STEREOTACTIC RADIOSURGERY/ STEROTACTIC RADIOTHERAPY FOR EPENDYMOMA

QUESTIONS TO BE ADDRESSED:

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

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

SUMMARY:

Background

- Ependymomas are rare, slow-growing tumours of the central nervous system which belong to a group of tumours called gliomas.
- They generally present in childhood and are the third most common childhood brain tumour.
- Recurrence rates for ependymomas are high.
- The main treatment is surgery, which is commonly followed by radiotherapy.
- Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are methods of delivering a strong and highly focused dose of radiation and they are considered as treatment options for ependymoma, particularly for recurrent cases.
- 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 ependymoma after previous surgery.
- No RCTs were found looking at the effectiveness of SRS/T for ependymoma compared to no treatment or other treatment modalities.
- One systematic review was found which included 13 case series (total of 138 patients) assessing the effectiveness of SRS/T in recurrent cases of ependymoma. An additional two retrospective case series (including 19 and 26 patients) were found.
- A wide range of survival rates was observed across the studies with 3-year survival rates ranging from 32% to 83%.
- It is not possible to determine the comparative clinical effectiveness of SRS/T for ependymoma based on case series.

Cost Effectiveness

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

Safety

- Few adverse events were reported.
- All events reported were of radiation necrosis.
- Two fatalities due to radiation necrosis were reported.

1 Context

1.1 Introduction

Ependymomas are rare, slow-growing tumours of the central nervous system and most commonly arise in children. They belong to a group of tumours called gliomas, which start in the glial cells (cells that support and protect neurones). Ependymomas arise from ependymal cells (a sub-type of glial cells) which line the cerebral ventricles and passageways in the brain and spinal cord. They can occur supratentorially (in an area of the brain located above the tentorium which includes the cerebrum), infratentorially (in an area of the brain located below the tentorium which includes the brain stem, cerebellum and fourth ventricle) or in the spinal cord. In children, most ependymomas are infratentorial tumours and arise in the fourth ventricle whereas in adults, ependymomas most commonly arise in the spinal cord.[1, 2]

The World Health Organisation (WHO) classifies ependymomas into three grades: Grade I are subependymoma and myxopapillary ependymomas (usually slow growing, benign neoplasms); Grade 2 are low-grade ependymomas (slow growing tumours of neoplastic ependymal cells); and Grade 3 are anaplastic ependymomas (malignant glioma of ependymal differentiation). The causes of ependymoma are not known. Symptoms of ependymoma depend on the location and size of the tumour. Intracranial ependymomas often present with symptoms of raised intracranial pressure such as nausea, vomiting, headaches, dizziness, visual disturbances and confusion. Symptoms of spinal cord ependymomas can include back pain, neck pain and numbness or weakness in the arms or legs. Diagnosis and staging of ependymomas can include a MRI or CT scan to determine the size and location of the tumour, a CSF examination and biopsy.[1-3]

Surgery is the first line treatment for ependymomas with the goal of maximum possible resection. In addition, radiotherapy is commonly used, even in some cases after complete resections. Other adjuvant therapies include second surgery and chemotherapy. The type of adjuvant therapy given can depend on the subtype of ependymoma, extent of tumour removal, tumour spread if any and patient's age. Newer techniques of radiotherapy such as stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are considered as options for treating ependymomas particularly in recurrent cases.[1]

1.2 Existing national policies and guidance

We found one national guideline that included specific recommendations for the management of ependymoma.[4] These neuro-oncology guidelines were produced by the London Cancer Brain and Spine Pathway Board in July 2014 and were reviewed in July 2015. The guidelines recommend the following management algorithm for ependymomas:

Complete resection	Grade I and Grade II	Surveillance
Complete resection	Grade III	Radiotherapy
Incomplete resection	Grade I	Surveillance or Radiotherapy
Incomplete resection	Grade I, II, III	Radiotherapy

For relapse, the guidelines state surgery may offer the best palliation and alternatives are radiosurgery or in rare cases re-irradiation. They state that ependymomas respond poorly to chemotherapy though there is some evidence for using cisplatin and etoposide.

The National Institute for Health and Care Excellence (NICE) is expected to publish guidelines of primary brain tumours and cerebral metastases in July 2018.

We found two international guidelines that included specific recommendations on the treatment of ependymoma.[5, 6]

The Alberta Health Services guidelines for adults with Grade II and III ependymomas published in May 2012 recommend that surgical resection and postoperative radiotherapy may be considered for known or suspected residual intracranial Grade II tumours. They state there is no evidence that the addition of chemotherapy to surgery or radiotherapy improves outcome. For Grade III tumours they state surgery plus radiotherapy represents the standard treatment and for patients with evidence of craniospinal spread, craniospinal irradiation should be considered. They state recurrent patients should be considered as candidates for chemotherapy or clinical trials. SRS/T is not included as one of the interventions considered for ependymomas.[5]

The 2011 National Comprehensive Cancer Network guidelines from the U.S. on central nervous system cancers recommend that radiosurgery be considered if geometrically favourable in patients with recurrent ependymoma who have not had prior radiotherapy or in patients with progression.[6]

2 Epidemiology

In the UK, approximately 9,700 people are diagnosed with tumours of the central nervous system each year. Around 2-5% of these are ependymomas (180-450 cases per year).[1, 7, 8]

Ependymomas generally present in early childhood. They are the third most common childhood brain tumour.[8] The National Registry of Childhood Tumours (NRCT) had a total of 748 registrations of ependymoma from 1977 to 2011 in children aged under 15 in Great Britain.[9] The occurrence of cerebral ependymomas peaks at an age of around 5 years and again at around 45 years, while spinal ependymomas generally occur in adults and peaks at an age of around 45 years.[10]

The National Cancer Intelligence Network has estimated survival rates for all ependymal tumours diagnosed in residents of England between 2001 and 2010. They found the survival for spinal ependymomas was better than for cerebral ependymomas with an estimated 5-year survival rate of just over 90% for spinal ependymomas compared to 70% for cerebral ependymomas. The survival rates in cerebral ependymomas decreased with increasing WHO Grade whereas spinal ependymomas were unaffected by WHO grade.[10] Other prognostic factors include the extent of tumour removal, location of the tumour, presence of metastases at diagnosis and age at diagnosis. Recurrence rates for ependymomas are high (around 50-70%) and the majority recur at the primary site.[4]

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 young children who cannot tolerate head mask fixation after a training period.[11, 12]

4 Findings

A literature search was performed on the 6th of November 2015 for ependymoma 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 ependymoma after previous surgery where further surgery was deemed too high risk. Case series with a sample size of five or fewer patients, case reports, conference papers, letters and commentary were excluded.

One relevant systematic review was found which looked at the effectiveness of SRS/T for the treatment of intracranial ependymomas in children.[13]

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

Two relevant case series looking at the clinical effectiveness or safety of SRS/T in ependymoma were found. Individual case series included in the systematic review were excluded as these results have already been summarised in the systematic review.[11, 14]

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

4.1 Evidence of effectiveness

Krieger et al 2009[13]

This systematic review assessed the effectiveness of SRS/T in children with intracranial ependymoma. Searches were conducted up to October 2008 and were limited, only searching Medline and PubMed with very few search terms. Therefore some studies may have been missed. In addition, very few details on methods were reported. For example no inclusion and exclusion criteria were stated so it is possible selection bias may have been introduced.

The review found 15 relevant studies, all of which were case series with sample sizes ranging from 2-39. Four studies (including a total of 13 patients) looked at the effectiveness of SRS/T at the time of initial disease presentation and 13 studies (including a total of 138 patients) looked at SRS/T at the time of recurrence. Although the systematic review's focus was on children, around half of the studies included in the review included adults. Follow-up times ranged from 2.5 months to 10 years and most studies used SRS dosing at 15-20 Gy.

The authors report that the best outcomes were obtained when SRS/T was used as a boost at the time of initial disease presentation with 12 out of 14 patients treated with an SRS/T boost upfront having prolonged survival. However this cannot be inferred to mean that SRS/T is more effective when given at time of tumour presentation compared to at time of recurrence because these results are based on small numbers and this subgroup of patients will have a better prognosis than those with recurrent disease.

The authors only present the overall survival outcome for all studies, but this isn't very useful because it is dependent on the length of follow-up which varied amongst the studies.

For SRS/T given at the time of recurrence, overall survival rates ranged from 12% to 100%. The higher survival rates (60-100%) were only seen in small studies with sample sizes ranging from 2-6 patients.

A more useful statistic for comparisons across the studies is the 3-year survival rate. The 3-year survival rate range for studies that included patients of all ages and for those that reported the rate separately for recurrent cases is 32-45%. The largest included case series (Kano et al 2009) with 39 patients (age range = 3-71 years) and a median follow-up of 24 months observed overall survival rates after SRS of 60%, 36% and 32% at 1,3, and 5 years, respectively. The progression-free survival rates reported for the same group of 39 patients (82%, 46% and 46% at 1, 3 and 5 years, respectively) were higher than the overall survival rates, which is not possible. We have contacted the authors for an explanation of this inconsistency, but have not had a response as yet. Twenty-five of the 39 patients died at a median of 20 months (range = 6-155 months) after SRS as a result of metastases (12 patients) or disease progression (13 patients).[15] The next largest included case series (Hodgson et al 2001) which included 25 children with ependymoma and a median follow-up of 24 months had an overall survival rate of 12%. The median progression-free survival was 8.5 months and 3-year progression-free survival rate was 22%.[16]

The included studies appear to be mostly small, retrospective, case series reporting on the outcomes of patients with recurrent ependymoma treated with SRS/T in a certain clinic over a defined time period. These studies are particularly prone to selection bias because patients seen in one clinic may not be representative of the wider ependymoma population. This is especially a problem in case series with small sample sizes. A further problem is, as case series do not include a control arm, it is not possible to compare results to no intervention or alternative interventions. In addition, the retrospective nature of the studies means that they rely 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/T for ependymoma based on case series.

Stauder et al 2012[14]

This is a retrospective case series of 26 patients who had SRS for recurrent intracranial ependymomas between 1990 and 2008 at the Mayo Clinic in the USA. The median age at diagnosis was 22 years (age range = 1-70), all but one patient had prior tumour resection (with two thirds having gross total resection) and around three quarters of patients had undergone prior external beam radiation therapy (EBRT). Patients were followed-up with MRI at intervals of 3-6 months after SRS for the first 2 years and then yearly thereafter. The median follow-up time was 3.1 years (range = 3.4 months to 13.1 years). It is worth noting that some of these patients will have been included in an earlier publication from the Mayo clinic which was included in the Krieger et al 2009 systematic review.[13]

One year and 3-year survival rates were 96% and 69%, respectively and the median survival time seen was 5.5 years. One year and 3-year local tumour control rates for all lesions treated were

85% and 72%, respectively. Ten patients (38%) were found to have had a local or marginal tumour recurrence and seven patients (27%) were found to have had a distant tumour progression. The one year progression-free survival rate was 80% and 3-year rate was 66%. Most (possibly all) patients required repeat SRS or alternative procedures after initial SRS, with ten patients undergoing a second SRS procedure, nine patients receiving chemotherapy, seven patients undergoing a craniotomy with tumour resection and two patients undergoing EBRT.

This is a retrospective case series with no inclusion/exclusion criteria stated other than having recurrent ependymoma treated with SRS from 1990-2008 at the Mayo Clinic. Therefore it is subject to the same biases described above. Reporting bias may be less of an issue, as the authors state that patients were identified through review of a prospectively maintained treatment database which contained data on pre-operative characteristics, radiosurgical dosimetry, post-operative imaging and clinical outcomes.

Combs et al 2006[11]

This is a retrospective case series of 19 patients with confirmed ependymomas, being treated with SRT at the University of Heidelberg from 1992 to 2003. The study included seven patients who were given SRT as re-irradiation for tumour progression after previous surgery. The remaining 12 patients received SRT as primary postoperative radiotherapy after surgical resection. The median age of the entire cohort at primary diagnosis was 15 years (age range = 1-60 years), two thirds had Grade 2 tumours and one third had Grade 3 tumours, and three quarters of patients had subtotal prior resection. Follow-up visits included an MRI and were initially conducted at 6 weeks after SRT, then every following 3-6 months. The median follow-up time was 32 months (range = 7-185 months).

The overall 5 and 10-year survival rates were 77% and 64%, respectively. The 3 and 5-year survival rates for SRT for tumour progression cases only were 83% and 50%, respectively. The progression-free survival rate for tumour progression cases only was 60% at 5 years. However this was higher than the 5-year survival rate of 50% for progression cases, which is not possible. We have contacted the authors for an explanation of this inconsistency, but have not had a response as yet, so the discrepancy remains unexplained.

Again, this is a retrospective case series with no inclusion/exclusion criteria stated other than having histologically confirmed ependymoma treated with SRT from 1992-2003 at the University of Heidelberg.

Table 1: Clinical effectiveness of SRS/ SRT for haemangioblastoma

Study	Patients	Intervention	Results and comments
Krieger et al 2009[13] Systematic review of case series	Total population: n=152 patients (from 14 studies) Relevant population (patients with disease recurrence at time of treatment): n=138 patients (from 13 case series) Inc/ex criteria: None stated Study characteristics: Year published: 1990-2009 Sample size (range): 2-39	SRS/T 15-20 Gy	For recurrent cases only: F/up range = 2.5 months to 10 years Overall survival rate (range): 12%-100% 3-year survival rate for studies that report outcome and include all ages (range): 32%-45% Toxicity 2/138 fatal adverse related events due to radiation necrosis
Stauder et al 2012[14] Retrospective case series USA	n=26 Inc/ex criteria: Patients undergoing SRS at the Mayo Clinic, Rochester Minnesota for recurrent ependymoma between 1990 and 2008. Baseline characteristics: Median age at diagnosis = 21.9 years (range 1.4-69.6) Grade 2 tumour = 15/26 (58%) Grade 3 tumour = 9/26 (34%) Grade 4 tumour = 2/26 (8%) Prior gross total resection = 16/26 (62%) Prior subtotal resection = 9/26 (35%) Previous cranial EBRT = 19/26 (73%) Median time to SRS from EBRT completion = 4.2 years (range 0.5-14.4 years)	Radiosurgery using the Leksell Gamma Knife. Median marginal dose = 18 Gy (range 12-24)	All patients were evaluated with MRI every 3-6 months after SRS for first 2 years and yearly thereafter. Median follow-up = 3.1 years (3.4 months to 13.1 years) Survival outcomes 1-year survival rate = 96% 3-year survival rate = 69% Median overall survival after SRS = 5.5 years. Tumour control Local tumour control achieved in 33/49 lesions (67%) Median time to progression = 14.7 months (range 2.9 months - 11.2 years) 1-year progression-free survival rate = 80% 3-year progression-free survival rate = 66% Local or marginal tumour recurrence rate = 10/26 (38%) Distant tumour progression rate = 7/26 (27%) Further treatment after initial SRS: Repeat SRS = 10/26 (38%) Chemotherapy = 9/26 (35%) Tumour resection = 7/26 (27%)

			EBRT = 2/26 (8%) Toxicity 2/26 had symptomatic radiation necrosis after SRS.
Combs et al 2006[11] Retrospective case series Germany	Total population n=19 Relevant population (patients with tumour progression): n=7 Inc/ex criteria: Patients with histologically confirmed ependymoma treated with SRT from January 1992 to December 2003 at the Department of Radiation Oncology, University of Heidelberg, Germany. Baseline characteristics for all patients: Median age at primary diagnosis = 15 years (range 1-60) Males = 10/19 (53%) Grade 2 tumour = 12/19 (63%) Grade 3 tumour = 7/19 (37%) Total resection = 5/19 (26%) Subtotal resection = 14/19 (74%)	Fractionated stereotactic radiotherapy (FRST) Median dose of 36 Gy for tumour progression cases.	Follow-up with MRI was 6 weeks after FSRT, then every 3-6 months. Median follow-up = 32 months (7-185) Sub-group results for SRT performed as re-irradiation for tumour progression cases Survival outcomes 3-year survival rate = 83% 5-year survival rate = 50% Toxicity No interruptions to SRT due to side effects. No severe treatment related toxicity > CTC (Common Toxicity Criteria) grade 2 observed.

4.2 Trials in progress

A search of clinicaltrials.gov on the 31st of December 2015 for ongoing trials looking at SRS/T for ependymoma found one relevant trial. The trial is a randomised controlled trial comparing stereotactic conformal radiotherapy (multiple non-coplanar fields using micromultileaf collimators under stereotactic guidance) to conventional radiotherapy in patients with primary intracranial tumours such as low-grade glioma, meningioma, craniopharyngiomas, ependymomas and other benign tumours considered for radical focal radiotherapy. The trial is being conducted in India and has randomised 200 patients and is now closed to recruitment. The main outcomes are incidence of neuropsychological and neuroendocrine function and progression free and overall survival. The trial is due to be completed in June 2017.

Another emerging treatment that has been used for ependymoma is proton beam therapy, but there were no trials found comparing the therapy to SRS/T.

4.3 Evidence of cost-effectiveness

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

4.4 Safety

No studies were found specifically looking at safety of SRS/T for ependymoma. 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 included studies.

Table 2: Adverse events associated with SRS/ SRT

Study	Safety results
Krieger et al 2009[13]	The authors report that the damage seen from SRS/T is relatively limited with two fatalities observed in the 14 included studies (including 152 patients), both due to radiation necrosis. They also noted that one of the included studies described an additional patient who required surgery for radiation necrosis with resultant notable disabilities. In the largest case series included (Kano et al 2009), 3 out of 39 patients (8%) had an adverse radiation effect, none of which led to an long-term adverse outcome.[15]
Stauder et al 2012[14]	Two out of 26 patients (8%) had pathologically confirmed radiation necrosis after SRS. Both had neurologic decline from radiation necrosis and underwent a craniotomy to attempt to stabilise their condition. No further adverse events are reported
Combs et al 2006[11]	The authors state that SRT was well tolerated by all patients and could be completed without interruptions due to side-effects and no serious side-effects were observed.

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 ependymoma after previous surgery where further surgery was deemed too high risk. We only found one systematic review which included 13 relevant case series and two additional retrospective case series which weren't included in the systematic review.[11, 13, 14] The studies were mostly small, retrospective, case series and ranged in size from 2-39 patients.

There was a wide range of survival rates observed across the studies, with 3-year survival rates ranging from 32% to 83%. The largest case series (Kano et al 2009) with 39 patients reported overall survival rates after SRS of 60%, 36% and 32% at 1,3, and 5 years, respectively.[15] The next largest case series (Stauder et al 2011) with 26 patients with recurrent ependymoma observed survival rates of 96% and 69% at 1 and 3 years, respectively; progression-free survival rates of 80% and 66% at 1 and 3 years, respectively; and local tumour control rates of 85% and 72% at 1 and 3 years, respectively. Interestingly, most patients (possibly all) in this series by Stauder et al required repeat SRS or alternative procedures after initial SRS, but it is not clear why there were so many additional treatments given.[14]

It is not possible to reliably determine the effectiveness of SRS/T for ependymoma based on the evidence found, because case series are prone to selection bias and they lack a control arm in which to make comparisons.

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

Few adverse events were reported. All were for radiation necrosis, two of which had fatal outcomes.

One relevant ongoing RCT was found which is comparing stereotactic conformal radiotherapy to conventional radiotherapy in patients with primary intracranial tumours including those with ependymomas.

5 Discussion and conclusions

There is a paucity of evidence surrounding the effectiveness of SRS/T for patients with residual, recurrent or progressive ependymoma after previous surgery where further surgery was deemed too high risk. We only found one systematic review of case series and two additional case series.[11, 13, 14]

The systematic review assessed the effectiveness of SRS/T in children with intracranial ependymoma, but it also included studies looking at adults. The review included 13 case series (with a total of 138 patients) that specifically looked at the effectiveness of SRS/T at time of recurrence. The studies were mostly small, retrospective, case series which ranged in size from 2-39 patients and had a wide range of follow-up times ranging from 2.5 months to 10 years. The systematic review only clearly reports the overall survival rate for each study (range = 12% to 100%), which makes comparisons across the studies difficult as they have different follow-up times. They do, however, report the 3-year survival rate range for studies that included patients of all ages and reported the rate separately for recurrent cases and this was 32-45%.[13] The largest case series included in the systematic review (Kano et al 2009) with 39 patients (age range = 3-71 years) observed overall survival rates after SRS of 60%, 36% and 32% at 1,3, and 5 years, respectively.[15] The quality of the reporting of the systematic review was poor making it difficult to critically appraise and extract results. Furthermore, the searches were carried out in October 2008 so the review is now out of date.

In addition to the systematic review, we found two retrospective case series, one of which (Stauder et al 2011) was published after the searches were conducted for the systematic review, and one appears to be missed from the review (Combs et al 2006).[11, 14]

The largest of the two (Stauder et al 2011), with 26 patients with recurrent ependymoma, observed survival rates of 96% and 69% at 1 and 3 years, respectively; progression-free survival rates of 80% and 66% at 1 and 3 years, respectively; and local tumour control rates of 85% and 72% at 1 and 3 years, respectively. Based on this series, there does appear to be a need for further intervention after initial SRS/T as the majority of patients (possibly all) required either repeat SRS or alternative procedures after initial SRS.[14]

The final case series (Combs et al 2006) included seven patients with confirmed ependymomas who were given SRT as re-irradiation for tumour progression after previous surgery. The 3 and 5-year survival rates after SRT were 83% and 50%.[11]

There were inconsistencies found with the progression-free survival rates reported for Kano et al 2009 and Combs et al 2006, as they were higher than the studies' overall survival rates which is not possible.

In summary, across the case series included in the systematic review and the additional two case series, a wide range of survival rates was observed, with 3-year survival rates ranging from 32% to 83%. This large range is to be expected, as the included studies were mostly small, retrospective, case series and therefore prone to selection bias. Their samples are likely to differ from each other and may not be representative of the wider ependymoma population. In addition, the lack of a control arm inherent in case series means that we can't compare results to those who received no treatment for recurrent ependymoma after previous surgery or who received alternative interventions. In the absence of an RCT, it is not possible to reliably determine the effectiveness of SRS/T for patients with ependymoma. We did find an ongoing RCT which compares stereotactic conformal radiotherapy to conventional radiotherapy in 200 patients with primary intracranial tumours including ependymomas. These results are expected to be released in June 2017.

Across the studies, few adverse events were reported, all of which were radiation necrosis. In total, two fatalities due to radiation necrosis were reported and three cases of craniotomies being required as a result of radiation necrosis
Unsurprisingly given the limited evidence base, no studies were found assessing the cost effectiveness of SRS/T for ependymoma.

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 ependymoma is limited. No randomised controlled trials, only small retrospective case series, were found. Lack of a control arm and the introduction of selection bias inherent in case series means that it is not possible to determine the clinical effectiveness of SRS/T for ependymoma 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 ependymoma. In the absence of reliable data on clinical effectiveness, it is impossible to establish cost-effectiveness.

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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7 Search Strategy

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

Population	Intervention	Comparison	Outcomes
Patients with ependymoma, 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")