NHS England

Evidence review: Efficacy, toxicity and cost-effectiveness of stereotactic ablative radiotherapy (SABR) in patients with cancer undergoing re-irradiation.

First published: June 2019

Updated: Not applicable

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1. Contents

2. Introduction

This review focuses on patients who have locally recurring tumours in the spine (generally metastatic tumours from a variety of primaries) or pelvis (prostatic, colorectal or gynaecological, either primary or metastatic, with or without lymph node involvement), which have been previously irradiated by conventional external beam radiotherapy (EBRT) or brachytherapy. Typically, treatment options are limited in these patients due to the harmful accumulated radiation dose in nearby healthy organs when re-irradiation occurs with conventional radiation therapy.

Stereotactic ablative radiotherapy (SABR or SBRT) offers a potential alternative by irradiating a precise region defined through imaging, thus sparing the healthy surrounding organs from harmful effects. SABR requires special equipment for positioning and targeting the radiation dose. It is delivered in 5 fractions (fx) or fewer in the context of re-irradiation.

The population that would be suitable for this intervention includes all patients with locally recurrent and previously irradiated pelvic or spinal tumours, who have a life expectancy of at least 6 months. There must be a period of at least 6 months since previous radiotherapy was last given in the same field. The expected number of patients who will be suitable for this intervention is around 500 patients per year annually in England (Policy Working Group Consensus).

Current standard treatment options may vary depending on the type of primary tumour being treated, but may include palliative measures, systemic chemotherapy or targeted treatments or surgery to the pelvic, spinal or para-aortic local recurrence.

SABR for locally recurrent and previously irradiated pelvic, spinal or para-aortic tumours has been investigated in the NHS England Commissioning through Evaluation (CtE) programme.

3. Summary of results

Following a systematic search of medical databases (see section 4: Methodology), 13 studies were identified which met the inclusion criteria for this review. These included:

- 1 systematic reviews reporting on pelvic tumours (Murray et al, 2017)
- 1 systematic review reporting on spinal metastases (Myrehaug et al, 2017)
- 9 non-comparative cohort studies on spinal metastases (Boyce-Fappiano et al, 2017; Chang et al, 2012; Choi et al, 2010; Garg et al, 2011; Hashmi et al, 2016; Mahadevan et al, 2011; Nikolajek et al, 2011; Ogawa et al, 2018; Sahgal et al, 2009)
- 2 non-comparative cohort studies on prostate cancer (Loi et al, 2018; Miszczyk et al, 2018).

The strongest evidence came from the two systematic reviews, although neither study reported pooled analyses or patient level data. Murray et al (2017), reporting on 205 patients with pelvic tumours, found that SABR delivered local control rates at 1-year

ranging from 51-100%. Overall survival ranged from 11.5-14 months (1-year survival was 46-52%). SABR was generally well tolerated with grade 3-4 toxicities occurring in 13 patients (6.3%). The systematic review included small retrospective case series of between 3 and 31 patients.

Myrehaug et al (2017), focusing on 405 patients with spinal metastases, reported median local control rates at 1-year of 76% (66-90%). Overall survival ranged from 10-22.5 months. The authors reported low crude rates of vertebral compression fractures (12%) and radiation induced myelopathy (1.2%), and no grade 3-4 toxicities. The systematic review included studies of between 37 and 180 patients, including one phase I controlled trial and a number of lower quality retrospective case series.

For the studies focusing on prostate cancer, local control ranged from 82-86%, while grade 3-4 genitourinary and gastrointestinal toxicities were seen in 3.7% and 2% of patients, respectively. Loi et al (2018) reported biochemical relapse free survival at 1-year of 80%.

There are severe limitations to the evidence for SABR re-irradiation with no published comparative studies and very high levels of heterogeneity in patient population and intervention among the studies. Furthermore, outcomes such as local control, progression free survival, and pain response are reported in different ways.

The outcome measured with the most consistency, median overall survival, was reported in 8 spinal metastases studies (ranging from 11-27 months in cohort studies and 10-22.5 months in Myrehaug et al's (2017) systematic review). Grade 3-4 toxicities have a low incidence rate (2-7.3% in the 5 studies that reported on this outcome). 2 studies indicated SABR re-irradiation significantly improves pain outcomes for patients with spinal metastases (Ogawa et al, 2018; Nikolajek et al, 2011).

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 10 for PICO table).

The PICO criteria were used to search for relevant publications in EMBASE, MEDLINE and Cochrane CDSR and CENTRAL (see section 10 for search strategy).

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

The titles and abstracts of the results from the literature searches were assessed 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 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 8 below).

5. Results

Clinical effectiveness - In patients with previously irradiated and locally recurrent spine, pelvic and para-aortic tumours, what is the clinical effectiveness of stereotactic ablative body radiotherapy to local tumours compared with no local treatment or local surgery or local conventionally fractionated radiotherapy?

All 13 included studies reported on at least one clinical effectiveness outcome. Boyce-Fappiano et al (2017); Chang et al (2012); Choi et al (2010); Garg et al (2011); Hashmi et al (2016); Loi et al (2018); Miszczyk et al (2018); Murray et al (2017); Myrehaug et al (2017); Sahgal et al (2009); Mahadevan et al (2011); Nikolajek et al (2011); and Ogawa et al (2018). As noted elsewhere in this report, none of the included studies were comparative. The studies also had high levels of heterogeneity in terms of the patient population; for example, spinal metastases studies had a wide variety of primary tumour locations, and demographic data was sparsely reported. None of the included studies provided evidence regarding para-aortic tumours. Additionally, the intervention incorporated a range of different doses and fractionation modalities, both within and across the studies. A summary of the notable outcomes are reported below:

Local control

Ten of the included studies reported local control (LC) rates. With the exception of Garg et al. (2011) which was prospective, the rest were retrospective case series. Two of the included studies (Murray et al, 2017; Myrehaug et al, 2017) were systematic reviews, mainly including evidence from small retrospective case series (of between 3 and 31 patients in Murray et al, and between 37 and 180 patients in Myrehaug et al).

Spinal metastases

There were a variety of different measures used with the two main being radiographic and neurological response rates. Myrehaug et al (2017), in a systematic review of 9 previous studies, reported 1-year local control of between 66% and 90% (in 6 studies focusing on re-irradiation SABR following initial conventional external beam radiation therapy [cEBRT])

and 81% (in 1 study on re-irradiation SABR following initial SABR). The study did not attempt any pooled analyses.

Boyce-Fappiano et al (2017) reported a local control (radiographic response) rate of 71% (29% progressed), with a median EQD2[1] of 34.67Gy at a median follow-up of 4 months. Chang et al (2012) reported a radiographic control rate of 78.6% at 2-year follow-up (mean EQD2 51.1Gy). Choi et al (2010) reported actuarial local control rate of 73% at 1-year, measured by follow-up MRI (median EQD2 15Gy). Garg et al (2011) reported 76% of patients were free from local progression at 1-year. The authors also reported actuarial freedom from neurologic deterioration of 92% at 1-year and 81% at 3-years. Hashmi et al (2016) reported a median time until local failure of 8.3 months (median EQD2 36Gy). The authors found single fractionation was a positive predictive factor for LC (compared to multiple-fractionation, Kaplan-Meier curve p=0.002) Nikolajek et al (2011) reported actuarial rates of freedom from local failure of 93% at 6-months, 88% at 12-months and 85% at 18-months (median dose 18Gy). Larger tumour volume was significantly associated with local failure (p=0.001). In this same study (Nikolajek et al 2011) larger tumour volume was significantly associated with local failure (p=0.001).

Pelvic tumours

For pelvic tumours generally (prostate, gynaecologic, rectal) Murray et al (2017), in a systematic review of 17 previous studies, reported rates of 1-year local control of between 51.4% and 100% (significantly associated with EQD2 >60Gy, p=0.04). The study did not attempt any pooled analyses.

The studies often provided further information for local control failures. For example, Sahgal et al (2009) noted that in 6 of the 17 local failures, they had to give a lower dose to respect spinal cord constraints. Boyce-Fapiano et al (2017) suggested that their LC rate of 71% could be improved with high doses, and noted the low rate of toxicity in their patients. Murray et al (2017) also concluded that LC rates are promising given the low levels of toxicity.

LC can be related to dose delivered and the size of the lesion being treated (Aubusaris et al 2012), but the substantial heterogeneity among these studies on both counts means that it is difficult to draw any firm conclusions about this outcome. Furthermore, Murray et al (2017) note that the evidence does not provide certainty on how or even if systemic treatments should be combined with SABR re-irradiation.

[1] EQD2 (Equivalent Dose in Gy-2 fractions) has been reported here to make it easier to compare doses between studies which used different fractionation schedules. This is also sometimes known as Biological Equivalent Dose (BED) but EQD2 is used to avoid confusion with Biological Effective Dose, which is also abbreviated to BED in some literature.

Progression free survival

Spinal metastases

Studies reported either the duration of time without progression or the proportion of patients without progression at a defined follow-up point. Chang et al (2012) reported a mean of 18.0 months for re-irradiated patients (mean dose 51.1Gy), which compared to 26 months for patients treated with EBRT alone (p=0.029). Mahadevan et al (2011) reported both a median 9-month local progression free survival and 93% of patients had improved or stable disease at final follow-up (median 12-months) although most patients had been lost to follow-up or died. Sahgal et al (2009) reported progression free survival rates of 85% at 1-year and 69% at 2-years (median EQD2 31Gy). Garg et al (2011) used a variety of dose regimens (27Gy/3fx in 50 patients; 30Gy/5fx in 8 patients; and 4Gy/5fx in 1 patient) but found no significant differences between these subgroups.

Prostate cancer

For prostate cancer Loi et al (2018) reported 80% of patients had biochemical relapse free survival at 1-year (SABR dose of 30Gy/5fx – EQD2 not reported); failure (i.e. relapse) was significantly associated with tumour grading of ≥3a (high risk) and ongoing androgen deprivation therapy [ADT] (p=0.014 and p=0.025, respectively). In studies focusing on prostate cancer, Loi et al (2018) reported biochemical response alongside median prostate specific androgen [PSA] decline (86% and 55.6% decline at 2-months; 82% and 77.1% decline at 6-months). Miszczyk et al (2018) reported 86.8% biochemical failure, which was significantly associated with months to PSA nadir following EBRT (hazard ratio 1.03, p=0.005) and neoadjuvant ADT before EBRT (HR 4.82, p=0.0218).

Overall and 1-year survival

The majority of studies reported median overall survival from start of SABR, although Choi et al (2010), Garg et al (2011), Hashmi et al (2016), and Murray et al (2017) also reported actuarial OS at 1-year follow-up.

Median OS

Spinal metastases

Myrehaug et al (2017), in a systematic review of 9 previous studies, reported median overall survival ranging from 10-22.5 months (in 7 studies). The study did not attempt any pooled analyses. In some of the studies subgroup analyses was used to explore the impact of certain parameters on survival. For example in Garg et al (2011) who reported a median overall survival of 22.5 months – patients receiving an initial dose of ≥35Gy had a significantly higher median survival time compared to <35Gy (33 vs. 21 months, Kaplan-Meier estimate p=0.01). The lowest median OS in spinal metastases studies was reported by Chang et al (2012) and Mahadevan et al (2011) with a median overall survival of 11 months for re-irradiated patients. In the Chang et al study the SABR dose was the highest of any study (median EQD2 51.1Gy), though it is unclear what influence this has on OS. The longest median OS was reported by Choi et al (2010) with their cohort achieving median overall survival of 27 months (median EQD2 15Gy). The authors did not discuss reasons for the longer OS but it is notable that the majority of patients were relatively young (<65) years and 93% had a relatively good performance status (Karnofsky

performance status of ≥70). Both these factors are considered good prognostic factors for OS. Nikolajek et al (2011) reported a median overall survival of 16.2 months (median EQD2 18Gy). Sahgal et al (2009) reported a median overall survival of 21 months (median EQD2 31Gy). Figure 1 shows the median OS survival rates reported for spinal re-irradiation.

Pelvic tumours

For pelvic tumours Murray et al (2017), in a systematic review of 17 previous studies, reported median overall survival rates ranging from 11.5-14 months in mixed primary pelvic tumour sites (2 studies), 26-40 months for colorectal cancer patients (2 studies) and 28 months for gynaecological cancer patients (1 study).

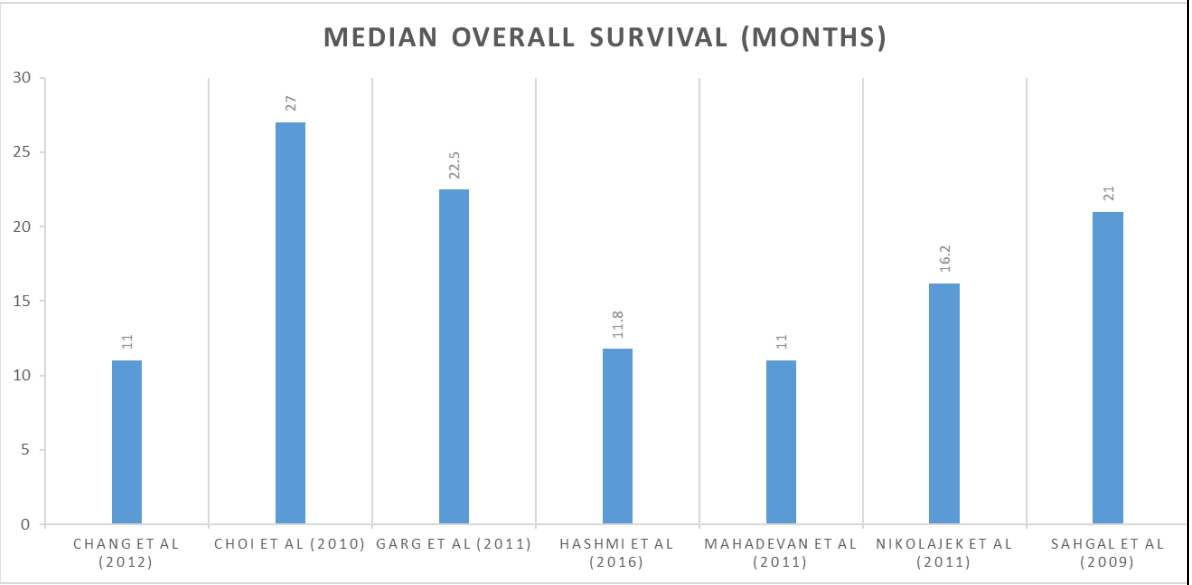

Figure 1 Median overall survival in spinal metastases primary studies

Actuarial OS

Spinal metastases

The results for actuarial OS were more consistent for spinal tumours. At 1-year follow-up, Garg et al (2011), Choi et al (2010) and Hashmi et al (2016) reported OS of 76%, 68% and 48%, respectively.

Pelvic tumours

Murray et al (2017), in a systematic review of 17 previous studies, reported differing 1-year overall survival rates depending on the primary tumour histology at 46-52% (mixed pelvic), 77-90% (colorectal) and 60% (gynaecological). The study did not attempt any pooled analyses.

Quality of life (pain)

Spinal metastases

Myrehaug et al (2017), in a systematic review of 9 previous studies, reported pain control of 65-81%, in 5 studies (4 subjective pain reporting, 1 using validated Brief Pain

Inventory). Studies reporting pain outcomes tended to report the number or proportion of patients experiencing pain or response rates to treatment. In the four studies that reported this outcome, the crude rate ranged from 81% to 87.6%, which was remarkably consistent across the studies (see Figure 2). Some studies used specific tools, such as Visual Analogue Score (VAS) or Numerical Pain Rating Scale (NPRS). For spinal metastases studies Boyce-Fappiano et al (2017) reported pain response in 81% of patients (5% were stable and 14% progressed), with a median EQD2 of 34.67Gy. Chang et al (2012) reported pain control rates at 2-year follow-up of 85.7% (mean dose 51.1Gy). Hashmi et al (2016) reported increased pain in 12.4% (median EQD2 36Gy). Mahadevan et al (2011) reported that, in patients suffering from pain at baseline, at 1-month follow-up 64.7% of patients reported improvement in pain, 20.6% stable and 14.7% progressed (35 lesions 5-6Gy/5fx; 46 lesions 8Gy/3fx). Nikolajek et al (2011) reported on 32 patients who suffered pain at baseline, in whom the median VAS improved from 6 to 4 ($p=0.0056$), with a median dose of 18Gy. Ogawa et al (2018) reported 52% of patients achieved complete pain response and 86% achieved partial or complete response[2]. NPRS also improved significantly (5.7 at baseline) at all follow-up points (1-3 months, 2.1 ($p<0.0001$), 4-6 months, 2.2 ($p<0.0001$), 7-9 months, 2.3 ($p=0.0005$) and 10-12 months, 1.6 ($p=0.0002$)). Median pain failure-free duration was 13 months and the 1-year pain failure-free rate was 55%. There were no significant correlations between pain results and primary tumour site, age, sex, performance status, initial radiation dose, or history of decompression surgery (mean EQD2 23.4Gy). Boyce-Fappiano et al (2017) commented on the importance of pain control to quality of life in patients with spinal metastases and noted their pain response result (81%) was comparable with a large previous case series reporting on first line SABR (86% in Gertzen et al, 2007).

[2] Complete response = score of 0 at treated site, no increase in analgesic requirements (oral morphine equivalent dose); partial response = score reduction of ≥2 with no increase in analgesic requirements, or analgesic reduction of ≥25% with no pain response.

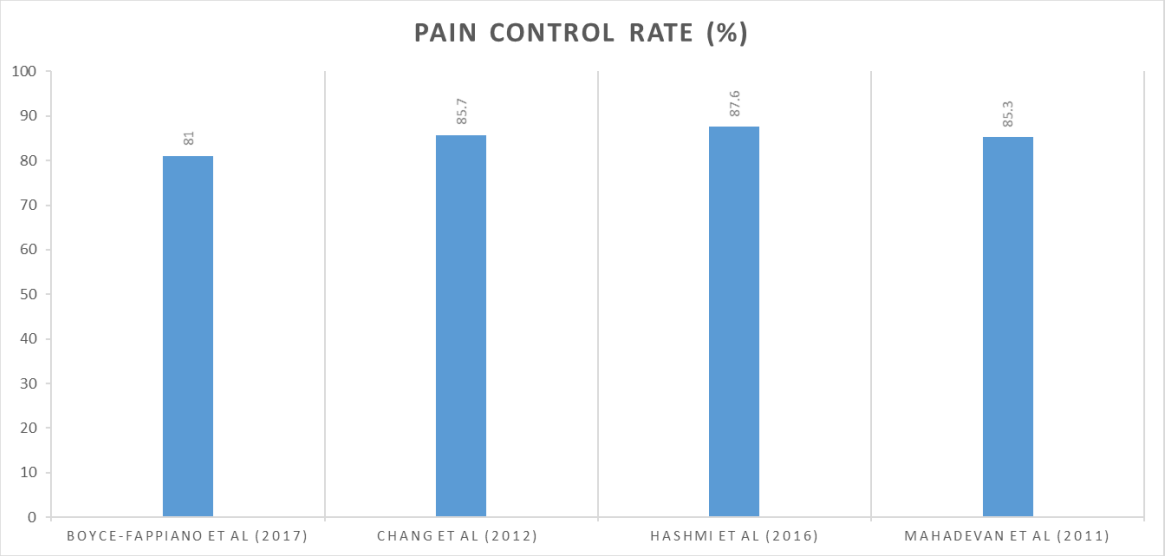

Figure 2 Pain control rate in spinal metastases studies

Pelvic tumours

Murray et al (2017), in a systematic review of 17 previous studies including 205 patients, reported pain improvements (in symptomatic patients) of 50-100%, in 4 different studies.

Prostate cancer

The two studies on prostate cancer did not report pain outcomes.

Safety and toxicity - In patients with previously irradiated and locally recurrent spine, pelvic and para-aortic tumours, what is the safety and toxicity of stereotactic ablative body radiotherapy to local tumours compared with no local treatment or local surgery or local conventionally fractionated radiotherapy?

Twelve of the 13 included studies reported on at least one safety outcome. Boyce-Fappiano et al (2017); Chang et al (2012); Choi et al (2010); Garg et al (2011); Hashmi et al (2016); Loi et al (2018); Miszczyk et al (2018); Murray et al (2017); Myrehaug et al (2017); Sahgal et al (2009); Mahadevan et al (2011); and Ogawa et al (2018). None of the included studies provided evidence regarding para-aortic tumours. Most studies used the CTCAE criteria for adverse events, but due to the heterogeneity among the studies, it is impossible to draw any conclusions about the safety profile of SABR relative to standard care.

The studies did not report any standardised quality of life outcome measures, such as the EQ5D questionnaire, but a number of studies did report pain outcomes, which have been included in this section.

Spinal metastases

The main side effect reported by spinal metastases studies was the incidence of vertebral compression fractures (VCFs), which ranged from 4.5% to 22%. This adverse event has

been observed both as an acute and late adverse effect and can result in pain and subsequent surgical interventions (Faruqi et al. 2017). Hashmi et al (2016) reported the lowest rate of VCFs in only 4.5% of lesions (median EQD2 36Gy). As the authors note, almost half of their patients undergone surgery prior to SABR, resulting in a cohort consisted mainly of patients at low risk of VCF, as those at high risk of VCF were likely to have undergone surgical stabilization prior to SABR re-irradiation. On the contrary, in Chang et al (2012), which reported the highest VCF rate (22%, mean dose 51.1Gy), almost half of their patients had lesions involving the presence of an epidural mass with large volume disease. The authors also do not report that any of their patients had undergone stabilisation surgery prior to SABR. As previously mentioned, the Chang et al. study also had the highest SABR dose (EQD2 51.1Gy). The combination of high SABR dose, lack of stabilisation surgery and presence of large volume disease, will have resulted in a population with higher risk for VCFs. Other studies reported intermediate rates of VCFs with Ogawa et al (2018) reporting VCFs in 5 patients (7.5%) and radiation induced myelopathy in 1 patient (mean EQD2 23.4Gy) and Boyce-Fappiano et al (2017) reported 77 VCFs (32.5% of lesions) although only 22 (9.3% of all lesions) were considered attributable to radiation (median EQD2 34.67Gy). Myrehaug et al (2017), in a systematic review of 9 previous studies, reported 12% of patients developed VCFs. The small study populations and heterogeneity among the studies make it difficult to make robust conclusions for the variability observed for this outcome.

Radiation myelopathy was also a side effect reported in some of the studies. It is a late toxicity side-effect resulting from the radiation-induced injury to the spinal cord and frequently associated with upper or lower extremity weakness, paresthesias, and urinary retention. In severe cases this can lead to paraplegia and even death (Marcus and Million 1990). The systematic review by Myrehaug et al (2017), reported that 1.2% of the patients developed symptomatic myelopathy. No other grade 3-4 events were reported (doses ranged from 20-30Gy in single or multiple (2-5) fractions). One more study by Choi et al (2010) also reported 1 patient who developed myelopathy. The patient died of progressive systemic disease 53 months after SABR (patient dose: 39.6Gy in 1.8 Gy fractions; total spinal cord dose of 40Gy). Garg et al (2011) reported 2 cases (3.3% of all patients) of severe (grade 3) neurotoxicity, while 18.6% of patients reported mild (grade 1-2) neurotoxicity and 20.3% mild gastrointestinal toxicity (dose: 27Gy/3fx). Mahadevan et al (2011) reported 40% of patients suffered grade 1 fatigue and 20% suffered grade 2 nausea at 1-month follow-up, while 30% had radiculopathy or lower limb weakness (35 lesions 5-6Gy/5fx; 46 lesions 8Gy/3fx). Sahgal et al (2009) reported 3 patients who suffered grade 1 or 2 events (nausea) and no patients suffered radiation-induced myelopathy or radiculopathy at ≥6-month follow-up (EQD2 31Gy).

Prostate cancer

Loi et al (2018) reported 8% rectal and 20% urinary acute grade 1-2 complications, during the 3 months following SABR. At subsequent follow-up (median 21.3 months) there were 6% rectal and 24% urinary complications (grade 1-2). One patient experienced grade 3 urinary and rectal complications (patient dose: 30Gy/5fx). Miszczyk et al (2018) reported 4.8% of patients suffered acute grade 2 gastrointestinal reactions, while 5.3%-9.1%

suffered acute grade 2 genitourinary reactions and 3.7% suffered acute grade 3 genitourinary reactions (EQD2 36.25Gy).

Pelvic tumours

Murray et al (2017), in a systematic review of 17 previous studies including 205 patients, reported overall 9 patients (4.4%) suffered grade 3 events and 6 (2.9%) suffered grade 4 events. Ten of the included studies reported no grade 3+ toxicities. The authors noted the 'surprising' low levels of toxicity and how the 'worst case' crude rate of 8.3% high-grade toxicities compares favourably with rates of 20-36% reported for hyperfractionated regimens (Guren et al, 2014).

Other adverse events were reported variously by the studies, with no consistent outcome measure used across the studies. Boyce-Fappiano et al (2017) reported adverse events in 11 patients (6.8%): 3 dysphagia/odynophagia, 5 sensory changes, weakness, or radiculopathy (however, median follow-up was very short at 4 months). Hashmi et al (2016) reported dysphagia in 11.3% of patients and dermatitis 3% (median dose 18Gy/1fx; median follow-up 8.1-months). Mahadevan et al (2011) reported 30% of patients had radiculopathy or lower limb weakness (35 lesions 5-6Gy/5fx; 46 lesions 8Gy/3fx; median follow-up 12-months). Nikolajek et al (2011) reported that of 22.2% of patients with sensory deficit, 1.8% experienced improvement while 3.7% regressed, and of 14 patients with motor deficit (26% of total cohort), 1 improved while 5 regressed (median dose 18Gy; median follow-up of 14.5 months).

Most studies used the CTCAE criteria for adverse events, but due to study heterogeneity, it is impossible to draw any conclusions about the safety profile of SABR relative to standard care. In addition, most studies did not have a long enough follow-up to adequately capture late toxicity increasing the risk of detection bias. Finally, a few studies did not report separately acute and late toxicity minimising the ability to estimate its overall impact on patients.

Cost effectiveness - In patients with previously irradiated and locally recurrent spine, pelvic and para-aortic tumours, what is the cost effectiveness of stereotactic ablative body radiotherapy to local tumours compared with no local treatment or local surgery or local conventionally fractionated radiotherapy?

We did not find any studies meeting the inclusion/exclusion criteria that focused on the cost-effectiveness of SABR re-irradiation.

Sub-groups - 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)?

In general, the studies did not report subgroup analyses, although Hashmi et al (2016) reported a median time until local failure of 8.3 months in the entire cohort but 8.2 months

in the single-fraction sub-group and 11.3 months in the multiple fraction subgroup, which was not statistically significant.

The literature was divided between spine (10 studies), prostate (2 studies) and pelvic (1 study with a mix of prostate, cervical, endometrial and rectal cancers). A notable difference between these studies was the large difference in the interval between initial EBRT and SABR: in spinal metastases studies, the interval ranged from 3-24.5 months, versus 76-101 months in prostate studies, and a median of 22 months for pelvic studies (Murray et al, 2017).

6. Discussion

Patterns of major findings, in perspective

The most consistently reported outcome was median OS in primary studies treating spinal metastases (see

Table 7), which ranged from 11-27 months (see Figure 1). Myrehaug et al (2017), in a systematic review of spinal metastases studies, reported median overall survival ranging from 10-22.5 months. Three spinal studies reported overall survival at 1-year follow-up (see

Table 7), ranging from 48-76%. Garg et al (2011), in a prospective case series, found that an initial SABR dose of ≥35Gy had significantly higher median survival time (33 vs. 21 months, Kaplan-Meier estimate p=0.01). A recent analysis of 100 cases of exenteration for advanced primary and recurrent pelvic colorectal cancer reported a 1-year OS at 76% and 50% at 2-years (in patients with the whole tumour removed within clear margins), providing indirect evidence that SABR re-irradiation potentially achieves the same degree of OS for this patient cohort (Milne et al. 2014).

Local control tends to be the primary focus of re-irradiation studies, although it was reported in various different ways (radiographic response, neurological response, local actuarial control at 6- and 12-months, biochemical response, and median time to local failure – see Table 2), with results ranging from 71-92% in the primary studies. Myrehaug et al (2017), in the spinal systematic review, reported LC rates of 66-90% and Murray et al (2017), in the pelvic systematic review, reported LC rates of 51.4-100%. Choi et al (2010) found that an interval between EBRT and SABR of ≤12 months significantly predicted local failure (multivariate analysis p<0.0006). Conversely, Garg et al (2011) found no significant differences between initial radiation <12-months prior vs. ≥12-

months. The heterogeneity of several aspects of the studies means it is difficult to say anything conclusive about this outcome.

Progression free survival (PFS) at 1-year was reported by 4 spinal metastases studies (76-93% - see

Table 5) and 1 prostate study (80% - see Table 8); only 1 study reported PFS at 2-years (69% - see Table 7). 2 studies reported length of PFS (9-18 months).

In prostate cancer studies, ongoing androgen deprivation therapy (ADT) was associated with statistically significantly worse outcomes in both Loi et al (2018) and Miszczyk et al (2018). Tumour grading of ≥3a (high risk) was associated with statistically significantly worse outcomes in Loi et al (2018).

Regarding toxicity, in the spinal metastases studies, vertebral compression fractures (VCFs) were reported by 5 studies, ranging from 4.5-22% (see Table 9). The rate of VCFs was highest in the study with the highest dose (51.1Gy in Chang et al, 2012). Serious adverse events (grade 3-4) were rare in all studies (0-3.4% spinal, 7.3% pelvic, and 2-3.7% prostate – see Table 11). A recent systematic review of studies using SABR in non-previously irradiated spinal metastases reported that VCF rates ranged from 5.7% to 39% (Faruqi et al. 2017). The reported range is similar to the VCF rate range identified in the re-irradiation studies included in this review (4.5%-22%). As a result it is reasonable to assume that there is indirect evidence that SABR re-irradiation does not increase the rate of VCF in this patient cohort.

Murray et al (2017), in a systematic review of 17 previous studies including 205 patients, reported overall 9 patients (4.4%) suffered grade 3 events and 6 (2.9%) suffered grade 4 events. Ten of the included studies reported no grade 3+ toxicities. The systematic review of patients undergoing pelvic re-irradiation (Murray et al. 2017), reported low levels of toxicity and a crude rate of 8.3% high-grade toxicities that compares favourably with rates of 20-36% reported for hyperfractionated regimens (Guren et al, 2014). On the contrary, two recent large sample size studies (one meta-analysis and an international registry) have reported high rates of surgical complications (32.1%-58.1%) and 30 day mortality rates of 1.6-1.8% (Barrera et al., 2019, PelvEx Collaborative, 2018).

Although no studies reported quality of life outcomes (such as a generic or cancer-specific questionnaire), most studies reported pain outcomes, albeit in a variety of ways (see Table 12). Four primary spinal metastases studies reported pain response or control rate (of 81-87.6%, see Table 12), while 2 studies reported change in VAS or NPRS[3] over baseline, with SABR delivering significant improvements in both studies (Nikolajek et al, 2011; Ogawa et al, 2018).

There is no discernible pattern to SABR dose, or the interval between EBRT and SABR. However, the spinal studies reporting overall survival shared similar EBRT treatment

[3] Visual Analogue Score or Numerical Pain Rating Scale

schedules (30-42.8Gy in 10-14fx). In the two prostate studies, EBRT and SABR doses were similar (72-76Gy and 30-36.25Gy, respectively), but the interval between irradiation modalities was more varied (76-101 months). Murray et al (2017), in a systematic review on pelvic patients, reported an EBRT dose of 80Gy and SABR dose of 30Gy in prostate patients. In non-prostate patients, EBRT dose was 45-50.4Gy and SABR dose was 15-60Gy.

Conflicting results

For spinal metastases, there was a very wide range of outcomes in the 3 studies reporting on grade 1-2 gastrointestinal toxicity (7.7-60%), though grade 3-4 events were far more closely matched (0-3.4%).

Chang et al (2012) reported high rates of VCFs (22%) compared to the other studies (4.5-12%). The authors highlighted the large size of the tumours being treated, which could be a possible explanation for the high rate of fractures. With the exception of one study (Garg et al, 2011), differences in dose appeared to have little impact on clinical outcomes (such as overall survival or local control) although due to the heterogeneity of the studies, this is very difficult to quantify.

Unexpected findings

SABR was shown to have very low toxicity profile in terms of grade 3-4 events, although the low quality of evidence could mean that some events were not captured by these studies.

Hashmi et al (2016), who reported the lowest rates of VCFs (4.5%), highlighted this was unexpectedly lower than previously reported in the literature (10-16%). The authors hypothesised that the high proportion of patients with previous surgery (46%) meant that high-risk patients would have had surgical stabilisation before treatment with SABR. A similar effect was observed in Thibault et al (2015).

Limitations/weaknesses

The quality of evidence is extremely low, with no comparative studies on SABR re-irradiation. Some studies had extremely short follow-up times (as little as 4 months median), which could skew the reported incidence of adverse events, for example. The retrospective nature of the majority of the studies severely limits our abilities to draw firm conclusions about many of the important outcomes. The strongest studies are two systematic reviews (Murray et al, 2017; Myrehaug et al, 2017) which did not report any pooled analyses. One of the non-comparative studies was conducted prospectively (Garg et al, 2011) and two had a sample size of 185 patients or greater (Chang et al, 2012; Hashmi et al, 2016). However, the grade of evidence was considered C (the lowest) for every outcome.

Principal implications of findings

The low quality of the studies (grade C for all outcomes) means that firm conclusions cannot be reached on the clinical effectiveness associated with OS, PFS and LC. The

results however, are more consistent for pain and toxicity related outcomes, which allows some inference of benefit despite the low quality study designs.

Recommendations for future research

In order to determine the relative clinical efficacy of SABR re-irradiation, prospective comparative studies are required. The STEREO-RE-PRO trial is currently recruiting (https://clinicaltrials.gov/ct2/show/nct03438552), a 3-arm trial which aims to investigate the efficacy of different doses (30Gy/5fx, 25Gy/5fx, 36Gy/6fx) in prostate cancer re-irradiation. However, we have not identified any ongoing studies comparing SABR with other treatment modalities. It should be highlighted that the treatment options for this group of patients is extremely limited and SABR re-irradiation may be the only treatment modality available. Therefore, it is unlikely that high-quality level I evidence (such as an RCT) will become available in the near future however.

7. Conclusion

This evidence review included 13 studies reporting on SABR re-irradiation in patients with pelvic tumours, prostate cancer, and spinal metastases. None of the included studies provided evidence regarding para-aortic tumours. The best evidence comes from 2 systematic reviews, although no pooled analyses were attempted and the studies included were of low quality. Rates of local control and overall survival can be seen as promising, but the heterogeneity of these studies and lack of comparative evidence means it is not possible to conclude whether or not SABR re-irradiation is an effective treatment option in this group of patients. The safety profile of SABR in this group of patients is encouraging with low levels of grade 3-4 adverse events, especially when viewed in light of higher adverse event rates in studies focusing on conventional radiotherapy. There is also low quality evidence from 2 studies indicating SABR re-irradiation significantly improves pain outcomes for patients with spinal metastases.

There is no published evidence on the cost-effectiveness of SABR re-irradiation. All available evidence is for an adult population only.

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8. Evidence Summary Table

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Boyce-Fappiano et al (2017)	P1 Retrospective case series	162 patients with 237 re-irradiated spine lesions, median age 64.3-yrs, 99 men (61%).	Initial treatment with conventional external beam radiation therapy (cEBRT). Median dose 30Gy/10fx. Median 10.2-month interval to stereotactic radiosurgery, with a median dose of 16Gy/1fx Median 4-month follow-up.	Primary Clinical effectiveness	Pain, neurological and radiographic response rates	Pain 81% (5% stable, 14% progressed), neurological 82% (9% stable, 9% progressed), radiographic 71% (29% progressed).	4	Direct	Single arm non-comparative case series - no randomisation, blinding, concealment. The study population and intervention are well matched to the scope although the patient population is heterogeneous with regard to primary tumour site. Pain and neurologic response are subjective outcomes and retrospective analysis is not reliable. Short-term follow-up does not allow capturing long-term toxicity.
				Primary Safety	Adverse effects	11 patients (6.8%): 3 (1.9%) dysphagia/odynophagia, 5 (3.1%) sensory changes, weakness or radiculopathy. 77 patients had vertebral compression; 22 (9.3%) were attributable to radiation.			

[4] See Appendix for detail

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Chang et al (2012)	P1 Retrospective cohort study	185 patients with spinal metastases. 54 SBRT re-irradiation (mean age 54.5) and 131 first line SBRT (mean age 50.1)	Re-irradiation cohort: initial EBRT (mean dose 39.2Gy$_2$) followed by 24.5 month interval to SBRT (mean dose 51.1Gy$_{2/10}$). Mean 17.3-month follow-up. First line SBRT mean dose 50.7Gy$_{2/10}$ Mean 23.7-month follow-up.	Primary Clinical effectiveness Primary Safety	Overall survival Progression free survival 2-yr pain/radiographic control rates Toxicity	Re-irradiation 20.7-months (mean), 11 months (median), first line SBRT 32.4-months (p=0.022). Re-irradiation 18.0-months, first line SBRT 26.0-months (p=0.029). Re-irradiation 85.7%/78.6%, first line SBRT 90.2%/90.2% (both non-significant) Overall 12 symptomatic vertebral compression fractures were seen (vertebroplasty in 5, conservative treatment in 7)	5	Direct	Retrospective cohort study comparing SBRT re-irradiation of initially EBRT treated spinal metastases with first-line SBRT. No randomisation, blinding, concealment, groups treated at different time points. The population, intervention and outcomes are well matched to the scope. The toxicity outcomes are poorly reported. The study treated lesions ranging from 1.3cm3 to 265cm3 resulting in a highly heterogeneous cohort potentially increasing the risk of toxicity and lowering efficacy for the largest lesions. The toxicity outcomes are poorly reported. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards.

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Choi et al (2010)	P1 Retrospective case series	42 patients with 51 spinal metastases (median age 57; 17 men (40%)).	Initial EBRT median dose 40 2-Gy, followed by median 19-month interval to SBRT median dose of 20Gy. Median 7-month follow-up.	Primary Clinical effectiveness Primary Safety	Actuarial local control (6 and 12 months) Survival (6 and 12 months) Median overall survival Toxicity	6-months: 87%; 12-months 73%. Interval between EBRT and SBRT ≤12 months significantly predicted local failure (multivariate analysis p<0.0006). 6-months: 81%; 12-months: 68%. 27 months. 1 patient developed lower extremity weakness, paresthesias, and urinary retention; the patient died of progressive systemic disease 53 months after SBRT.	4	Direct	Single arm non-comparative case series - no randomisation, blinding, concealment. The study population and intervention are well matched to the scope. Toxicity outcomes are poorly reported and the patient population is heterogeneous with regard to primary tumour site. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards.

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Garg et al (2011)	P1 Prospective case series	59 patients with 63 spinal metastases (median age 60; 35 men).	Initial conventional radiotherapy (median dose 30Gy) following >3month interval to SBRT (27Gy/3fx in 50 patients; 30Gy/5fx in 8 patients; and 4Gy/5fx in 1 patient). Mean 17.6-month follow-up.	Primary Clinical effectiveness Primary Safety	1-yr freedom from local progression Overall survival Neurological function Toxicity	76% Median overall survival time 22.5-months. Actuarial 1-yr survival 76%. Initial dose of ≥35Gy had significantly higher median survival time (33 vs. 21 months, Kaplan-Meier estimate p=0.01). Actuarial freedom from neurologic deterioration was 92% at 1-yr and 81% at 3-yrs. There were 2 cases of severe (grade 3) neurotoxicity.	5	Direct	Data was collected prospectively, but only in a single-arm study with no randomisation, blinding, concealment. The re-irradiation aspect of the study is a reanalysis of a previous paper. The study population and intervention are well matched to the scope. Pain response outcomes are not reported in this study. The study treated lesions ranging from 3.5cm^3 to 266cm^3 resulting in a highly heterogeneous cohort potentially increasing the risk of toxicity and lowering efficacy for the largest lesions. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards.

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Hashmi et al (2016)	P1 Retrospective case series	215 patients with 247 spinal metastases (median age 62; 48.6% male) treated at 7 institutions.	Initial cEBRT (median dose 30Gy/10fx) followed by a median 13.5 month interval to SBRT (median dose 18Gy/1fx) Median 8.1-month clinical follow-up	Primary Clinical effectiveness Primary Safety	Overall survival Local failure Adverse effects	Median length of survival was 11.8-months. Actuarial 6- and 12-month survival rates 64% and 48% respectively. Median time to local failure 8.3-months in the entire cohort (8.3-months in single-fraction SBRT subgroup). Overall: dysphagia in 11.3%, dermatitis 3%, increased pain 12.4%, vertebral compression fractures 4.5%.	5	Direct	Single arm non-comparative case series - with data collected from multiple institutions - no randomisation, blinding, concealment. The study population, intervention and outcomes are well matched to the scope although the patient population is heterogeneous with regard to primary tumour site. In addition, almost 50% of the patients underwent additional surgical treatment. The sample size is substantially larger than other studies of this type. Multi-centre international experience analysing a large cohort of patients means that the results are generalisable.

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Loi et al (2018)	P1 Retrospective case series	50 patients with recurrent prostate cancer (median prostate specific antigen (PSA) at relapse 2.6nmol/L)	Initial EBRT (median EQD2 dose 74Gy) followed by a median 76 month interval to SBRT (30Gy/5fx) Median 21.3-month follow-up.	Primary Clinical effectiveness	Biochemical response	2-months: 86% (median PSA decline 55.6%), 6-months: 82% (median PSA decline 77.1%).	4	Direct	Single arm non-comparative case series - no randomisation, blinding, concealment. The study intervention and outcomes are well matched to the scope. The patient population characteristics are poorly reported though tumour factors are largely homogeneous. Authors controlled for variations such as ADT use. This is a contemporary cohort with recruitment period starting from 2012, therefore, more comparable with current standards. With the exception of toxicity other clinical outcomes outside the scope of the review. Follow-up is long enough to allow captured of long-term toxicity. However, this was not consistent between patients (range 6.1-49.2 months).
					Oncologic outcome	54% no evidence of disease, 6% on androgen deprivation therapy (ADT) with stable PSA levels, 40% biochemical relapse.			
					Biochemical relapse free survival	1-yr: 80%. Failure significantly associated with tumour ≥3a (high risk) and ongoing ADT (p=0.014 and p=0.025 respectively).			
				Primary Safety	Toxicity	During and 3-months after rSBRT: 8% rectal and 20% urinary acute grade 1-2 complications. Subsequent follow-up: 6% rectal and 24% urinary grade 1-2 complications. 1 patient experienced grade 3 urinary and rectal complications.			

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Mahadevan et al (2011)	P1 Retrospective case series	60 patients with 81 epidural spinal metastases (median age 56; 36 males)	Initial EBRT (median dose 30Gy/10fx) followed by median 20-month interval to SBRT (35 lesions 5-6Gy/5fx; 46 lesions 8Gy/3fx). Median 12-month follow-up.	Primary Clinical effectiveness	Overall survival Local progression free survival Pain	Median 11 months (from initiation of SBRT). 9 months (most patients were lost to follow-up or died due to progressive systemic disease – at final follow-up 93% had improved or stable disease). Of 34 patients with pain at baseline 64.7% reported improvement at 1-month follow-up. 18% no longer needed pain medication and 47% needed less.	4	Direct	Single arm non-comparative case series no randomisation, blinding, concealment. The study population and intervention are well matched to the scope although the patient population is heterogeneous with regard to primary tumour site. Outcomes are poorly reported, particularly the dropout rate and reasons. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards. Most patients were lost to follow-up or died due to progressive systemic disease. Long-term follow-up, however, due to the unavailability of restaging imaging at progression following SABR, it is unknown if disease progression resulted from treatment failure or from out-of-field dissemination.
				Primary Safety	Neurologic outcomes Toxicity	30% had radiculopathy or lower limb weakness. At 1-month follow-up 40% suffered grade 1 fatigue and 20% suffered grade 2 nausea.			

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Miszczyk et al (2018)	P1 Retrospective case series	38 patients with recurrent prostate cancer (median age 71.6; median PSA at SBRT 3.26nmol/L). 55.3% of patients on ADT during study period. 9 patients had oligometastases.	Initial EBRT (median dose 76Gy – 1 patient brachytherapy (BT) alone, 3 patients EBRT with BT boost) followed by median 101-month interval to SBRT (median dose 36.25Gy) Median 14.4-month follow-up.	Primary Clinical effectiveness Primary Safety	Local control Gastrointestinal effects Genitourinary effects	86.8%. Biochemical failure significantly associated with months to PSA nadir following EBRT (hazard ratio 1.03, p=0.005) and neoadjuvant ADT before EBRT (HR 4.82, p=0.0218). 4.8% suffered acute grade 2 reactions. 5.3%-9.1% suffered acute grade 2 reactions, 3.7% suffered acute grade 3 reactions.	3	Direct	Single arm non-comparative case series no randomisation, blinding, concealment. The study intervention is well matched to the scope. However, the patient population is heterogeneous with regard to oligometastases and ADT use and the patient characteristics and outcomes are poorly reported. This is a contemporary cohort with recruitment period starting from 2012, therefore, more comparable with current standards. Follow-up is long enough to allow capturing long-term toxicity. However, this was not consistent between patients (range 1.6-46.4 months).

Murray et al (2017)	R1 Systematic review	205 patients (from 17 previously published studies) with either prostate (82 patients), cervical or endometrial (50 patients) or rectal lesions (50 patients). Some studies included both re-irradiated and irradiated patients.	Initial treatment was typically conventional RT (45-50.4Gy in non-prostate, 80Gy in prostate cases). Median interval between initial RT and SBRT was 22-months (based on reported means). SBRT dose ranged from 15Gy/3fx to 60Gy/3fx (median 30Gy/4.5fx) Median follow-up ranged from 3-38 months in re-irradiated only cohort, and from 12-31 months in the mixed cohort.	Primary Clinical effectiveness	Pain	Improvements in pain of 50-100% of patients were seen in 4 studies. Bleeding improved in 75% of patients in one study.	6	Direct	Systematic review of retrospective case series, with no pooled analysis of the results. The search methods are described briefly but they appear to be adequate for a systematic review of this kind. The search strategy is not reported. Individual study data is reported extensively in supplementary files.
					Radiological/clinical response	Complete or partial response or stable disease was seen in 86% (1 study). Complete response was seen in 40-60% (2 studies). Mixed cohort showed complete or partial response in 35-83% and stable disease in 5-40% (4 studies).			
					Local control	At 1-yr: 51.4-100% (success was associated with dose >60Gy)			
					Survival	Median overall survival ranged from 11.5-14 months with mixed primary tumour sites (2 studies), 26-40 months for colorectal patients (2 studies) and 28 months for gynaecological patients (1 study). 1-yr overall survival was 46-52%, 77-90% and 60% respectively for the same patient groups.			
				Primary Safety	Toxicity	Overall, 9 patients suffered grade 3			

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
						events and 6 suffered grade 4 events.			
Myrehaug et al (2017)	R1 Systematic review	405 patients (from 9 previously published studies) with spinal metastases.	Initial RT (either cEBRT or SBRT) median dose ranged from 24-40Gy (up to 14fx) SBRT doses ranged from 20-30Gy in single or multiple (2-5) fractions. Median follow-up ranged from 6.8-17.6 months.	Primary Clinical effectiveness Primary Safety	Overall survival Local control Pain control Adverse events	cEBRT->SBRT: median ranged from 10-22.5 months (7 studies). SBRT->SBRT: 6.8 months (1 study) cEBRT->SBRT: at 1-yr median ranged from 66-90% (7 studies). Progression was most common in epidural disease. SBRT->SBRT: at 1-yr 81% (1 study). Pain control was observed in 65-81% of cases (crude analysis of 5 studies) Of 186 spinal segments 12% developed vertebral compression fracture. Of 411 spinal segments 1.2% developed symptomatic myelopathy. No other grade 3-4 events reported.	6	Direct	Systematic review of retrospective case series, with no pooled analysis of the results. The search methods are described and the search strategy is reported; the methods are adequate for this kind of review. All included studies were GRADE scored as Low or Very Low quality (3 were prospective case series, 1 was described as a phase I/II study, and 5 were retrospective case series). There is no supplementary data provided on the individual studies and the patient population is poorly reported. Authors give three recommendations based on the evidence.

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Nikolajek et al (2011)	P1 Retrospective case series	54 patients with 70 spinal metastases (median age 56; 32 males)	Initial conventional RT (nBED Gy 2/2 median dose 42.8Gy) followed by a median 15-month interval to SBRT (median dose 18Gy). Median 14.5-month follow-up	Primary Clinical effectiveness	Freedom from local failure	Actuarial rates at 6-, 12- and 18-months: 93%, 88% and 85%. Larger tumour volume was significantly associated with local failure (p=0.001).	4	Direct	Single arm non-comparative case series - no randomisation, blinding, concealment. The study population, intervention and outcomes are well matched to the scope though the patient population is heterogeneous with regard to both primary tumour site and metastasis lesions treated. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards. However, VAS score was used to measure pain outcomes, which increases generalisablility.
					Overall survival	Median following SBRT: 16.2 months. Median following initial RT: 42 months.			
					Pain	Of 32 patients who suffered pain pre-SBRT the median VAS improved from 6 to 4 (p=0.0056)			
				Primary Safety	Adverse effects	Of 12 patients with sensory deficit, 1 experience improvement while 2 regressed. Of 14 patients with motor deficit, 1 improved while 5 regressed.			

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Ogawa et al (2018)	P1 Retrospective case series	66 patients with painful bone metastases (median age 65; 46 males)	Initial cEBRT (median dose 30Gy) followed by median 21-month interval to SBRT (24Gy/2fx in 51 patients, 30Gy/5x in 13 patients, and 35Gy/5fx in 2 patients) Median 10-month follow-up	Primary Clinical effectiveness	Pain	52% achieved complete pain response and 86% achieved partial or complete response.[5] Numerical pain rating scale improved significantly over baseline (5.7) at all follow-ups (1-3 months, 2.1 ($p<0.0001$), 4-6 months, 2.2 ($p<0.0001$), 7-9 months, 2.3 ($p=0.0005$) and 10-12 months, 1.6 ($p=0.0002$)). Median pain failure-free duration was 13 months and 1-year pain failure-free rate was 55%.	4	Direct	Single arm non-comparative case series - no randomisation, blinding, concealment – although the database has been set up prospectively. The study population, intervention and outcomes are well matched to the scope though the patient population is heterogeneous with regard to both primary tumour site and metastasis lesions treated. Additionally, the study only includes pain and toxicity outcomes. This is a contemporary cohort with recruitment period starting from 2012, therefore, more comparable with current standards. The authors do report detailed eligibility criteria. However, NPRS score was used to measure pain outcomes, which increases generalisability.
				Primary Safety	Toxicity	5 patients suffered vertebral compression fractures and 1 patient suffered radiation induced myelopathy.			

Use of SABR in previously irradiated tumours of the spine, prostate and pelvis									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score[4]**	**Applicability**	**Critical Appraisal Summary**
Sahgal et al (2009)	P1 Retrospective case series	39 patients with 60 spinal metastases (median age 58). 14 patients (23 lesions) had no previous RT.	25 patients (37 lesions) had initial RT (median dose 36Gy/14fx) followed by median 11-month interval to SBRT (median dose 24Gy/3fx, entire cohort) Median 8.5-month follow-up (entire cohort).	Primary Clinical effectiveness	Survival	Median survival time: 21 months. 2-yr survival probability: 45% (no significant differences between irradiated and re-irradiated groups).	3	Direct	Single arm non-comparative case series - no randomisation, blinding, concealment. The study population and intervention are well matched to the scope though the patient population is heterogeneous with regard to primary tumour site. Outcomes are poorly reported, particularly pain, and the study includes a mixed cohort of irradiated and re-irradiated patients. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards.
					Local control (shorter follow-up)	1- and 2-yr progression free probability 85% and 69% respectively (no significant differences between irradiated and re-irradiated groups). All 8 patients who failed to respond also suffered worsening of pain.			
				Primary Safety	Toxicity	3 patients suffered grade 1 or 2 events (nausea). No patients suffered radiation-induced myelopathy or radiculopathy (≥6-month follow-up).			

[5] Complete reponse = score of 0 at treated site, no increase in analgesic requirements (oral morphine equivalent dose); partial response = score reduction of ≥2 with no increase in analgesic requirements, or analgesic reduction of ≥25% with no pain response.

9. Grade of evidence table

Use of SABR in patients with previously irradiated tumours of prostate and pelvis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Local control	Loi et al (2018) Miszczyk et al (2018) Murray et al (2017)	4 3 6	Direct Direct Direct	C	Local control (LC) is usually reported as the proportion of patients for which the treated cancer lesion does not increase in size at a defined follow-up point after beginning treatment. Local control was reported in different ways depending on the tumour site (for example, prostate studies report prostate-specific antigen levels as a measure of biochemical response). The best evidence for patients undergoing pelvic and prostate re-irradiation came from a systematic review by Murray et al (2017) that included 205 patients from 17 studies and showed 1-yr local control of 51.4-100%. These outcomes show that local control is highly variable. Although Murray et al (2017) identified a clinical benefit when using doses of >60Gy, it is difficult to identify a clinical benefit from non-comparative studies There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations and reported outcomes.

Use of SABR in patients with previously irradiated tumours of prostate and pelvis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Progression free survival	Loi et al (2018)	4	Direct	C	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. PFS was defined based on biochemical control of a blood-circulating biomarker in some studies (for example, prostate studies report the prostate-specific antigen levels as a measure of biochemical response). The best evidence for this outcome is provided by the retrospective cohort study by Loi et al (2018) that analysed 50 patients with prostate cancer and found that 1-year biochemical relapse-free survival was 80% in prostate cancer patients. Non-comparative studies do not show a clear clinical benefit. Loi et al (2018) found failure was significantly associated with tumour stage ≥3a (high risk) and ongoing androgen-deprivation therapy (p=0.014 and p=0.025 respectively). There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence.

Use of SABR in patients with previously irradiated tumours of prostate and pelvis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Median overall survival	Murray et al (2017)	6	Direct	C	Median overall survival was reported as a length of time patients survive following treatment The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and reported a median OS of 11-14.5 months. Non-comparative studies do not show a clear clinical benefit. Various doses were used in different studies, which also limits validity. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations. However, the outcome measure is consistently reported in the studies included here.

Use of SABR in patients with previously irradiated tumours of prostate and pelvis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
1 year survival	Murray et al (2017)	6	Direct	C	This outcome was reported as a proportion of patients surviving at 1-year follow-up from re-irradiation. The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and that at 1-year follow-up 46-52% of patients survived. None of the studies compared SABR with another form of treatment so it is impossible to tell if it has a clinical benefit. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations.

Use of SABR in patients with previously irradiated tumours of prostate and pelvis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Adverse events	Loi et al (2018) Miszczyk et al (2018) Murray et al (2017)	4 3 6	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 in patients with cancer is usually recorded and graded according to the Common Toxicity Criteria Adverse Events (CTCAE). Studies reported acute and late toxicities although not consistently throughout the studies. Site-specific events were sometimes captured as adverse events (see below); there was not always a distinction made between radiotherapy and non-radiotherapy related morbidities. The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and reported that 7.3% of patients suffered grade 3-4 events. Non-comparative studies do not show a clear clinical benefit. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations and reported outcomes.

Use of SABR in patients with previously irradiated tumours of prostate and pelvis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Quality of life (pain)	Murray et al (2017)	6	Direct	C	Studies did not report any quality of life outcomes, with the exception of pain scores. These were reported either as a comparative before-after score (Visual Analogue Score or Numerical Pain Rating Scale) or as a proportion of patients who experience reduction, control of worsening of pain. The best evidence for patients undergoing pelvic re-irradiation came from a systematic review by Murray et al. (2017) that included 205 patients from 17 studies and reported pain improvement in 50-100% of patients. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations and reported outcomes.
Cost effectiveness	N/A				

Use of SABR in patients with previously irradiated tumours of the spine					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Local control	Boyce-Fappiano et al (2017) Chang et al (2012) Choi et al (2010) Garg et al (2011) Hashmi et al (2016) Myrehaug et al (2017) Sahgal et al (2009)	4 5 4 5 5 6 3	Direct Direct Direct Direct Direct Direct	C	Local control (LC) is usually reported as the proportion of patients for which the treated cancer lesion does not increase in size at a defined follow-up point after beginning treatment. Local control was reported in different ways depending on the tumour site. This outcome is also referred to as clinical/radiographic response in some studies. The best evidence for patients undergoing re-irradiation for spinal metastases comes from a systematic review by Myrehaug et al. (2017) that included 9 cohort studies and reported 1-yr local control rates of 66-90%. These outcomes show that local control is highly variable. It is difficult to identify a clinical benefit from non-comparative studies. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations and reported outcomes.

Use of SABR in patients with previously irradiated tumours of the spine					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Progression free survival	Chang et al (2012) Garg et al (2011) Mahadevan et al (2011) Nikolajek et al (2011)	5 5 4 4	Direct Direct Direct Direct	C	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. PFS was defined based on worsening neurological function in some studies. The best evidence is provided by the prospective cohort study by Garg et al. (2011) that analysed 59 patients with 63 spinal metastases and reported 76% of patients with progression free survival at 1-year follow-up. None of the studies compared SABR with another form of treatment so it is impossible to ascertain if it has a clinical benefit. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations.

Use of SABR in patients with previously irradiated tumours of the spine					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Median overall survival	Chang et al (2012) Choi et al (2010) Garg et al (2011) Hashmi et al (2016) Mahadevan et al (2011) Myrehaug et al (2017) Nikolajek et al (2011) Sahgal et al (2009)	5 4 5 5 4 6 4 3	Direct Direct Direct Direct Direct Direct Direct Direct	C	Median overall survival is reported as a length of time patients survive following treatment. The best evidence for patients undergoing re-irradiation for spinal metastases comes from a systematic review by Myrehaug et al. (2017) that included 9 cohort studies and reported median overall survival of 10-22.5 months. Non-comparative studies do not show a clear clinical benefit. Various doses were used in different studies, which also limits validity. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations. However, the outcome measure is consistently reported in the studies included here.

Use of SABR in patients with previously irradiated tumours of the spine					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
1 year survival	Choi et al (2010) Garg et al (2011) Hashmi et al (2016)	4 5 5	Direct Direct Direct	C	This outcome was reported as a proportion of patients surviving at 1-year follow-up from re-irradiation. The best evidence for this outcome is provided by the multi-centre cohort study by Hashmi et al (2016) that included 215 patients and found 48% of them surviving at 1-year follow-up. None of the studies compared SABR with another form of treatment so it is impossible to tell if it has a clinical benefit. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations.

Use of SABR in patients with previously irradiated tumours of the spine					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Adverse events	Boyce-Fappiano et al (2017) Chang et al (2012) Choi et al (2010) Garg et al (2011) Hashmi et al (2016) Mahadevan et al (2011) Myrehaug et al (2017) Ogawa et al (2018) Sahgal et al (2009)	4 5 4 5 5 4 4 6 4 3	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 in patients with cancer is usually recorded and graded according to the Common Toxicity Criteria Adverse Events (CTCAE). Studies reported acute and late toxicities although not consistently throughout the studies. There was not always a distinction made between radiotherapy and non-radiotherapy related morbidities. The best evidence for patients undergoing re-irradiation for spinal metastases comes from a systematic review by Myrehaug et al. (2017) that included 9 cohort studies and reported that 12% developed vertebral compression fractures (VCFs) and 1.2% developed symptomatic myelopathy. Non-comparative studies do not show a clear clinical benefit. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations and reported outcomes.

Use of SABR in patients with previously irradiated tumours of the spine					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Quality of life (pain)	Boyce-Fappiano et al (2017) Chang et al (2012) Hashmi et al (2016) Mahadevan et al (2011) Myrehaug et al (2017) Nikolajek et al (2011) Ogawa et al (2018)	4 5 5 4 6 4 4	Direct Direct Direct Direct Direct Direct Direct	C	Studies did not report any quality of life outcomes, with the exception of pain scores. These were reported either as a comparative before-after score (Visual Analogue Score or Numerical Pain Rating Scale) or as a proportion of patients who experience reduction, control of worsening of pain. The best evidence for patients undergoing re-irradiation for spinal metastases comes from a systematic review by Myrehaug et al. (2017) that included 9 cohort studies and found 65-81% of patients' pain was under control. Non-comparative studies do not show a clear clinical benefit although Nikolajek et al (2011) and Ogawa et al (2018) both showed a significant before-after improvement in VAS/NPRS. There are considerable uncertainties for this outcome due to the non-comparative and largely retrospective nature of the evidence, as well as the substantial heterogeneity in patient populations and reported outcomes.
Cost effectiveness	N/A				

10. Literature Search Terms

Table 1 PICO table agreed with NHS England

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 locally recurrent and previously irradiated pelvic, spinal or para-aortic tumours (primary or secondary). [Patients may have previously received standard care with standard treatment options that vary depending on the type of primary tumour being treated. Systemic treatments may include systemic chemotherapy, hormone treatments, molecular targeted treatments or palliative measures.]
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 (5 fractions or fewer) to locally recurrent and previously irradiated pelvic or spinal tumour in addition to standard care.
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 treatment Local treatment of tumour recurrence, which may be surgery or conventionally fractionated radiotherapy.
O – Outcomes Outcomes should be patient focussed and relate to those detailed in the PPP and the Research	*Critical to decision-making:* Local control (i.e. tumour regression/resolution OR no tumour progression within treatment field)

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; quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Progression free survival Median overall survival 1 year survival Acute and late radiotherapy toxicity (including, but not limited to, fatigue, nausea, diarrhoea and bone fracture) Quality of life Adverse events *Important to decision-making:* 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 Study sample size <30 patients.

11. Search Strategy

Total number of references: 1830

Total following de-duplication: 1254

- 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	(salvage treat* or salvage therap* or radiorecurrent or re-irradiat* or reirradiat* or repeat irradiat* or second irradiat* or secondary irradiat*).tw.	9628
2	Salvage Therapy/	13228
3	Re-Irradiation/	201
4	or/1-3	19473
5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	11342
6	(arc therap* or vmat).tw.	2815
7	radiosurg*.tw.	11519
8	exp Radiosurgery/	13787
9	or/5-8	22504
10	4 and 9	875
11	limit 10 to yr="2009 -Current"	723
12	(editorial or letter or case report or comment or news or conference abstract or Conference Paper or Conference Review).pt.	1880897
13	11 not 12	704

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

1	(salvage treat* or salvage therap* or radiorecurrent or re-irradiat* or reirradiat* or repeat irradiat* or second irradiat* or secondary irradiat*).tw.	16869
2	Salvage Therapy/	20351
3	Re-Irradiation/	860

4	or/1-3	29131
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	1981
11	limit 10 to yr="2009 -Current"	1790
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	1071

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

ID	Search	Hits
#1	(salvage treat* or radiorecurrent or re-irradiat* or reirradiat*):ti,ab,kw	2420
#2	[mh "Salvage Therapy"]	545
#3	[mh " Re-Irradiation"]	0
#4	{OR #1-#3}	2462
#5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*):ti,ab,kw	975
#6	radiosurg*:ti,ab,kw	617
#7	[mh Radiosurgery]	196
#8	(arc therap* or vmat):ti,ab,kw	570
#9	{OR #5-#8}	1714
#10	#4 and #9 with Cochrane Library publication date from Jan 2009 to present	55

12. Evidence selection

- Total number of publications reviewed: 1254

- Total number of publications considered relevant: 40
- Total number of publications selected for inclusion in this briefing: 13

13. References

ABUSARIS, H., HOOGEMAN, M. AND NUYTTENS, J. J. 2012. Re-Irradiation: Outcome, Cumulative Dose and Toxicity in Patients Retreated with Stereotactic Radiotherapy in the Abdominal or Pelvic Region. *Technology in Cancer Research & Treatment*, pp. 591–597

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14. Appendices

Tables of selected outcomes for discussion

Table 2 Local control, spinal metastases

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Radiographic response	Neurological response	Local actuarial control 6-months	Local actuarial control 12-months	Local actuarial control 18-months	Median time to local failure in months
Boyce-Fappiano et al (2017)	32.5Gy	10.2	34.67Gy	71%	82%	-	-		-
Chang et al (2012)	39.2Gy	24.5	51.1Gy	78.6%	-	-	-		-
Choi et al (2010)	40Gy	19	15Gy	-	-	87%	73%		-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	-	92%	-	76%		-
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	-	-	-	-		8.3
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)				93%		
Nikolajek et al (2011)	42.8Gy	15	18Gy			93%	88%	85%	
Myrehaug et al (2017) -	*24-40Gy (up to*	-	*20-30Gy (single or*	-	-	-	*66-90%*		-

systematic review	*14fx) (EQD2 not reported)*		*2-5fx) (EQD2 not reported)*						

Table 3 Local control, prostate (primary studies)

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Biochemical response 2-months	Biochemical response 6-months	PSA decline 2-months	PSA decline 6-months	Local control
Loi et al (2018)	74Gy	76	30Gy/5fx (EQD2 not reported)	86%	82%	55.6%	77.1%	
Miszczyk et al (2018)	76Gy	101	36.25Gy	-	-	-	-	86.8%

Table 4 Local control, pelvic

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Local control rate at 1-yr	Radiographic response
Murray et al (2017) – systematic review	*45-50.4Gy (non-prostate) 80Gy (prostate)*	*22*	*41.7-58Gy*	*51.4-100%*	*35-83%*

Table 5 Progression free survival, spinal metastases (primary studies)

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	PFS in months	Progression free survival probability 1-yr	Progression free survival probability 2-yr
Chang et al (2012)	39.2Gy	24.5	51.1Gy	18.0 (mean)	-	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	-	-	-
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	9 (median)	-	-
Sahgal et al (2009)	47Gy	11	31Gy	-	85%	69%

Table 6 Progression free survival, prostate (primary studies)

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Biochemical relapse free survival at 1-year
Loi et al (2018)	74Gy	76	30Gy/5fx (EQD2 not reported)	80%

Table 7 Overall survival, spinal metastases

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Median overall survival in months	Survival at 6-months	Survival at 12-months	Survival probability at 2-years
Chang et al (2012)	39.2Gy	24.5	51.1Gy	11	-	-	-
Choi et al (2010)	40Gy	19	15Gy	27	81%	68%	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	22.5	-	76%	-
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	11.8	64%	48%	-
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	11	-	-	-
Nikolajek et al (2011)	42.8Gy	15	18Gy	16.2	-	-	-
Sahgal et al (2009)	47Gy	11	31Gy	21	-	-	45%
Myrehaug et al (2017) - systematic review	*24-40Gy (up to 14fx) (EQD2 not reported)*	-	*20-30Gy (single or 2-5fx) (EQD2 not reported)*	*10-22.5*	-	-	-

Table 8 Overall survival, pelvic

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Median overall survival in months	Survival at 12-months
Murray et al (2017) – systematic review	*45-50.4Gy (non-prostate) 80Gy (prostate)*	*22*	*41.7-58Gy*	*11.5-14 (mixed primaries) 26-40 (colorectal) 28 (gynaecological)*	*46-52% (mixed primaries) 77-90% (colorectal) 60% (gynaecological)*

Table 9 Acute and late radiotherapy toxicity, spinal metastases

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Vertebral compression fractures (%)	Symptomatic myelopathy	Lower extremity weakness/ radiculopathy	Grade 1-2 neurotoxicity	Grade 1-2 gastrointestinal toxicity	Grade 3 neurotoxicity
Boyce-Fappiano et al (2017)	32.5Gy	10.2	34.67Gy	22 (9.3%)	-	5 (3.1%)	-	-	-
Chang et al (2012)	39.2Gy	24.5	51.1Gy	12 (22%)	-	-	-	-	-
Choi et al (2010)	40Gy	19	15Gy	-	-	1 (2.4%)	-	-	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	-	-	-	11 (18.6%)	12 (20.3%)	2 (3.4%)
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	11 (4.5%)	-	-	-	-	-

Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	-	-	18 (30%)	0	36 (60%)	0
Ogawa et al (2018)	30Gy	21	23.4Gy	5 (7.5%)	1 (1.5%)	-	-	-	-
Sahgal et al (2009)	47Gy	11	31Gy	-	0	0	-	3 (7.7%)	-
Myrehaug et al (2017) - systematic review	*24-40Gy (up to 14fx) (EQD2 not reported)*	-	*20-30Gy (single or 2-5fx) (EQD2 not reported)*	*22 (12%)*	*8 (1.2%)*	-	-	-	*0*

Table 10 Acute and late radiotherapy toxicity, pelvic

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Grade 3-4 events
Murray et al (2017) – systematic review	*45-50.4Gy (non-prostate) 80Gy (prostate)*	*22*	*41.7-58Gy*	*15 (7.3%)*

Table 11 Acute and late radiotherapy toxicity, prostate (primary studies)

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Grade 1-2 complications at 3-months	Grade 1-2 complications at final follow-up	Grade 3 complications at final follow-up

Loi et al (2018)	74Gy	76	30Gy/5fx (EQD2 not reported)	20% urinary 8% rectal	24% urinary 6% rectal	2% urinary 0% rectal
Miszczyk et al (2018)	76Gy	101	36.25Gy	7.4% gastro 25.9% genitourinary	4.8% gastro 5.3-9.1% genitourinary	0% gastro 3.7% genitourinary

Table 12 Pain, spinal metastases

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Pain response rate	Pain control rate	Improvement in pain at 1-month (patients)	Median VAS/NPRS improvement over baseline	Pain free at 1-yr (patients)	Median pain failure free in months
Boyce-Fappiano et al (2017)	32.5Gy	10.2	34.67Gy	81%	-	-	-	-	-
Chang et al (2012)	39.2Gy	24.5	51.1Gy	-	85.7% (at 2-yrs)	-	-	-	-
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	-	87.6%	-	-	-	-
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	-	-	64.7%	-	-	-
Nikolajek et al (2011)	42.8Gy	15	18Gy	-	-	-	Baseline **6** to **4** (p=0.0056)	-	-
Ogawa et al (2018)	30Gy	21	23.4Gy	86%	-	-	Baseline **5.7** to (1-3 months, **2.1** (p<0.0001), 4-6 months, **2.2**	55%	13

							(p<0.0001), 7-9 months, **2.3** (p=0.0005) and 10-12 months, **1.6** (p=0.0002)		
Myrehaug et al (2017) - systematic review	*24-40Gy (up to 14fx) (EQD2 not reported)*	*-*	*20-30Gy (single or 2-5fx) (EQD2 not reported)*	*-*	*65-81% (crude)*	*-*	*-*	*-*	*-*

Table 13 Pain, pelvic

Study	EBRT dose (EQD2)	Median interval in months	SABR dose (EQD2)	Pain response rate
Murray et al (2017) – systematic review	*45-50.4Gy (non-prostate) 80Gy (prostate)*	*22*	*41.7-58Gy*	*50-100%*

Quality of evidence scores detail

Template:

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. Is the research design appropriate for the aims and objectives of the research?	
3. Are the methods clearly described?	
4. Is the data adequate to support the authors' interpretation/conclusions?	
5. Are the results generalizable?	
Total	

Boyce-Fappiano (2017) 1+1+1+0+1=4

Chang (2012) 1+1+1+1+1=5

Choi (2010) 1+1+1+0+1=4

Garg (2011) 1+1+1+1+1=5

Hashmi (2016) 1+1+1+1+1=5

Loi (2018) 1+1+1+0+1=4

Mahadevan (2011) 1+1+1+0+1=4

Miszczyk (2018) 1+1+1+0+0=3

Murray (2017) 1+2+1+1+1=6

Myrehaug (2017) 1+2+1+1+1=6

Nikolajek (2011) 1+1+1+0+1=4

Ogawa (2018) 1+1+1+0+1=4

Sahgal (2009) 1+1+1+0+0=3