

Stereotactic ablative body radiotherapy for hepatocellular carcinoma or cholangiocarcinoma

Questions to be addressed

1. What is the clinical effectiveness of stereotactic ablative body radiotherapy for hepatocellular carcinoma or cholangiocarcinoma 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 hepatocellular carcinoma or cholangiocarcinoma 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 hepatocellular carcinoma and cholangiocarcinoma, two primary liver tumours, but there is uncertainty about the clinical and cost effectiveness of this approach.

Clinical effectiveness

- We found no randomised controlled trials.

Hepatocellular carcinoma

- We found two systematic reviews of the effectiveness of SABR for the treatment of hepatocellular carcinoma:
 - The authors of the first systematic review found no randomised trials or other controlled research. They included four uncontrolled studies of SABR for hepatocellular carcinoma. They did not meta-analyse the studies, but reported overall one-year survival rates of 33% to 100% after SABR.
 - The authors of the second review also found no randomised trials or other controlled research. They meta-analysed studies of conventional radiotherapy, SABR and charged particle therapy. Overall survival, progression-free survival and locoregional control were similar in people treated with charged particle therapy and SABR, both of which were reportedly superior to conventional radiotherapy. These results are not reliable.
- We found a systematic review of the safety of SABR for hepatocellular carcinoma. Of 65 people treated for hepatocellular carcinoma with SABR, four developed grade 5 radiation-induced liver disease (the most severe) and two developed grade 4 disease. The authors recommended that SABR should only be used with caution or in clinical trials.
- We found four controlled but unrandomised studies:
 - The first study compared results of trans-arterial chemo-embolisation with or without SABR in people with single hepatocellular carcinomas unsuitable for resection or

- ablation. Patients allocated to trans-arterial chemo-embolisation alone were older and had larger tumours. Participants who received both treatments had better outcomes, with higher rates of tumour response and disease-free survival, than those who received chemo-embolisation alone. Overall survival did not differ between the groups. The differences in co-morbidity and tumour size mean that the comparison of effectiveness in this study is unreliable.
- The second study had the same design as the first, though the two treatment groups showed fewer differences. Local recurrences was more common in the group treated with trans-arterial chemo-embolisation only than in those who received both treatments, and overall survival was longer in the latter group.
 - The third study compared a group of people who had undergone SABR for recurrent hepatocellular carcinoma with other contemporaneous patients who had received other treatments, or none. After multivariate adjustment for other prognostic variables, SABR was associated with longer survival. When the analysis was limited to pairs of patients whose recurrent tumours had similar characteristics, survival was also longer after SABR. A residual risk to this study's reliability arises from the possible existence of other confounders not measured and reported by the authors. The more important limitation on the usefulness of this study is the heterogeneous nature of the treatments in the control arm. It is not clear to which of these treatments SABR is superior and to which it might therefore be preferred.
 - The final study was a comparison of liver resection and SABR for early hepatocellular carcinoma. Survival was similar in the two groups. However, there were only 48 participants in the trial, meaning that it lacked power to detect any but the largest of differences; it was also subject to serious and unadjusted confounding.
- We found thirty uncontrolled studies of SABR for hepatocellular carcinoma. 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 reported the results of SABR in people with a single hepatocellular carcinoma either unsuitable for surgery or percutaneous treatment or who refused those treatments. Overall survival at one year was 95%, at two years 83% and at three years 70%.
 - The second study was of the effects of SABR in people with hepatocellular carcinoma unsuitable for other treatments. Most showed a partial response or no change in their tumour after treatment. Although local control was maintained at one year in 87% of participants, median overall survival was 17 months and median time to progression was six months.

Cholangiocarcinoma

- We found no systematic reviews of SABR for cholangiocarcinoma.
- We found six uncontrolled studies. We excluded four studies with ten or fewer 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 two studies for inclusion:
 - The first reported the results of SABR in people with unresectable cholangiocarcinoma. Median progression-free survival was less than seven months and median overall survival was less than eleven months. The authors concluded that the survival results in their study “appear no better than the survival outcomes achieved with external beam radiotherapy ... despite the use of a dose schedule of very high radiobiological potency.”
 - The second study reported results after a median of less than five months. Only a third of patients showed a response to treatment, and median survival was less

than a year. The authors concluded that “randomised controlled trials are needed to further define the role of [SABR] in the treatment of primary liver tumours.”

Cost effectiveness

- We found no studies of the cost effectiveness of SABR for hepatocellular carcinoma or cholangiocarcinoma.

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

Primary tumours in the liver are much less common than ones which have metastasised there from elsewhere. The commonest primary liver tumour is hepatocellular carcinoma, which often develops from liver cells affected by chronic liver disease such as cirrhosis or hepatitis. Cholangiocarcinoma is less common, and arises from the cells lining the bile ducts.

Hepatocellular carcinoma can be treated with surgical resection, liver transplantation, trans-catheter arterial chemo-embolisation, percutaneous ablation, systemic drug treatment, and external beam or stereotactic radiotherapy.

Cholangiocarcinoma can be treated with surgery in less advanced cases, and with radiotherapy. Chemotherapy may also be used.

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. It often requires fewer treatment sessions than other forms of radiotherapy to the liver.

4 Findings

In March 2015, we searched for evidence about the clinical and cost effectiveness of SABR for the treatment of hepatocellular carcinoma and cholangiocarcinoma.

The search strategy is in the Appendix.

4.1 Evidence of effectiveness

4.1.1 Hepatocellular carcinoma

We found three systematic reviews of SABR for the treatment of hepatocellular carcinoma:

- Tao and Yang reviewed studies of SABR for hepatocellular carcinoma and hepatic metastases (search date 2011).[1] The authors found no randomised trials or other controlled research. They included four uncontrolled studies of SABR for hepatocellular carcinoma. They did not meta-analyse the studies, but reported overall one-year survival rates of 33% to 100% after SABR. Tao and Yang contrasted these rates with those of 50% to 70% reported after other treatments such as resection, radiofrequency ablation and chemo-embolisation. However, the relevance of this comparison is uncertain, as SABR is sometimes used when other treatments are not feasible.
- The second systematic review was by Qi et al.[2] These authors included studies of people with hepatocellular carcinoma treated with photon therapy (including SABR), charged particle (proton and carbon ion) therapy or combined photon therapy and charged particle therapy. Qi et al found no controlled studies comparing charged particle therapy with photon therapy. They found twenty uncontrolled studies of charged particle therapy including a total of 1627 participants, thirty studies of SABR with 1473 participants and twenty-three studies of conventional radiotherapy with 2104 participants.

There were important differences between the three sets of participants in median age, tumour size, severity of cirrhosis and duration of follow-up. The authors also report a high degree of heterogeneity within all three groups of studies, but nevertheless meta-analysed them. Overall survival, progression-free survival and locoregional control were similar in people treated with charged particle therapy and SABR, both of which were reportedly superior to conventional radiotherapy. The frequency of adverse effects of treatment was also similar, except that there was significantly more late toxicity in the SABR group than in the charged particle therapy group.

Qi et al's review should be treated with great caution:

- The studies were too heterogeneous for meta-analysis to be reliable.
- The differences between studies in the three categories introduced what the authors admitted was a "high risk of bias".

- Selection bias was also likely to be present, with charged particle therapy and SABR probably offered to participants with a better prognosis.
 - The authors note that “the toxicity data are scarcely reported among studies, and as a result it is not possible to adequately compare acute and late treatment toxicity based on clinical data.” This casts doubt on their decision to report toxicity data.
- The third systematic review was of the safety of SABR and is summarised in Section 4.4 below.

We found no randomised trials.

We found four controlled but unrandomised studies (Table 1):

- Honda et al compared results of trans-arterial chemo-embolisation with or without SABR in people with single hepatocellular carcinomas unsuitable for resection or ablation.[3] Patients were allocated to trans-arterial chemo-embolisation alone if they had comorbidity which prevented SABR, had tumours near the digestive tract or declined SABR. These participants tended to be older, with larger tumours and to have received a different drug by chemo-embolisation than those who also received SABR; levels and types of co-morbidity were not reported.

Participants who received trans-arterial chemo-embolisation and SABR had better outcomes, with higher rates of tumour response and disease-free survival, than those who received chemo-embolisation alone. Overall survival did not differ between the groups. However, the differences in co-morbidity and tumour size mean that this study was undermined by confounding, and the better results when SABR was added to trans-arterial chemo-embolisation may be attributable to these underlying differences rather than the effects of treatment. Honda et al did not adjust their results for these confounders.

- Jacob et al’s study had the same design as Honda et al’s. [4] The authors recruited 161 participants with unresectable hepatocellular carcinoma at least 3cm in diameter who had not had previous treatment other than chemotherapy. One hundred and twenty-four patients had trans-arterial chemo-embolisation only, and 37 also had SABR. How the latter group was selected is not explained, beyond a statement that “referrals for adjuvant [SABR] ebbed and flowed according to the successes and failures of this treatment modality.”

Local recurrence was more common in the group treated with trans-arterial chemo-embolisation only than in those who received both treatments, and overall survival was longer in the latter group. These results may be attributable to selection bias arising from differences in patient characteristics in treatment regimes; there were however none apparent in the reported results. Unusually, Jacob et al did not report median follow-up, so differential loss to follow-up is another potential source of bias. The authors comment “the confirmation of [their results] will require this concept to be tested in a prospective, randomized clinical trial.”

- Huang et al compared a group of 36 patients who had undergone SABR for recurrent hepatocellular carcinoma with other contemporaneous patients who had received other treatments, or none. [5] After multivariate adjustment for other prognostic variables, SABR was associated with longer survival. When the analysis was limited to

pairs of patients whose recurrent tumours had similar characteristics, survival was also longer after SABR.

Huang et al made efforts to overcome the risk of confounding inherent in their unrandomised study. The multivariate adjustment and the pair-matching will have reduced the confounding effect of the variables that the authors measured. A residual risk to this study's reliability arises from the possible existence of other confounders not measured and reported by Huang et al. It is unclear why some participants had SABR and others did not, though the authors note that "the final treatment depended on patients' decisions." Perhaps patients who were not offered SABR or who declined it differed systematically from those who received it, for example in having more comorbidity or less resilience. The extent of residual confounding from any such effect cannot be gauged, but it would tend to bias the study in favour of SABR.

The more important limitation on the usefulness of Huang et al's study is the heterogeneous nature of the treatments in the control arm. There were seven of these, ranging from liver transplantation to no treatment at all. It is not clear to which of these treatments SABR is superior and to which it might therefore be preferred. With appropriate caution, Huang et al make no claim of therapeutic superiority for SABR, concluding merely that their study "supports that [SABR] is feasible".

- Yuan et al reported a comparison of liver resection and SABR for early hepatocellular carcinoma. [6] Survival was similar in the two groups. However, there were only 48 participants in the trial, meaning that it lacked power to detect any but the largest of differences. Not only was it unrandomised, but the participants allocated to surgery had less advanced liver disease and less systemic disease, which may explain their longer survival. Yuan et al did not adjust their results for these confounders.

We found thirty 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 (Table 1):

- Sanuki et al reported the results of SABR in 185 people with a single hepatocellular carcinoma either unsuitable for surgery or percutaneous treatment or who refused those treatments. [7] Patients who received a dose of more than 25 Gy to the bowels were excluded, introducing a potential bias in favour of SABR.

Overall survival at one year was 95%, at two years 83% and at three years 70%. There were ten local recurrences at a median of 21 months after SABR. Twenty-one (11%) participants died of disease progression, 23 (12%) died of liver failure and 8 (4%) died of other causes.

- Bujold et al carried out a study of the effects of SABR in 102 people with hepatocellular carcinoma unsuitable for other treatments. [8] Most showed a partial response or no change in their tumour after treatment. Although local control was maintained at one year in 87% of participants, median overall survival was 17 months and median time to progression was six months.

Table 1: Studies of SABR for hepatocellular carcinoma

Study	Patients	Intervention	Comparator	Outcomes	Comments
Honda et al [3] Hiroshima, Japan	68 people with a single hypervascular hepatocellular carcinoma, maximum diameter 3 cm. They were unsuitable for resection or ablative treatment.	Trans-arterial chemo-embolisation (TACE) with cisplatin (7 to 70 mg) or miriplantin (20 to 80 mg) plus SABR 48 or 60 Gy in 4 or 8 fractions over 4 to 10 days. Median age 70 years	TACE only Median age 73 years	Median follow-up: SABR + TACE 12.3 months, TACE only 30.2 months, P < 0.05. Complete response: SABR + TACE 29/30 (96%), TACE only 1/30 (3%), P < 0.001. Median disease-free survival SABR + TACE 15.2 months, TACE only 4.2 months, P = 0.029. Overall survival: SABR + TACE not yet reached, TACE only 40.9 months, P = 0.47.	Participants received TACE only if they declined SABR, had a tumour near the digestive tract or had co-morbidity. TACE participants were older, with larger tumours. They were more likely to have received cisplatin than miriplantin. Marked difference in duration of follow-up, The allocation bias and differences between the two arms mean this study is seriously confounded.
Jacob et al [4] Birmingham,	161 people with an unresectable hepatocellular carcinoma	Trans-arterial chemo-embolisation (TACE) not	TACE only (n = 124)	Median follow-up: not reported. Local recurrence: SABR + TACE 4/37 (11%), TACE-only 32/124	The basis on which patients were selected for SABR is not

Study	Patients	Intervention	Comparator	Outcomes	Comments
USA	previously untreated except with systemic chemotherapy Median age 63 years	further specified plus SABR 36 to 60 Gy usually in 3 fractions over up to 7 days (n = 37).		(26%), P = 0.042. Median overall survival: SABR + TACE 33 months, TACE-only 20 months, P = 0.02.	explained.
Huang et al [5] Taipei, Taiwan	174 people with a unresectable or medically inoperable recurrent hepatocellular carcinoma Median age 67 years	SABR 37 GY in 4 or 5 fractions over 4 or 5 consecutive days (n = 36)	Other contemporaneous patients, matched for stage, Cancer of the Liver Program score and "other combined therapeutic modalities" (n = 138): trans-arterial chemo-embolisation 77 (56%), liver transplantation 12 (9%), thalidomide 9 (7%), sorafenib 3 (2%), chemotherapy 1 (1%), radio-frequency ablation 3 (2%), no treatment 33 (24%). None received SABR. 28 pairs of patients were matched for recurrence stage and disease severity from the	Median follow-up: SABR 14 months, controls not reported. Complete response 22%, partial response 37%, stable disease 39%, progression 2%. SABR was associated with longer survival after adjustment for other prognostic variables: hazard ratio 2.39, 95% confidence interval (CI) 1.25 to 4.59, P = 0.009. Matched pairs analysis: 2-year survival SABR 73%, controls 42%, P = 0.013. Time to progression: SABR 8.6 months, controls 3.5 months, P value not reported.	Non-SABR participants had less advanced tumours (P = 0.007) but more adverse Child-Pugh* classification (P = 0.034).

Study	Patients	Intervention	Comparator	Outcomes	Comments
Yuan et al [6] Tianjin, China	48 people with stage 1** hepatocellular carcinoma) Patients allocated to surgery had less advanced cirrhosis (P < 0.05) and less systemic disease (P < 0.05). Median age 56 years	SABR 39 to 54 Gy in 3 to 8 fractions on consecutive days (n = 22).	two groups. Surgical resection (n = 26)	Median follow-up 53 months SABR: complete response: 11/22 (50%), partial response 9/22 (41%), stable disease 2/22 (9%). 1-year survival: SABR 73%, surgery 89%. 2-year survival: SABR 67%, surgery 73%. 3-year survival: SABR 57%, surgery 69%. Overall survival: P = 0.49.	No power calculation. Being small, the study could only have detected very large differences in survival. The comparison of survival is seriously confounded by differences between the two groups which are highly likely to influence prognosis.
Sanuki et al [7] Kamakura, Japan	221 people with a single hepatocellular carcinoma of maximum diameter 5cm, in whom surgery or percutaneous ablation was unfeasible, difficult or refused. Participants were treated with curative intent. Only 185 treated with SABR, see	SABR, 35 Gy (n = 48) or 40 Gy (n = 137) in 5 fractions over 5 to 9 days. Dose reduced by 5 Gy if the proportion on normal liver receiving at least 20 Gy exceeded 20%.	Uncontrolled	Median follow-up 31 months (35 Gy) and 23 months (40 Gy). 10 local recurrences at a median of 21 months after SABR. 21 (11%) participants died of progression, 23 (12%) died of liver failure and 8 (4%) died of other causes. Local control: 1 year 99%, 2 years 93%, 3 years 91%. Overall survival: 1 year 95%, 2 years 83%, 3 years 70%. Radiation dose did not affect	Participants excluded if they did not yet have 6 months follow-up (28/221, 13%) or received more than 25 Gy to the bowels (8/221, 4%). The second exclusion biases the study in favour of SABR by excluding those with poorer outcomes.

Study	Patients	Intervention	Comparator	Outcomes	Comments
	<p>comments.</p> <p>Median age 73 years</p>			<p>local control, recurrence-free survival, emergence of metastases or overall survival.</p>	
<p>Bujold et al [8]</p> <p>Toronto, Canada</p>	<p>102 people with hepatocellular carcinoma who were unsuitable for surgery, trans-arterial chemo-embolisation, radio-frequency ablation or alcohol ablation.</p> <p>Median age 69 years</p>	<p>SABR 24 to 54 Gy in 6 fractions over 2 weeks.</p>	<p>Uncontrolled</p>	<p>Median follow-up 31 months.</p> <p>Complete response 11/102 (11%), partial response 44/102 (43%), stable disease 45/102 (44%), 2 participants apparently missing.</p> <p>Local control at 1 year 87% (95% CI 78% to 93%)</p> <p>Median overall survival: 17 months (95% CI 10.4 to 21.3 months). Median time to progression 6 months (95% CI 3.4 to 6.4 months).</p>	<p>3 participants withdrawn from analysis because of progressive tumour venous thrombosis.</p>

* A classification system for patients with chronic liver disease, especially cirrhosis.

** A tumour of maximum 5 cm diameter, not involving nearby blood vessels.

4.1.2 Cholangiocarcinoma

We found six uncontrolled studies of SABR for cholangiocarcinoma. We excluded four studies with ten or fewer 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 two studies for inclusion (Table 2):

- Kopek et al reported the results of SABR in 27 people with unresectable cholangiocarcinoma.[9] Median follow-up was more than five years, longer than is usual for studies of this type. Median progression-free survival was less than seven months and median overall survival was less than eleven months. Kopek et al concluded that the survival results in their study “appear no better than the survival outcomes achieved with external beam radiotherapy ... despite the use of a dose schedule of very high radiobiological potency.”
- Ibarra et al treated participants with hepatocellular carcinoma and cholangiocarcinoma at three hospitals in the north-eastern United States. [10] The eleven people with cholangiocarcinoma were followed for a median of less than five months. Only a third of patients showed a response to treatment, and median survival was less than a year.

The authors concluded that “randomised controlled trials are needed to further define the role of [SABR] in the treatment of primary liver tumours.”

4.2 Trials in progress

We searched clinicaltrials.gov and found 24 uncontrolled studies of SABR for hepatocellular carcinoma. We found two randomised controlled trials of SABR versus trans-arterial chemo-embolisation (NCT02323360 and NCT02182687), one randomised trial of SABR plus trans-arterial chemo-embolisation versus trans-arterial chemo-embolisation alone (NCT02304445) and one randomised trial of sorafenib plus SABR versus sorafenib alone (NCT01730937). We also found an unrandomised trial of SABR plus trans-arterial chemo-embolisation versus trans-arterial chemo-embolisation alone (NCT01918683).

We found four uncontrolled studies in progress of SABR for cholangiocarcinoma.

4.3 Evidence of cost-effectiveness

We found no studies of the cost effectiveness of SABR for hepatocellular carcinoma or cholangiocarcinoma.

Table 2: Studies of SABR for cholangiocarcinoma

Study	Patients	Intervention	Comparator	Outcomes	Comments
Kopek et al [9] Aarhus, Denmark	27 people with unresectable cholangiocarcinoma. Median age 69 years	SABR 45 Gy in 3 fractions over 5 to 8 days	Uncontrolled	Median follow-up 5.4 years. Median progression-free survival: 6.7 months, 95% CI 2.3 to 11.2 months. Median overall survival: 10.6 months, 95% CI 4.8 to 16.3 months.	
Ibarra et al [10] Cleveland, New York and Rochester, United States	32 people with unresectable, untransplantable cholangiocarcinoma and a life expectancy of at least 3 months. Median age 66 years	Cleveland: median dose of 37.5 Gy in 3 fractions. New York: median dose 30 Gy in a single fraction. Rochester: 50 Gy in 10 fractions over 2 weeks.	Uncontrolled	Median follow-up 4.8 months. Median time to local progression: 4.3 months. Median overall survival: 11 months. At 3 months: complete response 11%, partial response 22%, stable disease 22%, progressive disease 44%.	Short follow-up

4.4 Safety

We found a systematic review of the safety of SABR for hepatocellular carcinoma and liver metastases (search date not stated). [10] The authors included studies of the SABR for liver tumours which reported a dose-volume constraint and liver toxicity; they used these to standardise doses and thereby to make studies more comparable.

The authors found eight suitable studies, only four of which included participants with hepatocellular carcinoma. They did not meta-analyse the results but reported that, of 65 people treated for hepatocellular carcinoma with SABR, four developed grade 5 radiation-induced liver disease (the most severe) and two developed grade 4 disease. This led them to recommend that SABR should only be used with caution or in a clinical trial.

Kopek et al reported that six of the 27 participants (22%) in their study developed “severely symptomatic” duodenal ulcers with bleeding, anaemia and either admission and/or transfusion. [9] Three patients developed duodenal stenosis.

Bujold et al report seven deaths in their study of 102 people with cholangiocarcinoma “at least possibly related to treatment.”[8] Five had liver failure, of whom two also had massive tumour thrombosis; the other two had cholangitis and duodenal haemorrhage.

4.5 Summary of section 4

4.5.1 *Hepatocellular carcinoma*

Neither of the systematic reviews yielded reliable information on the relative effectiveness and safety of SABR and other treatments for hepatocellular carcinoma.

Three of the controlled studies that we found were also inconclusive. The studies by Honda et al and Yuan et al were too confounded to be reliable, while the multiplicity of comparator treatments in Huang et al’s study undermined its usefulness. The results of the latter study cannot readily be applied to an individual patient, nor to policy-making, because it did not indicate the alternative treatment(s) to which SABR was apparently superior. Jacob et al’s results suggest there may be advantages from adding SABR to trans-arterial chemo-embolisation, but there are other explanations for the findings. Only 37 patients had SABR in this study, indicating the need for large studies to reach more definite conclusions.

The uncontrolled studies confirm the feasibility of SABR for hepatocellular carcinoma and indicate the likely outcomes for patients who receive the treatment, but provide no reliable information about the clinical effectiveness of SABR compared to best standard care.

The use of SABR in hepatocellular carcinoma carries a material risk of serious adverse effects.

4.5.2 *Cholangiocarcinoma*

The evidence about the use of SABR for cholangiocarcinoma is very limited. Taking all the studies that we found together yields a total of fewer than ninety participants. All the studies were uncontrolled and the two largest provide little evidence to support the treatment’s effectiveness. There is also little information on the risks of SABR for cholangiocarcinoma.

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 either hepatocellular carcinoma or cholangiocarcinoma.

There are no randomised trials for either indication.

Of the three controlled studies for hepatocellular carcinoma, two are unreliable because of unadjusted confounding, while the third compared SABR with too wide a range of alternative treatments to be interpretable. The uncontrolled studies indicate that some tumours are stable or regress following SABR, but provide no reason to conclude that it offers advantages over other approaches to management.

With respect to cholangiocarcinoma, a total evidence base reporting fewer than ninety participants and containing no controlled studies forms an insecure foundation for decision-making. The two larger studies report median survival of less than a year after SABR.

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

We found no conclusive evidence on this question.

Few studies have compared SABR with alternative treatments for hepatocellular carcinoma, and they have not produced reliable answers. The evidence about SABR for cholangiocarcinoma is scanty, and there are no comparative studies.

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

2. What is the cost effectiveness of stereotactic ablative body radiotherapy for hepatocellular carcinoma or cholangiocarcinoma 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 these indications.

8 Search Strategy (search date March 2015)

Population	Intervention	Comparator	Outcomes	Studies
Adults (18 years or over) with the hepatocellular carcinoma or cholangiocarcinoma 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 <ul style="list-style-type: none"> Survival Adverse events/complications No of treatments Quality of life (including patient self-reported outcome measures) Cost/cost-effectiveness Including resource utilisation, attendances Any other outcomes	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)"

9 References

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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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