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Abstract for Table of Contents
This chapter describes the technical aspects and the clinical results of conventional radiotherapy and modern stereotactic radiotherapy for pituitary adenomas. Systematic review of the published literature provides a factual basis for the comparison and the selection of appropriate radiation technique in patients with secreting and non-functioning pituitary adenomas not cured with surgery and medical therapy.
Introduction

External beam radiotherapy (RT) is generally used in patients with pituitary adenoma as second line treatment following surgery and medical therapy. In patients with secreting tumours it normalizes elevated serum hormone concentrations albeit with delay and in patients with unresectable progressive and recurrent non-functioning tumours it achieves excellent long-term tumour control. Hypothalamic-pituitary insufficiency is the most frequent late complication of treatment although serious late effects are uncommon. Modern techniques of high precision conformal and stereotactic RT delivery treat less normal tissue to high radiation doses than conventional RT with the aim of reducing late morbidity even further, although to demonstrate such benefit will require large long-term studies.

Radiotherapy techniques

Conventional radiotherapy

Conventional external beam RT for pituitary adenoma is given with photons using a linear accelerator. Practical steps in the preparation for treatment include patient immobilisation, CT and MRI imaging for accurate localisation of the tumour and computerised 3 dimensional (3D) planning to achieve localised delivery of radiation conforming to the shape of the tumour.
The precision of the treatment is aided by the use of immobilisation devices. The most frequently employed is an individually moulded, closely fitting plastic mask with a relocation accuracy of 2-5mm.

Imaging for treatment planning is performed in the treatment position (supine) in the immobilisation device using both CT and MRI which should be co-registered. The MRI visible mass and possible residual disease based on preoperative images and surgical notes are delineated and this is defined as the gross tumour volume (GTV). Based on the known technical uncertainty of planning, immobilisation and treatment delivery, a 3D margin is added to the GTV and this is defined as the planning target volume (PTV). The margin should be based on the actual measurement of uncertainty specific to the radiotherapy centre and for conventional RT is in the region of 5 to 10mm. The aim of conventional RT planning is to achieve a homogeneous dose to the PTV with the least dose to the surrounding normal tissue.

Conventional RT generally uses three fixed radiation fields – an anterior oblique field aimed at the pituitary through the forehead and two lateral opposing beams traversing through the temporal regions. Beams are shaped using a multi-leaf collimator (MLC) to conform to the shape of the tumour and to shield out normal structures and this is described as conformal radiotherapy.

MLC leaves may also be used to alter the intensity of radiation across the target and this is described as intensity-modulated radiotherapy (IMRT). Currently there is no advantage of IMRT over conformal radiotherapy in the treatment of pituitary adenomas."
Radiosurgery and stereotactic conformal radiotherapy

Stereotactic technique enables more precise localization of the tumour and the adjacent critical neural structures and is a further refinement of conformal radiotherapy. Stereotactic irradiation can be given either as single fraction radiosurgery (SRS) using a multi-headed cobalt unit (Gamma Knife - GK) or a linear accelerator, or as fractionated stereotactic conformal radiotherapy (SCRT) delivered as fractionated treatment on a linear accelerator.

Immobilisation for single fraction radiosurgery is traditionally with invasive neurosurgical type frames. For fractionated SCRT immobilisation is achieved with relocatable frames ², ³ with a relocation accuracy of 1-2 mm and more precisely fitting mask systems ⁴ with accuracy of 2-3 mm allowing for a smaller margin around the GTV.

Pituitary adenoma is delineated as for conventional RT on MRI, which is accurately co-registered with CT. The position of the tumour is defined using 3D co-ordinates with the aid of either external fiducial markers or fixed internal anatomical structures. Accurate identification of all parts of the tumour prior to treatment is essential for any modern RT technique and image interpretation is the cornerstone for successful treatment with any high precision delivery techniques employing small safety margins.
Linear accelerator beams are shaped with a narrow leaf multileaf collimator (MLC) of 3mm (micro-MLC) or 5mm (mini-MLC) leaf width. The leaves are automatically positioned to predefined shapes based on information transferred directly from the planning computer. The use of 4 to 6 rather than 3 beams improves the dose differential between the tumour and normal tissue and leads to further normal tissue sparing. There is no clear therapeutic gain using a larger number of fixed beams.

In SRS beams from multiple fixed Cobalt sources of a multi-headed cobalt unit (Gamma Knife) are collimated through a collimator helmet to produce small spherical high dose volumes ranging from 6 to 18mm diameter. Larger and/or non-spherical tumours, such as the majority of pituitary adenomas, are treated by a combination of several spheres described as a multiple isocentre technique. Computerised 3D planning determines the optimum number and distribution of isocentres and this can be aided by selective occlusion of GK collimator apertures.

**Comparison of conformal radiosurgery techniques**

The only published comparison of GK multiple isocentre technique and linear accelerator multiple fixed field treatment shows no clear advantage for either of the techniques in terms of sparing of normal tissue receiving high radiation doses with excellent conformity achieved with GK and linear accelerator fixed field treatments. The wide hemispheric distribution of multiple cobalt sources from GK increases the volume of normal brain receiving low radiation doses. Although the clinical
significance is at present uncertain, low dose whole brain irradiation may increase the risk of radiation-induced second malignancies.

While linear accelerator SCRT delivers a homogenous dose to the tumour, overlapping radiation spheres of multiple isocentres lead to inhomogeneous dose distribution in the target with small high dose regions (hot spots). In the absence of normal neural structures within the target this is unlikely to be of clinical importance in terms of toxicity. However, multiple isocentre treatment of tumours involving the cavernous sinus or the optic apparatus may produce hot spots within cranial nerves with a risk of late radiation damage.

In the early days of stereotactic radiotherapy, linear accelerators were adapted with fixed circular collimators to mimic GK dose distribution using the technique of multiple arc rotation. Four to six conformal fixed field SCRT technique produces superior dose distribution within and outside the target and has largely superseded the multiple arc multiple isocentre technique.

In summary, GK SRS and linear accelerator SCRT treat similar volumes of normal brain to high radiation doses. GK SRS produces dose inhomogeneity within the target and increases the volume of normal brain receiving low radiation doses (1-5%) while linear accelerator SCRT achieves homogenous target dose and tends to treat larger volumes of normal brain to medium-low doses (20-30%). The claimed benefit of GK SRS over linear accelerator SCRT is precision of relocation and patient convenience of a single treatment albeit with the added risk of single fraction radiation toxicity. This compares to the small inaccuracy of relocation of an
immobilisation device and inconvenience of multiple treatments though with lesser risk of morbidity. Whether such technical differences are likely to translate to different clinical outcomes is not clear.

The initial rationale for single fraction radiosurgery (SRS) was based on the perception of single high radiation dose as a surgical tool causing tissue destruction. While a large single dose of radiation results in a higher cell kill than the same dose given in a number of small fractions, it is also more toxic to normal tissues, particularly neural structures. The comparative benefit of different treatments is appropriately assessed by the differential effect on the tumour and normal tissue described as the therapeutic ratio.

**Dose fractionation**

The majority of pituitary adenomas requiring additional treatment with radiation lie in close proximity to the optic apparatus and the nerves of the cavernous sinus. The early enthusiastic use of high dose SRS for large adenomas containing the optic apparatus led to an unacceptably high incidence of optic radiation neuropathy. As the risk of radiation optic neuropathy following SRS is dose dependent, current practice aims to avoid irradiating the optic apparatus beyond single doses of 8 - 10Gy. Consequently radiosurgery is limited to small adenomas away from the optic apparatus (usually ≥ 5mm) and to radiation doses which do not cause tissue ablation.
Fractionated stereotactic radiotherapy (SCRT), as conventional RT, is given to doses of 45 - 50Gy at less than 2Gy per fraction which is below the tolerance dose of the central nervous system with minimal risk of structural radiation damage (<1%). The perceived benefit of single fraction radiosurgery over SCRT for pituitary adenoma has been based on radiobiological formalism defining equivalent doses and fractionation schemes through mathematically derived models 11, 12. Such models are not validated for single fraction treatments for benign tumours and theoretical claims for a benefit of single fraction radiosurgery over fractionated irradiation 13 are based on constants not derived from experimental data and therefore potentially misleading. Currently in terms of the there is no clear basis for improved therapeutic ratio of SRS over SCRT.

Clinical evidence

The efficacy of radiation treatment of pituitary adenoma should be assessed in terms of survival, actuarial tumour control (progression free survival) and quality of life (QOL). Information on the effect of different treatments on survival and QOL is limited and the principal efficacy endpoint reported in patients with non-functioning pituitary adenoma is progression free survival and late morbidity. In patients with secreting tumours the principal endpoints used are the normalization of elevated hormone concentrations, long-term tumour control and morbidity. As the delay in achieving normal hormonal status is largely related to pre-treatment hormone levels, assessment of the rate of decline is best made in relation to the initial level, with one appropriate measure the time to reach 50% of initial hormone level. “Control rate”
without indication of time and duration of follow-up and the proportion of patients achieving normal hormone levels without a clear relationship to pre-treatment values, may at first glance seem appealing, but they do not provide the appropriate measures of efficacy and are potentially misleading.

The reporting of outcome of different treatment techniques is affected by selection bias. Fractionated stereotactic radiotherapy (SCRT) to doses of 45-50Gy in 25-30 fractions, which are below the conventional radiation tolerance of surrounding normal structures including the optic chiasm, allow for the treatment of pituitary adenomas of all sizes including large tumours with suprasellar extension frequently encasing or in close proximity to the optic apparatus. The damaging effect of large single doses of radiation to critical normal structures dictates that patients treated with SRS have small tumours well away from the optic chiasm. The outcome data following GK SRS therefore represent results in patients with small adenomas generally after radical surgery.

**Efficacy and toxicity of conventional radiotherapy**

**Tumour control**

The 10 year PFS reported in seven large series of conventional external beam radiotherapy for pituitary adenoma is 80 - 94 % 14-23. In the largest series of over 411 patients, the 10 year progression free survival was 94% at 10 years and 89% at 20 years 14.
Hormone control

Acromegaly

The rate of reduction of GH after conventional therapy is reported as a 50% drop in 27 (+/- 5) months \(^{24}\). The rate of reduction of IGF-I is slower with normalisation in 60% of patients 5-10 years after treatment \(^{24}\).

Cushing’s Disease

50-100% patients treated with conventional radiation achieve normalisation of plasma and urinary cortisol with the majority normalising in the first two years after treatment \(^{25}\).

Prolactinoma

As radiotherapy is rarely used as the sole treatment for prolactinoma, information about the rate of decline of prolactin is limited. It is employed in occasional patients who fail surgery and medical therapy.

Toxicity

The toxicity of fractionated external beam radiotherapy is low with 1.5% risk of radiation-induced optic neuropathy \(^{14, 26}\) and 0.2% risk of necrosis of normal brain structures \(^{27}\). Although radiation is implicated in late cognitive impairment there is no clear evidence that small volume fractionated irradiation affects cognitive function in adults beyond the deleterious effect of surgery and the tumour itself \(^{28-30}\). The most frequent late morbidity of radiation is hypopituitarism likely to be primarily due to hypothalamic injury, although direct effect on the pituitary gland cannot be
excluded. In patients with normal pituitary function around the time of radiotherapy, hormone replacement therapy is required in 20-40% at 10 years.

Cranial irradiation is associated with an increased risk of developing a radiation induced brain tumour and this has been described in children receiving prophylactic cranial irradiation for ALL\textsuperscript{31, 32} and children treated with scalp irradiation for tinea capitis\textsuperscript{33}. The reported incidence of gliomas and meningiomas after radiotherapy for pituitary adenoma is in the region of 2% at 10-20 years\textsuperscript{34-37}. Although there is an increased incidence of cerebrovascular accidents and excess cerebrovascular mortality in patients with pituitary adenoma treated with radiation, the influence of radiation on its frequency is not defined\textsuperscript{38-41}.

**Efficacy and toxicity of GK SRS**

The systematic review of outcome of radiosurgery has been published previously\textsuperscript{42} and is summarised below with the addition of new studies. Between 1985 and 2006, 42 studies involving 1877 patients treated with GK radiosurgery were reported. The primary clinical outcome assessed was progression free survival (PFS), hormonal normalisation for secretory tumours and the frequency of adverse events.

**Hormone control**

Acromegaly

Although SRS data for 713 patients had been reported in 25 studies actuarial outcome data is limited (update of\textsuperscript{42}). Overall normalisation of serum growth
hormone concentrations were reported for 164 (23%) and decrease in 210 patients. No information on hormonal response was reported in over half of the patients and the reliability of the data is not clear. Studies where the rate of GH decline is related to pre-treatment serum growth hormone report a time to reaching 50% of initial level in the region of 2 years \(^ {43, \ 44}\) which is similar to the rate of decline following fractionated irradiation.

Cushing’s disease

The updated results of SRS for 269 patients in 21 studies reported normalisation of hormone level in 165 patients (61%), a decrease in 40 (15%) with no information on response in 50 patients. At a corrected median follow-up of 55 months, 61% of patients had normalisation of elevated hormone level \(^ {42}\). There is no data to demonstrate faster decline in elevated cortisol levels than achieved following conventional RT. Latest results in 90 patients with Cushing’s disease reported 54% (49/90) remission rate; of these 20% (10/49) subsequently relapsed suggesting poor efficacy of GK SRS\(^ {45}\).

Prolactinoma

SRS has been reported for 375 patients with prolactinoma in 19 studies. Although the serum prolactin concentrations normalised in 96 (26%) and decreased in 206 (55%) the results are difficult to disentangle from the effect of other interventions. The reported time to hormonal response (normalization or decrease) was 5 to 41 months after SRS. If we assume that follow-up time reported represents the median follow-up, 26% of patients had normalisation of prolactin level at a corrected median
follow-up of 25 months. The rate of decline of prolactin and comparison to conventional RT are not assessable from the available studies.

Tumour control in non-functioning pituitary adenoma

The results of SRS have been reported for 617 patients in 19 studies (update from 42). Five reported a “control rate” of more than 90% (weighted mean 96%) without specifying the length of follow-up or time of assessment 46-50. More recent studies report a 5 year PFS of 88 - 96% 51-53 and 3 years PFS of 94% - 95% 54, 55. The corrected (weighted) 5 year PFS is 92% 42, which is well below the results reported for conventional RT.

Toxicity of SRS

Hypopituitarism remains a frequent complication of SRS and has been reported in 4 - 66% of patients at an overall corrected median follow-up of 64 months 54, 56-62. While many studies do not record complications, 10% of 90 patients (9 cases) with Cushing’s disease developed cranial nerve deficit; 5 had ophthalmoplegia due to 3rd or 6th nerve palsies and 4 decrease in visual acuity presumed to represent optic radiation neuropathy 45. Similarly 10% patients with prolactinoma developed cranial nerve deficit after SRS 63.

Summary of GK radiosurgery

There is currently no evidence for faster decline of elevated hormone concentrations following GK SRS than has been reported after conventional therapy. Studies that take into account individual hormone concentrations show similar rate of decline as seen following fractionated irradiation 42, 44, 64. The majority of reports do not
provide appropriate information to assess the efficacy of GK radiosurgery in terms of tumour control in either secretory or non-functioning pituitary adenomas. On the limited evidence available the actuarial tumour control of small adenomas suitable for GK SRS appears inferior to the control rate achieved with fractionated irradiation given to adenomas of all sizes. The available information on comparative morbidity of SRS suggests a disturbingly high complication rate not seen with fractionated irradiation.

Efficacy and toxicity of linear accelerator SRS

Systematic review of linear accelerator stereotactic cranial irradiation has been reported previously. In the largest of 5 published studies of SRS, where 175 patients with pituitary adenomas were treated with a single fraction of 20 Gy, and followed for a minimum of 12 months (mean ± SD, 82 ± 37 months), the local “tumour control” rate was reported as 96% (at an unspecified time). The mean time from treatment to hormone normalization was 36 ± 24 months, with the overall probability of normalization of 34% at 3 years and 51% at 5 years. The results were not related to pre-treatment hormone levels. The reported side-effects at a relatively short follow-up included anterior pituitary dysfunction (12%), radiation-induced tissue damage (3%) and radiation-induced neuropathy (1%). Further four studies contain less than 30 patients with little information to assess the efficacy of treatment. The overall results of linear accelerator SRS are broadly comparable to GK SRS, although the follow-up is short and the endpoints in individual studies not
appropriate to provide meaningful comparative information on long-term tumour control and treatment-related toxicity.

**Efficacy and toxicity of linear accelerator SCRT**

Five studies of SCRT have been published and reviewed by us previously. Since that time an update of growth hormone (GH) secreting adenoma subgroup from a previous study was reported and we published the results from the Royal Marsden Hospital. Local control in secretory and non-secretory macroadenomas ranged from 85 - 100%. Twenty percent of patients needed new hormone replacement. Although studies report the proportion of patients who normalized their GH levels this is not related to pre-treatment values and the rate of decline of elevated hormone levels cannot be assessed.

The PFS in 92 patients treated at the Royal Marsden Hospital at a median follow-up of 32 months was 98% and 98% at 3 and 5 years and respective survival 98%. In patients with acromegaly 50% of baseline GH level was achieved in less than 2 years. The most frequently seen late toxicity was hypopituitarism, with 22% of patients experiencing deterioration in pituitary function.

In summary the early results of linear accelerator SCRT are within the range reported for conventional radiotherapy, and it is not possible to claim that either disease control or survival are significantly improved. The technical advantage of high precision stereotactic radiotherapy aims at reducing the amount of normal brain
receiving high radiation doses. It is hoped this will translate into further reduction in long-term toxicity. However, improvement in late morbidity has not yet been demonstrated and will require many years of follow-up and large cohorts of patients to obtain statistically meaningful results.

**Treatment of recurrent pituitary adenoma**

A small proportion of patients with pituitary adenoma progress after radiotherapy. Re-irradiation has been considered too risky because of the presumed cumulative damaging effect of radiation on normal brain, particularly the optic chiasm and cranial nerves. Primate spinal cord studies suggest that provided initial radiation is given to doses below conventional radiation tolerance, considerable recovery of latent radiation damage is seen two or more years after treatment 72. Re-irradiation using conventional techniques to repeat of initial radiation doses resulted in only a small risk of radiation optic neuropathy 73, 74. Stereotactic techniques can further reduce the radiation dose to sensitive surrounding structures, providing they are not in close proximity to the tumour. 11 patients with recurrent tumours treated with SCRT at the Royal Marsden Hospital have so far remained without late radiation optic neuropathy (unpublished). SRS for recurrent pituitary adenoma has to be restricted to tumours away from the optic chiasm and nerves. In patients with persistent hormone elevation SRS resulted in a decline of elevated hormone levels similar to that seen following SRS as primary therapy so far with no reported radiation optic neuropathy 75.
The available data does not provide sufficient information on long term tumour or hormonal control following reirradiation with SRS or SCRT. Reported evidence from conventional fractionated treatment suggests that fractionated treatment has acceptable efficacy and toxicity\textsuperscript{73, 74}.

**Conclusion**

Radiotherapy remains an effective treatment in patients with progressive pituitary adenomas not cured by surgery or medical therapy achieving excellent long term tumour and endocrine control. Hypopituitarism represents the most commonly reported late complication of radiotherapy with low incidence of other late effects.

There is much debate about the relative efficacy of SRS and SCRT. The efficacy of SCRT in terms of local tumour control is comparable to the results of conventional external beam radiotherapy. Currently reported results suggest that SRS achieves worse tumour control that fractionated treatment. The rate of decline of elevated hormone levels is no faster following single treatment compared to fractionated irradiation. The reported neurological toxicity of SRS is considerably higher than seen with fractionated irradiation at a relatively short follow up.

Treating less normal brain to high radiation doses with stereotactic irradiation is a clear technical improvement of modern radiotherapy which may in the future translate into clinical benefit as a reduction in the incidence of late effects of radiation. However, the relatively short follow-up requires caution in interpretation.
until more mature and reliable results are available both in terms of efficacy and late radiation induced toxicity.

A single fraction treatment may represent a convenient approach for patients with pituitary adenomas, but the technique is only suitable for small residual tumours well away from the optic chiasm. On the basis of the available evidence there is little justification for its use as it is associated with worse morbidity, inferior tumour control and in secreting tumours no faster hormone decline than seen with fractionated treatment. SRS cannot therefore be recommended as the appropriate treatment of non-functioning adenomas of any size and its use in patients with hormone secreting tumours remains questionable. Prospective studies comparing SRS with fractionated stereotactic radiotherapy may be of value to help define the comparative long-term efficacy and toxicity of the techniques. However the strongly held views about the relative merits of each technique largely based on the local availability of the equipment makes it unlikely that such studies will be carried out in the foreseeable future.

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