Stereotactic ablative body radiotherapy for spinal arteriovenous malformations, meningiomas and schwannomas

Questions to be addressed

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for spinal arteriovenous malformations, meningiomas and schwannomas which are considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for spinal arteriovenous malformations, meningiomas and schwannomas which are considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

Summary

Background

- Stereotactic ablative body radiotherapy (SABR) is a targeted mode of radiation therapy. It can be used to treat spinal arteriovenous malformations, meningiomas and schwannomas, but there is uncertainty about the clinical and cost effectiveness of this approach.

Clinical effectiveness

- We found no systematic reviews and no randomised trials of SABR for spinal arteriovenous malformations, meningiomas and schwannomas.
- We found seven uncontrolled studies, none of which included participants with arteriovenous malformations. We excluded three studies with fewer than ten participants with the indications covered by this review; including these very small uncontrolled studies would not have provided any further information on the effectiveness of SABR relative to other treatments.
- This left four studies for inclusion:
    - Gerstzen et al published a case series which included 35 participants with schwannoma and 13 with meningiomas treated with SABR. None of the participants with meningiomas progressed during follow-up. Most participants with schwannoma being treated for pain experienced a reduction in pain level that the authors deemed significant. Other patients showed an absence of radiological progression, though there is no reporting of how progression was defined or measured.
    - The same research group published results on a later set of patients. They report that there was no sub-acute or long-term spinal cord or cauda equina toxicity, nor evidence of tumour growth on serial imaging.
    - Sachdev et al reported a series of 87 participants, of whom 32 had a meningioma and 47 a schwannoma. About half of the meningiomas and schwannomas reduced in size after treatment, with the others nearly all stable. The authors also report

improvements in clinical state and pain, but do not describe how these were measured.
    - Gagnon et al studied pain and quality of life after SABR for benign and malignant spinal tumours. Only five of the two hundred participants in this study had meningioma, and only six had schwannomas. The authors do not report results according to the type of tumour. Overall, SABR was followed by improvements in pain which began within a month and continued throughout follow-up, a median period of one year.

Cost effectiveness

- We found no studies of the cost effectiveness of SABR for the treatment of spinal meningiomas. We found a Dutch study of the costs of three treatments for intracranial meningiomas. It reported that microsurgery was more expensive than radiosurgery using a linear accelerator and using a gamma knife.
- The value of this study is limited by the fact that it did not assess whether there were differences in the outcomes of the three treatments which might justify differences in costs. It is not clear whether all three treatments are equally suitable for all patients. The relevance of the study is limited by the inclusion of intracranial tumours rather than spinal ones, and the differences between health care costs between the NHS and the Dutch health care system.

Activity and cost

- No cost or activity data were available.

Equity issues

- We identified no specific equity issues.

1 Context

1.1 Introduction

Stereotactic ablative body radiotherapy (SABR) is a targeted mode of radiation therapy.

1.2 Existing national policies and guidance

We found no national policies or guidance based on systematic reviews of the evidence.

2 Epidemiology

Arteriovenous malformations (AVMs) are abnormal connections between arteries and veins. These vascular anomalies usually arise in the central nervous system, but can appear in any location. Although many AVMs are asymptomatic, they can cause pain, haemorrhage or focal neurological symptoms. The haemorrhage can be fatal.

Meningiomas are tumours arising from the meninges, the membranous layers surrounding the central nervous system. Most are benign, and many are asymptomatic. They can however cause seizures and focal neurological symptoms.

Schwannomas are tumours of the nerve sheath which produces the insulating myelin that covers peripheral nerves. They are usually benign but can produce symptoms from nerve compression.

All three of these lesions are usually treated surgically, but this can be difficult in surgically inaccessible sites or those near critical structures.

3 The intervention

Stereotactic ablative body radiotherapy (SABR) is a targeted mode of radiation therapy. It involves the use of radiation delivered from numerous angles so that only a small volume of tissue is exposed to the full dose. It can be delivered either as a single dose or in up to five fractions. It is an alternative to surgery or other forms of radiotherapy, especially in patients who cannot undergo surgery and for tumours that are hard to reach, located close to vital structures or subject to movement within the body.

4 Findings

In March 2015, we searched for evidence about the clinical and cost effectiveness of SABR for the treatment of spinal arteriovenous malformations, spinal meningiomas and schwannomas. Although the question specified for this review included only lesions considered unsuitable for surgery because of medical co-morbidity or because the lesion is inoperable, we included studies regardless of the operability of the lesion.

The search strategy is in the Appendix.

4.1 Evidence of effectiveness

We found no systematic reviews and no randomised trials.

We found seven uncontrolled studies, none of which included participants with AVMs (Table 1). We excluded three studies with fewer than ten participants with the indications covered by this review, with respectively seven, two and one relevant participants; including these very small uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments. This left four studies for inclusion:

- Gerstzen et al published a case series of patients with benign spinal tumours treated with SABR.[1] They included 35 participants with schwannoma and 13 with meningiomas, with median follow-up of 37 months. The authors do not report overall or progression-free survival, though these measures are less important for benign tumours. They report that none of the participants with meningiomas progressed during follow-up. The results for participants with schwannoma were reported according to the indication for treatment. Most of those being treated for pain experienced a reduction on pain level that the authors deemed significant. Other patients showed an absence of radiological progression, though there is no reporting of how progression was defined or measured.

- The same research group published results on a later set of patients.[2] The authors report that there was no sub-acute or long-term spinal cord or cauda equina toxicity, nor evidence of tumour growth on serial imaging. Again, they do not report overall or progression-free survival.

- Sachdev et al reported a series of 87 participants, of whom 32 had a meningioma and 47 a schwannoma.[3] About half of the meningiomas and schwannomas reduced in size after treatment, with the others nearly all stable. The authors also report improvements in clinical state and pain, but do not describe how these were measured.

- Gagnon et al studied pain and quality of life after SABR for benign and malignant spinal tumours.[4] Only five of the two hundred participants in this study had meningioma, and only six had schwannomas. The authors do not report results according to the type of tumour. Overall, SABR was followed by improvements in pain which began within a month and continued throughout follow-up, a median period of one year.

4.2 Trials in progress

We searched clinicaltrials.gov and found one study of SABR for spinal meningiomas, schwannomas and arteriovenous malformations (NCT01347307). It is an uncontrolled study of acute and late toxicity rates of SABR for the treatment of spine metastases and benign spine tumours. It is continuing but closed to recruitment.

The RSSearch Patient Registry-Long Term Study of Use of SRS/SBRT is a long-term registry of the use and outcomes of SABR (NCT01885299), which includes neoplasms, arteriovenous malformations of the central nervous system and trigeminal neuralgia. It is enrolling participants by invitation only.

Table 1: Studies of SABR for meningioma and schwannoma

Study	Patients	Intervention	Comparator	Outcomes	Comments
Gerstzen et al [1] Pittsburgh, USA	73 people with benign intradural extramedullary spinal tumours. 13 had meningiomas and 35 had schwannomas. 8% had had previous radiotherapy and 26% were being treated for post-surgical recurrence. Mean age 44 years	SABR, mean maximum tumour dose 21 Gy (meningiomas) and 22 Gy (schwannomas).	Uncontrolled	Median follow-up 37 months Meningiomas: no radiographic tumour progression detected. Pain relief not reported. Schwannomas: “Significant” pain relief*: 14/17** (82%). Radiosurgery as primary treatment (7 participants): 5 were “stable” at last follow-up, and one had tumour shrinkage. Lesion treated for progression after neurosurgery (6 participants): no further progression. Treated for neurological deficits (5 participants): 3 improved, 1 stabilised and 1 had open resection.	No information on how progression was defined and assessed. No reporting of progression-free or overall survival.
Gerstzen et al [2] Pittsburgh, USA	40 people with benign tumours. 8 had meningiomas and 15 had schwannomas. 55% were having primary treatment and 45% were being treated for post-surgical recurrence. Median age 55 years	SABR, mean prescribed dose 14 Gy in a single fraction (35 participants) and 18 to 21 Gy in 3 fractions (5 participants).	Uncontrolled	Median follow-up 26 months. No sub-acute or long-term spinal cord or cauda equina toxicity. “No evidence of tumor growth was seen on serial imaging in any case”.	No information on how progression was defined and assessed. No reporting of progression-free or overall survival.
Sachdev et	87 people with	SABR, mean	Uncontrolled	Median follow-up 29 months	Methods of

Study	Patients	Intervention	Comparator	Outcomes	Comments
al [3] Stanford, USA	103 benign intradural extramedullary spinal tumours. 32 had meningiomas and 47 had schwannomas. Participants were “not ideal” for surgery. Median age 53 years	prescribed dose 19.4 Gy, 43% in a single fraction, 32% in 2 fractions, 18% in 3 fractions and 7% in 4 or 5 fractions.		Meningiomas: 15/32 (47%) stable, 17/32 (53%) smaller. Schwannomas: 1/47 (2%) progressed, 24/47 (51%) stable, 22/47 (47%) smaller. “Most patients with symptomatic lesions and up-to-date clinical follow-up had improvement or long-term stability of their presenting clinical symptoms after radiosurgery.” 91% of participants with meningioma and 86% of those with schwannoma were "improved” after treatment. 57% of participants with meningioma and 53% of those with schwannoma had "improvement” in pain after treatment. Five participants died, but none of the deaths was attributed to the tumours.	ascertaining and measuring clinical improvement not described.
Gagnon et al [4] Washington DC, USA	200 people with primary or metastatic spinal tumours. 5 had meningiomas and 6 had schwannomas	SABR, mean dose 26.4 Gy in 3 fractions	Uncontrolled	Median follow-up 12 months. 95% follow-up. Median survival not reached in people. Results not presented by tumour type. For all participants: pain scores	

Study	Patients	Intervention	Comparator	Outcomes	Comments
	Median age 56 years			improved by 19 points on a 100 point scale at 1 month (P < 0.0001). There was continuing improvement over the course of follow-up (P = 0.049). There was no difference in the effects of treatment on pain between participants with benign and malignant tumours (P = 0.94). For all participants: quality of life changes over 3 years no significant change in physical component scores (P = 0.46). There was a change in mental component score (P = 0.01) but this was discounted by the authors because it “reflect[ed] the death of the sickest patients”.	

* Pain was measured on a 10-point visual analogue scale before and at every follow-up attendance, with the last recorded value used as a comparison. Pain improvement was defined as movement from 5 or more to 4 or less.

** Only 17 participants had pain at inception.

4.3 Evidence of cost-effectiveness

We found no studies of the cost effectiveness of SABR for the treatment of spinal meningiomas. We found a study of the costs of three treatments for intracranial meningiomas.[5] Although spinal meningiomas were outside the study's scope, we include it in case it is of interest. The authors compared the costs of treating intracranial meningioma with microsurgery, with radiosurgery using a linear accelerator and with gamma knife radiosurgery[1] at hospitals in Rotterdam and Tilburg, in the Netherlands. Costs were denominated in 2006 euros. They included the costs of diagnostic investigations, the procedure itself (including the depreciation of equipment) and follow-up costs for the first year, for 59 participants.

Patients receiving linear accelerator treatment reported worse health status before treatment, and those receiving microsurgery had larger tumours. Total costs were higher for microsurgery (€14,329, £10,460) than for radiosurgery with a linear accelerator (€3,060, £2,230) or gamma knife (€3,966, £2,900). Microsurgery was more expensive because of the eleven-day average inpatient stay.

The value of this study is limited by the fact that it did not assess whether there were differences in the outcomes of the three treatments which might justify differences in costs. Furthermore, it is not clear whether all three treatments are equally suitable for all patients: the patients undergoing microsurgery had larger tumours: more than half had a volume of more than 15 cm^3, whereas none of the tumours treated with radiotherapy were this large; most of the tumours with a volume of 11 to 15 cm^3 were treated surgically. The relevance of the study is limited by the inclusion of intracranial tumours rather than spinal ones, and the differences between health care costs between the NHS and the Dutch health care system.

4.4 Safety

The treatment of spinal arteriovenous malformations, meningiomas and schwannomas with SABR is not associated with a serious risk of adverse effects. Three participants in Gerszten et al's first study experienced mild muscle weakness in the leg as a result of radiation-induced damage to the spinal cord, which resolved fully in two cases.[1] One participant in Sachdev et al's study developed transient radiation myelitis.[3]

4.5 Summary of section 4

We found evidence that, after SABR, spinal meningiomas and schwannomas can show an unchanged or improved radiological appearance. There are also indications that patients' pain and overall physical condition may stabilise or improve, though this was not always well-reported. Quality of life is apparently not altered by treatment, though this has not been investigated for these tumours specifically.

We found no research comparing SABR with other treatments for spinal meningiomas and schwannomas, nor on how to identify those patients most likely to benefit. We found no

[1] Radiosurgery is a term sometimes used for single-fraction stereotactic radiotherapy; it is not a form of surgery. Gamma knife is a proprietary name for a machine to carry out stereotactic radiotherapy; it is not a knife.

studies of the treatment's cost effectiveness for these indications. It appears safe enough for routine use.

We found no evidence about the use of SABR for spinal arteriovenous malformations.

5 Cost and activity

No cost or activity data were available.

6 Equity issues

We identified no specific equity issues.

7 Discussion and conclusions

The evidence about the effectiveness of SABR for spinal meningiomas and schwannomas is scanty. There are indications that, after the treatment, tumours' size may remain the same or reduce, and that pain may be reduced after treatment. However, it is not clear whether or how often the effects of treatment are permanent, how soon the tumour may subsequently regrow nor how long any effects of treatment on symptoms persist. The outcomes of SABR have not apparently been compared with those of other treatments for spinal meningiomas and schwannomas, nor has the treatment's cost effectiveness been investigated.

We found no published research on the use of SABR for spinal arteriovenous malformations.

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for spinal arteriovenous malformations, meningiomas and schwannomas which are considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

   The available evidence on this question is inconclusive.

   After SABR, spinal meningiomas and schwannomas remain radiologically unchanged or become smaller. However, the extent to which this represents a departure from their natural history or an improvement on other forms of treatment is unclear. Furthermore, the published studies have median follow-up periods of two or three years, so the longer-term durability of this effect is not clear. There are reported reductions in pain after SABR, but quality of life is apparently not improved.

   We found no published evidence on the use of SABR to treat spinal arteriovenous malformations.

   On the basis of the evidence we found, it is not possible to delineate a reliable evidence-based role for SABR in treating these conditions.

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for spinal arteriovenous malformations, meningiomas and schwannomas which are considered not suitable for surgery (because of medical co-morbidity or because lesion is inoperable), compared to best standard care?

   We do not know. We found no health economic studies of SABR for spinal meningiomas, schwannomas and arteriovenous malformations.

8 References

1. Gerszten PC, Burton SA, Ozhasoglu C, et al. Radiosurgery for benign intradural spinal tumors. *Neurosurg* 2008; 62: 887-95.
2. Gerszten PC, Quader M, Novotny J Jr, Flickinger JC. Radiosurgery for benign tumors of the spine: clinical experience and current trends. *Technol Cancer Res Treat* 2012; 11: 133-9.
3. Sachdev S, Dodd RL, Chang SD, et al. Stereotactic radiosurgery yields long-term control for benign intradural, extramedullary spinal tumors. *Neurosurg* 2011; 69: 533-9.
4. Gagnon GJ, Nasr NM, Liao JJ, et al. Treatment of spinal tumors using cyberknife fractionated stereotactic radiosurgery: pain and quality-of-life assessment after treatment in 200 patients. *Neurosurg* 2009; 64: 297-306.
5. Tan SS, van Putten E, Nijdam WM, et al. A microcosting study of microsurgery, LINAC radiosurgery, and gamma knife radiosurgery in meningioma patients. *J Neurooncol* 2011; 101: 237-45.

9 Search Strategy (search date March 2015)

Population	Intervention	Comparator	Outcomes	Studies
Adults (18 years or over) with the following tumours who are not suitable for surgery because of medical co-morbidity or because lesion is technically inoperable. Spinal Arteriovenous Malformation (AVMs) Spinal Meningioma and Schwannoma	Stereotactic Ablative Body Radiotherapy (SABR)	Best supportive care	Clinical effectiveness • Survival • Adverse events/complications • No of treatments • Quality of life (including patient self-reported outcome measures) Cost/cost-effectiveness Including resource utilisation, attendances Any	Meta-analyses Systematic reviews Randomised controlled trials Prospective non-randomised clinical study Other clinical study* Conference abstracts* Health economics studies/models

1. Lung Neoplasms/

2. (sbrt or sabr).ti,ab.

3. Radiosurgery/

4. (stereotac* adj3 (radiother* or radiat* or irradiat* or radiosurg*)).ti,ab.

5. 2 or 3 or 4

6. Neoplasm Recurrence, Local/ and (Pelvic Neoplasms/ or exp nose neoplasms/ or exp pharyngeal neoplasms/ or exp Spinal Neoplasms/ or exp abdominal neoplasm/ or exp uterine neoplasms/)

7. Retreatment/ and (Pelvic Neoplasms/ or exp nose neoplasms/ or exp pharyngeal neoplasms/ or exp Spinal Neoplasms/ or exp abdominal neoplasm/ or exp uterine neoplasms/)

8. ((retreat* or re-irradiat* or reirradiat*) and ((pelvis or pelvic or nose or nasal or pharynx or pharyngeal or nasopharyn* or spine or spinal or abdomen or abdominal or gynaecolog* or gynecolog* or uter*) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?))).ti,ab.

9. ((residual or recur*) and ((pelvis or pelvic or nose or nasal or pharynx or pharyngeal or nasopharyn* or spine or spinal or abdomen or abdominal or gynaecolog* or gynecolog* or uter*) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?))).ti,ab.

10. exp Liver Neoplasms/

11. Cholangiocarcinoma/

12. ((liver or hepatic or hepatocell*) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?)).ti,ab.

13. cholangiocarcinoma?.ti,ab.

14. exp Prostatic Neoplasms/

15. ((prostate or prostatic) adj2 (cancer? or neoplasm? or carcinoma? or tumo?r?)).ti,ab.

16. Spinal Cord/ and Arteriovenous Malformations/

17. Spine/ and Arteriovenous Malformations/

18. Central Nervous System Vascular Malformations/

19. ((spine or spinal or central nervous system or cns) adj3 (arteriovenous malformation? or avm?)).ti,ab.

20. Meningioma/

21. ((spine or spinal or central nervous system or cns) adj3 meningioma?).ti,ab.

22. Neurilemmoma/

23. ((spine or spinal or central nervous system or cns) adj3 schwannoma?).ti,ab.

24. exp Kidney Neoplasms/

25. ((renal or kidney*) adj3 (cancer* or neoplas* or carcinoma* or malignan*)).ti,ab.

26. exp Lung Neoplasms/

27. ((lung or pulmonary) adj3 (cancer? or carcinoma? or neoplas* or tumo?r? or malignan*)).ti,ab.

28. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. 5 and 28

30. limit 29 to (english language and yr="2014 -Current")

31. limit 30 to "reviews (maximizes specificity)"

32. limit 30 to ("economics (maximizes sensitivity)" or "costs (maximizes sensitivity)")

33. limit 30 to "therapy (maximizes sensitivity)"