MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
02 09 2020

Agenda Item No	2.2
National Programme	Cancer
Clinical Reference Group	Radiotherapy
URN	1857

Title
Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) to the surgical cavity following resection of cerebral metastases (All ages).

Actions Requested	1. Support the adoption of the policy proposition.
	2. Recommend its approval as an IYSD.

Proposition
The policy proposition recommends that SRS/SRT should not be made routinely available for cerebral metastases following complete resection of the tumour. The policy has been developed based on the findings of an evidence review and in line with the standard Methods. It is important to note that NHS England does commission the use of SRS/SRT in people with partially resected cerebral metastases and where the disease returns post-surgery (NHS England Reference: NHSCB/ D05/P/d). This commissioning position is unaffected by the new policy proposition.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a not for routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Cancer programme confirms the proposition is supported by an: Impact Assessment; Consultation Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.

3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

A) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus observation following resection of cerebral metastasis

No	Outcome measures	Summary from evidence review
1.	Survival	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 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.
2.	Progression free survival	Not measured.

3.	Mobility	Not measured.
4.	Self-care	Not measured.
5.	Usual activities	Not measured.
6.	Pain	Not measured.
7.	Anxiety / Depression	Not measured.
8.	Replacement of more toxic treatment	Not measured.
9.	Dependency on care giver / supporting independence	Not measured.
10.	Safety	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. See above for limitations of Mahajan et al (2017).
11.	Delivery of intervention	Not measured.

No	Outcome measure	Summary from evidence review
1.	Local tumour recurrence-free rates	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 quality of life (QOL). See above for limitations of Mahajan et al (2017).
2.	Time to local recurrence (median time to radiographic evidence of new lesion)	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. See above for limitations of Mahajan et al (2017).
3.	Freedom from distant brain metastases (DBM)	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. See above for limitations of Mahajan et al (2017).

4.	Leptomeningeal disease (LMD)	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. See above for limitations of Mahajan et al (2017).
5.	Neurological death	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. See above for limitations of Mahajan et al (2017).
6.	Freedom from WBRT	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. See above for limitations of Mahajan et al (2017).

B Not measured.**) Stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) versus whole brain radiotherapy (WBRT) following resection of cerebral metastasis**

No	*Outcome measures*	*Summary from evidence review*
1.	Survival	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 quality of life.
2.	Progression free survival	Not measured.
3.	Mobility	Not measured.
4.	Self-care	Not measured.
5.	Usual activities	Not measured.
6.	Pain	Not measured.

7.	Anxiety / Depression	Not measured.
8.	Replacement of more toxic treatment	Not measured.
9.	Dependency on care giver / supporting independence	Not measured.
10.	Safety	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.
11.	Delivery of intervention	

No	Outcome measure	Summary from evidence review
1.	Cognitive deterioration-free survival	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 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.
2.	Neurological failure - cumulative incidence of neurological /cognitive failure (CINCF)	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)[1]. At 6 months: CINF rates in the SRT patients

[1] 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%)

		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.
3.	Neurological death - cumulative incidence of neurological/ cognitive death (CIND)	The two 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.
4.	Intracranial tumour progression	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.
5.	Surgical bed control	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.
6.	Local control	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 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.
7.	Distant brain control	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.
8.	Functional independence	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).

9.	Quality of life	Brown et al (2017) assessed quality of life by the change from baseline to 6 months in Functional Assessment of Cancer Therapy-Brain (FACT-Br) and Linear Analogue Self-Assessment (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). 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.
10.	Leptomeningeal disease (LMD)	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.
11.	Salvage treatment of relapses within the brain (rate)	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.

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

Patient Impact Summary
Not applicable – the policy proposition is not for routine commissioning and as such no patient impact summary has been completed.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
1) The proposal received the full support of the Cancer Programme of Care (PoC) on 23rd July 2020.