NHS England

Stereotactic radiosurgery or radiotherapy for recurrent or residual pituitary adenoma

NHS England

Evidence review: SRS/SRT for recurrent or residual pituitary adenoma

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Contents

1. Introduction

- Pituitary adenomas are usually benign and grow slowly to exert their harmful effects by pressure on surrounding structures or through hormone secretion. There are two main types of pituitary tumour - those that secrete hormones and cause clinical syndromes of hormone excess (functioning adenomas), and those that do not secrete hormones (non-functioning adenomas). While autopsy studies suggest pituitary tumours are found in 10% of the population the clinically relevant incidence is much lower.

- Non-functioning adenomas (prevalence 22.2 per 100,000) make up the largest group requiring primary surgery and potentially needing adjuvant treatment.

- Functioning adenomas secrete Prolactin (PRL) (prolactinomas), Growth Hormone (GH) (causing acromegaly), and Adrenocorticotrophic Hormone (ACTH, causing Cushings disease). Prolactinomas (prevalence 44.4/100,000) are usually treated medically. Cushing's disease (prevalence 1.2/100,000) and acromegaly (prevalence 8.6/100,000) are rare conditions primarily requiring surgery but frequently requiring subsequent radiation therapy. In the UK approximately 1100 operations are carried out on pituitary tumours as primary therapy each year.

- If intervention is required, surgery is the mainstay of active treatment. Residual tumour is common after surgery and can start to grow if it is a non-functioning tumour, or grow and continue to secrete hormones in the case of a functioning tumour. This may necessitate further treatment.

- Further surgery is possible but tends to have increased risk of complications and may have less favourable clinical outcomes than primary surgery. One meta-analysis of repeat surgical resection for residual/recurrent pituitary adenoma described a remission rate of 45.5% in GH-secreting tumours, 55.5% in ACTH-secreting tumours and 76.05% in non-functioning tumours. Complication rates were 20% and included diabetes insipidus, CSF leak and sinusitis[1].

- Adjuvant radiotherapy is used to treat residual or recurrent tumours. It has the advantages of being minimally invasive, having a lower risk of complications compared to repeat resection and appears to have better clinical outcomes. Conventional fractionated radiotherapy (CRT) has been the standard method of delivery. CRT is usually delivered via standard linear accelerators. Irradiation in the region of the pituitary gland can result in normal brain tissue being irradiated leading to damage to pituitary function (hypopituitarism), optic neuropathy, stroke, neurocognitive effects and secondary malignancy. One review of fractionated radiotherapy found it controlled tumour growth in 80-98% of patients with non-functioning adenomas and 67-89% for functioning tumours. Hypopituitarism is the most common side effect of pituitary irradiation with an incidence of 13-56%[2].

- Stereotactic Radiosurgery or Radiotherapy (SRS/SRT) is a highly conformal radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. SRS/SRT involves the delivery of a single dose or multiple (3-5 usually) treatments using stereotactic methods to accurately focus radiation beams on a target. The aim is to improve local control and reduce potential toxicity to nearby structures such as the optic apparatus. A multidisciplinary team of neurosurgeons, neuro-oncologists and neuro-radiologists should be involved in SRS case selection, treatment planning and delivery.

- SRS/SRT has a shorter recovery period and is usually delivered as a single or few treatments rather than many CRT fractions over several weeks. This results in potential advantages for patient experience, logistics and possibly overall service delivery.

2. Summary of results

- A total of 53 papers evaluating the effect and safety of stereotactic radiosurgery and radiotherapy were identified. The majority were retrospective case series that varied in size, baseline characteristics and treatment dosage.
- Outcome measures used and reported in each study varied. Follow up varied from median 2.8 to 12 years
- In non-functioning tumours *tumour control* was reported as 93.4% at median 36 months in the largest case series[3] and ranged from 75 to 100% in all other reporting studies[3,6,7,10-14,17-21,23-28,32-38,40,41,43,46]
- In functioning tumours *hormonal control* (normalisation of hormone levels with or without medication) was reported as 45.7% in the largest study[41] and ranged from 0 to 100% in all other reporting studies[4-6,9,11,15,17,19,22,25,28,29,30,31,33,35-39,42,44-46,49].
- The main adverse events identified were hypopituitarism (ranging between 0 to 39% in functional tumours and 0 to 38% in functioning tumours) and new/deteriorating visual dysfunction (ranging from 0% to 21% for non-functioning tumours and from 0% to 9% for functioning tumours).
- 6 non-randomised studies compared SRS/SRT [16,39,42-44]with conventional fractionated radiotherapy and suggest superior safety outcomes.

3. Methodology

- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by the NHS England Clinical and Public Health Leads of the Policy Working Group The following sources were searched for relevant publications: EMBASE, MEDLINE, Clinicaltrials.gov, NHS Evidence, Cochrane Library, and the National Institute for Health and Care Excellence (NICE) (see section 11 for search terms). National guidelines were examined and included where relevant.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Evidence was extracted from the selected trials and recorded in evidence summary tables (see section 7 below). Only outcomes specified in the PICO were extracted.
- All papers included in this evaluation were assessed as to their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. The evidence to support individual outcomes was graded, and quality was recorded in grade of evidence tables (see section 8 below).

4. Results

53 papers matching the PICO were identified. The majority (42 studies) were retrospective case series ranging in size, baseline characteristics and treatments used. There were 6 retrospective cohort studies comparing different interventions, 4 prospective cohort studies and 1 qualitative study. There was no randomisation or blinding in any study including the comparison studies. One study looked at health-related quality of life in patients who had been treated with SRS. There were no cost-effectiveness studies for this patient population.

The majority of patients had recurrent or residual pituitary adenoma despite ≥1 prior treatment (15% of patients were treatment naive due to operability or refusal of surgery - their outcomes could not be analysed separately). Patients underwent stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (SRT).

Outcomes assessed included progression-free survival (PFS), treatment response, disease progression and adverse events. Full details of the trial designs and outcomes are summarised in the evidence tables in section 7, below. Tumour/hormonal control or remission were the most common measures of effectiveness reported. There do not appear to be any internationally recognised standards of outcome reporting for pituitary adenomas so studies used different measures (documented for each study in section 7).

Dosage

Treatment dosage tended to differ between secretory and non-functioning adenomas. For non-functioning adenomas median marginal doses ranged from 13-20Gy[3,6,7,10-14,18,19,21,23,24,26,32-35,38,40,41,43,46] while for functioning adenomas this ranged from 15 to 35Gy[4-9,11,15-16,19,22,27,29-31,33,35,38,39]. Dosage was also dependant on other factors such as tumour size, previous radiotherapy and endocrine status.

Tumour response

This was reported as 93.4% at median 36 months in the largest case series[3] and 90% at 152 months in the series with the longest follow up[4]. Tumour response ranged from 86.4 to 100% in the 43 studies reporting this outcome[3-46]

Tumour response was found to depend on certain factors. In one multivariate analysis, tumour size >5cm[3] (OR 1.08, CI-1.02 to 1.13, p=0.006) and suprasellar extension (OR 2.10, CI 0.96-4.61, p=0.064) were found to increase the risk of progression[41].

Non-functioning tumours

Tumour control (TC), which refers to the absence of tumour growth/recurrence, was the most commonly reported outcome. This was reported as 93.4% at median 36 months in the largest case series[3] and 95% at 93 months in the series with the longest follow up[40]. TC ranged from 75 to 100% in 29 studies reporting this outcome [3,6,7,10-14,17-21,23-28,32-38,40,41,43,46]. In terms of the comparator studies, one cohort study[39] found SRS post-surgery to be superior to no intervention in maintaining tumour control at 10 years (95% in SRS group vs. 22% in no-intervention group). One

study[42] found SRS and SRT to be superior to conventional radiotherapy in terms of tumour control (5% vs. 13 % respectively – no confidence intervals given).

Complete tumour response, which is defined as the total disappearance of tumour identified on imaging, was reported to be 0% in the largest case series[41] and ranged from 0 to 1% in all 15 reporting studies[10,12-14,18,21,23,24,26,33,35,37-38,41,46]

Partial tumour response, defined as a sustained reduction of tumour volume identified on imaging, was reported in 41% in the largest case series[41]. 16 studies reported partial response in 8-100% of patients[10,12-14,18,21,23-24,26,32-33,37-38,41,43,46].

Stable disease (SD), defined as no change in tumour volume identified on imaging, was reported as 59% in the largest reporting case series[41] and ranged from 11% to 80% in the 13 studies[10,12-13,21,23-24,26,33,37,38,41,43,46] reporting this outcome.

Tumour growth/recurrence, defined as an increase in tumour volume identified on imaging or a return of a previously absent tumour, was reported by 27 studies [3,6,7,10-14,17-21,23-28,32-38,40,41,43,46] and ranged between 0 and 25%. The largest study[3] reported a rate of 6.6%.

Progression-free survival measured the proportion of patients alive and free of disease at a certain time point. In the studies reviewed the 5 and 10 year time point were most commonly used. In the largest case series[3] PFS was 95% and 85% at 5 and 10 years respectively following SRS. PFS in all 6 studies ranged from 93% to 100% to at 5 years and 85% to 88% at 10 years[3,24,26,28,34,43].

One study[42] found that SRS and SRT had a superior progression-free survival to conventional fractionated radiotherapy at 5 and 10 years ((SRS: 5yr-100% 10yr-100%; SRT: 5yr-92.8% (SE 3.6) 10 yr- 85.7% (SE 7.6); CRT: 5 yr- 86.9% (SE 6.2) 10 yr- 76.3% (SE 8.9)).

GH-secreting tumours

Tumour control (TC) refers to the absence of tumour growth/recurrence. This was reported as 96.9% at mean 54 months in the largest case series[41] and 100% at 152 months in the series with the longest follow up[4]. TC ranged from 88 to 100% in 27 studies reporting this outcome[4-6,8,11,15-17,19,20,25,28-31,33,35-39,41-42,44,46-48]. One study[17] found no significant difference in tumour control between SRS and conventional radiotherapy.

Complete tumour response, which is defined as the total disappearance of tumour identified on imaging, was reported to be 3% in the largest study[41] at mean 54 months and 29% in the study with the longest follow up[4] (152 months). It ranged from 0% to 29% in all 5 studies[4,33,37,41,46].

Partial tumour response, defined as a sustained reduction of tumour volume identified on imaging, was reported to be 20% in the largest study[41] at mean 54 months and 24% in the study with the longest follow up[4] (152 months). It ranged from 15% to 70% in all 9 studies[4,5,8,16,33,37,41,44,46].

Stable disease (SD), defined as no change in tumour volume identified on imaging, was reported to be 74% in the largest study[41] at mean 54 months and 47% in the study with the longest follow up[4] (152 months). It ranged from 30% to 85% in all 7 studies[4,5,33,37,41,44,46].

Tumour growth/recurrence, defined as an increase in tumour volume identified on

imaging or a return of a previously absent tumour, was reported to be 3% in the largest study[41] at mean 54 months and 0% in the study with the longest follow up[4] (152 months). It ranged from 0% to 10% in all 18 studies[4-6,8,11,1516,19,20,28-30,33,3741-42,44,46].

ACTH-secreting tumours

Tumour control refers to the absence of tumour growth/recurrence. This was reported as 88% at mean 58 months in the largest case series[41]. TC ranged from 33 to 100% in 19 studies reporting this outcome[6,8-9,11,17,19,20,25,28,35-39,41-42,45,46,48]. One study[17] found no significant difference in tumour control between SRS and conventional radiotherapy.

Complete tumour response, which is defined as the total disappearance of tumour identified on imaging, was reported to be 18% in the largest study[41] at mean 58 months and 0% in the other reporting study[46].

Partial tumour response, defined as a sustained reduction of tumour volume identified on imaging, was reported to be 12% in the largest study[41] at mean 58 months. It ranged from 12% to 50% in all 5 studies[8-9,41,45-46].

Stable disease (SD), defined as no change in tumour volume identified on imaging, was reported to be 59% in the largest study[41] at mean 58 months. It ranged from 44% to 59% in all 4 studies[9,41,45,46].

Tumour growth/recurrence, defined as an increase in tumour volume identified on imaging or a return of a previously absent tumour, was reported to be 12% in the largest study[41] at mean 58 months. It ranged from 0% to 67% in all 12 studies[6,8,9,11,17,19,20,28,41-42,45,46].

PRL-secreting tumours

Tumour control refers to the absence of tumour growth/recurrence. This was reported as 100% at mean 81.9 months in the largest case series[41]. TC ranged from 86 to 100% in 14 studies reporting this outcome[6,8,11,17,19,20,22,27-28,33,41-42,46,48]. One study[17] found no significant difference in tumour control between SRS and conventional radiotherapy.

Complete tumour response, which is defined as the total disappearance of tumour identified on imaging, was reported to be 62% in the largest study[41] at mean 56 months and ranged from 0 to 62% in all 6 reporting studies[8,22,27,33,41,46,48].

Partial tumour response, defined as a sustained reduction of tumour volume identified on imaging, was reported to be 39% in the largest study[41] at mean 56 months. It ranged from 25% to 57% in all 7 studies[8,22,27,33,41,46,48].

Stable disease (SD), defined as no change in tumour volume identified on imaging, was reported to be 0% in the largest study[41] at mean 56 months. It ranged from 0% to 75% in all 7 studies[8,22,27,33,41,46,48].

Tumour growth/recurrence, defined as an increase in tumour volume identified on imaging or a return of a previously absent tumour, was reported to be 0% in the largest study[41] at mean 56 months. It ranged from 0% to 14% in all 14 studies [6,8,17,19,20,22,27,28,33,41,42,46,48,].

Nelson's syndrome

One study[41] reported on tumour response in Nelson's syndrome. It found a tumour

control rate of 100%, complete response in 44%, partial response in 44%, stable disease in 11% and tumour growth/recurrence in 0%

LH/FSH secreting tumours

One study[46] reported on tumour response. It found a tumour control rate of 100%, complete response in 50%, partial response in 0%, stable disease in 50% and tumour growth/recurrence in 0%.

Hormonal response

Control or remission of hormonal hypersecretion is an important measure of disease control in functioning pituitary adenomas. Hormonal control (normalisation of hormone levels with or without medication) was reported as 45.7% in the largest study[41] but ranged from 0 to 100% across all reporting studies[4-6,9,11,15,17,19,22,25,28,29,30,31,33,35-39,42,44-46,49]. Tumour type, tumour size, initial hormonal level, and concomitant use of hormonal therapy have been shown to have an impact on the likelihood of hormonal remission[17,22,24,26,47,48].

GH-secreting tumours

Endocrine cure was defined by studies as normalisation of hormone levels without the need for anti-secretory medication. This was reported as 33% in the largest study at mean 54 months[41], EC in all 23 studies ranged from 0% to 47%[4-6,11,15,1719,25,28-31,33,35-39,41,46-48].

Hormonal normalisation/remission (HN) was defined as patients having normal levels of hormone but still requiring anti-secretory medication. This was reported 16.8% in the largest study[41] and ranged from 0% to 59% in 24 studies[4-6,8,11,15,19,25,28-31,33,35-39,41,42,44,46,47].

Hormonal improvement refers to a reduction in hormone levels but one that does not result in normalisation. HI was 15% in the largest study[46] at median 35 months and ranged from 0% to 80% in 18 studies[4,6,8,11,15,19,25,28-31,33,3536-39,44,46].

Hormonal deterioration refers to hormone levels that worsen post-treatment. HD was 0% in the largest study[45] and ranged from 0% to 17% in 18 studies[4-6,11,15,19,25,28-31,33,35,36,38,39,44,46].

ACTH secreting tumours

Endocrine cure was defined by studies as normalisation of hormone levels without the need for anti-secretory medication. This was reported as 78% in the largest study[41] at mean 54 months follow up, EC in all 14 reporting studies ranged from 0% to 100%[6,9,11,17,25,28,35-39,41,46,48].

Hormonal normalisation/remission (HN) was defined as patients having normal levels of hormone but still requiring anti-secretory medication. This was reported as 22% in the largest study[41] at mean 54 months and ranged from 0% to 67% in all 16 reporting studies[6,8,9,11,25,28,35-39,41,42,45,46].

Hormonal improvement (HI) refers to a reduction in hormone levels but one that does not result in normalisation. HI was 50% in the largest study[46] at median 35 months and ranged from 0% to 100% in 15 studies[6,8,9,11,17,25,28,35-39,41,45,46].

Hormonal deterioration (HD) refers to hormone levels that worsen post-treatment. HD was 0% in the largest study[45] and ranged from 0% to 33% in 15 studies[6,9,11,17,19,25,28,35-39,42,45,46].

PRL-secreting tumours

Endocrine cure was defined by studies as normalisation of hormone levels without the need for anti-secretory medication. This was reported as 17% in the largest study[41] at mean 54 months follow up, EC in all 17 reporting studies ranged from 0% to 100%[6,11,17,19,22,25,28,33,35-39,41,46,48,49].

Hormonal normalisation/remission (HN) was defined as patients having normal levels of hormone but still requiring anti-secretory medication. This was reported 26% in the largest study[41] at mean 54 months and ranged from 0% to 83% in all 17 reporting studies[6,8,11,19,22,25,27,28,33,36-39,41,42,46,49].

Hormonal improvement refers to a reduction in hormone levels but one that does not result in normalisation. HI was 29% in largest study[46] at median 35 months and ranged from 0% to 100% in all 14 reporting studies[6,8,11,19,22,25,28,36-39,46,49].

Hormonal deterioration refers to hormone levels that worsen post-treatment. HD was 14% in largest study[46] at mean 35 months and ranged from 0% to18% in all 14 reporting studies[6,11,19,25,28,33,36-39,42,46,49].

Nelson's tumour

Endocrine cure was 0% in one study[41].*Hormonal normalisation* was 17% and 50% in 2 studies[38,41] and *hormonal deterioration* was reported as 50% in one study[41].

Luteinising hormone (LH)/Follicle secreting hormone (FSH) secreting tumours

One study[46] found no change in hormonal hypersecretion following SRS.

Quality of Life

Quality of life was measured in one qualitative study[54] that used a validated WHO questionnaire. The study found that psychological domains were lowest in terms of satisfaction and there was a negative correlation between the number of symptoms reported (>6) and the quality of life score.

Safety

Hypopituitarism was a major complication monitored in most studies. It is defined as to any new deficit or deterioration in pituitary function identified after treatment. In non-functioning adenomas this was 21% in the largest study[3] at median 36 months and ranged from 0 to 39% in all 24 reporting studies[3,7,10-14,17-21,23-26,32,34-37,40,43,46]. For functioning adenomas the largest study reported a 13% rate at median 35 months and ranged from 0 to 38% in 14 studies[4,15,19-20,22,28,31,33,35,36,44-46,49]. In one comparative study involving SRS and CRT, those who underwent SRS had lower rates of hypopituitarism (2% in SRs v. 16% in CRT)[17]. However the difference in rates between SRS/SRT and CRT is less pronounced in other studies[35,43,44,45]. Factors found to influence the rate of hypopituitarism include visualisation of the gland[20], tumour size[26,29], dose given[51] and prior radiation therapy[24].

New visual dysfunction occurs as a result of radiation-induced toxicity to the optic chiasm. For non-functioning adenomas this was reported as 6.6% in the largest study[3] and ranged from 0% to 21% in all 25 studies[3,6,10-14,17,20,21,23-26,28,32-38,40,43,46]. For funtioning adenomas this was reported as 2.6% in the largest study[46] and ranged from 0% to 9% in all 25 studies[4-6,8,9,11,15-17,20,22,25,27-31,33,35-39,42,44-47,49]. Maximum dosage to the optic chiasm ranged from 8 to 11Gy (16 studies 8-9Gy, 10 studies 10-11Gy).

One series of 222 patients[53] treated with a range of doses found that the risk of visual dysfunction is minimal if dosage to the optic chiasm is kept below 12Gy (0% visual dysfunction <12Gy vs. 10% if >12Gy). In a comparative study with CRT[43], SRS/SRT led to fewer rates of visual dysfunction (1% in SRS/SRT vs. 11% in CRT).

New malignancy was not seen in any of the studies. One large retrospective study of new malignancy rates after SRS for benign intracranial tumours[53] found no difference in rate between the SRS group and the general population (4.4% vs. expected 5.2% rate at median 43.2 months).

Stroke was a rare occurrence and was only reported in 2 studies. 2/35 (5.7%) had TIAs at 72 and 134 months[29] and 1% had a stroke at 9 years in another study[13].

SRS vs. SRT

In studies (4 in total) that included both SRS and SRT there did not seem to be a significant difference in efficacy between the two treatment modalities. Tumour control rates were similar in 2 studies (88%vs.88%[43], and 88%vs.90%[44]) and hormonal normalisation was similar in two further studies (35% vs. 41%[28] and 20% vs. 20%[44]). In terms of safety patients undergoing SRS tended to have lower rates of hypothyroidism (10 vs. 23%[28], 0 vs. 6%[43] and 10 vs. 20%[44]) but equivalent rates of new visual dysfunction (4% vs. 3%[28], 0% vs. 2%[43]). No statistical testing was undertaken to quantify the significance of these differences. One study[45] had only included a single patient in the SRT group compared to 36 in the SRS group so was not included in this comparative analysis.

5. Discussion

53 published studies were included that reported on the efficacy and safety of SRS/SRT for recurring and residual tumours. However they tended to be of poor to moderate quality. The 6 comparator studies were retrospective, non-randomised and non-controlled. The other studies were retrospective case series. Approximately a quarter of studies had more than 100 patients but over half included only 9-40 patients.

The baseline characteristics of patients differed significantly in terms of tumour volume, tumour functional status and previous treatment. This an important limitation for the comparator studies as these characteristics have been shown to have an effect on both efficacy and safety outcomes (see results section).

The length of follow up also varied and ranged between 33 and 152 months. The studies with the shorter follow up may not have had sufficient time to record tumour response/recurrence, hormonal response/relapse or radiation-induced adverse events.

In addition to the limitations of the designs of the studies, there were problems with the reporting in several papers which may limit the applications of the findings. These included:

- inconsistency in the outcome criteria used between studies (there does not seem be an internationally recognised system to report outcomes in pituitary

adenoma). For example normalisation of GH was quoted as <2.5ng/ml in one study[44] and 1µg/ml in another[15].

- missing data and loss to follow up. This ranged from 10-50% for certain outcome measures[34,43,44,46.51]

While there are studies that have compared different radiation modalities, none directly compared SRS/SRT with repeat surgery and so judgements on efficacy and safety will be limited. The picture is further complicated by the fact that patients in most of the studies had a varied clinical history ranging from those with a primary presentation to those who have had multiple surgical interventions and previous fractionated radiotherapy. Most studies analysed these patients together and thus outcomes could not be split by baseline characteristics.

An analysis of efficacy and safety by tumour type was undertaken but was limited by studies often pooling outcomes rather than reporting them by specific tumour type. Additionally sub-groups by tumour type were often small so led to a wide range of outcomes when comparing all case series.

SRS/SRT appears to be effective in controlling the growth of recurrent/residual pituitary tumours and has a role in hormonal remission in the short to medium term. There is some evidence that SRS/SRT is more effective in achieving desired outcomes in non-functioning than functioning tumours. This is mostly due to the need to control hormonal secretion as well as tumour size in functioning tumours. SRS/SRT also appears to have variable effectiveness depending on the functioning tumour type – ACTH-secreting tumours had the best response followed by GH-secreting and PRL-secreting tumours. There were too few Nelson's and LH/FSH-secreting tumours reviewed to make a judgement on efficacy.

The data from the comparative studies is too limited to make any firm conclusions about efficacy relative to other treatment but suggests a reduced rate of adverse events in SRS/SRT compared to conventional fractionated radiotherapy. Additionally while SRS and SRT seem to have comparable efficacy, hypopituitarism may be higher in SRT as compared to SRS. However given the low numbers of patients, limited quality of these studies and lack of statistical testing this may not be a true difference.

It is difficult to discern whether some of the adverse events reported are attributable to the disease or to SRS/SRT, or whether both contributed to some degree. For example both SRS/SRT (radiation-induced toxicity) and disease progression (pressure effects of tumour) can lead to new visual deficit.

6. Conclusion

The published evidence on SRS/SRT for treatment residual/recurrent pituitary adenoma consists of retrospective case series, prospective cohort studies and non-randomised/controlled comparative studies. The major drawback of these types of study is the difficulty in understanding the true efficacy of an intervention due to a lack of control over factors that influence the outcomes being measured.

The evidence suggests a role for SRS/SRT in effective tumour control and to a lesser

degree, hormonal control. However a lack of randomised control trials mean it is difficult to make direct comparisons with standard care. The evidence suggests lower rates of adverse events in SRS/SRT compared to conventional fractionated radiotherapy but a lack of randomised control trials mean it is difficult to make direct comparisons with standard care.

7. Evidence Summary Table

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Sheehan et al. 2013	Retrospective case-series from 9 centres	512 patients with non-functional pituitary adenomas. Prior resection in 479 patients (93.6%) and prior fractionated external-beam radiotherapy in 34 patients (6.6%). Median age was 53 years.	SRS: Models U, B, C, 4C, or Perfexion Gamma Knife units (Elekta AB) were used Median dose of 16 Gy to the tumor margin. Median Maximum dose 32Gy (10 to 70) Median dose to optic chiasm 7.4Gy	Efficacy	Tumour control (stable/shrinkage)	438/469 (93.4%) at median 36 months	6	Direct. The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	Multi-centre trial – not all patients were followed at the same centre and some by the referring physician rather than the centre itself. Different SRS equipment used, possibility of different calibrations and efficacy. In 33 (6.4%) patients SRS was for primary disease so outside of PICO. However their results could not be analysed separately. 34 (6.6%) had prior fractionated radiotherapy No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. 42/512 patients were not assessable for response 50% had follow up of <3 years Actual proportion of tumour response/shrinkage unclear
					Tumour growth/recurrence	31/469 (6.6%) at median 36 months			
					Progression-free survival	98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years post-radiosurgery respectively			
					Time-to-reduction	Median 33 months			
				Safety	Hypopituitarism	91/432 (21%)			
					New visual dysfunction	29/442 (6.6%) developed new visual deficit			
					New CNS deficit	41/442 (9.3%) developed new CNS dysfunction			
Voges et al. 2006	Retrospective case-series	142 patients with pituitary adenomas. 105 were functional and 37 were non-functional 137 patients	SRT: Standard Linear accelerator. Upper limit for the therapeutic dose, was 20 Gy. The dose delivered to	Efficacy	Complete tumour response	5/142 (3.5%) at mean 82 months	6	Direct. The vast majority of the population studied appears representative of a patient group with residual/recurrent	Included treatment naïve patients (3.5%) 4 patients had previous adjuvant XRT Significant differences in treatment volumes between subgroups Restricted patients to those with dimensions <35mm No comparator group, and therefore no
					Partial tumour response	41/142 (28.9%) at mean 82 months			
					Stable tumour	91/142 (64.1%) at mean 82 months			
					Disease progression	5/142 (3.5%) – out of field recurrence at mean 38.5 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		underwent prior surgery. Of these 4 had adjuvant XRT. For 5 this was their primary treatment.	the anterior visual pathways was < 9 Gy. Follow up mean 82 months		Hormone normalisation	48/105 (45.7%) at mean 82 mths (TTN = 36.2 +/-24.0 mths)		pituitary adenoma. 5/142 (3.5%) had primary disease	randomisation or blinding. No evidence of efficacy compared to other treatment options, therefore insufficient evidence to guide treatment decisions. Time to adverse events unclear Outcome criteria: Hormonal normalization: 1) Fasting GH<2 ng/mL10 or mean GH <2 ng/mL11 and normal IGF-1 corrected for age and gender; 2) serum cortisol <25 mg/dL or normal 24-hour urinary free cortisol 3) normal serum ACTH; 4) normal free 3,5,30-triiodothyrone, free thyroxine, and TSH levels and a normal thyrotropin-releasing hormone test; and 5) normal serum prolactin levels. Endocrine cure was defined as normalization of hormone secretion without specific medication intake. Partial response/Tumour shrinkage ' reduction >25% in the greatest tumor dimension compared with baseline measurements in at least 2 reconstruction planes, Stable tumour - a reduction or increase 25%, and Progression- an increase >25%. A 'complete response when CT and/or MRI studies displayed no signal specific for tumor tissue.
					Endocrine cure	37/105 (37.5%) at mean 82 mths (TTC = 42.1 +/-25.0 mths)			
				Safety	Hypopituitarism	14/142 (12.3%)			
					New visual dysfunction	2/142 (1.4%)			
					Seizure	2/142 (1.4%)			
Kong et al. 2007	Retrospective comparison between SRS and SRT	125 patients with pituitary adenomas (54 functional and 71 non-functional) 64 had CRT,	CRT: The total dose delivered by was 50.4 Gy (range, 48–54 Gy) with daily dose of 2 Gy.	Efficacy	Tumour control (stable/response)	121/125 (97%) No sig difference between CRT and SRS	4	Direct. The vast majority of the population studied appears representative of a patient group with residual/recurrent	No randomisation, blinding or matching of patients between comparison groups. Differences in tumour size between groups (Median tumour volume for SRS = 3210 vs. 6021 for SRT) Differences in length of follow up) Mean
					Tumour growth/recurrence	4/125 (3%) at 36.8 months			
					Overall tumour response	39.5% at 2 years and 81.8% at 4 years			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		61 had SRS 8 patients had no prior surgery/RT Criteria: Maximum tumor dimension of 30 mm, and a distance 2 mm between the tumor and the optic apparatus.	SRS: Gammaknife radiosurgical Median dose (25.1 Gy (9 – 30) Max dose to optic chiasm <8Gy Follow up mean 36.8 months		Progression-free survival	99% at 2 years and 97% at 4 years.		pituitary adenoma.	follow up in SRT 46.4 months vs 25.4 months for SRS Not all effects on tumour volume presented (complete vs. partial vs. stable) Included treatment naïve patients with no separate analysis Hormone Normalisation (Remission): GH levels <1 ng/mL and normal IGF-1 values. Prolactinoma: Pl <20 ng/mL. In Cushing disease: normal cortisol levels, urinary free cortisol levels in the normal range, and resolution of clinical stigmata. Endocrine cure (Complete remission) remission state that fulfilled the criteria described above without requiring medications to suppress hormone secretion from the tumor.
					Endocrine cure	SRS: 14/32 (43.8%) (TTC = 26 months) CRT: 8/22 (36.4%) (TTC = 63 months) Multivariate analysis revealed SRS was significant predictor of endocrine remission vs. CRT (p=0.026) Overall 26.2% at 2 years and 76.3% at 4 years			
				Safety	Hypopituitarism	CRT: 10/64 (15.6%) (TT = median 84 months) SRS: 1/61 (1.6%) at 53 months			
					Visual dysfunction	0/95 (0%)			
Wilson et al. 2012	Retrospective comparison between SRS, SRT and CRT	171 patients with non-functioning adenoma 51 had SRS, 67 had FSRT and 53 had CRT. 9 patients had no prior surgery/RT	SRS: BRW head ring, SRT GTC head ring (both Radionics, Burlington, MA, USA) All treatment was delivered with 6 MeV photons	Efficacy	Tumour shrinkage	SRS: 4/51 (8%) at median 50 months follow up SRT: 12/67 (18%) at median 62 months follow up CRT: 2/53 (4%) at median 53 months follow up	5	Direct. The vast majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	No randomisation, blinding or matching of patients between comparison groups. Significant differences in tumour spread, prior treatment and adjacency to optic chiasm between groups. Different follow up periods. Gaps in data in CRT group. 20 patients were not assessable for response Included treatment naïve patients with no separate analysis
					Stable tumour	SRS: 41/51 (80%) at median 50 months follow up SRT: 47/67 (70%) at median 62 months follow up CRT: 32/53 (60%) at median 53 months follow up			
					Tumour growth/recurrence	SRS: 0/51 (0%) at median 50 months follow up SRT: 6/67 (9%) at median 62 months CRT: 7/53 (13%) at median 53			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						months follow up			
					Progression-free survival	5-year: SRS 100%, SRT 92.8% and CRT 86.9%.			
					Overall survival	SRS, SRT, CRT: 2 years: 100%, 96.8%, 95.5% 5 years: 100%, 91.6%, 83.4% 10 years: 100%, 91.6%, 79.2%			
				Safety	Hypopituitarism	4/67 (7%) in SRT group			
					Adverse events	SRS, SRT, CRT: Radiological: 0(0%),1(2%),3(6%) Visual: 0(0%),1(2%),6(11%) Memory: 1(2%), 0(0%), 2(4%) Epilepsy:1(2%),1(2%),3(6%)			
Wilson et al. 2013	Retrospective comparison between SRS, SRT and CRT	121 patients with GH-secreting Pituitary adenomas. 86 had SRS, 10 had SRT and 25 had CRT 20 patients had no prior surgery/RT	SRS: BRW head ring, SRT: GTC head ring (both Radionics, Burlington, MA, USA) Median dose: SRS: 20 Gy (14–25) SRT: 50 Gy (48.6–51.01) CRT: 55 Gy (40–104.8)	Efficacy	Hormone improvement	**GH:** SRS: 26/32 (81%) at mean 28.4 months SRT: 4/5 (80%) at mean 40 months CRT: No data **IGF-1**: SRS: 40/46 (87%) at mean 28.4 months SRT: 5/6 (83%) at mean 40 months CRT: No data	4	Direct The vast majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	SRT group was small (n=10) as compared to SRS group (n=86) No randomisation, blinding or matching of patients between comparison groups. Differences seen in tumour spread prior to treatment between groups. Different follow up periods. Gaps in data in CRT group. Large loss to follow up for hormonal evaluation: 84/121 (69%) had missing data Loss to follow up for tumour volume: 21/121 (17%) Endocrine remission: GH level <2.5 ng/mL as well as <5 ng/mL. IGF-1 levels were matched for sex and age with an upper limit of normal
					Hormone normalisation	**GH:** SRS: 12/32 (38%) at mean 28.4 months SRT: 2/5 (40%) at mean 40 months CRT: No data **IGF-1**: SRS: 16/46 (35%) at mean 28.4 months SRT: 4/6 (66%) at mean 40 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						CRT: No data			
					Hormonal deterioration	**GH:** SRS: 6/32 (19%) at mean 28.4 months SRT: 1/5 (20%) at mean 40 months CRT: No data **IGF-1**: SRS: 4/46 (9%) at mean 28.4 months SRT: 0/6 (0%) at mean 40 months CRT: No data			
					Tumour shrinkage	SRS: 18/79 (22%) at median 66 months SRT: 3/9 (33%) at median 61 months CRT: 0/12 (0%)			
					Stable tumour	SRS: 58/79 (73%) at median 66 months SRT: 6/19 (67%) at median 61 months CRT: 12/12 (48%)			
					Tumour growth/recurrence	SRS: 3/79 (4%) at median 66 months SRT: 0/9 (0%) at median 61 months CRT: 0/12			
					Progression-free survival	The 2 and 5 year progression free survival rate was 98.8% (SE 1.2) and 96.3% (SE 2.9) respectively.			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
				Safety	Adverse events	SRS, SRT, CRT: Radiological: 4(4%),0(0%),0(0%) Visual: 1(1%),0(0%),3(12%) Memory: 1(1%), 0(0%), 1(4%) Epilepsy:2(2%),0(0%),0(0%) Malignancy (Intra-crania)l: 1(1.1%), 0(0%), 0(0%) Malignancy – Extra-cranial 4(4.7%), 0(0%), 0(0%)			
					Hypopituitarism	17/86 (19.8%)			
					Mortality	6/86 (6.9%)			
Wilson et al. 2014	Retrospective comparison between SRS, SRT and CRT	50 patients with cortisol-secreting tumours. 36 had SRS, 1 had SRT and 13 had CRT	SRS: BRW head ring, SRT: GTC head ring (both Radionics, Burlington, MA, USA) Median dose: SRS: 20 Gy (17–25) SRS: 50 Gy, CRT: 90 Gy (50–100)	Efficacy	Hormone control	**Cortisol:** SRS: 9/36 (25%), 22/36 (61%) no data. At median follow up of 27 months**.** SRT: No data, CRT: No data **UFC:** SRS: 13/36 (36.1%), 5/86 (13.9%) no data. At median follow up of 27 month. SRT: No data, CRT: No data	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	No randomisation, blinding or matching of patients. Differences seen in tumour spread prior to treatment between groups. Different follow up periods. Gaps in data in CRT group. Large loss to follow up for hormonal evaluation: 25/50 (50%) had missing data Assessed target serum morning cortisol levels were <140 nmol/L and <50 nmol/L, as well as 24 hour urinary cortisol levels <276 nmol/24 hours and <55 nmol/24 hours
					Hormonal deterioration	**Cortisol:** SRS: 2/36 (5.6%) At median follow up of 27 months**.** SRT: No data**,** CRT: No data **UFC:** SRS: 4/36 (11.1%) At median follow up of 27 months**,** SRT: No data, CRT: No data			
					Tumour shrinkage	SRS: 14/36(39%) at median 66 months SRT: 0/1 (0%) at 69.6 months CRT: 0/13 (0%) at median 44.4 months			
					Stable tumour	SRS: 16/36(44%) at median 66 months SRT: 0/1(0%) at 69.6 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
						CRT: 6/13(46%) at median 44.4 months			
					Tumour growth/recurrence	SRS: 1(3%) at median 66 months SRT: 1/1(100%) at 69.6 months CRT: 0/13 (0%) at median 44.4 months			
					Progression-free survival	**2 year (SE):** SRS: 90%(6), SRT: 100% (0), CRT: 80%(18) **5 year: (SE)** SRS: 78% (9), SRT: 0% (0), CRT: 80% (18)			
					Overall survival	**2 year (SE):** SRS: 100%(0), SRT: 100% (0) , CRT: 80%(18) **5 year: (SE)** SRS: 100% (0) , SRT: 0% (0), CRT: 80% (18)			
				Safety	Hypopituitarism	5/36 (13.9%) had new endocrone dysfunction			
					New malignancy	Intracranial: 1/50 (2%)			
Park et al. 2011	Retrospective case-series	125 patients with non-functioning pituitary adenomas 110 (88%) post-surgical and 17 (14%) post-RT residual/recurrent disease 15 patients had no prior surgery/RT	SRS: Leksell Gamma Knife (U, B, C, 4C, or Perfexion, Elekta, Atlanta, Georgia) The median target volume was 3.5 cm3. The median prescription dose delivered to the tumour margin was 13 Gy	Efficacy	Tumour control	112/125 (89.6%) at median 64m	5	Direct The majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. However 47/125 patients had tumour <3mm to optic chiasm 15/125 had no prior treatment	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Differences in baseline characteristics on patient group including tumour size, spread, prior treatment. A sizable proportion of the population had tumour within 3mm (38%) of optic chiasm which falls out of the PICO of this review
					Tumour shrinkage	66/125 (53%) (TT=17.3m)			
					Tumour growth/recurrence	13/125 (10.4%) at median 64m			
					Stable tumour	46/125 (37%)			
					Progression-free survival	99%, 96%, and 78% at 1, 5, and 10 years, respectively			
				Safety	Hypopituitarism	30/125 (24%) at 24m			
					New CNS dysfunction	6/125 (4.8%) at 64m			
					New visual dysfunction	3/125 (2.4%) at 64m			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Iwata et al. 2011	Prospective cohort study	100 patients with recurrent non-functioning PA	SRT: CyberKnife system (Accuray). Dose was either 21Gy in 3 fractions or 25Gy in 5 fractions	Efficacy	Complete tumour response	1/100 (1%) at median 33 months	6	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Relatively short follow up
					Partial tumour response	29/100 (29%) at median 33 months			
					Stable tumour	65/100 (65%) at median 33 months			
					Disease progression	5/100 (5%) at median 33 months (TT=mean 35 months)			
					Overall survival	3-year: 98% (95% CI: 95–100%).			
					Progression-free survival	3-year: 98% (95% CI: 92–100%).			
				Safety	New visual dysfunction	1/58 (2%) at 36 months			
					Hypopituitarism	3/74 (4%) at median 33 months			
Castinetti et al. 2011	Retrospective case series	76 patients with functioning PA 27 had no prior treatment	SRS: Laskell Gamma knife	Efficacy	Hormonal normalisation	34/76 (44.7%) at mean 96 months	6	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 29/76 (38%) was not recurrent/ residual	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Tumour growth/recurrence	2/76 (4%) at 72 and 96 months			
				Safety	Hypopituitarism	16/76 (21%) at mean 132 months			
					New visual dysfunction	3/76 (4%) at mean 1 month (2 resolved by 6 months)			
Van dern Burgh et al. 2007	Retrospective comparative study	174 patients with non-functioning PA	SRS: Laskell Gamm Knife (group 1) (n=76)	Efficacy	Tumour control	Group 1: 72/76 (95%) at 120 months Group 2: 6/28 (22%) at 120 months (P<0.001 between groups)	6	Direct The population studied appears representative of a	No randomisation, blinding or matching of patients. Progression was defined as recurrence

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		All post-surgery	No intervention (group 2) (n=28)		Tumour growth/recurrence	Gp 1: 3/76 (4%), at median 23 months Gp 2: 16/28 (57%), at median 30 months		patient group with residual/recurrent pituitary adenoma.	of completely resected or regrowth of residual NFPA on CT or MRI
					Overall survival	Median standardized survival 0.97 (95% CI, 0.56 –1.39) in Groups 1 and 2 combined			
				Safety	Hypopituitarism	No difference between groups			
					Stroke	1/76 (1%)patients in group 1			
					Seizure	1/76 (1%) patients in group 1			
					New visual dysfunction	0/76 (0%)			
Puataweepong et al. 2015	Retrospective case-series	115 patients with PA. 75/115(65%) non-functioning 40/115 (35%) functioning. 65 (57%) recurrent disease 45 (37%) post-surgery 8/(6%) patients had no prior surgery/RT	SRS/SRT: linear accelerator-based system (6 MV dedicated LINAC; with X-Knife planning System version 3 &4, Radionics) 21/115 (18%) treated with SRS, 97/115 (82%) treated with FSRT.	Efficacy	Tumour control (stable/response)	112/115 (97%) at median 62 months	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 53/115 (43%) was not recurrent/ residual disease	No randomisation, blinding or matching of patients. Differences seen in tumour spread prior to treatment between groups. Different follow up periods. Complete response: a reduction of tumor size >25%. Partial response: a reduction in tumor size <25%. Tumors were considered stable if any change in size was < 10%. Tumor control was defined as the absence of radiologic tumor progression. Criteria for Hormone normalisation of functioning pituitary adenomas were defined as follow: 1) fasting GH levels <2.5 ng/ml and normal insulin like growth factor 1 (IGF-1) level in acromegaly; 2) normalized ACTH, cortisol levels and urine free cortisol level in Cushing disease; 3) prolactin levels <20 ng/ml in prolactinoma.
					Progression-free survival	6 years: 95% (SRS 93%, SRT 95%)			
					Hormone normalisation	15/115 (13%) at median 62 months (TT median =18 months)			
				Safety	Hypopituitarism	11/115 (9%) at median 62 months			
					New visual dysfunction	4/115 (3%) at median 62 months			
Leenstra	Retrospectiv	82 patients	SRS: Leksell	Efficacy	Tumour shrinkage	55/82 (67%) at median 63 months	5	Direct	No comparator group, and therefore no

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
et al. 2010	e case-series	with PA 53 (65%) non-functional , 29 (35%) functional 5 (6%) patients had no prior surgery/RT	Gamma Knife (Elekta Instruments, Norcross, Georgia). Median treatment volume of 2.9 cm^3 Median margin radiation dose was 20 Gy (range, 11.0-30.0); the median maximum radiation dose was 40 Gy (range, 27.5-60.0).		Stable tumour	26/82 (32%) at median 63 months		The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 5/82 (6%) was not recurrent/ residual disease	randomisation or blinding. No evidence of efficacy compared to other treatment options. Those with prior hypopituitarism and those who underwent prior radiotherapy were excluded
					Tumour growth/recurrence	1/82 (1%) at 13 months			
				Safety	Hypopituitarism	34/82 (41%) at a median of 32 months			
Zeiler et al. 2013	Retrospective case-series	86 patients with recurrent/residual PA 47 (55%) non-functional 56/86 (65%) had prior surgery.	SRS: Gamma Knife Average maximum dose for non-secreting adenomas was 28.6 Gy (range of 24 to 32 Gy) and 46.8Gy (range from 26 to 70 Gy) for secreting adenomas. The average	Efficacy	Tumour control	75/76 (98.6%) at mean 32.8 months	6	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. 10/86 (12%) patents lost to follow up Relatively short follow up
					Tumour shrinkage	42/76 (55.3%) at mean 32.8 months			
					Stable tumour	33/76 (43.4%) at mean 32.8 months			
					Tumour growth/recurrence	1/76 (1.3%) at 12.6 months			
					Hormonal improvement	18/47 (38%) at mean 32.8 months			
					Hormonal stability	13/47 (28%) at mean 32.8 months			
					Hormonal deterioration	2/47 (4%) at mean 32.8 months			
				Safety	Adverse events	Transient:: 18/76 pin site swelling/infection , 5/76 pin site dysesthesias , 4/76 visual blurring , 2/76 short term memory loss, 1/76			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
			total volume covered (TVC) was 4.7 cm3			ataxia			
					Hypopituitarism	11/76			
					New visual dysfunction	3/76			
Starke et. Al 2012	Retrospective case-series	140 patients with non-functioning PA 127 (91%) patients had recurrent adenomas prior surgery. 13 (9%) had no prior surgery/RT	SRS: Leksell Gamma Unit (Elekta Instruments) model U/C Margin dose 18Gy ± 4.9 (6–25) Maximum dose in 36Gy ± 10 (15–70)	Efficacy	Tumour control	113/125 (90%) at median 50.4 months	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 13/140 (9%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. 15/140 (11%) lost to follow up
					Progression-free survival	2, 5, 8, and 10 years: 98%, 97%, 91%, and 87%, respectively			
					Time-to-progression	Median 174 months			
				Safety	New visual dysfunction	15/115 (12.8%) at median 50.4 months			
					New CNS deficit	1/115 (1.1%) at median 50.4 months			
					Hypopituitarism	37/122 (30%) at median 50.4 months			
Mignone et al. 2006	Retrospective case-series	100 patients with non-functional PA 10 had prior adjuvant CRT 8(8%) had no prior surgery/RT	SRS: Gamma surgery using the Leksell Gamma Unit, model U and model C (both Elekta Instruments, Inc., Norcross, GA) Mean marginal dose was 18.5 Gy (range 5–25 Gy) Mean maximal dose was 41.5 Gy (range 10–70 Gy).	Efficacy	Tumour shrinkage	56/82 (68%) at mean 44.9 months	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	The results for the 8 patients with nor prior treatment were excluded in this table. 10 (10%) patients were lost to follow up No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Stable tumour	19/82 (23%) at mean 44.9 months			
					Tumour growth/recurrence	5/82 (11%) at mean 44.9 months			
				Safety	New visual dysfunction	1/100 (1%) at			
					hypopituitarism	12 (19.7%) at mean 26 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Jezkova et al. 2006	Retrospective case-series	96 patients with acromegaly. (GH > 2·5µg/l and increase in IGF-I, according to sex and age) 1 had prior adjuvant CRT 24(25%) had no prior surgery/RT	SRS: Leksell Gamma Unit model B (Elekta Instrument AB, Stockholm, Sweden) Mean marginal dose 32Gy and mean maximal was 63Gy	Efficacy	Hormonal normalization	48/96 (50%) at median 66 months	6	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 24/96 (25%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. All those with hypopituitarism received a dose >15Gy Hormone normalization: GH < 1µg/l with and normal IGF-1 at median 66 months
					Tumour shrinkage	60/96 (62·3%) at median 66 months			
					Tumour stable	36/96 (37.7%) at median 66 months			
				Safety	Hypopituitarism	26/96 (27%)			
Hayashi et. al 2010	Retrospective case-series	89 patients with residual/ recurrent PA 43/89 (48%) non-functional, 46/89 (52%) functional	SRS: Leksell Gamma Knife model C (Elekta Instruments, Stockholm, Sweden) Mean marginal dose 18.2 Gy (12 to 25) to non-functional tumors,and mean marginal dose 25.2Gy (12 to 35) Optic pathway <10gy	Efficacy	Tumour control	86/89 (97%) at mean 36 months	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. No clear hormonal evaluation criteria Maximal dose given unclear No long-term adverse events reported
					Tumour shrinkage	57/89 (64%) at mean 36 months			
					Stable tumour	29/89 (33%) at mean 36 months			
					Tumour growth/recurrence	3/89 (3%) at mean 36 months			
					Hormone normalization	18/46 (39%) at mean 36 months			
					Hormonal improvement	19/46 (41%) at mean 36 months			
				Safety	Visual dysfunction	2/89 (3%) Transient, 0 long-term			
					Hypopituitarism	0/89 (0%) at mean 36 months			
Castinetti et. al 2005	Prospective Cohort study	82 patients with acromegaly	SRS: Leskell Gamma Knife Unit model B	Efficacy	Hormonal normalisation	14/82 (17%) at mean 36 months	5	Direct The majority population studied	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment
					Hormonal	19/82 (23%) at mean 36 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		GH >2µg/ml and elevated age-adjusted IGF-I. 2 had prior CRT 19 patients had no prior surgery/RT	(Elekta Instruments, Stockholm, Sweden) Marginal dose (range 12–40 Gy)		improvement			appears representative of a patient group with residual/recurrent pituitary adenoma. 19/82 (23%) was not recurrent/ residual disease	options. Patients were considered in remission if they had a mean GH level of less than 2 g/liter and a normal age-adjusted IGF-I in off-treatment period. Those who were still on somatostatin agonists were considered uncured.
				Safety	Hypopituitarism	14/82 (17%) at mean 36 months			
					New visual dysfunction	1/82 (1%) (transient) at 1 month			
Liscak et al. 2007	Retrospective case series	140 patients with non-functioning PA 21 patients had no prior surgery 15 had tumour<3mm from optic chiasm	SRS: Leskell Gamma Knife Median marginal dose of 20Gy (12-35 Gy	Efficacy	Tumour control	140/140 100% at median 60 months	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 15/140 (10%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Tumour shrinkage	125/140 (89%) at median 60 months			
					Stable tumour	15/140 (11%) at median 60 months			
				Safety	Hypopituitarism	2/140 (1%) at 60 months			
Pollock et al. 2008	Retrospective case series	62 patients with non-functioning PA	SRS: Leksell Gamma Knife (Elekta Instruments, Norcross, GA). The median tumour margin dose was 16 Gy and median maximum radiation dose was 34.5 Gy	Efficacy	Tumour shrinkage	37/62 (60%) at median 64 months	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Stable tumour	23/62 (37%) at median 64 months			
					Tumour growth/recurrence	2/62 (3%) at median 64 months			
					Progression-free survival	3 and 7 years: 95%			
				Safety	Hypopituitarism	11/41 (27%) at median 12 months			
					New visual dysfunction	0/62 at median 64 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Marek et al. 2011	Prospective and retrospective case series	85 patients with: Group 1: 45 undergoing dose <15Gy (36 functioning, 9 non-functioning) Group 2: 40 undergoing dose>15Gy (38 functioning, 2 non-functioning) 38 patients had no prior surgery/RT	SRS: Leksell Gamma Knife model B (Elekta Instrument AB, Stockholm, Sweden). <15Gy dose – mean maximum = 60Gy, mean marginal = 31Gy >15Gy dose – mean maximal = 67Gy, mean marginal = 35Gy	Efficacy	Hormone normalisation	Group 1 (at median 73 months) Acromegaly: 42.8% Prolactinoma: 50% Cushings: 80% Group 2 (at median 135 months) Acromegaly: 65.2% Prolactinoma: 37.5% Cushings: 83.3%	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 38/85 (45%) was not recurrent/ residual disease	Baseline tumour and other characteristics between the two groups unclear Difference in follow up between the two groups No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Hormonal normalization: Acromegaly: normal IGF1 according to sex and age; Prolactinoma, prolactin (PRL) <619 mIU/l in non-pregnant women, PRL <430 mIU/l in postmenopausal women and PRL <375 mIU/l in men, patients with Cushing's disease, an 0800 h plasma cortisol and 24-h free urinary cortisol in the normal range, and either suppressibility of plasma cortisol after an overnight dexamethasone (1 mg) suppression test with 0800 h cortisol level below 84 nmol/l or the restitution of circadian variability of plasma cortisol levels.
					Hypopituitarism	Group 1: 1/45 (2%) Group 2: 29/40 (73%)			
Petrovich et. al 2003	Retrospective case series	79 patients with recurrent/residual PA 56 were non-functioning and 23 were functioning 4 had adjuvant CRT, 4 had	SRS: Leksell gamma knife (Elekta Instrument AB, Stockholm, Sweden). Median marginal dose of 15Gy. 8Gy at optic chiasm	Efficacy	Tumour shrinkage 1	23/79 (29%) at median 36 months	4	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	2 patients lost to follow up Shrinkage >50% volume reduction Stable tumour included growth <50% Hormone change criteria unclear No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Stable tumour 2	52/79 (67%) at median 36 months			
					Progression-free survival	1 year: 98%; at 2 years: 96%; and at 3 years: 94%			
					Hormonal normalisation	18/23 (78%) at median 36 months			
				Safety	Hypopituitarism	2/52 (4%) at median 36 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		CRT alone			New visual dysfunction	3/78 (4%) at median 36 months			
Runge et al. 2012	Retrospective case series	61 patients with residual/recurrent disease	SRS: Linac-RS The median marginal dose was 13 Gy, minimum 10 Gy, and maximum 20 Gy.	Efficacy	Tumour control	60/61 (98.3%) at median 83 months	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	Relatively long follow up of median 83 months Minimal distance 1-2mm from optic chiasm which means some patients are outside of PICO 16 patients underwent dosage from a micro-multileaf collimator versus 45 who underwent dosage from a circular collimator No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Tumour shrinkage	24/61 (40%) at median 83 months			
					Stable tumour	36/61 (68.3%) at median 83 months			
					Tumour growth/recurrence	1/61 (1.7%) at median 83 months			
				Safety	Hypopituitarism	4/41 (9.8%) at median 54 months			
					Seizure	1/61 (1.6%) at 11 months			
Surenko k et al. 2012	Retrospective case series	57 patients with PA 19 functioning, 38 non-functioning 29 no prior surgery	SRS: Synergy linear accelerator (Elekta, UK) head-on micro-MLC (micro multileaf collimator). Median marginal dose was 13 Gy (10-16 Gy) 83-95%	Efficacy	Tumour shrinkage	25/57 (43.9%), at median 31.5 months	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 29/57 (51%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Hormone evaluation levels unclear Relatively short follow up
					Stable tumour	23/57 (40.3%) at median 31.5 months			
					Tumour growth/recurrence	9/57 (15.8%) at median 31.5 months			
					Hormonal normalisation	8/13 (61.5%) at ? months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Iwata et al. 2016	Prospective cohort study	52 patients with GH-secreting PA	SRT: The CyberKnife system (Accuray, Sunnyvale, CA, USA) All irradiation was given once a day, 3–5 days a week. The dose was either 21 Gy in 3 fractions (41 pts)or 25 Gy in 5 fractions (11pts)	Efficacy	Overall survival	The 5-year: 100 % (95 % confidence interval [CI] 100–100 %).	6	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	Study used the Cortina consensus criteria which employs a stricter criterion on hormonal normalisation (random GH\1 ng/ml or nadir GH after an oral glucose tolerance test\0.4 ng/ml and the normalization of age- and sex-adjusted IGF-1. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Progression-free survival	The 5-year: 96 % (CI 90–100 %)			
					Local recurrence	3/52 (5.7%) at median 60 months			
					Hormonal normalisation	9/52 (17%) at median 60 months			
				Safety	Hypopituitarism	1/52 (2%) at median 60 months			
					New visual dysfunction	0/52 (0%) at median 60 months			
					Distant recurrence	2/52 (4%) at median 60 months			
Castro et al. 2010	Prospective cohort study	42 patients with PA (28 functioning and 14 non-functioning) 3 patients had no prior surgery	SRS: Leksell gamma unit model B (Elekta Instruments; Atlanta, GA, USA) The median dose was 12.5 Gy (9 -15 Gy) and 20 Gy (12 -28 Gy) for non-secretory and secretory adenomas, respectively	Efficacy	Tumour control	41/42 (98%) at median 42 months	4	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 3/42 (6%) was not recurrent/ residual disease	Hormone evaluation levels unclear. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Stable tumour :enlargement/ shrinkage <20% Tumour shrinkage volume reduction > 20%. Hormonal improvement = a decline in the measured hormonal level of more than 50% from the pre-treatment hormonal levels.
					Tumour shrinkage	4/42 (10%) at median 42 months			
					Stable Tumour	37/42 (88%) at median 42 months			
					Tumour growth/recurrence	1/42 (2%) at median 42 months			
					Hormone normalisation	14/28 (50%) at median 18 months			
					Hormone improvement	8/28 (28%) at median 15 months			
					Hormone stability	5/28 (18%) at ? months			
					Hormone deterioration	1/28 (4%) at ? months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
			Median target vol 1.3 cm3	Safety	Hypopituitarism	1/42 (2%) at median 42 months			
					New visual dysfunction	0/42 (0%) at median 42 months			
Kopp et al. 2013	Retrospective case series	37 patients with residual/recurrent PA 8 functioning and 29 non-functioning	SRT: An adapted Siemens-LINAC (6 MV) and a micro-multileaf collimator with a leaf width of 3 mm Most patients received a total dose of 50.4 Gy in 1.8 Gy per fraction, 5 times/ week (28 cases).	Efficacy	Tumour control	34/37 (91.9%) at median 57 months	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	Patients were reported as being in partial remission, if there was any tumor shrinkage, as stable disease, if there was no tumor shrinkage and progression if there was any tumor growth. Hormone evaluation levels unclear. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Tumour shrinkage	12 (32.4%) at median 57 months			
					Stable tumour	22 patients (59.5%) at median 57 months			
					Tumour growth/recurrence	3/37 (8.1%) at median 57 months			
					Hormonal normalisation	3/8 (38%) at a median follow-up of 3 months			
					Hormonal improvement	1/8 (12%) at 18 months			
				Safety	New visual dysfunction	1/37 (3%) at median 57 months			
					Hypopituitarism	15/37 (41%) at median 57 months			
					Mortality	4/37 (11%) at median 36 months			
Choi et al. 2003	Retrospective case series	42 patients with functioning PA 13 had prior surgery	SRS: Gamma Knife Mean marginal dose 28.5Gy (18-40) and mean maximal dose 54.1Gy (35 to 80)	Efficacy	Tumour control	31/32 (96.9%) at mean 42.5 months	4	Direct A minority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 29/42 (69%) was	High proportion (69%) of cases were for non-recurrent/residual disease Large loss to follow up 10/42 (27%) had no radiological follow up, No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Stable tumour :enlargement/ shrinkage
					Tumour shrinkage	13/32 (40.6%) at mean 42.5 months			
					Stable tumour	18/32 (66.9%) at mean 42.5 months			
					Tumour growth/recurrence	1/32 (3.1%) at mean 42.5 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					Hormonal improvement	35/42 (83.3%) at mean 6.8 months		not recurrent/ residual disease	<20% Tumour shrinkage volume reduction > 20%. Hormonal normalisation: PRL<20ng/ml, GH <5mIU/l, daily urine-free cortisol <90mg Hormonal improvement >50% reduction as compared to pre-treatment
					Hormonal normalisation	16/42 (38.1%) at mean 21 months			
				Safety	Hypopituitarism and visual dysfunction	0/42 (0%) at mean 42.5 months			
Iwai et al. 2005	Retrospective case series	31 patients with non-functioning PA All had prior surgery 1 had prior CRT	SRS: Gamma Knife unit (Elekta Instruments, Norcross, GA 4 patients treated via staged radiosurgery Median marginal dose was 14Gy (8 to 20)	Efficacy	Tumour shrinkage	18 patients (58.1%) at mean 59.8 months	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	13/31 patients followed up at other centres increasing the risk of inconsistent evaluation. 4/32 treated with staged radiosurgery vs. one treatment in others. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Stable tumour	9/31 (29.0%) at mean 59.8 months			
					Tumour growth/recurrence	4/31 (12.9%) at mean 59.8 months			
					Progression-free survival	5-year: 93%			
				Safety	New visual dysfunction	2/31 (6.5%) at ?			
					Hypopituitarism	2/31 (6.5%) at 2 and 5 years			
					Cyst enlargement	2/31 (6.5%) at 12 and 60 months			
					Stroke	1/31 at 108 months			
Ronchi et al. 2009	Retrospective case series	35 patients with GH-secreting PH 4 had prior CRT 3 had no prior treatment	SRS: Leksell Gamma Knife (GK) Median treatment dose 40 Gy, (30–80), Median marginal dose 20 Gy, (15–35) Median irradiated	Efficacy	Hormonal normalisation	17/35 (48.5%) at median 88 months	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 3/35 (5%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Complete tumour response: total disappearance of tumour on imaging Hormonal normalisation: GH <2.5 lg/l , IGF-I normal for age and post-glucose GH nadir <1 lg/l. Patients on SA treatment were considered to be controlled when they achieved GH <2.5
					Complete tumour response	6/35 (17%) at median 114 months			
					Tumour shrinkage	26% at 3, 34% at 7 and 43% at 10 years			
				Safety	Hypopituitarism	16/32 (50%) at median 100 months			
					TIA	2/32 (4%) at 72 and 132 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
			volume was 0.99 ml (0.2–3.7)						lg/l and normal IGF-I (only the latter in patients on Pegvisomant).
Diallo et al. 2015	Retrospective case series	34 patients with GH-secreting PA 4 had no prior treatment	SRT: LINAC (Clinac—Exactrac and Novalis Tx) Dosage of 50 Gy in 27 sessions at five sessions/ week. The delivered dose was 1.85 Gy per session,	Efficacy	Hormonal control	33/34 (97%) at mean 152 months	5	Direct The majority population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 4/34 (4%) was not recurrent/ residual disease	The hormonal control: normal IGF1 adjusted for age and sex with or without any medical treatment of acromegaly Endocrine cure/Remission: normal adjusted IGF1 without any medical treatment of acromegaly for a minimum of 3 consecutive months. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Endocrine cure	13/34 (38.2 %) at mean 62 months			
					Tumour shrinkage	18/34 (53 %) at mean 152 months			
					Stable tumour	16/34 (47%) at mean 152 months			
				Safety	Hypopituitarism	13/34 (39%) a mean 72 months			
					New visual dysfunction	0/34 (0%) at mean 152 months			
Wan et al. 2009	Retrospective case series	347 patients with functioning PA 47 had prior surgery	SRS: MASEP rotary gamma knife (MASEP instruments, Inc., Shenzhen, P.R. China) Mean marginal dose 22Gy (12-35)	Efficacy	Tumour control	318/347 (91.6%) at mean 67.3 months	5	Direct A minority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 47/347 (14%) was recurrent/ residual disease	Hormonal normlaisation: ACTH-producing PA: , 24 h urine cortisol < 200 µg/dL and the plasma cortisol level <2.5 µg/dL Prolactinomas: For nonpregnant women is <500 mU/L (20 µg/L) and for men <300 mU/L (12 µg/L). Acromegaly: GH <1 ng/ml (2.5 mU/L) after glucose ingestion and a normal (IGF-1) when matched for age and gender No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Hormonal normalisation	98/347 (28.2%) at mean 67.3 months			
				Safety	Hypopituitarism	6/347 (1.7%) at mean 67.3 months			
					Persistent Headache	1/347 (<1%)			
Roug et al. 2010	Retrospective case series	34 patients with GH-producing PA.	SRT: LINAC Dose 54 Gy in 27–30	Efficacy	Endocrine cure	10/34 (29%) at median 30 months	5	Direct A minority of the population studied appears	Hormonal improvement: Nadir GH<2.6 mU/l by oral glucose tolerance test and IGF1 below 2 S.D. of gender- and age-matched normal healthy individuals.
					Hormonal control	17/34 (50%) at median 30 months			
					Tumour control	31/34 (91%) median 32 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		28/34 had prior medical treatment only	fractions during 5.5–6 weeks		Tumour shrinkage	17/34 (50%) at median 32 months		representative of a patient group with residual/recurrent pituitary adenoma. 6/34 (18%) was recurrent/ residual disease	Hormonal control: above biochemical success irrespective of medicaltherapy status. Endocrine cure: Biochemical control as defined above without adjunctive medical therapy. IGF1 and nadir GH measured every 6 months after SRT. No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Stable tumour	14/43 (45%) at median 43 months			
					Tumour growth/recurrence	3/34 (9%) at median 23 months			
Schalin-Jantti et al. 2011	Retrospective case series	30 patients with PA 10 functioning, 20 non-functioning 5 had no prior surgery	SRT: Varian Clinac 600 CD, micro-multileaf collimator (m3; BrainLAB AG) or by Novalis (BrainLAB, AG). The total dose of 45Gy given in 25 fractions	Efficacy	Tumour shrinkage	18/30 (60%) at median 63 months	5	Direct A majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 5/30 (17%) was not recurrent/ residual disease	Imaging criteria: Tumour growth (Progressive disease): tumour growth >25%, Stable disease as <25% change in tumour volume or longest diameter, Tumour shrinkage (Partial response) as tumour shrinkage >25%, Complete response as no visible tumour. Hormonal normalisation: GH- unclear, IGF-1 age-adjusted range, PI <500mU/l for women and <300mU/l for men No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Complete response	3/30 (10%) at median 63 months			
					Stable tumour	9/30 (30%) at median 63 months			
					Hormonal improvement	7/10 (70%) at ? months			
				Safety	Transient events	Headache (8), local hair loss (7), taste/smell sensation (5), tiredness (3), eye-irritation (2), visual sensation (2), nausea (2) and allergy to the fixation mask(1)			
					Hypopituitarism	12/30 (40%) at ? months			
Sun et al. 2011	Retrospective case comparison	33 patients with PA 17 functioning, 16 non-	SRT: Brainlab or SynergyS Median	Efficacy	Tumour control	SRT: 22/23 (96%) at median 36 months SRS: 9/10 (90%) at median 36 months	5	Direct A majority of the population studied appears	No randomisation, blinding or matching of patients. Hormonal cure: Normalized hormone values in the absence of medical therapy

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		functioning 23 had SRT, 10 had SRS 4 patients had no prior surgery	dosage of 50.4 Gy (45.–54.) given over a median of 28 fractions (25-30). SRS: Leksell gamma knife Median dosage 16 Gy (14–16) for non-functioning and median dosage of 23 Gy (18–25) for functioning tumours		Hormonal cure	SRT: 5/10 (50%) at median 36 months SRS: 2/7 (29%) at median 36 months		representative of a patient group with residual/recurrent pituitary adenoma. 4/33 (12%) was not recurrent/ residual disease	
				Safety	New visual dysfunction	3/33 (10%) at 6 to 21 months			
					Hypopituitarism	2/33 (6%) at 21 and 22 months			
Cho et al. 2009	Retrospective case series	26 patients with residual/ recurrent PA 9 functioning, 17 non-functioning	SRT: CyberKnife (Accuray, Calif, USA) Total dose mean 1919cGy (1400- 2400) (mean±SD : Single fraction was performed in 5 cases, three fractions were performed in 21 cases.	Efficacy	Tumour control	24/26 (92.3%)	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Imaging criteria: Complete response - Gd-enhanced area disappears, and no regrowth is recognized at least four weeks after treatment Partial response (PR) Gd-enhanced area is reduced by more than 50%, and maintains this state at least four weeks after treatment Minor response (MR) Gd-enhanced area is reduced from 25% to 50%, and maintains this state at least four weeks after treatment No change (NC) Less than 50% reduction or less than 25% growth of
					Hormonal normalisation	9 (100%) at mean 16 months			
					Hormonal improvement	4/9 (44%) at mean 16 months			
				Safety	New visual dysfunction	2/26 at 36 and 40 months			
					Hypopituitarism	0/26 at mean 30 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
									Gd-enhanced area, maintained at least four weeks after treatment Progressive disease (PD) More than 25% growth of Gd-enhanced area Hormonal criteria: Hormonal (Endocrinological): Improvement: decline in the measured hormonal level > 50% from the pre-treatment Normalisation: Serum PRL < 20 ng/mL and a serum GH <5 mIU/L.
Liu et al. 2013	Retrospective case series	22 patients with prolactinomas 1 had prior CRT 7/22 had no prior surgery	SRS: Gamma knife devices (models U, B, C, 4C, and Perfexion; Elekta Instruments) Median margin dose was 15.0 Gy (12–25).	Efficacy	Tumour control	19/22 (86.4%) at median 37.5 months	5	Direct A majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 7/22 (31.8%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. All patients had cavernous sinus involvement Tumour Shrinkage: > 20% reduction in volume. Stable tumour <20% change in volume. Tumour growth > 20% increase volume Hormone normalization: normal serum prolactin level off DA (cure) or on DA. Hormonal improvement was defined as decreased but persistently elevated serum prolactin level. Hormonal deterioration was defined as persistently elevation in the serum prolactin level.
					Tumour shrinkage	12/22 (55%) at median 15.5 months			
					Tumour growth/recurrence	3/22 (13.6%) at ? months			
					Hormonal normalisation	6/22 (27.3%) at median 36 months			
					Hormonal improvement	12/22 (54.5%) at median 36 months			
					Hormonal deterioration	4/22 (18.2%) at median 36 months			
				Safety	New visual dysfunction	3/22 (13.6%) at ? months			
					Hypopituitarism	1/22 (4.5%) at 12 months			
Tanaka et al. 2010	Retrospective case series	22 patients with prolactinomas 1 had prior	SRS: Leksell Gamma Knife (Elekta Instruments,	Efficacy	Endocrine cure	4/22 (18%) at median of 34 months	5	Direct A minority of the population studied appears	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Hormonal normalisation	10/22 (45%) at median of 34 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		CRT 13 had no prior surgery	Norcross, Georgia, USA). Median marginal dose was 25.0 Gy (16.0 –30.0) and the median maximum dose was 50 Gy (32.0–60.0). Median treatment volume 2.2 cm3		Hormonal stability	8/22 (37%) at median of 34 months		representative of a patient group with residual/recurrent pituitary adenoma. 13/22 (59%) was not recurrent/ residual disease	Visual dysfunction in a patient with MS. Cause unclear Endocrine cure was assessed off dopamine agonist therapy for at least 3 months. Hormonal normalisation was normal levels on dopamine agonist therapy or symptom improvement
					Hypopituitarism	8/21 (38%) at median 19 months			
				Safety	New visual dysfunction	1/22 (4.5%) at 3 months			
					CSF leak	1/22 (4.5%) at 26 months			
Gopalan et al. 2011	Retrospective cases series	48 patients with non-functional PA. 1 patient had no prior surgery 3 patients had previous CRT	SRS: Leksell Gamma Unit Model U (Elekta Instruments, Norcross, Georgia) Mean marginal dose was 18.4 Gy (8-25) Mean maximal dose was 41.3 Gy (15-70 Gy).	Efficacy	Tumour shrinkage	35/47 (74.5%) at median 80.5 months (TT= mean 28 months)	5	Direct A majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 1/48 (2%) was not recurrent/ residual disease	Outcomes excluded for non-surgical patient where possible Time to visual dysfunction unclear No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Stable tumour	4/47 (8.5%) at median 80.5 months			
					Tumour growth/recurrence	8/47 (17.0%) at median 80.5 months (TT = mean 62.4 months)			
					Hypopituitarism	19/48 (39.6%) at range 12-120 months			
					New visual dysfunction	6/48 (12.5%)			
Devin et al. 2004	Retrospective cases series	35 patients with Cushing's disease 6 had no prior	SRS: Clinac 4 linear accelerator (Varian, Palo	Efficacy	Endocrine cure	4/35 (11%) at median 5.5 months	5	Direct A majority of the population studied appears	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Hormonal normalisation	13/35 (37%) at median 6 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		treatment	Alto, Calif., USA) Mean dose was 14.7Gy SD 4.00) 2 patients had more than one treatment		Tumour shrinkage	4/11 (36%) at median 33.5 months		representative of a patient group with residual/recurrent pituitary adenoma. 6/35 (2%) was not recurrent/ residual disease	Endocrine cure: Requiring steroid replacement therapy at some point after SRS and had no evidence of recurrent hypercortisolism thereafter. Hormonal normalisation: normal 24-hour urinary free cortisol without any adjunctive medical management.
					Stable tumour	6/11 (55%) at median 22 months			
					Tumour growth/recurrence	1/11 (10%) at 55 months			
				Safety	Hypopituitarism	14/35 (17%) at median 23 months			
Attanasio et al. 2003	Prospective cohort study	30 patients with acromegaly 4 had prior CRT 3 had no prior treatment	SRS: Gamma Knife Unit Model B The median margin dose was 20 Gy (15–35) The median irradiated volume was 1.43 ml	Efficacy	Hormone normalisation	7/30 (23%) at mean 24 months	4	Direct A majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 3/30 (10%) was not recurrent/ residual disease	GH and IGF-1 levels defined as normalisation unclear 11/30 lost to imaging follow up No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options. Tumour shrinkage: >25% reduction in volume
					Hormone improvement	18/30 (60%) at mean 24 months			
					Tumour shrinkage	11/19 (59%) at mean 24 months			
					Stable tumour	8/19 (41%) at mean 24 months			
				Safety	Hypopituitarism	2/30 (6.6%) at 24 and 72 months			
Tinnel et al. 2008	Retrospective case series	28 patients with functioning PA 3 had prior CRT 4 had no prior treatment	SRS: Gamma Knife Unit Model B and C Marginal dose 15-30Gy Target volume 0.19 to 10ml	Efficacy	Hormonal normalisation	12/25 (48%) at mean 36.3 months	4	Direct A majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 4/28 (14%) was not recurrent/ residual disease	Endpoint measures for imaging and endocrine levels were unclear No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options.
					Hormonal improvement	6/25 (24%) at mean 36.3 months			
					Hormonal stability	8/25 (32%) at mean 36.3 months			
					Hormonal deterioration	4/25 (16%) at mean 36.3 months			
					Tumour shrinkage	6/25 (24%) at mean 36.3 months			
					Stable Tumour	18/25 (72%) at mean 36.3 months			
					Tumour progression	2/25 (8%) at mean 36.3 months			
				Safety	Hypopituitarism	6/25 (24%) at mean 36.3 months			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
					New visual dysfunction	1/25 at 18 months			
Swords et al. 2009	Retrospective case series	25 patients with PA 17 functioning and 8 non-functioning All had previous CRT 2 had no prior surgery	SRS: Gamma Knife Mean marginal dose 13.2Gy (10-20) Modal target volume 1.04ml	Efficacy	Hormonal normalisation	3/7 (43%) at mean 36.4 months	4	Direct A majority of the population studied appears representative of a patient group with residual/recurrent pituitary adenoma. 2/25 (4%) was not recurrent/ residual disease	No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options Small numbers Tumour volume assessment only complete for non-functioning PA Hormone normalisation: GH <1.8 ng/ml. Other hormonal values unclear.
					Hormonal improvement	2/7 (29%) at mean 36.4 months			
					Tumour shrinkage	2/8 (25%) at mean 44.6 months			
					Stable tumour	4/8 (50%) at mean 44.6 months			
					Tumour growth/recurrence	2/8 (25%) at mean 44.6 months			
				Safety	Hypopituitarism	3/7 (43%) at median 36 months			
					New visual dysfunction	0/25 (0%) at median 36.4 months			
Swords et al. 2003	Retrospective case series	21 patients with PA 18 functioning and 3 non-functioning All had previous CRT	SRS: Linac adapted for stereotactic delivery of radiation therapy Modal marginal dose 10Gy (8-15) 2 patients received SRT (2-3 fractions)	Efficacy	Hormonal normalisation	7/18 (39%) at median 25 months	4	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	1/21 lost to follow up Time to recurrence unclear Small numbers No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options Hormonal normalisation: GH levels <5 mU/liter, <1.7 ng/ml) – other unclear
					Hormonal improvement	3/18 (17%) at median 25 months			
					Tumour shrinkage	3/20 (15%) at median 20.1 months			
					Stable tumour	16/20(80%) at median 33 months			
					Tumour growth/recurrence	1/20 (5%)			
				Safety	Hypopituitarism and visual dysfunction	0/21 at median 25 months			
Roberts et al. 2007	Retrospective case series	9 patients with GH-secreting PA 0 had prior	SRS: The Cyberknife Robotic Radiosurgical	Efficacy	Endocrine cure	4/9 (44%) at mean 25 months (TT = mean 12 months)	4	Direct The population studied appears representative of a	Previous treatment unclear Tumour response unclear Small numbers No comparator group, and therefore no
					Hormonal control	1/9 (11%) at mean 25 months (TT = mean 12 months)			

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		CRT 1/9 had no prior surgery	System (Accuray, Sunnyvale, CA, USA) Mean marginal dose of 20Gy (18-24) in 1-3 sessions		Tumour control	9/9 (100%) at mean 25.4 months		patient group with residual/recurrent pituitary adenoma.	randomisation or blinding. No evidence of efficacy compared to other treatment options Endocrine cure: normal serum IGF-1 level, using a gender and age-standardized normal range without concomitant use of medical therapy for at least 12 weeks. Hormonal control: Normal serum IGF-1 was attained only when medical therapy was added.
					Hypopituitarism	3/9 (33%) at mean 25.4 months			
					New visual dysfunction	0/9 (0%) at mean 25.4 months			
Pouratian et al. 2006	Retrospective case series	28 patients with prolactinoma All had prior treatment 4 had prior CRT 4 had no prior surgery	SRS: Leskell Gamm Knife Functioning adenomas: Mean maximum and marginal dose used was 42.2 (10–62.5) Gy and 18.6 (0.3–25) Gy, respectively. For non-functioning: Mean maximum and marginal dose used was 43.1 (10–62.5) Gy and 18.9 (0.3–25) Gy, respectively.	Efficacy	Endocrine cure	6/23 (26%) at mean 58 months (TT= mean 24.5 months)	4	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	Some patients treated for tumour <2mm from optic chiasm Small numbers No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options Endocrine cure: PI< 20 ng/ml and off a dopamine agonist. Imaging-criteria: Tumor shrinkage: >20% decrease in tumor volume; Stable tumour: volume between 20% less and 20% Tumor growth: >20% growth in tumor volume.
					Tumour shrinkage	13/28 (46%) at mean 52 months			
					Stable tumour	12/28 (43%) at mean 52 months			
					Tumour growth/recurrence	3/28 (11%) at mean 52 months			
				Safety	Hypopituitarism	8/28 (29%) at mean 52 months (TT = mean 44 months)			
					New visual dysfunction	2/28 (7.1%) at mean 52 months			
Hoybye et al.	Retrospective case	23 patients with non-	SRS: Gamma knife	Efficacy	Tumour control	23/23 (100%) at median 78 months	4	Direct The population	Tumour evaluation criteria unclear

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
2009	series	functioning PA All had prior surgery	Median maximum dose was 50 Gy (40–57.1) and median marginal dose 20 Gy (17.6–24.8)		Tumour shrinkage	18/23 (78%) at median 78 months		studied appears representative of a patient group with residual/recurrent pituitary adenoma.	Small numbers No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options
					Stable tumour	4/23 (12%) at median 78 months			
					Recurrence	1/23 at 60 months (outside field)			
				Safety	Transient adverse events	1/23 headache, 1/23 CN III paresis			
					Mortality	2/23 at 7 and 12 years			
Kopp et al. 2012	Retrospective case series	16 patients with non-functioning PA All had prior surgery	SRT The applied mean dose was 49.4 Gy (45.0–50.4 Gy) in 25 fractions	Efficacy	Tumour shrinkage	16/16 (100%) at median 63 months – mean 51%	4	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	Small numbers No comparator group, and therefore no randomisation or blinding. No evidence of efficacy compared to other treatment options
Cifarelli et al. 2012	Retrospective case series	217 patients with recurrent PA 131 functioning and 86 non-functioning	SRS: Leskell Gamma Knife Mean maximal dose was 44.6 Gy (10–70). Mean marginal dose was 19.9 Gy (1–30).	Safety	New visual dysfunction	9/217 (4%) at median 34 months (TT = range 6hrs to 34 months)	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma.	Only 110/217 were followed up by 36 months – 49% were lost to follow up by then No comparator group, and therefore no randomisation or blinding. Adverse events not compared to other treatment options
Elson et al. 2014	Retrospective comparative case series	33 patients with PA All had previous surgery 11 had CRT, 10 had IMRT,	CRT: Linac IMRT: Tomotherapy SRS: Leskell Gamma Knife Mean	Safety	Hypopituitarism	CRT: 15 new deficits IMRT: 4 new deficits SRS: 1 new deficit At median 24 months follow up	4	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	No randomisation, blinding or matching of patients between comparison groups. Small numbers

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
		12 had SRS	prescribed dose: CRT: 50.4Gy IMRT50.7Gy SRS: 15.8Gy						
Yang et al. 2014	Qualitative study	60 patients with PA following SRS	Cross sectional survey QoL: World Health Organization Quality of Life instrument short-form	Safety	Symptoms	Memory loss (31, 51.6%), Fatigue (28, 46.7%), Blurred vision (23, 38.4%), Headache (20, 33.3%), Sleep problems (19, 31.7%), and Altered libido (19, 31.7%)	5	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma	Patients were at a minimum 3 months post-SRS 25 of the original sample refused to take part No comparator group, and therefore no randomisation or blinding. Adverse events not compared to other treatment options
					Quality of Life	The lowest scoring items among the QOL domains were positive feelings (3.0360.74, psychological domain), followed by sexual activity (3.0760.78, social relationships domain), and vitality and fatigue (3.1360.79, physical health domain), indicating a moderate deterioration in QOL.			
Leavitt et al. 2013	Retrospective case series	222 patients with benign tumours adjacent to optic apparatus	SRS Median marginal dose was 18 Gy (12-30 Gy). Maximum dose 8.0 Gy (n=126), 8.1-10.0 Gy (n=39), 10.1-12.0 Gy (n=47), and >12 Gy (n=10)	Safety	New visual dysfunction	1/222 (0.5%) at mean 83 months Risk was 10% for dose>12Gy	4	Direct An unknown number of PA within the larger tumour group	Actual distances to optic chiasm unknown Relative number of tumour types unknown

Study reference	Study Design	Population characteristics	Intervention	Outcome measure type	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Rahman et al. 2014	Retrospective cohort study	2369 patients with cancer. Of these 39 were for pituitary adenomas	SRS	Safety	New malignancy	Observed rate 4.4% vs. expected 5.2% rate at median 43.2 months	6	Direct Only a minority of patients had pituitary adenoma 39/2369 (1.6%)	Relatively short follow-up Different cancers and doses given limit ability to apply results to pituitary adenoma
Yang et al. 2014	Qualitative - cross-sectional survey	60 patients who have undergone SRS for pituitary adenoma	SRS – CyberKnife	Safety	Symptoms	Number of symptoms 5.95 +/-5.05 Most common symptoms: Memory loss 51.6% Fatigue 46.7% Blurred vision 38.4% Headaches 33.3% Sleep problem 31.7% Altered libido 31.7%	6	Direct The population studied appears representative of a patient group with residual/recurrent pituitary adenoma. Number of patients receiving SRS as primary treatment unknown.	25 patients of those initially approached refused to participate. No significant difference between those who refused and those who participated. Symptom distress questionnaire not formally validated. Symptom distress: Questionnaire on 25 common symptoms observed in patients with pituitary tumours, patients evaluated the presence and levels of distress on the basis of their subjective perception. Symptom prevalence was calculated on the basis of whether the patient currently exhibited a certain symptom. Levels of symptom distress were evaluated using a 5-point Likert scale (distress levels 0, none; 1, mild; 2, moderate; 3, severe; and 4, extreme). QoL: This study used the WHOQOL-BREF Taiwan version comprising 28 items including overall QOL (one item), general health (one item), and the 4 domains regarding physical health (7 items), psychological (6 items), social relationships (4 items), and environmental factors (9 items). Questionnaire items use a 5-point Likert scale ranging from 1 to 5, with higher scores indicating better QOL
					Quality of life	Overall quality of life 3.4+/- 0.77 General health 2.8+/-1.05 Physical health 14.1+/-2.64 Psychological 13.5+/-2.61 Social relationships 13.8+/-2.14 Environmental factors 14.7+/-1.79			

8. Grade of evidence table

Outcome Measure	Reference	Quality of Evidence Score)	Applicability	Grade of Evidence	Interpretation of Evidence
Tumour control (TC)	Sheehan et al. 2013	6	Direct	B	Tumour control (TC) is a composite of all patients without any disease progression following SRS/SRT. This includes complete response, tumour shrinkage and stable tumour. **Non-functioning tumours** This was reported as 93.4% at median 36 months in the largest case series[3] and 95% at 93 months in the series with the longest follow up[40]. TC ranged from 75 to 100% in 29 studies reporting this outcome [3,6,7,10-14,17-21,23-28,32-38,40,41,43,46] **GH-secreting tumours** This was reported as 96.9% at mean 54 months in the largest case series[41] and 100% at 152 months in the series with the longest follow up[4]. TC ranged from 88 to 100% in 27 studies reporting this outcome[4-6,8,11,15-17,19,20,25,28-31,33,35-39,41-42,44,46-48]. **ACTH-secreting tumours** This was reported as 88% at mean 58 months in the largest case series[41]. TC ranged from 33 to 100% in 19 studies reporting this outcome[6,8-9,11,17,19,20,25,28,35-39,41-42,45,46,48]. **PRL-secreting tumours** This was reported as 100% at mean 81.9 months in the largest case series[41]. TC ranged from 86 to 100% in 14 studies reporting this outcome[6,8,11,17,19,20,22,27-28,33,41-42,46,48]. **Nelson's tumours** One study[41] reported on tumour response in Nelson's tumour. It found a tumour control rate of 100% **LH/FSH tumours** One study[46] reported on tumour response. It found a tumour control rate of 100% These results should be interpreted with caution; None of these trials were randomised. See appendix for response definitions.
	Van den Burgh 2007	6	Direct		
	Voges et al. 2006	6	Direct		
	Iwata et al. 2011	6	Direct		
	Park et al. 2011	5	Direct		
	Puataweepong et al. 2015	5	Direct		
	Leenstra et al. 2010	5	Direct		
	Wilson et al. 2012	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Wilson et al. 2014	5	Direct		
	Starke et al. 2012	5	Direct		
	Mignone et al. 2006	5	Direct		
	Jezkova et al. 2006	5	Direct		
	Hayashi et. al 2010	5	Direct		
	Runge et al. 2012	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Petrovich et. al 2003	5	Direct		
	Liscak et al. 2007	5	Direct		
	Pollock et al. 2008	5	Direct		
	Castro et al. 2010	5	Direct		
	Kopp et al. 2013	5	Direct		
	Choi et al. 2003	5	Direct		
	Iwai et al. 2005	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Diallo et al. 2015	5	Direct		
	Wan et al. 2009	5	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Sun et al. 2011	5	Direct		
	Cho et al. 2009	5	Direct		
	Liu et al. 2013	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Devin et al. 2004	5	Direct		
	Attanasio et al. 2003	4	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Tinnel et al. 2008	4	Direct		
	Swords et al. 2009	4	Direct		
	Swords et al. 2003	4	Direct		
	Roberts et al. 2007	4	Direct		
	Pouratian et al. 2006	4	Direct		
	Hoybye et al. 2009	4	Direct		
	Wilson et al. 2013	4	Direct		
	Kong et al. 2007	4	Direct		
	Kopp et al. 2012	4	Direct		
Complete response (CtR)	Voges et al. 2006	6	Direct	B	Complete tumour response was defined as the total disappearance of tumour on imaging **Non-functioning tumours** It was reported to be 0% in the largest case series[41] and ranged from 0 to 1% in all 15 reporting studies[10,12-14,18,21,23,24,26,33,35,37-38,41,46] **GH-secreting tumours** It was reported to be 3% in the largest study[41] at mean 54 months and 29% in the study with the longest follow up[4] (152 months). It ranged from 0% to 29% in all 5 studies[4,33,37,41,46]. **ACTH-secreting tumours** It was reported to be 18% in the largest study[41] at mean 58 months and 0% in the other reporting study[46]. **PRL-secreting tumours** It was reported to be 62% in the largest study[41] at mean 56 months and ranged from 0 to 62% in all 6 reporting studies[8,22,27,33,41,46,48]. **Nelson's tumours** One study[41] reported a complete response in 44%, **LH/FSH secreting tumours** One study[46] reported a complete response in 50%. These results should be interpreted with caution; None of these trials were randomised.
	Iwata et al. 2011	6	Direct		
	Diallo et al. 2015	5	Direct		
	Liu et al. 2013	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Sun et al. 2011	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Iwai et al. 2005	5	Direct		
	Mignione et al. 2006	5	Direct		
	Pollock et al. 2008	5	Direct		
	Hoybye et al. 2009	5	Direct		
	Park et al . 2011	5	Direct		
	Pouratian et al. 2006	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Liscak et al. 2007	5	Direct		
	Castinetti et al. 2009	6	Direct		
	Choi et al. 2003	5	Direct		
	Swords et al. 2003	4	Direct		
	Swords et al. 2009	4	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Kopp et al. 2012	5	Direct		
Partial response (PR)	Voges et al. 2006	6	Direct	B	Tumour shrinkage represents any sustained volume reduction in tumour **Non-functioning tumours** It was reported as 59% in the largest reporting case series[41] and ranged from 11% to 80% in the 13 studies[10,12-13,21,23-24,26,33,37,38,41,43,46] **GH-secreting tumours** It was reported to be 20% in the largest study[41] at mean 54 months and 24% in the study with the longest follow up[4] (152 months). It ranged from 15% to 70% in all 9 studies[4,5,8,16,33,37,41,44,46]. **ACTH-secreting tumours** It was reported to be 12% in the largest study41 at mean 58 months. It ranged from 12% to 50% in all 5 studies[8-9,41,45-46]. **PRL-secreting tumours** It was reported to be 39% in the largest study[41] at mean 56 months. It ranged from 25% to 57% in all 7 studies[8,22,27,33,41,46,48]. **Nelson's tumours** One study[41] reported a complete response in 44%, **LH/FSH secreting tumours** One study[46] reported a complete response in 0%. These results should be interpreted with caution; None of these trials were randomised.
	Iwata et al. 2011	6	Direct		
	Wilson et al. 2012	5	Direct		
	Wilson et al. 2014	5	Direct		
	Park et al. 2011	5	Direct		
	Leenstra et al. 2010	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Mignone et al. 2006	5	Direct		
	Jezkova et al. 2006	5	Direct		
	Hayashi et. al 2010	5	Direct		
	Liscak et al. 2007	5	Direct		
	Pollock et al. 2008	5	Direct		
	Petrovich et. al 2003	5	Direct		
	Runge et al. 2012	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Castro et al. 2010	5	Direct		
	Kopp et al. 2013	5	Direct		
	Choi et al. 2003	5	Direct		
	Iwai et al. 2005	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Diallo et al. 2015	5	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Liu et al. 2013	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Devin et al. 2004	5	Direct		
	Wilson et al. 2013	4	Direct		
	Attanasio et al. 2003	4	Direct		
	Tinnel et al. 2008	4	Direct		
	Swords et al. 2009	4	Direct		
	Swords et al. 2003	4	Direct		
	Pouratian et al. 2006	4	Direct		
	Hoybye et al. 2009	4	Direct		
	Kopp et al. 2012	4	Direct		
Stable Disease	Voges et al. 2006	6	Direct	B	Stable tumour indicates no growth or reduction in tumour volume on

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
(SD)	Iwata et al. 2011	6	Direct		imaging **Non-functioning tumours** It was reported in 41% in the largest reporting case series[41]. 16 studies reported partial response in 8-100% of patients[10,12-14,18,21,23-24,26,32-33,37-38,41,43,46] **GH-secreting tumours** It was reported to be 74% in the largest study[41] at mean 54 months and 47% in the study with the longest follow up[4] (152 months). It ranged from 30% to 85% in all 7 studies[4,5,33,37,41,44,46] **ACTH-secreting tumours** It was reported to be 59% in the largest study[41] at mean 58 months. It ranged from 44% to 59% in all 4 studies[9,41,45,46]. **PRL-secreting tumours** It was reported to be 0% in the largest study[41] at mean 56 months. It ranged from 0% to 75% in all 7 studies[8,22,27,33,41,46,48]. **Nelson's tumours** One study[41] reported a complete response in 11%, **LH/FSH secreting tumours** One study[46] reported a complete response in 50%. These results should be interpreted with caution; None of these trials were randomised.
	Wilson et al. 2012	5	Direct		
	Wilson et al. 2014	5	Direct		
	Park et al. 2011	5	Direct		
	Leenstra et al. 2010	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Mignone et al. 2006	5	Direct		
	Jezkova et al. 2006	5	Direct		
	Hayashi et. al 2010	5	Direct		
	Liscak et al. 2007	5	Direct		
	Pollock et al. 2008	5	Direct		
	Petrovich et. al 2003	5	Direct		
	Runge et al. 2012	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Castro et al. 2010	5	Direct		
	Kopp et al. 2013	5	Direct		
	Choi et al. 2003	4	Direct		
	Iwai et al. 2005	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Diallo et al. 2015	5	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Liu et al. 2013	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Devin et al. 2004	5	Direct		
	Wilson et al. 2013	4	Direct		
	Attanasio et al. 2003	4	Direct		
	Tinnel et al. 2008	4	Direct		
	Swords et al. 2009	4	Direct		
	Swords et al. 2003	4	Direct		
	Pouratian et al. 2006	4	Direct		
	Hoybye et al. 2009	4	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Kopp et al. 2012	4	Direct		
Tumour growth/recurrence (TG)	Voges et al. 2006	6	Direct	B	Tumour growth/recurrence indicates an increase in volume on imaging or recurrence **Non-functioning tumours** It was reported by 27 studies [3,6,7,10-14,17-21,23-28,32-38,40,41,43,46] and ranged between 0 and 25%. The largest study[3] reported a rate of 6.6%. **GH-secreting tumours** It was reported to be 3% in the largest study[41] at mean 54 months and 0% in the study with the longest follow up[4] (152 months). It ranged from 0% to 10% in all 18 studies[4-6,8,11,1516,19,20,28-30,33,3741-42,44,46] **ACTH-secreting tumours** It was reported to be 12% in the largest study[41] at mean 58 months. It ranged from 0% to 67% in all 12 studies[6,8,9,11,17,19,20,28,41-42,45,46] **PRL-secreting tumours** It was reported to be 0% in the largest study[41] at mean 56 months. It ranged from 0% to 14% in all 14 studies [6,8,17,19,20,22,27,28,33,41,42,46,48,]. **Nelson's tumours** One study[41] reported a complete response in 0%, **LH/FSH secreting tumours** One study[46] reported a complete response in 0%. These results should be interpreted with caution; None of these trials were randomised.
	Van den Burgh 2007	6	Direct		
	Iwata et al. 2011	6	Direct		
	Wilson et al. 2012	5	Direct		
	Wilson et al. 2014	5	Direct		
	Park et al. 2011	5	Direct		
	Leenstra et al. 2010	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Mignone et al. 2006	5	Direct		
	Jezkova et al. 2006	5	Direct		
	Hayashi et. al 2010	5	Direct		
	Liscak et al. 2007	5	Direct		
	Pollock et al. 2008	5	Direct		
	Petrovich et. al 2003	5	Direct		
	Runge et al. 2012	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Castro et al. 2010	5	Direct		
	Kopp et al. 2013	5	Direct		
	Choi et al. 2003	4	Direct		
	Iwai et al. 2005	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Diallo et al. 2015	5	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Liu et al. 2013	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Devin et al. 2004	5	Direct		
	Wilson et al. 2013	4	Direct		
	Attanasio et al. 2003	4	Direct		
	Tinnel et al. 2008	4	Direct		
	Swords et al. 2009	4	Direct		
	Swords et al. 2003	4	Direct		
	Pouratian et al. 2006	4	Direct		
	Hoybye et al. 2009	4	Direct		
	Kopp et al. 2012	4	Direct		
Progression-free	Sheehan et al. 2013	6	Direct	B	Progression-free survival is the proportion of patients alive and free of

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
survival (PFS)	Wilson et al. 2012	6	Direct		disease at a certain time point. In the studies on non-functioning tumours reviewed the 5 and 10 year time point were most commonly used. This was 95% and 85% at 5 and 10 years following SRS respectively in the largest case series[3]. PFS in all 6 studies ranged from 93% to 100% to at 5 years and 85% to 88% at 10 years[3,24,26,28,34,43]. These results should be interpreted with caution; None of these trials were randomised.
	Iwata et al. 2016	6	Direct		
	Puataweepong et al. 2015	5	Direct		
	Iwai et al. 2005	5	Direct		
	Pollock et al. 2008	5	Direct		
	Petrovich et al. 2003	4	Direct		
	Wilson et al. 2013	4	Direct		
	Kong et al. 2007	4	Direct		
	Gopalan et al. 2011	5	Direct		
Endocrine cure (EC)	Kopp et al. 2013	4	Direct	B	Endocrine cure is defined as normal levels of hormone **without** the need for medication. **GH-secreting tumours** This was reported as 33% in the largest study at mean 54 months[41], EC in all 23 studies ranged from 0% to 47%[4-6,11,15,1719,25,28-31,33,35-39,41,46-48]. **ACTH-secreting tumours** This was reported as 78% in the largest study[41] at mean 54 months follow up, EC in all 14 reporting studies ranged from 0% to 100%[6,9,11,17,25,28,35-39,41,46,48]. **PRL-secreting tumours** This was reported as 17% in the largest study[41] at mean 54 months follow up, EC in all 17 reporting studies ranged from 0% to 100%[6,11,17,19,22,25,28,33,35-39,41,46,48,49]. **Nelson's tumours** One study[41] reported a endocrine cure of 0%, **LH/FSH secreting tumours** One study[46] reported a endocrine cure of 0%. These results should be interpreted with caution; None of these trials were randomised.
	Diallo et al. 2015	5	Direct		
	Liu et al. 2013	5	Direct		
	Puataweepong et al. 2015	5	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Sun et al. 2011	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Tanaka et al. 2010	5	Direct		
	Wilson et al. 2013	4	Direct		
	Zeiler et al. 2013	6	Direct		
	Kong et al. 2007	4	Direct		
	Petrovich et al. 2003	5	Direct		
	Voges et al. 2006	6	Direct		
	Castro et al. 2010	5	Direct		
	Roberts et al. 2007	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Swords et al. 2003	4	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Swords et al. 2009	4	Direct		
	Tinnel et al . 2008	4	Direct		
	Anastasio et al. 2003	4	Direct		
	Castinetti et al. 2005	5	Direct		
	Castinetti et al. 2009	6			
	Devin et al. 2004	5	Direct		
	Hayashi et al. 2012	5	Direct		
Hormonal normalisation	Voges et al. 2006	6	Direct	B	Hormonal normalisation is defined as normal levels of hormone **with** the need for medication. **GH-secreting tumours** This was reported 16.8% in the largest study[41] and ranged from 0% to 59% in 24 studies[4-6,8,11,15,16,19,25,28-31,33,35-39,41,42,44,46,47] **ACTH-secreting tumours** This was reported 22% in the largest study[41] at mean 54 months and ranged from 0% to 67% in all 16 reporting studies[6,8,9,11,25,28,35-39,41,42,45,46]. **PRL-secreting tumours** This was reported 26% in the largest study[41] at mean 54 months and ranged from 0% to 83% in all 17 reporting studies[6,8,11,19,22,25,27,28,33,36-39,41,42,46,49]. **Nelson's tumours** This was 17 and 50% in 2 studies[38,41] **LH/FSH secreting tumours** One study[46] reported a normalisation rate of 0%. These results should be interpreted with caution; None of these trials were randomised.
	Castinetti et al. 2009	6	Direct		
	Diallo et al. 2015	5	Direct		
	Liu et al. 2013	5	Direct		
	Puataweepong et al. 2015	5	Direct		
	Roug et al. 2010	5	Direct		
	Sun et al. 2011	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Tanaka et al. 2010	5	Direct		
	Wilson et al. 2012	5	Direct		
	Wilson et al. 2013	4	Direct		
	Wilson et al. 2014	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Cho et al. 2009	5	Direct		
	Castro et al. 2010	5	Direct		
	Pouratian et al. 2006	5	Direct		
	Roberts et al. 2007	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Swords et al. 2009	4	Direct		
	Tinnel et al . 2008	4	Direct		
	Wan et al. 2009	5	Direct		
	Anastasio et al. 2003	4	Direct		
	Castinetti et al. 2005	5	Direct		
	Choi et al. 2003	5	Direct		
	Hayashi et al. 2012	5	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Jezkova et al. 2006	5	Direct		
Hormonal improvement (HI)	Iwata et al. 2016	5	Direct	B	Hormonal improvement refers to an improvement in hormonal levels but that remain above normal levels. This was reported 16.8% in the largest study[41] and ranged from 0% to 59% in 24 studies[4-6,8,11,15,19,25,28-31,33,35-39,41,42,44,46,47] **GH-secreting tumours** HI was 15% in largest study[46] at median 35 months and ranged from 0% to 80% in 18 studies[4,6,8,11,15,19,25,28-31,33,3536-39,44,46]. **ACTH-secreting tumours** HI was 50% in largest study[46] at median 35 months and ranged from 0% to 100% in 15 studies[6,8,9,11,17,25,28,35-39,41,45,46]. **PRL-secreting tumours** HI was 29% in largest study[46] at median 35 months and ranged from 0% to 100% in all 14 reporting studies[6,8,11,19,22,25,28,36-39,46,49]. **Nelson's tumours** One study[46] reported an improvement rate of 0%. **LH/FSH secreting tumours** One study[46] reported an improvement rate of 0%. These results should be interpreted with caution; None of these trials were randomised.
	Kopp et al. 2013	4	Direct		
	Diallo et al. 2015	4	Direct		
	Liu et al. 2013	5	Direct		
	Puataweepong et al. 2015	4	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Sun et al. 2011	5	Direct		
	Surenkok et al. 2012	5	Direct		
	Tanaka et al. 2010	5	Direct		
	Wilson et al. 2013	4	Direct		
	Wilson et al. 2014	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Kong et al. 2007	4	Direct		
	Cho et al. 2009	5	Direct		
	Petrovich et al. 2003	5	Direct		
	Voges et al. 2006	6	Direct		
	Castro et al. 2010	5	Direct		
	Roberts et al. 2007	5	Direct		
	Ronchi et al. 2009	5	Direct		
	Swords et al. 2003	4	Direct		
	Swords et al. 2009	4	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Tinnel et al . 2008	4	Direct		
	Choi et al. 2003	5	Direct		
	Devin et al. 2004	4	Direct		
	Hayashi et al. 2012	5	Direct		
Hormonal deterioration (HD)	Iwata et al. 2016	5		B	Hormonal deterioration refers to an increase in hormonal levels after treatment **GH-secreting tumours** HD was 0% in largest study[45] and ranged from 0% to 17% in 18 studies[4-6,11,15,19,25,28-31,33,35,36,38,39,44,46]. **ACTH-secreting tumours** HD was 0% in largest study[45] and ranged from 0% to 33% in 15 studies[6,9,11,17,19,25,28,35-39,42,45,46]. **PRL-secreting tumours** HD was 14% in largest study[46] at mean 35 months and ranged from 0% to18% in all 14 reporting [studies6,11,19,25,28,33,36-39,42,46,49.] **Nelson's tumours** One study[46] reported an deterioration rate of 0%. **LH/FSH secreting tumours** One study[46] reported an deterioration rate of 0%. These results should be interpreted with caution; None of these trials were randomised.
	Kopp et al. 2013	4			
	Diallo et al. 2015	5			
	Liu et al. 2013	5			
	Puataweepong et al. 2015	4			
	Roug et al. 2010	5			
	Schalin-Jantti et al. 2011	5			
	Sun et al. 2011	5			
	Surenkok et al. 2012	5			
	Tanaka et al. 2010	5			
	Wilson et al. 2013	4			
	Wilson et al. 2014	5			
	Zeiler et al. 2013	6			
	Kong et al. 2007	4			
	Petrovich et al. 2003	5			
	Castro et al. 2010	5			
	Roberts et al. 2007	5			
	Ronchi et al. 2009	5			
	Swords et al. 2003	4			

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Swords et al. 2009	4			
	Tinnel et al . 2008	4			
	Wan et al. 2009	5			
	Anastasio et al. 2003	4			
	Devin et al. 2004	4			
	Hayashi et al. 2012	5			
Hypopituitarism	Sheehan et al. 2013	6	Direct	B	Hypopituitarism refers to a deficiency in endocrine function from the pituitary gland following treatment in this context. In **non-functioning** adenomas this was 21% in the largest study[3] at median 36 months and ranged from 0 to 39% in all 24 reporting studies[3,7,10-14,17-21,23-26,32,34-37,40,43,46]. For **functioning** adenomas the largest study[46] reported a 13% rate at median 35 months and ranged from 0 to 38% in 14 studies[4,15,19-20,22,28,31,33,35,36,44-46,49]. These results should be interpreted with caution; None of these trials were randomised.
	Voges et al. 2006	6	Direct		
	Iwai et al. 2005	6	Direct		
	Van Den Burgh et al. 2007	6	Direct		
	Elson et al. 2014	5	Direct		
	Iwata et al. 2011	6	Direct		
	Leenstra et al. 2010	5	Direct		
	Roug et al. 2010	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Sheehan et al. 2014	5	Direct		
	Tanaka et al. 2010	5	Direct		
	Wilson et al. 2012	5	Direct		
	Wilson et al. 2013	4	Direct		
	Wilson et al. 2014	5	Direct		
	Petrovich et al. 2003	5	Direct		
	Liscak et al. 2007	5	Direct		
	Pollock et al. 2008	5	Direct		
	Mingione et al. 2006	5	Direct		
	Castro et al. 2010	5	Direct		
	Park et al. 2011	5	Direct		
	Pouratian et al. 2006	5	Direct		
	Roberts et al. 2007	5	Direct		
	Ronchi et al. 2009	5	Direct		

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
	Runge et al. 2012	5	Direct		
	Starke et al. 2012	5	Direct		
	Swords et al. 2009	4	Direct		
	Attanasio et al. 2003	4	Direct		
	Castinetti et al. 2005	5	Direct		
	Devin et al. 2004	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Jezkova et al. 2006	5	Direct		
	Marek et al. 2011	5	Direct		
New visual dysfunction (VD)	Sheehan et al. 2013	6	Direct	B	New visual dysfunction refers to any new or deterioration in visual acuity or fields after treatment For **non-functioning** adenomas this was reported as 6.6% in the largest study[3] and ranged from 0% to 21% in all 25 studies[3,6,10-14,17,20,21,23-26,28,32-38,40,43,46]. For **functioning** adenomas this was reported as 2.6% in the largest study[46] and ranged from 0% to 9% in all 25 studies[4-6,8,9,11,15-17,20,22,25,27-31,33,35-39,42,44-47,49] These results should be interpreted with caution; None of these trials were randomised.
	Voges et al. 2006	6	Direct		
	Iwata et al. 2011	6	Direct		
	Wilson et al. 2012	5	Direct		
	Park et al. 2011	5	Direct		
	Puataweepong et al. 2015	5	Direct		
	Zeiler et al. 2013	6	Direct		
	Starke et. Al 2012	5	Direct		
	Mignone et al. 2006	5	Direct		
	Hayashi et. al 2010	5	Direct		
	Petrovich et. al 2003	5	Direct		
	Kopp et al. 2013	5	Direct		
	Iwai et al. 2005	5	Direct		
	Schalin-Jantti et al. 2011	5	Direct		
	Sun et al. 2011	5	Direct		
	Cho et al. 2009	5	Direct		
	Liu et al. 2013	5	Direct		
	Tanaka et al. 2010	5	Direct		
	Gopalan et al. 2011	5	Direct		
	Tinnel et al. 2008	4	Direct		
	Pouratian et al. 2006	4	Direct		
	Cifarelli et al. 2012	5	Direct		
	Leavitt et al. 2013	4	Direct		
New malignancy	Rahman et al. 2014	5	Indirect	C	New malignancy is defined as new cancer being diagnosed unrelated to the primary tumour

Outcome Measure	Reference	Quality of Evidence	Applicability	Grade of	Interpretation of Evidence
					One large cohort study[53] on SRS for benign intracranial tumours found the observed rate of new malignancy was 4.4% vs. expected 5.2% rate at median 43.2 months These results should be interpreted with caution; None of these trials were randomised.
Stroke	Ronchi et al. 2009	6	Direct	C	Stroke refers to any cerebrovascular incident after treatment 2 studies reported incidence of stroke at 1% and 5.7% at mean 103 and 108 months respectively[29,13] These results should be interpreted with caution; None of these trials were randomised.
	Iwai et al. 2005	6			
Quality of Life	Yang et al. 2014	6	Direct	C	Quality of life outcomes looked at physical and psychological aspects of health as well as social relationships and environmental factors. The single study[54] found that The most common symptoms reported by patients after SRS were memory loss, fatigue, blurred vision, headache, sleep problems, and altered libido. The highest and lowest scores for QOL were in the environmental and psychological domains, respectively There was no control group to compare to

9. Fact Sheet

Intervention Fact Sheet	
What is the intervention	Stereotactic radiosurgery (SRS) and Stereotactic Radiotherapy (SRT) refer to targeted radiation treatment that is designed to minimise harmful side effects to normal body tissue surrounding a tumour
What is the intervention for?	Treating patients with pituitary tumour that has returned or not responded to previous therapy
Who might consider taking it?	Patients with pituitary tumour that has returned or not responded to previous therapy
Who should not take it?	Patients for whom SRS/SRT is contraindicated or deemed unsuitable
Benefits **What difference did the intervention make?** • What was the effect on the size of the tumour? • What was the effect on abnormal hormone secretion **Harms** **Did the intervention have side effects?** • Were there life-threatening side effects? • Were there any other serious side-effects?	• SRS/SRT stopped tumour growth or reduced tumour size in 75 to 100% of study participants in 43 studies reviewed. • SRS/SRT reduced abnormal hormonal secretion in 45.7% of study participants in the largest study[13] (range of 0 to 100% in all 31 studies reviewed). • 93 to 100% of study participants did not have any growth in tumour, recurrence or increased abnormal hormone levels at 5 years in 8 studies reviewed. • 85 to 88% of study participants did not have any growth in tumour, recurrence or increased abnormal hormone levels at 10 years in 8 studies reviewed. • In the largest study[3] 21% of participants developed new hormonal deficits that required replacement therapy after SRS/SRT treatment (range of 0 to 38% in 34 studies reviewed). • 6.6% of study participants developed new visual problems in the largest study[3] after SRS/SRT treatment (range of 0 to 21% in 32 studies reviewed).

10. Literature Search Terms

Search strategy *Indicate all terms to be used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	• *Adults with pituitary tumours with residual tumour remaining after surgery that is sufficiently far from the optic apparatus and brainstem to allow organ at risk preservation doses to be achieved.* • *Adults with pituitary tumours with recurrent tumour growing after surgery that is sufficiently far from the optic apparatus and brainstem to allow organ at risk preservation doses to be achieved.*
I – Intervention Which intervention, treatment or approach should be used?	• Stereotactic radiosurgery (treatment given as a single dose) • Stereotactic radiotherapy (hypofractionated treatment of no more than 5 fractions)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Surgery • Fractionated radiotherapy • Drugs for the treatment of excessive prolactin secretion • Drugs for the treatment of excessive growth hormone (GH) secretion • Drugs for the treatment of excessive adrenocorticotrophic hormone (ACTH , Cushing's disease) treatment.
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*<u>Critical to decision-making:</u>* • *Control of symptoms caused by pressure or hormone secretion* • *Adverse events including optic neuropathy, secondary malignancy and stroke* • *Patient experience* • *Recurrence of tumour* • *Progression free survival (non functioning adenoma)* • *Reduction in medication requirements* • *Normalisation/improvement in hormone levels* • *Development of hypopituitarism* • *Radiological control of tumour* • *Neurological deficit* *<u>Important to decision-making:</u>* *Cost effectiveness*
Assumptions / limits applied to search	
Inclusion Criteria	English, Year 2000 onwards Case series, case reports, cohort studies, randomised controlled trial, comparator studies, systematic reviews, meta-analyses
Exclusion Criteria	Studies older than 10 years

11. Search Strategy

CINAHL

1. CINAHL; exp *PITUITARY NEOPLASMS/ OR exp *ACTH-SECRETING PITUITARY ADENOMA/ OR exp
*GROWTH HORMONE-SECRETING PITUITARY ADENOMA/ OR exp *ADENOMA, PITUITARY/; 356 results.
2. CINAHL; (pituitary ADJ (tumo?r* OR cancer OR adenoma*)).ti,ab; 171 results.
3. CINAHL; exp *PROLACTINOMA/; 52 results.
4. CINAHL; prolactinoma.ti,ab; 56 results.
5. CINAHL; exp *RADIOSURGERY/ OR exp *STEREOTAXIC TECHNIQUES/; 713 results.
6. CINAHL; (stereotactic ADJ (radiosurgery OR treatment*)).ti,ab; 229 results.
7. CINAHL; "stereotactic radiotherapy".ti,ab; 101 results.
8. CINAHL; (SRS OR SRT).ti,ab; 843 results.
9. CINAHL; ("pituitary irradiation" AND .).ti,ab; 0 results.
10. CINAHL; 1 OR 2 OR 3 OR 4; 446 results.
11. CINAHL; 5 OR 6 OR 7 OR 8; 1630 results.
12. CINAHL; 10 AND 11; 6 results.
13. CINAHL; 9 AND 11; 0 results.
14. CINAHL; 12 [Limit to: Publication Year 2010-2016]; 4 results.

Cochrane

ID	Search	Hits
#1	MeSH descriptor: [ACTH-Secreting Pituitary Adenoma] explode all trees	11
#2	MeSH descriptor: [Prolactinoma] explode all trees	40
#3	prolactinoma.tw	0
#4	(pituitary ADJ (tumo?r* or cancer or adenoma*)) .tw	63
#5	MeSH descriptor: [Radiosurgery] explode all trees	250
#6	MeSH descriptor: [Stereotaxic Techniques] explode all trees	406
#7	(stereotactic ADJ (radiosurgery or treatment*)) .tw	10
#8	"stereotactic radiotherapy" .tw	7
#9	(SRS or SRT) .tw	37
#10	"pituitary irradiation" .tw	0
#11	#1 or #2 or #3 or #4	113
#12	#5 or #6 or #7 or #8 or #9	451
#13	#11 and #12	0

EMBASE

Database: Embase <1974 to 2016 August 01> Search Strategy:

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1 hypophysis/ or exp *hypophysis adenoma/ or exp *adenomatoid tumour/ (55184)
2 (pituitary adj (tumo?r* or cancer or adenoma*)).tw. (19079)
3 exp *prolactinoma/ (2890)
4 prolactinoma.tw. (2216)
5 exp *stereotactic radiosurgery/ or exp *stereotactic treatment/ (2297)

6 (stereotactic adj (radiosurgery or treatment*)).tw. (6348)
7 "stereotactic radiotherapy".tw. (2751)
8 (SRS or SRT).tw. (12916)
9 "pituitary irradiation".tw. (341)
10 1 or 2 or 3 or 4 (68430)
11 5 or 6 or 7 or 8 (19226)
12 10 and 11 (398)
13 9 and 11 (10)
14 limit 12 to yr="2010 -Current" (191)
15 limit 13 to yr="2010 -Current" (2)

Medline

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1 exp *acth-secreting pituitary adenoma/ or exp *adenomatoid tumour/ or exp *prolactinoma/ (2348)
2 (pituitary adj (tumo?r* or cancer or adenoma*)).tw. (15850)
3 prolactinoma.tw. (1766)
4 exp *Radiosurgery/ or exp *Stereotaxic Techniques/ (16053)
5 (stereotactic adj (radiosurgery or treatment*)).tw. (4473)
6 "stereotactic radiotherapy".tw. (1775)
7 (SRS or SRT).tw. (8958)
8 "pituitary irradiation".tw. (296)
9 1 or 2 or 3 (17891)
10 4 or 5 or 6 or 7 (25530)
11 9 and 10 (498)
12 8 and 10 (14)
13 limit 11 to yr="2010 -Current" (176)
14 limit 12 to yr="2010 -Current" (1)

NHS Evidence Search: stereotactic and pituitary (drugs and technologies) =129 results

TRIP: "pituitary "~10 (stereotactic or) from:2010 to:2016 =110 results

Notes

A test search was originally undertaken using EMBASE to gauge the sensitivity of the terms and the numbers. The free text search terms in the search strategies were subsequently revised slightly. The TRIP search yielded no guidelines, so the overall results were downloaded. The CINAHL search yielded some results, but when the duplicates were removed these turned out to be duplicates of the citations in the other databases. Most of citations from the NHS Evidence search related to patient information and are unlikely to be relevant. The Cochrane search yielded no results when the condition and intervention terms were combined.

12. Evidence selection

- Total number of publications reviewed: 185
- Total number of publications considered relevant: 139
- Total number of publications selected for inclusion in this briefing: 52

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14. Appendix

There are no international consensus criteria on measuring outcomes for pituitary adenoma. Below is the general definitions used by most studies in the review. More detailed criteria will be found in section 7.

Outcome	Definition
Complete tumour response (CtR)	The total disappearance of tumour identified on imaging
Partial tumour response (PtR)	The sustained reduction of tumour volume identified on imaging
Stable Tumour (ST)	No identified change in tumour volume identified on imaging
Tumour growth/recurrence (TG)	An increase in tumour volume identified on imaging or a return of a previously absent tumour
Progression-free survival (PFS)	The proportion of patients alive and free of disease at a certain time point.
Hormonal normalization (HN)	Hormone levels reduced to normal reference levels but remain on anti-secretory medication.
Endocrine cure (EC)	Hormone levels reduced to normal reference levels without the need for any anti-secretory medication.
Hormonal improvement (HI)	Hormonal levels closer to normal reference levels, but remaining above normal limits.
Hormonal deterioration (HD)	Hormone levels further away normal reference levels.
Hypopituitarism	New deficit or deterioration in pituitary function
New visual dysfunction	New deficit or deterioration in visual function