CPAG Summary Report for Clinical Panel – Efficacy, toxicity and cost-effectiveness of stereotactic ablative radiotherapy (SABR) for patients with metachronous, extracranial oligometastatic cancer (all ages) [URN: 1908]

The Benefits of the Proposition (only non-comparative studies are included)		
No	*Outcome measures*	*Summary from evidence review*
1	Survival	Median overall survival is reported as the length in time a patient survives following treatment or when they were recruited for the study. Actuarial overall survival is reported as the proportion of patients surviving at a defined follow-up point, such as 1- or 2-years after beginning treatment. The best evidence on median overall survival is provided by the randomised controlled trial (RCT) by Palma et al. (2019), which compared SABR to standard care: survival was 46 and 28 months, respectively. Actuarial survival at 1- and 2-years was 86% and 70% for SABR, and 86% and 60% for standard care. The clinical benefit to the patient group is demonstrated by the results of the study by Palma et al. (2019) showing that the use of SABR in patients with controlled primary tumours and one to five oligometastases (only 5% of the patients had 5 metastases) leads to an increase of approximately 13 months in overall survival. There is variability between the results reported by Palma et al. (2019) and the rest of the evidence. However, there were similar findings in studies run under similar conditions, such as Sutera et al., 2019 that recruited a contemporary cohort of patients with oligometastases from different primary cancers with various lesion locations. Palliative radiotherapy does not aim to cure the disease and there is little, grade C evidence to compare the effect of SABR on survival with other curative treatments such as surgery (please see table below). The Palma et al. study although powered to detect a difference in overall survival, was also designed with a less rigorous statistical analysis (phase II design with lower statistical power). Overall, there is good quality evidence for this outcome. **CtE** The Commissioning through Evaluation (CtE) scheme collected data on a number of outcomes, including survival. Data was collected on 1422 patients from 17 different centres around the country. Survival rates were high in the CtE analysis with 1-year survival of 92.3% and 2-year survival of 79.2% (due to the length of follow-up it was not possible to calculate median overall survival but

		it was estimated as higher than 24 months). However, the results varied considerably depending on the location of the primary tumour – for example, 2-year survival rates ranged from 33.5% for oesophageal cancer to 94.6% for prostate cancer.
2.	Local control	Local control (LC) is the proportion of patients for which the treated metastasis does not increase in size at a defined follow-up point after beginning treatment. The best evidence on local control is provided by three retrospective case-control studies comparing SABR with surgery for lung oligometastatic disease or RFA for liver lesions. In all three studies, LC with SABR was not statistically significantly different to either of the comparators. The clinical benefit to the patient group is that a less invasive treatment such as SABR can provide equivalent results. The evidence provided should be interpreted with caution given that these were retrospective and underpowered studies with often not well-matched populations between the two treatment arms. **CtE** The results from the CtE project showed slightly lower levels of local control compared to the published literature with 1-year local control rates of 86.9% and 2-year local control rates of 72.3%. However, the CtE used a different definition of local control to the published studies so the results are not easily comparable.
3.	Progression free survival	Progression free survival (PFS) is the length of time during which the disease does not worsen, or the proportion of patients without worsening disease at a defined follow-up point after beginning treatment. There is significant variability on how different studies report this outcome. The best evidence on PFS is provided in the study by Palma et al. (2019), which compared SABR to standard care: PFS was 12 and 6 months, respectively. PFS at 1- and 2-years was 53% and 40% for SABR, and 22% and 15% for standard care. The clinical benefit to the patient group is demonstrated by the results of the study by Palma et al. (2019) showing that the use of SABR in patients with controlled primary tumours and one to five oligometastases (only 5% of the patients had 5 metastases) leads to an increase of approximately 6 months in PFS. PFS was reported as a secondary outcome (i.e. the studies were not designed with PFS as the main focus) and some studies used different definitions depending on the site of the metastases. Standard care does not aim to cure the disease and there is little, low quality evidence to compare the effect of SABR on PFS with other curative treatments such as surgery. Overall, there is some uncertainty about this outcome.

		CtE The CtE report did not include progression free survival as one of its outcomes.
4.	Mobility	In most studies, quality of life (QoL) was measured using cancer-specific questionnaires, such as the European Organization for Research and Treatment of Cancer (EORTC) or Functional Assessment of Cancer Therapy: General (FACT-G). The best evidence on quality of life are provided by two RCTs. Ost et al. (2018) reported similar QoL between SABR and active surveillance in patients with prostate cancer at 3 months and 2 years follow-up using the EORTC score. Palma et al (2019) also reported equivalent FACT-G scores between SABR and standard care at 6-month follow-up. From all 5 studies included in the review, none of the studies reported a difference in quality of life with SABR. The evidence is considered medium quality for this outcome due potential serious risks of bias. Most studies had a very short follow-up for QoL outcomes, which could mean they failed to capture the effect of late toxicity on QoL. Prostate cancer patients in particular have relatively good prognoses and QoL is an important factor in treatment decisions for these patients. **CtE** The CtE did not report outcomes for QoL as seen in the published literature, but it did report on 'patient experience' with 93% (1136 out of 1227 patients) saying they were 'likely' or 'extremely likely' to recommend SABR to family or friends.
5.	Self-care	
6.	Usual activities	
7.	Pain	
8.	Anxiety / Depression	
9.	Replacement of more toxic treatment	*Not specified in the protocol*
10.	Dependency on care giver / supporting independence	*Not specified in the protocol*
11.	Safety	Most studies reported treatment-related toxicity using the CTCAE criteria (grade 1-2 are minor adverse events, grade 3-4 severe and grade 5 death). The Palma et al. (2019) RCT reported increase in severe toxicity and grade 5 deaths with SABR compared with standard care. In addition, comparative evidence on toxicity is provided by three retrospective studies comparing SABR with surgery for lung oligometastatic disease or RFA for liver lesions. None of the three studies reported grade 4-5 toxicity and two studies reported low grade 3 toxicity (<5%).

		The clinical benefit to the patient group is that SABR can be as effective as surgery or RFA without an increase in severe toxicity. The evidence provided should be interpreted with caution given that these were retrospective and underpowered studies with often not well-matched populations between the two treatment arms. With the exception of Palma et al. (2019) that reported increased severe toxicity and grade 5 events with SABR compared to standard care the rest of the published literature consistently reports low toxicity with SABR. Given the above inconsistency, however, the evidence on the safety of SABR are downgraded to low quality. **CtE** The analysis of CTCAE adverse events showed 5.8% (95% CI 4.7-7.2%) of patients suffered grade 3 events, while 1.8% (95% CI 1.2-2.7%) suffered grade 4 events. No patient suffered grade 5 toxicity.
12.	Delivery of intervention	*Not specified in the protocol*
13.	Cost-effectiveness	*No applicable studies were found during the evidence review.* **CtE** Using data from the CtE report, a cost-effectiveness analysis was performed, which compared SABR to surgery in patients with oligometastases of the liver. Initial analysis showed that SABR results in more gains in quality-adjusted life years and lower cost compared to surgery, although using data from the CtE – which showed overall survival and local control were worse with SABR – the economic model showed surgery to be more cost-effective. However, there is considerable uncertainty about this outcome due to different prognoses for the patients involved in these studies.