NHS England

Evidence review: Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) to the surgical cavity following resection of a cerebral metastasis

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Contents

1 Introduction

Introduction

- Cerebral metastasis is the spread of cancer cells from the original site they were formed (the primary tumour) to the brain, forming a secondary tumour (Tse 2018). The term can be used interchangeably with brain metastases. Cerebral metastases are the most frequent intracranial tumours in adults and arise as a consequence of cancer elsewhere in the body, most commonly from primary cancer of the lung, breast and skin (melanoma). By contrast, carcinomas of the prostate, oesophagus, and oropharynx and non-melanoma skin cancers rarely metastasize to the brain (Loeffler 2018).
- Brain metastases are an increasingly common complication of systemic cancers and represent a significant source of morbidity and mortality in cancer patients. However, with developments in systemic cancer treatments; the prognosis is improving (Lin and DeAngelis 2015). For this reason, cerebral metastases are now more frequently referred for active treatment. The number of people diagnosed with brain metastases is likely to continue to rise as a consequence of both improved detection of small metastases by magnetic resonance imaging (MRI) and better control of extracerebral disease resulting from improved systemic therapy (Loeffler 2018).
- Approximately 60% of patients with brain metastases have subacute symptoms. Symptoms are usually related to the location of the tumour and may include headache, nausea, vomiting, seizures, photophobia, nuchal rigidity, neurocognitive dysfunction, and motor dysfunction (Tse 2018).
- Medical management of brain metastatic disease consists mainly of symptom control and has mainly focused on treating cerebral oedema, headache, and seizure. Other options are radiation therapy (whole brain radiation, focal beam, and stereotactic radiation therapy), chemotherapy, combined therapies, experimental therapies, and integration therapy (Tse 2018).
- The optimal treatment strategy aims to address the balance between intracranial disease control and neurocognitive sequelae of both the disease and the treatment (NICE 2018).

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- There is no relevant NICE Technology Appraisal Guidance (with statutory requirement for NHS organisations to make funding available), clinical guidelines or quality standards specifically for the use of stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) to surgical cavity following resection of a cerebral metastasis. However, NICE published Clinical Guideline (NG 99) - Brain tumours (primary) and brain metastases in adults in July 2018 (NICE 2018). The guideline made the following recommendation regarding stereotactic radiosurgery/radiotherapy to the surgical cavities;

“Consider adjuvant stereotactic radiosurgery/radiotherapy to the surgical cavities for people with one to three brain metastases that have been resected”.

The indication and epidemiology

- Cerebral metastases are the most common intrinsic brain tumours in adults, with estimates of incidence ranging from 6-40% of patients with cancer (Davis et al 2012). Approximately, 20–40% of cancer patients with primary extracranial cancer will develop brain metastases during the course of their disease. Median survival without treatment is estimated at one month, and increases to three to 12 months when cranial radiation

therapy is used (Lamba et al 2017).

Standard treatment and pathway of care

- Traditionally, brain metastases have been treated with surgical resection followed by whole brain radiotherapy (WBRT) to decrease the rates of local recurrence, distant brain recurrence and neurologic cause of death (Lamba et al 2017).
- However, WBRT is associated with potentially greater short and long term side effects than SRS or SRT and is therefore now only used where SRS or SRT treatments are not feasible, such as in cases with too many metastases or leptomeningeal disease (NICE 2018, Brown et al 2017).

The intervention

- Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are highly conformal radiotherapy treatments to a precisely delineated target area of the brain, delivered using stereotactic localisation techniques (Lippitz et al. 2014). SRS is delivered as a single treatment known as a fraction, and SRT in two to five fractions or treatments. SRS and SRT can be delivered on an outpatient basis via various technologies including Gamma Knife, Cyberknife and modified Linear Accelerator (LINAC). During treatment the patient is fitted with a head frame, or a custom thermoplastic mask, which immobilises their head for the treatment session. The conformity and precision of SRS and SRT is thought to result in greater preservation of healthy tissue surrounding the target area, causing less functional deficit in the area and higher local control than WBRT (Lippitz et al. 2014).

Rationale for use

- SRS delivers high-dose radiation to a discrete volume within the brain. Because SRS spares healthy brain functional tissue, it confers a theoretically favourable alternative to WBRT and is being increasingly utilized in the management of brain metastases (Scheitler-Ring et al 2016).

2 Summary of results

- We found three randomised control trials (RCT), fulfilling the PICO criteria for inclusion; the results of these trials were reported in four publications. One RCT of moderate quality (Mahajan et al 2017) compared SRS with observation in 128 patients who had resection of one to three brain metastases. Another moderate quality RCT (Brown et al 2017) compared SRS to the surgical cavity with WBRT in 194 patients with one resected metastatic brain lesion. A third low quality non-inferiority RCT[1] (Kepka et al 2016) compared SRT to the surgical cavity with WBRT in 59 patients with a total or subtotal resection of single brain metastases. A further publication by Kepka et al (2017) reported on quality of life outcomes in the two treatment arms of the same study.
- We did not find any studies assessing the cost effectiveness of post-surgical SRS/SRT to tumour site resection in comparison with observation or WBRT.

[1] A non-inferiority trial aims to demonstrate that the test product (SRS/SRT) is not worse than the comparator (WBRT) by more than a pre-specified amount (in this case -20%). A non-inferiority study design is used when one treatment is superior to another in terms of an important criterion which does not require statistical validation, for example, convenience for the patient

Clinical effectiveness

2.1 SRS versus observation following resection of cerebral metastases

- The RCT by Mahajan et al (2017) (n = 128) showed a significant reduction in local tumour recurrence-free rates for patients who received SRS compared with those who were observed only at 12 months (HR 0.46, [95% CI 0.24 to 0.88], p=0.015). It also reported a longer time to local recurrence: SRS not reached (NR) [95% CI 15.6 months to NR] vs observation 7.6 months [5.3 to NR].
- In the RCT by Mahajan et al (2017), at median follow up 11.1 months (4.8 to 20.4), there were no significant differences in median overall survival time 18 months (95% CI 13 months to NR) in the observation arm (39 events) and 17 months (95% CI 13 to 22 months) in the SRS arm (46 events) (HR 1.29, [95% CI 0.84 to 1.98], p=0.24).
- Mahajan et al (2017) reported no significant difference in neurological death (the proportion of deaths that were from a neurological cause) between those who received SRS post-surgical resection of brain metastases (22/46) 48% and those who were managed by observation (25/39) 64%; difference 16% [95%CI -5 to 37], p=0.13.
- There was no significant difference at 12 months between SRS and observation in terms of freedom from distant brain metastases (DBM) (HR 0.81, [95% CI 0.51 to 1.27], p=0.35), leptomeningeal disease (LMD) (HR 1.4 [95%CI 0.6 to 3.4], p=0.46), nor freedom from WBRT; HR 0.8 [95%CI 0.47 to 1.37], p=0.42.
- The results of this trial should be treated with caution because it was a single specialist cancer site study and might have selected a sub-group of patients who required treatment at a specialist site.

2.2 SRS versus WBRT following resection of cerebral metastases

- The RCT by Brown et al (2017) (n = 194) showed a significantly longer median cognitive deterioration-free survival with SRS 3.7 months [95% CI 3.5 to 5.06] compared with WBRT 3.0 months [95%CI 2.86 to 3.25]; HR 0.47 [95% CI 0.35 to 0.63], p<0.0001. At six months a significantly lower proportion of SRS patients had experienced cognitive deterioration 52% compared with WBRT 85%; difference -33.6% [95% CI -45.3 to -21.8], p=0.00031.
- In the RCT by Brown et al (2017), changes from baseline in functional independence (as assessed by activities of daily living index) were significantly better with SRS than with WBRT at three months, but not at six months. At three months: SRS (n=70) 6% decline, 11% improvement vs WBRT (n=66) 12%, 2%; p=0.036. At six months: SRS (n=66) 5% decline, 8% improvement vs WBRT (n=48) 15%, 2%; p=0.1. Brown et al (2017) also reported a significant increase in the duration of stable or better functional independence with SRS compared to WBRT (HR 0.56, [95% CI 0.32 to 0.906], p=0.034).
- In the study by Brown et al (2017), surgical bed control was not significantly better for either SRS or WBRT at three months: 95.9% of SRS patients [95% CI 92.0 to 99.9] vs WBRT 93.5% [95% CI 88.7 to 98.7] were assessed to have good surgical bed control. However, WBRT was significantly more effective at maintaining surgical bed control at 12 months; the corresponding control rates at 12 months were: SRS 60.5% [95%CI 51.3 to 71.3] vs WBRT 80.6% [95%CI 73.0 to 89.1], p = 0.00068.
- Brown et al (2017) also reported that local control and distant brain control were significantly better maintained with WBRT than with SRS. At 12 months local control rates were: SRS 61.8% [95%CI 52.8 to 72.3] vs WBRT 87% [95%CI 80.5 to 94.2], p=0.00016.

At 12 months, distant brain control rates were: SRS 64.7% [95%CI 55.8 to 75.0] vs WBRT 89.2% [95%CI 83.1 to 95.8], p=0.00045.

- Brown et al (2017) reported no significant difference in the proportion of patients free from LMD between patients treated with SRS vs WBRT. At 12 months: SRS 92.8% [95% CI 87.8 to 98.1] vs WBRT 94.6% [95%CI 90.1 to 99.3], p=0.62.
- In the study by Kepka et al (2016) salvage treatment of relapses within the brain was undertaken in nine of 11 (81%) patients from the SRT arm and in six of 10 (60%) patients from the WBRT arm; p=0.128. All patients from both arms who received only local treatment (SRT and/or surgery) for salvage, ultimately died from progression in the brain.
- Brown et al (2017) reported no significant difference in overall survival between SRS and WBRT following resection of a single brain metastasis; HR 1.07 [95% CI 0.76 to 1.5], p=0.70, at a median follow up of 11.1 months (for entire population); 22.6 months (for those who had not died). The RCT by Kepka et al (2016) (n = 59) showed significant improvement in overall survival at two years with WBRT compared with SRT when calculated on an intention-to treat basis: HR 1.8 [95%CI 0.99 to 3.30], p=0.046. However, the difference was not significant when calculated on a per protocol[2] basis: HR 1.4 [95% CI 0.91 to 2.71], p=0.332.
- Kepka et al (2016) showed no significant difference between SRT and WBRT in the cumulative incidence of neurological/cognitive failure (CINCF) at two years follow-up (HR 1.32 [95%CI 0.74 to 2.36], p=0.31.
- Kepka et al (2016) showed no significant differences between SRT and WBRT in total intracranial progression (SRT 58% vs WBRT 36%; p=0.133), relapse in the tumour bed (SRT 26% vs WBRT 25%; p=1) or progression at new sites in the brain (distant brain recurrence) (SRT 42% vs WBRT 21%; p=0.128) at a median follow-up of 29 months. However, Brown et al (2017) showed that the time to intracranial tumour progression was significantly shorter for those who received SRS compared with WBRT (HR 2.45, [95% CI 1.62 to 3.72]), p<0.0001.
- Kepka et al (2016) showed an increase in cumulative incidence of neurological death (CIND) with SRT compared with WBRT at two years follow-up (HR 2.51, [95%CI 1.19 to 5.29]), p=0.015.
- Evidence from Brown et al (2017) (SRS n= 65; WBRT n=64) showed no differences between the treatment groups in quality of life (QOL) at six months as measured by both linear analog self-assessment (LASA) (mean difference, 14.9 [95% CI 3.5 to 26.2], p=0.24) and Functional Assessment of Cancer Therapy-Brain (FACT-Br) (mean difference, 2.9 [95% CI -4.5 to 10.3], p=0.31); Kepka et al (2017) showed no significant difference between the treatment groups at two months (SRT 65.9 vs WBRT 61.4, p=0.6) or five months (SRT 55.7 vs WBRT 67.1, p=0.19), using different scoring systems (European Organisation for Research and Treatment of Cancer quality of life questionnaire C30 and BN20 questionnaires [EORTC-QLQ-C30 and QLQ-BN20 questionnaires]).
- These results should be treated with caution because not all patients were available for assessment of functional independence and quality of life questionnaire completion was low in the study by Brown et al (2017). In addition, in the study by Kepka et al (2016, 2017) the assumptions used in the calculation of the sample size were reported to be imprecise, leading to underestimation of the number of patients needed to demonstrate non-inferiority and therefore risk of statistical hazard.

[2] In the SRT arm, 21 patients (72%) were treated per protocol, whereas 29 (97%) of the WBRT arm received the assigned treatment.

Safety

2.3 SRS versus observation following resection of cerebral metastases

- Mahajan et al (2017) reported no adverse events related to SRS treatment. They also reported no treatment related deaths with either SRS or observation.

2.4 SRS versus WBRT following resection of cerebral metastases

- Brown et al (2017) reported a lower proportion of patients with at least one treatment-related toxic effect, or toxic effects possibly related to treatment for SRS (51%) vs WBRT (71%). There were also fewer grade 3 or worse toxic effects that were possibly related to SRT treatment (12%) vs WBRT (18%). The significance of these differences was not reported.
- Brown et al (2017) reported on the proportion of patients with all grade 3 or worse toxic effects (SRS 39% vs WBRT 40%); hearing impairment (SRS 3% vs WBRT 8%); cognitive disturbances (SRS 3% vs WBRT 5%); Grade 2 or worse CNS necrosis (SRS 4% vs WBRT 0%) or death from adverse events unrelated/unlikely related to treatment (SRS 7% vs WBRT 11%). The significance of these differences was not reported.
- Kepka et al (2017) reported a significantly higher incidence of drowsiness and appetite loss with WBRT (assessed as part of the HRQOL assessments) at two months, but not at five months; at two months the mean score (SD) for drowsiness in the SRT group was 19.9 (27.5) vs WBRT 36.2 (25.1), p=0.048. At five months this was SRT 19.3 (17.0) vs 29.4 (19.5), p=0.24. Corresponding measure for appetite loss were: at two months SRT 8.9 (19.8) vs WBRT 30.2 (30.7), p=0.03; at five months SRT 35.1 (32.3) vs 25.8 (33.4), p=0.93.

Cost effectiveness

- No studies assessing the cost effectiveness of post-surgical SRS/SRT to tumour site resection in comparison with observation or WBRT were identified.

Conclusion

- Evidence from one moderate quality RCT suggests that, in patients who have undergone surgical resection of at least one metastatic brain tumour, SRS to the local cavity was more effective than observation in reducing local recurrence. However, there was no significant difference between groups in terms of overall survival, neurological death and distant brain disease. Impact on quality of life was not assessed.
- Evidence from a moderate quality RCT suggests that SRS is better at preventing cognitive decline, maintaining functional independence and is associated with longer median cognitive deterioration-free survival compared with WBRT. However, there was no significant difference between SRS and WBRT in terms of overall survival.
- WBRT is more effective than SRS in reducing recurrence rates of tumours both at the resection sites and distant from the resection. WBRT also appears to be better at delaying or preventing intracranial tumour progression and preserving intracranial control, apart from LMD for which the rates were no different.
- Neither the improved intracranial control from WBRT, nor reduced cognitive decline from SRS/SRT has been shown to result in a significant difference in QOL as assessed in the

studies identified.

- However, these results, especially regarding QOL, are inconclusive because of limitations to the studies.
- Better designed larger studies on the comparative effects of SRS/SRT vs observation or WBRT on quality of life and well-conducted cost effectiveness studies are required to determine whether SRS/SRT, compared to observation or WBRT should be routinely available for post-resection of brain metastases in the NHS.

3 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 9 for PICO).
- The PICO was used to search for relevant publications in the following sources Embase, MEDLINE, Cochrane library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 01 January 2009 and 18 January 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.
- Using established hierarchy of evidence criteria[3], the best quality and most reliable studies which matched the PICO were selected for inclusion in this review. As randomised evidence was available, non-randomised studies were excluded.
- 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).

4 Results

We found three RCTs fulfilling the PICO criteria for inclusion the results of these trails were reported in four publications. One RCT compared SRS with observation and two compared SRS/SRT with WBRT. Mahajan et al 2017 compared SRS with observation in 128 patients who had resection of one to three brain metastases. One RCT by Brown et al (2017) compared SRS to the resected tumour site with WBRT in 194 patients with one resected metastatic brain lesion. The RCT by Kepka et al (2016) was a non-inferiority study that compared SRT with WBRT in 59 patients with a total or subtotal resection of one brain metastases. A further publication by Kepka et al (2017) reported on quality of life outcomes from the same study.

[3] https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

We did not find any studies assessing the cost effectiveness of post-surgical SRS/SRT to tumour site resection in comparison with observation or WBRT.

What is the clinical effectiveness of routine SRS and SRT applied to the surgical cavity in patients following surgical resection of cerebral metastases compared with observation or WBRT?

The clinical effectiveness outcomes reported in the RCTs included: overall survival, cognitive deterioration free survival, neurocognitive failure, intracranial tumour progression, surgical bed control, local tumour recurrence, distant brain control, functional independence, leptomeningeal disease and quality of life.

4.1 SRS versus observation following resection of cerebral metastases

Local tumour recurrence-free rates at 12 months
Mahajan et al (2017) reported a significantly higher local tumour recurrence-free rate with SRS compared with observation alone. At 12 months: 72% of SRS [95%CI 60 to 87] vs 43% of observation patients [31 to 59] remained free from recurrence; HR 0.46 [0.24 to 0.88], p=0.015.

Time to local recurrence
The median times to local tumour recurrence were significantly longer with SRS compared with observation in the Mahajan et al (2017) study; SRS not reached [95% CI 15.6 months to not reached] vs observation 7.6 months [5.3 to not reached], p value not reported.

Overall survival
Mahajan et al (2017) found no significant difference in overall survival between SRS and observation. The median survival rate (median follow up 11.1 months; range 4.8 to 20.4) for SRS was 17 months [95% CI 13 to 22] compared to 18 months for observation [13 to NR]; HR 1.29 [0.84 to 1.98], p=0.24.

Neurological death
Mahajan et al (2017) reported no significant difference in the proportion of deaths that were from a neurological cause between patients who received SRS post-surgical resection of brain metastases (22/46) 48% and those who were managed by observation (25/39) 64%; difference 16% [95%CI -5 to 37], p=0.13.

Freedom from distant brain metastases (DBM)
Mahajan et al (2017) reported no significant difference in DBM. At 12 months, the rates of DBM were: SRS 42% [95% CI 30 to 58] vs observation 33% [22 to 49]; HR 0.81 [0.51 to 1.27], p=0.35.

Leptomeningeal disease (LMD)
Mahajan et al (2017) reported no significant difference between LMD rates in the SRS vs observation groups. At 12 months: SRS 28% [95% CI 12 to 40] vs observation 16% [4 to 26], HR 1.4 [0.6 to 3.4], p=0.46.

Freedom from WBRT
Mahajan et al (2017) reported no significant difference in freedom from WBRT rates between SRS and observation; SRS 16 months [95% CI 10.1 to NR] vs observation 15 months [8.6 to 42.5]; HR 0.8 [0.47 to 1.37], p=0.42.

4.2 SRS versus WBRT following resection of cerebral metastases

Cognitive deterioration-free survival
The RCT by Brown et al (2017) (N=194) reported a significantly longer median cognitive deterioration-free survival with SRS 3.7 months [95% CI 3.5 to 5.06] compared with WBRT 3.0 months [2.86 to 3.25]; HR 0.47 [0.35 to 0.63], p<0.0001. At six months a significantly lower proportion of SRS patients had experienced cognitive deterioration 52% compared with WBRT 85%; difference -33.6% [-45.3 to -21.8], p=0.00031.

Functional independence
In the RCT by Brown et al (2017), changes from baseline in functional independence (as assessed by activities of daily living index) were significantly better with SRS than with WBRT at three months, but not at six months. At three months: SRS (n=70) 6% decline, 11% improvement vs WBRT (n=66) 12%, 2%; p=0.036. At six months: SRS (n=66) 5% decline, 8% improvement vs WBRT (n=48) 15%, 2%; p=0.1.

The median duration of stable or better functional independence in the study by Brown et al (2017), was significantly better with SRS than with WBRT: SRS median not yet reached [95% CI 17.6 to not yet reached] vs WBRT 14.0 months [8.4 to 27.0]; HR 0.56 [0.32 to 0.906], p=0.034.

Surgical bed control
In the study by Brown et al (2017), the surgical bed was not significantly better controlled by either SRS or WBRT at three months: 95.9% of SRS patients [95% CI 92.0 to 99.9] vs WBRT 93.5% [88.7 to 98.7] were assessed to have good surgical bed control. However, WBRT was significantly more effective at maintaining surgical bed control at 12 months; the corresponding control rates at 12 months were: SRS 60.5% [51.3 to 71.3] vs WBRT 80.6% [73.0 to 89.1], p = 0.00068.

Local control
Local control was significantly better maintained with WBRT than with SRS in the RCT by Brown et al (2017). At 12 months local control rates were: SRS 61.8% [95%CI 52.8 to 72.3] vs WBRT 87% [80.5 to 94.2], p=0.00016.

Distant brain control
Distant brain control was significantly better maintained with WBRT than with SRS in the RCT by Brown et al (2017). At 12 months, distant brain control rates were: SRS 64.7% [95%CI 55.8 to 75.0] vs WBRT 89.2% [95%CI 83.1 to 95.8], p = 0·00045.

Progression at new sites in the brain (distant brain recurrence)
In the study by Kepka et al (2016), there was no significant difference in distant brain recurrence between SRT and WBRT at a median follow-up of 29 months. Distant brain recurrence rates were: SRT 42% vs WBRT 21%; p=0.128.

Leptomeningeal disease (LMD)
Brown et al (2017) reported no significant difference in the proportion of patients free from LMD between patients treated with SRS vs WBRT. At 12 months: SRS 92.8% [95% CI 87.8 to 98.1] vs WBRT 94.6% [90.1 to 99.3], p=0.62.

Overall survival
Brown et al (2017) found no significant improvement in the overall survival between SRS/SRT vs WBRT at a median follow up of 11.1 months (for entire population); 22.6 months (for those who had not died). The median overall survival was 12.2 months with SRS [95% CI 9.6 to 16.0] compared to 11.6 months with WBRT [9.9 to 18.0]; HR 1.07 [0.76 to 1.5], p=0.70. The non-inferiority RCT by Kepka et al (2016) (n = 59) reported an improvement in two-year overall

survival rate (median follow up 29 months [range 8 to 45]) on intention-to-treat analysis of 10% for SRT [0 to 22] compared with 37% for WBRT [19 to 55], p=0.046; HR 1.8 [0.99 to 3.30]. However, when calculated on a per protocol basis[4], the difference was no longer significant: SRT 14% [0 to 31] vs WBRT 30% [12 to 48], p=0.332; HR 1.4 [0.91 to 2.71].

Cumulative incidence of neurological/cognitive failure (CINCF)
The non-inferiority RCT by Kepka et al (2016) did not demonstrate non-inferiority between SRT and WBRT in terms of neurological/cognitive failure at six months (its primary outcome)[5]. The difference in CINCF at six months was SRT 72% vs WBRT 63%; difference -8 [95% CI -34 to 17] The corresponding scores at 24 months were: SRT 75% [58 to 93] vs WBRT 62% [43 to 80], HR 1.32 [0.74 to 2.36], p=0.31.

Intracranial tumour progression
The RCT by Kepka et al (2016) reported no significant difference in intracranial tumour progression rates: SRT 58% vs WBRT 36%; p=0.133. However, in the RCT by Brown et al (2017), the median time to intracranial tumour progression was significantly shorter in the SRS group at 6.6 months [95% CI 5.15 to 8.90], 66 events, compared with 27.5 months for WBRT [14.85 to not reached], 34 events; HR 2.45 [1.62 to 3.72], p<0.0001.

Relapse in tumour bed
Kepka et al (2016) reported no significant difference in rates of relapse at the tumour bed between SRT 26% vs WBRT 25%, p=1.

Salvage treatment of relapses
In the study by Kepka et al (2016) salvage treatment of relapses within the brain was undertaken in nine of 11 (81%) patients from the SRT arm and in six of 10 (60%) of patients from the WBRT arm; p=0.128. All patients from both arms who received only local treatment (SRT and/or surgery) for salvage, ultimately died from progression in the brain.

Cumulative incidence of neurological death (CIND)
Kepka et al (2016) reported that, at two years, cumulative incidence of neurological death (CIND) rate for the SRT group was significantly greater for SRT compared to WBRT: SRT 66% [95% CI 46 to 86] vs WBRT 31% [14 to 49], p=0.015; HR 2.51 [1.19 to 5.29].

Quality of life (QOL)
In the RCT by Brown et al (2017), there were no significant differences between the treatment groups in quality of life (QOL) at six months as measured by both linear analog self-assessment (LASA) (mean difference, 14.9 [95% CI 3.5 to 26.2] p=0.24) and Functional Assessment of Cancer Therapy-Brain (FACT-Br) (mean difference, 2.9 [95% CI -4.5 to 10.3] p=0.31). Kepka et al (2017) showed no significant difference between the treatment groups at two months (SRT 65.9 vs WBRT 61.4, p=0.6) or five months (SRT 55.7 vs WBRT 67.1, p=0.19), using different scoring systems (European Organisation for Research and Treatment of Cancer quality of life questionnaire C30 and BN20 questionnaires [EORTC-QLQ-C30 and QLQ-BN20 questionnaires]).

[4] In the SRT arm, 21 patients (72%) were treated per protocol, whereas 29 (97%) of the WBRT arm received the assigned treatment.
[5] The authors assumed a 20% non-inferiority margin in CINCF at 6 months. The authors stated that they did not demonstrate non-inferiority because the 95%CI included the non-inferiority margin (-20%)

What is the safety of routine SRS and SRT applied to the surgical cavity in patients following surgical resection of cerebral metastases compared with observation or WBRT?

4.3 SRS versus observation following resection of cerebral metastases

Mahajan et al (2017) reported no adverse events related to SRS treatment. They also reported no treatment related deaths with either SRS or observation.

4.4 SRS versus WBRT following resection of cerebral metastases

Brown et al (2017) reported a lower proportion of patients reporting at least one treatment-related toxic effect, or toxic effects possibly related to treatment for SRS (51%) vs WBRT (71%). However the significance of these differences was not reported. The rates of grade 3 or worse toxic effects possibly related to treatment were lower (SRS 12% vs WBRT 18%). Brown et al (2017) also reported the proportion of patients with all grade 3 or worse toxic effects (SRS 39% vs WBRT 40%); hearing impairment (SRS 3% vs WBRT 8%); cognitive disturbances (SRS 3% vs WBRT 5%); Grade 2 or worse CNS necrosis (SRS 4% vs WBRT 0%) or death from adverse events unrelated/unlikely related to treatment (SRS 7% vs WBRT 11%). Kepka et al (2017) reported a significantly higher incidence of drowsiness and appetite loss with WBRT (assessed as part of the HRQOL assessments) at two months, but not at five months; at two months the mean score (SD) for drowsiness in the SRT group was 19.9 (27.5) vs WBRT 36.2 (25.1), p=0.048. At five months this was SRT 19.3 (17.0) vs 29.4 (19.5), p=0.24. Corresponding measure for appetite loss were: at two months SRT 8.9 (19.8) vs WBRT 30.2 (30.7), p=0.03; at five months SRT 35.1 (32.3) vs 25.8 (33.4), p=0.93.

What is the cost effectiveness of routine SRS and SRT applied to the surgical cavity in patients following surgical resection of cerebral metastases compared with observation or WBRT?

We did not find any studies assessing the cost effectiveness of post-surgical SRS/SRT to tumour site resection in comparison with observation or WBRT.

From the evidence selected, are there any sub-groups of patients who would gain greater benefit from routine SRS or SRT applied to the surgical cavity compared with observation or WBRT?

The evidence identified did not include any suitable sub-group analysis or other comparison that can help identify sub-groups of patients who would gain greater benefit from routine SRS or SRT compared with observation or WBRT.

5 Discussion

The study by Mahajan et al (2017) provides moderate quality evidence for the effectiveness of SRS compared with observation only. In this study, SRS significantly improved local tumour recurrence-free rate compared with observation alone. Time to local recurrence was also improved. There were also no adverse events related to SRS treatment, and there was no difference in neurological death. The study however showed no overall survival benefits between groups. Without some measure of the impact of SRS on quality of life, it is difficult make any meaningful interpretation of the reduction in local recurrence.

The studies by Brown et al (2017) and Kepka et al (2016) provide moderate to low quality evidence on how SRS compares with WBRT in terms of clinical effectiveness and safety. In these studies the effects of SRS on local recurrence of metastases, total intracranial control and distant recurrence appear significantly diminished compared with WBRT, although there was no significant difference in LMD control, which is one of the more important prognoses of poor intracranial control. WBRT therefore appears to offer better intracranial control than SRS, but there was no overall survival benefit; therefore any benefits from the improved intracranial control, with WBRT, will depend on the effect on other outcomes like the patients' neurological function, cognitive deterioration, functional independence and quality of life. Brown et al (2017) reported a significantly longer cognitive deterioration-free survival with SRS compared to WBRT. The study also reported an improved median duration of stable or better functional independence with SRS than with WBRT. Kepka et al (2016) reported a higher rate of cumulative incidence of neurological death with SRT, compared with WBRT, but this study was of low quality and was not sufficiently powered to demonstrate its primary outcome; therefore that result needs to be treated with caution.

Both Brown et al (2017) and Kepka et al (2017) measured QOL and did not report any significant differences in QOL between SRS/SRT and WBRT. The cognitive loss and decline in functional independence, recognised as side effects for WBRT, did not therefore impact on the patients' global health status. This result should however be interpreted with caution because of the low rate of compliance for HRQOL evaluation in both studies.

There was a slightly higher rate of treatment related toxicities with SRS compared with WBRT (significance not reported), but there were no significant difference in occurrence of the high grade toxicities.

Better designed larger studies on the comparative effects of SRS/SRT vs observation or WBRT on quality of life and cost effectiveness analyses are required to fully establish the relative benefits of these treatment strategies following surgical resection of brain metastases.

These results should be interpreted carefully due to limitations in the study design that may have affected the results. The study by Mahajan et al (2017) was of moderate quality, but subject to the bias of being a single specialised centre study; the results could be skewed by the patients being drawn out of the population for specialised care. The 12 month local tumour-free recurrence rate for surgery alone was lower than that previously reported, but this could have been due to more frequent surveillance. The more reliable evidence on SRS vs WBRT is from the study by Brown et al, but there are limitations in the methodology that could have biased some of the results. Surgical bed control after SRS was worse than reported in previous studies, and only 129/194 patients (65 in the SRS and 64 in the WBRT groups) completed the QOL questionnaires at baseline and had at least one subsequent assessment. In addition, functional independence change from baselined values were available for 70/98 SRS patients and 48/96 WBRT patients at three months. The study by Kepka et al (2016, 2017) was an underpowered non-inferiority study that failed to demonstrates its primary outcome. The authors reported that their assumptions used in the calculation of the sample size were imprecise leading to underestimation of the number of patients needed to demonstrate non-inferiority. Any results from this study are therefore at risk of statistical hazard.

6 Conclusion

We found moderate evidence that, in patients who have undergone surgical resection of at least one metastatic brain tumour, SRS, to the local cavity was more effective than observation in reducing local recurrence. However, there was no significant difference between groups in terms of overall survival, neurological death and distant brain disease.

We found moderate evidence for a longer median cognitive deterioration-free survival with SRS compared with WBRT, but WBRT is more effective that SRS/SRT in reducing recurrence rates of tumours both at the resection sites and distant from the resection. It is also better at delaying or preventing intracranial tumour progression and preserving intracranial control, apart from LMD for which the rates were no different. SRS on the other hand is better at preventing cognitive decline and maintaining functional independence. However, there was no significant difference between SRS and WBRT in terms of overall survival.

Neither the improved intracranial control from WBRT, nor reduced cognitive decline from SRS/SRT resulted in a significant difference in QOL as assessed in the studies identified. However, these results, especially regarding QOL, are inconclusive because of limitations to the studies.

Better designed larger studies on the comparative effects of SRS/SRT vs observation or WBRT on quality of life and well-conducted cost effectiveness studies are required to determine whether SRS/SRT, compared to observation or WBRT should be routinely available for post-resection of brain metastases in the NHS.

7 Evidence Summary Table

For abbreviations see list after each table

a) Stereotactic radiosurgery (SRS) versus observation for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Mahajan et al 2017	P1 - Single centre RCT United States of America	N = 128 Age >3 years with a Karnofsky performance Score ≥ 70, complete resection of 1 to 3 brain metastases (max diameter ≤ 4 cm). No participants had a history of previous radiotherapy to the brain, or of resection of metastases (prior to those required for the trial). There were no significant differences in the baseline characteristics in both patient groups. Median follow up 11.1 months (IQR 4.8 to 20.4)	SRS (n = 64) to the tumour bed; Single session of 12 to 16 Gy (depending on cavity volume). **Versus** Observation, OBS (n = 68)	Primary Clinical effectiveness	Local tumour recurrence-free rates	At 12 months: SRS 72% [95%CI 60 to 87] vs OBS 43% [31 to 59]; HR 0.46 [0.24 to 0.88], p=0.015	8	Direct	The method of randomisation was appropriately described. Allocation was done with stratification factors. Patients and treating physicians (except neuroradiologists) were not masked with respect to treatment group. This could have biased the results for the more subjective outcomes like recurrence. The primary and secondary analyses were a modified ITT that excluded ineligible patients from the analysis and preserved original treatment assignment. All patients were accounted for at the end of the study. The study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care. The 12 month local tumour-free recurrence rate for surgery alone was lower than that previously reported, but this could have been due to more frequent surveillance.
				Secondary Clinical effectiveness	Time to local recurrence (median time to radiographic evidence of new lesion)	SRS NR [95% CI 15.6 months to NR] vs OBS 7.6 months [5.3 to NR] (p value not reported)			
				Secondary Clinical effectiveness	Overall survival time (median time from randomisation to death)	SRS 17 months [95% CI 13 to 22] (46 events) vs OBS 18 months [13 to NR] (39 events); HR 1.29 [0.84 to1.98], p=0.24			
				Secondary Clinical effectiveness	Neurological death (proportion of deaths from a neurologic cause)	SRS (22/46) 48% vs OBS (25/39) 64%; difference 16% [-5% to 37%], p=0.13			
				Secondary Clinical effectiveness	Freedom from DBM	At 12 months: SRS 42% [95% CI 30 to 58] vs OBS 33% [22 to 49]; HR 0.81 [0.51 to 1.27], p=0.35			
				Secondary Clinical effectiveness	Freedom from WBRT	SRS 16 months [95% CI 10.1 to NR] vs OBS 15 months [8.6 to 42.5]; HR 0.8 [0.47 to 1.37], p=0.42			
				Secondary Clinical effectiveness	LMD	At 12 months: SRS 28% [95% CI 12 to 40] vs OBS 16% [4 to 26], HR 1.4 [0.6 to 3.4], p=0.46			
				Secondary Safety	Adverse events related to stereotactic frame or SRS treatment	SRS 0% vs OBS 0%			
				Secondary Safety	Treatment related deaths	SRS 0% vs OBS 0%			

a) Stereotactic radiosurgery (SRS) versus observation for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Baseline characteristics between the patient groups were similar							

ADL - Activities of daily living; cGy - centigray (dose unit for radiotherapy); CINCF - Cumulative incidence of neurological/cognitive failure; CIND - Cumulative incidence of neurological death; COWAT - Controlled Oral Word Association Test; DBM - Distant brain metastases; EORTC - European Organisation for Research and Treatment of Cancer; FACT-Br - Functional Assessment of Cancer Therapy-Brain; Gy - Gray; HR - Hazard ratio; HRQOL - Health-related Quality of Life; HVLT-R - Hopkins Verbal earning Test-Revised; ITT - Intention to treat; LASA - Linear Analog Self-Assessment; LMD - Leptomeningeal disease]; NR - Not reached; (p value not reported) - No significance reported; OBS - Observation; P1 Primary research using quantitative approaches; PP - Per protocol; QOL - Quality of life; RR - Risk Ratio; SRS - Stereotactic Radiosurgery; SRT - Stereotactic Radiotherapy; TMT - Trial Marking Test; WBRT - Whole-brain radiotherapy

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Brown et al 2017	P1 – multicentre RCT (48 institutions in USA and Canada)	N = 194 adult patients (age ≥ 18 years) with one resected metastatic brain lesion; resection cavity < 5.0 cm. 23% had 2 to 4 Metastases. No previous cranial radiation. Prior	SRS (n = 98) to the tumour bed; 12 to 20 Gy single fraction (dose depending on cavity volume). **Versus** WBRT (n = 96) 30 Gy in ten daily fractions or 37.5 Gy in 15 daily fractions of 2.5 Gy (fraction schedule predetermined at treating	Primary Clinical effectiveness	Overall survival (median time from randomisation to death from any cause)	SRS vs. WBRT 12.2 months [95% CI 9.6 to16.0] vs 11.6 months [9.9 to18.0]; HR 1.07 [0.76 to1.5], p=0.70	8	Direct	The method of randomisation and allocation was appropriately described. There was no concealment of allocation to the investigator or the patients. Patients, clinicians, and study statisticians were not masked to treatment assignment, but the graders of cognitive assessments were masked to treatment assignment. All patients were accounted for and efficacy analyses were carried out on the intention to treat (ITT) basis. Local control was determined by the treating physician rather than by central review, which could have created some inconstancies in the results. Other potential limitations to the study includes the fact that the surgical bed control after SRS was worse than reported in previous studies,
				Primary Clinical effectiveness	Cognitive deterioration-free survival (median time from randomisation to a drop of greater than 1 SD from baseline in at least one of six cognitive tests	SRS vs. WBRT 3.7 months [95% CI 3.5 to 5.06] vs 3.0 months [2.86 to 3.25]; HR 0.47 [0.35 to 0.63], p<0.0001			
				Primary Clinical effectiveness	Cognitive deterioration-free survival (median time; stratified for age,	SRS vs WBRT 3.7 months vs 3.1 months; HR 0.47 [95% CI 0.35 to 0.64], p<0.0001			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		systemic therapies (chemotherapy) were permitted. Baseline characteristics between the patient groups were similar. Median follow up 11.1 IQR 5.1 to 18) months for entire population; 22.6 months for those who had not died	centre)		extracranial disease, control status, number of metastases, histology & cavity size)				including single-institution clinical trials of SRS to the surgical cavity compared with observation after completed resection of brain metastases. Only 129/194 patients (65 in the SRS and 64 in the WBRT groups) completed the QOL questionnaires at baseline and had at least one subsequent assessment. Functional independence change from baseline values were available for 70/98 SRS patients and 48/96 WBRT patients at three months. Almost all patients (93/98 SRS vs 92/96) WBRT were evaluable for treatment toxic effects.
				Secondary Clinical effectiveness	Intracranial tumour progression	SRS Median 6.6 months [95% CI 5.15 to 8.90], 66 events vs WBRT 27.5 months [14.85 to not reached], 34 events; HR 2.45 [1.62 to 3.72], p<0.0001			
				Secondary Clinical effectiveness	Cognitive deterioration	At 6 months: SRS vs. WBRT 52% vs. 85%, difference -33.6% [95% CI -45.3 to -21.8], p=0.00031			
				Secondary Clinical effectiveness	**Quality of life** (change from baseline FACT-Br and LASA)	**At 3 months: FACT-Br** SRS (n=65) 9.5% vs WBRT (n=64) 8.9%; mean difference, 0.9 [95% CI -6.5 to 7.7] p = 0.35 **At 6 months: FACT-Br** SRS (n=65) 11.8% vs WBRT (n=64) 8.9%; mean difference, 2.9 [95% CI -4.5 to 10.3] p = 0.31 **At 6 months: LASA** SRS (n=65) 40.4% vs WBRT (n=64) 25.5%; mean difference, 14.9 [95% CI 3.5 to 26.2] p = 0.24			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Clinical effectiveness	**Functional independence** change from baseline (Barthel ADL index)	At 3 months: SRS (n=70) 6% decline, 11% improvement vs WBRT (n=66) 12%, 2%; p=0.036. At 6 months: SRS (n=66) 5% decline, 8% improvement vs WBRT(n=48) 15%, 2%; p=0.1			
				Secondary Clinical effectiveness	**Functional independence** Median duration of stable or better functional independence	SRS median not yet reached [95% CI 17.6 to not yet reached] vs WBRT 14.0 months [8.4 to 27.0]; HR 0.56 [0.32 to 0.906], p=0.034			
				Secondary Clinical effectiveness	Cognitive deterioration in long term survivors; assessed by HVLT-R recognition, Immediate and delayed recall; COWAT; TMT-A/B	At 3 months: SRS (n=27) 37% vs WBRT(n=27) 89%; p=0.00016 At 6 months; SRS (n=26) 46% vs WBRT(n=26) 88%, p=0.0025 At 9 months: SRS (n=25) 48% vs WBRT(n=26) 81%, p=0.020 At 12 months: SRS (n=25) 60% vs WBRT(n=23) 91%, p=0.0188			
				Secondary Clinical effectiveness	Intracranial tumour control in long term survivors	At 6 months: SRS (n=26) 70.4% [95% CI 55.1 to 89.9] vs WBRT(n=26) 92.6% [83.2 to 100], (p value not reported)			
				Secondary Clinical		At 12 months: SRS (n=25) 40.7% [25.9 to 64.2] vs WBRT(n=23) 81.5% [68.1			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				effectiveness		to 97.5]; HR 3.12 [1.4 to 6.94], p=0.0033			
				Secondary Clinical effectiveness	Surgical bed control	At 3 months: SRS 95.9% [95% CI 92.0 to 99.9] vs WBRT 93.5% [88.7 to 98.7] (p value not reported) At 6 months: SRS 80.4% [72.8 to 88.7] vs WBRT 87.1% [80.5 to 94.2] (p value not reported) At 12 months: SRS 60.5% [51.3 to 71.3] vs WBRT 80.6% [73.0 to 89.1], p = 0.00068			
				Secondary Clinical effectiveness	Local control	At 3 months: SRS 84.7% [95% CI 77.9 to 92.1] vs WBRT 96.7% [93.2 to 100] (p value not reported) At 6 months: SRS 69.4% [60.8 to 79.1] vs WBRT 92.5% [87.3 to 98.0] (p value not reported) At 12 months: SRS 61.8% [52.8 to 72.3] vs WBRT 87% [80.5 to 94.2], p = 0.00016			
				Secondary Clinical effectiveness	Distant brain control	At 3 months: SRS 88.7% [95% CI 82.6 to 95.2] vs WBRT 96.8% [93.3 to100] (p value not reported) At 6 months: SRS 72.1% [63.7 to 81.6] vs WBRT 94.6% [90.1 to 99.3] (p value not reported)			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						At 12 months: SRS 64.7% [55.8 to 75.0] vs WBRT 89.2% [83.1 to 95.8], p = 0.00045			
				Secondary Clinical effectiveness	Leptomeningeal disease (LMD)	At 3 months: SRS 98.0% [95% CI 95.2 to 100] vs WBRT 97.9% [95.0 to 100] (p value not reported) At 6 months: SRS 93.9% [89.2 to 98.7] vs WBRT 96.8% [93.3 to 100] (p value not reported) At 12 months: SRS 92.8% [87.8 to 98.1] vs WBRT 94.6% [90.1 to 99.3], p=0.62			
				Secondary Clinical effectiveness	Total intracranial brain control	At 3 months: SRS 79.6% [95% CI, 72.0 to 88.0] vs WBRT 90.4% [84.7 to 96.6] (p value not reported) At 6 months: SRS 55.1% [46.1 to 65.9] vs WBRT 80.8% [73.1 to 89.2] (p value not reported) At 12 months: SRS 36.6% [28.1 to 47.8] vs WBRT 72.1% [63.6 to 81.8], p=0.0001			
				Secondary Safety	Patients reporting at least one treatment toxic effect	SRS (n=93) 76% vs WBRT (n=92) 86% (p value not reported)			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Secondary Safety	Grade 3 or worse toxic effects	SRS 39% vs WBRT 40% (p value not reported)			
				Secondary Safety	Hearing impairment	SRS 3% vs WBRT 8% (p value not reported)			
				Secondary Safety	Cognitive disturbances	SRS 3% vs WBRT 5% (p value not reported)			
				Secondary Safety	Toxic effects possibly related to treatment	SRS 51% vs WBRT 71% (p value not reported)			
				Secondary Safety	Grade 3 or worse toxic effects possibly related to treatment	SRS 12% vs WBRT 18% (p value not reported)			
				Secondary Safety	Grade 2 or worse CNS Necrosis	SRS 4% vs WBRT 0% (p value not reported)			
				Secondary Safety	Death from adverse events unrelated/unlikely related to treatment	SRS 7% vs WBRT 11% (p value not reported)			
Kepka et al 2016 (Clinical effectiveness) Kepka et al 2017 (Quality of life)	P1 - Non-inferiority multicentre RCT. Poland	N = 59. Median age 60 (30 to 78) years with a Karnofsky performance Score ≥ 70, life expectancy > 6 months. Total or subtotal resection of single brain metastases. All participants	SRT (n = 29) 15 to 18 Gy at isodose line. For cavities >5 cm, 25 Gy in 5 fractions over 5 days. **Versus** WBRT (n = 30) 30 Gy in ten fractions delivered 5 times weekly	Primary Clinical effectiveness	CINCF difference	At 6 months: SRT 72% vs WBRT 63%; difference -8 [95% CI -34 to 17] (p value not reported) At 24 months; SRT 75% [58 to 93] vs WBRT 62% [43 to 80], p=0.31; HR 1.32 [0.74 to 2.36]	6	Direct	The results of this study were reported in two separate reports; Kepka et al (2016) reported the CINCF and CIND rates, relapse intracranial progression as well as overall survival, while Kepka et al (2017) reported the QOL outcomes. The method of randomisation was not described and it is not reported whether there was any concealment of allocation. The authors assumed a 20% of non-inferiority margin in CINCF at 6 months. The authors stated that they did not demonstrate non-inferiority because the 95%CI included the non-inferiority margin (-20%) The authors reported that their assumptions
				Secondary Clinical effectiveness	CIND rates	At 2 years: SRT 66% [95% CI 46 to 86] vs WBRT 31% [14 to 49], p=0.015; HR 2.51 [1.19 to 5.29]			
				Secondary Clinical	Overall survival at 2 years	ITT analysis: SRT 10% [95% CI 0 to 22] vs WBRT 37% [19 to 55], p=0.046;			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		had surgical resection of the metastasis prior to trial entry. No previous brain irradiation. Median follow up 29 months (8-45) There were more female patients in the SRT arm 18 (62%) vs 11 (38%) compared with the WBRT group with 15 (50%) males and 15 (50%) females.		effectiveness		HR 1.8 [0.99 to 3.30] PP analysis: SRT 14% [95% CI 0 to 31] vs WBRT 30% [12 to 48], p=0.332; HR 1.4 [0.91 to 2.71]			used to calculate the sample size were imprecise which led to underestimation of the number of patients needed to demonstrate non-inferiority. The data source used to select the non-inferiority margin used was not stated. The authors reported that their study was underpowered and at risk of statistical hazard. Patients with both total and subtotal resections were included; a higher proportion of patients in the SRT group had subtotal resections (17% vs 10% (p value not reported). There was no limitation of patients based on cavity size; the mean sizes for each patient group were not reported, but the study was reported to include patients with larger cavities (>5cm) than was permitted in other studies. Another limitation of this study was that, in the SRT arm, 21 patients (72%) were treated per protocol, whereas 29 (97%) of the WBRT arm received the assigned treatment. However, none of the patients were lost to follow up results were analysed both on an ITT and PP basis. The primary end point of the study was cumulative neurological/cognitive failure. However, cognitive function was measured using Mini-Mental State Examination (MMSE) test score. MMSE is used for assessing patients for treatment of dementia, but is not established as an adequately sensitive measure of cognitive changes.
				Secondary Clinical effectiveness	Total intracranial progression	SRT 58% vs WBRT 36%; p=0.133			
				Secondary Clinical effectiveness	Relapses in tumour bed	SRT 26% vs WBRT 25%; p=1			
				Secondary Clinical effectiveness	Progression at new sites in the brain including LMD (distant brain recurrence)	SRT 42% vs WBRT 21%; p=0.128			
				Secondary Clinical effectiveness	Salvage treatment of relapses within the brain (rate)	SRT 81% vs WBRT 60%; p=0.128			
				Secondary Clinical effectiveness	Global health status (HRQOL) measured by QLQ-C30 and OLQ-BN20 questionnaire	At baseline SRT mean 66 (SD 20.6) vs WBRT 66.7 (17.3), p=0.94 At 2 months SRT 65.9 (24.6) vs WBRT 61.4 (25.7), p=0.6 At 5 months SRT 55.7 (26.9) vs WBRT 67.1 (23.7), p=0.19			
				Secondary Safety	Drowsiness measured by QLQ-C30 and OLQ-BN20 questionnaire	At baseline mean SRT 19.9 (SD 24.6) vs WBRT 23.6 (18.6), p=0.51 At 2 months SRT 19.9 (27.5) vs WBRT 36.2			

b) Stereotactic radiosurgery (SRS) versus whole brain radiotherapy (WBRT) for resected brain metastatic tumours									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						(25.1), p=0.048 At 5 months SRT 19.3 (17.0) vs 29.4 (19.5), p=0.24			
				Secondary Safety	Appetite loss measured by QLQ-C30 and OLQ-BN20 questionnaire	At baseline: SRT mean 4.4 (SD 11.6) vs WBRT 9.0 (15.0), p=0.49 At 2 months SRT 8.9 (19.8) vs WBRT 30.2 (30.7), p=0.03 At 5 months SRT 35.1 (32.3) vs 25.8 (33.4), p=0.93			

ADL - Activities of daily living; cGy - centigray (dose unit for radiotherapy); CINCF - Cumulative incidence of neurological/cognitive failure; CIND - Cumulative incidence of neurological death; COWAT - Controlled Oral Word Association Test; DBM - Distant brain metastases; EORTC - European Organisation for Research and Treatment of Cancer; FACT-Br - Functional Assessment of Cancer Therapy-Brain; Gy - Gray; HR - Hazard ratio; HRQOL - Health-related Quality of Life; HVLT-R - Hopkins Verbal earning Test-Revised; ITT - Intention to treat; LASA - Linear Analog Self-Assessment; LMD - Leptomeningeal disease]; MMSE - Mini-Mental State Examination; NR - Not reached; (p value not reported) - No significance reported; OBS - Observation; P1 Primary research using quantitative approaches; PP - Per protocol; QOL - Quality of life; RR - Risk Ratio; SRS - Stereotactic Radiosurgery; SRT - Stereotactic Radiotherapy; TMT - Trial Marking Test; WBRT - Whole-brain radiotherapy

8 Grade of Evidence Table

For abbreviations see list after each table

a) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus observation following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall Survival	Mahajan et al 2017	8	Direct	B	The overall survival was defined as the time from randomisation to date of death. At median follow up 11.1 months (4.8 to 20.4), the moderate quality RCT by Mahajan et al (2017) (n= 128) showed no difference in median overall survival, following resection of a single brain metastasis between patients who received SRS 17 months [95% CI 13 to 22] and those who were observed (OBS) 18 months [13 to NR]; HR 1.29 [0.84 to 1.98], p=0.24. The effect of treatment on overall survival is important for patients with brain metastases because of the low life expectancy in these patients if untreated. The estimated median survival time without treatment is two months. This study suggests that SRS treatment following resection for brain metastases has no significant effect on survival compared with OBS, as it neither prolongs nor reduces how long the patients survive for. Although there is no difference in survival, without some measure of the relative impact of SRS vs observation on quality of life, it is difficult to make any meaningful interpretation of this result. The results should also be interpreted with caution because the study was subject to the bias of being a single specialised centre study which means that the results may not be generalisable.
Local tumour recurrence-free rates	Mahajan et al 2017	8	Direct	B	The assessment of local tumour-free recurrence includes radiographic evidence of a new contrast-enhancing lesion contiguous with or within the resection cavity as confirmed by the neuroradiologist. Mahajan et al (2017), in a moderate quality RCT of patients undergoing surgical resection for 1 to 3 brain metastases (n=128), found that SRS administered to the resected cavity significantly lowers local recurrence compared to observation alone. At 12 months: tumour recurrence-free rates were: SRS 72% [95%CI 60 to 87] vs OBS 43% [31 to 59]; HR 0.46 [0.24 to 0.88] p=0.015. This result suggests SRS to the surgical bed following surgical resection of brain metastases significantly lowers the risk of tumour recurrence in the vicinity of the resection cavity. Local failures often require further surgery or WBRT; therefore this result might be an important factor for avoiding these further interventions. Although there was a reduction in recurrence, these results alone do not tell us whether this reduction translates to a positive impact on QOL. The results should also be interpreted with caution because the study was subject to the bias of being a single specialised centre study which means that the results may not be generalisable.

a) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus observation following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Time to local recurrence (median time to radiographic evidence of new lesion)	Mahajan et al 2017	8	Direct	B	Time to local recurrence refers to the median time to radiographic evidence of a new lesion. Mahajan et al (2017) reported a significantly longer time to local recurrence with SRS Median not reached [95% CI 15.6 months to not reached] vs OBS 7.6 months [5.3 to not reached] This result indicates the SRS treatment to the brain resection site following surgery to brain metastases prevents recurrence to the resection site for longer than in patients whose postoperative management consists of observation only. Local failures often require further surgery or WBRT; therefore this result might be an important factor for avoiding these further interventions. Although there was a longer time to recurrence, these results alone do not tell us whether the effects on quality of life are the same. The results should also be interpreted with caution because the study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care.
Neurological death	Mahajan et al 2017	8	Direct	B	Death was categorised as neurologic if metastatic brain disease was the proximate cause of death or systemic if the patient died from extracranial disease. Neurological death rates were reported as the proportion of deaths in each group that were neurologic. Mahajan et al (2017) reported no significant difference in proportion of neurological deaths between patients who received SRS post-surgical resection of brain metastases (22/46 events) 48% and those who were managed by OBS (25/39 events) 64%; difference 16% [-5 to 37], p=0.13. The results suggest no difference in neurological death between treatment with SRS post-surgical resection and observation. The results should be interpreted with caution because the study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care.
Freedom from distant brain metastases (DBM)	Mahajan et al 2017	8	Direct	B	Distant brain metastases (DBM) was defined as the development of a new lesion separate from the surgical site. Mahajan et al (2017) reported no significant difference in rates of freedom from DBM at 12 months; SRS 42% [95% CI 30 to 58] vs OBS 33% [22 to 49]; HR 0.81 [0.51 to 1.27], p=0.35. This outcome is likely to be valued by patients. The results suggest that SRS to the brain resection site is no more effective than observation in preventing DBM. The results should be interpreted with caution because the study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care.

a) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus observation following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Leptomeningeal disease (LMD)	Mahajan et al 2017	8	Direct	B	Leptomeningeal disease (LMD) is a rare complication of cancer in which the disease spreads to the membranes (meninges) surrounding the brain and spinal cord. LMD occurs in approximately 5% of people with brain metastases and is usually terminal. The risk of LMD may also increase after surgical resection of brain metastases. Mahajan et al (2017) reported no significant difference in LMD rates between patients receiving SRS to the resection site and OBS only. At 12 months: LMD rates in SRS treated patients was 28% [95% CI 12 to 40] vs OBS 16% [4 to 26], HR 1.4 [0.6 to 3.4], p=0.46. Absence of LMD is likely to be valued by patients. These results represent evidence that SRS to the surgical bed, compared with OBS does not increase the risk of this important complication. This result is also consistent with the evidence of there being no significant difference in overall survival between the two patient groups. The results should also be interpreted with caution because the study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care.
Freedom from WBRT	Mahajan et al 2017	8	Direct	B	Freedom from WBRT was defined as the time to WBRT from randomisation. Mahajan et al (2017) reported no significant difference in freedom from WBRT rates between SRS and observation; SRS 16 months [95% CI 10.1 to NR] vs OBS 15 months [8.6 to 42.5]; HR 0.8 [0.47 to 1.37], p=0.42. The aim of SRS in this clinical setting is to minimize local recurrence and therefore the need for WBRT and the associated adverse effects. However this benefit would not be realised if patients subsequently had to receive WBRT. These results should be interpreted with caution because the patients were treated at the physician's discretion. The results should also be interpreted with caution because the study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care.
Adverse events	Mahajan et al 2017	8	Direct	B	Adverse events (AE) were not specifically defined by Mahajan et al (2017). However, the World Health Organisation defines an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention, in this case SRS for brain metastases. Adverse events related to SRS were recorded at each clinical visit. Mahajan et al (2017) reported no adverse events related to placement of a stereotactic frame or treatment with SRS. There were no treatment related deaths. Prevention of adverse events is likely to be valued by patients, as they can be serious and/or require hospitalisation. The results should be interpreted with caution because the study was subject to the bias of being a single specialised centre study and the results could be skewed by the patients being drawn out of the population for specialised care.

ADL - Activities of daily living; cGy - centigray (dose unit for radiotherapy); CINCF - Cumulative incidence of neurological/cognitive failure; CIND - Cumulative incidence of neurological death; COWAT - Controlled Oral Word Association Test; DBM - Distant brain metastases; EORTC - European Organisation for Research and Treatment of Cancer; FACT-Br - Functional Assessment of Cancer Therapy-Brain; Gy - Gray; HR - Hazard ratio; HRQOL - Health-related Quality of Life; HVLT-R - Hopkins Verbal earning Test-Revised; ITT - Intention to treat; LASA - Linear Analog Self-Assessment; LMD - Leptomeningeal disease]; MMSE - Mini-Mental State Examination; NR - Not reached; (p value not reported) - No significance reported; OBS - Observation; P1 Primary research using quantitative approaches; PP - Per protocol; QOL - Quality of life; RR - Risk Ratio; SRS - Stereotactic Radiosurgery; SRT - Stereotactic Radiotherapy; TMT - Trial Marking Test; WBRT - Whole-brain radiotherapy

b) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Overall Survival	Brown et al 2017 Kepka et al 2016	8 6	Direct	B	The overall survival was measured as the median time from randomisation to death from any cause. The moderate quality RCT by Brown et al (2017) (n = 194), at a median follow up of 11.1 months (for entire population); 22.6 months (for those who had not died), showed no difference in median overall survival, following resection of a single brain metastasis, between SRS 12.2 months [95% CI 9.6 to 16.0] and WBRT 11.6 months [9.9 to 18.0]; HR 1.07 [0.76 to1.5], p=0.70. This study suggests that SRS treatment following resection for brain metastases has no significant effect on survival compared with WBRT as it neither prolongs nor reduces how long the patients survive for. The effect of treatment on overall survival is important for patients with brain metastases because of the life expectancy in these patients. Although the study shows no difference in survival, these results alone do not tell us about the relative impact SRS/SRT vs WBRT on QOL.
Cognitive deterioration-free survival	Brown et al 2017	8	Direct	B	Cognitive deterioration-free survival was defined by Brown et al (2017) as the median time from randomisation to a drop of greater than 1 SD from baseline in at least one of six cognitive tests. The moderate quality RCT by Brown et al (2017) reported that that median cognitive deterioration-free survival was longer with SRS 3.7 months [95% CI 3.5 to 5.06] compared with WBRT 3.0 months [2.86 to 3.25]; HR 0.47 [0.35 to 0.63], p<0.0001. At 6 months a significantly lower proportion of SRS patients had experienced cognitive deterioration 52% compared with WBRT 85%. Mean difference -33.6% [95% CI -45.3 to -21.8], p=0.00031. Postoperative adjuvant WBRT is normally given after surgical resection of brain metastases, to improve intracranial control, but it negatively affects cognitive function and therefore quality of life. Because SRS/SRT is delivered more precisely to the tumour bed, achieving a similar intracranial control without cognitive deterioration is expected to improve quality of life. Results from the study by Brown et al (2017) suggest that patients who are treated with SRS after surgery are less likely to suffer cognitive deterioration compared to patients who have WBRT. Cognitive function is an especially important endpoint in this patient population given the absence of a substantiated survival advantage with adjuvant radiotherapy. The results were similar when the patients were stratified for age, extracranial disease

b) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					control status, number of brain metastases histology and size of resection cavity, suggesting they are generalisable. However, the results still have to be interpreted with caution because the patients and clinicians were not blinded to the treatment allocation, which could have led to some bias. However, the neurocognitive assessment test graders were not aware which treatment groups the patients belonged to.
Neurological failure - cumulative incidence of neurological /cognitive failure (CINCF)	Kepka et al 2016	6	Direct	C	Cumulative incidence of neurological/cognitive failure (CINCF) was defined as a worsening of neurological status by one point or more within the five point MRC scale or a worsening of the Mini-Mental State Examination (MMSE) test score by three or more points compared to the baseline core or neurological death; whichever occurred first. A low quality non-inferiority RCT by Kepka et al (2016) failed to demonstrate non-inferiority of SRT compared to WBRT after surgery of single brain metastases in terms of neurocognitive functioning at 6 months (its primary outcome)[6]. At 6 months: CINF rates in the SRT patients were 72% compared to WBRT 63%; difference -8 [95% CI -34 to 17]. At 24 months; SRT 75% [58 to 93] vs WBRT 62% [43 to 80], p=0.31; HR 1.32 [0.74 to 2.36]. These results do not give us any conclusive information about the relative impact of the two treatments on neurocognitive function because the study was not adequately powered to demonstrated non-inferiority of SRT to WBRT. These results should be interpreted with caution because the study was not adequately powered, and because cognitive function was measured by MMSE scores which is a test for assessing patients for dementia treatment. It is not well-established as a sensitive tool for measuring cognitive deterioration due to brain metastases or radiotherapy.
Neurological death - cumulative incidence of neurological/ cognitive death (CIND)	Kepka et al 2016	6	Direct	C	The 2 year cumulative incidence of neurological/cognitive deaths (CIND) was defined by Kepka et al (2016) as the proportion of patients that had died due to a neurological cause within 2 years from randomisation. A low quality RCT by Kepka et al (2016) reported that, at 2 years CIND rates for the SRT group was 66% [95% CI 46 to 86] vs WBRT 31% [14 to 49]; HR 2.51 [1.19 to 5.29] p=0.015. This indicates that patients who received SRT after tumour resection for brain metastases are potentially more likely to die from a neurological cause than patients who received WBRT. This would suggest a neuroprotective effect of WBRT over SRT. These results must be interpreted with caution because the study was underpowered and therefore at the risk of statistical hazard.

[6] The authors assumed a 20% of non-inferiority margin in CINCF at 6 months. The authors stated that they did not demonstrate non-inferiority because the 95%CI included the non-inferiority margin (-20%)

b) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Intracranial tumour progression	Brown et al 2017	8	Direct	B	Intracranial tumour progression is the time from randomisation to recurrence in the local surgical bed, progression of unresected metastases, distant brain recurrence, or development of LMD. The moderate quality RCT by Brown et al (2017) reported a significantly shorter intracranial progression period with SRS treatment post brain metastases resection: Median 6.6 months [95% CI 5.15 to 8.90], 66 events compared with the WBRT: 27.5 months [14.85 to not reached], 34 events; HR 2.45 [1.62 to 3.72], p<0.0001. At 12 months: a significantly lower proportion of SRS patients had total intracranial brain control: 36.6% [28.1 to 47.8] compared with the WBRT patients: 72.1% [63.6 to 81.8], p=0.0001. Surgical bed control, local control and distant control were all significantly better in the WBRT patients, but there was no difference in development of LMD. The results were similar when only 48 long term survivors (≥12 months after randomisation) were included in the analysis. At 12 months: SRS (n=25) 40.7% vs WBRT (n=23) 81.5%; HR 3.12 [1.4 to 6.94], p=0.0033. These results suggest that compared with SRS, WBRT treatment after metastatic brain resection is better at controlling the progression of brain metastases. These results are potentially important in the management of brain metastases. However, the value of this outcome on its own is uncertain, unless accompanied by improvements in overall survival and quality of life. In addition, local control was determined by the treating physician rather than central review. Neither the patients nor the physician were blinded to the treatment, which could have created bias.
	Kepka et al 2016	6	Direct		
Surgical bed control	Brown et al 2017	8	Direct	B	Surgical bed control refers to lack of tumour recurrence at the surgical bed of the resected metastases. Brown et al (2017) reported that surgical bed control was numerically but not significantly better in SRS patients at 3 months but not at 12 months. At 3 months: 95.9% of SRS patients [95% CI 92.0 to 99.9] vs WBRT 93.5% [88.7 to 98.7] were assessed to have good surgical bed control. However, the corresponding rates at 12 months were: SRS 60.5% [51.3 to 71.3] vs WBRT 80.6% [73.0 to 89.1], p = 0·00068. These results suggest that SRS to the surgical bed may provide better short term control but that longer term control is better with WBRT. Local recurrence often requires further surgery or WBRT; therefore this result might be an important factor for avoiding these further interventions However, these results must be interpreted with caution because, in this study, surgical bed control after SRS was worse than reported in previous RCTs. In addition local control was determined by the local physician rather than by central review, which could have created some bias.
	Kepka et al 2016	6	Direct		
Local control	Brown et al 2017	8	Direct	B	Local control means that tumour did not recur at the unresected metastases treated with SRS. Brown et al (2017) reported that local control was significantly better in the WBRT patients

b) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					at 3 months, 6 months and at 12 months. At 12 months: 61.8% of SRS patients [95% CI 52.8 to 72.3] vs WBRT 87.1% [80.45 to 94.2], p=0.00016 were assessed to have good local control. These results suggest that WBRT provides better local control than SRS. Local recurrence often requires further surgery or WBRT; therefore this result might be an important factor for avoiding these further interventions. However, these results must be interpreted with caution because, local control was determined by the local physician rather than by central review, which could have created some bias.
Distant brain control	Brown et al 2017	8	Direct	B	Distant brain control means that a new tumour did not appear at a site not treated. Brown et al (2017) reported that distant brain control was significantly better in the WBRT patients at 3 months, 6 months and at 12 months. At 12 months: 64.7% of SRS patients [95% CI 55.8 to 75.0] vs WBRT 89.2% [83.1 to 95.8], p=0.00045 were assessed to have good distant control. These results suggest that WBRT provides better distant brain control than SRS. However, these results must be interpreted with caution because, distant brain control was determined by the local physician rather than by central review, which could have created some bias.
Functional independence	Brown et al 2017	8	Direct	B	Brown et al (2017) assessed functional independence by the median duration of stable or better functional independence as assessed by the Barthel ADL Index as a score that fell by at least 10% below the baseline level. Brown et al (2017) reported that median duration of better functional independence was higher in the SRS patients: median not yet reached [95% CI 17.6 to not yet reached] compared with the WBRT 14.0 months [8.4 to 27.0]; HR 0.56 [0.32 to 0.906], p=0.034. This result indicates that SRS treated patients maintain better functional independence, which could potentially improve quality of life. However, the result should be treated with caution because not all patients were available for this outcome: SRS (66/98) vs WBRT (48/96).
Quality of life	Brown et al 2017	8	Direct	B	Brown et al (2017) assessed quality of life by the change from baseline to 6 months in FACT-Br and LASA. A quality of life index gives a measure of how much a disease stage compromises general health and well-being of the patients compared to normal health which is given an index of 1. Brown et al (2019) reported FACT-BR scores at 6 months compared with baseline. A clinically significant improvement from baseline was noted more frequently in the SRS group than with the WBRT group for physical wellbeing, whereas there were not significant differences between treatment groups in social, emotional or functional wellbeing, brain-specific concern or overall FACT-Br (MD 2.9 [95%CI 4.5 to 10.3], p=0.31).
	Kepka et al 2017	6			

b) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					For LASA there was no significant improvement from baseline in overall mental, physical or emotional wellbeing, nor in the overall QOL at 6 months (MD 14.9 [95%CI 3.5 to 26.2], p=0.24). These results suggest that patients who undergo SRS post-resection and those who receive WBRT experience no significant differences in terms of QOL improvement, or the effects on QOL appear to be the same. The results should be treated with caution because; only 129 out of 194 patients completed QOL questionnaires at baseline and had at least one subsequent assessment: SRS (65/98) vs WBRT (64/96). The tools were also self-assessments, which could have created further bias as the patients were not blinded to the treatment they received.
Leptomeningeal disease (LMD)	Brown et al 2017	8	Direct	B	Leptomeningeal disease (LMD) is a rare complication of cancer in which the disease spreads to the membranes (meninges) surrounding the brain and spinal cord. LMD occurs in approximately 5% of people with brain metastases and is usually terminal. The risk of LMD may also increase after surgical resection of brain metastases. As a measure of total intracranial control, Brown et al (2017) observed the rate of LMD in patients treated with SRS or WBRT post brain tumour resection. They observed no significant difference in the percentage of patients free from LMD at 3 months, 6 months and 12 months. LMD control rate, at 12 months was: SRS 92.8% [87.8 to 98.1] vs WBRT 94.6% [90.1 to 99.3], p=0.62. These results represent moderate evidence that SRS to the surgical bed, compared with WBRT does not increase the risk of this important complication. This result is also consistent with the evidence of there being no significant difference in overall survival between the two patient groups. These results need to be interpreted with caution because LMD was not a primary outcome specified by the authors and the report does not specify whether the study was adequately powered to show a difference in this outcome.
	Kepka et al 2016 Kepka et al 2017	6	Direct		
Salvage treatment of relapses within the brain (rate)	Kepka et al 2016 Kepka et al 2017	6	Direct	C	The rates of patients requiring salvage treatment for relapses within the brain were recorded in the study by Kepka et al (2016). These were patients who had relapses perceived by the physicians to warrant further treatment with SRT or further surgery. In the study by Kepka et al (2016) salvage treatment of relapses within the brain was undertaken in nine of 11 (81%) patients from the SRT arm and in six of 10 (60%) patients from the WBRT arm; p=0.128. All patients from both arms who received only local treatment (SRT and/or surgery) for salvage, ultimately died from progression in the brain. The short survival rates following brain metastases means avoiding any interference with quality of life due to further treatments or surgery would be of value to patients. The results of this non-inferiority study should be treated with caution because the assumptions used in the calculation of the sample size were reported to be imprecise. This is likely to lead to underestimation of the number of patients needed to demonstrate non-inferiority and therefore risk of statistical hazard.

b) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Adverse events	Brown et al 2017	8	Direct	B	Adverse events (AE) were not specifically defined by Brown et al (2017). However, the WHO defines an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention, in this case SRS for brain metastases. Brown et al (2017) reported a higher proportion of WBRT patients experiencing at least one treatment toxic effect, or toxic effects possibly related to treatment SRS (51%) vs WBRT (71%). However the significance of these differences was not reported. The rates of grade 3 or worse toxic effects possibly related to treatment were not as remarkable (SRS 12% vs WBRT 18%). They also reported the proportion of patients with all grade 3 or worse toxic effects (SRS 39% vs WBRT 40%); hearing impairment (SRS 3% vs WBRT 8%); cognitive disturbances (SRS 3% vs WBRT 5%); Grade 2 or worse CNS Necrosis (SRS 4% vs WBRT 0%) or death from adverse events unrelated/unlikely related to treatment (SRS 7% vs WBRT 11%). These results suggest that, although adverse effective unrelated to treatment may be similar between SRS and WBRT, toxic effects related to treatment might be more frequent with WBRT. These results are uncertain because the statistical significances of the observed differences between the groups were not reported.

ADL - Activities of daily living; cGy - centigray (dose unit for radiotherapy); CINCF - Cumulative incidence of neurological/cognitive failure; CIND - Cumulative incidence of neurological death; COWAT - Controlled Oral Word Association Test; DBM - Distant brain metastases; EORTC - European Organisation for Research and Treatment of Cancer; FACT-Br - Functional Assessment of Cancer Therapy-Brain; Gy - Gray; HR - Hazard ratio; HRQOL - Health-related Quality of Life; HVLT-R - Hopkins Verbal earning Test-Revised; ITT - Intention to treat; LASA - Linear Analog Self-Assessment; LMD - Leptomeningeal disease]; MMSE - Mini-Mental State Examination ; NR - Not reached; (p value not reported) - No significance reported; OBS - Observation; P1 Primary research using quantitative approaches; PP - Per protocol; QOL - Quality of life; RR - Risk Ratio; SRS - Stereotactic Radiosurgery; SRT - Stereotactic Radiotherapy; TMT - Trial Marking Test; WBRT - Whole-brain radiotherapy

9 Literature Search Terms

<table>
<tr><th colspan="2">PICO Table</th></tr>
<tr><td>P – Patients / Population
Which patients or populations of patients are we interested in? How can they be best described? Are there sub-groups that need to be considered?</td><td>Patients of all ages, with one or more cerebral metastases, where one or more metastases have been recently surgically resected.</td></tr>
<tr><td>I – Intervention
Which intervention, treatment or approach should be used?</td><td>Postoperative SRS/SRT to the surgical cavity.

[For info
• SRS is delivered in a single fraction.
• SRT is delivered in 2-5 fractions.]</td></tr>
<tr><td>C – Comparison
What is/are the main alternative/s to compare with the intervention being considered?</td><td>• Observation
[For information: this might be a watch and wait strategy with active surveillance]
• Whole-brain radiotherapy (WBRT)</td></tr>
<tr><td>O – Outcomes
What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.</td><td><u>Critical to decision-making:</u>
• Overall survival
• Quality of life
• Safety
<u>Important to decision-making:</u>
• Rate of local recurrence
• Development of distal brain metastases
• Complications due to irradiation (oedema, radionecrosis and neurological deficit)
• Steroid dependency
• Leptomeningeal disease
• Cognitive decline
• Measures of cost-effectiveness</td></tr>
<tr><td colspan="2">Assumptions / limits applied to search
Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.

<u>Inclusion Criteria:</u>
• Systematic review
• Randomised controlled trials
• Cohort studies
• English language
• Human studies only
• All ages

<u>Exclusion Criteria:</u>
• Abstracts
• Letters
• Commentaries
• Conference papers
• Papers published more than 10 years ago
• Studies without comparators (including before and after studies)
• Case control studies
• Case series/reports</td></tr>
</table>

10 Search Strategy

We searched Medline, Embase and Cochrane Library limiting the search to papers published in England from **1st January 2009 to 18th January 2019**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 18 January 2019
Embase search:

1. brain metastasis/
2. ((brain or cereb* or cranial* or intracranial*) adj5 metasta*).ti,ab.
3. 1 or 2
4. exp *radiosurgery/
5. (stereotactic adj2 (radiotherap* or radiation therap*)).ti,ab.
6. (srs or srt).ti,ab.
7. (gamma knife or gammaknife or cyber knife or cyberknife or linear accelerator or linac).ti,ab.
8. 4 or 5 or 6 or 7
9. *cancer surgery/ or *cytoreductive surgery/
10. (post-operat* or postoperat* or post-surg* or postsurg* or resect*).ti,ab.
11. (cavity or cavities).ti,ab.
12. metastasectom*.ti,ab.
13. 9 or 10 or 11 or 12
14. 3 and 8 and 13
15. (exp animals/ or nonhuman/) not human/
16. (editorial or letter or note or "review" or conference*).pt. or case report/ or case report.ti.
17. 15 or 16
18. 14 not 17
19. limit 18 to (english language and yr="2008 -Current")
20. 3 and 8
21. limit 20 to (english language and yr="2008 -Current" and "reviews (maximizes specificity)")
22. 19 or 21

11 Evidence Selection

- Total number of publications reviewed: 116
- Total number of publications considered potentially relevant: 19
- Total number of publications selected for inclusion in this briefing: 3

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	Mahajan A, Ahmed S, McAleer M, Weinberg J, Li J, Brown P, Settle S, Prabhu S, Lang F, Levine N, McGovern S, Sulman E, McCutcheon I, Azeem S, Cahill D, Tatsui C, Heimberger A, Ferguson S, Ghia A, Demonte F, Raz, S, Guha-Thakurta N, Yang J, Sawaya R, Hess K and Rao G. 2017. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled phase 3 trial. *The Lancet Oncology*, 18(8): 1040-1048.	Included
2	Lamba N, Muskens I, DiRisio A, Meijer L, Briceno V, Edrees H, Aslam B, Minhas S, Verhoeff J, Kleynen C, Smith T, Mekary R and Broekman M. 2017. Stereotactic radiosurgery versus whole-brain radiotherapy after intracranial metastasis resection: a systematic review and meta-analysis. *Radiation Oncology*, 12(1): 106	Excluded This is a systematic review of retrospective studies of SRS and WBRT (cohort studies) with pooled analysis. RCTs which provide a higher level of evidence are available for inclusion.
3	Brown P, Ballman K, Cerhan J, Anderson S, Carrero X, Whitton A, Greenspoon J, Parney I, Laack N, Ashman J, Bahary J, Hadjipanayis C, Urbanic J, Barker F, Farace E, Khuntia D, Giannini C, Buckner J, Galanis E and Roberge D. 2017. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *The Lancet Oncology*, 18(8):1049-1060.	Included

12 References

Brown P, Ballman K, Cerhan J, Anderson S, Carrero X, Whitton A, Greenspoon J, Parney I, Laack N, Ashman J, Bahary J, Hadjipanayis C, Urbanic J, Barker F, Farace E, Khuntia D, Giannini C, Buckner J, Galanis E and Roberge D. 2017. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *The Lancet Oncology*, 18(8):1049-1060.

Davis F, Dolecek T, McCarthy B and Villano J. 2012. Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. *Neuro-Oncology*, 14(9): 1171-1177.

Kępka L, Tyc-Szczepaniak D, Bujko K, Olszyna-Serementa M, Michalski W, Sprawka A, Trąbska-Kluch B, Komosińska K, Wasilewska-Teśluk E and Czeremszyńska B. 2016. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: Results from a randomized trial. *Radiotherapy and Oncology*, 121(2): 217-224.

Kepka L, Tyc-Szczepaniak D, Osowiecka K, Sprawka A, Trąbska-Kluch B and Czeremszynska B. 2017. Quality of life after whole brain radiotherapy compared with radiosurgery of the tumor bed: results from a randomized trial. *Clinical and Translational Oncology*, 20(2): 150-159.

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