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Pituitary adenoma

The incidence of second tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone

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ABSTRACT

Background and purpose: To assess and compare the incidence of intra- and extracranial tumours and mortality in pituitary adenoma patients treated with postoperative radiotherapy and surgery alone.

Patients and methods: A total of 462 pituitary adenoma patients were treated between 1959 and 2008 at the University Medical Center Groningen in The Netherlands. Postoperative radiotherapy was administered on indication in 236 patients.

Results: The median follow-up time was 14 (range 1–49) years in patients treated with radiotherapy and 6 (range 1–34) years in patients treated with surgery alone. Three radiotherapy patients developed an intracranial tumour compared to one patient treated with surgery alone. The numbers of extracranial tumours per follow-up year were 6.5 (95% CI 2.5–10.5) and 5.1 (95% CI 1.9–8.2) in patients treated with and without a technique with vertex field and central body axis irradiation and 7.1 (CI 95% 2.9–11.2) in surgery alone patients. Forty-five patients treated with radiotherapy died compared to twenty-four patients treated with surgery alone (log-rank test RR 1.26, 95% CI 0.77–2.08, $p = 0.36$).

Conclusion: In this study postoperative radiotherapy and a radiotherapy treatment technique with vertex field and central body axis irradiation were not associated with an increased incidence of second tumours and mortality in pituitary adenoma patients.

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In most pituitary adenoma patients (non-functioning adenomas (NFA), growth hormone (GH) secreting and adrenocorticotrophic hormone (ACTH) secreting adenomas), surgery is the treatment of first choice. Postoperative radiotherapy is usually applied in case of certain indications as an adjuvant treatment modality such as: (1) in order to prevent tumour progression after incomplete resection; (2) in case of secreting adenomas where hormonal control cannot be achieved with surgery alone; and (3) as salvage treatment in case of local recurrence after surgery. Several studies have shown that postoperative radiotherapy results in an excellent long term local tumour control with a 10-year progression free survival of 90–97% [1–5] and an improvement of excessive hormonal secretion [6,7].

Despite the benefits of postoperative radiotherapy regarding local and hormonal control, the role of radiotherapy has been debated, in particular because of concerns related to long term side effects, such as the induction of second tumours and associated with it a negative impact on mortality. Based on these concerns, some

investigators proposed to withhold or postpone radiotherapy to pituitary adenoma patients [8].

In pituitary adenoma patients several studies have reported on the impact of the disease itself, on the risk of developing tumours and on mortality. An increased incidence of tumours has been reported [9,10], as well as an increased incidence of mortality [11–13]. However, other studies indicated that tumour incidence [14] and mortality [15,16] were not increased.

Several other investigators evaluated the risk of radiotherapy on developing second tumours and the impact on mortality in pituitary adenoma patients. Some reported on an increased risk for second intracranial [17–19] or extracranial [20] tumours and an increase in mortality [21,22] in patients treated with surgery and radiotherapy. However, no firm support for an increased incidence of second intracranial [20,23] or extracranial [17,19] tumours and mortality [4,15] was found by others.

All these previous studies compared the incidence of second tumours and mortality in pituitary adenoma patients treated with surgery and radiotherapy with the incidence observed in a normal reference population. As a consequence, potential other patient or treatment related factors that may be responsible for the increased incidence in tumours and mortality were not taken into account.

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To properly evaluate the concerns related to radiotherapy on second tumour induction and mortality a direct comparison should be made with similar patients treated with surgery alone. However, even in this clinical non-randomisation setting it remains difficult to prove a causal effect of radiotherapy on second tumour induction and mortality.

Therefore, the main objective of this study was to assess and compare the incidence of intra- and extracranial second tumours and mortality among pituitary adenoma patients treated with postoperative radiotherapy versus surgery alone.

Patients and methods

Patients and follow-up

A total of 462 pituitary adenoma patients (217 males and 245 females) underwent treatment from January 1959 to March 2008 at the University Medical Center Groningen. All patients were treated with surgery as primary treatment with or without postoperative radiotherapy. The patient and treatment characteristics are shown in Table 1. The diagnosis was based on the patient's clinical history and presentation, endocrine evaluation, pituitary imaging, and all confirmed by histopathological findings. Ultimately, 256 patients turned out to have a NFA (55%), 139 patients a GH-secreting adenoma (30%), and 67 patients an ACTH-secreting adenoma (15%), including Cushing's disease ($n = 61$) and Nelson's syndrome ($n = 6$).

Second tumours and death events were retrieved by reviewing retrospectively the hospital records. The second tumours were divided in intra- and extracranial tumours.

All patients were followed from the onset of surgery until January 2009 or date of death. For patients who were not seen in the hospital for follow-up appointments after January 2008 information requests were sent to the referring hospital or general practitioner. The median follow-up time after pituitary adenoma diagnosis for the entire cohort was 9 (range 1–49) years. For patients treated with radiotherapy this was 14 (range 1–49) years and 6 (range 1–34) years in patients with surgery alone. The total follow-up time consisted of 5161 patient-years. For patients treated with radiotherapy this was 3575 patient-years compared to 1586 patient-years in patients treated with surgery alone. A total of 202 pituitary adenoma patients (155 radiotherapy and 47 surgery alone patients) were followed-up for more than 10 years.

Postoperative radiotherapy

The indication to administer postoperative radiotherapy was discussed in a multidisciplinary team in which the neurosurgeon, endocrinologist, radiation oncologist and all other relevant medical disciplines are involved. The indications for radiotherapy were: (1) postoperative for local control of tumour growth or hormone excess in case of residual disease after incomplete resection, or (2) salvage treatment in patients with recurrent disease after surgery.

Table 1
Characteristics of the pituitary adenoma patients.

	RT+	RT–	Total
Number of patients	236	226	462
Sex (male/female)	110/126	107/119	217/245
Age at diagnosis (y) [*]	46 (10–83)	51 (19–81)	47 (10–83)
Age at end of follow-up (y) ^{**}	62 (21–89)	57 (23–89)	60 (21–89)
Number of patients alive at end of follow-up	191 (81%)	202 (89%)	393 (85%)
Duration of follow-up (y) [*]	14 (1–49)	6 (1–34)	9 (1–49)
Type of adenoma ^{***}			
Non-functioning adenoma ^{**}	143 (61%)	113 (50%)	256 (55%)
GH-secreting adenoma	69 (29%)	70 (31%)	139 (30%)
ACTH-secreting adenoma ^{**}	24 (10%)	43 (19%)	67 (15%)
Primary treatment [†]			
Transsphenoidal surgery [*]	172 (73%)	218 (96%)	390 (84%)
Craniotomy [*]	64 (27%)	8 (4%)	72 (16%)
Second surgical treatment	40 (17%)	22 (10%)	62 (14%)
Extent of surgery [†]			
Complete resection [*]	12 (5%)	117 (52%)	129 (28%)
Incomplete resection [*]	209 (89%)	95 (42%)	304 (66%)
Unknown	15 (6%)	14 (6%)	29 (6%)
Postoperative radiotherapy			
Age at radiotherapy (y)	49 (19–84)	–	–
Time between first surgery and RT (y)	1 (1–32)	–	–
Radiotherapy dose:			
≤44 Gy	4 (2%)	–	–
45–49 Gy	173 (73%)	–	–
≥50 Gy	55 (23%)	–	–
Unknown	4 (2%)	–	–
Radiotherapy technique:			
Technique with vertex field	80 (34%)	–	–
Technique without vertex field	153 (65%)	–	–
Unknown	3 (1%)	–	–

Abbreviations: RT+: patients with postoperative radiotherapy; RT–: patients with surgery alone; y: year; Gy: Gray.

Data are given as absolute numbers, median (range) and percentages.

RT+ versus RT–:

^{*} $p < 0.001$.

^{**} $p < 0.01$.

^{***} $p < 0.05$.

The patients in this cohort were diagnosed and treated from 1959 to 2008, a time period of almost 50 years. Due to improvements over time in neurosurgery treatment and better imaging techniques (CT/MRI), less postoperative radiotherapy was needed and the indication for postoperative radiotherapy declined.

External beam radiotherapy was applied in 143 (61%) patients with a NFA, 69 (29%) patients with a GH-secreting adenoma and in 24 (10%) patients with an ACTH-secreting adenoma. All radiotherapy data were retrieved from the individual radiotherapy patient charts. The median radiation dose was 45 Gy (range 30–55 Gy). Most patients received a radiation fractionation scheme of 25 daily fractions of 1.8 Gy in 5 weeks.

Patients were treated with radiotherapy from 1962 to 2008. One patient was treated with 200 kV X-rays and two patients with Cobalt-60. All other patients were treated with external beam radiotherapy with 4–18 MeV photons.

The radiation dose to the tumour was prescribed at the tumour encompassing isodose in the time period 1962–1990. From 1991 to 2008 the dose was prescribed at a central point in the tumour according to the recommendations of the International Commission on Radiation Units and Measurements.

In the time period 1962–2008 different radiotherapy techniques were used for the treatment of pituitary adenoma. Some techniques included a vertex field with a radiation beam configuration entering through the top of the head. As a consequence, the entire axial length of the body is irradiated and various extracranial organs may be exposed to radiotherapy and possibly increasing the chances of developing second extracranial tumours [24]. For this reason, the radiotherapy patients were divided into a group irradiated with ($n = 80$) or without ($n = 153$) a radiotherapy technique with vertex field and central body axis irradiation. The incidence of extracranial tumours was assessed and compared between these two radiotherapy groups and the surgery alone group.

Statistical methods

The incidence of second tumours occurring after pituitary adenoma diagnosis in patients treated with postoperative radiotherapy were compared to patients treated with surgery alone.

Because the surgery alone patients did not receive radiotherapy, registration of tumours started from the date of pituitary adenoma diagnosis, allowing a direct comparison of both treatments from a fixed point in time.

A left-censored log-rank test with stratification for sex was used for investigating the risk for tumours.

The number of second tumours per follow-up year were calculated per treatment group because of differences in time of follow-up between patients treated with postoperative radiotherapy and surgery alone.

To answer the question if patients treated with radiotherapy have an increased overall mortality compared to patients treated with surgery alone, death events in pituitary adenoma patients

who received radiotherapy were compared to patients who underwent surgery alone. Both treatment groups were compared to an age and sex related reference population according to the standardized mortality rate (SMR). SMR is a ratio between observed and expected numbers of death events. The expected death events were calculated using the annual published life tables of the Central Office of Statistics (CBS) accounting for year of birth and gender (<http://www.cbs.nl>). Age at diagnosis was transformed to median life expectancy (MLE) using the annual life tables of the CBS according to gender. MLE at pituitary adenoma diagnosis in patients treated with radiotherapy were compared to the patients treated with surgery alone with the Mann–Whitney–U test.

There is an inverse correlation between age and life expectancy. Therefore, in the time to event analysis of longitudinal follow-up, the age at start of follow-up must be taken into consideration. In conventional methods like Cox regression analysis and log-rank test this problem is solved by using age as an independent risk factor. However, because age is related to other risk factors of life expectancy, such as gender and year of birth, it is unclear to what extent this correction for age is related to life expectancy and to what extent to these other risk factors. To avoid this methodological bias it is recommended to use age itself instead of surviving time as the time base in analyses [25]. This way, participants of the same age are compared. Additionally, by using age as the time scale, control for calendar period and/or birth cohort effects can be achieved by stratifying the model on birth cohort. Age at the event (death or second tumour) instead of surviving time is the outcome parameter.

Because of the difference in age at start of follow-up, left-censoring is used: the patient is only used in the calculations after reaching the age at start of follow-up. Also right-censoring is applied: the patient does not participate in the analyses at ages higher than that at the end of follow-up.

Cox-regression analysis, log-rank test and Kaplan–Meier curves can be performed without objection this way.

A log-rank test was used to calculate the relative risk of death events in patients treated with postoperative radiotherapy compared to patients treated with surgery alone.

Data are expressed as mean \pm SD, median (interquartile range) or percentages when appropriate. Two-tail p -values <0.05 were considered significant. SPSS 16.0 and Excel 2003 were used for data analysis.

Results

Incidence of intracranial tumours

Four (two males and two females) out of 462 pituitary adenoma patients developed an intracranial tumour after pituitary adenoma diagnosis (Table 2).

Three intracranial tumours (1.3%) developed in patients treated with postoperative radiotherapy compared to one intracranial

Table 2

Characteristics of the individual pituitary adenoma patients diagnosed with intracranial tumour and treated with postoperative radiotherapy or surgery alone.

Type of intracranial tumour	Type of adenoma	Sex	Age at pituitary adenoma diagnosis	Age at intracranial tumour diagnosis	Time since RT in years	Total pituitary RT dose in Gray	No. of RT fields	Location in RT field
Meningioma	NFA	M	42	56	14	50	2 and 5	Y
Meningioma	GH	F	36	57	20	50	3	Y
NFA metastasis	NFA	M	25	37	10	45	5	Y
Glioblastoma multiforme	NFA	F	50	56	N/A	N/A	N/A	N/A

Abbreviations: RT: radiotherapy; F: female; M: male; Y: yes; NFA: non-functioning adenoma; GH: growth-hormone; ACTH: adrenocorticotropic hormone; N/A: not applicable, this patient was treated with surgery alone.

tumour (0.4%) in a patient treated with surgery alone. These numbers were too small for statistical analysis on extent of exposure between the two treatment groups.

Two patients treated with postoperative radiotherapy developed meningiomas. Both patients received radiotherapy after incomplete resection and were treated with a total radiotherapy dose of 50 Gy in daily fractions of 2 Gy. The NFA patient had a localized right fronto-parietal meningioma at a scar place at the skull from the right-sided craniotomy procedure. This patient was operated upon and 11 years after surgery, no evidence of recurrence of meningioma was seen on magnetic resonance (MR) imaging. The GH-secreting adenoma patient had a 1.5 cm large meningioma located at the processus clinoideus anterior on the left side. Repeated MR imaging during a 9 year follow-up period revealed no evidence of progression. Both patients were alive at the end of follow-up of this study.

A tumour at the skull base was found in one male NFA patient 10 years after radiotherapy because of an incomplete resection. This patient received a total dose of 45 Gy in daily fractions of 1.8 Gy. Histological analysis after surgery showed a metastasis of NFA without malignant transformation. At the end of follow-up of this study, and 7 years later after the diagnosis of metastasis of NFA, this patient was still alive.

One female NFA patient developed a glioblastoma multiforme after treatment with surgery alone. The diagnosis was confirmed histologically. She died of glioblastoma multiforme 7 months after the initial diagnosis.

None of these 4 patients were diagnosed with extracranial tumours.

Incidence of extracranial tumours

Thirty-one (16 males and 15 females) of the 462 patients developed 33 extracranial tumours after the date of pituitary adenoma diagnosis (Supplementary material).

Twenty patients (11 males and 9 females) treated with postoperative radiotherapy were diagnosed with a total of 22 extracranial tumours compared to eleven patients treated with surgery alone (Supplementary material). The number of extracranial tumours per follow-up year were 6.5 (95% CI 2.5–10.5) in patients treated with a radiotherapy technique with a vertex field and central body axis irradiation compared to 5.1 (95% CI 1.9–8.2) in patients treated without a radiotherapy technique with vertex field and central body axis irradiation and 7.1 (CI 95% 2.9–11.2) in patients treated with surgery alone.

Two radiotherapy patients developed each two extracranial tumours. The first was a male GH-secreting adenoma patient who developed a basal cell carcinoma located at the hairy part of the head at an age of 59 years 13 years after radiotherapy. At the age of 73 years he was diagnosed with metastatic melanoma of unknown primary origin 26 years after radiotherapy. The second ACTH-secreting female adenoma patient developed a basal cell carcinoma at the back 9 years after radiotherapy at an age of 47 years and a second basal cell carcinoma located at the flank one year later. Both patients had been treated with a radiotherapy technique with vertex field and central body axis irradiation with a total radiotherapy dose of 45 Gy in daily fractions of 1.8 Gy.

The age at pituitary adenoma diagnosis and age at tumour diagnosis is shown in Fig. 1 for patients treated with postoperative radiotherapy compared to patients treated with surgery alone.

Incidence of death events

Sixty-nine out of 462 patients died during follow-up. In 236 postoperative radiotherapy patients 45 deaths were observed compared to 41.26 expected and in 226 surgery alone patients 24

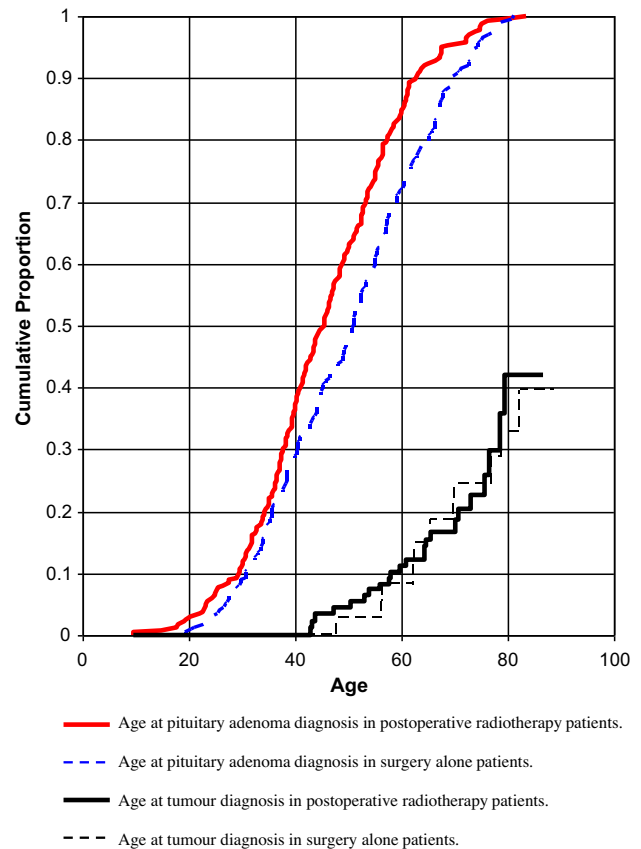


Fig. 1. Age at pituitary adenoma diagnosis and age at tumour diagnosis in patients treated with postoperative radiotherapy compared to patients treated with surgery alone.

deaths were observed compared to 27.74 expected (log-rank test RR 1.26, 95% CI 0.77–2.08, $p = 0.36$). Age at pituitary adenoma diagnosis and age at death is shown in Fig. 2 for patients treated with postoperative radiotherapy compared to patients treated with surgery alone and compared to the expected age of death in the Dutch reference population. There was an increased incidence of death events in the entire study population compared to an age and sex related Dutch reference population (SMR 1.47, 95% CI 1.18–1.75, $p = 0.0016$; Fig. 2).

Discussion

This study did not demonstrate that postoperative radiotherapy in pituitary adenoma patients has a negative impact on the incidence of second intra- and extracranial tumours and mortality compared to patients treated with surgery alone. First, three intracranial tumours developed in patients treated with radiotherapy compared to one tumour in a patient treated with surgery alone, which numbers were too small for statistical analysis on extent of exposure. Lack of significance does not mean that there is no difference between treatment with postoperative radiotherapy or surgery alone but that the differences and absolute risk between the treatment groups on developing an intracranial tumour is small. Second, the yearly incidence of extracranial tumours was not different in patients treated with surgery alone compared to patients treated with postoperative radiotherapy. Moreover, a radiotherapy technique with a vertex field and central body axis irradiation was not associated with an increased incidence of second extracranial tumours. Finally, this study showed a slightly increased incidence of death events in the entire study population

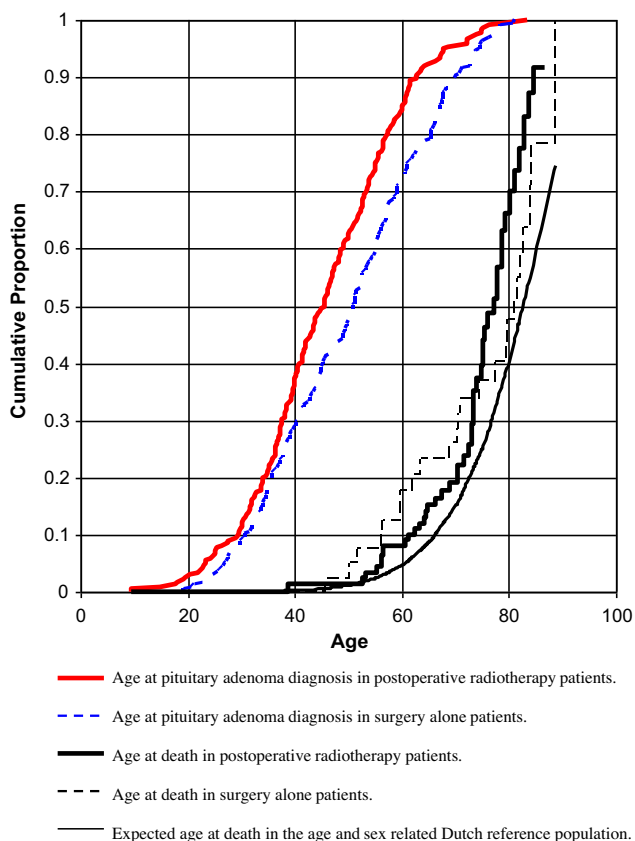


Fig. 2. Age at pituitary adenoma diagnosis and age at death in patients treated with postoperative radiotherapy compared to patients treated with surgery alone and compared to the expected age of death in the Dutch reference population.

compared to an age and sex related Dutch reference population. There was no difference in death events in patients treated with radiotherapy compared to patients treated with surgery alone.

In the present study the median follow-up time for patients treated with postoperative radiotherapy was 14 (range 1–49) years compared to 6 (range 1–34) years in patients treated with surgery alone. Despite a longer follow-up time for patients treated with radiotherapy no difference was seen in the incidence of second tumours or death events between the two treatment groups.

In previous studies the incidence of second tumours and mortality in pituitary adenoma patients treated with radiotherapy were compared with a normal reference population instead of patients treated with surgery alone.

Our results confirm those of other investigators who did not find an increased incidence of intracranial tumours in patients treated with surgery and radiotherapy compared to a reference population with a median follow-up time of 8 (range 0.08–28) and 14 (range 0.1–38) years [20,23]. However, Brada et al. reported a cumulative risk of intracranial tumours after radiotherapy, ranging from 1.3% to 2% over the first 10 years and from 1.9% to 2.4% over the first 20 years [17,19]. The relative risk for developing intracranial tumours in patients treated with radiotherapy was 9.4 (95% CI 3.1–22) compared to that observed in a normal reference population. Eleven of the 426 patients (2.6%) developed a second intracranial tumour (5 meningiomas, 4 gliomas, 1 meningial sarcoma and 1 primitive neuroectodermal tumour). The median follow-up time was 12 (range 0–38) years [19]. A study by Tsang et al. reported a cumulative risk of second glioma after radiotherapy of 1.7% at 10 years and 2.7% at 15 years [18]. The relative risk of developing a malignant brain tumour was 16 (95% CI 4.4–41).

Four of the 305 irradiated patients (1.3%) developed gliomas of the brain. The median follow-up time was 7.9 (range 0.1–19.7) years [18].

These studies do not provide sound evidence that radiotherapy per se is the only causal factor because the comparison with regard to the incidence of brain tumours were made with the general population instead of non-irradiated pituitary adenoma patients. Moreover, the absolute observed numbers in these studies are small and based on a few incident cases (2.6% and 1.3%) and are accompanied by wide confidence intervals.

In the present study two patients treated with radiotherapy developed a meningioma and one patient developed a metastasis of a NFA. Meningiomas are the most common diagnosed second intracranial tumours after cranial radiotherapy, mainly developed in patients irradiated in childhood for brain tumours, leukaemia and tinea capitis [26,27]. Radiation-induced meningioma differs from “spontaneous meningiomas” with regard to the patient’s age at diagnosis, location, multiplicity, aggressive biological behaviour and the rate of tumour recurrence [27,28]. Spontaneous meningiomas are generally diagnosed in the 5th or 6th decade of life while radiation-induced meningioma presents at a younger age with incidence peaks in the second and third decade of life [26,27]. In this study, the age of meningioma diagnosis was 56 years for the NFA patient and 57 years for the GH-secreting patient and developed at 14 and 20 years after radiotherapy. There is a tendency for shorter latency in patients treated with higher doses and larger treatment volumes [26,27]. Although the median follow-up time of 14 years in this study might be short to develop meningioma, it is comparable to the study by Erfurth et al. [23] who did not find an increased incidence of intracranial tumours, and has a longer median follow-up time compared to the studies by Brada et al. [19] and Tsang et al. [18] who did find an increased incidence of intracranial tumours. The meningiomas diagnosed in our study may represent a late complication of postoperative radiotherapy. However, a higher incidence of second intracranial tumours could also be explained by a genetic trait that predisposes to both pituitary adenomas and intracranial tumours. This hypothesis is supported by the findings of Jones et al. that reported on the co-occurrence of glioma or meningioma in pituitary adenoma patients treated with surgery alone [29]. In the present study one NFA patient developed a glioblastoma multiforme 6 years after treatment with surgery alone. In the patients treated with surgery alone meningioma was not diagnosed. In the patient with a metastasis of NFA the role of radiotherapy in the development of metastasis of NFA without malignant transformation is unknown because of this extreme rare disease.

Our results on extracranial tumours confirm those of other investigators who reported no excess risk of second extracranial tumours in patients treated with radiotherapy compared to incidence rates observed in a reference population [17,19]. However, in the study by Bliss et al. 30 extracranial tumours were diagnosed out of 269 pituitary adenoma patients treated with radiotherapy compared with an expected incidence of 17.5 (95% CI 12–26, $p < 0.01$) in an age and gender-matched population. The pituitary adenoma patients were treated with two lateral opposed fields or an anterior and two lateral opposed fields. The reporting of second extracranial tumours was possibly more complete than in the reference population due to regular review.

This study showed no difference in death events in patients treated with postoperative radiotherapy compared to patients treated with surgery alone. Postoperative radiotherapy in pituitary adenoma patients is given on indication as an adjuvant treatment after surgery. The purpose of the study was to compare death events between patients treated with postoperative radiotherapy and surgery alone and therefore the cause of death was irrelevant. The results of this study regarding a slightly increased incidence of

death events in the entire study population irrespective of treatment compared to an age and sex related Dutch reference population can be explained by the uncontrolled disease itself in some patients, like in acromegaly and Cushing's disease, and hypopituitarism [11–13,30,31] in both treatment groups.

In conclusion, in this current study postoperative radiotherapy for pituitary adenoma patients was not associated with an increased incidence of second tumours and mortality compared to patients who are treated with surgery alone. Furthermore, a radiotherapy technique with a vertex field and central body axis irradiation was not associated with an excess risk of second extracranial tumours. In patients treated with radiotherapy second tumours registration requires lifelong follow-up and a consequent documentation in cancer registries as well as registration of tumours in patients treated with surgery alone. In most cases the benefits of postoperative radiotherapy outweigh the absolute small risk of second tumour induction. We believe that postoperative radiotherapy should therefore not be avoided as an adjuvant treatment modality to pituitary adenoma patients with otherwise uncontrolled disease who can benefit from it.

Disclosure

All the authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2012.04.024>.

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