External beam radiotherapy has been used extensively in the management of patients with pituitary disease. However, in view of advances in the techniques of radiotherapy planning and administration, neurosurgery and pharmacological manipulation of the pituitary, there are a growing number of questions and controversies surrounding the current and future use of pituitary radiotherapy in the management of pituitary disease.

Introduction

External beam radiotherapy has a history of use in pituitary disease dating back ~ 100 years [1]. The technique then described utilized three ‘crossfire’ fields of radiotherapy that focused on the pituitary, and radiation was administered in several small fractionated doses. The rationale for a multiple-field technique and fractional delivery of radiotherapy was to spare normal surrounding tissue from the effects of ionizing radiation. To a large extent, the techniques described 100 years ago form the basis of current conventional external beam radiotherapy (Figure 1).

Pituitary radiotherapy has been utilized to treat a wide array of pituitary and para-pituitary pathologies, although a coherent evidence base for such practice is far from complete. There is a dearth of randomized controlled trials describing the use of radiotherapy in the context of managing pituitary disease. Nevertheless, pituitary radiotherapy has remained central to the management of patients with functioning and non-functioning pituitary adenomas, craniopharyngiomas and other pathologies in and around the pituitary fossa. This review identifies and discusses specific clinically relevant controversial aspects of pituitary radiotherapy that will inform clinical decision-making.

What are the clinically relevant complications of contemporary pituitary radiotherapy?

Techniques in the planning and delivery of radiotherapy have changed enormously over the past two decades. It is important to revisit historical concerns pertaining to the risks associated with pituitary radiotherapy in light of modern practice. It is also imperative that clinicians have a clear understanding of the currently perceived complications so that balanced and informed discussions can take place with patients.

Hypopituitarism and possible links to cerebrovascular disease

Hypopituitarism is an inevitable consequence of pituitary irradiation and quantitatively is the most significant problem associated with pituitary radiotherapy. The speed of onset of hypopituitarism is variable but is related to the total and fractional doses of radiotherapy [2]. Several studies have confirmed that patients with hypopituitarism have twice the risk of dying of all causes compared with matched controls [3–5]. A large prospective study by Tomlinson et al. [5] showed a significant increase in deaths due to circulatory, respiratory and cerebrovascular causes, findings also confirmed by others [6]. Moreover, the mortality ratio was higher in patients with hypopituitarism who had been treated with radiotherapy compared with those who were not treated in this way (Figure 2). A large proportion of this excess resulted from a significant increase in cerebrovascular disease-associated deaths in radiotherapy-treated patients. Whether this represented a direct causal relationship between radiotherapy and cerebrovascular disease remains to be determined. From a study of 342 patients exposed to a combination of pituitary surgery and radiotherapy [7], it would appear that radiotherapy-dependent variables (e.g. maximum absorbed dose, biologically equivalent dose, number of fractions, field size) were no different between patients who died from a cerebrovascular accident and those who did not experience a cerebrovascular accident. The only difference between these two groups of patients was the duration of symptoms associated with hypopituitarism, suggesting that states of untreated hormone deficiency might be more directly implicated in the pathogenesis of cerebrovascular disease in hypopituitarism, rather than radiotherapy per se. This is an important area where further research should be focused.

Secondary tumour formation

Exposure to ionizing radiation increases the risk of malignant transformation. The magnitude of this excess risk following pituitary radiotherapy is a widely debated issue. The majority of cases of intracranial tumours following pituitary radiotherapy have been published as case reports, thus making it impossible to derive a denominator and thus assess the true incidence of this
potential complication. Moreover, published reports are weighted towards describing the unusual, and an association might be one of ascertainment rather than causation.

In some studies, the risk of intracerebral neoplasm formation in pituitary patients treated with radiotherapy has been estimated to be as high as 2.4% at 20 years (relative risk 28.6 compared with the incidence in the general population) [8], with latencies of over 30 years described [9–11]. However, a more conservative estimate of risk has been calculated by meta-analysis, suggesting the standard incidence ratio of a secondary brain tumour to be increased approximately sixfold [12]. Patients with pituitary tumours represent a highly selected group of individuals who receive disproportionately frequent imaging of the central nervous system. Thus, the incidence of associated intracranial neoplasms cannot be directly compared with that observed in the general population but instead should be compared with those patients with pituitary tumours treated by surgery alone. Large cohort studies of such patients have not yet been reported but are crucial to provide a more direct assessment of the true excess risk of intracranial tumour formation following pituitary radiotherapy.

A literature review encompassing a 22-year period identified similar numbers of meningiomas in irradiated pituitary patients compared with unirradiated pituitary patients [13]. Gliomas were more frequently described in association with pituitary radiotherapy but, again, there were no available denominators to determine the true incidence of these tumours [13]. Data in this area are suboptimal and it remains to be determined what the true increased risk of secondary intracranial tumour formation is when compared with an appropriate group of pituitary patients who have not received radiotherapy.

**Radiation effects on the optic apparatus**

The optic chiasm is radiosensitive, and blindness caused by radiotherapy-induced chiasmal damage has been well documented [14–19]. A 1–2% risk of radiotherapy-induced damage to the visual pathways is sometimes quoted [20–26], with a latency of between two months and four years following irradiation [14,16,18,19]. The risk of chiasmal damage is directly related to the total administered dose and the dose per fraction of radiotherapy, and probably occurs secondary to damage to the vasa nervorum [15,17]. If modern radiotherapy planning and dosing schedules are used, however, damage to the optic chiasm is extremely rare [27]. No cases of optic neuropathy were reported after a ten-year follow-up of 332 patients treated with a radiation dose of 4500 cGy in 180 cGy daily doses [28]. Thus, with careful planning and delivery of external beam radiotherapy, radiation-induced damage to the optic chiasm should remain of historical interest but should not confer significant risk to the patient.

**Possible effects of pituitary radiotherapy on neurocognitive and neuropsychological function**

Several aspects of neurocognitive and neuropsychological function have been examined in patients following pituitary radiotherapy, although the results often vary [15,28–33]. Several independent variables, including the effects of surgery, radiotherapy and hypopituitarism, act in concert to cloud the relative contribution of each to changes in quality of life, neurocognitive function and neuropsychological behaviour. Furthermore, the endpoints in such assessments are often ‘soft’. Poor social adjustment, anxiety, depression and memory deficits have been reported to varying degrees following pituitary surgery and/or radiotherapy [13,15,29–32,34]. However, the full impact of neurocognitive and neuropsychological sequelae that result from radiotherapy to the pituitary region have been inadequately studied. Prospective studies in this area are required to determine the relative
contributions of hormone-deficiency states, surgery and radiotherapy.

When and under what circumstances should pituitary radiotherapy be used in the management of patients with nonfunctioning pituitary adenomas?

Transsphenoidal debulking surgery is the initial treatment for patients with large nonfunctioning pituitary tumours. Frequently, a residual postoperative tumour remnant will remain that has the potential to regrow. Regrowth rates following surgery performed in the 1960s were as high as 75% at ten years [35–38], leading to the introduction of postoperative adjuvant pituitary radiotherapy in some patients – principally those with a large tumour remnant or perceived ‘aggressive’ tumour. More recent studies have assessed the efficacy of modern surgery alone in effecting the long-term definitive treatment of patients with nonfunctioning pituitary tumours. In a group of 132 such patients who received surgery but no postoperative radiotherapy on the grounds that they were deemed to have a low risk of tumour regrowth, based principally on radiological and histopathological findings [39], tumour expansion occurred in 32% after a follow-up duration of 20 years [40].

Our group addressed the potential importance of postoperative radiotherapy in preventing the regrowth of nonfunctioning tumour remnants, by analysing the outcome in two groups of patients receiving disparate postoperative management with respect to the application of pituitary radiotherapy [41]. One group (n = 63) routinely were given radiotherapy following initial debulking pituitary surgery, whereas the other group (n = 63) rarely received such treatment. Progression-free survival was 93% at five, ten and 15 years for patients treated with postoperative radiotherapy. By contrast, patients who did not receive radiotherapy had recurrence-free survival rates of 68%, 47% and 33% at five, ten and 15 years, respectively [41] (Figure 3). Administration of postoperative radiotherapy was the only independent prognostic indicator of tumour regrowth. In a further study of 122 patients with nonfunctioning pituitary tumours, 108 did not receive postoperative radiotherapy [42]. The five-year progression-free survival rate was 48% in the unirradiated group. Taken together, data from the above studies [40–42] suggest that surgery alone for nonfunctioning pituitary tumours is associated with a high rate of regrowth of tumour remnants and that administration of postoperative radiotherapy can significantly reduce the likelihood of this occurrence. Bearing in mind the aforementioned potential hazards associated with pituitary radiotherapy, the decision to treat with adjuvant radiotherapy is based on a careful assessment of the balance of benefit and risks in individual patients.

Ten-year follow-up data from our own study [41] showed that 53% of patients who were not treated with radiotherapy had no evidence of tumour regrowth, and in the presence of complete tumour clearance, regrowth rates at five years without radiotherapy are low (6–16%) [42,43]. Clinical [44], pathological [45] and molecular markers [46–51] of tumour regrowth potential are currently unreliable but the presence of cavernous sinus extension preoperatively and suprasellar extension postoperatively are independent predictors of tumour regrowth [42]. In general, if there is residual postoperative tumour that is clear of the optic chiasm, most centres adopt a watchful waiting strategy utilizing sequential MRI scanning to detect early evidence of tumour regrowth. In the presence of tumour expansion, pituitary radiotherapy is arranged. In those with a ‘significant’ tumour remnant, radiotherapy might be considered but at present there is no satisfactory definition of ‘significant’. With complete macroscopic clearance, regrowth rates are low [42,43], although when the tumour remnant is confined to the sella, without radiotherapy there is a 32% risk of regrowth [40]. It remains open to speculation that there might be a threshold of size of tumour remnant that is ‘safe’ to observe following surgery. Postoperative radiotherapy is administered in some centres if tumour remnants have supra- or extrasellar extension, and some advocate this approach for significant intrasellar tumour remnants. Tumours with cavernous sinus extension preoperatively should also be considered as being at high risk of regrowth postoperatively [42]. All patients with nonfunctioning pituitary tumours, irrespective of the administration of radiotherapy, require life-long imaging, owing to the possibility of late tumour regrowth.

Types of pituitary radiotherapy: does radiosurgery have a role?

Conventional fractionated external beam radiotherapy concentrates an X-ray beam on a target volume (the whole pituitary fossa and any tumour extension beyond) by a crossfire technique of several ports, each directed at a target, while the patient’s head is immobilized in a tight-fitting mask (Figure 1). Megavoltage radiotherapy is given in daily doses of 150–200 cGy, four to five times per week over a five to six week period, up to a total dose of ~4500–5000 cGy [15,52].

Radiosurgery can be defined as the precise stereotactic delivery in a single session of a high radiation dose to a delimited target with sharp fall-off radiation at target

**Figure 3.** Actuarial progression-free survival in 126 patients with nonfunctioning pituitary tumours who received radiotherapy (RT) or did not receive RT (No RT). Follow-up time is defined as the time since initial pituitary surgery. Number of patients in the study: 93 at five years; 56 at ten years; 30 at 15 years; 14 at 20 years. Adapted, with permission, from [41].
It enables delivery with a high degree of precision, such that a necrotizing dose is administered to the tumour, with relatively little irradiation to the surrounding tissues [53,54], theoretically minimizing the risk of potential complications. The potential downside to this rapid fall-off in radiotherapy is the possibility of missing deposits of tumour not identified on high-resolution imaging used to plan radiosurgery.

Radiosurgery can be delivered using photon techniques that include gamma-knife surgery using cobalt-60 γ-radiation-emitting sources and the linear accelerator (LINAC) method, and proton-beam therapy using heavy charged particles [55,56]. Published data on the efficacy of pituitary radiosurgery (recently extensively reviewed in [57]) have concentrated predominantly on small functioning pituitary tumours. A potential advantage of pituitary radiosurgery is the claim that there is a faster decline in elevated hormone levels in functioning tumours, although presently there are only limited and relatively short-term data on both the efficacy and toxicity of radiosurgery. To date, there have been no randomized controlled trials comparing radiosurgery with conventional external beam radiotherapy. Long-term prospective studies, ideally with randomization between radiosurgery and external beam radiotherapy, are needed to delineate relative long-term efficacy and toxicity in a clinically representative cohort of patients.

Pituitary radiosurgery has been used as a salvage procedure in patients with residual or recurrent pituitary tumour remnants that are inaccessible to transsphenoidal surgery. This is particularly pertinent to nonfunctioning pituitary adenomas, where no effective medical therapy is available to control disease activity. Early results of pituitary radiosurgery for residual and recurrent nonfunctioning pituitary adenomas show promising results in terms of disease control, with a low rate of additional pituitary hormone deficiencies [58–62]. Longer term follow-up of these cohorts of patients will help to determine whether radiosurgery might offer clinically relevant advantages over conventional fractionated pituitary radiotherapy.

Radiotherapy for craniopharyngiomas
Craniopharyngiomas are challenging tumours to manage, given their propensity for regrowth, morbidity [63,64] and mortality [5,65]. Although optimal primary therapy is gross surgical removal, this is often technically not feasible, and in a recent report of 121 cases was successfully achieved in only 18% [66]. When gross clearance is achieved, recurrence-free survival is good (74–100% at ten years [66–69]). In the presence of partial clearance and no radiotherapy, regrowth rates are around 60% at ten years [66–68,70]. By contrast, regrowth rates of 10–33% have been documented in patients who had partial surgical clearance followed by external beam radiotherapy [66,68,71,72]. Gamma-knife radiosurgery has also been successfully used for disease control [73].

The presence of tumour regrowth appears to confer a negative impact on ten-year survival, which falls from 99% in those with no recurrence to 70% in those experiencing tumour regrowth [66]. These data strongly support the practice of postoperative radiotherapy in patients with partial surgical clearance. However, a potential complication of radiotherapy for craniopharyngiomas is the possibility of clinical deterioration owing to cyst enlargement in up to 14% during radiotherapy [74]. Intracavity irradiation using 32P is advocated by some for cystic craniopharyngiomas, and a recent report showed tumour cyst control of 70% at ten years, with worsening vision, thought to be a result of irradiation, in 8% and additional endocrine deficiencies developing in 29% [75].

In the minority of patients in whom a gross clearance is achieved, it is unlikely that postoperative radiotherapy is routinely required.

Does pituitary radiotherapy have a role in the contemporary management of patients with acromegaly?
Historically, pituitary surgery has been employed as the treatment of choice in patients with acromegaly. At centres that have great experience in managing such patients, long-term remission is seen in over 85% with microadenomas, although this figure falls to around 50% in the presence of a macroadenoma [76]. Patients who are not cured by surgery alone (overall, ~36% in our series
Radiotherapy-induced hypopituitarism and its associated mortality is a real concern, whereas other complications of radiotherapy are less clearly defined and quantified. Further research is required to clarify the extent of these complications. In view of the significant advances in radiotherapy planning and delivery, it is important for clinicians to have a clear and contemporary view of the true risk versus benefit profile of pituitary radiotherapy, to inform clinical decision-making (Table 1).

External beam radiotherapy does have a role in a subgroup of patients with postoperative remnants of nonfunctioning pituitary tumours. In most patients with craniopharyngioma, gross surgical clearance is not feasible, and postoperative radiotherapy significantly reduces the risk of tumour expansion in this group of patients. Although pituitary radiosurgery is widely used in some centres with an interest in this therapy modality, it has a limited role in conventional clinical practice, although future research might provide an evidence base to identify groups of patients in whom this mechanism of delivery of ionizing radiation could become the standard approach. Finally, despite highly effective medical therapies, pituitary radiotherapy will continue to have a role in managing subgroups of patients with acromegaly. In each clinical scenario in which pituitary radiotherapy is considered, a careful assessment of the risk versus benefit profile is required.

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References

Table 1. Possible factors to consider before utilizing pituitary radiotherapy

<table>
<thead>
<tr>
<th>Generic</th>
<th>Use of prior pituitary RT&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td></td>
<td>Degree of hypopituitarism</td>
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<td>Risk factors for cerebrovascular disease</td>
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<td>Patient age</td>
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<tr>
<td>Nonfunctioning adenomas</td>
<td>Size, location and extension of postoperative residual tumour</td>
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<tr>
<td>Acromegaly</td>
<td>Availability, efficacy and cost of medical therapy</td>
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<tr>
<td>Craniopharyngioma</td>
<td>Degree of initial surgical tumour clearance&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Pituitary radiosurgery</td>
<td>Convenience of single-fraction treatment versus multiple attendances for conventional external beam pituitary radiotherapy</td>
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<td></td>
<td>Inadequate response to prior external fractionated RT&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Surgically inaccessible pituitary tumour</td>
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<td></td>
<td>Growth hormone or adrenocorticotrophic hormone-secreting adenomas&lt;sup&gt;d&lt;/sup&gt;</td>
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<sup>a</sup>As a result of dose-limiting factors, a second course of conventional external beam pituitary radiotherapy is not indicated. However, pituitary radiosurgery might be considered following conventional external beam pituitary radiotherapy.

<sup>b</sup>In the presence of gross total surgical clearance, radiotherapy is frequently withheld.

<sup>c</sup>Functioning or nonfunctioning tumours.

<sup>d</sup>Some centres use pituitary radiosurgery as a first-line radiotherapy technique (before conventional external beam pituitary radiotherapy). However, with this approach, there is heavy reliance on precision radiosurgery technology that cannot take into account the subjective nature of interpretation of modern imaging. It thus carries a risk of missing parts of a tumour that would normally be included in the larger radiation fields used in conventional external beam radiotherapy.

[76] require adjuvant therapy, which historically has included postoperative pituitary radiotherapy. However, there are now substantial data showing sustained efficacy of somatostatin analogues in achieving satisfactory control of growth hormone secretion, insulin-like growth factor-I concentrations [77,78] and, more recently, causing tumour shrinkage in the majority of cases, at least in the short term [79,80]. Collectively, these observations raise the possibility of using long-term medical therapy, while sparing patients the potentially negative consequences of pituitary radiotherapy. As such, the role of pituitary radiotherapy in the modern management of acromegaly remains a subject for debate [81,82].

Recently, Ayuk et al. [83] reported the outcome of a cohort of patients with acromegaly, a large proportion of whom were subjected to pituitary radiotherapy. They described a significant increase in mortality in patients who had been treated with radiotherapy when compared with those who had not. More specifically, the excess mortality was primarily a result of an increased death rate from cerebrovascular disease. Pituitary radiotherapy might have generic negative effects on cerebrovascular disease-associated risk factors which might be compounded by the already adverse cardiovascular risk profile seen in patients with acromegaly. On balance, it is difficult to propose a role for radiotherapy in acromegalic patients who have satisfactory disease control on somatostatin analogues. However, in those with inadequate response to surgery and currently available medical therapies, whether in terms of tumour growth and/or hypersecretion, radiotherapy remains a useful adjunct within the therapeutic armamentarium for acromegaly. Other issues, such as relative costs, newer medical therapies (the growth hormone receptor antagonist pegvisomant) and newer modes of delivery of radiotherapy, are also important variables, fuelling the ever more complex equation of how to optimize management in patients with acromegaly.

Conclusions
Pituitary radiotherapy has a long history of use in pituitary disease and is likely to continue to be an important adjunctive treatment for some time to come. Radiotherapy-induced hypopituitarism and its associated variables, fuelling the ever more complex equation of how to optimize management in patients with acromegaly.


Peace, K.A. et al. (1998) Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transphenoidal surgery or medication. *Clin. Endocrinol. (Oxf.)* 49, 391–396


Free journals for developing countries

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