (0.1–54.5)	<.001
GHT	328 (93.7)	442 (96.9)	.03
GH dose, mg/d [median (range)]	0.27 (0.04–1.3)	0.28 (0.06–1.1)	.21
Duration of GHT, y [median (range)]	3.4 (0.03–15.1)	6.7 (0.04–20.2)	<.001
Smoking[c]			.27
Yes	91 (32.6)	101 (26.9)	
Former	68 (24.4)	97 (25.8)	
No	120 (43.0)	178 (47.3)	
Alcohol use[d]	114 (50.7)	143 (46.7)	.37
Use of anticoagulant medication[e]	21 (6.0)	25 (5.5)	.76
Use of antiplatelet medication[e]	67 (19.2)	94 (20.7)	.60
CVE	16 (4.6)	53 (11.6)	<.001

Abbreviations: IGHD, isolated GHD; ADH, antidiuretic hormone; PRL, prolactin. Variables are presented as number (percentage) unless stated otherwise.

[a] Continuous variables were tested with either the Student's *t* test or the Mann-Whitney *U* test. Categorical variables were examined with the χ^2 test.

[b] Time from surgery or primary radiotherapy for the NFPA or first confirmation of the NFPA on pituitary imaging when no surgery or radiotherapy was initiated until start of GH treatment.

[c] Missing (n = 151).

[d] Missing (n = 275).

[e] Missing (n = 3).

intracranial tumor in addition to a NFPA. Median duration between NFPA and secondary intracranial tumor diagnosis was 12.7 (0.7–42.4 range) years. Of the five patients with a secondary intracranial tumor who received GHT, for a median time of 8.3 (0.2–13.2 range) years, GHT was started 0.22, 8.9, and 11.2 years, respectively, before the secondary intracranial tumor diagnosis in three patients and 2.3 and 30.1 years, respectively, after the diagnosis in two patients. In the former group, GHT was stopped around the time of tumor diagnosis.

Of all non-IRR patients, two (0.6%) developed a secondary intracranial tumor, whereas five of all IRR patients (1.1%) developed a secondary intracranial tumor. Median radiation dose did not differ significantly between IRR patients who did or did not develop a second tumor [45.5 (44–51) vs. 46.0 (5–60) Gy, $P = .76$].

Mortality

In the total study population, 54 deaths (6.7%), at a mean age of 68.4 (10.2 standard deviation) years, were observed. Median time between NFPA diagnosis and death was 11.8 (0.6–54.5 range) years and 32 patients (59.3%) were males.

Of the 69 patients who developed a CVE during follow-up, 17 (24.6%) died, due to a CVA in six cases (35.4%). Two of the seven patients with a secondary intracranial neoplasm (40%), both with a glioma, died 2 and 6 months, respectively, after the second tumor diagnosis. Of all deceased patients, 32 (59.3%) had received radiotherapy.

In the Cox proportional hazard analyses on the association between radiotherapy and mortality risk, no significant interaction with gender was found. After adjustment for relevant confounders (age, gender, treated ACTH insufficiency, and GHT), mortality was not significantly different between IRR and non-IRR patients (Table 5).

Discussion

To our knowledge, this is the largest cohort of NFPA patients in which the occurrence of CVEs, secondary intra-

Table 2. Characteristics of NFPA Patients With and Without a CVE During Follow-Up

	No CVE	CVE	*P* Value[a]
Patients, n	737 (91.4)	69 (8.6)	
Gender			.47
Males	448 (60.8)	45 (65.2)	
Females	289 (39.2)	24 (34.8)	
Age at NFPA diagnosis, y [mean (SD)]	48.1 (13.2)	49.8 (13.7)	.33
Extension of pituitary insufficiency, IGHD	24 (3.3)	0 (0.0)	.26
Three or more other pituitary hormone deficits	513 (69.6)	49 (71.0)	.81
Pituitary surgery	687 (93.2)	67 (97.1)	.30
Radiotherapy	403 (54.7)	53 (76.8)	<.001
Radiotherapy dose, Gy [mean (SD)][b]	46.2 (5.7)	45.6 (8.6)	.54
Dose of radiotherapy ≥50 Gy[b]	184 (58.6)	24 (63.2)	.59
Onset of GHD, childhood onset	5 (0.7)	0 (0.0)	1.00
GHT	704 (95.5)	66 (95.7)	.96
Duration of GHT, y [median (range)]	5.1 (0.03–20.2)	5.7 (0.4–15.2)	.40
Prior history of CVE[c]	21 (2.9)	1 (1.4)	.71

Abbreviation: IGHD, isolated growth hormone deficiency. Variables are presented as number (percentage) unless stated otherwise.

[a] Continuous variables were tested with either the Student's *t* test or the Mann-Whitney *U* test. Categorical variables were examined with the χ^2 test.

[b] Missing (n = 104).

[c] Missing (n = 8).

cranial tumors, and mortality was examined and compared between IRR and non-IRR patients. IRR men had a 3-fold increased risk of developing a CVE compared with non-IRR men. No association was observed in women. Only seven patients developed a secondary intracranial tumor, including five IRR patients. Radiotherapy was not associated with mortality after adjustment for relevant confounders.

Several studies have explored the incidence of cerebrovascular disease in IRR PA patients. In a study by Sattler et al (16), postoperative radiotherapy, in comparison with surgery alone, was not associated with an increased risk of stroke in a cohort of 462 patients. However, the number of strokes in the total study population, 25 (5.4%), was relatively low, which may have limited the ability to detect differences. Compared with the expected number of strokes in a Dutch reference population, the incidence in PA patients was increased (16). Similarly, two other studies found increased incidences of cerebrovascular disease in IRR PA patients compared with a normal reference population (8, 14), whereas in another early study, this was not observed (26).

Except for the study by Sattler et al (16), all of these studies compared the CVE incidence in IRR PA patients with the incidence in a normal reference population (8, 14, 16, 26). Comparison with non-IRR PA patients may be more informative because in that way potential disease-related factors apply to both groups. Another difference between previous studies and the present study is the inclusion of different types of PAs. This may have influenced the results because GH-producing PAs, for instance, have been associated with an increased risk of cerebrovascular diseases (14, 15).

In our study, an increased CVE risk was observed only in IRR men. Gender differences have also been reported by others but notably with poorer outcomes for women (8, 14, 15, 17). Gonadal insufficiency and (inadequate) hormonal replacement therapy have been proposed as possible contributing factors to explain the differences between the two genders (17, 27). Although ACTH insufficiency occurred more often in IRR patients than in non-IRR patients in our study, the percentage of patients receiving gonadal replacement therapy was similar in both groups. Possibly, due to the low occurrence of CVEs in women, the power to detect an association was too low. Interestingly, in a previous study from our registry regarding GHT and

Table 3. Cox Proportional Hazard Analyses for the Association Between Radiotherapy and the Risk of Developing a CVE Over Time, According to Gender, in Patients With a NFPA

	CVE			
	Crude Model HR (95% CI)	*P* Value	Model 1 HR (95% CI)	*P* Value
Males				
No IRR	Reference		Reference	
IRR	2.51 (1.11–5.67)	.03	2.99 (1.31–6.79)	.01
Females				
No IRR	Reference		Reference	
IRR	0.62 (0.26–1.46)	.27	0.79 (0.32–1.93)	.61

Abbreviation: HR, hazards ratio. Analyses were stratified for gender (*P* value interaction term for gender, .02). Model 1 was adjusted for age at the diagnosis of NFPA.

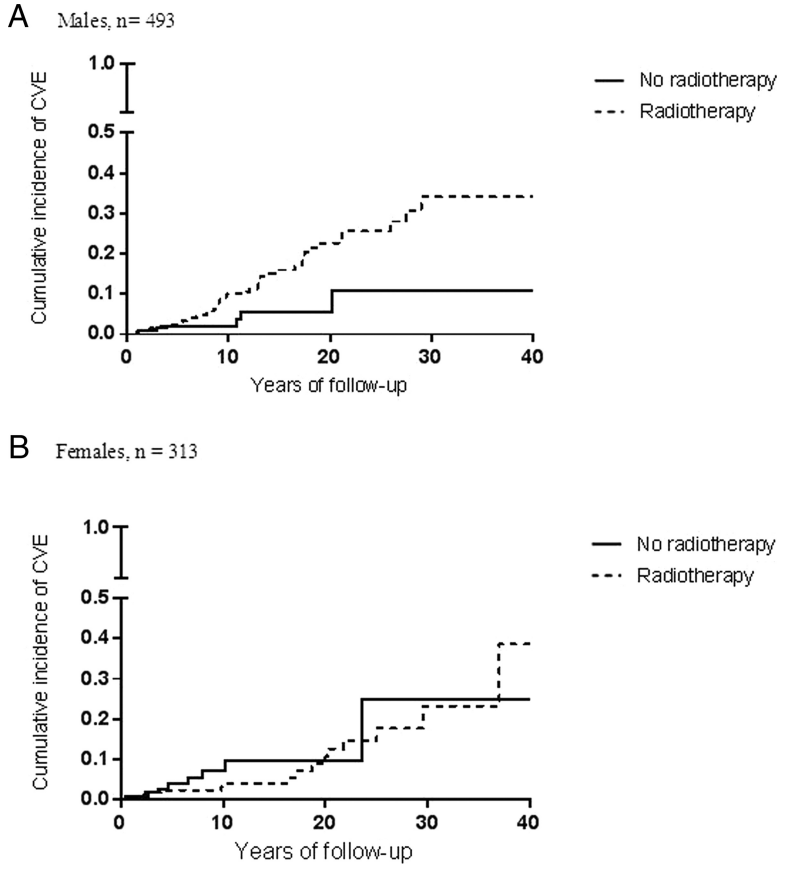

Figure 1. Kaplan-Meier curves of the cumulative incidence of cerebrovascular events in IRR and non-IRR patients with a NFPA. A, Males (n = 493). B, Females (n = 313).

mortality, mortality due to cardiovascular diseases was increased in women but not in men (25). However, mortality due to CVA was not significantly different between the two genders (25).

In a recent systematic review, an increased CVE risk after radiotherapy for various types of head or neck cancer was demonstrated, which is in line with our results (28). However, data regarding possible underlying pathological mechanisms are scarce. A possible mechanism is the directly damaging effect of radiation to the cerebral vasculature (28–30), which may result in the development of clinically significant stenosis (28).

Hypopituitarism, especially GHD, has been associated with an increase in cardiovascular risk factors (31) and has therefore been proposed as another contributing factor (17). In patients with hypopituitarism, increased cerebrovascular mortality has been described (27, 32). However, the influence of radiotherapy in this relationship is unclear. Erfurth et al (17) hypothesized that the long-term effects of inadequately substituted or unsubstituted pituitary insufficiency, possibly in combination with the effects of radiotherapy on the cerebral vasculature, may contribute to the increased cerebrovascular disease mortality in women. Although data on the duration of unsubstituted hypopituitarism were not available in the present study, multiple regression analyses did not identify substituted pituitary deficiencies as a relevant confounder. Likewise, GHT, which was used in approximately 95% of the patients, was not a relevant confounder either, which suggests that GHT did not substantially contribute to the increased CVE risk in IRR men in the present study, even though the duration of GHT tended to be longer in men who developed a CVE compared with those who did not.

Another study reported that the extent of pituitary surgery (macroscopic or biopsy/none) and higher radiotherapy dose were possible risk factors for CVAs (14). In our

Table 4. Characteristics of Patients With a NFPA Who Developed a Secondary Intracranial Tumor During Follow-Up

	Gender	Age at Diagnosis NFPA, y	Secondary Intracranial Tumor Type	Time Between NFPA and Secondary Intracranial Tumor, y	GHT	Pituitary Surgery	Radiotherapy Type/Dose, Gy	Time Between Radiotherapy and Secondary Intracranial Tumor, y
IRR	Male	49	Vestibular schwannoma	0.7	Yes	Yes	External/45	0.3
	Male	33	Meningioma	27	No	Yes	External/46	27
	Male	36	Meningioma	1	Yes	Yes	External/na	0.8
	Female	17	Meningioma	42	Yes	Yes	External/44	First IRR: 42; second IRR: 34
	Male	57	Malignant glioma	13	Yes	Yes	External/51	12
Non-IRR	Female	54	Malignant glioma	1	Yes	Yes	na	na
	Male	51	Meningioma	24	No	Yes	na	na

Abbreviation: na, not applicable or data not available.

Table 5. Cox Proportional Hazard Analyses for the Association Between Radiotherapy and Mortality Risk in Patients With a NFPA

	Mortality					
	Crude Model		Model 1		Model 2	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Non-IRR	Reference		Reference		Reference	
IRR	0.56 (0.32–0.98)	.04	0.90 (0.50–1.63)	.73	0.89 (0.46–1.58)	.62

Abbreviation: HR, hazards ratio. Analyses were not stratified for gender (*P* value interaction term for gender, .41). Model 1 was adjusted for age at diagnosis of NFPA and gender. Model 2 was adjusted for age at diagnosis of NFPA, gender, treated ACTH insufficiency, and GH therapy.

study, pituitary surgery did not emerge as a relevant factor in the analyses.

Although our radiation dose data should be interpreted with caution, doses did not significantly differ between patients who did and did not develop a CVE. This is in accordance with the study by Erfurth et al, in which several radiation parameters were not significantly associated with cerebrovascular death (17).

Whether radiotherapy induces secondary intracranial tumor formation in PA patients is still a matter of discussion. Two studies, with relatively few observed cases, found relative risks of 10.5 [95% confidence interval (CI) 4.3–16.7] and 16 (95% CI 4.4–41), respectively, in PA patients in comparison with a reference population (18, 19). Another study reported a standard incidence ratio of 5.2 (95% CI 1.9–11.31) (33). However, intracranial tumors may be detected earlier in PA patients than in persons from a normal population because PA patients are subject to close follow-up, including regular brain imaging.

In the present study, no firm indications were observed for an increased risk of secondary intracranial tumors. These results are in line with other published series (20–22).

Similar to other studies (18–20, 22, 33), meningiomas and gliomas were the most frequently encountered secondary intracranial tumors. It has been suggested that meningiomas tend to develop later after radiotherapy than gliomas and that they may occur as late as 30 years after radiotherapy (19, 34). In the present study, a meningioma was diagnosed in one IRR patient 42 years after the first radiotherapy. However, in another IRR patient, a meningioma was found within 1 year after radiotherapy, which therefore questions its relationship with the radiotherapy. In the one IRR who developed a glioma, the diagnosis was made 12 years after radiotherapy, which is in line with the latency period of 8–15 years for gliomas reported by Tsang et al (18).

Except for one patient who was irradiated twice, the radiation dose did not differ between patients who did and did not develop a secondary intracranial tumor. An increased risk of meningiomas with higher radiation doses has been described (35). With the advent of newer radiation techniques offering the ability for more localized radiation, it has been postulated that the occurrence of long-term side effects may decrease (29). Nevertheless, long-term follow-up studies comparing older and newer radiation techniques are scarce (36).

Because associations have been observed between higher IGF-1 levels and neoplasms, concerns have been raised about the potential oncogenic effect of GHT (37). Although a full evaluation of this particular subject is beyond the scope of the present study, only three patients had received GHT prior to the development of a secondary intracranial tumor. Additionally, in a previous study, we did not find increased malignancy-related mortality in patients receiving GHT (25), which is in agreement with other published data (38).

Radiotherapy was not associated with mortality in the present study. Several studies have described increased mortality, mainly due to cerebrovascular diseases, in patients with hypopituitarism and/or PAs (15, 27, 32). Comparison and interpretation of these studies, however, are complicated due to a wide variation in underlying disorders, treatment modalities, definitions, and duration of follow-up.

In a previous study from our registry, cerebrovascular mortality was significantly higher in IRR patients than in non-IRR patients receiving GHT (25). All-cause mortality, however, did not differ between the two groups. This was also observed in the present study, in which we further analyzed potential influencing factors. After adjustment for age and other relevant confounders, including GHT, mortality was similar in IRR and non-IRR patients. This is in agreement with the findings by Sattler et al (20). Tomlinson et al (27) observed no effect of radiotherapy on mortality in a subanalysis with hypopituitary patients with a NFPA.

A major strength of the present study includes the large cohort of NFPA patients, which enables comparison of IRR and non-IRR patients. In addition, thorough registration of events was ensured through (bi-)annual monitoring by specially trained nurses. However, it should be

taken into account that, because the database was set up around the start of GHT, events before that date could have been underreported, even though data were also retrospectively collected. Also, the follow-up time differed between IRR and non-IRR patients because the indication for radiotherapy gradually declined through the years due to improvements in imaging and surgical techniques (16). This may have influenced the results. However, differences in follow-up time have also been observed in other published series comparing IRR and non-IRR patients (16, 20, 33). Details on stroke type and radiotherapy protocol were unfortunately not available in the present study.

The clinical decision to administer radiotherapy was not randomized in this observational study. However, due to the nature of NFPAs and the long-term follow-up required to detect long-term adverse events, randomized controlled trials may not be feasible. Finally, it should be kept in mind that only NFPA patients with severe GHD, and not those with an intact GH-IGF-1 axis, were included in the study population. Nevertheless, as such, the study population provides useful information.

In conclusion, in this large cohort of NFPA patients, a 3-fold increased risk of CVE was demonstrated in IRR men compared with non-IRR men but not in women. Furthermore, secondary intracranial tumors were not encountered more often in IRR patients than in non-IRR patients, and radiotherapy was not associated with increased mortality. Although possible causative underlying mechanisms remain to be elucidated, these data suggest that pituitary radiotherapy may increase the risk of CVE, especially in men. The benefits of radiotherapy should be carefully balanced against potential long-term side effects. Continuous surveillance of IRR patients is required. Further prospective research is needed to evaluate long-term effects and the safety of radiotherapy in NFPA patients.

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