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Radiosurgery for pituitary adenomas

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Introduction

Radiotherapy has been successfully employed in the management of patients with pituitary adenoma. It achieves excellent long-term tumour control and frequently leads to normalization of elevated serum hormone concentrations albeit with delay. There are well documented late effects of irradiation of which hypothalamic-pituitary insufficiency is the most frequent. Serious late complications are uncommon with overall risk generally < 2%. Nevertheless, the perception, largely based on selected studies of early use of radiation, is that radiotherapy is damaging and the effectiveness is questioned. Into this scenario comes radiosurgery offering an apparent quantum leap in radiation technology that combines neurosurgical terminology of surgery and stereotaxy with more advanced means of radiation delivery. The impression is of surgical precision added to the science of radiation. Have the new techniques altered the management of patients with pituitary adenoma or is the new technology the emperor’s new clothes?

In an attempt to provide an objective answer we present a systematic review of the literature published between 1985 and 2003 on the efficacy of radiosurgery in patients with pituitary adenomas and at least 6 months follow-up excluding single case reports and non-peer reviewed chapters. As critical interpretation of this data requires both an understanding of current radiotherapy technology and the improvements and the results of conventional treatment, they are discussed first.

Advances in radiotherapy technology

The aim of modern techniques is to achieve localised radiation delivery. Three principal advances have enabled this – improvement in patient immobilisation, modern imaging combined with precise image co-registration and more localised means of giving radiation aided by 3 dimensional (3D) planning. Despite the perception that it is the technique of delivery which is the major determinant of modern localised radiotherapy, it is the combination of better
immobilisation and high-definition co-registered 3D imaging which is responsible for most of the gain in sparing normal tissue.

**Improvements in the technique of radiation delivery**

**Immobilisation**

In conventional radiotherapy, patients are usually immobilised in an individually shaped plastic mask. The head has some freedom to move (3-5mm) (Gildersleve, et al., 1995) and to avoid missing the tumour as a result of the movement during a course of fractionated radiotherapy a safety margin is included in planning. Better immobilization is achieved through more precise and firmer fixation with relocatable frames (Gill, et al., 1991; Graham, et al., 1991) and more precise fitting mask systems (Karger, et al., 2001). The usual gain is an improvement in relocation accuracy to 1-2 mm for relocatable frames and 2-3mm for mask systems allowing for a smaller margin. Invasive neurosurgical type frames are used for single fraction radiosurgery with ≤1mm accuracy.

**Tumour localisation**

Stereotactic techniques initially adopted from neurosurgery have enabled more precise localisation of tumours and critical neural structures. Pituitary adenoma position is described using 3D co-ordinates defined from external markers (fiducial markers). Fixed internal anatomical structures may be used to define the 3D space and fiducial markers may in the future become redundant. Tumour localization has also improved using data from CT and MRI which are co-registered. The extent of the adenoma and the position of critical structures such as the optic chiasm and nerves are best localised on MRI while co-registered CT scans provide the appropriate X-ray absorption information for radiotherapy planning.
Radiotherapy planning has also independently improved with the use of 3D displays and 3D methods of calculation of dose distribution. It is therefore relatively easy to depart from the arrangement of three fixed fields in a single plane used in conventional radiotherapy.

It is axiomatic that high precision treatment delivery with little margin for error demands that all parts of the tumour are identified and treated. Expert neuroradiology interpretation has therefore become an essential component of modern radiotherapy practice. Nevertheless, rapid advances in imaging often outstrip image interpretation which, at times, inevitably becomes subjective and compares unfavourably with accuracy demanded of the precision radiotherapy technique. Pragmatically, a reasonable and safe approach is to accept regions of “uncertainty” as representing potential tumour involvement, providing inclusion does not result in unacceptable treatment toxicity.

**Treatment delivery**

The aim of all high precision techniques is to minimise the radiation to normal tissue for equivalent dose of radiation to the target. There are two ways of achieving it. Shaping the radiation beams to conform to the shape of the tumour reduces radiation exposure to surrounding normal brain and this is the principle of conformal radiotherapy. Increasing the number of beams is believed to lead to a greater dose differential between the target and surrounding normal tissue with further normal tissue sparing.

**Linear accelerator**

Linear accelerator beams can be shaped with lead alloy blocks mounted onto an external tray or by altering the shape of the aperture at linear accelerator head with a multi-leaf collimator (MLC). This results in the reduction in volume of normal brain receiving high doses of radiation when compared to square or rectangular beams (Kaushal, et al., 1990). The available MLCs
consist of individual leaves of 3mm (micro-MLC), 5mm (mini-MLC) and 10 mm (conventional) width. The leaves are automatically positioned to predefined shapes based on information transferred directly from the planning computer. There is little data to demonstrate a difference in normal tissue sparing between 3mm or 5mm leaves.

High precision conformal radiation using stereotactic techniques which includes better immobilisation, imaging and conformation, is described as stereotactic conformal radiotherapy (SCRT) and is usually delivered as fractionated treatment. Using more than 3 beams separated in space reduces the amount of normal brain receiving high radiation doses but this is at the cost of increasing the volume of brain receiving low doses. The benefit for increasing the number of beams is, however, only seen for arrangement of 4 to 6 beams. Although there is a perception that higher number of beams improves dose differential, studies of 3D dose distribution demonstrate not only lack of further normal tissue sparing, but, frequently detriment at high dose levels for more than 6 beams (Perks, et al., 1999), (Ajithkumar, et al., Submitted). Techniques of dynamic shaping with MLC leaves adjusting to the tumour shape during rotation of the linear accelerator around the tumour are, on present evidence, also no better than a 4 - 6 fixed field technique (Solberg, et al., 2001) (Ajithkumar et al, Submitted)

In modern radiotherapy practice, MLC leaves can be used to modulate the intensity as well as altering the shape of the radiation beam and this is described as intensity modulated radiotherapy (IMRT). Studies of dose distribution in tumour and normal tissue show no benefit for IMRT compared to fixed field SCRT in the treatment of pituitary adenoma (Khoo, et al., 1999) (Low, et al., In preparation).

Multiheaded cobalt unit

The technique of focussed radiation with multiple cobalt sources was developed by Leksel prior to the routine use of linear accelerators which
superceded cobalt as the high energy radiation source. In multi-headed cobalt unit (Gamma Knife - GK) 201 cobalt sources are arranged in a hemisphere and focused with a collimator helmet onto a central target. This results in small spherical high dose volumes ranging from 6-18mm diameter. Multiple radiation spheres are combined in a multiple isocentre technique to conform to the shape of larger and non-spherical tumours which would include the majority of pituitary adenomas considered suitable for radiation treatment. Computerised 3D planning determines the optimum number and distribution of isocentres and this can be aided by selective occlusion (plugging) of collimator apertures. GK irradiation performed as a single treatment given with a patient immobilised in a fixed frame is described as stereotactic radiosurgery (SRS).

Comparison of conformal radiosurgery techniques

The only published comparison of GK multiple isocentre techniques 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 (Yu, et al., 1999). The wide spatial separation of GK sources leads to an increase in the volume of normal brain receiving low doses although the clinical significance is at present not clear. With GK, overlapping radiation spheres of multiple isocentres produce small high dose regions (hot spots). This may not be of clinical relevance in terms of toxicity if there are no normal structures within the target. Multiple isocentre treatment of tumours involving the cavernous sinus or the optic apparatus (or in close proximity to them) may produce hot spots in cranial nerves with a risk of late radiation damage.

In the early days of radiosurgery, linear accelerators were adapted to mimic GK dose distribution through multiple arcs of rotation equivalent to hemispheric distribution of radiation sources (sometimes described as SMART). This produces spherical high dose volumes which are not size limited. For the treatment of non-spherical lesions conformation can be achieved with multiple isocentre technique similar to the GK technique. Such treatment on a linear accelerator is highly time and manpower intensive. The
4-6 conformal fixed field technique produces superior dose distribution within and outside the target (Laing, et al., 1993) and has largely superseded 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%) and linear accelerator SCRT the volumes of medium-low doses (20-30%). The only claimed benefit of GK SRS over linear accelerator SCRT is precision of single treatment compared to the small inaccuracy of relocation of immobilisation device with multiple treatments.

**Fractionation**

The principal difference between radiosurgery (SRS) and fractionated stereotactic radiotherapy (SCRT) is in the number of radiation treatments. The term radiosurgery is reserved for radiation given in one large dose (single fraction) and the term radiotherapy is used for treatment given in multiple, usually daily, doses (fractionated treatment). The term fractionated radiosurgery is an attempt to cash in on the apparent marketing superiority of “radiosurgery” over “radiotherapy” and is inappropriate.

The initial rationale for single fraction radiosurgery was based on the perception of single high radiation dose as a surgical tool causing tissue destruction. There is little doubt that 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, however, the differential effect between tumour and normal tissue damage embodied in the concept of therapeutic ratio, which should provide the measure for comparing the efficacy of treatments. In this respect, large single doses of radiation are more toxic to normal tissue, particularly the brain than similar doses given in a fractionated manner.

Given that the majority of pituitary adenomas lie in close proximity to the optic apparatus and the nerves of the cavernous sinus it is perhaps not surprising
that early enthusiastic use of high dose SRS for large pituitary adenomas containing the optic apparatus led to an unacceptably high incidence of optic radiation neuropathy (Rocher, et al., 1995). As the risk of radiation optic neuropathy following SRS is dose dependent (Leber et al., 1998; Tishler, et al., 1993), current practice aims to avoid irradiating the optic apparatus beyond single doses of 8-10Gy. This means limiting radiosurgery to small adenomas away from the optic apparatus (usually ≥ 5mm) and using lower doses which do not cause tissue ablation.

The belief in the benefit of single fraction radiosurgery for pituitary adenoma and for that matter, other benign tumours, has also been based on radiobiological formalism which defines equivalent doses and fractionation schemes through biologically derived models (Gutin et al., 1991; Steel, 1993). While such models may be appropriate for malignant tumours when the number of radiation fractions changes, they are not validated for single fraction treatment and biological constants which are necessary to calculate such equivalent doses do not exist for benign tumours. Publications claiming theoretical benefit of single fraction radiosurgery over fractionated irradiation (Larson et al., 1993) are based on constants not derived from experimental data and may therefore be misleading.

**Clinical evidence**

There are several important caveats in the critical interpretation of data in clinical studies of the efficacy of radiation treatment of pituitary adenoma. The first relates to the endpoints. While effectiveness may be best assessed in terms of survival, tumour control (as actuarial progression free survival) and quality of life (QOL) information on the effect of different treatment modalities on survival and QOL is limited and the main reported efficacy endpoints in patients with non-functioning pituitary adenoma are progression free survival and late morbidity. In patients with secreting tumours the principal endpoints used are the normalization of elevated hormone concentrations and long-term tumour control. The delay in achieving normal hormonal status is largely
related to pre-treatment hormone levels; the higher the pretreatment concentration the longer it will take to normalise. To assess the rate of decline it is therefore necessary to either incorporate individual patient data or make it independent of the initial level. One appropriate measure is the time necessary to reach 50% of initial hormone level.

Results of SRS are frequently reported as "control rate" without the dimension of time, failing to take into account the duration of follow-up of individual patients. Such data, although at first glance appealing, do not provide the appropriate measure of efficacy and are potentially misleading.

The second caveat is that basic radiobiological considerations (discussed above) introduce case selection bias. Conventional external beam radiotherapy to doses of 45-50Gy in 25-30 fractions is below the conventional radiation tolerance of surrounding normal structures including the optic chiasm. Consequently, there is no restriction to the size of pituitary adenoma suitable for standard dose fractionated radiotherapy and all reported series include not only intrasellar tumours but also (and often predominantly) large adenomas 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 third is an observation that the majority of publications are retrospective single arm studies and as radiation equipment is expensive, individual institutions may have a necessary vested interest in amortising the costs involved leading to reporting and publication bias.

**Efficacy and toxicity of conventional radiotherapy**

The 10 year progression free survival reported in seven large series of conventional external beam radiotherapy for pituitary adenoma is 80-94% (Brada, et al., 1993) (Sheline, 1974) (Erlichman et al., 1979) (Halberg &
1998) (Grigsby, et al., 1988) (Gittoes, et al., 1998). In the largest series of
over 411 patients, the 10 year progression free survival was 94% at 10 years
and 89% at 20 years (Brada et al., 1993).

In acromegaly, the rate of reduction of GH after conventional therapy is a 50%
drop in 27 (+/- 5) months (Biermasz et al., 2000). It has also been expressed
as halving of mean growth hormone level in a population of acromegalic
patients in about 2 years (Ciccarelli, et al., 1989). The rate of reduction of IGF-
I is slower with normalisation in 60% of patients 5-10 years after treatment
(Biermasz et al., 2000; Biermasz et al., 2000). In Cushings disease, the
normalisation of plasma and urinary cortisol has been reported in 50-100% of
patients. A detailed prospective study of 30 adults demonstrated remission in
all patients 60 months after radiotherapy with the majority normalising in the
first two years after treatment (Estrada, et al., 1997). There is limited
information about the rate of decline of prolactin as radiotherapy is rarely used
as the sole treatment for prolactinoma.

The toxicity of fractionated external beam radiotherapy is low with 1.5% risk of
radiation optic neuropathy (Brada et al., 1993) (Tsang, et al., 1994) and 0.2%
risk of necrosis of normal brain structures (Becker, et al., 2002). Although
radiation is blamed for potential cognitive impairment, there is no clear
evidence that small volume fractionated irradiation affects cognitive function
beyond the deleterious effect of surgery and the pituitary adenoma (Grattan-
Smith, et al., 1992) (Peace, et al., 1997). The most frequent late morbidity of
radiation is hypopituitarism likely to be primarily due to hypothalamic injury. In
patients with normal pituitary function around the time of radiotherapy
hormone replacement therapy is required is 20-40% at 10 years. The most
feared late effect of radiation for pituitary adenoma is the development of
second radiation induced brain tumour. The reported frequency is in the
region of 2% at 10-20 years (Brada, et al., 1992; Tsang, et al., 1993) (Erfurth,
et al., 2001). 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

**Efficacy and toxicity of GK SRS**

Between 1985 and 2003, 29 studies involving 1153 patients treated with GK radiosurgery were reported either as abstract, conference article or peer reviewed article (Tables 1-5). According to the manufacturers of Gamma Knife, 18166 patients received radiosurgery for pituitary adenoma from 126 centres around the world to December 2002.

Primary clinical outcome assessed was progression free survival (PFS). When PFS data was not available, the reported surrogate endpoints of efficacy in individual studies were extracted. Secondary outcomes included hormonal normalisation for secretory tumours and adverse events. As summary measure mean progression free survival at a specific time point weighted for initial sample size was calculated. For hormonal response and adverse events, descriptive methods and pooled reported figures were used.

a) **Hormone secreting adenomas**

**Acromegaly** (Table 1)

SRS data for 361 patients have been reported in 19 studies. The median follow-up ranged from 6 months to 5.4 years. Normalisation of serum growth hormone concentrations were reported for 136 patients (38%) (including 6 who had normal serum growth hormone concentrations prior to SRS). In 85 patients growth hormone concentrations decreased, in 3 they remained unchanged and in 6 they increased. Response was not reported in the remaining 131 patients. Time to response ranged from 3 to 24 months. At a corrected median follow up of 29 months, 38% of patients had normalisation of serum growth hormone concentrations.

In an early report of 16 patients with acromegaly treated with GK SRS, the median time to reaching normal serum growth hormone (GH) level was
shorter than in a comparative historical control series of 58 patients treated with conventional fractionated therapy (Landolt, et al., 1998). As SRS patients had lower pre-treatment GH concentrations (indeed, some were normal) than conventionally treated patients, it is, therefore, not possible to conclude that the rate of decline for the two techniques of irradiation is different. A more recent study reported changes in serum growth hormone concentrations in 30 patients after SRS. These reached 50% of baseline 1.5 – 2 years after treatment with a slower reduction in IGF-I levels (Attanasio, et al., 2003).

**Cushing’s disease** (Table 2)

SRS data has been reported for 208 patients in 19 studies. The median follow up ranged from 6 months to 17 years. 121 patients (58%) had normalisation of hormone level, 39 (19%) had decrease, 9 had unchanged levels, 5 had increase in hormone and response was not reported in the remaining 34. Time to hormonal response ranged from 6 months to 3 years. At a corrected median follow-up of 55 months, 58% of patients had normalisation of elevated hormone level.

**Prolactinoma** (Table 3)

Data following SRS has been reported for 330 patients with prolactinomas in 16 studies. The median follow up ranged from 6 to 45 months. The serum prolactin concentrations normalised in 87 patients (26%), decreased in 204 (62%) and were unchanged in 4. Serum prolactin concentrations increased in 9 patients and no data is available for the rest. The rate of hormone decline varied. Seven studies involving 109 patients reported time to hormonal response (normalization or decrease) ranging from 5 months to 41 months. The “corrected” mean time to hormone normalisation is 29 months. 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 29 months.
b) Non-functioning adenoma (Table 4)

The results of SRS have been reported for 273 patients with non-functioning pituitary adenoma in 11 studies. Five studies reported a “control rate” of more than 90% (mean weighted 96%) without specifying time or length of follow-up (Izawa, et al., 2000; Mokry, et al., 1999; Pan, et al., 1998; Sheehan, et al., 2002; Wowra et al., 2002). One recent study (Petrovich, et al., 2003) reported a 3 year progression free survival of 94% in a cohort of patients with both secretory and non-secretory tumours.

Complications

Hypopituitarism was reported in 4-66% of patients at an overall corrected median follow-up of 64 months (6 studies) (Degerblad, et al., 1986; Hoybye, et al., 2001; Morange-Ramos, et al., 1998b; Petrovich et al., 2003; Pollock, et al., 2002; Sheehan, et al., 2000). In many studies, visual complications were not evaluated or indeed mentioned.

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 decline (Attanasio et al., 2003; Choi, et al., 2003). 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. Of the 29 published studies, only one reported actuarial progression free survival (Petrovich et al., 2003). Because of short follow-up and patient selection there is insufficient information regarding late morbidity although individual cases have been reported.
**Linear accelerator SRS**

Systematic review of literature, ignoring early experience which was abandoned (Rocher et al., 1995), yielded only three studies of linear accelerator SRS (Mitsumori, et al., 1998; Voges, et al., 1996; Yoon, et al., 1998). Voges et al reported 26 patients treated with a single fraction SRS to a dose of 10-27 Gy (mean 21.1 Gy) and followed for ≥6 months. Patients with Cushing’s disease, Nelson syndrome and prolactinoma had no significant endocrinological response but serum growth hormone concentrations decreased within 6 - 36 months in 12 patients with acromegaly (Voges et al., 1996; Yoon et al., 1998). In a study of 24 patients with pituitary adenoma <3 cm diameter, 9 of 11 patients with prolactinoma and 2 (of 2) patients with combined growth hormone and prolactin secreting tumours reached normal hormone level within one year, although some patients already had normal levels prior to SRS (Yoon et al., 1998). Actuarial tumour control was not reported. Seven of 24 patients developed hormone deficiency and none had visual problems after linear accelerator SRS. In the report of Mitsumori et al (Mitsumori et al., 1998), the 3-year tumour control rate of 18 patients treated in this way was 77% including patients who had recurred after previous radiotherapy. A third of patients with secreting tumours had hormonal normalisation at a mean of 8.5 months. Three patients developed radiation necrosis of the temporal lobe and 23% patients needed new hormonal replacement (Mitsumori et al., 1998). In summary the reported literature of linear accelerator SRS is limited. Nevertheless the results published so far are broadly equivalent to those reported for GK SRS with little information on long term tumour control and no clear evidence of faster decline in hormone levels.

**Linear accelerator SCRT**

There are four published reports of SCRT in patients with pituitary adenoma (Coke, et al., 1997; Jalali, et al., 2000; Milker-Zabel, et al., 2001; Mitsumori et al., 1998). Local control in secretory and non-secretory macroadenomas was 100% in 19 patients (Mitsumori et al., 1998) at a mean follow-up of 10 months
and 85% at 3 years in 30 patients (Coke et al., 1997). Normalization of elevated hormone concentrations was reported in over 50% patients within a mean of 18 months. Twenty percent of patients needed new hormone replacement (Mitsumori et al., 1998). In a study of 63 patients 5-year local progression free survival was 93% at a mean follow-up of 38 months (Milker-Zabel et al., 2001). Twenty percent of patients with secreting adenomas had normalization and 31% a reduction in serum hormone concentrations.

The 2-year actuarial progression free and overall survival in the Royal Marsden Hospital experience of 22 patients (13 non-functioning and nine secretory) was 100%. Newly initiated hormone replacement therapy was required in five patients (Jalali et al., 2000). An update of 99 patients with 2 year median follow-up (26 followed for > 3 years) shows a 97% 3 and 5 year actuarial progression free survival (unpublished).

The early results of linear accelerator SCRT are within the range reported for conventional radiotherapy. The short follow-up doesn’t allow for any conclusion about long term efficacy or late side effects. While the technical advantages of stereotactic radiotherapy may translate into a meaningful clinical benefit in terms of minimizing long term toxicity this has not yet been demonstrated and will require many years of follow-up and larger cohorts to obtain statistically meaningful results.

**Treatment of recurrent pituitary adenoma**

A small proportion of patients with pituitary adenoma progress after radiotherapy. Treatment with further radiation has been considered risky because of presumed cumulative damaging effect of radiation of normal brain, particularly optic chiasm and nerves. Stereotactic techniques offer the option of avoiding irradiation of sensitive structures providing they are not in close proximity to the tumour and both SRS and SCRT have been used in this situation.
Before resorting to high precision technique, it is worth noting that there is considerable recovery of latent radiation damage after 2 years when first treatment was to doses below conventional radiation tolerance. This means that late recurrences (after 5 years or more) following conventional doses of 45Gy in 25 fractions can be relatively safely reirradiated to more or less the same dose with small risk of radiation optic neuropathy using conventional techniques (Flickinger et al., 1989) (Schoenthaler, et al., 1992).

Nevertheless, SCRT can further reduce the dose to the optic apparatus and we have used it in 10 patients with recurrent tumours after previous irradiation so far without late effects (unpublished). Long term outcome data is not available. SRS, as in primary therapy, has to be restricted to tumours away from the optic chiasm and nerves. SRS has been employed as an additional treatment in patients with persistently elevated hormone concentrations. The rate of decline of elevated hormone levels is similar to that seen following SRS as primary therapy so far with no reported radiation optic neuropathy (Swords, et al., 2003).

The available data does not provide sufficient information on the efficacy of reirradiation with SRS or SCRT on long term tumour or hormonal control. Reported evidence from conventional fractionated treatment suggests that fractionated treatment has acceptable efficacy and toxicity (Flickinger et al., 1989; Schoenthaler et al., 1992).

**Conclusion**

Technical advances have improved the delivery of radiation to intracranial tumours with significant reduction in radiation dose to the normal brain. Treating less brain to higher radiation doses during radiotherapy of pituitary adenoma is undoubtedly a reasonable goal in itself and may in the future translate into a clinical benefit. However, enthusiastic acceptance should be tempered by caution. The reliance on precision technology without taking into account the subjective nature of interpretation of modern imaging, carries the
risk of missing parts of the tumour previously included in larger radiation fields used in conventional therapy.

The debate about the relative merits of equipment (gamma knife or linear accelerator) and fractionation of treatment (Brada et al., 1999) continues largely fuelled by enthusiasm and vested interests. On the evidence available, there is little to justify the claim for the superiority of GK radiosurgery over fractionated conventional or stereotactic radiotherapy. The paucity of data on progression free survival argues for caution in the use of single fraction radiosurgery to achieve long term tumour control. The claim for faster decline of elevated hormone concentrations in patients with secreting tumours remains unsubstantiated. The only argument in favour of SRS for secreting tumours (that are almost by definition small and well away from the optic chiasm) is convenience of single fraction treatment. There is clearly a need for prospective studies to define the long term efficacy and toxicity of SRS particularly in comparison to fractionated conventional and stereotactic radiotherapy.

Fractionated SCRT offers a more localised irradiation compared to conventional fractionated radiotherapy. The use of standard dose/fractionation provides some reassurance about its long term efficacy and toxicity, although data on long term tumour control, survival and late morbidity are also lacking. As with SRS, SCRT should also be used with caution and evaluated in long term studies.

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<table>
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<th>response to treatment</th>
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<td>5/0</td>
</tr>
<tr>
<td>Zhang '00 (Zhang, et al., 2000)*</td>
<td>68</td>
<td>6 to 52</td>
<td></td>
<td></td>
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<td>25/26-3yr</td>
<td>24/26 - 3 yr</td>
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<tr>
<td>Izawa '00 (Izawa, Hayashi, Nakaya, Satoh, Ochial, Hori, &amp; Takakura, 2000)**</td>
<td>29</td>
<td>&gt;6</td>
<td>93</td>
<td></td>
<td>0</td>
<td>12</td>
<td>15/2</td>
</tr>
<tr>
<td>Pollock '02 (Pollock, Nippoldt, Stafford, Foote, &amp; Abboud, 2002; Petrovich, Yu, Giannotta, Zee, Apuzzo, 2003)**</td>
<td>26</td>
<td>36</td>
<td>42%</td>
<td>0</td>
<td>16% (seri)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>(Attanasio, Epaminonda, Motti, Giugni, Ventrella, Cozzi, 2003)**</td>
<td>6</td>
<td>36</td>
<td>100%</td>
<td>nil</td>
<td>4%#</td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 1: Radiosurgery for acromegaly (review of literature 1986-2003)
<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>43</th>
<th>97#</th>
<th>nil</th>
<th>nil</th>
<th>6</th>
<th>5/0</th>
<th>3/9</th>
<th>6/9</th>
<th>6.8#</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
<td>361</td>
<td>28.5$</td>
<td></td>
<td>136</td>
<td>85/3</td>
<td>6</td>
<td></td>
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<td>3-24£</td>
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</tbody>
</table>

* meeting report/abstract  **peer reviewed article  # figure from the whole series of both secretory and non-secretory tumours
1-3 patients had normal GH prior to radiosurgery  $weighted mean  £range

2 - CR – complete response; PR-partial response; NC – no change; PD- progressive disease; Resp- response; SD-stable disease; NA – not available
Table 2  Radiosurgery for Cushing's disease (review of literature 1986-2003)

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>follow-up (months)</th>
<th>control rate (%)</th>
<th>5 or 10yr PFS</th>
<th>Late effects</th>
<th>response to treatment</th>
<th>time to response</th>
</tr>
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<tr>
<td>Dagerbald ‘86 (Degerblad, Rahn, Bergstrand, &amp; Thoren, 1986)</td>
<td>29</td>
<td>3-9 yr</td>
<td>76</td>
<td>NA</td>
<td>55%</td>
<td>CR</td>
<td>22</td>
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<tr>
<td>Ganz ‘93 (Ganz, Backlund, &amp; Thorsen, 1993)</td>
<td>4</td>
<td>18</td>
<td>nil</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pollock 94** (Pollock, Kondziolka, Lunsford, &amp; Flickinger, 1994)</td>
<td>15</td>
<td>26</td>
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<td>NA</td>
<td>8/11</td>
<td>2/11</td>
<td>1/11</td>
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<td>Seo 95** (Seo, et al., 1995)</td>
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<td>24</td>
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<td>nil</td>
<td>2</td>
<td>nil</td>
<td>nil</td>
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<tr>
<td>Martinez ‘98* (Martinez, Bravo, Burzaco, &amp; Rey, 1998)</td>
<td>3</td>
<td>26-45</td>
<td>NA</td>
<td>nil</td>
<td>nil</td>
<td>2/0</td>
<td>3</td>
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<tr>
<td>Pan L ’98* (Pan, Zhang, Wang, Wang, &amp; Xu, 1998)</td>
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<td>29</td>
<td>95</td>
<td>NIL</td>
<td>NIL</td>
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<td>20</td>
<td>66</td>
<td>0</td>
<td>16%#</td>
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<td>2/0</td>
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<td>1</td>
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<td>56</td>
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<tr>
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<td>&gt;6</td>
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<th>Study</th>
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<th>Progression</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
<th>Resp</th>
<th>SD</th>
<th>NA</th>
<th>24/33</th>
<th>9/33</th>
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<td>24/33</td>
<td>9/33</td>
<td>0</td>
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<tr>
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<td>0</td>
<td>66%</td>
<td>83%</td>
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<td>36</td>
<td>1</td>
<td>16%#</td>
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<td>94# (3 yr)</td>
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<td>0</td>
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<td>Petrovich '03 (Petrovich, Yu, Giannotta, Zee, &amp; Apuzzo, 2003)</td>
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<td>36</td>
<td>94# (3 yr)</td>
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<td>4%#</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
<td>22</td>
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<td>43</td>
<td>97#</td>
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<td>nil</td>
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<td>0</td>
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<td>4/7</td>
<td>6.8#</td>
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<tr>
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<td>121</td>
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* meeting report/abstract **peer reviewed article # figure from the whole series of both secretory and non-secretory tumours $weighted mean £range
CR – complete response; PR-partial response; NC – no change; PD- progressive disease; Resp- response; SD stable disease; NA – not available
Table 3 Radiosurgery for prolactinoma (review of literature 1986-2003)

<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>follow-up (months)</th>
<th>control rate (%)</th>
<th>5 or 10yr PFS(%)</th>
<th>Late effects</th>
<th>response to treatment</th>
<th>time to response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<td>visual</td>
<td>hormonal</td>
<td></td>
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<td></td>
<td></td>
<td>hypopituitarism</td>
<td>PD</td>
<td>Resp</td>
</tr>
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<tr>
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<td>0</td>
<td>0</td>
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<tr>
<td>Pan L '98* (Pan, Zhang, Wang, Wang, &amp; Xu, 1998)</td>
<td>27</td>
<td>29</td>
<td>95</td>
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<td>0</td>
<td>8(4)¹</td>
<td>16</td>
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<td>4</td>
<td>20</td>
<td>NA</td>
<td>0</td>
<td>16%</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Lim '98* (Lim, Leem, Kim, Rhee, &amp; Kim, 1998)</td>
<td>19</td>
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<td>1#</td>
<td>1#</td>
<td>10</td>
<td>6/2</td>
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</tr>
<tr>
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<td>98</td>
<td>0</td>
<td>3</td>
<td>13</td>
<td>6</td>
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<tr>
<td>Kim '99* (Kim, Lee, &amp; Sim, 1999)</td>
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<td>83</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>15</td>
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<tr>
<td>Hayashi '99* (Hayashi, Izawa, Hiyama, Nakamura, Atsushi, Sato, Nakaya, Sasaki, Ochiai, Kubo, Hori, &amp; Takakura, 1999)</td>
<td>13</td>
<td>&gt;6</td>
<td>NA</td>
<td>15%</td>
<td>69%</td>
<td>85%</td>
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<td>&gt;24</td>
<td>NA</td>
<td>1</td>
<td>1/0</td>
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<td>Kim '99* (Kim, Huh, Chang, Park, &amp; Chung, 1999)</td>
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<td>5</td>
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<td>-</td>
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<td>8</td>
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<tr>
<td>Study</td>
<td>Patients</td>
<td>Follow-Up</td>
<td>CR (4%)</td>
<td>PR</td>
<td>NC</td>
<td>PD</td>
<td>Resp</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
<td>----</td>
<td>----</td>
<td>----</td>
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</tr>
<tr>
<td>Pollock '02* (Pollock, Nippoldt, Stafford, Foote, &amp; Abboud, 2002)</td>
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<td>26</td>
<td>29</td>
<td>0</td>
<td>16%</td>
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<tr>
<td>Petrovich '03 (Petrovich, Yu, Giannotta, Zee, &amp; Apuzzo, 2003)</td>
<td>12</td>
<td>36</td>
<td>94#</td>
<td>nil</td>
<td>4#</td>
<td>10</td>
<td>0</td>
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<td>Choi '03 (Choi, Chang, Chang, Ha, Park, &amp; Chung, 2003)</td>
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<td>97#</td>
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<td>Nil</td>
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</table>

* meeting report/abstract;  **peer reviewed article;  #  figure from the whole series of both secretory and non-secretory tumours $weighted mean £range

1- 4 patients had normal prolactin before radiosurgery, CR – complete response; PR-partial response; NC – no change; PD- progressive disease; Resp- response; SD stable disease; NA – not available
<table>
<thead>
<tr>
<th>Author</th>
<th>No of patients</th>
<th>follow-up (months)</th>
<th>control rate (%)</th>
<th>5 or 10 yr PFS</th>
<th>Late effects</th>
<th>response to treatment</th>
<th>time to response (months)</th>
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<td>hormonal PR/NC PD PD</td>
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<td>PR</td>
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<td>Resp</td>
<td>SD</td>
<td>NA</td>
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<td>98</td>
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<td>Petrovich 2003</td>
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<td>(Petrovich, Yu, Giannotta, Zee, &amp; Apuzzo, 2003)**</td>
<td>56</td>
<td>36</td>
<td>100</td>
<td>94%</td>
<td>nil</td>
<td>0</td>
<td>4%#</td>
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<tr>
<td>Total</td>
<td>273</td>
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</tbody>
</table>

* meeting report/abstract     ** peer reviewed article

CR – complete response; PR-partial response; NC – no change; PD- progressive disease; Resp- response; SD stable disease; NA – not available
References:


