NHS England

Evidence review: Efficacy, toxicity and cost-effectiveness of stereotactic ablative radiotherapy (SABR) in patients with metachronous extracranial oligometastatic cancer.

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2 Introduction

Metastatic cancer is diagnosed in approximately 140,000 patients in England per year (Cancer Research UK (CRUK), 2018). If not treated in time malignant tumours often spread by means of distant metastases. In 1995, Hellman and Weichselbaum coined the term oligometastatic disease (Hellman and Weichselbaum, 1995), hypothesising that some patients enter a transitional state between localised disease and widespread, incurable metastatic spread. During this period, patients have a limited number of clinically detectable metastases, removal or ablation of which may prolong survival or even be curative. Oligometastatic disease has since been further defined as fewer than 5 metastases.

The most common sites of cancer metastases are the lymph nodes, lungs, bones, and liver. When the cancer has spread to other parts of the body, many patients will be treated with systemic chemotherapy or targeted treatments, given with palliative intent (to control symptoms and extend life expectancy). Radiotherapy is given to help to manage pain and symptoms, but the duration of symptom control from conventional radiotherapy doses is 6 months on average. For patients with oligometastatic disease (fewer than 5 metastases) their prognosis tends to be substantially better than for patients with more widespread metastases. For this reason, optimising local control for as long as possible is vital.

Stereotactic ablative radiotherapy (SABR) refers to the precise irradiation of an image-defined extra-cranial lesion and is associated with the use of a high radiation dose delivered in a small number of fractions (8 or fewer). The technique requires specialist positioning equipment and imaging to confirm correct targeting. It allows sparing of the surrounding healthy normal tissues.

The population that would be suitable for this intervention would be all patients with extracranial metachronous oligometastatic cancer from any primary site. Metachronous disease refers to development of metastases more than 6 months after a primary cancer is treated. Patients who also have intracranial metastases as well as extracranial metastases should not be excluded from this review regarding the treatment of their extracranial metastases with SABR. However, this review will not cover the treatment of intracranial metastases with stereotactic radiotherapy/radiosurgery, as this indication is referred to in another published NHS England policy (Clinical Commissioning Policy: Stereotactic Radiosurgery/Radiotherapy for Cerebral Metastases (2013)).

It is estimated that 2200 patients with extracranial oligometastatic disease (synchronous or metachronous) would be suitable for SABR treatment annually in England (Policy Working Group consensus).

Current standard care depends on primary cancer type, but is often systemic chemotherapy, hormone therapy or targeted systemic treatment options. Treatments for metastases include surgical excision, radio-frequency, or microwave ablation, locally delivered chemotherapy and conventionally fractionated external beam radiotherapy. SABR for extracranial oligometastases has been investigated in clinical trials and in the NHS England Commissioning through Evaluation (CtE) programme. It has been suggested that stereotactic ablative radiotherapy for oligometastatic disease not only leads to a longer duration of tumour control but could also lead to an improvement in overall survival.

The objective of this review is to examine the clinical effectiveness, safety and cost effectiveness of SABR for the treatment of oligometastases compared with no local treatment or local or local treatment to oligometastases in patients with oligometastatic cancer and to identify any subgroups of patients who may greater benefit from SABR.

3 Summary of results

Sixteen studies met the inclusion criteria for clinical effectiveness and safety (Kunos et al. 2012, Stintzing et al. 2013, Comito et al. 2014, Navarria et al. 2014, Filippi et al. 2016, Lodeweges et al. 2017, Ricco et al. 2017, Warren et al. 2017, Andratschke et al. 2018, Klement et al. 2018, Lee et al. 2018, Mahadevan et al. 2018, Ost et al. 2018, Siva et al. 2018, Palma et al. 2019, Sutera et al. 2019).

Two studies reported results of a randomised controlled trial (RCT) (Ost et al. 2018, Palma et al. 2019).

There were four non randomised comparative studies (Stintzing et al. 2013, Filippi et al. 2016, Lodeweges et al. 2017, Lee et al. 2018). Three of them compared SABR with surgery (Filippi et al., 2016, Lee et al., 2018, Lodeweges et al., 2017) for treating patients with pulmonary metastases and one (Stintzing et al. 2013) compared SABR with RFA for treating patients with liver oligometastases. Six studies were prospective non-comparative cohort studies (Kunos et al. 2012, Comito et al. 2014, Navarria et al. 2014, Warren et al. 2017, Siva et al. 2018, Sutera et al. 2019).

Finally, four studies were large registries mainly of retrospectively collected data (Ricco et al. 2017, Andratschke et al. 2018, Klement et al. 2018, Mahadevan et al. 2018).

SABR effect on overall survival

Twelve studies reported the impact of SABR treatment on overall survival. All of the studies reported actuarial survival and 9 of the studies additionally reported median overall survival. The strongest evidence is provided by a phase II RCT by Palma et al. (2019)[1] that analysed patients with oligometastases from various primary tumours and in various locations. The authors reported a median overall survival of 41 months (95% CI 26-not reached) with SABR and 28 months (95% CI 19-33, HR: 0.57, p=0.09) with standard care (comprising of palliative radiotherapy and/or chemotherapy). The study concluded that the use of SABR in patients with controlled primary tumours and up to 5 oligometastases leads to an increase of approximately 13 months in OS (median OS = 41 months, 1-year OS of 86% and 2-year OS of 70%) compared to standard care. The SABR-COMET RCT was adequately powered to detect a difference in OS between SABR and standard care, however, it was designed as a phase II RCT (Palma et al. 2019) requiring a confirmatory phase III study to demonstrate if the OS advantage is true. The findings of SABR-COMET, is corroborated by a prospective cohort study (Sutera et al. 2019) with a median overall survival of 42.3 months (95%CI 27.4-not reached). Both studies recruited a contemporary cohort, and had comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various metastases locations. Although some studies reported smaller median survival with SABR, for example Kunos et al. 2012 reported only 20.2 months median overall survival (95% CI 10.9-29.5), they were characterised by potential sources of bias such as short follow-up duration, recruiting only patients from a single primary diagnosis, treated with palliative intent, and in some cases recruiting patients for almost two decades, making the population, intervention and other aspects of the patient treatment and follow-up less comparable to a contemporary cohort.

[1] Throughout the document the references Palma et al. (2019) and SABR-COMET are used interchangeably.

There is good evidence to confirm the superiority of SABR against standard care (RCT by Palma et al. 2019), albeit to the expense of a higher rate of toxicity with the intervention, and more importantly grade 5 (G5) adverse events (i.e. deaths).

Four other comparative studies, provided weak evidence that SABR is non-inferior to surgery in the case of pulmonary metastases, and to radiofrequency ablation (RFA) for liver metastases. However, the evidence provided should be interpreted with caution given that these were retrospective and underpowered studies.

SABR effect on progression free survival

Ten of the included studies reported progression-free survival (PFS) with SABR as a secondary outcome. The strongest evidence for this outcome is provided by SABR-COMET. The authors concluded that use of SABR doubles the PFS from 6 months with standard care to 12 months (HR: 0.47, 95% CI 0.3-0.6, p=0.0012).

SABR effect on local control

Ten studies reported the impact of SABR treatment on local control (LC). The majority of the evidence comes from non-comparative cohort studies, with three case-control series. The studies report local control rates of 83-97% at 1 year and 71-95% at 2 years. Lower lesion size and higher overall dose received improved LC. However, primary tumour histology did not affect the outcome in most studies. The study reported 91% and 80% local control rates at 1- and 2-years, respectively. In all three comparative studies LC with SABR was not statistically significant to either surgery or RFA. However, the evidence provided should be interpreted with caution given the retrospective nature and small sample sizes of these studies.

SABR effect on toxicity

Fourteen of the included studies provided results on toxicity. The strongest evidence comes from two RCTs, one investigating patients with oligometastases from different primary cancers with various lesion locations. The second RCT investigated only patients with prostate-related oligometastatic disease. Almost all studies used the Common Terminology Criteria for Adverse Events (CTCAE) criteria to record toxicity information; however, often the reporting was poor, failing to distinguish between acute and chronic toxicity.

With the exception of the RCT by Palma et al. (2019), no other study reported grade 5 toxicity with SABR. On the contrary, all previous studies reported a favourable toxicity profile with SABR in patients with oligometastatic disease with absence of grade 4 and grade 5 acute and chronic toxicity and very low rates of grade 3 events. In the case of the second RCT (Ost et al., 2018), there was only a low incidence of grade 1 toxicity reported with SABR. It should be noted, however, that (Ost et al. 2018) only included patients with prostate cancer.

Limitations of the evidence

Unlike the scope of the review, that includes patients with extracranial oligometastatic disease independent of the primary tumour histology and location of metastases, most existing evidence is focused either on a single histology (for example prostate or colorectal cancer) or location (pulmonary or liver metastases) and it is therefore difficult to generalise their findings. With the exception of the two RCTs, none of the other studies was adequately powered to detect a difference between the intervention and the comparator. Among other potential sources of bias

we note the short follow-up duration in some studies, patients treated with palliative intent, and in some cases recruiting patients for almost two decades, making the population, intervention, and other aspects of the patient treatment and follow-up less comparable to a contemporary cohort. None of the studies included children.

Because of the heterogeneity in treatment doses and schedules used, the optimal dose and fractionation of SABR, and the optimal number of lesions treatable with acceptable risk remain unknown from the current evidence.

Finally, although the RCT by Palma et al. 2019 was powered to detect a difference in overall survival, this was calculated on the basis of a phase 2 study design (with an alpha of 0.20). A phase 3 trial adequately powered for survival and toxicity will be required to provide definitive evidence of the overall benefit.

4 Methodology

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 11 for PICO table).

The PICO criteria were used to search for relevant publications in EMBASE, MEDLINE and Cochrane CDSR and CENTRAL (see section 12 for search strategy).

The search dates for publications were between 01/01/2009 and 08/03/2019.

The searches retrieved 4791 records. Following de-duplication in EndNote X7, 3729 records were assessed for relevance using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.

Evidence from all 16 papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).

The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 10).

5 Results

1. In patients with oligometastatic cancer, what is the clinical effectiveness of stereotactic ablative body radiotherapy to the extracranial oligometastases compared with no treatment or local treatment to oligometastases?

All 16 included studies reported on at least one clinical effectiveness outcome (Andratschke et al., 2018, Comito et al., 2014, Filippi et al., 2016, Klement et al., 2018, Kunos et al., 2012, Lee et al., 2018, Lodeweges et al., 2017, Mahadevan et al., 2018, Navarria et al., 2014, Ost et al., 2018, Palma et al., 2019, Ricco et al., 2017, Siva et al., 2018, Stintzing et al., 2013, Sutera et al., 2019, Warren et al., 2017).

Median overall survival

Nine of the included studies reported median survival. One study was the SABR-COMET RCT (Palma et al., 2019) that compared SABR with standard of care in patients with oligometastatic disease from different primary tumours, and one was a case-control study comparing SABR with RFA (Stintzing et al., 2013) for liver metastases. The rest of the studies were non-comparative cohorts (Comito et al., 2014, Kunos et al., 2012, Navarria et al., 2014, Sutera et al., 2019) and 3 registries (Andratschke et al., 2018, Klement et al., 2018, Mahadevan et al., 2018). Figure 1 shows the median overall survival achieved with SABR for these studies. Details for OS per study are presented in table 5.

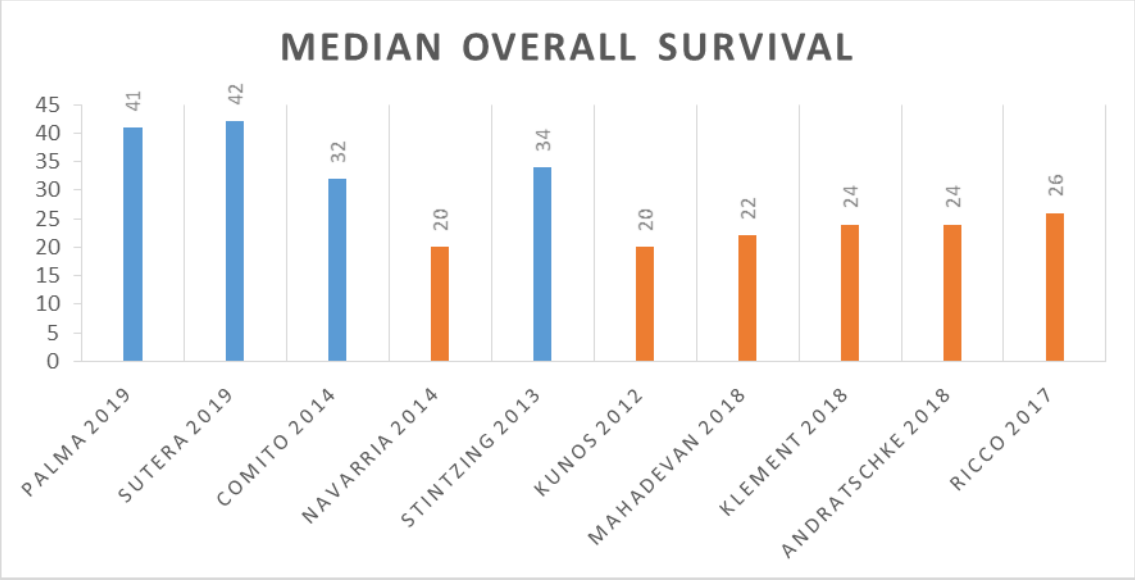

Figure 1: Median overall survival in months for patients treated with SABR. The studies are arranged based on recruitment dates starting from the most recent. All studies in orange had less than 20-months median follow-up time.

The shortest median OS reported was reported by (Kunos et al., 2012) at 20.2 months (95% CI 10.9-29.5), however, the study had a short follow-up (median 15 months), recruited only patients with gynaecological malignancies and some of the patients were treated with a low biologically

equivalent dose (BED). Oligometastatic patients are expected to have a longer survival as is evident from the findings of Palma et al (2019) for the control group that received standard care and achieved 28 months median overall survival (95%CI 19-33).

The longest median overall survival was reported by (Sutera et al., 2019) at 42.3 months (95%CI 27.4-not reached). Similar findings were reported by Palma et al (2019) at 41 months (95%CI 26-not reached). These two studies both recruited a contemporary cohort. They used comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various lesion locations, although there were differences on the individual proportions with a notably lower percentage of prostate cancer metastases for Sutera et al's (2019) study.

Some of the included studies reported the following variables influencing survival analysis[2]:

- Karnofsky Performance Status (Sutera et al., 2019, Klement et al., 2018).
- Primary diagnosis (Sutera et al., 2019, Andratschke et al., 2018).
- Metastasis size (Klement et al., 2018, Andratschke et al., 2018)
- Primary controlled (Klement et al., 2018)
- Solitary metastasis (Klement et al., 2018)

Actuarial overall survival

Twelve studies reported actuarial survival. One study was an RCT (Palma et al., 2019), three were case-control studies comparing SABR with surgery (Filippi et al., 2016, Lee et al., 2018, Lodeweges et al., 2017) for pulmonary metastases. The rest of the studies were non-comparative cohorts (Comito et al., 2014, Navarria et al., 2014, Siva et al., 2018, Sutera et al., 2019) and 3 registries (Andratschke et al., 2018, Klement et al., 2018, Mahadevan et al., 2018). Figure 2 and Figure 3 show the 1- and 2-year overall survival achieved with SABR for these studies. Details for OS per study are presented in table 5.

Actuarial overall survival was a primary outcome in a number of the included studies, however, it is unknown if any of them was adequately powered to detect a difference either from historically reported results or vs. a comparator (standard care, surgery, RFA). Studies reported mainly OS at 1- and 2-years post treatment.

[2] Only studies reporting multivariable analysis are included.

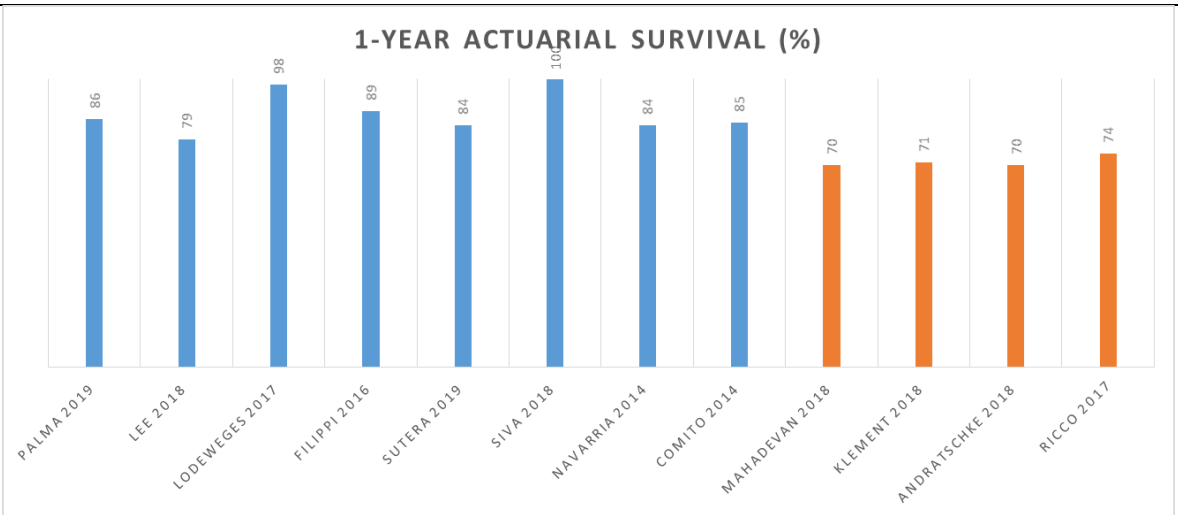

Figure 2: 1-year actuarial survival rates with SABR, in orange are results from registries.

The lowest rates for 1- and 2-year OS (approximately 70% and 47% respectively), were reported by the 4 registry analyses (Andratschke et al., 2018, Klement et al., 2018, Mahadevan et al., 2018, Ricco et al., 2017). These studies recruited patients for almost two decades starting in some cases from 1997, making the population, intervention and other aspects of the patient treatment and follow-up less comparable to a contemporary cohort. The highest 1- and 2-year OS was reported by Siva et al. (2018) a study that included only patients with prostate cancer and with bone/nodal metastases, all considered as good prognostic factors for OS.

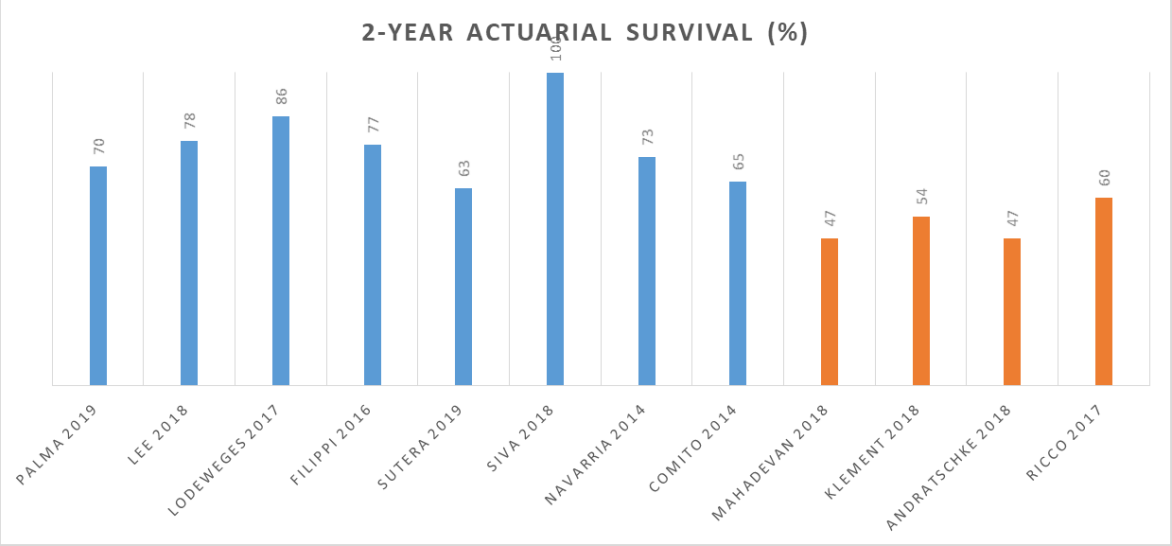

Figure 3: 2-year actuarial survival rates with SABR, in orange are results from registries.

The best evidence on actuarial survival is provided by the Palma et al. (2019) RCT that reported 86% and 70% with SABR vs. 86% and 60% with standard care (data extracted from the Kaplan-Meier curves graph included in the publication). There is consistency between the results reported by Palma et al. (2019) and the rest of the evidence as the 1-year OS rates in the rest of the literature ranged between 70-100%. The differences in the included population, study designs

and treatment received, could account for the outliers. The results were less consistent for the 2-year OS rates with rates between 47-100%.

Results of comparative studies

Three retrospective case-control studies compared SABR with surgery (Filippi et al., 2016, Lee et al., 2018, Lodeweges et al., 2017) for pulmonary metastases. All three studies reported equivalent results between SABR and surgery (metastasectomy). However, it should be noted that these were retrospective case-control studies with small sample sizes and without estimated sample size calculations. The SABR cohorts included in these studies usually had more adverse prognostic factors such as having larger tumours and higher incidence of synchronous extra-pulmonary disease (Lee et al., 2018), being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval (Lodeweges et al., 2017). Two of the studies (Filippi et al., 2016), used propensity scoring to account for the differences between SABR and the comparator.

The overall survival achieved with SABR reported from these studies is comparable to those of the largest international retrospective pulmonary metastasectomy analysis, according to which the 1- and 2-year survival rates for complete resection were approximately 85% and 70%, respectively (Pastorino et al., 1997). More recent studies have confirmed similar findings (Onaitis et al., 2009).

Local control

Ten of the included studies provided results on local control. Three of these were case-control studies comparing SABR with surgery for lung oligometastatic disease (Lee et al., 2018, Lodeweges et al., 2017) or RFA (Stintzing et al., 2013) for liver lesions. The rest of the studies were non comparative cohorts (Comito et al., 2014, Navarria et al., 2014, Siva et al., 2018, Sutera et al., 2019) and registries (Andratschke et al., 2018, Mahadevan et al., 2018, Ricco et al., 2017). Figure 4 shows the 1- and 2-year LC rates achieved with SABR for these studies. Details for LC rates per study are presented in table 6.

When studies reported separate outcomes between radical and palliative radiotherapy doses the results for the high BED only have been included in the graph. With the exception of the (Andratschke et al., 2018) study, which reported a 1-year LC of 76%, the rest of the studies reported values of 83-97%. In (Andratschke et al., 2018) the authors report a number of reasons for the relatively low LC in comparison with other studies, such as the recruitment of patients over almost two decades starting from the late 1990s, and the fact that that some patients received low BED (which has been consistently associated with poor LC across the studies). Indeed, based on Andratschke et al's. 2018 subgroup analysis, the size of the lesion and the BED affected LC, and patients treated after 2003 had a better LC than patients treated in earlier years.

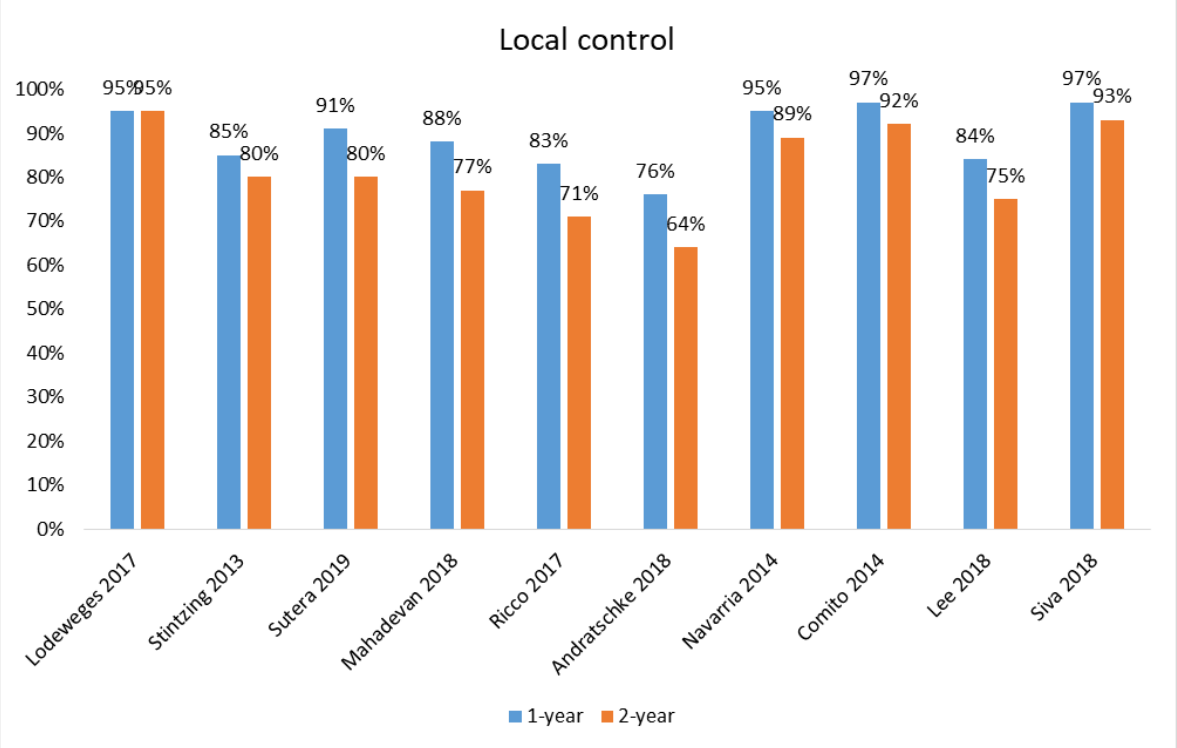

Figure 4: 1- and 2-year LC rates with SABR. When studies reported separate outcomes between radical and palliative radiotherapy doses the results for the high BED only have been included in the graph.

Results of comparative studies

Three studies were case-control studies comparing SABR with surgery for lung oligometastatic disease (Lee et al., 2018, Lodeweges et al., 2017) or RFA (Stintzing et al., 2013) for liver lesions. In all three studies, LC with SABR was not statistically significantly different to either surgery (Lee et al., 2018, Lodeweges et al., 2017) or RFA (Stintzing et al., 2013). However, all studies were retrospectively conducted with high risk of bias. Figure 5 shows the 1- and 2-year LC rates achieved with SABR vs. surgery and RFA for these studies.

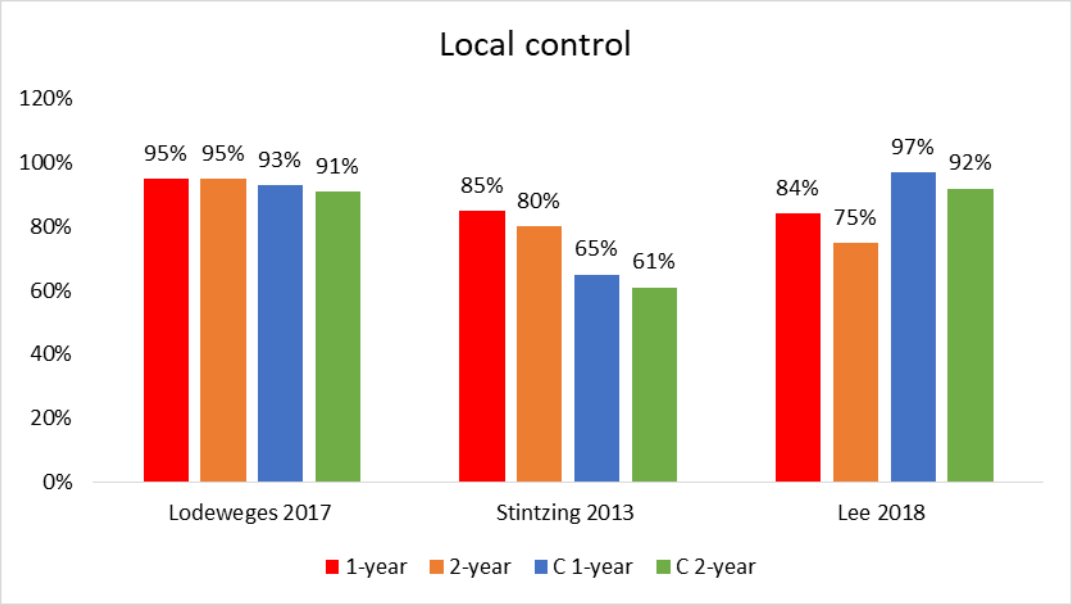

Figure 5: LC rates comparing SABR with surgery (Lee 2018, Lodeweges 2017) and RFA (Stintzing 2013). Red and orange columns show the 1- and 2-year LC achieved with SABR, respectively. Blue and green columns show the 1- and 2-year LC rates achieved with the comparator.

Effect of lesion size

In (Lodeweges et al., 2017) lesion size did not influence LC (HR =1.03, 95% CI: 0.73- 1.45). However, overall the study included small lesions with a mean size of 1.9 cm. In studies including lesions with higher size variability such as (Mahadevan et al., 2018, Andratschke et al., 2018, Ricco et al., 2017) LC was better for tumours of smaller size.

Effect of dose

With the exception of (Navarria et al., 2014) a number of studies reporting LC and performing subgroup analysis based on dose confirmed the impact of that variable on LC. It should be noted, however, that in (Navarria et al., 2014) the authors used high radiotherapy doses (BED10 dose >100Gy) to treat all metastases resulting in very homogenous cohort that is difficult to separate with subgroup analysis based on dose.

Effect of primary histology

With the exception of (Andratschke et al., 2018), which found worse LC rates in patients with colorectal cancer (CRC) metastases, all other studies that analysed results based on primary cancer diagnosis found no impact on LC (Mahadevan et al., 2018, Ricco et al., 2017). The above

findings from the literature reflect the results reported by a recent study investigating the dose-response relationship in oligometastatic disease that shows that after median follow-up 16 months, local tumour control was observed in 86.7% of the secondary lung tumours. Furthermore, although a strong dose-response relationship was observed for the overall cohort, this was not influenced by the primary cancer site within the metastatic cohort (Guckenberger et al., 2016).

Progression free survival

Ten of the included studies reported progression-free survival with SABR as a secondary outcome. The studies used different definitions of progression depending on the histology, location of metastases and follow-up schedule and therefore, the results of PFS from the included studies are less reliable than those reported for OS and LC. One of the studies was the SABR-COMET RCT (Palma et al., 2019), 5 were prospective non comparative cohorts (Comito et al., 2014, Kunos et al., 2012, Navarria et al., 2014, Siva et al., 2018, Sutera et al., 2019) and 4 were non-randomised comparative (Filippi et al., 2016, Lee et al., 2018, Lodeweges et al., 2017, Stintzing et al., 2013). Details for PFS rates per study are presented in table 7.

Progression-free survival ranged from 24%-83%. The most significant evidence for this outcome is reported by Palma et al (2019) with a doubling in PFS in favour of SABR. Six months median PFS (95% CI 3.4-7.1) in the standard care group vs. 12 months (6.9-30.4) in the SABR group (HR 0.47, 95% CI 0.30-0.76, p=0.0012). Although (Sutera et al., 2019) reported a lower median PFS of 8.7 months (95% CI, 6.6-13.1) the 95% CI overlapped. Both studies recruited a contemporary cohort, and had comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various lesion locations, although there were differences on the individual proportions with a notably lower percentage of prostate cancer metastases for the Sutera et al. (2019) study.

Quality of life

Five of the included studies reported quality of life (QoL) with SABR as a secondary outcome. Two of the studies were RCTs (Ost et al., 2018, Palma et al., 2019) and the rest were prospective non comparative cohorts (Siva et al., 2018, Sutera et al., 2019, Warren et al., 2017). Details for QoL per study are presented in table 9.

With the exception of 1 study (Warren et al., 2017), all studies used cancer-specific questionnaires to assess quality of life. None of the studies reported a difference in quality of life with SABR. More specifically, the RCT by Ost et al. (2018) found that QoL was similar at baseline and at 1-year post treatment, between patients with oligometastases from prostate cancer treated with SABR with those who were on active surveillance. This is a significant finding for this patient population with relatively good prognosis, as one of the factors influencing treatment decisions is whether treatment will affect quality of life. A prospective cohort study also reached a similar conclusion in this patient cohort, with no significant changes observed between baseline and up to 2 years post treatment.

The RCT by Palma et al. (2019) also found no difference in QoL between patients treated with SABR and those receiving standard care at 6 months post treatment. Sutera et al. (2019) reached the same conclusion for a similar patient population with no major differences between baseline and at 9 months in patients treated with SABR.

Finally, a prospective cohort study (Warren et al., 2017) reported the quality of life changes in patients with liver metastases only using the generic tool EQ5D. The mean utility score remained stable between baseline and at 6 months post treatment.

Although two of the studies contributing evidence for QoL are RCTs the current evidence is weak as QoL was not an adequately powered outcome in any of the studies. This is easily demonstrated in the case of Sutera et al. (2019) where changes in QoL were significant at 6 and 12 months but not at 9 months, which questions the validity of the result. All authors have noted that the lack of changes in QoL, indicates that SABR does not significantly adversely affect quality of life. However, it is common for patients whose health and subsequent QoL deteriorates to be lost to follow-up, resulting in detection bias and inability to accurately measure QoL outside an adequately powered phase 3 RCT.

Quality of life was a secondary outcome in all studies, therefore, none of them was adequately powered to detect a difference either from baseline or vs. a comparator (standard care or active surveillance). With the exception of (Siva et al., 2018) that reported QoL results for up to 2 years after treatment, the other studies captured only a relatively short post-treatment interval potentially failing to capture the effect of late toxicity on QoL. For some of the subgroups that active surveillance is a common treatment strategy (such as with patients with prostate cancer) because of relatively good prognosis, one of the factors weighting in treatment decisions is whether treatment will affect their QoL. Unfortunately, the current literature cannot provide conclusive answers for this outcome.

2. In patients with oligometastatic cancer, what is the safety of stereotactic ablative body radiotherapy to the extracranial oligometastases compared with no treatment or local treatment to oligometastases?

Fourteen of the included studies provided results on toxicity. Two studies were RCTs (Ost et al., 2018, Palma et al., 2019), three studies were case-control studies comparing SABR with surgery for lung oligometastatic disease (Lee et al., 2018, Lodeweges et al., 2017) or RFA (Stintzing et al., 2013) for liver lesions. The rest of the studies were non comparative cohorts (Comito et al., 2014, Navarria et al., 2014, Siva et al., 2018, Sutera et al., 2019, Warren et al., 2017, Kunos et al., 2012) and registries (Andratschke et al., 2018, Mahadevan et al., 2018, Ricco et al., 2017). Almost all studies used the CTCAE criteria to record toxicity information. However, often the reporting was poor, failing to distinguish between acute and chronic toxicity. Table 7 shows the toxicity rates reported for SABR in these studies.

The 3 deaths reported in Palma et al. (2019) that were attributed to SABR were in 2 patients treated for pulmonary metastases and 1 patient treated for an adrenal metastasis. The first patient, had a prior non-small cell lung cancer (NSCLC) and a history of chronic kidney disease, and

underwent SABR for two lung lesions and a liver lesion. All 3 lesions were treated within the expected normal tissue tolerance, meaning that they received a radiation dose that has low risk to cause toxicity. The patient developed symptoms of severe pneumonitis 2 months after SABR that did not respond to treatment and the patient died in hospital. The second patient with pulmonary metastases was treated for a single lung lesion. All normal tissue doses were within tolerance. Approximately 1 year later, he developed dyspnoea and left-sided chest pain, and was found to have a large pulmonary abscess at the treated location. Scans also showed widespread progressive disease. The patient was started on antibiotics but declined further treatment, and died in hospital. The third patient, was treated for an adrenal metastasis from colon cancer with a background history of Crohn's disease. The risk of gastrointestinal injury from SABR was high and discussed with the patient, and for that reason the gastric radiation dose was kept to a minimum. Several months after SABR, the patient was started on steroids for base of tongue swelling that proved benign. Shortly after starting steroids, the patient developed a perforated gastric ulcer requiring urgent operative intervention. Intra-operatively, the surgeon noted that the perforation occurred in the posterior gastric wall near the adrenal gland in an area of fibrosis, which corresponded to the area of treatment. In the post-operative period, the patient experienced an acute-on-chronic subdural haemorrhage and died (Palma et al., 2019).

With the exception of the SABR-COMET RCT (Palma et al., 2019) no other study reported Grade 5 toxicity with SABR. On the contrary, all previous studies reported a favourable toxicity profile with SABR in patients with oligometastatic disease with no Grade 4 and Grade 5 acute and chronic toxicity and very low rates of Grade 3 events. This finding highlights the significance of adherence to follow-up and avoiding bias during the collection of toxicity information. For example in all registry studies the retrospective data collection resulted in under-reported toxicity rates as noted by the authors of those studies. In the case control studies, patients who received different interventions had different follow-up schedules and often different toxicity profiles (Lee et al., 2018).

In the case of the second RCT by Ost et al. (2018), there were only 6 cases (17%) of G1 toxicity with metastasis-directed treatment. After removing the few cases treated with surgery, there were only two (8%) incidents of SABR-related toxicity, one associated with acute loose stools, and one with acute muscle soreness. No G2 or G5 toxicity was observed. The toxicity for all cases was well documented and assessed in the metastasis-directed treatment group without any patients lost to follow-up.

Treatment-related toxicity was a secondary outcome in all studies, therefore, none of them was adequately powered to detect a difference compared with a comparator (standard care, active surveillance, surgery, RFA). Evidence for an increase in severe toxicity with SABR is provided by the Palma et al. (2019) RCT that reported grade 5 deaths (4.5%, 95% CI 0-10%) with SABR but not with standard care. There is however, inconsistency between the results reported by Palma et al. (2019) and the rest of the evidence as no other study has reported grade 5 deaths with SABR. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care (Palma et al., 2019) and active surveillance (Ost et al., 2018) the impact of severe toxicity is clinically very important. The inconsistency between the toxicity results reported in Palma et al. (2019) and the rest of the literature, in combination with

toxicity being measured as a secondary outcome in all studies results in low quality evidence for this outcome.

3. **In patients with extracranial oligometastatic cancer, what is the cost effectiveness of stereotactic ablative body radiotherapy to the extracranial oligometastases compared with no treatment or local treatment to oligometastases?**

No eligible economic analyses comparing SABR with no treatment or local treatment were identified as part of this review.

4. **From the evidence selected, are there any subgroups of patients who may benefit from stereotactic ablative body radiotherapy to local tumours more than the wider population of interest (for example, by primary tumour type)?**

It is not possible from the current evidence to discern any subgroups of patients that may benefit from SABR more than the wider population. There is weak evidence that local control with SABR is only dependent on size and administered dose rather than primary tumour histology. Further research should aim to provide support for the overall survival benefits for tumour-specific groups in adequately powered phase 3 trials.

6 Discussion

Sixteen studies provide evidence relevant to the scope of this review. There is good quality evidence (Grade A) that SABR significantly increases median overall survival in comparison with standard care in patients with extracranial oligometastases in various locations. There is also moderate quality evidence that SABR results in high local control and low quality of evidence that the result achieved with SABR is similar to that achieved by surgery (for pulmonary oligometastases) or RFA (for liver oligometastases).

Low quality evidence suggests that SABR may be linked to severe toxicity. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care and active surveillance, the impact of severe toxicity is clinically very important and should be investigated further in future studies and using real world data.

There is low quality evidence suggesting that the QoL after SABR treatment is equivalent to that experienced by patients receiving standard care or active surveillance. Literature addressing QoL focused particularly on patients with prostate cancer, who have a relatively good prognosis. One of the factors influencing treatment decisions is whether treatment will affect patients' QOL; therefore this outcome is clinically important and should be investigated further in future studies.

The main limitation of the evidence is that with the exception of the RCT by Palma et al. (2019) most studies were non-comparative and so cannot inform the clinical efficacy and safety of SABR versus comparators. In addition, most studies had a relatively short follow-up schedule. Although

a short follow-up duration is appropriate for studying cancers with poor prognoses, in the case of oligometastatic disease is not appropriate and it can bias the reported survival analysis. The 4 retrospective case-control comparative studies have high risk of bias for patient selection and detection and are underpowered to detect differences between the two cohorts. Although some studies reported subgroup analysis, the low numbers of patients and the high risk of bias do not allow robust conclusions to be drawn.

The main implication from the available evidence is that the use of SABR in patients with controlled primary tumours and one to five oligometastases may lead to an increase of approximately 13 months in overall survival, with a doubling of progression-free survival. The inconsistency between the reported toxicity results in the literature does not allow robust conclusions about the safety of SABR compared to standard care or other comparators.

In the future, phase 3 trials are needed to confirm the benefit in overall survival in comparison with other metastases-directed treatments such as surgery and RFA, to determine whether tumour sub-groups derive differing levels of benefit, to define the maximum number of metastases and to investigate the impact of SABR on toxicity and QoL.

7 Conclusion

The available evidence from the literature supports the use of SABR in adult patients with metachronous extracranial oligometastases (up to 5 metastases). There is evidence of clinically and statistically significant improvement in overall survival, progression free survival, and local control. These findings, however, will need to be confirmed by an adequately powered phase III RCT. A conclusion about the safety profile of SABR in this population is less clear as the majority of the evidence, reported low levels of severe toxicity and absence of grade 5 toxicity. The exception to this is the report of grade 5 toxicity by the SABR-COMET RCT (4.5%) as a secondary outcome measure. Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care and active surveillance, the impact of severe toxicity is clinically important and should be investigated further in future studies and using real world data.

Because of the heterogeneity in treatment doses and schedules used, the optimal dose and fractionation of SABR, and the optimal number of lesions treatable with acceptable risk, remain unknown from the current evidence.

No published evidence exist on the cost-effectiveness of SABR compared with any of the comparators.

8 Evidence Summary Tables

Table 1: Comparative studies

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Palma et al., 2019) - NCT01446744	RCT Multicentre International (Canada, Netherlands, UK, Australia) Recruitment period 2012-2016	99 patients with various oligometastases from various primary cancers (21% prostate*, 20% breast*, 14% colorectal*) 95% of the patients had ≤4 metastases Median time to metastases was 2.4 years	Patients were randomised (2:1) to SABR (n=66) or standard care (n=33) Total dose: SABR = 30-60Gy in 3-8 fractions, single fractions of 16-24Gy were permitted for brain or vertebrae metastases Standard care= 8-30Gy in 1-10 fractions Median 24 months follow-up.	Primary Clinical effectiveness	Overall survival Progression free survival Local control	OS: -Median = 28 months (95%CI 19-33) standard care vs 41 months (95%CI 26-not reached) SABR, (HR 0.57, 95%CI 0.3-1.1, p=0.09) -1 year = 86% in both groups -2 year = 60% standard care vs. 70% SABR PFS: -Median = 6 months (95%CI 3.4-7.1) standard care vs. 12 months (95%CI 6.9-30.4) SABR, (HR 0.47, 95%CI 0.3-0.76, p=0.0012) -1 year = 22% standard care vs. 53% SABR -2 year = 15% standard care vs 40% SABR LC: 49% standard care vs 75% SABR,	9	Direct	Randomised, due to the nature of the intervention, blinding was not possible. The study population and intervention are well matched to the scope, with comparable % of prostate and colorectal cancer primary diagnoses. The groups were well matched with the exception of a higher % of prostate cancer (21% for SABR vs 6% for the control group) and a lower % of colorectal cancer in the SABR group (14% for SABR vs. 27% for the control group). The exact number of further cycles of systemic therapy, and the drugs used, could not be reliably ascertained as patients were often treated at other centres during the follow-up period. The study was adequately powered for the primary outcome, however, the

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Safety	Toxicity QoL	absolute increase 26% (95%CI 10-41) Quality of life was similar between arms at baseline and remained comparable at 6-months. Adverse events: -G2 = 6% in standard care vs. 16% in SABR -G3 3% in standard care vs. 7% in SABR -G5 0% in standard care vs. 5% in SABR The only side effect experienced with standard care was fatigue. Patients receiving SABR had fatigue, dyspnoea, pain. Grade 5: 4.5% (3 deaths)			overall survival outcomes were better than the a priori estimates of survival used in the sample size calculation, Progression was measured objectively using either PET or CT imaging. CI were reported
(Ost et al., 2018) - NCT01558427	RCT multicentre Belgium	62 patients with oligorecurrent prostate cancer All patients had less than 3 metastases	Patients were randomised (1:1) to initial metastasis-directed therapy (MDT) or active surveillance	Primary Clinical effectiveness	ADT-free survival	ITT: Median ADT-free survival was 13 months (80%CI, 12 to 17 months) for the surveillance group and 21 months (80% CI,	9	Direct	Randomised, due to the nature of the intervention, blinding, and concealment was not possible. The study population and intervention are well

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
	Recruitment period 2012-2016	Mean time to metastases was approximately 6 months	In the MDT group, SBRT (n = 25) and surgery in 6 patients Total dose = 30Gy in 3 fractions Median 3 years follow-up.			14 to 29 months) for the MDT group (HR: 0.60 [80% CI, 0.40 to 0.90]; log-rank p= 0.11).			matched to the scope, however, 6 patients in the intervention group received surgery rather than SABR. The study was adequately powered for the primary outcome. Progression was measured objectively using either PET or CT imaging. Quality-of-life scoring was performed and scored using appropriate tools namely the EORTC QLQ-C30 supplemented with the QLQ-PR25. Toxicity was assessed using the CTCAE criteria.
				Secondary Clinical effectiveness Safety	Local control Quality of life Adverse events	Quality of life was similar between arms at baseline and remained comparable up to 1-year follow-up. Six patients developed grade 1 toxicity in the MDT arm. No grade 2 to 5 toxicity was observed.			

(Lee et al., 2018)	Retrospective case-control study single-centre Korea Recruitment period unknown	51 patients with pulmonary oligometastases from various primary cancers (35.3% colorectal*) All patients had less than 3 metastases Mean time to metastases was approximately 30 months	21 patients received SABR and 30 metastasectomy Total dose = 60Gy in 3 fractions or 48Gy in 4 fractions Median follow-up: 14 months	Primary Clinical effectiveness	Overall survival Local control Progression free survival	OS: -1 year = 95% surgery vs 79.5% SABR -2 years = 81.8% surgery vs 68.2% SABR (p=0.534) LC: 1 year= 96.6% surgery vs 83.5% SABR 2 year = 91.5% surgery vs 75.2% SABR (p=0.163) PFS: 1 year= 51.1% surgery vs 23.8% SABR 2 year = 46% surgery vs 11.9% SABR (p=0.02)	4	Direct	Retrospective, no randomisation, blinding, concealment. The 2 groups well not well matched with SABR patients having larger tumours and higher incident of synchronous extra-pulmonary disease. It is unknown if the study was adequately powered, when the patients were recruited and the follow-up period was short. CI are not reported.
				Primary Safety	Toxicity	85.7% of the SABR cohort developed radiation pneumonitis: -grade 1 in 12 (57.1%), -grade 2 in 5 (23.8%), and -grade 3 in 1 (4.8%). Two patients experienced grade 1 and 2 rib fractures, one and two patients experienced grade 1 and 2 chest wall pain, respectively. In the surgery group:			

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						-1 patient experienced acute bleeding requiring surgical intervention. -1 patient had acute respiratory distress syndrome requiring intensive medical care -1 patient experienced grade 3 nausea and required fluid treatment.			

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Lodeweges et al., 2017)	Retrospective case-control study single-centre Netherlands Recruitment period 2007-2010	101 patients with pulmonary oligometastases from various primary cancers (57% colorectal*) 97% of patients had ≤ 4 metastases Mean time to metastases was approximately 16 months	42 patients received SABR and 68 metastasectomy Total dose = 60Gy in 3 fractions or 48Gy in 4 fractions Median follow-up: 7.6 years	Primary Clinical effectiveness	Overall survival Local control Progression free survival	OS: -1 year = 87% (76–93) surgery vs 98% (84–100) SABR -2 years = 74% (61–82) surgery vs 86% (71–93) SABR (p > 0.05) LC: 1 year= 93% (83–97) surgery vs 95% (80–99) SABR 2 year = 91% (79–96) surgery vs 95% (80–99) SABR (p > 0.05) PFS: 1 year= 56% (43–66) surgery vs 49% (34–63) SABR 2 year = 35% (23–46) surgery vs 27% (14–41) SABR (p > 0.05)	7	Direct	Retrospective, no randomisation, blinding, concealment. A small percentage of patients had more than 4 lesions. SABR was considered a second choice treatment after surgery and as result the groups were different the baseline clinical characteristics (in favour of surgery). The 2 groups well not well matched with SABR patients being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval. The authors used propensity scoring to account for the baseline differences among the 2 groups The study did not report a sample size calculation. The study had long follow-up.

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Filippi et al., 2016)	Retrospective case-control study single-centre Italy Recruitment period 2005-2012	170 patients with pulmonary oligometastases from colorectal cancer The majority of patients had less than 3 metastases Mean time to metastases was more than 2 years	28 patients received SABR and 142 metastasectomy Total dose = 26Gy in 1 fraction or 45Gy in 3 fractions or 55Gy in 10 fractions and 60Gy in 8 fractions Median follow-up: SABR = 27 months Surgery= 46 months	Primary Clinical effectiveness Primary Safety	Overall survival Local control Progression free survival Toxicity	OS: -1 year = 96% surgery vs 89% SABR -2 years = 82% surgery vs 77% SABR (p=0.134) The results of PFS are considered unreliable because different follow-up protocols were applied in the two cohorts. SABR: -Radiation pneumonitis grade 3 = 14.4% -Chronic chest pain grade 3 = 3.55 Surgery: No major complications and only one death within 30 days were observed among the surgical population.	5	Direct	Retrospective, no randomisation, blinding, concealment. A small percentage of patients had more than 4 lesions. The 2 groups were well matched, however, they were unbalanced in terms of numbers. The authors used propensity scoring to account for the baseline differences among the 2 groups The study did not report a sample size calculation. The study had unbalanced follow-up between the 2 groups reducing the ability to detect differences between the 2 cohorts.

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Stintzing et al., 2013)	Retrospective case-control study Single-centre Germany Recruitment period 2005-2011	60 patients with liver oligometastases from colorectal cancer The majority of patients had a solitary lesion Median time to metastases was 12 months	30 patients received SABR and 30 RFA Total dose = 26Gy in 1 fraction Median follow-up was 23 months	Primary Clinical effectiveness Primary Safety	Overall survival Local control PFS Adverse effects	OS: Median = 34.4 months (19.9-48.9) SABR vs 52.3 (31.1-73.6) RFA (p=0.06) LC: -1 year = 65% RFA vs 85% SABR -2 years = 61% surgery vs 80% SABR (p>0.05) Local PFS: Median= 6.0 months (1.9–10) RFA vs 34.4 months (3.4–65.4) SABR (p<0.001) No patient develop grade 3 or higher toxicity.	5	Direct	Retrospective, no randomisation, blinding, concealment. Baseline characteristics did not differ significantly between the groups. The study did not report a sample size calculation. It is unknown if the follow-up was consistent between the 2 groups.

* The cancer types with the highest % representation in the sample
Quality of evidence score: The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence included in the report.
HR: Hazard ratio, ITT = intention to treat, LC = local control, OS = overall survival , 95% CI = 95% confidence interval

Table 2: Non-comparative studies

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Sutera et al., 2019) NCT01345552	Prospective cohort Multicentre Ireland/US Recruitment period 2011-2017	147 patients with oligometastases from various primary cancers (21.8% lung* and 21.2% colorectal*) 97.2% of the patients had ≤4 metastases Mean time to metastases was not reported	All patients received SABR with changes in total dose and fractionation depending on treatment site Total dose = 18-60Gy in 1-5 fractions Median 41.3 months follow-up.	Primary Clinical effectiveness	Overall survival Local control PFS	OS: -Median = 42.3 months (27.4-∞) -1 year = 84% -2 year = 63% -5 year = 43% LC: -Median = not reached -1 year = 91% -2 year = 83% -5 year = 75% PFS: -Median = 8.7 months (95%CI, 6.6-13.1) -1 year = 47% -2 year = 27% -5 year = 17%	7	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population and intervention are well matched to the review scope. The study did not report a sample size calculation. Progression was measured objectively using CT imaging, however, the 6 months interval beyond the 1st year raises concerns about detection bias. Quality-of-life scoring was performed and scored using an appropriate tool namely the 27-item Function Assessment of Cancer Therapy-General (FACT-G). The fact that changes in QoL were significant at 6 and 12 months but not 9 months questions the validity of the result. Confidence intervals were reported
				Secondary Safety QoL	Adverse events	QoL did not change at completion, 6 weeks, 3 months, and 9 months after treatment. The changes were significant at 6 and 12 months. Adverse events Acute: -G2 = 7.5% -G3 = 2% Late: -G2 = 1.4% -G3 = 1.4%.			

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Navarria et al., 2014)	Prospective cohort Single centre Italy Recruitment period 2010-2012	76 patients with pulmonary oligometastases from various primary cancers (24% lung* and 38% colorectal*) Number of patients with ≤4 metastases not reported Median time to metastases = 24 months	All patients received SABR with changes in total dose and fractionation depending on treatment site Total dose = 60Gy in 3/8 fractions or 48Gy in 4 fractions The majority of patients received 48Gy in 4 fractions. Median 18 months follow-up.	Primary Clinical effectiveness Primary Safety	Overall survival Local control Progression free survival Toxicity	OS: -Median = 20 months -1 year = 84% -2 year = 73% -3 year = 73% LC: -1 year = 95% -2 year = 89% -3 year = 89% PFS: -1 year = 83% -2 year = 70% -3 year = 70% No acute or late grade2+ pulmonary toxicity, chest pain or rib fracture was observed.	7	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population and intervention are well matched to the review scope. The study did not report a sample size calculation. Progression was measured objectively using CT or PET imaging, however, not all patients were subjected to the same follow-up assessment raising concerns about detection bias. Confidence intervals were not reported

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Siva et al., 2018) U1111-1140-7563	Prospective cohort Single-centre Australia Recruitment period 2013-2014	33 patients with bone and lymph nodes oligometastases from prostate cancer All patients had ≤3 metastases Mean time to metastases was not reported	All patients received SABR with a single fraction of 20Gy Total dose = 20Gy in 1 fraction 2 years follow-up. Patients were followed-up with PSA, CT scans and NaF PET at 1 year.	Primary Clinical effectiveness Secondary Safety	Overall survival Local control Progression free survival Toxicity QoL	OS: -1 year = 100% -2 year = 100% LC: -1 year = 97% (95%CI 91-100%) -2 year = 93% (95%CI 84-100%) PFS: -1 year = 58% (95%CI 43-77%) -2 year = 39% (95%CI 25-60%) Adverse events: -G1 = 48% -G2 = 15% -G3 = 3% (vertebral fracture) The most common adverse event was G1 fatigue. There was no significant difference from baseline QoL	7	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population and intervention are well matched to the scope. However, the presence of only bone and lymph nodes metastases may have favourably skewed the results for toxicity and OS. The study was powered to detect a 15% acute G3 toxicity Progression was measured objectively using CT or PET imaging. Confidence intervals were reported

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Warren et al., 2017)	Prospective cohort Single-centre Australia Recruitment period 2013-2014	31 patients with liver oligometastases from various primary cancers (41% colorectal cancer*) All patients had ≤3 metastases Mean time to metastases was not reported All patients had Child-Pugh A liver function.	Total dose not reported but treatment was delivered in 3-6 fractions 6 months follow-up.	Primary Safety	Toxicity QoL Pain	No grade 3+ acute or late toxicities Mean EQ-5D score at baseline was 0.857, which remained stable across the entire study period. The mean visual analogue score at baseline was 65.8 and remained unchanged throughout treatment and follow-up.	6	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population is matching the review scope. There was a decrease in compliance for measuring QoL. This is a well-recognised problem in quality QoL research and minimises the validity of the results. EQ-5D is not a cancer specific QoL tool. The study did not report a sample size calculation. Short follow-up duration. Confidence intervals were not reported.

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Comito et al., 2014)	Prospective cohort Single-centre Italy Recruitment period 2010-2013	82 patients (mixed pulmonary and liver metastases) with oligometastases from colorectal cancer All patients had ≤3 metastases Mean time to metastases was > 12 months for 76% of the patients .	All patients received SABR with changes in total dose and fractionation depending on treatment site Total dose = 60Gy in 3 fractions, 48Gy in 4 fractions or 75Gy in 3 fractions Median 24 months follow-up.	Primary Clinical effectiveness Primary Safety	Overall survival Local control PFS Adverse effects	OS: Median = 32 months -1 year = 85% -2 year = 65% -3 year = 43% LC: -1 year = 90% -2 year = 80% -3 year = 75% PFS: Median= 14 months -1 year = 56% -2 year = 40% -3 year = 40% -G2 acute toxicity = 70% -G3+ = 0% The most common side effect was fatigue	6	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population is matching the scope. The study did not report a sample size calculation. Short follow-up duration. Confidence intervals were not reported.

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Kunos et al., 2012)	Prospective cohort Single centre USA Recruitment period 2009-2011	50 patients with oligometastases from gynaecologic cancer (50% ovarian cancer*) 96% of the patients had ≤3 metastases Mean time to metastases was not reported	All patients received the same SABR treatment Total dose = 24Gy in 3 fractions Median 15 months follow-up.	Primary Clinical effectiveness Primary Safety	Overall survival Local control PFS Adverse effects	OS: Median = 20.2 (95% CI, 10.9, 29.5) months LC: -1 year = 100% PFS: Median= 7.8 (95% CI, 4.0-11.6) months Acute -G1 = 26% -G2 = 50% -G3 = 4% -G4 = 2% The most common side effect was fatigue	6	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. Low BED The study population is partially matching the scope as it only includes people with gynaecologic cancer. The study did not report a sample size calculation. Short follow-up duration. Confidence intervals were reported.

* The cancer types with the highest % representation in the sample
Quality of evidence score: The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence included in the report.
HR: Hazard ratio, ITT = intention to treat, LC = local control, OS = overall survival , 95% CI = 95% confidence interval

Table 3: Registries

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
(Mahadevan et al., 2018) RSSearch registry NCT01885299	Retrospective cohort Multicentre International (USA, Germany, Australia) Recruitment period 2005-2017	447 patients with pulmonary oligometastases from various primary cancers (12.2% lung* and 44.3% colorectal*) Median number of metastases was not reported. Mean time to metastases was not reported	All patients received SABR with changes in total dose and fractionation depending on treatment site Median dose = 45Gy (12–60Gy) delivered in a median of 3 fractions Median 14 months follow-up.	Primary Clinical effectiveness	Overall survival Local control	OS: -Median = 22 months -1 year = 70% -2 year = 47% LC for BED≥100Gy: -Median = 52 months -1 year = 88%% -2 year = 77%	5	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. Toxicity data was not available for all patients. The study population and intervention are matched to the review scope. Recruitment period was over a decade starting from early 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises
				Secondary Safety	Adverse events	There was no grade 3+ toxicity reported The most common toxicity was fatigue			

Use of SABR to treat Oligometastatic disease in patients with cancer									
Study reference	**Study Design**	**Population characteristics**	**Intervention/ Comparators**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									concerns about detection bias. Follow-up duration was short. Confidence intervals not reported.

(Ricco et al., 2017) RSSearch registry NCT01885299	Retrospective cohort Multi-centre International (USA, Germany, Australia) Recruitment period 2004-2015	447 patients with pulmonary oligometastases from various primary cancers (16.6% lung* and 25.7% colorectal*) Median number of metastases was 1. Mean time to metastases was not reported	Patients received SABR with changes in total dose and fractionation depending on treatment site Median dose = 50Gy (8–60Gy) delivered in a median of 3 fractions Median 13 months follow-up.	Primary Clinical effectiveness	Overall survival Local control	OS: -Median = 26 months -1 year = 74% -2 year = 60% -3 year = 33% -5 year = 22% LC: -Median = 53 months -1 year = 80% -3 year = 59% -5 year = 46% There was no statistical difference in LC rates based on primary tumour types.	5	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding, and concealment was not possible. The study population and intervention are matched to the review scope. Recruitment period was over a decade starting from early 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Follow-up duration was short. Confidence intervals not reported.
(Klement et al., 2018)	Retrospective cohort Multi-centre	637 patients with pulmonary oligometastases from various primary	Patients received SABR with changes in total dose and	Primary Clinical effectiveness	Overall survival Local control	OS: -Median = 23.5 (21.4-26.6) months	5	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding,

DEGRO registry	International (Germany, Switzerland) Recruitment period 1997-2014	cancers (30.5% lung* and 21.9% colorectal*) 99% of the patients had ≤4 metastases. Median number of metastases was 1. Mean time to metastases was not reported	fractionation depending on treatment site Median dose = 50Gy (8–60Gy) delivered in a median of 3 fractions Median 13 months follow-up.	 Secondary Safety	Progression free survival Toxicity	-1 year = 71% (67%-75%) -2 year = 60% (45%-54%) -3 year = 33% (29%-39%) Pneumonitis: -G2 = 4% -G3 = 1% -G5 = 1 patient			and concealment was not possible. The study population and intervention are matched to the review scope. Recruitment period was over a decade starting from early 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Toxicity data was not available for all patients. Follow-up duration was short. Confidence intervals were reported
(Andratschke et al., 2018) DEGRO registry	Retrospective cohort Multi-centre	474 patients with liver oligometastases from various primary cancers (13.3%	Patients received SABR with changes in total dose and fractionation	Primary Clinical effectiveness	Overall survival Local control	OS: -Median = 24 months -1 year = 70% -3 year = 29%	5	Direct	Non-randomised, lack of control, due to the nature of the intervention, blinding,

	International (Germany, Switzerland) Recruitment period 1997-2015	breast* and 48.1% colorectal*) 100% of the patients had ≤4 metastases. Median number of metastases was 1. Mean time to metastases was not reported	depending on treatment site Median dose and number of fractions not reported Median 15 months follow-up.	Primary Safety	Adverse effects	-5 year = 15% LC: -1 year = 77% -2 year = 64% -3 year = 56% G1-2 acute toxicity = 23% G3 acute toxicity < 1% No G4 or G5 toxicity The most common side effects were fatigue, nausea, diarrhoea. Chronic: G1-2 toxicity = 10% G3 acute toxicity = 1.4% No G4 or G5 toxicity The most common side effects were fatigue, nausea, diarrhoea.			and concealment was not possible. The study population and intervention are matched to review scope. Recruitment period was over a decade starting from early 2000s. The intervention may be less comparable with current standards of SABR delivery. Some patients received low doses of SABR (BED<100Gy). The study did not report a sample size calculation. Progression was measured objectively using mainly CT imaging, however, not all patients had the same follow-up schedule. This raises concerns about detection bias. Toxicity data, especially long-term was not available for all patients. Follow-up duration was short. Confidence intervals were not reported

* The cancer types with the highest % representation in the sample
Quality of evidence score: The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence included in the report.
HR: Hazard ratio, ITT = intention to treat, LC = local control, OS = overall survival , 95% CI = 95% confidence interval

9 Summary studies results per outcome

Table 4: Survival

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Palma et al. 2019 (SABR-COMET) RCT 25 N = 99	41 (95% CI 26-not reached)	Standard care 28 (95% CI 19-33)	0.57 0.3-1.1 P=0.09	Contemporary cohort, OS is primary outcome and power calculation is reported.
Stintzing et al. 2013 Case control 23.3 N = 60	34.4	RFA 52.3	NR NR P=0.06	Heavily pre-treated population, single fraction SABR
Sutera et al. 2019 Cohort 41.3 N = 147	42.3 months (95% CI 27.4-not reached)	NA	NA NA NA	Contemporary cohort, population and intervention comparable to SABR-COMET
Mahadevan et al. 2018 Registry 14 N = 427	22	NA	NA NA NA	Not contemporary cohort, only liver metastases, some patients received low BED
Klement et al. 2018 Registry 13 N = 637	23.5 months (95% CI 21.4–26.6)	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Andratschke et al. 2018 Registry 15 N = 474	24	NA	NA NA NA	Not contemporary cohort, only liver metastases, some patients received low BED
Ricco et al. 2017 Registry 13 N = 447	26	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Navarria et al. 2014 Cohort 18 N = 76	20	NA	NA NA NA	Only treated patients with pulmonary metastases, high BED
Comito et al. 2014 Cohort 24 N = 82	32	NA	NA NA NA	Only treated patients with CRC and visceral metastases (liver and pulmonary), high BED
Kunos et al. 2012 Cohort 15 N = 50	20.2 (95% CI 10.9-29.5)	NA	NA NA NA	Only treated women with gynaecologic cancer, low BED

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Palma et al. 2019 RCT 25 N = 99	SABR -1 year =86% -2 year =70%	Standard care -1 year =86% -2 year =60%	NR NR NR	Contemporary cohort, OS is primary outcome and power calculation is reported.
Lee et al. 2018 Case control 13.7 N = 51	SABR -1 year =79% -2 year =68%	Surgery -1 year =95% -2 year=82%	p=0.53	The 2 groups were not well matched with SABR patients having larger tumours and higher incident of synchronous extra-pulmonary disease. There were no significant differences in OS between treatment groups after dividing patients according to the presence or absence of synchronous metastases.
Lodeweges et al. 2017 Case control 7.6 years N = 110	SABR -1 year =98% (95% CI 84-100%) -2 year =86% (95% CI 71-93%) -3 year = 64% (95% CI 48-77%) -5 year = 45% (95% CI 30-59%)	Surgery -1 year = 87% (95% CI 76-93%) -2 year = 74% (95% CI 61-82%) -3 year = 63% (95% CI 51-73%)	0.76 0.38-1.54 NR	SABR was considered a second choice treatment after surgery and as result the groups' baseline clinical characteristics were not well matched (in favour of surgery). The 2 groups well not well matched with SABR patients being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval. The authors used propensity scoring to

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
		-5 year = 41% (95% CI 29-53%)		account for the baseline differences among the 2 groups
Filippi et al. 2016 Case control 27 N = 170	SABR -1 year = 89% -2 year =77%	Surgery -1 year = 96% -2 year = 82%	1.28 0.58-2.82 p=0.54	The 2 groups were well matched, however, they were unbalanced in terms of numbers. The authors used propensity scoring to account for the baseline differences among the 2 groups.
Sutera et al. 2019 Cohort 41.3 N = 147	-1 year = 84% -2 year = 63% -3 year = 50% -5 year = 43%	NA	NA NA NA	Contemporary cohort, population, and intervention comparable to SABR-COMET.
Siva et al. 2018 Cohort 24 N = 33	-1 year = 100% -2 year = 100%	NA	NA NA NA	Only included prostate cancer patients. This patient cohort historically has better OS rates.
Navarria et al. 2014 Cohort 18 N = 76	-1 year = 84% -2 year = 73% -3 year = 73%	NA	NA NA NA	Only treated patients with pulmonary metastases, high BED

Overall Survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Comito et al. 2014 Cohort 24 N = 82	-1 year = 85% -2 year = 65% -3 year = 43%	NA	NA NA NA	Only treated patients with CRC and visceral metastases (liver and pulmonary), high BED
Mahadevan et al. 2018 Registry 14 N = 427	-1 year = 70% -2 year = 47% -3 year = 30% -5 year = 5%	NA	NA NA NA	Not contemporary cohort, only liver metastases, some patients received low BED
Klement et al. 2018 Registry 13 N = 637	-1 year = 71% (95% CI 67%-75%) -2 year = 60% (95% CI 45%-54%) -3 year = 33% (95% CI29%-39%) -5 year = 20%	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Andratschke et al. 2018 Registry 15 N = 474	-1 year = 70% -2 year = 47% -3 year = 29% -5 year = 15%	NA	NA NA NA	Same as previously.
Ricco et al. 2017 Registry 13 N = 447	-1 year = 74% -2 year = 60% -3 year = 33% -5 year = 22%	NA	NA NA NA	Not contemporary cohort, only pulmonary metastases, some patients received low BED
Abbreviations: BED, biologically effective dose; CI, confidence interval; CRC, colorectal cancer; LC, local control; OS, overall survival; RFA, radiofrequency ablation; RT, radiotherapy				

Table 5: Local control

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Lodeweges et al. 2017 Case control 7.6 years N = 110	-1 year =95% (95% CI 80-99%) -2 year =95% (95% CI 80-99%) -3 year = 90% (95% CI 70-97%) -5 year = 83% (95% CI 57-94%)	Surgery -1 year = 93% (95% CI 83-97%) -2 year = 91% (95% CI 79-96%) -3 year = 85% (95% CI 70-93%) -5 year = 81% (95% CI 65-90%)	0.8 (local recurrence) 0.24-2.65 > 0.05	Small lesions (mean size = 1.9 cm). However, lesion size did not influence LC (HR =1.03, 95% CI 0.73-1.45). LC was assessed with RECIST 1.1 and CT.
Stintzing et al. 2013 Case control 23.3 N = 60	-1 year = 85% -2 year = 80%	RFA -1 year = 65% -2 year = 61%	NR NR -1-year = 0.09 - 2-year = 0.20	Heavily pre-treated population, single fraction SABR. Average size lesions (mean=3.4 cm). Size and number of metastases matched between the 2 cohorts. CT or MRI was used for assessing LC.
Sutera et al. 2019 Cohort 41.3 N = 147	-Median = not reached -1 year = 91% -2 year = 80% -3 year = 75% -5 year = 75%	NA	NA NA NA	Contemporary cohort. Population, and intervention comparable to Palma et al., 2019. Small lesions (median=2.3 cm). LC was assessed with RECIST and CT.

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Mahadevan et al. 2018 Registry 14 N = 427	-Median = 51 months -1 year = 80% -2 year = 70% -3 year = 65% -5 year = 47%	NA	NA NA NA	LC was assessed with RECIST but imaging test used and frequency of follow-up not reported. Small tumours (<40 cm^3) had improved LC (p=0.0014). 1- and 2-year LC rates for BED10 ≥ 100 Gy were 87.5% and 77.2%, respectively, compared to 1- and 2-year LC rates for BED 10 < 100 Gy of 71.8% and 59.6% (p<0.0001). No difference in LC based on primary histology.
Ricco et al. 2017 Registry 13 N = 447	-Median = 53 months -1 year = 80% -2 year = 65% -3 year = 59% -5 year = 46%	NA	NA NA NA	LC was assessed with RECIST but imaging test used and frequency of follow-up not reported. Some patients received low BED. Improved LC was observed for lesions that received SABR doses of BED ≥100Gy. No difference in LC based on primary histology.
Andratschke et al. 2018 Registry 15 N = 474	-1 year = 76% -2 year = 64% -3 year = 56% -5 year = 50%	NA	NA NA NA	Some patients received low BED. Different follow-up frequency and imaging modalities used between

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
				centres. The size of the lesion and the BED affected LC.
Navarria et al. 2014 Cohort 18 N = 76	-1 year = 95% -2 year = 89% -3 year = 89%	NA	NA NA NA	Only pulmonary metastases, high BED. LC was assessed with RECIST using CT and/or FDG-PET/CT. No correlation between delivered doses and local control was present.
Comito et al. 2014 Cohort 24 N = 82	All -1 year = 90% -2 year = 80% -3 year = 75% High BED -1 year = 97% -2 year = 92% -3 year = 83% Low BED -1 year = 85% -2 year = 70% -3 year = 70%	NA	NA NA NA	Only CRC population, liver and pulmonary metastases, high BED. Mean lesion size was 3.3 cm. The difference in LC between the subgroup of lesions treated with ≥60 Gy (n = 58) and those irradiated with <60 Gy (n = 52) was statistically significant.

Local control				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Lee et al. 2018 Case control 14 N = 51	-1 year = 83.5% -2 year = 75.2%	Surgery -1 year = 96.6% -2 year = 91.5%	NR NR P=0.163	High BED. The tumour size in the SABR group was larger than in the surgery group (median 2.5 vs. 1.25 cm; p = 0.015). Details on follow-up and how LC was assessed are not reported.
Siva et al. 2018 Cohort N = 33	-1 year = 97% (95% CI 91-100%) -2 year = 93% (95% CI 84-100%)	NA	NA NA NA	LC was assessed using RECIST and CT and 18F-NaF PET imaging (at 12 months only).
Abbreviations: BED, biologically effective dose; CT, computerised tomography; CRC, colorectal cancer; CI, confidence interval; LC, local control; RFA, radiofrequency ablation; RT, radiotherapy				

Table 6: Progression free survival

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Palma et al. 2019 RCT 25 N = 99	-Median = 12 months -1 year = 53% -2 year = 40%	Standard care -Median = 6 months -1 year = 22%	0.47 0.3-0.76 P= 0.0012	Contemporary cohort. Comparator was standard care.

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
		-2 year = 15%		PFS was defined as time from randomisation to disease progression at any site or death.
Lee et al. 2018 Case control 14 N = 51	-1 year = 24% -2 year = 12%	Surgery -1 year = 51% -2 year= 46%	NR NR p=0.53	The 2 groups well not well matched with SABR patients having larger tumours and higher incident of synchronous extra-pulmonary disease. There were no significant differences in PFS between treatment groups after dividing patients according to the presence or absence of synchronous metastases.
Lodeweges et al. 2017 Case control 7.6 years N = 110	-1 year = 49% (95% CI 34-63%) -2 year =2 7% (95% CI 14-41%)	Surgery -1 year = 56% (95% CI 43-66%) -2 year = 35% (95% CI 23-46%)	NR NR NR	PFS not defined. Comparator was surgery. The 2 groups well not well matched with SABR patients being older, having received higher rates of prior treatment, and having a shorter median metastasis free interval.

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
Filippi et al. 2016 Case control SABR = 27 months Surgery= 46 months N = 170	-1 year = 58% -2 year = 25%	Surgery -1 year = 80% -2 year = 62%	1.28 0.58-2.82 p=0.54	PFS was defined as the time from the date of the treatment for lung metastases (SABR or surgery) to the date of progression (death or first local/distant recurrence) or of the last follow-up. The results of PFS are considered unreliable because different follow-up protocols and sample sizes were applied in the two cohorts.
Stintzing et al. 2013 Case control 23 N = 60	34.4 months (3.4-65.4)	RFA Median= 6.0 months (1.9-10)	NR NR p<0.001	The comparator was RFA. The study had unbalanced follow-up between the 2 groups reducing the ability to detect differences between the 2 cohorts.
Sutera et al. 2019 Cohort 41.3 N = 147	-Median = 8.7 months (95% CI, 6.6-13.1) -1 year = 47% -2 year = 27% -5 year = 17%	NA	NA NA NA	PFS was defined as the time from completion of SABR to documentation of new distant metastases.
Siva et al. 2018 Cohort	-1 year = 58% (95% CI 43-77%) -2 year = 39% (95% CI 25-60%)	NA	NA NA	PFS was defined based on imaging.

Progression free survival				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Quality**
24 N = 33			NA	
Navarria et al. 2014 Cohort 18 N = 76	-1 year = 83% -2 year = 70% -3 year = 70%	NA	NA NA NA	Only pulmonary metastases. PFS was not defined. Progression was measured objectively using CT or PET imaging, however, not all patients were subjected to the same follow-up assessment.
Comito et al. 2014 Cohort 24 N = 82	-Median = 14 months -1 year = 56% -2 year = 40% -3 year = 40%	NA	NA NA NA	Only CRC population, liver and pulmonary metastases. Progression included any intra- or extra-hepatic and pulmonary disease progression.
Kunos et al. 2012 Cohort 15 N = 50	Median= 7.8 months (95% CI 4.0-11.6)	NA	NA NA NA	Progression was defined as distant disease relapse.
Abbreviations: CRC, colorectal cancer; PFS, progression free survival; QoL, quality of life				

Table 7: Toxicity

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Palma et al. 2019 RCT 25 N = 99	-Grade 2 = 16% -Grade 3 = 7% -Grade 5 = 5%	Standard care -Grade 2 = 6% -Grade 3 = 3% -Grade 5 = 0%	Absolute increase= 20% Grade 2/3 =5-34% Grade 5 = 1-10% NR	Toxicity was evaluated at each follow-up visit using the CTCAE version 4.0. The most common treatment related toxic effects of Grade 2 or worse in the SABR group were fatigue (n=4), dyspnoea (n=2) and pain (including muscle, bone, and other, total n=8). There were three treatment related Grade 5 events in the SABR group due to deaths from radiation pneumonitis (n=1), pulmonary abscess (n=1), and subdural haemorrhage after surgery to repair a SABR-related perforated gastric ulcer (n=1).
Ost et al. 2018 RCT 24	-Grade 1 = 8% -Grade 2-5 = 0%	Active surveillance -Grade 1-5 = 0%	NR	Toxicity was assessed in the metastasis-directed therapy group using CTCAE for patients undergoing

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
N = 62				SABR and the Clavien-Dindo classification for patients who underwent surgery. Only 2 episodes (loose stools and muscle pain) of acute Grade 1 toxicity were observed with SABR.
Stintzing et al. 2013 Case control 23.3 N = 60	-Grade 1 = 6% -Grade 2 = 0% -Grade 3+ = 0%	RFA -Grade 1 = 8% -Grade 2 = 7.5% -Grade 3+ = 0%	NR NR NS	Heavily pre-treated population, single fraction SABR
Sutera et al. 2019 Cohort 41.3 N = 147	Acute: -Grade 2 = 7.5% -Grade 3 = 2% Late: -Grade 2 = 1.4% -Grade 3 = 1.4%	NA	NA NA NA	Contemporary cohort. Population and intervention comparable to Palma et al., 2019 Unclear how acute and late toxicity were defined
Warren et al. 2017 Cohort 6 N = 31	-Grade 1 = Unknown -Grade 2 = Unknown -Grade 3 = 0% -Grade 4 = 0%	NA	NA NA NA	Toxicity was assessed using CTCAE. No grade 3 or 4 acute or late toxicities nor classic or non-classic radiation-induced liver disease cases were reported.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Mahadevan et al. 2018 Registry 14 N = 427	-Grade 1 = Unknown -Grade 2 = Unknown -Grade 3 = 0%	NA	NA NA NA	Toxicity data was not available from all centres for all patients.
Klement et al. 2018 Registry 13 N = 637	-Grade 2 = 4% -Grade 3 = 1% -Grade 5 = 1 patient	NA	NA NA NA	Toxicity data was not available from all centres for all Patients. Toxicity was mainly associated with pneumonitis.
Andratschke et al. 2018 Registry 15 N = 474	Acute: Grade 1- 2= 23% Grade 3 < 1% Grade 4 = 0% Grade 5 = 0% Late: -Grade 1-2 = 10% -Grade 3 = 1.4% -Grade 4 = 0% -Grade 5 = 0%	NA	NA NA NA	Acute toxicity was scored according to the CTCAE criteria during and up to 3 months after SABR. Toxicity beyond 3 months (late) was graded using the RTOG/EORTC criteria. Acute toxicity data was available for only 73% of the patients. Grade 1–2 toxicity consisted mostly of fatigue, nausea, and diarrhoea. Chronic toxicity data was available for only 44% of the patients and consisted of fatigue, nausea, diarrhoea, liver enzyme elevation, and jaundice.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Navarria et al. 2014 Cohort 18 N = 76	Acute: Grade 1-5 = 0% Late: -Grade 1 = 80% (mostly radiological fibrosis in <25% of lung volume) -Grade 2 = 0% -Grade 3 = 0% -Grade 4 = 0% -Grade 5 = 0%	NA	NA NA NA	Toxicity was assessed in the MDT group using CTCAE. It is unclear what cut-off the authors used to separate acute and late toxicity. No major pulmonary toxicity, chest pain or rib fracture occurred.
Comito et al. 2014 Cohort 24 N = 82	Acute -Grade 2 = 70% -Grade 3 = 0% -Grade 4 = 0% -Grade 5 = 0%	NA	NA NA NA	Acute and late toxicity were scored by the CTCAE criteria, however, the authors do not clarify the time frame for separating between acute and late toxicity. The most frequent side effects were fatigue (60%) and transient hepatic transaminase increase (25%) for liver metastases treatment. No patients developed RILD, chest pain or rib fracture.
Kunos et al. 2012 Cohort 15 N = 50	Acute and late -Grade 1 = 26% -Grade 2 = 50% -Grade 3 = 4%	NA	NA NA NA	Acute (within a month after SABR) and late (after a month post SABR) toxicity were scored by the CTCAE criteria. The most frequent adverse

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
	-Grade 4 = 2%			events were grade 1 or 2 fatigue (20%) and grade 1 or 2 nausea (12%). The incidence of grade 3 or grade 4 possible SABR-related non-haematological toxicities was 6%. It is not possible to distinguish between acute and late toxicity events from the authors reporting of the results.
Lee et al. 2018 Case control N = 51	Radiation pneumonitis: -Grade 1 = 57.1% -Grade 2 = 23.8% -Grade 3 = 4.8% Rib fractures -Grade 1 = 9% -Grade 2 = 9% Chest wall pain -Grade 1 = 5% -Grade 2 = 9%	Surgery -1 patient experienced acute bleeding requiring surgical intervention. -1 patient had acute respiratory distress syndrome requiring intensive medical care	NR NR NR	There were differences in patients' baseline characteristics and toxicity profiles.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
		-1 patient experienced grade 3 nausea and required fluid treatment.		
Filippi et al. 2016 Case control N = 170	Radiation pneumonitis -Grade 1 = 21.4% -Grade 2 = 14.4% Chronic chest pain -Grade 2 = 3.5% -Grade 3 = 3.5%	One death within 30 days was observed among the surgical population. No other major complications were observed.	NR NR NR	Acute and late toxicity were scored by the CTCAE criteria. It is not possible to distinguish between acute and late toxicity events from the authors reporting of the results.
Siva et al. 2018 Cohort N = 33	-Grade 1 = 48% -Grade 2 = 15% -Grade 3 = 3% (vertebral fracture requiring spinal instrumentation)	NA	NA NA NA	The study estimated the sample size based on the assumption that grade 3 toxicity rate would be 10.5%, and the probability of no greater than 15% of patients in the sample suffering a grade 3 or higher acute toxicity would be 80%. The most common side effect was fatigue.

Toxicity				
Reference **Design** **Follow-up (months)** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Abbreviations: CTCAE, common terminology criteria for adverse events; CI, confidence interval; MDT, multidisciplinary team; NA, Not applicable; NR, Not reported; RFA, radiofrequency ablation; RILD, Radiation-induced liver disease;				

Table 8: Quality of life

Quality of life				
Reference **Design** **Follow-up (months)*** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
Palma et al. 2019 RCT 6 N = 99	82.6 (SD 16·6)	Standard care 82.5 (SD 16.4)	NA NA p=0.99	QoL was evaluated at each follow-up visit using the Functional Assessment of Cancer Therapy: General (FACT-G) tool. QoL was similar between arms at baseline and remained comparable at 6-months.
Ost et al. 2018 RCT 12 N = 62	Values not reported as results presented only on graphs	Active surveillance Values not reported as	NR NR NR	QoL was evaluated at each follow-up visit using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life

Quality of life				
Reference **Design** **Follow-up (months)*** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
		results presented only on graphs		Questionnaire QLQ-C30 and QLQ-PR25 tools. QoL was similar between arms at baseline and remained comparable at 1-year. The questionnaire completion rate was 97% at baseline, 89% at 3 months, and 84% at 1 year.
Sutera et al. 2019 Cohort 12 N = 147	NR	NA	NA NA NR	QoL was evaluated at each follow-up visit using the Function Assessment of Cancer Therapy-General (FACT-G) tool. QoL was similar between baseline, 6 weeks, 3 months, and 9 months after treatment. The fact that changes in QoL were significant at 6 and 12 months but not 9 months questions the validity of the result.
Warren et al. 2017 Cohort 6 N = 31	Mean EQ-5D-3L utility score at baseline = 0.857 (SD = 0.0258). Mean utility score at 6 months = 0.799 (SD = 0.0650)	NA	NA NA $p > 0.05$	QoL was evaluated at each follow-up visit using the EQ-5D-3L.

Quality of life				
Reference **Design** **Follow-up (months)*** **Study size**	**SABR**	**Comparator**	**HR** **95% CI** **p-value**	**Comments**
				QoL was similar between baseline and each follow-up up to 6 months.
Siva et al. 2018 Cohort 24 N = 33	Baseline = 77 (95% CI 70 - 84) 2 years = 69 (95% CI 61 - 77)	NA	NA NA NA	QoL was evaluated at each follow-up visit using the EORTC QLQ and BM22 tools. QoL was similar between baseline and each follow-up up to 2-years.
Abbreviations: CTCAE, common terminology criteria for adverse events; CI, confidence interval; MDT, multidisciplinary team; RFA, radiofrequency ablation; RILD, Radiation-induced liver disease;				

10 Grade of evidence table

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Median overall survival	Palma, 2019 Stintzing, 2013 Sutera, 2019 Navarria, 2014 Comito, 2014 Kunos, 2012	9 5 7 7 6 6	Direct Direct Direct Direct Direct Direct	A	*Median overall survival is reported as the length in time a patient survives following treatment or when they were recruited for the study.*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Mahadevan, 2018 Klement, 2018 Andratschke, 2018 Ricco, 2017	5 5 5 5	Direct Direct Direct Direct		*Median overall survival was reported in months, defined either as time from randomisation or from SABR treatment to death from any cause.* *The best evidence on actuarial survival is provided by the Palma et al. (2019) RCT that was adequately powered as a phase II RCT to detect a difference. The study compared SABR to standard care (46 vs. 28 months, HR: 0.57, [95%CI 0.3-1.1], p=0.09).* *There is variability between the results reported by Palma et al. (2019) and the rest of the evidence, however, there is good agreement in cases were a similar population and intervention was studied. For example, similar findings were reported by Sutera et al. (2019) at 42.3 months (95%CI 27.4-not reached). Both studies recruited a contemporary cohort, and had comparable populations and interventions. They recruited patients with oligometastases from different primary cancers with various lesion locations, with differences however on the individual proportions with a notably lower percentage of prostate cancer metastases for the Sutera 2019 study.*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					The clinical benefit to the patient group is demonstrated by the results of Palma et al. 2019 showing that the use of SABR in patients with controlled primary tumours and one to five oligometastases leads to an increase of approximately 13 months in overall survival. *Good quality evidence* *There is some uncertainty to the conclusion reached by Palma et al. 2019 as it is a phase 2 screening design in which the α level is set higher than the 0.05 level that is used for a phase 3 design, recognising that even if the phase 2 trial is positive (i.e. if the ultimate p value is less than 0.20), such a positive result is not usually considered definitive without a subsequent phase 3 trial.*
Actuarial overall survival	Palma, 2019 Lee, 2018 Lodeweges, 2017 Filippi, 2016 Sutera, 2019 Siva, 2018 Navarria, 2014 Comito, 2014 Mahadevan, 2018	9 4 7 5 7 7 7 6 5	Direct Direct Direct Direct Direct Direct Direct Direct Direct	A	*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.* *Actuarial overall survival was a primary outcome in a number of the included studies, however, none of them reported sample size calculations. It*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Klement, 2018 Andratschke, 2018 Ricco, 2017	5 5 5	 Direct Direct Direct		*is therefore, unknown if they were adequately powered to detect a difference either from historically reported results or vs. a comparator (standard care, surgery, RFA). Studies reported mainly OS at 1- and 2-years post treatment. Few studies with long-term follow-up also reported OS at 5 years post treatment.* *The best evidence on actuarial survival is provided by the Palma et al. (2019) RCT that reported 86% and 70% with SABR vs. 86% and 70% with standard care.* *There is consistency between the results reported by Palma et al. (2019) and the rest of the evidence as the reported 1-year overall survival rates ranged between 70-100% with differences in the included population and treatment that could account for the outliers, studies reporting either close to 70% or to 100% OS rates. The results were less consistent for the 2-year OS rates with rates between 47-100%.* *Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care (Palma et al., 2019) and active surveillance (Ost*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					et al., 2018) long-term actuarial survival beyond 2-years is more clinically meaningful. *Good quality evidence*
Local control	Stintzing 2013 Sutera 2019 Navarria 2014 Comito 2014 Lee 2018 Mahadevan 2018 Andratschke 2018 Ricco, 2017 Siva 2018 Lodeweges	5 7 7 6 4 5 5 5 7 7	Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct	C	*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.* *LC was a secondary outcome in 10 studies, however, it is not known if any of them was adequately powered to detect a difference either from historically reported results or vs. a comparator (surgery, RFA) as sample size calculations were not reported. Studies reported mainly LC at 1- and 2-years post treatment. RECIST was used to measure LC in almost all studies.* *The best comparative 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.*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					The clinical benefit to the patient group is that a less invasive treatment such as SABR can provide equivalent results. *The comparative 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. Low quality evidence.*
Progression-free survival	Palma 2019 Comito 2014 Kunos 2012 Navarria 2014 Siva 2018 Sutera 2019 Filippi 2016 Lee 2018 Lodeweges 2017 Stintzing 2013	9 6 6 7 7 7 5 4 7 5	Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct	B	*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.* *Ten of the included studies reported progression-free survival with SABR as a secondary outcome.* *The strongest evidence for this outcome is provided by SABR-COMET. The authors concluded that use of SABR doubles the PFS from 6 months with standard care to 12 months (HR: 0.47, 95% CI 0.3-0.6, p=0.0012).*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					The clinical benefit to the patient group is demonstrated by the results is that SABR can increase PFS by approximately 6 months in comparison with standard care. *PFS was reported as a secondary outcome (i.e. the studies were not designed with PFS as the 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.* *There is some uncertainty to the conclusion reached by Palma et al. 2019 as it is a phase 2 screening design in which the α level is set higher than the 0.05 level that is used for a phase 3 design, recognising that even if the phase 2 trial is positive (i.e. if the ultimate p value is less than 0.20), such a positive result is not usually considered definitive without a subsequent phase 3 trial.*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Toxicity	Palma 2019 Ost 2018 Stintzing 2013 Warren 2017 Lee 2018 Filippi 2016 Sutera 2019 Warren 2017 Navarria 2014 Comito 2014 Kunos 2012 Siva 2018 Mahadevan 2018 Klement 2018 Andratschke 2018	9 9 5 6 4 5 7 6 7 6 6 7 5 5 5	Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct Direct	C	*Toxicity is defined based on the number and severity of adverse events a patient can experience after undergoing treatment.* *Treatment-related toxicity was a secondary outcome in all studies, therefore, none of them was adequately powered to detect a difference either from baseline or vs. a comparator (standard care, active surveillance, surgery, RFA).* *The best evidence on toxicity is provided by the Palma et al. (2019) RCT that reported higher toxicity with SABR, and specifically grade 5 deaths 4.5%, 95%CI 0-10) with SABR but not with standard care.* *There is inconsistency between the results reported by Palma et al. (2019) and the rest of the evidence as no other study has reported an increase in severe toxicity and especially G5 deaths with SABR.* *Given the relatively good prognosis of patients with oligometastatic disease and the high rates of overall survival achieved with standard care (Palma et al., 2019) and active surveillance (Ost et*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					al., 2018) the impact of severe toxicity is clinically very important. *Low quality evidence due to downgrading the Palma et al. (2019) findings for serious risk of bias and serious inconsistency for this outcome.*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Quality of life	Palma 2019 Ost 2018 Siva 2018 Sutera 2019 Warren 2017	9 9 7 7 6	Direct Direct Direct Direct Direct	B	*Quality of life was a secondary outcome in all studies, therefore, none of them was adequately powered to detect a difference either from baseline or vs. a comparator (standard care or active surveillance).* *With the exception of (Siva et al., 2018) which reported QoL results for up to 2 years after treatment, the other studies captured only a relatively short post-treatment interval potentially failing to capture the effect of late toxicity on QoL* *None of the studies reported a difference in quality of life with SABR.* *The prostate population includes patient with a relatively good prognosis. One of the factors weighting in treatment decisions is whether treatment will affect their quality of life.* *Medium quality evidence due to downgrading the results for serious risk of bias.*

Use of SABR to treat extracranial oligometastases					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
QoL = quality of life *RFA = radiofrequency ablation* *OS = overall survival*					

11 Literature search terms – PICO table

P –Population and Indication Describe the relevant population and indication provided previously including if necessary disease severity or duration, previous treatment, new or recurrent symptoms, any specific co-morbidities and other population factors (for example, age range). Add details of any subgroups or stratifications for which separate evidence may be required.	Patients who have extracranial oligometastatic cancer of any tumour type (metachronous disease) with fewer than 5 metastases. Studies with a small % of patients with 5 lesions (<5%) were considered eligible for inclusion. Metachronous disease was defined as the diagnosis of metastases more than 6 months after the primary cancer. In cases where this was not adequately reported the corresponding authors were contacted for further information. Patients eligible for the review who also had intracranial metastases were included. Patients may have had or be having standard care, which differs depending on primary tumour site: systemic treatments (chemotherapy, hormone treatment or molecular targeted treatments) may be given alone or with local treatment of metastases.
I – Intervention Describe the intervention details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	Stereotactic ablative body radiotherapy (8 fractions or fewer) to oligometastases (dose and fractionation dependent on site of metastasis and proximity to organs at risk).
C – Comparators What is/are the main alternative/s to compare with the intervention being considered? Describe the comparator details provided previously including if necessary details of treatment, mode of delivery, size/frequency/duration of dose, position of intervention in treatment pathway (e.g. first/second line/salvage) and any background / concomitant medication	• No local oligometastases treatment/palliative care alone • Local treatment to oligometastases with conventionally fractionated radiotherapy, surgical excision, radio-frequency or microwave ablation and/or locally delivered chemotherapy either in combination or as single therapies.
O – Outcomes Outcomes should be patient focussed and relate to those detailed in the PPP and the Research Questions covering clinical effectiveness, safety and cost effectiveness as required. Examples will be topic specific but might include intermediate or short-term outcomes; mortality; morbidity;	*Critical to decision-making:* • Median overall survival • 1 year survival • 2 year survival • Local control at 1 year and 2 years (i.e. tumour regression/resolution OR no tumour progression within treatment field) • Progression free survival • Acute and late radiotherapy toxicity (including, but not limited to, fatigue, nausea, diarrhoea and bone fracture)

quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	• Quality of life • Adverse events <u>*Important to decision-making:*</u> • Cost effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
Study design	Case reports, resource utilisation studies
In addition to the above criteria, any study with a patient population of <30 patients was also excluded.	

12 Search Strategy

Total number of references: 4791

Total following de-duplication: 3729

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 07, 2019
- 8th March 2019

1	(((solitar* or isolate*) adj4 metasta*) or ((one or two or three or four or multi* or numerous) adj3 metastas*)).tw.	27584
2	(oligomet* or oligo-met* or oligo met*).tw.	1432
3	exp Neoplasm Metastasis/	191806
4	sc.fs.	151606
5	or/1-4	318046
6	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	11342
7	(arc therap* or vmat).tw.	2815
8	radiosurg*.tw.	11519
9	Radiosurgery/	13787
10	or/6-9	22504
11	5 and 10	4266
12	limit 11 to yr="2009 -Current"	3039
13	(editorial or letter or case report or comment or news).pt.	1880897
14	12 not 13	2920

- Embase 1974 to 2019 Week 09
- 8th March 2019

1	((solitar* or isolate*) adj4 metasta*).tw.	8954
2	(oligomet* or oligo-met* or oligo met*).tw.	2867
3	((one or two or three or four or multi* or numerous) adj3 metastas*).tw.	31647
4	or/1-3	41744
5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	20863
6	(arc therap* or vmat).tw.	7217
7	radiosurg*.tw.	17079
8	exp Radiosurgery/	61567
9	or/5-8	72601
10	4 and 9	3640
11	limit 10 to yr="2009 -Current"	3128
12	(editorial or letter or case report or comment or news or conference abstract or Conference Paper or Conference Review).pt.	5688078
13	11 not 12	1606

- Cochrane (CDSR and CENTRAL)
- 8th March 2019

ID	Search	Hits
#1	((solitar* or isolate*) NEAR/4 metasta*):ti,ab,kw	129
#2	(oligomet* or oligo-met* or oligo met*):ti,ab,kw	353
#3	((one or two or three or four or five or six or multi* or numerous) NEAR/3 metastas*):ti,ab,kw	2512
#4	[mh /SC]	3199
#5	(Pastorino et al.-#4)	5574
#6	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*):ti,ab,kw	975
#7	radiosurg*:ti,ab,kw	617
#8	[mh Radiosurgery]	196
#9	(arc therap* or vmat):ti,ab,kw	570

#10	(Franceschini et al.-#9)	1714
#11	#5 and #10 with Cochrane Library publication date from Jan 2009 to present	265

13 Evidence selection

- Total number of publications reviewed: 3729
- Total number of publications considered relevant: 166
- Total number of publications selected for inclusion in this briefing: 16

14 References

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15 Appendices

15.1 Quality of evidence scores

15.1.1 Comparative studies

Palma (2019)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**2**
5. Are the results generalizable?	**2**
Total	**9**

Ost (2018)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**2**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**2**
5. Are the results generalizable?	**1**
Total	**9**

Lee (2018)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**1**
2. Is the research design appropriate for the aims and objectives of the research?	**0**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**

5. Are the results generalizable?	**1**
Total	**4**

Lodeweges (2017)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**7**

Filippi (2016)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**1**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**5**

Stintzing (2013)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**1**
2. Is the research design appropriate for the aims and objectives of the research?	**0**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**5**

15.1.2 Non-comparative studies

Sutera (2019)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**7**

Navarria (2014)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**7**

Siva (2018)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**7**

Warren (2017)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**6**

Comito (2014)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**0**
5. Are the results generalizable?	**1**
Total	**6**

Kunos (2012)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**1**
3. Are the methods clearly described?	**2**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**0**
Total	**6**

Mahadevan (2018)

Each quality item is scored as follows:	**Score**

• **Yes= 2** • **In part = 1** • **No= 0**	
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**0**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**5**

Ricco (2017)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**0**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**5**

Andratschke (2018)

Each quality item is scored as follows: • **Yes= 2** • **In part = 1** • **No= 0**	**Score**
1. Are the research questions/aims and design clearly stated?	**2**
2. Is the research design appropriate for the aims and objectives of the research?	**0**
3. Are the methods clearly described?	**1**
4. Is the data adequate to support the authors' interpretation/conclusions?	**1**
5. Are the results generalizable?	**1**
Total	**5**