# Stereotactic ablative body radiotherapy for previously irradiated tumours of the pelvis, spine and nasopharynx

## Questions to be addressed

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for re-irradiation of tumours of the pelvis, spine and nasopharynx which had received previous radiotherapy, compared to best standard care?

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for re-irradiation of tumours of the pelvis, spine and nasopharynx which had received previous radiotherapy, 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 previously irradiated tumours of the nasopharynx, spine and pelvis, but there is uncertainty about the clinical and cost effectiveness of this approach.

### *Clinical effectiveness*

- We found no randomised trials or systematic reviews.

*Spinal tumours*

- We found no controlled studies, but found two uncontrolled studies:
    - The first reported a series of participants with spinal metastases which had previously been treated with external beam radiotherapy. One-year local progression-free survival was 76% and median overall survival of 22.5 months.
    - Participants in the second study also had spinal metastases, some of which had previously been irradiated. The results for those with and without previous irradiation were not reported separately, but were not significantly different. The overall median survival was 21 months, and one-year and two-year progression-free survival rates were 85% and 69% respectively.

*Pelvic tumours*

- We found no controlled studies, but found two uncontrolled studies:
    - The first reported results from people with abdominal and pelvic tumours which had previously been irradiated. Local control rates were 64% at one year and 53% at two years. Overall survival rates were 52% and 37% respectively, and median overall survival was 14 months.

- The second series was of 16 people with recurrent carcinoma in the lateral pelvis. Median disease-free survival was 8.3 months and median overall survival was 11.5 months. One-year survival was 46%.

*Nasopharyngeal tumours*

- We found two controlled studies:
  - The first reported 74 people with previously irradiated, persistent or recurrent nasopharyngeal cancer treated with either SABR or brachytherapy from radioactive gold grains. Rates of local treatment failure and overall survival were similar in the two arms of this study.
  - The second controlled study was of people with recurrent nasopharyngeal cancer treated with conformal radiotherapy or SABR. The study reported similar two-year local control and cancer-specific survival after the two treatments.

- We found ten uncontrolled studies. We excluded studies with fewer than a hundred participants; including these small uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments. This left two studies for inclusion:
  - The first study reported on people who had residual disease after conventional radiotherapy. Overall survival after three years was 86%, and after five years was 76%. Disease-free survival rates were 79% and 74% respectively.
  - The second study reported on people treated with fractionated or unfractionated SABR for nasopharyngeal carcinomas in which previous radiotherapy had not been fully successful. Local control was better after fractionated SABR, perhaps because the dose was higher, but survival was similar.

***Cost effectiveness***

- We found no studies of the cost effectiveness of SABR for previously irradiated tumours of the spine, pelvis and nasopharynx.

***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. It can be used to treat previously irradiated tumours of the nasopharynx, spine and pelvis, but there is uncertainty about the clinical and cost effectiveness of this approach.

## 1.2 Existing national policies and guidance

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

# 2 Epidemiology

Various tumours may arise in the pelvis, spine and nasopharynx. Pelvic tumours include colo-rectal, prostatic and gynaecological carcinomas, all of which may metastasise to regional lymph nodes. Spinal tumours are often metastases, and nasopharyngeal carcinomas may not be cured by initial treatment or may recur locally.

After initial treatment, which may include surgery, radiotherapy and/or chemotherapy, recurrences and metastases from these tumours may be treated with SABR.

# 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.

After previous radiotherapy, local recurrences of and metastases from pelvic, spinal and nasopharyngeal tumours may be difficult to treat. Further external beam radiotherapy might produce adverse effects if high doses have already been given, and radiotherapy may make subsequent surgery technically difficult. SABR may be offered under these circumstances.

# 4 Findings

In March 2015, we searched for evidence about the clinical and cost effectiveness of SABR for the treatment of previously irradiated tumours in the pelvis, spine and nasopharynx. We excluded studies in which only some of the participants had received previous radiotherapy unless those participants' results were separately reported, and studies where another treatment was given alongside SABR.

The search strategy is in the Appendix.

## 4.1 Evidence of effectiveness

We found no randomised trials or systematic reviews.

### *4.1.1 Spinal tumours*

We found no controlled studies, but found two uncontrolled studies (Table 1):

- Garg et al reported a series of participants with spinal metastases which had previously been treated with external beam radiotherapy.[1] They reported one-year local progression-free survival of 76% and median overall survival of 22.5 months. The patients also reported pain relief after SABR, though this result was not clearly described.

- Participants in Sahgal et al's study also had spinal metastases, some of which had previously been irradiated.[2] The results for those with and without previous irradiation were not reported separately, but were not significantly different. The overall median survival was 21 months, and one-year and two-year progression-free survival rates were 85% and 69% respectively.

### *4.1.2 Pelvic tumours*

We found no controlled studies, but found two uncontrolled studies (Table 2):

- Abusaris et al reported results from 27 people with abdominal and pelvic tumours which had previously been irradiated.[3] Twenty-one of the twenty-seven recurrences were pelvic, and rectal cancer was the commonest primary.

  Pelvic recurrences were not separately reported. Local control rates were 64% at one year and 53% at two years. Overall survival rates were 52% and 37% respectively, and median overall survival was 14 months.

- Dewas et al's series was of 16 people with recurrent carcinoma in the lateral pelvis.[4] They reported median disease-free survival of 8.3 months and median overall survival of 11.5 months. One-year survival was 46%.

#### *4.1.3 Nasopharyngeal tumours*

We found two controlled studies (Table 3):

- Chua et al treated 74 people with previously irradiated, persistent or recurrent nasopharyngeal cancer with either SABR or brachytherapy from radioactive gold grains.[5] The study was unrandomised, but the authors aimed to match participants in the two arms for variables that might influence their prognosis.

  Rates of local treatment failure and overall survival were similar in the two arms of Chua et al's study. The study was small and lacked a power calculation, so may have been underpowered.

- The second controlled study was by Ozyigit et al.[6] Participants with recurrent nasopharyngeal carcinoma treated before June 2007 had conformal radiotherapy, while after that date they had SABR. The study was small and reported similar two-year local control and cancer-specific survival after the two treatments. It may also have been underpowered.

We found nine uncontrolled studies. We excluded studies with fewer than a hundred participants; including these small uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments. This left one studies for inclusion (Table 3):

- Liu et al reported on 136 people who had residual disease after conventional radiotherapy.[8] Overall survival after three years was 86%, and after five years was 76%. Disease-free survival rates were 79% and 74% respectively.

- Chua et al reported on people treated with fractionated or unfractionated SABR for nasopharyngeal carcinomas in which previous radiotherapy had not been fully successful.[7] Local control was better after fractionated SABR, perhaps because the dose was higher, but survival was similar

### 4.2 Trials in progress

We searched clinicaltrials.gov and found two relevant studies, both uncontrolled:

- In the first study, people with recurrent squamous cell carcinoma of the head and neck who have received prior radiotherapy will receive SABR plus chemotherapy (NCT02057107). This study is now recruiting in Pittsburgh.
- In the second study, people with limited spinal metastases and prior radiotherapy will receive SABR (NCT01290562). This study is now recruiting in Toronto.

### 4.3 Evidence of cost-effectiveness

We found no studies of the cost effectiveness of SABR for previously irradiated tumours of the pelvis, spine and nasopharynx.

## 4.4 Safety

*Spinal tumours*

Garg et al reported two participants with grade 3 neurological toxicity; one developed lumbar plexopathy and foot-drop and the other had persistent neuropathic pain, paraesthesia and foot-drop.[1] Twenty patients had milder adverse effects.

*Pelvic tumours*

Toxicity in Dewas et al's series was limited to grade 1 and 2, affecting seven of the sixteen participants.[2] Abusaris et al also reported only grade 1 and 2 toxicity.[3]

*Nasopharyngeal tumours*

Chua et al reported that 22% of patients developed brain necrosis, 5% developed cranial neuropathy and a further 5% developed pituitary insufficiency.[5] Other complications included haemorrhage from a carotid artery aneurysm, headaches, palatal fistula and neuroendocrine deficiencies. Liu et al report serious complications in five patients (21%) in the SABR arm, including cranial neuropathy, carotid blow-out and brain necrosis.[8]

**Table 1: Studies of SABR for spinal tumours**

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| Garg et al [1]<br><br>Houston, USA | 59 people with previously irradiated spinal metastases<br><br>Median age 60 years | SABR 27 Gy in 3 fractions (n = 50), 30 Gy in 5 fractions (n = 8) or 20 Gy in 5 fraction (n = 1). | Uncontrolled | Median follow-up 17.6 months.<br><br>16 local spine fractures<br><br>1-year local progression-free survival 76%.<br><br>Median overall survival 22.5 months.<br><br>Preservation of neurological function: 1 year 92%, 3 year 81%.<br><br>Pain relief versus baseline (details not fully explained): 1 month P = 0.07, 3 months P = 0.04, 6 months P = 0.03. | |
| Sargal et al [2]<br><br>San Francisco, United States | 39 people with spinal or paraspinal metastases, of whom 25 had prior spinal irradiation.<br><br>Median age of these 25 was 59 years. | SABR 24 Gy in 1 to 5 fractions | Uncontrolled | Median follow-up 8.5 months<br><br>Median survival 21 months for both previously irradiated and non-irradiated participants (P = 0.41 for comparison of two categories of participant). From the authors' Figure 1, median survival for the former category appears to be about 21 months also.<br><br>Median progression-free survival | Short follow-up |

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| | | | | not reached. 1-year and 2-year progression-free survival 85% and 69% respectively, similar in previously irradiated and non-irradiated participants (P = 0.09). | |

**Table 2: Studies of SABR for pelvic tumours**

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| Abusaris et al [3]<br><br>Rotterdam, the Netherlands | 27 people with recurrent cancer in an area previously treated with external beam radiotherapy.<br><br>Primaries were rectal (48%), cervical (22%), ovarian (7%), sarcoma (7%) and other (15%).<br><br>78 of recurrences were pelvic.<br><br>Median age 59 years | SABR, 2 to 6 fractions of 6 to 20 Gy each. Median dose 34 Gy, range 8 to 60 Gy. | Uncontrolled | Median follow-up not reported.<br><br>Local control: 1 year 64%, 2 years 53%.<br><br>Overall survival: 1 year 52%, 2 years 37%.<br><br>Median overall survival 14 months, range 2 to 56 months. | Pelvic and abdominal recurrences not separately reported. |
| Dewas et al [4]<br><br>Lille, France | 16 people with a lateral pelvic recurrence after treatment with external beam | SABR 36 Gy in 6 fractions over 3 weeks. | Uncontrolled | Median follow-up 10.6 months.<br><br>Median disease-free survival 8.3 months. | |

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| | radiotherapy or brachytherapy.<br><br>Primaries were anal (38%), rectal (25%), cervical (25%), uterine (6%), bladder (6%).<br><br>Median age 55 years | | | Median overall survival 11.5 months. 1-year survival 46%. | |

**Table 3: Studies of SABR for nasopharyngeal tumours**

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| Chua et al [5]<br><br>Hong Kong | 74 people with nasopharyngeal carcinoma recurring after previous radical radiotherapy.<br><br>Median age 46 years. | SABR 12 to 18 Gy, single fraction | Brachytherapy with gold grains to give a uniform dose of 60 Gy at 0.5 cm from plane of implantation | Median follow-up 42 months.<br><br>3-year local failure rate: SABR 68%, brachytherapy 78%, P = 0.098.<br><br>3-year overall survival rate: SABR 78%, brachytherapy 66%, P = 0.74. | A small and potentially underpowered study.<br><br>Participants were matched for type of local failure (persistent or recurrent), previous local failure (yes or |

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| | | | | | no), T-stage at treatment, gender and age. There may be residual confounding.<br><br>This study may have participants in common with Chua et al.[7] |
| Ozyigit et al [6]<br><br>Ankara, Turkey | 67 people with locally recurrent nasopharyngeal carcinoma, previously treated with intensity-modulated radiation therapy.<br><br>Median age not reported, though about 46 years | SABR 30 Gy over 5 fractions<br><br>Participants treated after June 2007, n = 24 | Conformal radiotherapy (CRT), median dose 57 Gy.<br><br>Participants treated before June 2007, n = 27 | Median follow-up 24 months.<br><br>2-year local control: SABR 82%, CRT 80%, P = 0.57.<br><br>Cancer-specific survival: SABR 64%, CRT 47%, P = 0.4. | A small and potentially underpowered study. |
| Chua et al [7]<br><br>Hong Kong | 125* people with residual nasopharyngeal cancer after external beam radiotherapy. | Unfractionated SABR, 12.5 Gy, n = 43, or fractionated SABR: 18 Gy in 2 to 4 | Uncontrolled with respect to this review question | Median follow-up: fractionated SABR 24 months, unfractionated SABR 40 months.<br><br>Local control: at 1 year | Participants receiving the two regimes were matched in pairs for the type of local |

| Study | Patients | Intervention | Comparator | Outcomes | Comments |
|---|---|---|---|---|---|
| | Median age not reported but about 45 years | fractions (persistent disease), 48 Gy in 4 to 6 fractions (recurrent disease), n = 43. | | fractionated SABR 91%, unfractionated SABR 70%; at 3 years fractionated SABR 83%, unfractionated SABR 51%, P = 0.003.<br><br>Overall survival: at 1 year fractionated SABR 78%, unfractionated SABR 98%; at 3 years fractionated SABR 61%, unfractionated SABR 66%, P = 0.031 | failure, retreatment T-stage and tumour volume.<br><br>This study may have participants in common with Chua et al.[5] |
| Liu et al [8]<br><br>Beijing, China | 136 people with residual nasopharyngeal cancer after external beam radiotherapy.<br><br>Median age 43 years | SABR 2 to 10 Gy over 2 to 8 fractions | Uncontrolled | Median follow-up 66 months.<br><br>Overall survival: 3 years 86%, 5 years 76%.<br><br>Disease-free survival: 3 years 79%, 5 years 74%. | |

* Only 86 of these were used in the matched pairs design.

## 4.5 Summary of section 4

*Spinal tumours*

Uncontrolled studies indicate the feasibility of SABR for previously irradiated spinal tumours, but do not indicate its effect on symptoms, quality of life or survival.

*Pelvic tumours*

Similarly for pelvic tumours, we found only uncontrolled studies. These confirm that the treatment is feasible, but provide little further useful information on its value relative to other treatments, or none at all.

*Nasopharyngeal tumours*

The controlled studies that we found indicate that SABR is of apparently similar effectiveness to brachytherapy and to three-dimensional conformal radiotherapy, though in both cases the studies were potentially underpowered. Fractionation may allow larger doses and achieve better local control, but this does not appear to lead to longer survival.

For all indications, there is a risk of adverse effects, but these were reported more frequently after SABR for nasopharyngeal tumours.

# 5 Cost and activity

No cost or activity data were available.

# 6 Equity issues

We identified no specific equity issues.

# 7 Discussion and conclusions

There is no conclusive evidence to support the clinical effectiveness of SABR for any of the three indications reviewed here.

*Spinal tumours*

We found only very limited evidence about the effectiveness of SABR for previously irradiated spinal tumours; there was not enough evidence to draw definite conclusions.

*Pelvic tumours*

Again, the evidence we found about the effectiveness of SABR for previously irradiated pelvic tumours was not substantial enough to support definite conclusions.

*Nasopharyngeal tumours*

Although we found more evidence about the use of SABR for previously irradiated nasopharyngeal tumours, including controlled studies, the evidence was also inconclusive. The controlled studies did not show any specific advantages of the treatment versus alternative treatments, nor versus supportive care.

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for re-irradiation of tumours of the pelvis, spine and nasopharynx which had received previous radiotherapy, compared to best standard care?

   We found no conclusive evidence on this question.

   There are apparently few studies which have compared SABR with alternative treatments for tumours previously treated with radiotherapy, and they do not indicate that it offers advantages to patients.

   On the basis of the evidence which we found, it is not possible to delineate a reliable evidence-based role for SABR in treating these tumours in people with previous radiotherapy.

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for re-irradiation of tumours of the pelvis, spine and nasopharynx which had received previous radiotherapy, compared to best standard care?

   We do not know. We found no health economic studies of SABR for these indications.

## 8 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 | Stereotactic Ablative Body Radiotherapy (SABR) | Best supportive care | Clinical effectiveness<br>• Survival<br>• Adverse events/complications<br>• No of treatments<br>• Quality of life | |

| | | | | |
|---|---|---|---|---|
| because lesion is technically inoperable.<br><br>Re-irradiation of Pelvis, Nasopharynx and Spine | | | (including patient self-reported outcome measures)<br><br>Cost/cost-effectiveness Including resource utilisation, attendances<br><br>Any other outcomes | |

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)"

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### *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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