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Mortality following pituitary radiotherapy

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Abstract External beam radiotherapy has been used in the management of pituitary adenomas for nearly a century, preventing tumor regrowth following surgery for non-functioning pituitary adenomas and suppressing functional hypersecretion in those which are hormonally active. However, it has been linked with a number of potentially significant complications including formation of secondary intracranial tumors, cognitive impairment, hypopituitarism and cerebrovascular disease, as well as increased mortality.

Radiation may cause a variety of vascular injuries and hemodynamic changes to the cerebral vasculature, and several authors have reported cerebrovascular complications and an increase in cerebrovascular mortality in patients receiving radiotherapy for pituitary and other central nervous system tumors.

Ten years following pituitary radiotherapy, over 50% of patients develop deficiencies in one or more anterior pituitary hormones. A number of studies have demonstrated increased mortality in patients with hypopituitarism, predominantly due to cerebrovascular and cardiovascular disease. However, no clear answer has emerged with regards to causation, and pituitary radiotherapy has only been linked directly to mortality in one of these studies.

Questions remain unanswered, and the use of conventional external beam radiotherapy in the management of pituitary disease must involve a critical risk-benefit analysis in each case.

Keywords Pituitary · Radiotherapy · Mortality · Hypopituitarism · Cerebrovascular

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Introduction

External beam radiotherapy has been used in the management of hormonally active and non-functioning pituitary adenomas for nearly a century [1]. Administered post-operatively, radiotherapy significantly reduces the likelihood of tumor regrowth following surgery for non-functioning pituitary adenomas [2, 3]. When used in patients with acromegaly, conventional fractionated radiotherapy lowers growth hormone levels to less than 2.5 μg/L in 60% of patients by 10 years and in 77% of patients by 20 years [4]. Conventional pituitary irradiation has also been shown to be a useful adjunctive treatment for adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas [5] and resistant or giant prolactinomas [6]. However, over the years a number of potentially significant complications of pituitary radiotherapy have been described, including the formation of secondary intracranial tumors [7, 8], damage to the optic nerves [9, 10] and impaired neurocognitive function [11]. Of particular relevance is the development of hypopituitarism and a link to cerebrovascular disease, as both of these conditions are associated with increased mortality in patients with pituitary disease. This article explores the evidence linking pituitary irradiation with increased mortality. As stereotactic radiosurgery is a relatively new technique with few long-term outcome studies, the article will focus on conventional fractionated external beam radiotherapy.

Cerebrovascular disease following pituitary radiotherapy

Several authors have reported cerebrovascular complications in patients receiving radiotherapy for central nervous

system tumors. These include cases of documented arteriographic changes within the radiation fields in children and adults suffering strokes following irradiation [12, 13] and Moya-moya syndrome with severe stenosis or occlusion of the internal carotid arteries [14]. In a series of 156 patients receiving radiotherapy for non-functioning pituitary adenomas, the incidence of cerebral infarction was found to be elevated in those treated with higher equivalent doses [15]. Similarly, in another study of 331 patients with pituitary adenomas treated with surgery and radiotherapy, increasing doses of radiotherapy were associated with increasing risk of cerebral infarction [16]. In this study, the relative risk of first cerebrovascular accident compared to the general population was 4.1 [95% confidence intervals (CI) 3.6–4.7].

Debate surrounds the exact cause of the increased cerebrovascular risk seen in patients treated with radiotherapy, but it is thought that radiation may cause a variety of vascular injuries and hemodynamic changes to the cerebral vasculature [17].

Cerebrovascular mortality following pituitary radiotherapy for non-functioning adenomas

Not surprisingly, the increased incidence of cerebrovascular disease seen in patients treated with pituitary radiotherapy is reflected in an increase in cerebrovascular mortality in these patients. Having determined the incidence of cerebrovascular accidents in a cohort of patients with predominantly non-functioning pituitary adenomas treated with surgery and radiotherapy [16], Brada et al. went on to assess cerebrovascular mortality within the group [18]. In the cohort of 334 patients representing a total of 4,982 person-years, 79% had been treated with transcranial or transsphenoidal surgery and all patients had received radiotherapy. Deaths from cerebrovascular disease accounted for 26% of the total. There were 33 deaths from cerebrovascular disease, compared with 8.04 expected, leading to an estimated relative risk (RR) of death from cerebrovascular disease of 4.11 [95% CI 2.84–5.75]. There was a statistically significant difference in the relative risk of cerebrovascular deaths in women (RR 6.93 [95% CI 4.29–10.60]) compared with men (RR 2.4 [95% CI 1.24–4.20]). The authors also found that patients who had debulking surgery were at greater risk than those who had no surgery or biopsy alone (RR 5.19 [95% CI 3.50–7.42] versus 1.33 [95% CI 0.27–3.88]). The relative risk of cerebrovascular deaths in patients with non-functioning tumors was 3.65 [95% CI 2.26–5.58], compared with 5.23 [95% CI 2.25–10.30] in patients with hormonally active tumors.

Impact of pituitary radiotherapy on mortality in acromegaly

In the West Midlands Acromegaly Study, we reported on outcome in 419 patients with acromegaly, of whom 324 were alive and 95 deceased [19]. Compared to the general population, all cause mortality was significantly increased with a standardized mortality ratio of 1.26 [95% CI 1.03–1.54, $p < 0.05$]. The excess mortality was due predominantly to cerebrovascular disease with small but non-significant increases due to cardiovascular and respiratory disease. No significant increase in mortality was identified in patients where therapy achieved a post-treatment growth hormone less than 4 mU/L (2 μg/L), but survival was reduced in the cohort failing to achieve this target, with a standardized mortality ratio of 1.31 [95% CI 1.03–1.66, $p = 0.05$].

The use of external radiotherapy (total dose ranging from 45 to 50 Gy in 30 treatments via three ports) was associated with increased mortality, with a standardized mortality ratio of 1.58 [95% CI 1.22–2.04, $p = 0.005$] which was highly significant. The excess mortality was predominantly due to cerebrovascular disease, with a standardized mortality ratio of 4.42 [95% CI 2.71–7.22, $p = 0.005$] (Table 1). A comparison of 211 patients who received external radiotherapy with 206 who did not, controlled for age and sex, confirmed a poor outcome in the former with a rate ratio of 1.67 [95% CI 1.10–2.56, $p = 0.02$]. This effect was consistent despite controlling for the effects of growth hormone, insulin-like growth factor-1, tumor size, tumor extension (beyond sella) or hypopituitarism (any deficient axis).

In the Finnish Nationwide Survey of Mortality in Acromegaly, treatment with radiotherapy was also associated with increased mortality [20]. Of 334 patients with acromegaly, 116 had been treated with radiotherapy. The standardized mortality ratio for irradiated patients was 1.69 [95% CI 1.05–2.58, $p < 0.001$], which was significantly higher than in the general population, whilst the standardized mortality ratio for those not treated with radiotherapy was 0.94 [95% CI 0.62–1.37]. Cerebrovascular disease was a common cause of death among patients who had been treated with radiotherapy.

Data from the Spanish Acromegaly Study also examined the link between radiotherapy and mortality [21]. Patients who died were twice as likely to have been treated with radiotherapy than those who survived.

Thus, recent evidence suggests that mortality is increased in patients with acromegaly treated with conventional radiotherapy. This increased mortality remains consistent even after controlling for the effects of growth hormone and insulin-like growth factor-1, and is thus not directly linked to disease activity. It is established that

Table 1 All cause and cause specific mortality in patients with acromegaly treated with radiotherapy [19]

Cause	Observed deaths	Expected deaths	SMR (95% CI)	*p*
All cause	59	37.4	1.58 (1.22–2.04)	0.005
Cerebrovascular	16	3.6	4.42 (2.71–7.22)	0.005
Cardiovascular	20	12.5	1.60 (1.03–2.48)	0.096
Respiratory	7	4.0	1.75 (0.84–3.68)	0.261
Malignancy	12	12.0	1.00 (0.57–1.76)	1.000

non-acromegalic patients with hypopituitarism have increased mortality [22–25], and around half of all patients treated with radiotherapy develop new anterior hormone deficiencies by 10 years [26]. However, in only one of the studies discussed above was hypopituitarism linked to a trend towards increased mortality [19]. This lends support to the theory that the increased mortality seen in patients with acromegaly treated with radiotherapy may be due to the direct effects of radiation on cerebral vasculature. Nonetheless, further studies are required to define the contribution of hypopituitarism to any increase in mortality in patients with acromegaly.

Hypopituitarism and excess mortality following pituitary radiotherapy

Hypopituitarism occurs almost invariably following pituitary radiotherapy; over 50% of patients treated with pituitary radiotherapy will develop deficiencies in one or more anterior pituitary hormones over the following decade [27–29]. The speed of onset of hypopituitarism is related to the dose of radiotherapy, and the incidence increases with time from treatment [27, 28]. Despite the observed differing sensitivities of anterior pituitary cell types to pituitary radiotherapy, deficiencies may occur in an unpredictable sequence and may take many years to develop, making regular life-long full endocrine testing mandatory in these patients.

A number of studies have examined mortality in patients with hypopituitarism and found increased mortality compared with age-matched controls, predominantly due to cerebrovascular and cardiovascular disease [22–25]. The overall standardized mortality ratio in these studies was around 2, with females appearing to be more severely affected.

Of a total of 1,863 patients included in these studies, nearly 50% had been treated with pituitary radiotherapy. In two of these studies, treatment with radiotherapy was not associated with increased mortality [22, 23], and in the third, as almost all patients had received radiotherapy post-operatively, any possible contribution of radiotherapy to the increased cerebrovascular mortality could not be evaluated [24]. However, in the large prospective study from the West Midlands region of the United Kingdom, comprising over 1,000 patients and 181 deaths, treatment with radiotherapy was associated with a significantly increased mortality rate [25]. Standardized mortality ratio was 2.32 [99% CI 1.71–3.14, $p = 0.004$] in the 353 patients with hypopituitarism that had been treated with cranial radiotherapy, compared to 1.87 [99% CI 1.62–2.16] in the general cohort of patients with hypopituitarism. The excess mortality was caused to a significant degree by a marked increase in cerebrovascular deaths in patients who underwent radiotherapy (standardized mortality ratio 4.36 [99% CI 2.48–7.68, $p = 0.001$]). The authors also reported higher mortality in patients who had been diagnosed at a younger age, with a standardized mortality ratio of 4.87 in the group younger than 20 years, decreasing to 1.0 in those older than 60 years. This is of particular relevance as over half of the radiotherapy-treated patients were younger than 50 years at the time of treatment.

While the studies above confirm the excess mortality seen in patients with hypopituitarism, no clear answer has emerged with regards to causal relation. It is difficult to be certain about the individual contribution of various risk factors in the very heterogeneous population of hypopituitary patients. As well as the direct effects of radiation on cerebral vasculature, some authors have suggested that deficiencies in specific pituitary hormones may contribute to the increased vascular mortality seen in these patients. Growth hormone secretion is the most vulnerable of the anterior pituitary hormones following radiation damage to the hypothalamo-pituitary axis, followed by the gonadotrophins [27, 30]. Based on the assumption that most patients with hypopituitarism would be growth hormone deficient, Rosen and Bengtsson speculated that growth hormone deficiency might explain the premature death from vascular disease seen in their series; however, no evidence was available to support this speculation [22]. By contrast, the only endocrine factor implicated in the excess mortality in the West Midlands study was untreated gonadotrophin deficiency, with sex steroid replacement significantly reducing mortality [25].

A recent study examining risk factors for cerebrovascular mortality in 342 patients with pituitary disease treated with surgery and radiotherapy provides a useful contribution to the field [31]. The study compared radiation regimens and duration of symptoms of hypopituitarism

between 31 subjects who died from cerebrovascular disease and a matched control group of 62 patients from the same cohort of hypopituitary patients who had not died from cerebrovascular disease. No significant differences were found between the two groups in maximum absorbed dose, maximum biological equivalent dose, field size or number of fractions. The only difference between the patients who died from cerebrovascular disease and the control group was the duration of symptoms of hypopituitarism, lending support to the hypothesis that untreated hormone deficiencies may be more directly implicated in the increased cerebrovascular mortality seen in hypopituitarism than radiotherapy per se. Of interest, however, is that in all the patients who died from cerebrovascular disease, the lesion was localized within the irradiated area of the brain.

Conclusion

The link between pituitary radiotherapy and cerebrovascular mortality remains the subject of much debate and discussion. Both human and animal studies have shown that exposure to therapeutic doses of radiotherapy can lead to atherosclerosis-like occlusive disease, and increased cerebrovascular mortality has been demonstrated in patients with secretory and non-functioning pituitary adenomas treated with external beam radiotherapy. As well as the direct effects of radiation on cerebral vasculature, some authors have suggested that deficiencies in specific pituitary hormones may contribute to the increased vascular mortality seen in these patients.

However, a causal link has not been proven, and there may be a number of alternative explanations for the increased mortality seen in these patients. The patients may have had more severe or aggressive pituitary disease, necessitating the use of radiotherapy. Alternatively, they may have had significant comorbidities, making them poor surgical candidates and leaving radiotherapy as the only treatment option.

Despite these possibilities, the existing evidence points to a persistent association between pituitary radiotherapy and cerebrovascular mortality. Further studies are required to elucidate causation, but in the interim the future use of radiotherapy, particularly in younger patients, needs to be set in the context of aggressive cerebrovascular risk stratification and reduction.

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