Clinical Commissioning Policy: Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) to the surgical cavity following resection of cerebral metastases (all ages) [URN: 1857]

Commissioning Position

Summary

A final decision as to whether stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) to the surgical cavity following resection of cerebral metastases (all ages) will be not for routine commissioning will made by NHS England following a recommendation from the Clinical Priorities Advisory Group. The proposal is: Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) is not recommended to be available as a treatment option through not for routine commissioning for the treatment of the surgical cavity following resection of cerebral metastases within the criteria set out in this document.

Executive Summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain language summary

About cerebral metastases

Cerebral metastasis is the formation of a secondary tumour in the brain. A metastasis is the spread of cancer cells from the original place they were formed (the primary tumour) to another part of the body, where a new, secondary tumour is formed. Multiple tumours are called 'metastases'. Cerebral metastases most commonly arise from primary cancers of the lung, breast and skin but can arise from other cancers.

About current treatments

The treatment of cerebral metastases is dependent on a number of factors such as: the size of a cancer as compared to the amount of space taken up by the tumour (total tumour volume), the position of the tumour in the brain, the type of cancer the metastasis has arisen from, whether the primary tumour itself is stabilised and overall health and fitness (functional status) of the patient.

Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT), is often the primary treatment for cerebral metastases. SRS and SRT are radiotherapy treatments which can

precisely target an area of the brain. This means that the irradiation of healthy tissue surrounding the tumour is limited. SRS is delivered as a single treatment, known as a fraction, and SRT in two to five fractions. SRS and SRT are delivered on an outpatient basis.

In some cases, the cerebral metastasis is too large for SRS / SRT and surgical removal is the alternative treatment option. In most cases, surgery will result in the metastasis being completely removed. Following surgery, it is standard practice to closely monitor patients (observation), which involves an MRI every three months. If imaging shows evidence that the tumour has returned at the site of surgery (surgical cavity), then SRS or SRT may be offered, in accordance with the clinical commissioning policy: SRS / SRT for Cerebral Metastases (NHS England, 2013).

Where it is not possible to completely remove the metastasis with surgery (incomplete surgical removal), the standard practice is to offer SRS / SRT shortly after surgery, in accordance with the clinical commissioning policy: SRS / SRT for Cerebral Metastases (NHS England, 2013).

About the new treatment

Some centres are now offering SRS / SRT to the surgical cavity, shortly following complete surgical removal of a metastasis, in accordance with NICE Guideline 99, relating to the management of primary brain tumours and brain metastases in adults (NICE, 2018) which recommends that use of SRS / SRT should be considered in these cases. The policy considers whether this practice should be routinely commissioned.

What we have decided

NHS England has carefully reviewed the evidence to treat the surgical cavity of one or more completely resected cerebral metastases shortly after surgery with SRS or SRT. We have concluded that there is not enough evidence to make the treatment available at this time.

Links and updates to other Policies

This policy links to:

- NHS England (2013). Clinical Commissioning Policy: Stereotactic Radiosurgery / Stereotactic Radiotherapy for Cerebral Metastases. NHS England. Accessed 30 October 2018: https://www.england.nhs.uk/wp-content/uploads/2013/04/d05-p-d.pdf

Committee discussion

The Clinical Priorities Advisory Group are asked to consider the evidence and the policy proposition. See the committee papers (link) for full details of the evidence.

The condition

Cerebral metastasis is the formation of a secondary tumour in the brain. Multiple tumours are called ‘metastases’. Cerebral metastases most commonly arise from primary cancers of the lung, breast and skin but can arise from other cancers.

Current treatments

The primary treatment options vary depending on a number of factors and include SRS, SRT, surgery, and drug treatments. Sometimes surgery is required to remove the metastases because the cerebral metastases are too large for SRS or SRT to be offered as the primary treatment, or a tissue diagnosis is required, or for patient preference.

Following surgery, metastases will have been either completely or incompletely resected. If metastases have been incompletely resected then patients may be offered post-operative SRS /

SRT to the tumour in the surgical cavity; this is already commissioned under clinical commissioning policy: SRS / SRT for Cerebral Metastases (NHS England, 2013).
The standard practice after complete surgical resection of a cerebral metastasis at most centres is observation. Observation involves an MRI every three months, if post-operative imaging shows evidence of tumour recurrence in the surgical cavity at a later date then SRS or SRT to the surgical cavity may be offered. This use of SRS or SRT is commissioned under the current policy: SRS / SRT for Cerebral Metastases (NHS England, 2013).

Some centres are now using SRS / SRT to treat the surgical cavity shortly following complete surgical removal of a metastasis, in accordance with NICE Guideline 99 (NICE, 2018) which recommends that SRS / SRT should be considered in these cases. However, this use of SRS / SRT is not currently commissioned by NHS England.

This policy proposition considers whether SRS / SRT to the surgical cavity following complete removal of cerebral metastases should be routinely offered shortly after surgery.

Proposed treatments

The proposed intervention involves routinely offering SRS or SRT to the surgical cavity of completely resected cerebral metastases shortly after surgery.

SRS and 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. The conformity and precision of SRS and SRT is considered to result in greater preservation of healthy tissue surrounding the target area, causing less functional deficit in the area and higher local control than whole-brain radiotherapy (WBRT) (Lippitz et al. 2014). It is thought that routinely treating the surgical cavity with SRS or SRT can reduce tumour recurrence and improve the patient's quality of life.

Epidemiology and Needs Assessment

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; Bradley and Mehta, 2004), however, this could be higher due to missed diagnoses when systemic cancer has become too advanced. Cerebral metastases most commonly arise from primary cancers of the lung, breast and skin (melanoma), together, these cancers account for 67-80% of cases (Nayak et al., 2011) (Barnholtz-Sloan et al. 2004). The estimated median survival time for patients with cerebral metastases without treatment is approximately two months (Langley et al. 2013), however, with developments in cancer treatments, the prognosis is improving. As a result, cerebral metastases are now more frequently referred for active treatment.

There are few estimates of the number of patients living with cerebral metastases in England each year. Kurian et al. (2017) suggest 16,000. According to 2014/15 HES data, 1,023 patients underwent a craniotomy for removal of a secondary brain tumour in England (GIRFT, 2016). As a result, the Policy Working Group estimated that approximately 1,000 people per year would be eligible for post surgical treatment with SRS / SRT in England.

Evidence summary

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

<u>Evidence review summary</u>

- 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

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.

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.

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

- 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.

Safety

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.

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.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposition needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Cerebral metastases	These are tumours in the brain that result from the spread of metastatic cancer cells from a primary site outside of the brain. The term can be used interchangeably with brain metastases and this policy covers all such metastases.
Fractionation	Is the term describing how the full dose of radiation is divided into a number of smaller doses called fractions. The fractions are given as a series of treatment sessions which make up a radiotherapy course.
Stereotactic Radiosurgery (SRS) and Stereotactic Radiotherapy (SRT)	A highly conformal radiotherapy treatment to a precisely delineated target volume, delivered using stereotactic localisation techniques. The basic principle of SRS and SRT is the destruction of abnormal tissues by administration of a large and highly focused dose/s of radiation. The procedure allows radiation to be concentrated in the target area and thus helps spare the surrounding tissue as much as possible. SRS / SRT is delivered using a Cyberknife, Gammaknife and modified linear accelerator.
Radiotherapy	The safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation.
Whole-brain radiotherapy (WBRT)	Involves irradiating the whole brain and is now only used in cases where SRS, SRT or surgery are not feasible.

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