



# Risk of second brain tumour after radiotherapy for pituitary adenoma or craniopharyngioma: a retrospective, multicentre, cohort study of 3679 patients with long-term imaging surveillance

Ross Hamblin, Ashley Vardon, Josephine Akpalu, Metaxia Tampourlou, Ioannis Spiliotis, Emilia Sbardella, Julie Lynch, Vani Shankaran, Akash Mavilakandy, Irene Gagliardi, Sara Meade, Claire Hobbs, Alison Cameron, Miles J Levy, John Ayuk, Ashley Grossman, Maria Rosaria Ambrosio, Maria Chiara Zatelli, Narendra Reddy, Karin Bradley, Robert D Murray, Aparna Pal, Niki Karavitaki

## Summary

**Background** Radiotherapy is a valuable treatment in the management algorithm of pituitary adenomas and craniopharyngiomas. However, the risk of second brain tumour following radiotherapy is a major concern. We assessed this risk using non-irradiated patients with the same primary pathology and imaging surveillance as controls.

**Methods** In this multicentre, retrospective cohort study, 4292 patients with pituitary adenoma or craniopharyngioma were identified from departmental registries at six adult endocrine centres (Birmingham, Oxford, Leeds, Leicester, and Bristol, UK and Ferrara, Italy). Patients with insufficient clinical data, known genetic predisposition to or history of brain tumour before study entry (n=532), and recipients of proton beam or stereotactic radiotherapy (n=81) were excluded. Data were analysed for 996 patients exposed to 2-dimensional radiotherapy, 3-dimensional conformal radiotherapy, or intensity-modulated radiotherapy, and compared with 2683 controls.

**Findings** Over 45246 patient-years, second brain tumours were reported in 61 patients (seven malignant [five radiotherapy, two controls], 54 benign [25 radiotherapy, 29 controls]). Radiotherapy exposure and older age at pituitary tumour detection were associated with increased risk of second brain tumour. Rate ratio for irradiated patients was 2.18 (95% CI 1.31–3.62, p<0.0001). Cumulative probability of second brain tumour was 4% for the irradiated and 2.1% for the controls at 20 years.

**Interpretation** Irradiated adults with pituitary adenoma or craniopharyngioma are at increased risk of second brain tumours, although this risk is considerably lower than previously reported in studies using general population controls with no imaging surveillance. Our data clarify an important clinical question and guide clinicians when counselling patients with pituitary adenoma or craniopharyngioma on the risks and benefits of radiotherapy.

**Funding** Pfizer.

**Copyright** © 2022 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license

## Introduction

Tumours of the sellar region account for 18% of all brain tumours,<sup>1</sup> with 88% of them being pituitary adenomas or craniopharyngiomas.<sup>2</sup> For those patients requiring active treatment, primary management is usually surgery aiming for total or partial tumour resection and, in cases of functioning pituitary adenomas, for remission of the hormonal hypersecretion.<sup>3</sup> Radiotherapy has been used in pituitary tumours for over a century,<sup>4</sup> and despite the advances in surgery and medical treatments, it remains a valuable tool in the management algorithm of primary or recurrent pituitary adenomas and of craniopharyngiomas.<sup>5–7</sup> Irradiation, however, is associated with late toxicities.<sup>5</sup> Amongst them, hypopituitarism has been the most well established,<sup>5</sup> whereas other late effects, including the risk of a second brain tumour, remain controversial—mainly due to their rarity and the long latency period required until they become apparent.

The association between ionising radiation and subsequent neoplasms is well recognised.<sup>8</sup> Cancer survivors who have received cranial irradiation during childhood have an increased risk of a second brain tumour, both when compared with healthy population controls,<sup>9</sup> and with non-irradiated children with the same primary disease.<sup>10</sup> Comparatively, the risk of a second brain tumour in an adult offered cranial radiotherapy for a brain tumour is less definitive.<sup>11</sup> Notably, reports based on the US Surveillance, Epidemiology and Results (known as SEER) cancer registries, suggest that there is an increased risk of a second brain tumour, but this is seen in both irradiated and non-irradiated adult patients compared with the general population.<sup>12</sup>

Studies investigating the risk of second brain tumours in cohorts of irradiated patients with pituitary adenomas or craniopharyngiomas specifically have yielded discordant

Lancet Diabetes Endocrinol 2022

Published Online

June 30, 2022

[https://doi.org/10.1016/S2213-8587\(22\)00160-7](https://doi.org/10.1016/S2213-8587(22)00160-7)

See Online/Comment

[https://doi.org/10.1016/S2213-8587\(22\)00171-1](https://doi.org/10.1016/S2213-8587(22)00171-1)

Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

(R Hamblin MBChB,

A Vardon MBChB,

J Akpalu MBChB,

M Tampourlou MD, J Ayuk MD,

N Karavitaki PhD); Centre for

Endocrinology, Diabetes and

Metabolism, Birmingham

Health Partners,

Birmingham, UK (R Hamblin,

A Vardon, J Akpalu,

M Tampourlou, J Ayuk,

N Karavitaki); Department of

Endocrinology (R Hamblin,

A Vardon, J Akpalu,

M Tampourlou, J Ayuk,

N Karavitaki) and

Department of Oncology

(S Meade MBChB),

Queen Elizabeth Hospital,

University Hospitals

Birmingham NHS

Foundation Trust,

Birmingham, UK; Oxford

Centre for Diabetes,

Endocrinology and

Metabolism (I Spiliotis PhD,

E Sbardella MD,

Prof A Grossman MD,

A Pal DPhil) and Department

of Clinical Oncology

(C Hobbs MSc), Oxford

University Hospitals NHS

Foundation Trust, Oxford,

UK; Department of Diabetes

and Endocrinology, Leeds

Teaching Hospitals NHS

Trust, St James's University

Hospital, Leeds, UK

(J Lynch BA,

V Shankaran MBBS,

R D Murray MD);

Department of Diabetes and Endocrinology, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK (A Mavilakandy MBChB, M J Levy MD, N Reddy MD); Section of Endocrinology and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy (I Gagliardi MD, M R Ambrosio MD, Prof M C Zatelli MD); Bristol Haematology and Oncology Centre (A Cameron MBChB) and Department of Endocrinology, Bristol Royal Infirmary (K Bradley DPhil), University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

Correspondence to: Dr Niki Karavitaki, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK  
n.karavitaki@bham.ac.uk

## Research in context

### Evidence before this study

We searched Medline, Embase, and Cochrane Library Central Databases using search terms: ("radiotherapy", OR "radiation", OR "radiation induced", OR "radiotherapy induced") AND ("pituitary adenoma", OR "pituitary tumo\*", OR "craniopharyngioma") AND ("second\*", OR "subsequent", OR "new") AND ("brain", OR "intracranial", OR "CNS") AND ("neoplasm", OR "tumo\*", OR "cancer", OR "malignancy"). 865 articles were identified from a search period ranging from 1947 to Jan 14, 2022. The last search was conducted on Jan 23, 2022. Case reports, studies without comparisons with non-irradiated participants, duplicate studies, those with overlapping populations, animal studies, as well as studies focusing on stereotactic or proton beam therapy, were excluded. 11 relevant retrospective cohort studies were identified looking at development of second brain tumours following radiotherapy for pituitary tumours in adults. There were no randomised control trials or meta-analyses. Data on the risk of a second brain tumour were conflicting, ranging from no risk to risk 16 times higher than that of the general population. All studies had methodological limitations, including the use of population controls without detailed imaging surveillance, small sample size, few case events, and selection biases. Current conclusions are thus, restricted, and the major concern on the true risk of a second brain tumour following radiotherapy for pituitary adenoma or craniopharyngioma remains to be addressed.

### Added value of this study

To our knowledge, this is the first study assessing the risk of a second brain tumour using a large cohort of non-selected

patients with pituitary adenomas or craniopharyngiomas treated or not treated with irradiation (2-dimensional radiotherapy [2DRT], 3-dimensional conformal radiotherapy [3DCRT], or intensity-modulated radiotherapy [IMRT] offered to most affected individuals during adult life), and observed for 45 246 patient-years, as defined strictly by imaging monitoring. We have shown that radiotherapy is associated with an increased risk of a second brain tumour (rate ratio 2.18 [95% CI 1.31–3.62], adjusted hazard ratio 1.82 [1.10–3.02]), the magnitude of which is more conservative than previous estimates.

### Implications of all the available evidence

These data suggest that radiotherapy (2DRT, 3DCRT, or IMRT) is associated with an 82% increase in the risk for a second brain tumour in irradiated patients compared with non-irradiated patients. This estimation is much lower than what has previously been reported in studies relying on general population controls, who in contrast to those exposed, undergo no imaging surveillance. The results inform clinical practice when counselling patients regarding this low risk. Appropriate follow-up protocols need to be established, which should also be based on research clarifying the acceptability, psychological impact on patients, safety of extra imaging studies, and cost of such surveillance. These protocols also need to consider the frequency of imaging monitoring dictated by the type and behaviour of each pituitary tumour. Further methodologically sound studies clarifying this risk in patients offered radiotherapy with other irradiation techniques are warranted.

outcomes; thus, some have suggested an increased risk of a second brain tumour,<sup>13–18</sup> whereas others could not confirm this finding.<sup>19–23</sup> The reasons for such disparity can in part be attributed to the low incidence of second brain tumours, the considerable follow-up period required given the tumour latency after radiotherapy, and to differences in study design and methodology. Many studies have estimated the risk of the irradiated cases based on expected rates of brain tumours in the general population,<sup>14,15,17,18</sup> a control group which, comparatively, is not subject to regular imaging surveillance, thereby restricting detection of possible asymptomatic second brain tumours. Furthermore, studies are challenged by small sample sizes,<sup>15,16,18,22</sup> very few observed events,<sup>17,19–21,23</sup> and wide CIs in the reported risks.<sup>14,16,18,22</sup> Moreover, the presence of selection biases,<sup>13,22,23</sup> including retrieval of patient cohorts from pharmaceutical industry registries or pituitary hormone deficiency databases,<sup>13,23</sup> the analysis of patients with non-functioning pituitary adenomas alone,<sup>23</sup> or the exclusion of those with acromegaly and Cushing's disease,<sup>22</sup> have restricted the potential to extrapolate the conclusions drawn to the non-selected cohorts encountered in routine clinical practice.

To overcome these limitations and seek an answer to this clinically important question, we performed a large multicentre study of patients offered radiotherapy for pituitary adenomas or craniopharyngiomas, and we estimated the risk of a second brain tumour in this population by comparing it with a control group of non-irradiated patients diagnosed with the same pathology, during a long imaging follow-up period.

## Methods

### Study design and participants

We conducted a multicentre, retrospective cohort study involving six adult endocrine centres (Queen Elizabeth Hospital Birmingham, Birmingham, UK; Churchill Hospital, Oxford, UK; Leeds Teaching Hospitals NHS Trust, Leeds, UK; University Hospitals of Leicester NHS Trust, Leicester, UK; Bristol Royal Infirmary, Bristol, UK, and Section of Endocrinology and Internal Medicine, Department of Medical Sciences, University of Ferrara, Ferrara, Italy).

All patients with a history of a pituitary adenoma or a craniopharyngioma detected before Dec 31, 2013, and managed with or without radiotherapy, were eligible for

inclusion. The cases were identified from the databases of each participating centre. Exclusion criteria were incomplete information in the medical records, absent or limited (second scan performed less than 3 months since tumour detection) imaging follow-up, a history of a CNS tumour detected either before, or at the time of (synchronous) pituitary tumour detection, a genetic predisposition to CNS tumours (eg, multiple endocrine neoplasia, neurofibromatosis or tuberous sclerosis), or a history of radioactive implants in the pituitary gland. Patients who had received stereotactic or proton beam radiotherapy were also excluded from the analyses.

Patients were in two groups, irradiated (exposure) or non-irradiated (control). Demographic, clinical, imaging, and, where applicable, relevant radiotherapy data were collected. Information on the diagnosis, management and outcomes of the patients diagnosed with a second brain tumour were also recorded.

An overview of the study design and number of participants included and excluded is highlighted in figure 1.

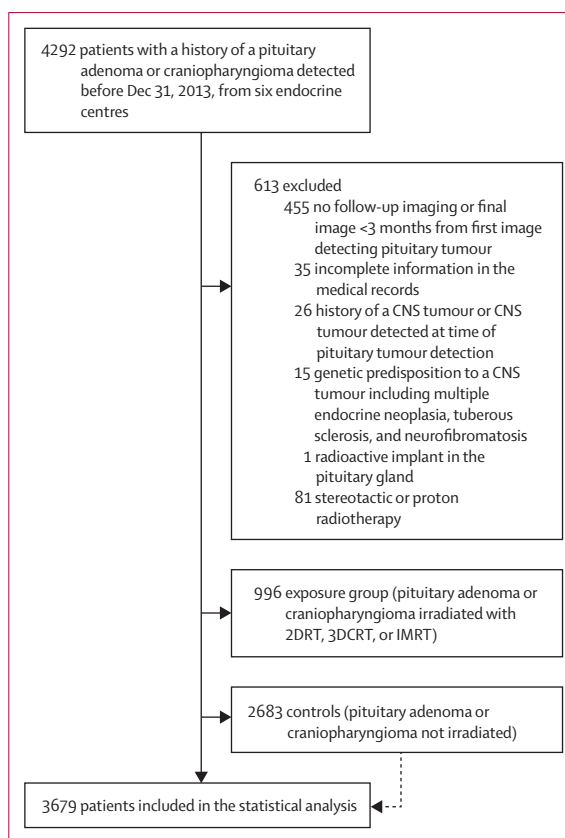
The study involved no intervention beyond routine patient care, and anonymised data were collected on a specific proforma. Institutional approval was obtained from each site before the contribution of retrospective data. Each site has patient consent waivers.

### Statistical analysis

Follow-up was defined by imaging dates, from time of radiotherapy until last imaging in the exposure group, and from time of pituitary tumour detection until last imaging in the control group. To prevent immortal time bias, the period of observation preceding delivery of radiotherapy in the exposure group (ie, interval between date of pituitary tumour detection and date of radiotherapy administration) was added to patient-years at risk for the control group. Percentages were used for categorical variables and medians with ranges for continuous variables.

A second brain tumour progression-free curve was generated by the Kaplan-Meier method, and the differences between the exposed and control groups were assessed by the log-rank test. Cox regression analysis was used to estimate the effect of a range of factors on second brain tumour development and hazard ratios (HR) with 95% CI were calculated. No significant departure from proportional hazards assumptions was identified for any of the variables. The incidence rate of second brain tumours with 95% CIs was estimated from the number of cases of second brain tumour divided by the amount of person-time at risk in each group (Mid-P exact test).

Given that this was a retrospective cohort study, we performed no calculation of power or sample size. The level of statistical significance was set at  $p < 0.05$ . Statistical analyses were conducted with IBM SPSS statistics for Windows (version 28; IBM, Armonk, NY, US) and by using Open Epi (version 3.01).



**Figure 1: Flowchart showing the cases selection process**

CNS=central nervous system. 2DRT=2-dimensional radiotherapy. 3DCRT=3-dimensional conformal radiotherapy. IMRT=intensity-modulated radiotherapy.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

Data for a total of 3679 patients (996 [27.1%] irradiated, 2683 [72.9%] controls) were analysed. Radiotherapy modalities included 2-dimensional radiotherapy (2DRT) in 453 (45.5%), 3-dimensional conformal radiotherapy (3DCRT) in 497 (49.9%), and intensity-modulated radiotherapy (IMRT) in 43 (4.3%) cases; in three patients (0.3%), radiotherapy modality was unknown, but was neither stereotactic nor proton radiotherapy. Patient characteristics, including age, sex, and pituitary tumour subtype are summarised in table 1 (excluded patients due to absent or short imaging follow-up were similar in age, sex, and tumour type). Based on the available records, radiotherapy was offered over a 5–6 weeks period, and the median total dose for pituitary adenomas was 45 Gy (IQR 45.00–45.00) over 25 fractions (IQR 25.00–25.00); for craniopharyngiomas it was 50.1 Gy (IQR 50.00–54.00) over 30 fractions (IQR 27.50–30.00). Median follow-up for the total group

	Irradiated group (n=996)	Control group (n=2683)	Total (n=3679)
<b>Sex</b>			
Male	558 (31.6%)	1207 (68.4%)	1765
Female	435 (22.8%)	1475 (77.2%)	1910
No information	3	1	4
Age at pituitary tumour detection, years*	43 (2-83 [31-57])	46 (1-93 [32-60])	..
<b>Tumour type</b>			
Craniopharyngioma	173 (48.9%)	181 (51.1%)	354
Functioning somatotroph adenoma (acromegaly)	174 (28.3%)	441 (71.7%)	615
Prolactinoma	73 (8.5%)	786 (91.5%)	859
Functioning corticotroph adenoma (Cushing's disease)	50 (24.6%)	153 (75.4%)	203
Non-functioning pituitary adenoma	526 (32.1%)	1114 (67.9%)	1640
Thyroid stimulating hormone secreting adenoma	0	6	6
Adenoma type unknown	0	2	2
<b>Pituitary adenoma size</b>			
Microadenoma	27 (3.8%)	679 (96.2%)	706
Macroadenoma	755 (31.3%)	1660 (68.7%)	2415
Unknown	41 (20.1%)	163 (79.9%)	204
Age at radiotherapy administration, years	47 (34-60)	NA	NA
<b>Type of radiotherapy</b>			
2DRT	453 (45.5%)	NA	NA
3DCRT	497 (49.9%)	NA	NA
IMRT	43 (4.3%)	NA	NA
Not specified†	3 (0.3%)	NA	NA
Imaging follow-up, years	12.3 (6.97-19.30)	8.5 (4.47-14.56)	9.3 (5.00-16.02)
Imaging follow-up, patient-years	13 910	31 336	45 246

Data are n, n (%), median (IQR), or median (range [IQR]), unless otherwise specified. NA=not applicable. 2DRT=2-dimensional radiotherapy. 3DCRT=3-dimensional conformal radiotherapy. IMRT=Intensity-modulated Radiotherapy. \*In 177 (4.8%) of 3679 patients, the pituitary tumour was diagnosed before the age of 18 years. †Not stereotactic radiosurgery or proton radiotherapy.

**Table 1: Patient characteristics**

was 9.3 years (IQR 5.00–16.02); 12.3 (IQR 6.97–19.30) for the irradiated, and 8.5 years (IQR 4.47–14.56) for the controls. There were 45 246 patient-years at risk for the total cohort of patients: 13 910 for the irradiated and 31 336 for the controls. At last follow-up, 90% of the patients had MRI and 10% had CT.

Second brain tumours were detected in 61 patients: 30 in the irradiated (at median age 65 years [range 26–87]) and 31 in the control group (at median age 63 years [range 25–97]). Seven second brain tumours were malignant, five of which occurred in the irradiated group (three glioblastomas and two astrocytomas), and two in the control group (one glioblastoma and one astrocytoma) (appendix p 1). 54 second brain tumours were benign (25 in the irradiated individuals and 29 in the controls), including 48 meningiomas (two atypical), four acoustic neuromas, one neurocytoma and one

low-grade glioma (appendix p 1–6). Median age at second brain tumour detection was 63.5 years (range 25.0–97.0) for benign tumours, and 58 years (range 26.0–81.0) for malignant tumours (appendix pp 1–6). Eighteen tumours (12 benign and six malignant) were confirmed histologically. Location of the tumours is shown in table 2. Median latency period following radiotherapy completion was 8.3 years (range 7.5–27.3) for malignant tumours, and 17.7 years (range 3.0–50.8) for benign ones.

The cumulative probability of a second brain tumour at 10-year, 15-year, and 20-year follow-up for irradiated patients was 0.9% (95% CI 0.3–1.5%), 2.1% (0.9–3.3%), and 4% (2.0–6.0%), respectively, and for the control group 0.9% (0.5–1.5%), 1.6% (0.8–2.4%) and 2.1% (1.1–3.1%), respectively (figure 2). In the total group, the incidence rate for second brain tumours was 2.16 per 1000 patient-years in the exposed, and 0.99 per 1000 patient-years in the control group, giving a rate ratio of 2.18 (95% CI 1.31–3.62, p<0.0001). For the pituitary adenoma group, the incidence rate for second brain tumours was 2.07 per 1000 patient-years in the exposed, and 1.07 per 1000 patient-years in the control group, giving a rate ratio of 1.94 (95% CI 1.12–3.32, p=0.018). For the craniopharyngioma group, the incidence rate for second brain tumours was 2.63 per 1000 patient-years in the exposed, and 0.31 per 1000 patient-years in the control group, giving a rate ratio of 8.34 (95% CI 1.23–193.20, p=0.026; table 3).

Cox regression analysis showed that sex or type of pituitary tumour were not predictors of a second brain tumour, whereas radiotherapy exposure and older age at pituitary tumour detection were (HR 1.73 [95% CI 1.05–2.86] and HR 1.36 per decade [1.15–1.61], respectively). Following adjustment for age at pituitary tumour detection, radiotherapy exposure remained a predictor of a second brain tumour (HR 1.82 [1.10–3.02]). Detailed HRs are presented in table 4.

After exclusion of patients who were irradiated before the age of 18 years (n=66), the risk of a second brain tumour remained raised (unadjusted HR 1.74, 95% CI 1.04–2.98, adjusted for age at pituitary tumour detection 1.73, 1.03–2.90). Data analysis after excluding patients who received IMRT provided similar results: after adjustment for age at pituitary tumour detection, the HR for a second brain tumour in the irradiated patients was 1.77 (95% CI 1.06–2.95).

Radiotherapy was offered to 460 patients before the year 2000 (in ten of them before 1970) and to 536 patients after the year 2000. The period of radiotherapy administration (<2000 or ≥2000), type of radiotherapy (2DRT or 3DRT) or participating centre were not predictors of developing a second brain tumour, whereas older age at radiotherapy exposure was a predictor (HR 1.43 per decade, 95% CI 1.097–1.865).

The management of the benign second brain tumours in the control group consisted of surgery (n=6) or

See Online for appendix

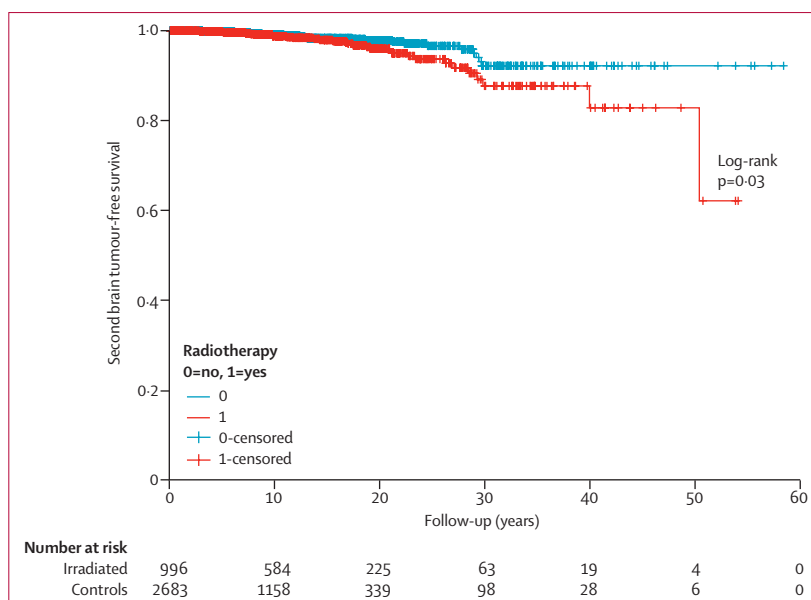
	N
<b>Irradiated group</b>	
Cavernous sinus or parasellar region	7
Cerebellopontine angle	5
Frontal lobe	4
Middle cranial fossa	4
Temporal lobe	3
Anterior hemispheric fissure	2
Parafalcine region	2
Cerebellum	2
Parietal lobe	1
<b>Controls</b>	
Parasagittal or parafalcine region	7
Parietal lobe	6
Temporal lobe	4
Frontal convexity	4
Parasellar region	2
Cerebellopontine angle	2
Posterior fossa	2
Frontal lobe	1
Sphenoid	1
Central skull base	1
Lateral ventricle	1

**Table 2: Location of second brain tumours**

surveillance (n=22), whereas in the irradiated group, it was surgery (n=5), stereotactic radiosurgery (n=5), both surgery and stereotactic radiosurgery (n=1), or surveillance (n=13). The management of two patients with benign tumours was unknown (one irradiated, and one control). The management and outcomes of the seven patients with malignant tumours (five irradiated and two non-irradiated), as well as of those with benign tumours are shown in the appendix (pp 1–6).

## Discussion

This study reports that of 3679 patients with a pituitary adenoma or craniopharyngioma, over 45 246 patient-years and defined strictly by imaging monitoring (and not by last clinical review), 996 who had undergone radiotherapy had 2·18 (95% CI 1·31–3·62) relative risk of a second brain tumour as compared with the non-irradiated patients. The association of radiotherapy with second brain tumours is in agreement with some earlier studies,<sup>13–18</sup> however, our results suggest that the magnitude of this risk is more conservative than previous estimates.<sup>13–15,18</sup> Indeed, Minniti and colleagues<sup>15</sup> and Tsang and colleagues<sup>18</sup> in cohorts of 426 and 305 irradiated patients, respectively, reported risks of 10·5 (95% CI 4·3–16·7), and 16 (95% CI 4·4–41) times higher than that of the general population, respectively. Furthermore, Norberg and colleagues,<sup>16</sup> in a cohort of 298 irradiated patients reported a standard incidence ratio of 5·2 (95% CI 1·9–11·3). These studies



**Figure 2: Cumulative probability of second brain tumour-free survival in the irradiated and the non-irradiated patients**

are compromised, however, by not using appropriate controls, as the general population is not subject to the systematic imaging surveillance offered to irradiated patients with a history of pituitary tumour. This increases the likelihood of under-reporting, particularly asymptomatic brain tumours in the control group, and thus, overestimating the risk of those irradiated. Our approach of using as controls non-irradiated patients with a pituitary tumour undergoing imaging monitoring, allowed the generation of more credible estimates.

Interestingly, Burman and colleagues,<sup>13</sup> in a study comparing 3236 irradiated and 4927 non-irradiated patients with sellar tumours (most of which were pituitary adenomas or craniopharyngiomas), reported relative risks of 3·34 (95% CI 1·06–10·6) for malignant brain tumours and 4·06 (95% CI 1·51–10·9) for meningiomas. Selection bias needs to be considered as the patients were retrieved from the KIMS—Pfizer International Metabolic Study—database, in which only individuals with growth hormone deficiency are enrolled. Furthermore, the authors acknowledged the potential limitations associated with incomplete adverse events reporting encountered in surveillance databases. In contrast to the above findings, Erfurth and colleagues,<sup>22</sup> in a cohort of 325 patients irradiated for a pituitary tumour, identified three patients with second brain tumours, and by using data from the Swedish Cancer Registry, provided a standardised incidence ratio of 2·7 with 95% CI ranging between 0·6 and 7·8. In this study, patients with acromegaly, Cushing's disease or those exposed to growth hormone replacement therapy as children, were excluded.

	Patients		Cases		Patient-years		Incidence rate, per 1000 patient-years, (95% CI)		Rate ratio, (95% CI)
	Radiotherapy	Controls	Radiotherapy	Controls	Radiotherapy	Controls	Radiotherapy	Controls	Radiotherapy vs controls
Total	996	2683	30	31	13 910	31 336	2.16 (1.48–3.04)	0.99 (0.68–1.39)	2.18 (1.31–3.62) p<0.0001
Pituitary adenomas	823	2502	24	30	11 625	28 158	2.07 (1.32–3.07)	1.07 (0.72–1.52)	1.94 (1.12–3.32) p=0.018
Craniopharyngiomas	173	181	6	1	2285	3178	2.63 (0.96–5.71)	0.31 (0.004–1.75)	8.34 (1.23–193.20) p=0.026

**Table 3: Number of patients, of second brain tumours, and patient-years in each group, incidence rates per 1000 patient-years and rate ratio (irradiated vs controls)**

	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age at pituitary tumour detection	1.36 per decade (1.15–1.61), p<0.001	..
<b>Radiotherapy exposure</b>		
Total number of patients	1.73 (1.05–2.86), p=0.03	1.82 (1.10–3.02), p=0.02*
Group of patients who received irradiation after the age of 18 years	1.74 (1.04–2.98), p=0.04	1.73 (1.03–2.90), p=0.04*
Patients with pituitary adenoma	1.48 (0.86–2.55), p=0.15	1.55 (0.90–2.66), p=0.11*
Patients with craniopharyngioma	9.33 (1.10–79.08), p=0.04	8.91 (1.03–77.05), p=0.047
Patient sex	1.01 (0.61–1.67), p=0.97	..
<b>Type of pituitary tumour</b>		
Craniopharyngioma	ref (1)	..
Functioning somatotroph adenoma (acromegaly)	2.09 (0.86–5.10), p=0.11	..
Functioning corticotroph adenoma (Cushing's disease)	1.02 (0.26–3.96), p=0.97	..
Prolactinoma	0.97 (0.38–2.48), p=0.94	..
Non-functioning pituitary adenoma	1.26 (0.53–2.99), p=0.60	..
Thyroid stimulating hormone secreting adenoma†	..	..

\*Following adjustment for age at pituitary tumour detection. †Only 6 cases, statistics not shown.

**Table 4: Hazard ratios for second brain tumour**

In our study, the cumulative probability of a second brain tumour in the irradiated group was estimated to be 0.9% at 10 years and 4.0% at 20 years; this is compared with 0.9% at 10 years and 2.1% at 20 years in the control group. Given very few cases with follow-up longer than 40 years, our data beyond this period need to be interpreted with caution. Previous studies have reported lower rates at 20 years ranging between 1.3% and 2.4%;<sup>15–17</sup> the systematic imaging monitoring which our follow-up relied on is a potential explanation of our rates. The median latency after radiotherapy was 8.3 years for malignant tumours (glioblastoma or anaplastic astrocytoma) and 17.7 years for benign or atypical ones (23 meningiomas and two acoustic neuromas), comparable with previous reports. In a study of patients with radiation-induced malignant gliomas, Elsamadicy and colleagues<sup>24</sup> described a median latency period of 10.5 years following radiotherapy for pituitary adenomas, whereas in an analysis of patients with radiation-induced meningioma,

Yamanaka and colleagues<sup>25</sup> found an average latency period of 20.3 years (SD 8.3 [95% CI 16.4–24.2]) for 20 patients irradiated for a pituitary adenoma. In contrast, Burman and colleagues<sup>13</sup> reported a longer latency period of 27 years (range 6–46) for malignant brain tumours after radiotherapy for craniopharyngiomas or pituitary adenomas, but this is probably the result of the study design and survivor bias, as the authors acknowledge. Two second brain tumours in our irradiated group were detected between 3 and 5 years after the radiotherapy. Although an association or causality with the irradiation exposure cannot be firmly supported, reports of similar latency intervals are available in the published literature.<sup>17,20,26</sup>

Based on the adjusted for age HR for second brain tumour for the total group of patients (1.82), radiotherapy is associated with an 82% risk increase compared with the controls. HR for craniopharyngiomas was 8.91 with, however, wide 95% CIs (1.03–77.05) due to the small number of cases and of second brain tumour events. In the pituitary adenoma group, HR of 1.55 and the 95% CI of 0.90–2.66 point towards a permissive role of radiotherapy for second brain tumour (in this group, rate ratio was 1.93 [95% CI 1.12–3.32]).

We found that older age at pituitary tumour detection was a predictor of developing a second brain tumour. This is in accord with the view that increasing age is associated with rising incidence of primary brain tumours, including glioblastomas, meningiomas and vestibular schwannomas, with a peak incidence in individuals aged in their late 60s or early 70s.<sup>27</sup> Of note, in our cohort, older age at radiotherapy exposure was associated with a higher risk of a second brain tumour. In contrast, Burman and colleagues<sup>13</sup> in a study of selected patients from the KIMS database reported that younger age at radiotherapy was associated with the development of malignant brain tumours and meningiomas. This finding is in keeping with the results of childhood cancer survivors studies, which indicate a link between younger age at irradiation and the risk of a second brain tumour, although genetic factors and other cancer treatments might also play a role in this age group.<sup>9</sup> It should be noted, however,

that our multicentre study of adult endocrine centres mostly included patients who received radiotherapy during adult life (median age 47 years), and is not representative of the paediatric population.

The proportions of our patients exposed or not to radiotherapy differed according to tumour type. Cox regression analysis showed that type of pituitary tumour was not a significant factor associated with increased risk of second brain tumour and this is in agreement with previously published reports.<sup>13,15</sup> Particularly for patients with acromegaly, in a meta-analysis of four studies reporting the incidence of second brain tumours after radiotherapy, the weighted relative risk of a second brain tumour in patients with growth hormone-secreting adenomas versus non-growth hormone-secreting ones was 1.9, but with 95% CI ranging between 0.7 and 4.6.<sup>28</sup>

The strengths of our study include the review of what is to the best of our knowledge the largest cohort of non-selected patients irradiated for a pituitary adenoma or craniopharyngioma, plus the use of a control group of non-irradiated patients with the same primary pathology aiming to minimise the effect of a potential link between these pituitary tumours and development of a second brain tumour. All participants had imaging surveillance, resulting in a total of 45 246 patient-years, and the duration of follow-up was determined by the last imaging rather than the date of last clinic review or date of death as used in other reports.<sup>13,15,16,22</sup> Exclusion of patients with syndromes predisposing to CNS tumours and adjustment for several confounding factors are further strengths.

Limitations include the retrospective nature of the study; thus, a causal relationship between radiotherapy and development of a second brain tumour cannot be proven. It could be argued though, that prospective studies aiming to investigate this topic might not be practically feasible. In a number of second brain tumours (n=43/61), the diagnosis relied on imaging criteria and no histological analysis. Ascertainment bias associated with the review of the images of irradiated versus non-irradiated patients cannot be excluded. Less frequent imaging follow-up potentially adopted after the first decade could have introduced bias in the time to diagnosis of asymptomatic brain tumours. We had no detailed information on the dose distribution to the tumour and the brain, and very few cases of malignant brain tumours (n=7) did not allow robust analyses on the risk of individual tumours. Finally, the effect of environmental factors or family history were not ascertained. The inclusion of patients from centres other than those taking part in our study, would enhance the generalisability of our findings.

Our multicentre study has addressed a major concern on a late toxicity of radiotherapy in adults which, due to its rarity and long-latency, has been difficult to investigate with a methodologically sound approach. We have shown that second brain tumours are approximately twice as common in those treated with

radiotherapy, compared with those treated without it and this estimation is much lower than that which has previously been reported in studies relying on general population controls. Notably, malignant tumours were detected in few patients. Therefore, given the beneficial role of radiotherapy in the control of craniopharyngiomas and recurrent or aggressive pituitary adenomas, the very few events of second brain tumours should not preclude its use in the management algorithm of these tumours.<sup>6,7,29</sup> Although an aetiological relationship between radiotherapy for pituitary adenomas or craniopharyngiomas and development of a second brain tumour cannot be proven, our data inform clinical practice and can guide clinicians when counselling this group of patients on the risks and benefits of radiotherapy. As the evolution of radiotherapy delivery continues and pre-radiotherapy imaging becomes more accurate, further adequately powered studies exploring other irradiation techniques (in combination with appropriate controls and follow-up to allow for prolonged latency periods), remain necessary to confirm their potential more optimal risk profile.

#### Contributors

NK conceived, planned, and supervised the study; RH and NK had access to all the raw data, wrote the manuscript, and, with input from all co-authors, contributed patient information and verified all clinical and treatment details. The corresponding author had final responsibility for the decision to submit for publication.

#### Declaration of interests

AC has received a grant from Health Education England for a radiotherapy contouring analysis website tool in 2020. MCZ is a consultant for Novartis, Eli Lilly, and Genzyme. KB has received honoraria from HRA Pharma and Ipsen UK for talks and professional consultancy services; conference and travel grants from Novo Nordisk; and has completed a National Health Service service development project with Novartis. RDM has received research funding from Pfizer, Sandoz, and Ipsen; consultancy fees from Takeda, Sandoz, and Diurnal; conference grant from Recordati Rare Diseases UK; and honoraria for talks from Pfizer, Ipsen, Sandoz, and Novartis. RH has received a conference grant from Recordati Rare Diseases UK. NK has received honoraria from Pfizer, Ipsen, HRA Pharma and Recordati Rare Diseases for lectures; research funding from Pfizer, Ipsen, and Shire and has served as a member in Scientific Advisory Boards for Pfizer, Ipsen, and Recordati Rare Diseases. All other authors declare no competing interests.

#### Data sharing

The study protocol and statistical analysis plan for this project are available on request from the corresponding author. Individual patient data protected by local clinical governance for each participating centre are not available for sharing.

#### Acknowledgments

The study was supported by an Independent Investigator Research Grant from Pfizer. The sponsor was not involved in any part of the study, including the design, data collection, analysis, or interpretation of the results.

#### References

- Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014–2018. *Neuro Oncol* 2021; 23 (suppl3): 1–105.
- Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol* 2007; 156: 203–16.
- Melmed S. Pituitary-tumor endocrinopathies. *N Engl J Med* 2020; 382: 937–50.

- 4 Bécélère A. The radio-therapeutic treatment of tumours of the hypophysis, gigantism, and acromegaly. *Archives of the Roentgen Ray* 1909; **14**: 142–50.
- 5 Ntali G, Karavitaki N. Efficacy and complications of pituitary irradiation. *Endocrinol Metab Clin North Am* 2015; **44**: 117–26.
- 6 Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev* 2006; **27**: 371–97.
- 7 Tampourlou M, Ntali G, Ahmed S, et al. Outcome of nonfunctioning pituitary adenomas that regrow after primary treatment: a study from two large UK centers. *J Clin Endocrinol Metab* 2017; **102**: 1889–97.
- 8 Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. *Lancet* 2018; **392**: 432–46.
- 9 Bowers DC, Nathan PC, Constine L, et al. Subsequent neoplasms of the CNS among survivors of childhood cancer: a systematic review. *Lancet Oncol* 2013; **14**: e321–28.
- 10 Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2009; **101**: 946–58.
- 11 Lee JW, Wernicke AG. Risk and survival outcomes of radiation-induced CNS tumors. *J Neurooncol* 2016; **129**: 15–22.
- 12 Kutsenko A, Berrington de Gonzalez A, Curtis RE, Rajaraman P. Risk of second benign brain tumors among cancer survivors in the surveillance, epidemiology, and end results program. *Cancer Causes Control* 2014; **25**: 659–68.
- 13 Burman P, van Beek AP, Biller BM, Camacho-Hübner C, Mattsson AF. Radiotherapy, especially at young age, increases the risk for de novo brain tumors in patients treated for pituitary/sellar lesions. *J Clin Endocrinol Metab* 2017; **102**: 1051–58.
- 14 Brada M, Ford D, Ashley S, et al. Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma. *BMJ* 1992; **304**: 1343–46.
- 15 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. *J Clin Endocrinol Metab* 2005; **90**: 800–04.
- 16 Norberg L, Johansson R, Rasmuson T. Intracranial tumours after external fractionated radiotherapy for pituitary adenomas in northern Sweden. *Acta Oncol* 2010; **49**: 1276–82.
- 17 Erridge SC, Conkey DS, Stockton D, et al. Radiotherapy for pituitary adenomas: Long-term efficacy and toxicity. *Radiother Oncol* 2009; **93**: 597–601.
- 18 Tsang RW, Laperriere NJ, Simpson WJ, Brierley J, Panzarella T, Smyth HS. Glioma arising after radiation therapy for pituitary adenoma. A report of four patients and estimation of risk. *Cancer* 1993; **72**: 2227–33.
- 19 Brown PD, Blanchard M, Jethwa K, et al. The incidence of cerebrovascular accidents and second brain tumors in patients with pituitary adenoma: A population-based study. *Neurooncol Pract* 2014; **1**: 22–28.
- 20 Bliss P, Kerr GR, Gregor A. Incidence of second brain tumours after pituitary irradiation in Edinburgh 1962–1990. *Clin Oncol (R Coll Radiol)* 1994; **6**: 361–63.
- 21 Sattler MG, van Beek AP, Wolffebuttel BH, et al. The incidence of second tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone. *Radiother Oncol* 2012; **104**: 125–30.
- 22 Erfurth EM, Bülow B, Mikoczy Z, Svahn-Tapper G, Hagmar L. Is there an increase in second brain tumours after surgery and irradiation for a pituitary tumour? *Clin Endocrinol (Oxf)* 2001; **55**: 613–16.
- 23 van Varsseveld NC, van Bunderen CC, Ubachs DH, et al. 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. *J Clin Endocrinol Metab* 2015; **100**: 1104–12.
- 24 Elsamadicy AA, Babu R, Kirkpatrick JP, Adamson DC. Radiation-induced malignant gliomas: a current review. *World Neurosurg* 2015; **83**: 530–42.
- 25 Yamanaka R, Hayano A, Kanayama T. Radiation-induced meningiomas: an exhaustive review of the literature. *World Neurosurg* 2017; **97**: 635–44.
- 26 Cullinan N, Cryan J, O’Sullivan C, et al. Radiation-induced glioblastoma multiforme within 4 years of cranial irradiation for paediatric craniopharyngioma-case report and review of the literature. *Neuro Oncol* 2016; **18** (suppl 3): 20–21.
- 27 Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro Oncol* 2019; **21**: 1357–75.
- 28 Burman P, Dekkers OM. A permissive role of growth hormone (GH) in the development of second brain tumors after radiotherapy? *Endocrine* 2017; **57**: 356–58.
- 29 Raverot G, Burman P, McCormack A, et al. European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *Eur J Endocrinol* 2018; **178**: 1–24.