Stereotactic ablative body radiotherapy for oligometastatic disease

QUESTIONS TO BE ADDRESSED

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for oligometastatic disease considered unsuitable for surgery, compared to best standard care?

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for oligometastatic disease considered unsuitable for surgery, 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 small numbers of metastatic tumour deposits, but there is uncertainty about the clinical and cost effectiveness of this approach.

Clinical effectiveness

- We found one randomised trial. It reported no significant survival advantage from adding SABR to a cisplatin-based chemotherapy regime in patients with cerebral metastases from lung cancer.
- We found four systematic reviews:
    - The first reviewed evidence about the treatment of metastatic head and neck cancer. The authors found 12 studies of the use of SABR. None of the studies was randomised, and all but two were uncontrolled. No clear conclusions can be drawn from this review.
    - The second was a systematic review of the treatment of oligometastatic non-small cell lung cancer. All the studies were uncontrolled. Outcomes varied, but half of the participants in the studies progressed within a year.
    - The third review was of the treatment of tumours metastatic to the adrenal gland, again all uncontrolled. Despite evident heterogeneity, the authors meta-analysed the results, concluding that surgical adrenalectomy produced better results than SABR.
    - The fourth review was of the treatment of pulmonary metastases. These studies were also uncontrolled and heterogenous, but, when meta-analysed, indicated that two-year survival was about 50 per cent.

- We found 32 uncontrolled studies of SABR for oligometastatic disease. We included those reporting at least 75 participants. Including further uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments. There were six such studies, resulting in seven publications:

- Comito et al reported results in 82 people with colorectal metastases in the liver or lung. Most tumours responded to SABR, and three-quarters of survivors showed local tumour control at three years. Median disease-free survival was 32 months.
- Fumagalli et al reported a series of people with hepatic or pulmonary metastases. Most tumours responded to SABR, and local control was maintained at two years in two-thirds of participants. However, median disease-free survival was less than seven months and only one in ten participants was alive and disease-free at two years.
- Jereczek-Fossa et al's study included people with metastases mainly in the brain, bone and lymph nodes. Forty-six percent of lesions responded to SABR. Over three years, more than four out of five patients progressed despite treatment, and more than two-thirds died.
- Navarria et al reported results from treating lung metastases. Sixty per cent of lesions showed a complete response to treatment, and a further 29% had a partial response. Despite this, median survival was only 20 months. Longer-term results may have been statistically unstable and less reliable.
- Milano et al's cohort had a high proportion of women with metastatic breast cancer. Those participants had better results, with 47% survival to six years, compared with only 9% for the other primary sites. Milano et al investigated several other potentially important prognostic factors but none were significant.
- Milano et al published a separate report of people from the above cohort whose metastases were confined to a single organ. After median follow-up of 23 months, 61%had died.
- Wang et al reported the effects of SABR in reducing pain from spinal metastases.

Cost effectiveness

- We found no studies of the cost effectiveness of SABR for oligometastatic disease.

Activity and cost

- NHS England has agreed to pay £1296 per patient for the planning of treatment, and £712 per SABR fraction. For three-fraction treatment, the total cost is £3432.
- No activity data were available.

Equity

- 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 small numbers of metastatic tumour deposits, 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

If not treated in time, malignant tumours often spread by means of distant metastases. In 1995, Hellman and Weichselbaum coined the term oligometastatic disease, hypothesising that some patients enter a transitional state between localised disease and widespread, incurable metastatic spread.[1] During this period, patients have a limited number of clinically detectable metastases, removal or ablation of which may prolong survival or even be curative. An alternative hypothesis is that patients with apparently oligometastatic disease often also harbour many occult deposits which will progress and limit life expectancy, whatever local treatments are used for the manifest disease.

Neither of these views is universally accurate. There are patients in both these categories, though it is difficult to separate them prospectively. Oncologists are more likely to treat metastases with curative intent in patients whose primary tumour has been treated with apparent success, whose metastases appear small and few in number and whose prognosis would be materially improved by treating them. Other relevant factors are the patient's age, comorbidity and performance status.

Treatments for metastases include surgical excision, radio-frequency or microwave ablation, locally delivered chemotherapy and external beam radiotherapy. Another treatment option is SABR.

3 The intervention

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 (sometimes called stereotactic radiosurgery) 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 January 2015, we searched for evidence about the clinical and cost effectiveness of SABR for the treatment of oligometastatic disease in the lung, liver, bone, soft tissues or lymph nodes. We included all metastases, regardless of the site of the primary tumour. There is no universally agreed definition of the maximum number of metastases considered "oligometastatic", so we did not use this criterion in our search.

The search strategy is in the Appendix.

4.1 Evidence of effectiveness

We found four systematic reviews (Table 1):

- Florescu and Thariat systematically reviewed published evidence about the treatment of metastatic head and neck cancer (search date 2012).[2] The review contained only limited information on how it was carried out.

  The authors found 12 studies of the use of SABR, with a variety of durations, treatment regimens, inclusion and exclusion criteria and follow-up. This made it impossible to meta-analyse the results or even to draw general conclusions. None of the studies was randomised. All but two were uncontrolled, and so provide no information on the benefits for patients of SABR versus other treatment options.

  Of the controlled studies, the first evaluated pulmonary metastasectomy, with SABR as a treatment for participants less suitable for surgery.[3] Survival was similar after the two treatments. The other controlled study included participants with brain metastases who received surgery, whole brain radiotherapy, surgery plus whole brain radiotherapy, radiosurgery (i.e. SABR) or supportive care.[4] No conclusive results about the effectiveness of SABR emerged from this study.

  Florescu and Thariat's review provides no reliable information on the outcomes of SABR versus other treatments for metastatic head and neck cancers.

- Ashworth et al published a systematic review of the treatment of oligometastatic non-small cell lung cancer (search date 2012).[5] The authors included studies of people with tumours of that histological type and fewer than six metastases. Studies were included whether or not the primary was controlled. The review was rigorously carried out and thoroughly reported.

  Ashworth et al found no randomised trials, and none of the studies was apparently controlled. They found five studies of SABR, but disappointingly do not report details of the regimes or the results according to the mode of treatment. They do report a wide range of outcomes among the studies of all interventions, with five-year survival ranging from 8.3 to 86 percent. Half of the participants in the studies progressed within a year.

- Gunjar et al reviewed systematically the treatment of tumours metastatic to the adrenal gland (search date 2012).[6] They included studies regardless of the extent of control of the primary or the number of metastases.

  Gunjar et al found nine published studies of SABR for adrenal metastases, reporting 178 participants. All studies were uncontrolled, and there were a wide range of total radiation doses (from 10 to 60 Gy) delivered in one to eighteen fractions. Sixty-eight percent of patients had lung cancer.

  The authors apparently carried out no tests for heterogeneity but nevertheless pooled the results. At two years, the rate of local control was 63%, and overall survival was 19%. The results from the studies of adrenalectomy were better – 84% and 46% respectively. Although the studies of the two treatments were not comparable, Gunjar

et al concluded that “surgery appears to be the most reasonable option, given the large body of retrospective data … and the apparently acceptable complication rates.”

The heterogeneity of the studies in Gunjar et al’s review casts doubt on the appropriateness of pooling the studies, but their results provide no basis for a conclusion that SABR is a better alternative to surgery.

- Siva et al carried out a similar review of the treatment of pulmonary metastases (search date 2009).[7] The authors included six studies of unfractionated treatment reporting a total of 148 participants, and 13 studies of fractionated treatment, in 334 people. All studies were uncontrolled, and they varied widely in dosage regimens, lesion size, maximum number of metastases, duration of follow-up and reported outcomes.

  As undeterred by this heterogeneity as Gunjar et al, Siva et al pooled the results. The unfractionated studies reported a weighted two-year local control rate of 79% (range 48% to 91%) and a two-year overall survival rate of 50% (range 33% to 73%). The corresponding figures for fractionated treatment are 78% (67% to 96%) and 54% (33% to 89%).

  Again, these pooled results must be treated with caution because of the studies’ heterogeneity.

We found one randomised controlled trial.[8] Lim et al randomised 105 people with non-small cell lung cancer and cerebral metastases to either stereotactic radiosurgery followed by chemotherapy or chemotherapy alone. Overall survival and progression-free survival for cranial disease were similar in the two groups.

We found 33 uncontrolled studies of SABR for oligometastatic disease. We included those reporting at least 75 participants; including further uncontrolled studies would have not provided any further information on the effectiveness of SABR relative to other treatments. There were seven such studies (Table 2):

- Comito et al studied 82 people with one to three colorectal metastases in the liver or lung.[9] Median overall survival was 32 months, with 43% of participants surviving to 3 years. Rates of local control were higher than overall survival, suggesting that occult metastases were often responsible for participants’ deaths.

- Fumagalli et al reported a series of 90 heavily pre-treated participants with five or fewer hepatic or pulmonary metastases.[10] Most had a single metastasis. Seventy-two per cent of tumours showed a response to SABR, and local control was maintained at two years in two-thirds of participants. However, the effect on longevity was modest: median disease-free survival was less than seven months and only one in ten participants was alive and disease-free at two years.

- Jereczek-Fossa et al’s study included 95 people with up to five metastases in a wider range of organs, mainly brain, bone and lymph nodes.[11] Thirty-one percent of lesions were primary tumours. Despite a bias in the ascertainment of response rates likely to inflate them, only 46% of lesions responded to SABR. Over three years, more than four out of five patients progressed despite treatment, and more than two-thirds died.

- Navarria et al reported 76 participants treated for no more than five lung metastases.[12] These authors used higher doses of radiation than Jereczek-Fossa et al, and reported better survival. Sixty per cent of lesions showed a complete response to treatment, and a further 29% had a partial response. Despite this, median survival was only 20 months. The reported rates of local control (89%), progression-free survival (70%) and overall survival (73%) were the same at two and at three years. It is likely that some patients with metastatic cancer would experience loss of local control, progression or death in the third year after treatment. Perhaps these results were based on small numbers of potentially unrepresentative longer-term survivors, and may therefore be statistically unstable and less reliable.

- Milano et al's cohort had a high proportion of women with metastatic breast cancer.[13] All the participants had a maximum of five metastases. The results for the breast cancer participants were better, with 47% survival to six years, compared with only 9% for the other primary sites. Milano et al investigated several other potentially important prognostic factors but none significantly affected outcomes.

- Milano et al published a separate study of 77 patients from the above cohort whose metastases were confined to a single organ.[14] After median follow-up of 23 months, 47 (61%) had died.

- Wang et al reported results from 149 people with mechanically stable, non-cord-compressing spinal metastases.[15] The number reporting no pain from bone metastases increased from 26% before treatment to 54% six months after treatment.

4.2 Trials in progress

We searched clinicaltrials.gov using the search terms "stereotactic" AND "radiotherapy" AND "metastases" AND ("randomised" OR "randomized"). This search yielded 67 trial, all apparently randomised. For example, there is a randomised trial of surgery plus whole brain radiotherapy versus radiosurgery plus whole brain radiotherapy for solitary brain metastases (NCT00124761). Another trial is comparing radiofrequency ablation with stereotactic body radiation therapy for colorectal liver metastases (NCT01233544).

4.3 Evidence of cost-effectiveness

We found no studies of the cost effectiveness of SABR for oligometastatic disease.

4.4 Safety

Fumagalli et al reported that hepatic SABR was associated with nausea, vomiting, gastritis and pain.[10] Adverse effects of lung treatment included asthenia, radiation pneumonitis and pleural effusion. Side effects were generally mild and uncommon.

The other studies reported similar toxicity results.

Table 1: Systematic reviews of SABR for oligometastatic disease

Review	Studies included	Intervention	Comparator	Outcomes	Comments
Florescu and Thariat [2]	12 studies of SABR given with curative intent to people with head and neck squamous cell carcinoma.	SABR, limited and incomplete information on dose and regimen and on participants	10 uncontrolled studies. One unrandomised comparison versus pulmonary metastasectomy, with SABR for those unsuitable for surgery. One comparison with surgery, whole brain radiotherapy, surgery plus whole brain radiotherapy, radiosurgery or supportive care.	The studies were not meta-analysed. The two comparative studies provided no reliable results about the relative effects of SABR and alternative treatments.	Inclusion and exclusion criteria unclear. Limited reporting of study quality. No definition of the oligometastatic state
Ashworth et al [5]	5 studies of SABR for non-small cell lung cancer and fewer than six apparent metastases, as part of a review of all treatments.	SABR, further details not specified.	None	The studies were not meta-analysed. The authors do not report the results of SABR separately from those of other treatments.	
Gunjar et al [6]	9 studies of SABR for adrenal metastases, reporting 178 participants	SABR (10 to 60 Gy) delivered in 1 to 18 fractions, most commonly 5 fractions.	None	Weighted 2-year local control: 63% Weighted 2-year overall survival: 19%	No definition of the oligometastatic state Marked but unquantified heterogeneity. Appropriateness of meta-analysis doubtful.
Siva et al [7]	19 studies of	Unfractionated:	None	Unfractionated treatment:	No definition of

Review	Studies included	Intervention	Comparator	Outcomes	Comments
	SABR for pulmonary metastases	15 to 30 Gy. Fractionated: 33 to 60 Gy in 3 to 6 fractions		2-year local control rate 79% (range 48% to 91%). 2-year overall survival rate of 50% (range 33% to 73%). Fractionated treatment: 2-year local control rate 78% (67% to 96%). 2-year overall survival rate 54% (33% to 89%).	the oligometastatic state Marked but unquantified heterogeneity. Appropriateness of meta-analysis doubtful.

Table 2: Studies of SABR for oligometastatic disease

Study	Participants	Intervention	Comparator	Outcomes	Comments
Lim et al [8] Seoul, Korea	96 people with non-small cell lung cancer and 1 to 4 synchronous cerebral metastases with maximum diameter 3cm. Median age 58 years, 76% under 65 years	Unfractionated SABR at a "high" dose, followed within 3 weeks by cisplatin-based chemotherapy.	Randomised controlled trial. Comparator was the cisplatin-based chemotherapy regime used in the SABR arm.	Median follow-up 43 months. Median overall survival: SABR + chemo 14.6 months (95% confidence interval 9.2 to 20), chemo only 15.3 months (7.2 to 23.4), hazard ratio 1.2 (0.77 to 1.89, P = 0.418). Progression-free survival for cranial disease: SABR + chemo 9.4 months (95% confidence interval 4.2 to 14.6), chemo only 6.6 months (2.9 to 10.3), hazard ratio not reported, P = 0.248. Overall response rate: SABR + chemo 57%, chemo only 37%, P = 0.011.	Participants in the SABR arm had more cerebral metastases (P = 0.026) but the total volume of metastases was similar and the chemotherapy-only group had more extra-cranial metastases
Comito et al [9]	82 people with 1 to 3 colorectal metastases in liver	Lung: 48 Gy in four fractions (n = 54) or 60	Uncontrolled	Median follow-up 2 years. Median overall survival 32 months.	

Study	Participants	Intervention	Comparator	Outcomes	Comments
Rozzano, Italy	or lung which were otherwise untreatable, no progressive or untreated disease elsewhere. 112 metastases Mean age 68 years.	Gy in 3 fractions (n = 6). Liver: 75 Gy in 3 fractions (n = 52).		Response: complete 44/112 (39%) lesions, partial 28/112 (25%), stable 22/112 (20%), progressive 18/112 (16%). Local control: 1 year 90%, 2 years 80%, 3 years 75%. Overall survival: 1 year 85%, 2 years 65%, 3 years 43%.	
Fumagalli et al [10] Lille, France	90 people (52 men) with 1 to 5 pulmonary or hepatic metastases unsuitable for surgery. WHO performance status > 3, lesions < 100mm (liver) and < 70mm (lung). 71% had a single metastasis, 85% had previous chemotherapy and 27% had had more than three cycles. All were naïve to radiotherapy. Median age 65 years	SABR, 6 to 60 Gy in 3 to 6 fractions over two weeks	Uncontrolled	Median follow-up 17 months. Response: complete 52%, partial 20%, stable 9%, progressive 20%. 21 patients died and 17 were apparently disease-free. Local control: 1 year 85%, 2 years 66%. Disease-free survival: 1 year 27% (95% confidence interval (CI) 18% to 37%), 2 years 10% (4% to 20%). Median disease-free interval: 6.7 months. On univariate analysis, risk of local treatment failure was higher with adenocarcinoma (hazard ratio (HR) 2.74, 95% CI 0.95 to 7.88, P = 0.036*). Probability of disease-free survival was lower with lung lesions than liver lesions (HR 0.47, 95% CI, 0.23 to 0.95, P = 0.02), and higher with previous chemotherapy (HR 4.51, 95% CI 1.1 to 18.5, P = 0.007).	
Jereczek-Fossa et al [11]	95 people (43 men) with 1 to 5 metastases in	SABR 24 to 30 Gy in 3 fractions.	Uncontrolled	Median follow-up 12 months. Response: complete 15/87 (17%), partial	Response assessment only performed

Study	Participants	Intervention	Comparator	Outcomes	Comments
Milan, Italy	which other local treatments were contra-indicated. 118 lesions. Median age 65 years.			25/87 (29%), stable 34/87 (39%), progressive 13/87 (15%). Three-year rates: local control 67.6%, progression-free survival 18.4%, overall survival 31.2%. Visceral lesions were associated with poorer cause-specific survival (P = 0.015) and overall survival (P = 0.041)	in 87 (74%) of participants. The worse prognosis patients were probably less likely to attend for radiological follow-up, introducing bias.
Navarria et al [12] Milan, Italy	76 people (54 men) with 1 to 5 metastases including at least one unresectable or inoperable lung metastasis, a controlled primary tumour, no progressive disease for > 6 months, other metastases stable or had responded to previous treatment. 118 lesions. 27 participants had more than one lung lesion treated. Median age 68 years	SABR, 48 to 60 Gy in 3 to 8 fractions.	Uncontrolled	Median follow-up 18 months (range 6 to 45 months). Response: complete 71/118 (60%), partial 33/118 (29%), stable 4/118 (3%), progressive 10/118 (9%). Median survival 20 months. At 1 year: local control 95%, progression-free survival 83%, overall survival 84%. At 2 years: local control 89% progression-free survival 70%, overall survival 73%. At 3 years: local control 89%. progression-free survival 70%, overall survival 73%.	These results may have been based on small numbers of potentially unrepresentative longer-term survivors, and may therefore be statistically unstable and less reliable.
Milano et al [13]	121 people with 1 to 5 extra-cranial	SABR, mostly 50 Gy in 10	Uncontrolled	Breast cancer participants (39): median follow-up 4.5 years. Other participants	

Study	Participants	Intervention	Comparator	Outcomes	Comments
Rochester, United States	metastases and Karnofsky performance status of at least 70. Median age 60 years	fractions.		(82): median follow-up 1.7 years. *All participants* Overall survival: 2 years 50%, 4 years 28%, 6 years 20%. *Breast cancer participants* Local control: 2 years 87%, 4 years 87%, 6 years 87%. Overall survival: 2 years 74%, 4 years 54%, 6 years 47%. *Non-breast cancer participants* Local control: 2 years 74%, 4 years 68%, 6 years 65%. Overall survival: 2 years 39%, 4 years 16%, 6 years 9%. The differences in local control and overall survival between breast cancer and other participants were significant (P = 0.0005 and P < 0.00001 respectively).	
Milano et al [14] Rochester, United States	77 people (27 men) with 5 or fewer metastases, confined to one organ: liver (42 (55%), lung 21 (27%), bone 9 (12%), lymph nodes 5 (7%). Median age 60 years	SABR, mostly 50 Gy in 10 fractions.	Uncontrolled	Median follow-up 23 months. 56 (73%) of participants developed further metastases, in 82% of these patients in the same organ. Mortality: all sites 47/77 (61%). Liver metastases 30/42 (71%), lung metastases 14/21 (67%), bone metastases 1/9 (11%), lymph metastases 2/5 (40%).	
Wang et al [15]	149 people with one or two mechanically	SABR, 27 to 30 Gy, typically	Uncontrolled	No pain from bone metastases, measured by the Brief Pain Inventory: before SABR 39/149 (26%), 6 months after SBRT	

Study	Participants	Intervention	Comparator	Outcomes	Comments
Houston, United States	stable, non-cord-compressing spinal metastases (166 lesions). Participants had a Karnofsky performance status score of at least 40, and an MRI scan documenting spinal or paraspinal metastasis within 4 weeks of enrolment. Median age 58 years	delivered in 3 fractions given every other day.		55/102 (54%), P < 0·0001). BPI-reported pain reduction from baseline to 4 weeks after SBRT: baseline mean 3.4, (SD 2.9) on the BPI pain-at-its-worst item at baseline, 4 weeks 2.1 [SD 2.4], effect size 0.47, P = 0.00076. Strong opioid use: baseline 43/149 (29%), 20/100 (20%) of 100 at 6 months, P = 0.011. Progression-free survival: 1 year 80.5% (95% CI 72.9% to 86.1%), 2 years 72.4% (63.2 to 79.7%).	

* This result appears anomalous, in that a hazard ratio 95% confidence interval that includes 1 is only compatible with a P-value of at least 0.05.

4.5 Summary of section 4

The evidence indicates that SABR can be effective in partially or completely ablating some patients' metastases. Whether this leads to prolonged survival versus other treatment options or supportive care cannot be ascertained from the available research.

There is little evidence on how well SABR compares in other respects to other treatments, nor on how to identify those patients most likely to benefit. We found no studies of the treatment's cost effectiveness. It appears safe enough for routine use.

5 Cost and activity

NHS England has set tariff prices for SABR used as part of its commissioning through evaluation scheme:

- Preparation code for planning – SC41Z £1,296
- Treatment code - SC31Z £178 per fraction

Three-fraction treatment is expected to be the standard treatment, at a price of £3,432. Market Forces Factor will be applied to these prices.

No activity data were available.

6 Equity issues

We identified no specific equity issues.

7 Discussion and conclusions

The evidence indicates that SABR can cause metastatic tumours to regress or even disappear from radiological images. However, the rationale for the use of SABR in patients with oligometastases is that it will materially prolong survival, so radiological changes are of only limited relevance.

We found no reliable evidence to support survival improvements from SABR. All the studies that we found reported that many patients with treated oligometastases progressed and died of disseminated disease, perhaps because there were occult metastases present at the time of treatment. The sole randomised trial showed no benefit from adding SABR to chemotherapy for cerebral metastases.

Studies report a number of longer-term survivors, but this cannot be attributed to SABR. These patients might have had a good prognosis for other reasons and with other treatments, or with none. The results of the randomised trial do not support the hypothesis that SABR lengthens survival.

Results varied substantially between studies, perhaps because of variations in dose or in participants. This indicates the uncertainties involved in selecting patients and prescribing treatment. We found little evidence about how to select the patients for SABR.

In 2012, Milano et al set out the questions that remained unanswered:[13]

- What, if any, benefit does SABR offer for patients with limited metastases?
- Which patients are most likely to derive a benefit from SABR?
- What are the optimal radiation dose fractionation schemes in terms of efficacy and toxicity?
- What radiobiological mechanisms are relevant in the treatment of the targeted tumour, as well as remote disease sites?

We found no more recent evidence that addressed these questions. Until more progress has been made in resolving them, it will be difficult to define an evidence-based role for SABR in treating oligometastatic cancer.

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for oligometastatic disease considered unsuitable for surgery, compared to best standard care?

   We found no conclusive evidence on this question. Few studies have compared SABR with alternatives, and they have not been designed so that reliable answers emerged. On the basis of the evidence we found, it is not possible to delineate a reliable evidence-based role for SABR in treating metastatic cancer with curative intent.

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for oligometastatic disease considered unsuitable for surgery, compared to best standard care?

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

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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9 Search Strategy (search date March 2015)

Population	Intervention	Comparator	Outcomes	Studies
Adults (18 years or over) with oligometastatic disease (lung/liver/bone/soft tissue/nodal) who are not suitable for surgery because of medical co-morbidity or because lesion is technically inoperable.	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)"

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