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Original Article

Efficacy and safety of external beam radiation therapy in non-functioning pituitary adenomas: a case–control, nested in a cohort study

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Abstract

Background and objectives: Recurrence is frequent in surgically treated non-functioning pituitary adenomas (NFPA). The use of radiation therapy (RT) to prevent recurrence has to be weighted against the potential side effects, particularly, hypopituitarism. Our objective was to evaluate the efficacy and safety of RT in postoperative patients with NFPA with adenoma remnant.

Patients and methods: The 3- and 5-year outcome of 51 patients with NFPA with a remnant after surgery that received RT (cases) was compared with that of 61 subjects who did not receive RT (controls). Cases and controls were matched for postoperative remnant size, cavernous sinus invasion, age and gender.

Results: Tumour volume decreased in the radiated group from a median of 1,601 mm^3 to 816 mm^3 after 5 years of follow-up ($p = 0{\cdot}01$, 50% tumour volume reduction). In the non-radiated controls median tumour volume decreased at 3 years but increased again after 5 years (baseline 1,415 mm^3, 5 years 1,204 mm^3, $p = 0{\cdot}93$). Recurrence rate was 4% for the radiated group and 29% for the controls (OR 0·10, 95% CI 0·01–0·04, $p = 0{\cdot}02$). Although pituitary hormone deficiencies at baseline were more prevalent in the radiated group, after 5 years, both groups showed a significant worsening of pituitary function. No RT-related side effects were recorded.

Conclusion: Postoperative RT is effective in preventing tumour regrowth in NFPA patients with postoperative remnants. The fact that hypopituitarism is highly prevalent even in non-radiated patients should allow a more generalised use of this treatment modality.

Keywords: hypopituitarism; non-functioning pituitary adenoma; radiation therapy

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INTRODUCTION

The treatment of choice for non-functioning pituitary adenomas (NFPA) is transsphenoidal surgery (TSS).[1–3] Tumour recurrence rates can be as low as 20% and as high as 49%, depending on the series.[1,4] Since these tumours do not produce a syndrome of hormonal hypersecretion, the diagnosis of recurrences relies on clinical (visual impairment signs) an imaging data [magnetic resonance imaging (MRI) showing the presence of tumour].[2,3] Patients who are left with significant tumour remnants after TSS are likely to recur after long-term follow-up.[1,4,5] Although tumour regrowth is usually slow and it can be monitored with serial pituitary imaging studies, in many patients it can be clinically significant and generate compressive complications.[2,3] A minority of NFPA are actually silent corticotroph adenomas that are known to behave more aggressively and recur more frequently.[6] However, in the majority of patients with NFPA, an accurate prediction of recurrence remains an elusive goal.[4,7] Thus, in this scenario, the risk of a significant tumour recurrence has to be established primarily based on the size and location of the remnant after surgery. On the other hand, even tumours that are completely removed by surgery also have a risk, albeit lower, of recurrence and a careful clinical and imaging follow-up is indicated.[1,3,4]

There is extensive evidence supporting the effectiveness of external beam radiation therapy (XRT) in preventing recurrences of NFPA after surgery.[8–11] However, the decision to submit a patient to XRT is not always an easy one. Some centres recommend postoperative XRT routinely to all NFPA patients, even in those with complete resection of their tumours, whereas others do so on a more individual basis, taking into account the size and location of the remnant and the pituitary hormone status. One of the major disadvantages of XRT is the induction of hypopituitarism, which may impact quality of life; however, many of these patients already have one or more anterior pituitary hormone deficiencies because of the tumour itself and/or to the surgical procedure.[1,3,12,13] The purpose of this study was to establish whether or not the adjunctive use of XRT in patients with NFPA is effective and safe in preventing tumoural recurrences using a case–control design.

METHODS

Patient population

Both our local ethics and scientific committees approved the study; all patients signed an informed consent. Both, cases and controls were selected from a large database ($n = 450$) of patients diagnosed with and treated for NFPA between January 2000 and December 2010 at our centre. In the case group, we included patients with NFPA who had been submitted to TSS and later on (1–2 years after surgery) received XRT because of the presence of a tumour remnant (defined as a >5 mm lesion, readily identifiable on MRI). The control group consisted of patients with NFPA, who had undergone TSS but who did not receive XRT, despite the presence of a tumour remnant. Both the radiated, and the non-radiated patients were free of tumour compressive symptoms and their pituitary hormone deficiencies were adequately replaced. Groups were carefully matched for age, gender, tumour volume and presence of cavernous sinus invasion. Imaging and hormonal information was gathered at baseline, and thereafter yearly, the end-points being tumour regrowth and the development of new pituitary hormone deficiencies.

The same two neuroradiologists evaluated baseline and follow-up MRIs; tumour volume was calculated using the DeChiro Nelson formula[14]:

$$volume = (sagital \times coronal \times axial\ diameters)\,\pi/6$$

Panhypopituitarism was diagnosed when three or more hormone deficiencies could be documented. Hypocortisolism was defined by a morning serum cortisol below 3 μg/dL; insulin-induced hypoglycemia was performed in borderline cases when am cortisol was between 3 and 10 μg/dL. Central hypothyroidism was defined by a free T4 below 0·5 ng/dL irrespective of the TSH level; and the diagnosis of central hypogonadism was established when the serum estradiol level was below 10 pg/mL in females and the serum total testosterone was below 300 ng/dL in males. Anterior pituitary

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Table 1. *Baseline characteristics*

	Cases ($n = 51$)	Controls ($n = 67$)	p
Age (mean ± SD)	56.2 ± 11.7	53.4 ± 12.3	0·52
Female (%)	45	46	0·60
Cavernous sinus invasion (%)	71	72	0·56
Tumour volume before XRT, median (interquartile ranges)[a]	1,601 mm^3 (697–1,538)	1,415 mm^3 (565–3,854)	0·50
Pituitary hormone deficiencies before XRT (%)			
Hypogonadism	73	40	<0·001
Hypothyroidism	71	43	<0·001
Hypocortisolism	53	24	<0·001
Panhypopituitarism	49	17	<0·001

Note: [a] In the non-radiated controls, this refers to tumour volume at matching time.
Abbreviations: SD, standard deviation; XRT, external beam radiation therapy.

hormones, as well as testosterone, estradiol, IGF-1, cortisol and free T4 were all measured by commercially available assays.

Radiation therapy (RT) protocol

Three-dimensional, conformal, external beam radiotherapy was administered by means of a lineal accelerator, at a mean total dose of 52 Gy (range 50–57), delivered as 2–2·5 Gy daily fractions, 5 days a week, over 5 weeks. Optic apparatus radiation dose was kept below 50·4 Gy using a multi-leave collimator.

Statistical analysis

For quantitative variables, data are presented as medians and interquartile ranges or means ± SD depending on data distribution, which was determined using the Shapiro-Wilks test. Differences in categorical variables were analysed by the χ^2-test. The Wilcoxon's signed-rank test was used to compare medians among the groups. A step wise, lineal, multiple regression analysis was performed to explore which patient characteristic was associated with tumour volume reduction in both groups. A p-value of $<0·05$ was considered statistically significant. Statistical software package consisted of STATA version 11.0 and SPSS version 16.

RESULTS

Baseline characteristics (Table 1)

The case group consisted of 51 patients (45% women) with a mean age of 56·2 ± 11·7 years; XRT was administered 2–8 months after the last pituitary surgery and the median follow-up was 5 years. The control group included 67 non-radiated patients (46% women), whose mean age was 53·4 ± 12·3 years. Median tumour remnant volume before radiation therapy (RT) was similar between cases and controls (cases: 1,601 mm^3, controls: 1,415 mm^3). A similar proportion of subjects in both groups had cavernous sinus invasion (cases: 71%, controls: 72%). The number of pituitary surgeries was similar among patients who did and those who did not receive XRT (39% one, 41% two and 20% three). Immunohistochemical analysis of tumour tissue revealed the same proportion of gonadotroph, null cell and corticotroph tumours in both groups.

Tumour volume changes

Median tumour volume decreased progressively in the radiated group from a baseline value (after last surgery, before XRT) of 1,601 mm^3 (697–1,538), to 1,124 mm^3 (382–2,638) and 816 mm^3 (92–1,866) after 3 and 5 years of follow-up, respectively ($p = 0·01$); tumour volume reduction in the radiated subjects after 5 years of follow-up was 50% (Figure 1). In contrast, in the non-radiated controls median tumour volume apparently decreased at 3 years follow-up but in fact increased again after 5 years [baseline 1,415 mm^3 (565–3,854), at 3 years 1,066 mm^3 (227–3,351), at 5 years 1,204 mm^3 (620–2,623), $p = 0·93$] (Figure 1). Lineal regression analysis revealed a tumour volume reduction in the radiated patients of 388 mm^3/year ($p = 0·02$, 95% CI: −714 to −62), whereas in the non-radiated patients a tumour

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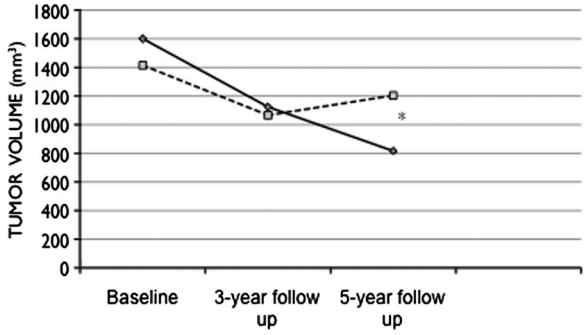

Figure 1. Median tumour volumes at baseline, 3 and 5 years of follow-up, in the radiated (solid line) and control groups (dotted line). Note: *p = *0·03.*

volume increment of 592 mm^3/year was documented ($p = 0{\cdot}05$, 95% CI: 12–1,198). The estimated tumour recurrence rate was 4% (2 out of 51) for the radiated group and 29% (20 out of 67) for the non-radiated controls (OR 0·10, 95% CI 0·01–0·04, $p = 0{\cdot}02$).

Pituitary hormone deficiencies and XRT-related adverse events

The group of radiated patients had a higher prevalence of pituitary hormone deficiencies after the last surgery than the non-radiated group (Figure 2); in fact, this was the main reason for avoiding XRT in the control group. At 5 years follow-up, pituitary hormone deficiencies had increased significantly in both groups; TSH deficiency was present in 80% of cases and 68% of controls, gonadotrophin deficiency in 95% of cases and 50% of controls, Adrenocorticotropic hormone deficiency 62% of cases and 42% of controls and panhypopituitarism in 60% of cases and 38% of controls (Figure 2). No cerebrovascular events, cases of optic neuritis, secondary tumours or deaths were recorded.

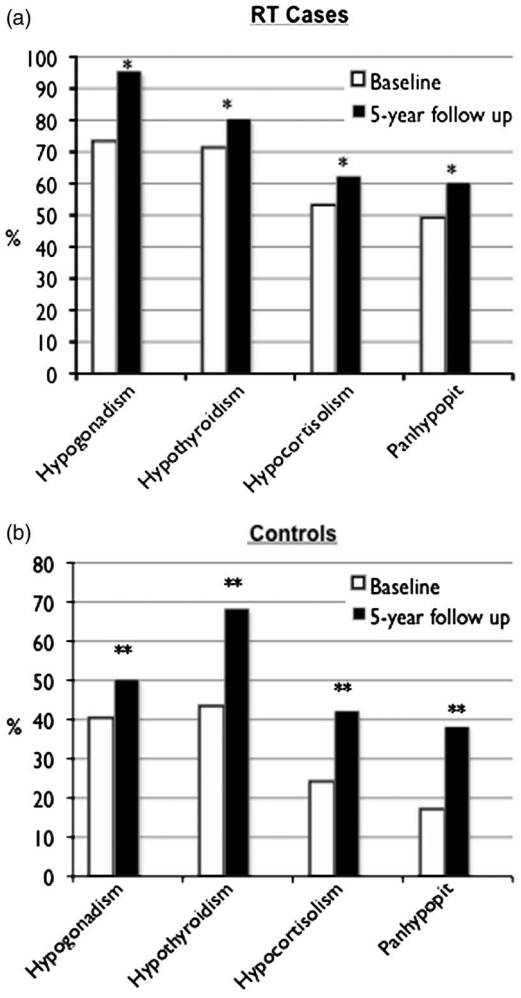

Figure 2. Prevalence of pituitary hormone deficiencies at baseline and after 5 years of follow-up in the radiated (a, *p < *0·001), and non-radiated controls (b,* **p < *0·01).*

DISCUSSION

Pituitary surgery remains the primary treatment of choice for NFPA.[1–3] However, a significant proportion of these tumours will recur upon long-term follow-up.[1–4] Unfortunately, there are neither clinical/imaging characteristics, nor histopathological features or biomarkers capable of accurately predicting recurrences and therefore indicate the need for prophylactic therapeutic interventions such as postoperative XRT.[4,7] Although the efficacy of postoperative XRT in preventing tumour regrowth has been documented, most if not all published studies have been retrospective and suffer from a selection bias whereby XRT is reserved for the largest or more invasive tumours.[8–11] On the other hand, the potential side effects of radiation, particularly the development of pituitary hormone deficiencies, preclude a more generalised use of this therapeutic tool.[15–17] Hypopituitarism because of NFPA has been associated with a decreased quality of life and in some studies, with increased mortality.[16,18] Studies in this regard have shown rather discrepant results,

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likely because of the myriad of variables involved in determining life quality and expectancy in this scenario, including the adequacy of hormone replacement.[16,18] Thus, in view of the available data, withholding XRT in patients with a complete adenoma resection and no evidence of a tumour remnant on postoperative MRI seems undoubtedly reasonable, particularly if the patient has few or no anterior pituitary hormone deficiencies. However, a significant proportion of NFPA are large and invasive and complete surgical resection is not always possible.[5,19] Therefore the fundamental question is whether XRT should be administered routinely to patients with evident tumour remnants after pituitary surgery.

In the present study we have used a case–control design to overcome these caveats and have confirmed that RT is highly effective in reducing tumour remnant volume and regrowth. The main reason for withholding XRT in the control group was in fact the relatively well-preserved pituitary function in these patients (the other reason being patient's and/or treating physician's preference). We did not include cases with complete adenoma resection and tumour remnant volumes were similar in both cases and controls. Only two of the 51 (4%) patients who received XRT had recurred after 5 years, whereas 20 of the 67 (29%) who did not receive XRT showed tumour regrowth at the end of the follow-up period.

Recurrence rates for patients with NFPA who do not receive postoperative XRT can be as low as 9%[13,17] and as high as 50%,[12–19] at follow-up periods that range between 5 and 10 years. Multivariate analyses performed in some of these studies show that the presence of an extraselar remnant, an incomplete resection of the adenoma and cavernous sinus invasion are all associated with an increase risk of recurrence.[12,17,19] In our study, multivariate analysis revealed that the use of XRT in NFPA patients effectively prevents tumour regrowth.

Although the development of pituitary hormone deficiencies has traditionally been an argument against the use of XRT, hypopituitarism is highly prevalent in patients with NFPA at diagnosis and is unlikely to improve after surgery, even in those subjects who do not undergo XRT. Our data confirms this notion, since the non-radiated group of patients also showed a significant worsening of pituitary function upon follow-up, likely as a result of previous pituitary surgeries but also because of the effects of the growing adenoma itself.

Although cases of radiation-induced damage to the optic chiasm have been well documented,[15] the use of modern techniques with carefully planned dosing schedules has made this complication an extremely rare event.[8,9] Accordingly, no cases of optic neuropathy were documented in our patients. The development of secondary brain tumours after XRT for pituitary adenomas has also been a concern and has been estimated to be around 2·4% at 20 years of follow-up.[9,20,21] Although our patients have only been followed for 5 years, so far no cases of secondary brain tumours have been detected.

A reduced life expectancy has been reported in patients with pituitary tumours treated with both surgery and RT.[21–24] This increased mortality rate, which in the majority of cases is due to cardiovascular and cerebrovascular causes, has been related to hypopituitarism.[18,23,24] In contrast to GH-secreting pituitary adenomas, where XRT has been associated to an increased mortality rate,[25] in NFPA the contributory role of XRT is still a matter of debate.[9] All patients included in our study are alive and no cardiovascular or cerebrovascular events have occurred. We are aware that our patients have been followed for only 5 years and thus need long-term surveillance to be able to ascertain whether those who received XRT have a higher mortality rate than those who did not.

Based on the present case–control study we can conclude that postoperative conventional XRT is a highly effective intervention to prevent tumour regrowth in patients with NFPA showing tumour remnants on imaging studies. The fact that hypopituitarism is highly prevalent even in non-radiated patients should allow a more generalised use of this treatment modality.

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Conflict of interest

The authors declare that they have no conflict of interest.

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