CPAG Summary Report for Clinical Panel – 1603: Stereotactic radiosurgery/radiotherapy for functioning and non-functioning pituitary adenomas

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured.	
2.	Progression free survival (PFS)	B	Progression-free survival is the proportion of patients alive and free of disease at a certain time point. The studies on non-functioning tumours measured progression-free survival and the 5 and 10 year time points were most commonly used. This was 95% and 85% at 5 and 10 years following SRS respectively in the largest case series (Sheehan et al 2013) (n=512). These results should be interpreted with caution. This study did not have a comparator group and was not randomised. Sheehan et al enrolled patients from many different centres so the type of equipment used to deliver the SRS was different and the accuracy of the follow up data collected relied on the referring physician. 42/512 patients in this study could not be assessed for a response. 50% of patients had follow up of less than 3 years which may not have been sufficient time to assess both the long term treatment effects and side effects. The main drawback of this study design (case series) is that it is difficult to fully attribute the outcomes to the treatment as there is a lack of control over other factors that could influence the outcomes being measured.

3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review
12	Tumour control (TC)	B	Tumour control (TC) is a combined measure 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 (Sheehan et al 2013). **GH-secreting tumours** This was reported as 96.9% at mean 54 months in the largest case series (Voges et al 2006) (n=142). **ACTH-secreting tumours** This was reported as 88% at mean 58 months in the largest case series (Voges et al 2006). **PRL-secreting tumours** This was reported as 100% at mean

			81.9 months in the largest case series (Voges et al 2006). **Nelson's tumours (ACTH secreting tumours which develop following the removal of both adrenal glands for the treatment of Cushing's disease)** One study (Voges et al 2006) reported on tumour response in Nelson's tumour. It found a tumour control rate of 100%. **LH/FSH tumours** One study (Zeiler et al 2013) (n=86) reported on tumour response. It found a tumour control rate of 100%. These results should be interpreted with caution. Voges et al and Zeiler et al did these not have a comparator group or were randomised. The case series vary in size, baseline characteristics of the patients selected and dosage of SRS/SRT administered to patients. In the Zeiler et al study 10/86 (12%) of patients were lost to follow up and the follow up period was relatively short. This may not have allowed enough time for both treatment effects and/or side effects to be monitored. The main drawback of the study design is that it is difficult to fully attribute the outcomes to the treatment as there is a lack of control over other factors that could influence the outcomes being measured. For critical appraisal of Sheehan et al (2013) see Section 2.
13	Tumour re-growth/recurrence	B	Tumour re-growth/recurrence indicates an increase in size on imaging or reappearance of disease.

			Non-functioning tumours The largest study (Sheehan et al 2013) reported a rate of 6.6%. **GH-secreting tumours** It was reported to be 3% in the largest study (Voges et al 2006) at mean 54 months. **ACTH-secreting tumours** It was reported to be 12% in the largest study (Voges et al 2006) at mean 58 months. **PRL-secreting tumours** It was reported to be 0% in the largest study (Voges et al 2006) at mean 56 months. For critical appraisal of Sheehan et al (2013) see Section 2. For critical appraisal of Voges et al (2006) see Section 12.
14	Endocrine cure	B	Endocrine cure (EC) is defined as normal levels of hormone without the need for medication. **GH-secreting tumours** This was reported as 67% in the largest study at mean 54 months (Lee et al 2014). **ACTH-secreting tumours** This was reported as 78% in the largest study (Voges et al 2006) at mean 54 months follow up. **PRL-secreting tumours** This was reported as 17% in the largest study (Voges et al 2006) at mean 54 months follow up. **Nelson's tumours** One study reported on this measure for this group (Voges et al 2006). They reported an endocrine cure of 0%.

			LH/FSH secreting tumours One study (Zeiler et al 2013) reported an endocrine cure of 0%. These results should be interpreted with caution. The main drawback of the study design (Lee et al 2014) is that it is difficult to fully attribute the outcomes to the treatment as there is a lack of control over other factors that could influence the outcomes being measured. For critical appraisal of Voges et al (2006) see Section 12. For critical appraisal of Zeiler et al (2013) see Section 12
15	Hormonal normalisation	B	Hormonal normalisation is defined as normal levels of hormone however the patient still needs medication. **GH-secreting tumours** This was reported as 16.8% in the largest study (Voges et al 2006). **ACTH-secreting tumours** This was reported as 22% in the largest study (Voges et al 2006) at mean 54 months. **PRL-secreting tumours** This was reported as 26% in the largest study (Voges et al 2006) at mean 54 months. **Nelson's tumours** This was 50% in the Voges et al (2006) study. **LH/FSH secreting tumours** One study (Zeiler et al 2013) reported a normalisation rate of 0%. For critical appraisal of Voges et al (2006) see Section 12. For critical appraisal of Zeiler et al (2013) see Section 12
16	Hormonal	B	HI is an improvement in hormone

	improvement (HI)		levels but they remain higher than normal. This was reported as 16.8% in the largest study (Voges et al 2006). **GH-secreting tumours** HI was 15% in the largest study (Zeiler et al 2013) at median 35 months. **ACTH-secreting tumours** HI was 50% in the largest study (Zeiler et al 2013) at median 35 months. **PRL-secreting tumours** HI was 29% in the largest study (Zeiler et al 2013) at median 35 months. . **Nelson's tumours** One study (Zeiler et al 2013) reported on this outcome in this group and reported an improvement rate of 0%. **LH/FSH secreting tumours** One study (Zeiler et al 2013) reported on this outcome in this group and reported an improvement rate of 0%. For critical appraisal of Voges et al (2006) see Section 12. For critical appraisal of Zeiler et al (2013) see Section 12
17	Hormonal deterioration	B	Hormonal deterioration refers to an increase in hormonal levels after treatment **GH-secreting tumours** HD was 0% in the largest study (Wilson et al 2013) (n=121). **ACTH-secreting tumours** HD was 0% in the largest study (Wilson et al 2013).

			PRL-secreting tumours HD was 14% in the largest study (Zeiler et al 2013) at mean 35 months. **Nelson's tumours** One study (Zeiler et al 2013) reported a deterioration rate of 0%. **LH/FSH secreting tumours** One study (Zeiler et al 2013) reported a deterioration rate of 0%. These results should be interpreted with caution Wilson et al did have a comparator group but there was no randomisation, blinding or matching of patients between the comparison groups. There were differences in baseline characteristics between the groups and the follow up period. In the Wilson et al study 20 patients were not assessable for a response. For critical appraisal of Zeiler et al (2013) see Section 12
18	Hypopituitarism	B	Hypopituitarism is defined as a deficiency in the hormone regulation function of the pituitary gland. In this case it is a side effect of the SRS/SRT treatment. In non-functioning adenomas this was 21% in the largest study (Sheehan et al 2013) at median 36 months. For functioning adenomas the largest study (Zeiler et al 2013) reported a 13% rate at median 35 months. For critical appraisal of Sheehan et al (2013) see Section 2. For critical appraisal of Zeiler et

			al (2013) see Section 12
19	New visual dysfunction	B	New visual dysfunction refers to any newly occurring deterioration in existing visual acuity or fields after treatment For non-functioning adenomas this was reported as 6.6% in the largest study (Sheehan et al 2013). For functioning adenomas this was reported as 2.6% in the largest study (Zeiler et al 2013). For critical appraisal of Sheehan et al (2013) see Section 2. For critical appraisal of Zeiler et al (2013) see Section 12
20	New malignancy	C	New malignancy is defined as new cancer being diagnosed unrelated to the primary tumour One large cohort study (Rahman et al 2014) 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. Follow up for this study was relatively short so may not have been adequate to assess all adverse events. Only 39 of the total patient cohort (n=2369) had pituitary adenomas and patients received different doses of SRS. Results were presented for the whole study cohort.

21	Stroke	C	Stroke refers to any cerebrovascular incident after treatment Two studies reported incidence of stroke at 1% and 5.7% at mean 103 (Roberts et al 2007) and 108 months respectively (Iwai et al 2005). Both study designs were retrospective case series with no comparator group. In the Roberts et al study there were small numbers of patients (n=9) limiting applicability of the findings. Only 1/9 patients had prior surgery. In the Iwai et al study 13/31 patients were followed up at referring centres increasing the possibility of inconsistency in the evaluation.
22	Quality of life	C	Quality of life investigates the physical, social, environmental and psychological impact of treatment. The single study (Yang et al 2014) (n=60) 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 with. 25% of the original sample did not take part in the follow up.