STEREOTACTIC RADIOSURGERY/ STEROTACTIC RADIOTHERAPY FOR HAEMANGIOBLASTOMA

QUESTIONS TO BE ADDRESSED:

1. What is the evidence for the clinical effectiveness of stereotactic radiosurgery/ stereotactic radiotherapy for haemangioblastoma compared to other treatment modalities?

2. What is the evidence for the cost-effectiveness of stereotactic radiosurgery/ stereotactic radiotherapy for haemangioblastoma compared to other treatment modalities?

SUMMARY:

Background

- Haemangioblastomas are rare benign tumours of the central nervous system that develop from blood vessel cells.
- They tend to occur in middle age and approximately a quarter of cases are associated with von Hippel-Lindau (VHL) disease involving multiple lesions.
- The main treatment is surgery. However, vascularity, critical location or multiple small lesions can make complete resection impossible.
- In these cases and for recurrent tumours, radiotherapy can be used including newer methods such as stereotactic radiosurgery and stereotactic radiotherapy
- Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are methods of delivering a strong and highly focused dose of radiation.
- The precise nature of SRS/T means that there is less risk of causing damage to surrounding healthy tissue and therefore are associated with fewer side effects than standard external beam radiotherapy.

Clinical Effectiveness

- There is limited evidence surrounding the effectiveness of SRS/T for patients with residual, recurrent or progressive haemangioblastoma after previous surgery.
- No RCTs were found looking at the effectiveness of SRS/T for haemangioblastoma compared to no treatment or other treatment modalities.
- One large retrospective case series was found of 186 patients with haemangioblastoma treated with SRS and four small case series, ranging in size from 21 to 35 patients.
- In the largest case series, the survival rate after SRS was 94%, 90% and 74% at 3, 5 and 10 years, respectively and the local tumour control rate was 92%, 89% and 79% at 3, 5 and 10 years, respectively.
- It is not possible to determine the comparative clinical effectiveness of SRS/T for haemangioblastomas based on case series.

Cost Effectiveness

- No studies were found assessing the cost effectiveness of SRS/T for haemangioblastomas.

Safety

- Few adverse radiation effects were reported across the series, although there was one death due to refractory peritumoral oedema.

1 Context

1.1 Introduction

Haemangioblastomas are rare benign tumours of the central nervous system that develop from blood vessel cells. The majority of cases (around 75%) are sporadic and involve a single lesion in the cerebellum, brainstem, or upper cervical spinal cord which very rarely spreads. Approximately a quarter of cases are associated with von Hippel-Lindau (VHL) disease (an autosomal dominant genetic syndrome) and these tend to involve multiple lesions. The tumours can be solid or cystic. Symptoms are predominantly as a result of increased intracranial pressure and include headaches, vomiting, balance and coordination problems, visual disturbances, confusion and back and neck pain.[1, 2]

Surgical resection is usually the main treatment. However, vascularity, critical location or multiple small lesions can sometimes make complete resection impossible. In these cases and for recurrent tumours, radiotherapy can be used, including newer methods such as radiosurgery and stereotactic radiotherapy.[3]

1.2 Existing national policies and guidance

We found no national policies and guidance on the treatment of haemangioblastomas.

2 Epidemiology

Haemangioblastomas are rare, accounting for around 2% of all brain tumours. This would roughly equate to around 190 new cases of haemangioblastoma per year in the UK.[4] Haemangioblastomas most often occur in the posterior fossa (a small space in the skull which contains the brainstem and cerebellum) and the second most common location is the spinal cord. Haemangioblastomas usually develop in middle age and rarely in children. Patients with haemangioblastomas tend to have a high survival rate if total resection is possible. Local recurrences after complete tumour resection seem to be more frequent in patients with von Hippel-Lindau (VHL) disease, in patients diagnosed at a young age, and in patients with multiple haemangioblastomas. The recurrence rate varies in different surgical series but is generally less than 25%.[5]

3 The intervention

Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are methods of delivering a strong and highly focused dose of radiation. In SRS, treatment is delivered as a single dose. In SRT, it is delivered as a hypofractionated treatment, of not more than five fractions. The precise nature of SRS/T means that there is less risk of causing damage to any healthy tissue surrounding the target area for treatment. For this reason, there are fewer side effects associated with SRS/T compared to standard external beam radiotherapy. Generally SRS/T are used for smaller lesions (ideally less than 3cm). They tend to be used for tumours such as secondary brain tumours, recurrent gliomas, small low grade brain tumours, vestibular schwannomas, meningiomas, pituitary adenomas and chordomas. SRS/T can be delivered using standard linear accelerators or using specially designed devices such as Gamma Knife or Cyberknife. Long-term side effects of SRS/T are rare. Around one in ten patients develop radiation necrosis (small area of dead cells in the treated area). Most people who develop necrosis have no symptoms, but

occasionally symptoms from swelling can occur, which may require steroids or in extreme cases surgery to remove the dead cells. Deep sedation or general anaesthesia are usually required for people (such as young children) who won't tolerate head mask fixation after a training period.[6]

4 Findings

A literature search was performed on the 6th of November 2015 for haemangioblastomas and stereotactic radiosurgery or radiotherapy. The search was run on Medline, Embase, Cochrane Library, TRIP and NICE Evidence Search, and was limited to English language results from 2000 onwards.

The search strategy used is detailed in section 7, and a detailed summary of the studies included in this review can be found in Table 1. Studies were included that specifically looked at patients with residual, recurrent or progressive haemangioblastoma after previous surgery. Case series with a sample size of fewer than 20 relevant patients, case reports, conference papers, letters and commentary were excluded.

No RCTs were found looking at the effectiveness of SRS/T for haemangioblastomas compared to no treatment or other treatment modalities.

One large retrospective case series was found (Kano et al 2015) looking at the clinical effectiveness or safety of SRS/T in haemangioblastomas, which included 186 patients, 156 of whom had had prior surgery.[7] In addition, four other case series were found, which ranged in size from 21 to 35 patients.[3, 8-10] Case series that reported earlier results for patients included in the Kano et al 2015 case series were excluded.

No studies evaluating the cost effectiveness of SRS/T for haemangioblastomas were found.

4.1 Evidence of effectiveness

Kano et al 2015[7]

This was the largest case series found, which included 186 patients (517 tumours) with intracranial haemangioblastomas treated with SRS, between 1990 and 2010, in six centres in the USA and Japan. Eighty patients had 335 haemangioblastomas associated with VHL (98 of which were recurrent or residual tumours) and 106 patients had 182 sporadic haemangioblastomas (162 of which were recurrent or residual tumours). The majority of patients (84%) had had prior surgery: 70 VHL patients (single surgery in 32 patients and multiple surgeries in 38) and 86 patients with sporadic haemangioblastoma (single surgery in 53 patients and multiple surgeries in 33). The median target volume was 0.2 cm^3 in patients with VHL and 0.7 cm^3 in patients with sporadic haemangioblastomas. The median margin dose was 18 Gy in patients with VHL and 15 Gy in patients with sporadic haemangioblastomas. Patients were followed-up by MRI at intervals of 3–6 months after SRS. The majority of the results were not reported separately for those patients with residual, recurrent or progressive tumours after prior surgery.

The median follow-up after SRS was 5 years (range 0.5–18). For the entire series, overall survival after SRS was 94% at 3 years, 90% at 5 years, and 74% at 10 years. In a multivariate analysis, factors associated with longer patient survival after SRS included the absence of neurological deficits (p = 0.02, HR 15.11, 95% CI 1.46–157.0) and fewer tumours (p = 0.02, HR = 0.21, 95% CI 0.06–0.79). No statistically significant difference was observed in survival between

patients with VHL-associated haemangioblastomas and those with sporadic haemangioblastomas (p = 0.28).

The overall local tumour control rate (defined as tumour volume regression or prevention of additional tumour growth) was 92% at 3 years, 89% at 5 years, and 79% at 10 years. For VHL patients only, the local tumour control rate after SRS was 99%, 95%, 93% and 82% at 1, 3, 5 and 10 years, respectively, and for sporadic haemangioblastomas patients it was lower at 94%, 87%, 81% and 75%, respectively.

Overall, the rate of developing a new tumour or recurrence of residual tumour was 5% at 1 year, 18% at 3 years, 33% at 5 years, and 54% at 10 years. The rate was much higher for VHL patients than for sporadic patients, with VHL patients having a rate of new tumour development of 7%, 21%, 43% and 84% at 1, 3, 5 and 10 years, respectively, and sporadic patients having a rate of developing a recurrence of residual tumour of 4%, 16%, 24% and 29% at 1, 3, 5 and 10 years, respectively.

In the entire series, for those patients that underwent SRS for recurrent tumours, the 5-year local tumour control rate was 86% and, for those with residual tumours it was 87%. In VHL patients with further new tumours, the 5-year local control rate was 90% and in sporadic haemangioblastoma patients with recurrence it was also 90%. No statistically significant difference was observed in local tumour control rate in patients who underwent SRS for residual, recurrent, or new tumours (VHL) or recurrences of residual tumour from the original tumour (sporadic) (p = 0.558).

Around 20% of patients (38/186 patients) required additional treatment (SRS, resection or cyst aspiration) for tumour progression and a further 20% (37/186 patients) for new tumours or recurrence.

The large sample size of this case series means that its results are less likely to be subject to selection bias and chance compared to the smaller case series found and therefore are more likely to be applicable to the wider haemangioblastoma population. However, as with all case series, it does not have a control arm so it is not possible to compare results to no treatment or alternative treatments. Furthermore, the retrospective nature of the series means that results are based on case notes which can be incomplete and may introduce reporting bias, as those with worse outcomes are likely to have more detailed notes. For these reasons, it is not possible to reliably assess the comparative effectiveness of SRS for haemangioblastoma based on this study.

Smaller case series[3, 8-10]

An additional four smaller, retrospective, case series were identified which ranged in size from 21 to 35 patients with haemangioblastoma treated with SRS at a median/mean dose of 16-21 Gy and median/mean follow-up period ranging from 4 to 8 years. Two studies were conducted in the USA, one in China and one in Japan, and they included patients treated with SRS in the 1990s and 2000s. The majority of patients had had prior surgery (range across series = 84-96%) and hence were likely to be having SRS treatment for recurrent or residual tumours, or further new tumour in the case of VHL patients. Across the four case series, the 3-year tumour control rates ranged from 82% to 92% and the 5-year tumour control rates ranged from 71% to 92%.

Again, these studies are subject to selection bias and reporting bias inherent in case series, and no comparisons can be made to alternative treatments or no treatment due to the lack of a control arm.

Table 1: Clinical effectiveness of SRS/ SRT for haemangioblastoma

Study	Patients	Intervention	Results and Comments
Kano et al 2015[7] Retrospective case series North America & Japan	n=186 (517 tumours) Inc/ex criteria: Patents with haemangioblastoma who were treated with SRS between 1990 and 2010 at participating centres of the North American Gamma Knife Consortium and Japanese Gamma Knife centres Baseline characteristics: Median age = 47 years (range =14-89) Male = 94/186 (51%) Sporadic haemangioblastoma (HB) = 106/186 (57%) VHL HB = 80/186 (43%) Single prior surgery = 85/186 (46%) Multiple prior surgery = 71/186 (38%) Residual tumours = 83/517 (16%) Recurrent tumours = 177/517 (34%) Median target volume = 0.24cm^3 (0.01-39.5)	Radiosurgery Median margin dose = 16 Gy (range = 8-31.4) Median maximum dose = 30 Gy (range = 6-60)	Median follow-up = 5 years (range = 0.5-18) Overall survival rate: At 3 years = 94% (Sporadic = 91%; VHL = 97%) At 5 Years = 90% (Sporadic = 88%; VHL = 82%) At 10 years = 74% (Sporadic = 71%; VHL = 77%) No significant difference in survival between patients with VHL-associated haemangioblastomas and those with sporadic haemangioblastomas found (p = 0.28) Rate of developing a new tumour or recurrence of residual tumour from the original tumour after SRS: At 1 year = 5% (Sporadic = 4%; VHL = 7%) At 3 years = 18% (Sporadic = 16%; VHL = 21%) At 5 years = 33% (Sporadic = 24%; VHL = 43%) At 10 years = 54% (Sporadic = 29%; VHL = 84%) Local tumour control rate: At 1 year = not reported (Sporadic = 94%; VHL = 99%) At 3 years = 92% (Sporadic = 87%; VHL = 95%) At 5 years = 89% (Sporadic = 81%; VHL = 93%) At 10 years = 79% (Sporadic = 75%; VHL = 82%) 5 year local tumour control rate: For recurrent tumours = 86% For residual tumours = 87% No difference in local tumour control rate in patients who underwent SRS for residual, recurrent, or new tumours (VHL) or recurrences of residual tumour from the original tumour (sporadic) (p = 0.558) Additional treatment: For sporadic haemangioblastomas: 23 patients (22%) required additional treatment (SRS for 4 patients, resection for 14 patients and cyst aspiration for 5 patients) for treated tumour. 13 patients (12%) required additional treatment (SRS for 10 patients, resection for 2 patients and cyst aspiration for 1 patient) for progression recurrences of residual tumour from the original tumour.

			For VHL-associated haemangioblastomas: Fifteen patients (19%) required additional treatment (SRS for 2 patients, resection for 8 patients and cyst aspiration for 5 patients) for treated tumour. 24 patients (30%) required additional treatment (SRS for 13 patients, resection for 10 patients and cyst aspiration for 1 patient) for progression recurrences of new tumours. Toxicity Adverse radiation events (ARE) = 13/186 (7%) ARE managed successfully with steroids = 10/186 patients (5%) One patient required ventriculoperitoneal shunt due to hydrocephalus 14 months after SRS One patient underwent cyst drainage 6 months after SRS One patient with refractory peritumoral oedema died one month after SRS.
Hanakita et al 2014[8] Retrospective case series Japan	n=21 (57 tumours) Inc/ex criteria: Patients with intracranial haemangioblastomas treated with SRS between January 1991 and June 2010 at the University of Tokyo Hospital (not a centre contributing patients to Kano et al 2015) Baseline characteristics: Median age = 41 years (range = 19–84) Male = 11 patients (52%) VHL HB = 14 patients (67%) Sporadic HB = 7 patients (33%) Prior surgery = 20 patients (95%) Median individual tumour volume = 0.13 cm^3 (range = 0.004–9.5)	Radiosurgery using gamma knife surgery Median marginal dose Gy = 18 (range = 14–20) Median max dose Gy = 40 (range = 28–45)	Median follow-up = 96 months (range = 3–235) Local tumour control rate: At 3 years: = 92%, At 5 years = 92% At 10 years = 80% Additional treatment: 10 tumours in 7 patients showed tumour progression (3 sporadic lesions in 3 patients and 7 VHL-related lesions in 4 patients). Of these: 7 tumours in 5 patients received surgical resection 2 tumours in 2 patients underwent additional SRS 1 tumour in 1 patient was treated by hypofractionated radiotherapy with Cyberknife Toxicity: Radiation-induced adverse events were observed in 3 patients (1 sporadic and 2 VHL). • One patient with VHL showed peritumoral oedema and transient worsening of balance sense with dizziness at 4 months after the second SRS. Symptoms improved within 1 year of treatment. • One patient with sporadic haemangioblastoma showed intratumoral haemorrhage on the radiographic image 24 months after SRS, but patient did not show any neurological deterioration during follow-up.

			• One patient with VHL revealed transient hydrocephalus due to stenosis of the fourth ventricle outlets caused by cerebellar oedema with peritumoral enhancement at 7 months after the second SRS. Symptoms improved within 8 months of treatment.
Moss et al 2009[3] Retrospective case series USA	n=31 (92 tumours) Inc/ex criteria: Patients with haemangioblastoma who were treated with radiosurgery at Stanford University Medical Centre between 1991 and 2006 (not a centre contributing patients to Kano et al 2015) Baseline characteristics: Mean age = 41 years (range = 18–81) Males = 20 patients (65%) VHL HB = 26 patients (84%) Prior surgery (mean = 2.9 resections) = 26 patients (84%) No. of lesions presenting with radiographic evidence of tumour progression = 39 (42%) Spinal tumours = 16 (17%) Mean no. of tumours = 2.8 (range = 1–10) Mean tumour volume = 1.8 cm^3 (range = 0.058–65.4)	Frame-based linear accelerator radiosurgery or cyberknife image-guided radiosurgery Median dose = 21 Gy (range = 12–40)	Median follow-up = 69 months (range = 5–164) Local tumour control rate: At 3 years = 85% At 5 years = 82% For spinal lesions only: At 3 years = 92% At 5 years = 92% Of the 41 tumours presenting with pain and/or neurological deficits, symptoms attributed to 36 lesions (88%) improved or resolved after radiosurgery. Toxicity: • 5 patients (11 tumours) developed radiation necrosis (as determined by postradiosurgery positron emission tomographic imaging) • 3 patients (4 tumours) had radiographic evidence of • necrosis discovered on serial imaging studies, but were asymptomatic. • 2 patients (7 tumours) experienced symptoms of numbness in a dermatomal distribution, extremity weakness, and new-onset headaches.
Wang et al 2005[9] Retrospective case series China	n= 35 (93 tumours) Inc/ex criteria: Patients with haemangioblastoma who were treated with radiosurgery between 1993 and 2001 at Huashan Hospital and Shanghai Gamma Knife Hospital	Radiosurgery using gamma knife surgery (GKS) Mean prescription dose placed at the target	Mean follow-up = 66 months (range = 24–114) Tumour control rate: At 1 year = 94% At 2 years = 85% At 3 years = 82% At 4 years = 79% At 5 years = 71%

	Baseline characteristics: Mean age = 36 years (range 16–61) Males = 28 patients (80%) Recurrent tumours = 18 patients (51%) Residual tumours = 11 patients (31%) Mean prior no. of operations per patient = 2.4 (1-5) Solitary tumours = 17 patients (49%) Multiple tumours = 18 patients (51%) Mean maximum tumour diameter = 13 mm (range = 5–55)	margin = 17.2 Gy (range 12–24) Mean maximum radiation dose = 35.6 Gy (range 20–50)	Additional treatment: 8 patients underwent open surgery because of tumour-associated cyst enlargement (4 patients) or the development of new tumours (4 patients) after GKS. 5 patients required a second GKS due to the development of new tumours after initial GKS. Toxicity: Not reported
Jahawar et al 2000[10] Retrospective case series USA	n= 27 patients (29 tumours) Inc/ex criteria: Patients with haemangioblastoma who were treated with radiosurgery at the University of Pittsburgh and the Mayo Clinic over an 11 year period (no dates specified, may include some patients included in Kano et al 2015). Baseline characteristics: Mean patient age = 32 years (range = 14-75) VHL HBL = 14 patients (52%) Sporadic HBL = 13 patients (48%) Prior surgery = 26 patients (96%) Median number of previous resections = 2 (range = 1-6) Prior external beam radiation therapy = 2 patients (7%) Mean tumour volume = 2.2 ml	Radiosurgery using the the 201 source cobalt-60 Leksell Gamma-knife Mean dose delivered to the tumour margin = 16.1 Gy (11.7-20) Mean maximum dose = 32.5 Gy (range = 26-40)	Mean follow-up = 4 years (range = 0.5-9) Survival outcomes: Median survival = 6.5 years Actuarial 5 year survival rate = 75:1% (+/-11:5%) Tumour control: Actuarial rate of freedom from progression: At 2 years = 84.5% (+/-7:1%) At 5 years = 75.2% (+/-8.9%) 5/7 (71%) tumours that ultimately failed to be controlled by radiosurgery were recurrent tumours after prior resection. Additional treatment: 3 patients (12%) underwent reoperation at a median of 10 months following radiosurgery. 2 patients had drainage of tumour-associated cysts six and twelve months after radiosurgery. 1 patient had placement of a ventriculo-peritoneal shunt for progressive hydrocephalus.

	(range = 0.36-27)		Toxicity: Resolved within 24 hours of treatment: Headaches n=2 Nausea and vomiting n=1 No delayed complications identified.

4.2 Trials in progress

A search of clinicaltrials.gov on the 10th of January 2016 showed no current, ongoing trials for SRS/T for haemangioblastomas.

4.3 Evidence of cost-effectiveness

No studies were found assessing the cost-effectiveness of SRS/T for haemangioblastomas.

4.4 Safety

No studies were found specifically looking at safety of SRS/T for haemangioblastomas. Instead toxicity findings from the studies included in this review have been used. Toxicity results are also summarised in Table 1 for each included study.

Table 2 summarises adverse events associated with SRS/ SRT in the five included studies.

Table 2: Adverse events associated with SRS/ SRT

Study	Safety results
Kano et al 2015[7]	Thirteen patients (7%) developed adverse radiation effects after SRS, including one patient who died due to refractory peritumoral oedema. The majority of patients (10 patients) were managed successfully with oral steroids. One patient required placement of a ventriculoperitoneal shunt due to hydrocephalus 14 months after SRS and one patient underwent cyst drainage 6 months after SRS.
Hanakita et al 2014[8]	Three patients (14%) developed adverse radiation effects after SRS, all of which resolved. One patient had an intratumoral haemorrhage, but no neurological deterioration during follow-up, and two patients had peritumoral oedema, including one who developed transient hydrocephalus.
Moss et al 2009[3]	Five patients (16%) with 11 tumours developed adverse radiation effects after SRS. Three patients (4 tumours) had radiographic evidence of necrosis, but were asymptomatic, and two patients (7 tumours) experienced symptoms of numbness in a dermatomal distribution, extremity weakness, and new-onset headaches. It was not reported whether these symptoms resolved.
Wang et al 2005[9]	No complications were reported.
Jahawar et al 2000[10]	Three patients (11%) developed minor adverse radiation effects of headaches, nausea and vomiting, all of which resolved within 24 hours of treatment. No delayed complications were identified.

4.5 Summary of section 4

There is a limited evidence base surrounding the effectiveness of SRS/T for patients with residual, recurrent or progressive haemangioblastoma after previous surgery where further surgery was deemed too high risk. No randomised controlled trials were found, only retrospective case series. One recently published, large, case series (Kano et al 2015) was found of 186 patients with haemangioblastomas treated with SRS, the majority of which had had prior surgery.[7] The other case series ranged in size from 21 to 35 patients and did not add any further information to Kano et al 2015.[3, 8-10] The majority of results were not reported separately for those patients with residual, recurrent or progressive tumours after prior surgery.

In the largest case series (Kano et al 2015), the overall survival rate after SRS was 94%, 90% and 74% at 3, 5 and 10 years, respectively and the overall local tumour control rate was 92%, 89% and 79% at 3, 5 and 10 years, respectively. For those patients that underwent SRS for recurrent or residual tumours, the 5-year local tumour control rate was just over 85%.[7] Across the smaller

case series, the 3-year tumour control rates ranged from 82% to 92% and the 5-year tumour control rates ranged from 71% to 92%. No relevant ongoing studies were found. Few adverse radiation effects were observed. One death due to refractory peritumoral oedema was reported.

It was not possible to reliably determine the comparative effectiveness of SRS/T for haemangioblastoma based on the evidence found, because case series are prone to selection bias and they lack a control arm against which to make comparisons. We do not know what would have happened to patients if they were not treated or had alternative treatments.

No studies were found that assessed the cost-effectiveness of SRS/T for haemangioblastoma.

5 Discussion and conclusions

The evidence surrounding the clinical effectiveness of SRS/T for patients with residual, recurrent or progressive haemangioblastoma after previous surgery where further surgery was deemed too high risk is limited. We only found five retrospective case series in which patients with haemangioblastoma were treated with SRS and a large proportion of these had previous surgery.[3, 7-10] The majority of results were not reported separately for those patients with residual, recurrent or progressive tumours after prior surgery and it was not a condition of the studies for SRS to be only given in cases where further surgery was too risky.

The most recently published case series and also the largest (Kano et al 2015) included 186 patients (517 tumours) with intracranial haemangioblastomas treated with SRS in six centres in the USA and Japan between 1990 and 2010.[7] Eight-four percent of patients had prior surgery with 85 patients having had previous single surgery and 71 patients having had multiple surgeries. The median follow-up after SRS was 5 years (range 0.5–18).

The overall survival rate after SRS was 94%, 90% and 74% at 3, 5 and 10 years, respectively. Factors associated with longer patient survival after SRS were the absence of neurological deficits ($p = 0.023$, HR 15.11, 95% CI 1.46–157.0) and fewer tumours ($p = 0.021$, HR = 0.21, 95% CI 0.06–0.79). The overall local tumour control rate was 92%, 89% and 79% at 3, 5 and 10 years, respectively. For those patients that underwent SRS for recurrent or residual tumours, the 5-year local tumour control rate was just over 85%. For the entire series, the rate of developing a new tumour or recurrence of residual tumour was 5% at 1 year, 18% at 3 years, 33% at 5 years, and 54% at 10 years. Around 40% of patients required additional treatment (SRS, resection or cyst aspiration) for tumour progression (38/186 patients) or for new tumours or recurrence (37/186 patients).

The smaller case series ranged in size from 21 to 35 patients.[3, 8-10] The results reported across these smaller case series are consistent with those of Kano et al 2015, with the 3-year tumour control rates ranging from 82% to 92% and the 5-year tumour control rates ranging from 71% to 92%. Kano et al 2015 observed tumour control rates at the higher end of these ranges, and this large case series is likely to give a more reliable estimate of the treatment effect as it is less prone to selection bias and chance findings. However, the reliance of the studies on case notes, as is the case for all these retrospective case series, means that reporting bias may have been introduced with patients with worse outcomes being likely to have more complete notes. Few adverse radiation effects were reported across all the included series, although there was one death due to refractory peritumoral oedema observed in Kano et al 2015.

Case series do not have a control arm, so in the absence of a randomised controlled trial, it was not possible to compare results to no intervention or alternative interventions and hence reliably

determine the comparative clinical effectiveness of SRS/R in patients with haemangioblastoma. No ongoing relevant randomised controlled trials or other study designs were found. The cost-effectiveness of SRS/T cannot be determined because the data do not allow us to reliably quantify the clinical effectiveness.

1. What is the evidence for the clinical effectiveness of stereotactic radiosurgery/ stereotactic radiotherapy for haemangioblastoma compared to other treatment modalities?

The evidence surrounding the clinical effectiveness of SRS/T for haemangioblastoma is limited. No randomised controlled trials were found. Only one large retrospective case series and four small retrospective case series were found, all of which reported high tumour control and survival rates over many years of follow up. However, lack of a control arm and the possibility of selection bias inherent in case series means that it was not possible to determine the clinical effectiveness of SRS/T for haemangioblastoma compared to other treatments.

2. What is the evidence for the cost-effectiveness of stereotactic radiosurgery/ stereotactic radiotherapy for haemangioblastoma compared to other treatment modalities?

No studies were found assessing the cost-effectiveness of SRS/T for haemangioblastoma.

6 References

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7 Search Strategy

Table 3: Population, Intervention, Comparator and Outcomes (PICO)

Patients / Population	Intervention	Comparison	Outcomes
Patients with haemangioblastoma, residual, recurrent or progressive after previous surgery where further surgery deemed too high risk	Stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT)	Surgery Fractionated radiotherapy Proton beam therapy	Clinical effectiveness • Long-term tumour control / cure rate • Proportion of patients free from progressive symptoms • Proportion of patients with maintenance/improvement of quality of life • Incidence and nature of adverse events • Need for repeat or alternative procedures • Recovery time after treatment Cost effectiveness/Cost of treatment

Search date: 6th November 2015
Databases searched: We searched Medline, Embase, Cochrane, Trip and NICE Evidence search – limited to English and 2000 onwards. We excluded case reports, conference papers, letters and commentary.
This was a combined search for papers on ependymoma, haemangioblastoma, pilocytic astrocytoma and trigeminal schwannoma, each of which is the subject of a separate evidence review. Only the results for pilocytic astrocytoma are considered in this review

Embase search strategy

1 ependymoma/
2 (ependymoma? or ependymal glioma? or subependymal glioma?).ti,ab.
3 1 or 2
4 hemangioblastoma/
5 (h?emangioblastoma? or angioblastoma?).ti,ab.
6 4 or 5
7 pilocytic astrocytoma/
8 (pilocytic astrocytoma? or cystic cerebellar cytoma? or pilomyxoid astrocytoma?).ti,ab.
9 7 or 8
10 neurilemoma/ and (trigeminal nerve/ or trigeminal nerve disease/)
11 (trigeminal adj2 (schwannoma? or neuroilemoma?)).ti,ab.
12 10 or 11
13 3 or 6 or 9 or 12
14 exp stereotactic procedure/
15 (stereotactic* or stereotaxic* or sbrt or srt or srs or radiosurg* or radio-surg*).ti,ab.
16 (gammaknife or gamma knife or linac or cyberknife or cyber knife).ti,ab.
17 14 or 15 or 16
18 13 and 17
19 case report/
20 conference*.pt.
21 19 or 20
22 18 not 21
23 limit 22 to (english language and yr="2000 -Current")