REVIEW

Radiotherapy for non-functioning pituitary adenomas

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Abstract

The initial management of large non-functioning pituitary adenomas is surgical debulking. In some cases, postoperative radiotherapy (RT) is administered in order to reduce the likelihood of tumour regrowth. Historically, there have been concerns surrounding a number of potentially significant complications of pituitary RT. Recent contributions to the literature, however, suggest that pituitary RT may be less hazardous than was originally thought. This article reviews the evidence relating to the potential side-effects of RT and weighs these risks against the clinically beneficial effects of preventing pituitary tumour regrowth.

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Introduction

Non-functioning pituitary adenomas (NFAs) are common tumours of the anterior pituitary and are the most frequent indication for pituitary surgery. Despite extensive efforts, little is known of their pathogenesis (reviewed in 1–3). ‘Clinically non-functioning pituitary adenomas’ comprise a heterogeneous array of tumour subtypes that are derived from a variety of pituitary cell types (4, 5). The initial management of large non-functioning pituitary macroadenomas is surgical debulking to relieve mass effects on adjacent structures, principally the optic chiasm. With surgery alone, however, a significant proportion (30–50%; 6–12) of NFAs will regrow and therefore require further treatment, sometimes up to 20 years after the initial surgery. In an effort to reduce the likelihood of tumour regrowth after surgery, postoperative pituitary radiotherapy (RT) is often employed, although the necessity, efficacy and potential complications of this treatment modality are the subjects of much debate. In this review, we endeavour to subject the available literature to a critical analysis and to provide a practical approach to the use of pituitary RT in the management of patients with NFAs.

Postoperative radiotherapy reduces the risk of regrowth of NFAs

During the 1960s, pituitary surgery generated poor long-term remission/cure rates for NFAs, tumour regrowth at 10 years being noted in up to 75% of subjects (13–16). These observations spurred clinicians into adopting an adjuvant mode of therapy –

namely pituitary RT – in an effort to reduce the excessive rates of regrowth. The majority of subsequent studies (see Table 1) have supported a role for RT, although in none of these has RT been randomly assigned to patients. When RT has been used, there has been significant selection bias, the tendency being to reserve RT for the largest or more aggressive pituitary tumours. The limitations of these studies and the lack of any randomised controlled trials of the use of postoperative RT versus other treatment modalities have served to fuel the continuing dilemma over the role of postoperative RT in the management of patients with pituitary tumours (17).

It has been suggested that the poor results of surgery alone (performed in the 1960s) may have reflected poor surgical technique, which was often performed using a transcranial approach with unsophisticated imaging modalities. More recent studies have reassessed the efficacy of modern surgery alone to determine whether it is an effective and definitive treatment for NFAs. Data from Oxford, UK, would argue against this, however. Bradley *et al.* (18) described a series of 132 patients with NFAs; 98 of these patients were advised not to receive adjuvant RT. The criteria used for withholding RT were as follows: (a) the absence of radiological or surgical evidence of parapituitary invasion; (b) complete surgical removal as reported by the surgeon at the time of the operation; (c) the absence of suprasellar extension 2 months postoperatively; and (d) no evidence of histological features of aggressive tumour behaviour (mitoses or poor cellular differentiation). After 13 years of follow-up, 8 patients out of 73 showed evidence of tumour regrowth. A recent re-examination of outcomes in this cohort of patients, however,

Table 1 Studies comparing recurrence rates of pituitary adenomas following surgery with or without RT.

Study	Follow-up period	Recurrence rate after surgery (%)	Recurrence rate after surgery + RT (%)
Ciric <i>et al.</i> , 1983 (7)	6 months–14 years	28	6
Ebersold <i>et al.</i> , 1986 (8)	4 years–8 years	16	9
Chun <i>et al.</i> , 1988 (9)	2 years–18 years	19–22	2–10
McCollough <i>et al.</i> , 1991 (11)	5 years–21 years	N/A	5
Comtois <i>et al.</i> , 1991 (12)	1 year–16 years	21	N/A

revealed that of the 65 patients followed, tumour recurrence was found in 21 (32%) after a total follow-up period of 20 years (19). Hence, despite the employment of what appeared to be markers of a good prognosis, approximately one-third of tumours regrew when treated with surgery alone.

We have previously described the rates of regrowth of NFAs in 2 cohorts of patients who received disparate postoperative management with respect to the application of pituitary RT (6). One group ($n = 63$) was treated in a centre that routinely administered RT after initial debulking pituitary surgery, whereas the other group ($n = 63$) was treated in a unit that rarely adopted this approach. The actuarial progression-free survival was 93% at 5, 10 and 15 years for patients treated with postoperative RT. In comparison, patients who did not receive RT had recurrence-free survival rates of 68, 47 and 33% at 5, 10 and 15 years respectively (6). We, like others, found no independent prognostic indicators of tumour regrowth other than the administration of RT in the postoperative period (20). Taken together, the data from Birmingham and Oxford show that the results of surgery alone for NFAs is poor and that administration of postoperative RT can significantly reduce the chance of tumour regrowth.

Complications of radiotherapy – how significant are they?

There is compelling evidence that RT prevents regrowth of NFAs following debulking surgery. However, over many decades a number of potentially significant complications of pituitary RT have been described; some represent justified concerns, whilst others are less well substantiated and require further

analysis. The following text reviews the literature relating to the potential side-effects of RT.

The immediate side-effects of RT are mild and include nausea and lassitude that may last up to 1–2 months after treatment. Diminished taste and olfaction can last for up to 6 months. Hair loss at entry sites may persist for up to 1 year after RT (4). The more significant potential complications of RT are discussed below.

Hypopituitarism

Quantitatively, the most significant problem following RT is radiation-induced hypopituitarism that occurs as a result of direct damage to the pituitary and also secondary to hypothalamic damage, as is evidenced by appropriate pituitary responses to administration of exogenous hypothalamic releasing hormones (21–23). Up to 50% of patients develop panhypopituitarism following pituitary surgery and RT (21–24). The speed of onset is related to the total and fractional doses of RT (21, 22), and the incidence of hypopituitarism increases with time from exposure. Littlely *et al.* (21) examined the incidence of hypopituitarism following RT: at 5 years after exposure, all patients were found to be growth hormone deficient, 91% were gonadotrophin deficient, 77% were corticotrophin deficient and 42% were thyrotrophin deficient. Despite the observed relative sensitivities of secretory cell types to pituitary RT, deficiency states may occur in an unpredictable sequence; thus, full endocrine testing is obligatory in all patients after pituitary RT. Furthermore, deficiency states may take up to 20 years to develop, stressing the importance of long-term follow-up for these patients (20, 22, 25).

Table 2 Studies showing mortality rates in patients with hypopituitarism.

Study	SMR (females) ¹	SMR (males) ¹	Overall (SMR)
Rosén & Bengtsson 1990 (28)	2.83	1.45	1.81
Bates <i>et al.</i> , 1996 (66)	2.29	1.50	1.73
Bulow <i>et al.</i> , 1997 (29)	2.93	1.91	1.73
Bates <i>et al.</i> , 1999 (67)	1.20	1.30	1.20
Tomlinson <i>et al.</i> , 2000 (26)	2.29	1.57	1.87

¹ SMR, standard mortality ratio.

The implications of hypopituitarism go beyond the inconvenience of taking life-long pituitary-hormone-replacement therapy. A number of reports have confirmed that patients with hypopituitarism have significantly increased mortality (standardised mortality ratio ~ 2 ; see Table 2), although the precise reasons for this excess have not been fully elucidated. A recent large study has confirmed increased mortality, especially in female patients with hypopituitarism (26). Major causes of excess mortality in this cohort were circulatory, respiratory and cerebrovascular in nature – findings that were also confirmed by others (27). Uncorrected growth hormone (GH) deficiency may be a contributing factor in the excess mortality in hypopituitary patients (28, 29), although the doses of other pituitary hormones used in replacement therapy might also be of relevance.

The prevalence of hypopituitarism in patients treated for NFAs cannot be attributed solely to the effects of pituitary RT. A significant proportion of patients have hypopituitarism at the time of diagnosis. Tsang *et al.* (22) found that 20–50% of patients have varying degrees of hypopituitarism at presentation. Following RT, hypopituitarism requiring hormone replacement with thyroxine, glucocorticoid and sex hormone was noted in 65, 68 and 67% of patients respectively (see Fig. 1). Radiation was reported to be a contributory cause in 23, 16 and 13% of cases respectively. In addition, patients treated with trans-sphenoidal surgery alone have significant rates of hypopituitarism (19).

Radiation-induced tumour formation

In the early 1960s, a number of case reports of parasellar fibrosarcomas were described in patients with pituitary adenomas who received RT following

pituitary surgery. X-ray treatment had previously been implicated in the development of meningiomas and gliomas in children who received scalp irradiation for conditions such as ringworm (30, 31). The majority of cases of intracranial tumours following pituitary RT have been published as case reports, thus making it impossible to assess the true incidence of this potential complication. Moreover, published reports are weighted towards describing the unusual, and an association may be one of ascertainment rather than causation.

In some studies, the risk of intracerebral neoplasm formation has been estimated to be as high as 1–2%, sometimes occurring with a latency of 8–15 years (31–33). However, it is important to appreciate that patients with pituitary tumours represent a highly selected group of individuals who receive disproportionately frequent imaging. Thus, the incidence cannot be directly compared with that observed in the general population, and instead should be compared with those patients with pituitary tumours treated with surgery alone. It is also noteworthy that a recent study has detected a 3.9-fold excess of malignancies (albeit extracerebral neoplasms) in patients with NFAs, compared with the general population, suggesting that the incidence of tumours may be higher, irrespective of the treatment modality (34).

Jones (35) reviewed the world literature (encompassing a 22-year period) on the subject of secondary tumour formation following pituitary RT: 16 cases of meningiomas were found in irradiated patients, but 19 cases were also detected in unirradiated pituitary patients. Gliomas were present in 18 irradiated patients and in 9 patients who were not irradiated. Again, there were no available denominators to allow the true incidence of these tumours to be determined. Clearly, the data in this area are suboptimal, although there is no clear causal link between pituitary RT and

Figure 1 Proportion of patients with hypopituitarism attributable to the causes shown during follow-up for pituitary tumours. Data for thyrotrophin, adrenocorticotrophin and gonadotrophin deficiencies are shown (22).

secondary intracranial tumours. However, there may be a common aetiological association between pituitary tumours, meningiomas and gliomas.

Damage to the optic chiasm

The optic chiasm is radiosensitive, and blindness due to RT-induced chiasmal damage has been well documented (25, 36–39). A 1–2% risk of radiotherapy-induced damage to the visual pathways has been quoted (40–45), with a latency of between 2 months to 4 years following irradiation (25, 37, 39). Gadolinium-enhanced magnetic resonance imaging (MRI) scanning has been instrumental in determining the pathological basis of radiation injury to the optic chiasm; such injuries have been shown to be due to damage to the vasa nervorum (36, 38). The risk of chiasmal damage is directly related to the total dose administered and the dose per fraction of RT. With modern RT planning and dosing schedules, however, damage to the optic chiasm is extremely rare. Jones (30) found no cases of optic neuropathy after a 10-year follow-up of 332 patients treated with 4500 cGy in daily doses of 180 cGy. Radiation-induced damage to the optic chiasm is of theoretical and historical interest but offers no identifiable risk when carefully planned RT is administered.

Neuropsychological changes following pituitary radiotherapy

A number of aspects of quality of life and neurocognitive function have been examined in patients following pituitary RT, though the results have been discrepant (30, 36, 46–48). A number of independent variables, such as the effects of surgery, RT, and hypopituitarism, act in concert to cloud the relative contribution of each to changes in quality of life. Furthermore, the end points in such assessments are often 'soft'. Poor social adjustment, mood disorders (including depression and memory deficits) have been reported following pituitary RT (35, 46–48). Symptoms of depression and anxiety have been found to be more prevalent in patients treated with pituitary RT than in those treated with surgery alone (36, 48). Others have noted greater memory deficits in patients treated with a combination of surgery and RT than in those treated with either treatment modality alone. The full impact of the neurocognitive sequelae that result from limited-field RT to the pituitary region has been inadequately studied. More research is required to determine the relative contributions of hormone deficiencies, surgery, and RT to any neurocognitive dysfunction (36, 44).

Which tumours should be treated with pituitary radiotherapy?

The 10-year follow-up data from our own study (6) showed that 53% of patients who were not treated with

RT showed no evidence of tumour regrowth. Furthermore, a study by Lillehei *et al.* (49) revealed that following radical tumour clearance (resulting in an empty sella upon postoperative MRI), the rate of tumour regrowth without RT was 6% after 5 years. These data suggest that a significant proportion of NEAs will not regrow despite the absence of RT. Ideally, therefore, a means of predicting the regrowth potential of NEAs is required to allow targeted therapy of those tumours with regrowth potential. At present, however, there are no reliable clinical (10), radiological (19), pathological (50) or molecular parameters (51–56) that predict the likelihood of tumour recurrence.

Decisions relating to the administration of RT are often made after an initial postoperative MRI scan at 4–6 months (6, 18). If there is a 'significant' tumour remnant, RT is often requested, but at present there is no definition of 'significant'. We know from the Oxford data (19) that even when the tumour remnant is confined to the sella, without RT there is a 32% risk of regrowth. Data from Lillehei *et al.* (49) show that with no macroscopic tumour remnant on MRI, the risk of regrowth is very low. It remains open to speculation as to whether there is a threshold size of tumour remnant that is safe to leave after surgery and which has minimal regrowth potential. At present, RT is usually administered to tumour remnants with supra- or extrasellar extension, and some advocate this approach for significant intrasellar tumour remnants.

A frequent approach used for small intrasellar tumour remnants (and empty sella) is a policy of observation with sequential MRI scanning to detect early evidence of tumour expansion. In the presence of tumour regrowth, RT is organised, and, because most NEAs are slow growing, most patients will avoid a second debulking operation. All patients with NEAs, irrespective of the administration of RT, require life-long imaging because of the possibility of late regrowth(s).

Types of pituitary radiotherapy; does radiosurgery have a role?

Conventional fractionated external-beam RT concentrates an X-ray beam on a target volume (the whole fossa and any tumour extension beyond) by means of a crossfire technique involving several ports, each of which is directed at the target; the patient's head is immobilised in a tight-fitting mask. Supravoltage RT is given in daily doses of 200 cGy 4–5 times per week over a 5–6-week period up to a total dose of 4500–5000 cGy (4, 36, 57).

Radiosurgery is the precise stereotactic delivery (in a single session) of a high-radiation dose to a delimited target, with a sharp fall-off of radiation at the target margins. It allows delivery with a high degree of precision such that a necrotising dose is administered to the tumour with relatively little irradiation to

surrounding tissues (17, 57, 58). Such selective destruction of tumour is an attainable therapeutic goal because of great advances in diagnosis and imaging (57, 59).

Three forms of radiosurgery are available, as follows: proton-beam therapy using heavy charged particles (protons); gamma knife surgery using cobalt-60 gamma radiation-emitting sources focused on a specific fixed point; and linear acceleration (LINAC), which also uses photons and focuses on a stationary point but involves a moving gantry (17, 58–60). There are a number of published small series of outcomes following pituitary radiosurgery that have concentrated on small functioning pituitary tumours (59–64); the results have generally been disappointing. It does appear, however, that the time required to achieve a reduction in hormone secretion is significantly reduced following radiosurgery as opposed to conventional external-beam radiotherapy (65). Radiosurgery is a relatively new technique and the initial disappointing results may reflect relative user-inexperience. The periods of follow-up in these studies have also been rather short. There are few data relating to radiosurgery for NFAs, thus at present there is no accepted role for this treatment in the management of NFAs. In the future, however, radiosurgery may prove useful in treating tumours and tumour remnants that extend into the cavernous sinus, a site that is inaccessible to surgery.

Conclusions

All patients with NFAs require life-long follow-up imaging to detect evidence of tumour regrowth. Despite major advances in diagnostic and surgical techniques, the results of trans-sphenoidal surgery alone are poor. Postoperative tumour remnants have been shown to regrow in a significant proportion of patients, often many years after the initial surgery. RT is an important adjuvant treatment in the management of non-functioning pituitary tumours, which, when administered during the postoperative period, significantly reduces the chance of regrowth. Hypopituitarism is a frequent and significant complication of pituitary RT. Damage to the optic chiasm can be avoided by careful planning, dosing, and administration of the RT. Further data are required to evaluate more fully the risks of neurocognitive dysfunction in patients exposed to pituitary RT. Although there is no direct evidence for secondary intracranial tumour development following pituitary RT, there are insufficient data to report a conclusive relative risk for this potential complication.

Currently, there is no reliable indicator of tumour regrowth following surgery, though most centres advocate RT for large postoperative tumour remnants. Small, intrasellar, postoperative tumour remnants are often tracked by sequential MRI scanning and RT requested in the presence of tumour expansion. Ideally, an accurate and reliable means of predicting tumour

behaviour in the postoperative period is required to allow targeted therapy for tumours with regrowth potential. In the absence of any clinical, radiological or pathological indicators of tumour regrowth potential, the most realistic expectation for the future lies with a novel molecular marker. Until such a test becomes available, efforts are being made to improve MRI surveillance to allow more accurate assessment of tumour volume with a view to quantitatively defining a 'safe' tumour remnant.

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