STEREOTACTIC RADIOSURGERY/ STEROTACTIC RADIOTHERAPY FOR TRIGEMINAL SCHWANNOMA

QUESTIONS TO BE ADDRESSED:

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

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

SUMMARY:

Background

- Trigeminal schwannomas are slow growing, benign, nerve sheath tumours associated with the 5th cranial nerve.
- Trigeminal schwannomas (TS) are rare and figures from a number of case series suggest they account for between 1% and 8% of all intracranial schwannomas.
- Surgical resection is the preferred first-line treatment for TS where a total or near total resection can be achieved. However, since these tumours are adjacent to critical neurovascular structures complete removal is difficult and often results in new post-operative neurological deficits.
- Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) can be used in cases of incomplete surgical resection to treat residual tumour or to treat tumours that have progressed or recurred following surgery.

Clinical Effectiveness

- There are few published studies reporting outcomes of patients with TS and the use of SRS/SRT following surgery. The research available is limited to retrospective case series over many years reporting results from a combination of patients for whom SRS/SRT is either the initial intervention or used to treat residual tumour or tumour recurrence following surgery.
- This review identifies seven studies (range 4 to19) which reported separate outcomes of patients who received SRS/SRT following surgery.
- Three studies reported reduction in tumour size in 37.5% to 75% of patients, stable tumour state in 16.6% to 50% of patients and increase size of tumour in 8.1% to 12.5% of patients following prior surgery and SRS/SRT.
- Four studies reported that between 9.1% and 75% of patients had an improvement in some or all of their previous neurological deficits. Where symptoms remained stable or unchanged, the rate varied between 9.1% and 81.8%. Four studies described transient SRS/SRT induced symptoms in 9.1% to 50% of patients.
- Progression-free survival (PFS) at one year (100%), three years (80%), five years (80%) and ten years (80%) was reported by one study (n=11); a second study (n= 19) reported PFS at five years (81%) and ten years (73%).

Cost Effectiveness

- We did not identify any studies about the cost-effectiveness of SRS/SRT for trigeminal schwannoma in patients with residual, recurrent or progressive tumours after previous surgery where further surgery is deemed too high risk.

Safety

- Four studies described transient SRS/SRT induced symptoms in 9.1% to 50% of patients. They included headache, pain, numbness, muscle weakness, blurred vision. A symptomatic transient flare phenomenon occurred in two patients involving rapid increase in tumour size which subsequently decreased in size (one patient) and stabilised (one patient). All were transient conditions and were resolved by last follow-up. One study reported masseter muscle atrophy in 28.5% of patients following SRS but did not state if these were transient or permanent symptoms.

1 Context

1.1 Introduction

Trigeminal schwannomas (TS) are slow growing, benign, nerve sheath tumours associated with the 5th cranial nerve[1].

They generally arise in the skull base and typically cause facial pain (trigeminal neuralgia). As they enlarge they can grow further into the cavernous sinus or into the posterior fossa, causing double vision, loss of coordination and other symptoms of brainstem compression. Some patients are asymptomatic and tumours may be an incidental finding of other investigations [2]. Tumours are classified based on anatomical location and extension into other areas. Ramina [2] describes a classification of six tumour types ordered from A-F in increasing surgical challenge.

Surgical resection is the preferred first-line treatment for TS where a total or near-total resection can be achieved. These tumours are adjacent to critical neurovascular structures which make complete removal difficult often resulting in new post-operative neurological deficits [1].

Stereotactic radiosurgery and stereotactic radiotherapy can be used in cases of incomplete surgical resection to treat residual tumour [3] or to treat tumours that have progressed or recurred following surgery [1]. The questions to be addressed in this review concern the use of these interventions in patients with trigeminal schwannoma, and residual, recurrent or progressive tumours after previous surgery, where further surgery is deemed too high risk.

1.2 Existing national policies and guidance

We did not identify any guidance from the National Institute of Health and Care Excellence (NICE) on stereotactic radiosurgery or stereotactic radiotherapy for trigeminal schwannomas.

2 Epidemiology

Trigeminal schwannomas are rare and figures from a number of case series suggest they account for between 1% and 8% of all intracranial schwannomas [2]. In a large case series of 111 patients seen between 1961 and 1994 at one Russian hospital, TS accounted for 0.3% of the 37,000 intracranial tumours and 5.8% of intracranial neuromas undergoing surgery during that period. Of

the 111 patients, 71% were females [4]. TS tends to occur in middle aged patients with the highest incidence between the ages of 38 and 40 [2].

3 The intervention

The interventions of interest in this review are stereotactic radiosurgery and stereotactic radiotherapy.

Stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) use focused radiation beams to deliver radiation to a specific target with minimal radiation exposure to normal adjacent tissue. In stereotactic radiosurgery the radiation is delivered in a single treatment whilst in SRT the treatment is fractionated over a number of sessions. This allows for high doses to be delivered within the target while maintaining an acceptable safety profile. SRS and SRT are alternatives or adjuncts to invasive surgery where tumours are hard to reach and close to neurovascular systems. A fixation device is used to immobilise the head and scans are taken in order to plan the treatment for the tumour. [1].

The outcomes of interest are long term tumour control, proportion of patients free from progressive symptoms, improvement or worsening of neurological deficits and the frequency and nature of adverse events.

4 Findings

A search of Medline, Embase, Cochrane Library, TRIP and NICE Evidence was performed on the 6th November 2015 for studies published in English since 2000. Case reports, conference papers, letters and commentary were excluded. Details of the search strategy are provided in Section 7.

We found seven uncontrolled observational studies with a total of 78 patients (range 4 to 19) with TS who received SRS/SRT following prior surgery.

We did not identify any studies comparing SRS or SRT with other treatments. The identified studies included tumours of varying anatomy and histology. In order to prioritise the best available evidence we have only included studies with results reported separately for patients with residual tumours or tumour recurrence following surgery.

There were a number of reasons why studies identified by the literature search did not meet the criteria for inclusion in this review. These included:

- The intervention was not SRS or SRT.
- There was no separate reporting of results for trigeminal schwannoma patients receiving SRS or SRT following prior surgery.

4.1 Evidence of effectiveness

All studies were retrospective reviews of patients at single institutions. The median follow-up periods ranged from 36.5 months to 147.9 months. Of the seven included observational studies, six [1,3,5,6,7,8] described outcomes of patients who received SRS as either an initial treatment or as a secondary treatment following surgical resection. All the studies reported some separate results for those with prior resection. The seventh study [9] included a comparison of the

outcomes of SRS versus SRT for patients who received the treatment as an initial or secondary intervention following prior resection.

The number of patients treated with SRS/SRT in each case series ranged from 22 to 56. The sub-set of these patients who had received SRS/SRT following prior surgery ranged from four to 19.

Tumour control was reported by three of the seven studies. The proportion of patients with decreased tumour size in each study was 3/8 (37.5%), 3/4 (75%) and 9/12 (75%). [5, 6, 8] The proportion of stable tumours was 4/8 (50%), 1/4 (25%), and 2/12 (16.6%) [5,6,8]. An increase in tumour size was seen in 1/8 (8.3%) and 1/12 (12.5%) patients [5, 8].

Four studies reported some effect of the intervention on neurological deficits [1,6,7,9] with three [1,6,9] describing the proportion of patients that reported improvement in some or all of their previous neurological deficits. These proportions were 1/11 (9.1%), 3/4 (75%), 6/10 (60%) respectively [1,6,9]. Where symptoms remained stable or unchanged the rate varied between 1/11 (9.1%) 3/4 (75%) 3/10, (30%), [1,6,9]. The proportion of patients experiencing transient SRS/SRT induced symptoms were 1/11 (9.1%) and 2/4 (50%) [1,6]. A further study reported 2/9 (22.2%) patients who had a flare of dramatically worsening transient symptoms following SRS. The two patients were admitted to hospital and received medication to reduce symptoms which resolved within a month and both patients were asymptomatic at last follow-up. The final study[7] reported that four out of 14 (28.5%) patients had symptom deterioration following SRS but did not specify if they were transient or permanent and did not describe whether the remaining patients (10/14, 71.5%) symptoms had improved or remained unchanged.

Progression-free survival (PFS) at one year (100%), three years (80%), five years (80%) and ten years (80%) was reported by one study [1]. The five and ten year PFS calculated in a second study was 81% and 73% respectively [3]; in the same study, there was no significant difference in PFS between patients who had undergone previous surgery and those who had not p=0.58).

All small case series including the seven identified in this review (retrospective, uncontrolled, un-blinded, observational studies) are confounded by a high likelihood of bias and are considered low grade evidence. The wide range in percentage of different outcomes is a reflection of the small numbers in each case series

Table 1: Clinical effectiveness of SRS/ SRT for trigeminal schwannomas

Study	Population	Intervention	Results	Comments
Hasegawa et al (2013)[3] Retrospective review of patients at one centre treated since 1991 Japan	Patients receiving SRS for TS N=53 (19 with prior surgery) Median age 53 years (range 21 to 81)	SRS	Median follow-up period (for total study population) 98 months (range 4 to 241). For patients with prior craniotomy (n=19), PFS (from SRS): • 5 years: 81% • 10 years: 73% A comparison of PFS in patients who had received or not received prior treatment was not significant (p=0.58) Other results were not reported separately for patients with prior surgery	Of the 53 patients, 34 received SRS as an initial treatment and 19 patients had undergone 1 or 2 craniotomies before SRS
Champ et al (2012)[9] Retrospective review of patients at one centre treated between 1996 and 2011 US	Patients receiving SRS or SRT for TS following surgery N=23(19 with prior surgery) Median age 37 years (range 16 to 75)	SRS n= 10 (3 with prior surgery) SRT n= 13 (7 with prior surgery) 1 lost to follow-up	Median follow-up period (for total study population) 36.5 months (range 0 to 120) Functional outcome • 6 (60%) improvement of some/all symptoms at last follow-up; • 3 (30%) patients' symptoms were stable at last follow-up • 2 (20%) patients had transient dramatic worsening of symptoms that required hospital admission and were resolved within a month The 10th patient had follow-up of 0 months Tumour control at 5 and 10 years was achieved for 94% of whole sample. Not reported separately for patients with prior surgery	The total study sample included 23 patients. Only the results for the 10 patients who received prior surgery are reported (9 subtotal resection, 1 biopsy) Of the 10 patients, 9 received SRS/ SRT for residual tumour and 1 received SRS / SRT for recurrence
Kano et al (2009)[1] Retrospective review of patients at one centre treated between 1989	Patients receiving SRS for TS N= 33 (11 with prior surgery) Median age 49.5 years (range 15.1 to 82.5)	SRS	Mean follow-up (for total study population) 72 months (range 7.2 to 147.9) For patients with prior resection (n=11): Recurrence-free rate 81.1% PFS (from SRS) • 1 year: 100% • 3 years: 80%	Of the 33 patients, 22 received SRS as an initial treatment and 11 had undergone a previous tumour resection.

and 2005 US			• 5 years: 80% • 10 years: 80% Functional outcome after SRS/SRT: • 1 patient showed an improvement in neurological symptoms • 1 patient had worse neuropathy. • 9 patients' symptoms were unchanged.	
Sheehan et al (2007)[5] Retrospective review of patients at one centre treated between 1989 and 2005 US	Patients receiving SRS for TS N=25 (8 with prior surgery) Mean age 50 years (range 19 to 76) Mean follow-up 48.5 months (range 12 to104 months)	SRS	For patients with prior resection (n=8): • 3 (37.5%) tumour decreased in size • 4 (50%) tumour remained stable • 1 (12.5%) tumour enlarged	The 8 patients with prior resection presented at a mean interval of 23.3 months (range 6 to 66 months) following surgery.
Phi et al (2007)[6] Retrospective review of patients at one centre treated between1997 and 2004	Patients receiving SRS for TS N=22 (4 with prior surgery) Median age 52 years (range 27 to 73)	SRS	Median follow-up (for total study population) 46 months (range 24 to 79) For patients with prior resection (n=4): Tumour size: • 3 patients tumour decreased in size • 1 patient tumour remained stable after 79 months follow-up Functional outcome: • 1 patient showed improvement in trigeminal pain • 3 patients had a range of symptoms – some improving some persisting New or worsening symptoms • 2 patients had new transient symptoms :	Of the 22 patients 4 had undergone prior surgery.
Pan et al (2005)[7] Retrospective	Patients receiving SRS for TS N=56 (14 with prior	SRS	Mean follow-up (for total study population) 68 months (range 27 to 114) For patients with prior surgery (n=14) Functional outcome:	Of the 56 patients, 14 had undergone prior surgery

review of patients at one centre treated between 1993 and 2001 China	surgery) Mean age 42 years (range 8 to 67)		• 4 patients had a deterioration in symptoms after SRS Other results were not reported separately for patients with prior surgery	
Nettel et al (2004)[8] Retrospective review of patients at one centre treated between 1987 and 2001 US	Patients receiving SRS for TS N=23 (12 with prior surgery) Median age 47 years (range 15 to 82)	SRS	Median follow-up (for total study population) 40 months (range 12 to 146) For patients with prior surgery (n=12) Tumour size: • 9 patients tumour decreased • 1 patient tumour increased and repeat SRS • 2 patients tumour remained unchanged Other results were not reported separately for patients with prior surgery	Of the 23 patients, 12 had undergone one or more prior resections

PFS – progression-free survival; SRS – stereotactic radiosurgery; SRT – stereotactic radiotherapy; TS – trigeminal schwannomas

4.2 Trials in progress

We did not identify any trials in progress on SRS/T for trigeminal schwannoma from clinicaltrials.gov (search date 8/01/2016).

4.3 Evidence of cost-effectiveness

We did not identify any studies assessing the cost-effectiveness of SRS/T for trigeminal schwannomas.

4.4 Safety

Table 2 summarises adverse events for all 7 included studies for the total study populations. Separate results for patients receiving SRS/SRT after prior surgery are included where available.

Table 2: Adverse events associated with SRS/ SRT after prior surgery

Study	Safety results for all patients in study	Safety results for patients receiving SRS/SRT after prior surgery
Hasegawa et al (2013)[3]	Ten percent of patients (n=5) had worsened facial numbness or pain in spite of no tumour progression, indicating adverse radiation effect.	No separate safety results for prior surgery available.
Kano et al (2009)[1]	Symptoms reported: • Increased peritumoural T2 signal changes resolved following treatment with corticosteroids (2 patients) • Transient trigeminal neuropathy (3 patients) • Trigeminal pain (1 patient) • Abducent nerve palsy (2 patients)	Symptoms were reported in 1 of 11 patients receiving SRS following surgery • Transient trigeminal neuropathy (1 patient)
Champ et al (2012)[9]	Symptoms were reported in 7 patients. One had received SRS and 6 received SRT. • Dizziness (2 patients) • Blurry vision (2 patients) • Discomfort along cranial nerve (1 patient) • Headache (1 patient) • Paresthesia (2 patients) • Facial pain (2 patients) • Dysarthria (1 patient) • Rapid increase tumour size(2 patients)	Symptoms were reported in 5 patients (50%); all had received SRT • Dizziness (2 patients) • Blurry vision (2 patients) • Discomfort along cranial nerve (1 patient) • Headache (1 patient) • Paresthesia (1 patient) • Facial pain (1 patient) • Dysarthria (1 patient)
Sheehan et al (2007)[5]	Symptoms • Facial pain (3 patients)	No separate safety results for patients with prior surgery available.
Phi et al (2007)[6]	Symptoms reported in 6 patients: • Abducent nerve palsy • Trigeminal pain • Facial hypesthesia • Dysesthia • Masseter weakness	Symptoms reported in 2 patients following surgery and treatment with SRS. • Transient masseter weakness (1 patient) • Transient trigeminal pain (1 patient)
Pan et al	Symptoms reported in 9 patients	Symptoms reported in 2 patients following SRS

2005	• Facial numbness (5 patients) • Masseter weakness (1 patient) • Atrophy in the masseter and temporal muscles (3 patients)	after prior surgery: • Masseter weakness (1 patient) • Atrophy of masseter and temporal muscles (1 patients)
Nettel et al (2004)[8]	Symptoms reported in 2 patients • Worsening light touch sensory loss • Facial weakness	No separate safety results for patients with prior surgery available.

4.5 Summary of section 4

There are few published studies reporting outcomes of the use of SRS/SRT in patients with TS with prior surgery. The available research is limited to uncontrolled observational studies. These are retrospective case series conducted over many years and which report results from a combination of patients for whom SRS/SRT was the initial intervention or was offered following surgery which did not remove the whole lesion or where there was a recurrence. This review includes seven papers (range all patients 22 to 56, range those with prior surgery, 4 to19) which reported separate outcomes of patients who received SRS/SRT following surgery.

Three studies reported reduction in tumour size in 37.5% to 75% of patients, stable tumour state in 16.6% to 50% of patients and increase size of tumour in 8.1% to 12.5% of patients following prior surgery and SRS/SRT.

Four studies reported that between 9.1% and 75% of patients had an improvement in some or all of their previous neurological deficits. Where symptoms remained stable or unchanged, the rate varied between 9.1% and 81.8%. Four studies described transient SRS/SRT induced symptoms in 9.1% to 50% of patients. They included headache, pain, numbness, muscle weakness, blurred vision and rapid increase in tumour size. A symptomatic transient flare phenomenon occurred in two patients involving rapid increase in tumour size which subsequently decreased in size (one patient) and stabilised (one patient)All were transient conditions and were resolved by last follow-up. The wide range in percentage of different outcomes is a reflection of the small numbers in each case series.

Two studies calculated PFS at ten years as 80% [1] and 73%[3]. A comparison [3] between those receiving initial SRS/SRT treatment and those receiving it following surgical resection showed no difference in PFS (p=0.58).

We did not identify any studies assessing the cost-effectiveness of SRS/T for trigeminal schwannomas.

5 Discussion and conclusions

The questions posed at the outset of this review are addressed in turn below.

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

There is an absence of reliable appropriately controlled studies with which to assess the effectiveness of SRS/SRT to treat the recurrence or residual tumours following surgery. Across

the studies patients with a decrease in tumour size outnumber patients with an increase in tumour size (15 vs 2); patients with a reduction in symptoms were similar in number to those whose symptoms worsened (10 vs 9), with seven patients having unchanged symptoms. Worsening symptoms as a result of SRS/SRT resolved themselves by last follow-up.

All small case series such as those identified in this review (retrospective, uncontrolled, un-blinded, observational studies) are confounded by a high likelihood of bias and are considered low grade evidence. On balance the findings of the seven case series indicate the merit in pursuing more rigorous studies focussed on efficacy and safety. Given the rare occurrence of these tumours, multi-site studies would be necessary to gather statistically useful information.

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

We did not identify any studies on the cost-effectiveness of radiosurgery/ stereotactic radiotherapy for trigeminal schwannoma for patients with residual, recurrent or progressive tumours, after previous surgery, where further surgery is deemed too high risk.

6 References

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7 Search Strategy

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

Patients/ population	Patients with trigeminal schwannoma, residual, recurrent or progressive after previous surgery where further surgery deemed too high risk
Intervention	Stereotactic radiosurgery / stereotactic radiotherapy
Comparison	Surgery Fractionated radiotherapy Proton beam therapy
Outcomes	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: Medline, Embase, Cochrane, TRIP and NICE Evidence Search
Limited to studies published in English from 2000 onwards.
Case reports, conference papers, letters and commentary excluded.
This was a combined search for papers on ependymoma, haemangioblastoma, pilocytic astrocytoma and trigeminal schwannoma. Only the results for trigeminal schwannoma 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")