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Stereotactic radiosurgery for treatment of patients with brain metastases[1]

Extract

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The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

The aim of the present investigation is

to assess the benefit of treatment with single-session stereotactic radiosurgery (SRS) with linear accelerators or cobalt-60-gamma radiation sources (also in combination with surgical resection) versus treatment with microsurgical resection (also in combination with whole brain radiation therapy, WBRT) or WBRT

in each case in patients with one or a few brain metastases requiring treatment. The focus of the assessment was on patient-relevant outcomes.

Conclusion

A total of 7 randomized controlled trials (RCTs) were included in the present assessment. These were assigned to 2 different comparisons, depending on the control intervention investigated.

For the comparison of single-session SRS versus microsurgical resection (Comparison 1), a treatment-inherent advantage of SRS with regard to length of hospital stay was found. However, due to the risk of publication bias of a relevant magnitude, no conclusion regarding a greater benefit or harm of either treatment option could be drawn for this comparison across outcomes. Nor could valid conclusions be drawn regarding a comparable benefit of SRS.

Due to the intervention-specific differences in invasiveness and length of hospital stay, the present results suggest that single-session SRS in patients with one or a few brain metastases may have the potential to be a necessary treatment alternative to resection. The prospects of success of a testing study for this comparison must be considered very low due to the known recruitment problems.

For the comparison of single-session SRS versus WBRT (Comparison 2), data from a total of 6 randomized trials could be used, of which 1 had a high and 5 had a moderate qualitative certainty of results across outcomes. In terms of all-cause mortality, across studies, overall the data provide no hint of a greater benefit or harm of any of the treatment options. In addition, the available results do not suggest with sufficient certainty that SRS provides at least comparable overall survival versus WBRT. With regard to memory performance as a subcomponent of cognitive function, there was a hint of a greater benefit of SRS, but not for other components of cognitive function, such as speech fluency or executive functions. For the outcomes of activities of daily living, adverse events and treatment-related complications, and health-related quality of life, there was no hint of a greater benefit or harm of any of the treatment options. For the outcome of neurological function, no usable data were identified. Beyond the results reported in the studies, single-session SRS has treatment-inherent advantages over WBRT in terms of repeatable application of the intervention and in terms of treatment-related burden. Thus, a hint of a greater benefit of SRS can be also be derived for the comparison of single-session SRS versus WBRT in the overall assessment across outcomes.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
COWAT	Controlled Oral Word Association Test
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5 Dimensions
GTV	gross tumour volume
Gy	Gray
HR	hazard ratio
HRQoL	health-related quality of life
HVLT-R	Hopkins Verbal Learning Test – Revised Version
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KPS	Karnofsky Performance Score
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
OR	odds ratio
PTV	planning target volume
QLQ-BN20	Quality of Life Questionnaire – Brain Cancer Module
QLQ-C30	Quality of Life Core Questionnaire
RCT	randomized controlled trial
SRS	stereotactic radiosurgery
TMT-A/-B	Trail Making Test –Part A / B
WBRT	whole brain radiation therapy

1 Background

Brain metastases are a common neurological complication of systemic cancers in which metastases of an extracranial malignant tumour occur in the brain. They usually indicate terminal cancer and limited life expectancy [1]. Untreated, patients with brain metastases from a solid tumour have a median life expectancy of 1 to 2 months; individual patients in certain subgroups, such as those with human epidermal growth factor receptor 2 (HER2)-positive breast cancer or certain genotypes of non-small-cell lung cancer (NSCLC), appear to have slightly longer survival periods [2].

About 8 to 20 % of all patients with cancer develop brain metastases; they occur 10 times more frequently than primary brain tumours [1,3]. According to the German Brain Tumour Society, patients with lung cancer are the most frequently affected (40 to 60%), followed by patients with breast cancer (15 to 20%) and malignant melanoma (10 to 15%) [4]. The annual incidence is currently 8.3 to 14.3 per 100,000 people per year in the United States [1,5]. These numbers may increase in the future, because improved imaging techniques can also detect small metastases and improved systemic therapies can better control the underlying disease [5,6].

The presence of brain metastases must be expected whenever a cancer patient develops neurological symptoms, which may include headaches, seizures, and focal neurological deficits, as well as cognitive impairment and difficulties in walking [1].

Diagnostic imaging options include magnetic resonance imaging with a contrast agent or computed tomography, which has lower sensitivity [5]. Subsequently, if the primary tumour is known, all necessary assessment options for staging should be used to depict primary cancer activity and extracranial metastases. If the primary tumour is not known (in approx. 20% of cases, brain metastases are diagnosed at the same time or before the primary tumour is diagnosed [5]), imaging techniques should be used to detect the primary tumour. If these are inconclusive, either resections should then be performed or, if these are not indicated, biopsies of the brain metastases should be taken [1,3].

Before treatment is started, the patient is first classified using a prognostic scoring system. In addition, the necessity of supportive therapy must be considered, for example, with regard to seizures, oedema-related symptoms, or fatigue [1].

Depending on the size and location of the brain metastases, the control of the primary tumour and the general condition of the affected patients, different treatment options are available. According to current guidelines, microsurgical resection of operable brain metastases is indicated in the following cases: for a limited (1 to 3) number of newly diagnosed brain metastases (especially with a diameter of 3 cm or more), for lesions with necrotic or cystic changes, for oedema or effects caused by the tumour mass, for brain metastases located in the posterior fossa and associated with hydrocephalus, and for brain metastases located in regions with an increased risk of symptoms [3,7,8].

Stereotactic radiosurgery (SRS) can be a suitable alternative to resection, particularly in the case of smaller brain metastases with a diameter of up to 3.5 cm or of brain metastases that are difficult to access surgically (e.g., at the brain stem) or of concomitant diseases with a high surgical risk [7,8]. In this radiosurgical treatment, the mostly single-session, high-dose and precise irradiation is performed with fixation of the skull using linear accelerators or devices with cobalt-60 gamma radiation sources [2]. The large dose decrease at the edge of the metastases treated is intended to spare the surrounding healthy tissue and thus reduce the risk of radiation-induced damage [7]. In contrast, in whole brain radiotherapy (WBRT), the radiation dose is divided in several treatment sessions and the entire brain of the patient is irradiated. 50 to 60% of patients with a single resected metastasis develop local recurrence within 6 to 12 months after resection. Both WBRT and SRS can also be used for adjuvant treatment after resection to irradiate the postoperative resection cavities and/or additional unresected brain metastases [2].

2 Research question

The aim of the present investigation is

- to assess the benefit of treatment with single-session SRS with linear accelerators or cobalt-60-gamma radiation sources (also in combination with surgical resection) versus treatment with microsurgical resection (also in combination with WBRT) or WBRT

in each case in patients with one or a few brain metastases requiring treatment. The focus of the assessment was on patient-relevant outcomes.

3 Methods

The target population of the benefit assessment is patients with one to a few brain metastases requiring treatment. The test intervention was single-session SRS with linear accelerators or cobalt-60 gamma radiation sources (SRS60G), also in combination with surgical resection. Microsurgical resection, also in combination with WBRT, or WBRT were considered as the control intervention.

The following patient-relevant outcomes were considered in the investigation:

- Mortality
- Morbidity (especially cognitive impairment and other neurological disorders such as seizures or paralysis)
- Health-related quality of life
- Adverse events (AEs) and treatment-related complications

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

The systematic literature search for studies was performed in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the HTA Database.

The following sources of information and search techniques were additionally used: study registries, queries to manufacturers, documents sent by the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), documents made available from hearing procedures, and queries to authors.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Because no maximum limit in the number of metastases is defined for the present research question on one or a few brain metastases, the selection of relevant study populations was primarily based on the single-session implementation of the study intervention. Data were extracted into standardized tables. To assess the qualitative certainty of results, criteria across outcomes and outcome-specific criteria for the risk of bias were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were organized according to outcomes and described.

In addition to the comparison of the results of the individual studies, metaanalyses and sensitivity analyses were to be conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter is the case if no data are available or the available data do not permit classification into one of the 3 other categories. In that case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

4 Results

4.1 Information retrieval results

Information retrieval yielded a total of 7 RCTs relevant to the research question. Furthermore, 6 ongoing studies comparing SRS versus WBRT were identified. In addition, 5 discontinued and 1 completed study without reported results were identified.

The search strategies for bibliographic databases and study registries are included in the appendix. The last search took place on 16 April 2021.

The completed study without reported results (NCT00460395 [9]) compared SRS with resection (potentially with adjuvant WBRT). According to the information in the study registry, 64 patients were recruited. An associated publication on the study protocol or results or other documents could not be identified. In response to repeated inquiries, the sponsor of the study provided feedback, which suggested that the study had been completed as indicated in the study registry entry, but the associated manuscript was not accepted and published, despite multiple submissions to scientific journals. Submission of the study results to IQWiG was rejected with reference to the lack of peer review. Reasons for the lack of publication of the results in the study registry entry were not provided upon request.

For another study without reported results already identified for the preliminary report NCT00075166 [10], the sponsor of the study has since provided the information that the actual status differs from the study registry entry and that the study was discontinued due to recruitment difficulties after the only patient recruited dropped out (without having received treatment).

Table 1: Study pool of the benefit assessment

Study		**Documents available**		
	Full-text publication (in scientific journals)	**Registry entry / results report from study registries**	**Study report of manufacturer (not publicly accessible)**	**Other documents**
SRS versus resection				
Muacevic 2008	yes [11]	no / no	no	no
SRS versus WBRT				
Brown 2017	yes [12]	yes [13] / yes	no	no
El Gantery 2014[a]	yes [14]	no / no	no	no
Hartgerink 2021	yes [15,16]	yes [17] / no	no	no
Kayama 2018	yes [18]	yes [19,20] / no	no	no
Kepka 2016	yes [21,22]	yes [23] / no	no	no
Raman 2020	yes [24]	yes [25] / no	no	no[b]

a. For the present assessment, only the data comparing SRS versus WBRT were used from this 3-arm study.
b. Data were provided by e-mail after a query to the authors.

SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy

4.2 Characteristics of the studies included in the assessment

Because of the different comparators (resection plus WBRT or WBRT alone), the studies included were divided into 2 comparisons:

4.2.1 Studies comparing SRS versus resection

In 1 of the 7 studies included, single-session SRS was compared with microsurgical resection followed by WBRT in adult patients with 1 resectable brain metastasis. This study, Muacevic 2008, conducted in Germany between 1999 and 2003, included only patients in good general health (Karnofsky Performance Score [KPS] ≥ 70) and a life expectancy of at least 4 months and whose single brain metastasis did not exceed 3 cm in diameter. The mean age of the patients was 54.3 (SRS group) and 58.3 years (control group). In both groups, the primary tumour was most frequently (32.3% and 36.4%) located in the lung. Following randomization, with a target study duration of at least 4 years, all patients included were followed up for at least 12 months. SRS was performed by gamma knife using a mean radiation dose at the tumour margin of 21 Gray (Gy). Depending on the radiosensitivity of the primary tumour, this dose range varied from 14 to 20 Gy (e.g., for breast cancer) and 20 to 27 Gy (e.g., for melanoma or hypernephroma). The mean maximum dose was reported to be 41 Gy. In the control group, brain metastasis was treated using standard neurosurgical techniques with the goal of complete resection of the metastasis. The dose of WBRT following within 14 days was 40 Gy distributed over 20 fractions. In addition to adjuvant systemic therapies (e.g. corticosteroids), renewed radiosurgery, microsurgery, or additional WBRT were possible in both study arms for recurrent or progressive brain metastases. The decision on the necessity and choice of therapy was up to the medical staff. The study group states that recruitment was slow due to reservations by the participating physicians regarding the treatment options; as a result, the study was terminated prematurely and included only 64 of the 242 patients originally planned.

4.2.2 Studies comparing SRS versus WBRT

In 6 of the 7 studies included, the comparison of single-session SRS with WBRT was investigated. In this regard, radiotherapy in 3 of these 6 studies (Brown 2017, Kayama 2018, and Kepka 2016) was adjuvant following resection of the brain metastases. Data for neoadjuvant use of either therapy before resection of brain metastases were not found.

In Brown 2017 [12], a total of 194 adult patients with 1 brain metastasis at 48 US and Canadian study centres were randomized after prior surgical resection. In addition to the resected brain metastasis, whose resection cavity had to measure less than 5 cm, up to 3 additional unresected brain metastases with a maximum diameter < 3 cm could exist. The patients included were a median of 61 (SRS group) and 62 years old (WBRT group). In approximately half of these patients, the brain metastases originated from primary lung cancer. Treatment in the intervention group consisted of single-session SRS to irradiate the resection cavity. The radiation dose used ranged from 12 to 20 Gy depending on the volume of the respective resection cavity. Treatment in the control group consisted of adjuvant WBRT with a radiation dose of 30 Gy distributed over 10 sessions (alternatively 37.5 Gy distributed over 15 sessions).

In addition, previously untreated brain metastases were treated with SRS in both study groups. Here, the radiation dose of SRS varied between 20 and 24 Gy in the intervention arm and between 18 and 22 Gy in the control arm, depending on the size of the lesion. Only memantine was mentioned as a possible concomitant therapy to improve cognitive function during SRS or WBRT. Systemic chemotherapy was allowed both until study entry and after completion of the study interventions. For subsequent treatment of progression or recurrence, the study protocol suggested different treatment algorithms depending on the number of brain metastases, the control of the primary disease, and individual patient preferences. The decision on concomitant chemotherapy was up to the medical staff. The study was conducted between 2011 and 2015. The median follow-up duration was 11.1 months for all patients and 22.6 months for patients who did not die during the course of the study. To test for non-inferiority of SRS versus WBRT with respect to overall survival, a non-inferiority hazard ratio (HR) threshold of 1.3 was specified.

Kayama 2018 [18] is a study to test the non-inferiority of postoperative SRS versus WBRT in terms of overall survival. The noninferiority threshold was defined as an HR of 1.385, which should correspond to a median 2.5-month reduction in overall survival for the SRS group. A total of 271 adult patients, each with 1 to 4 previously resected brain metastases, of which no more than 1 metastasis was allowed to exceed 3 cm in diameter, were randomized in 43 Japanese study centres between 2006 and 2014. Across groups, approximately 73.4% of all patients had only 1 intracranial metastasis. In addition, approximately 56% of all patients had at least 1 additional extracranial metastasis (e.g. lung, liver, and bone). The mean age of patients was 63 (SRS arm) and 61 years (WBRT arm); nearly half had primary lung cancer. The treatment strategy in the intervention group was to provide adjuvant SRS or WBRT exclusively to patients who had a residual brain metastasis (or metastases) or unresected lesions after surgery (approx. 60% of all patients included) and/or newly identified lesions with a maximum diameter of 3 cm (or, alternatively, with a macroscopic gross tumour volume [GTV] of $\leq$ 10 ml). There was no specific treatment of postoperative resection cavities after total resection. As a result, 47 (35.1%) of the 134 randomized patients in the SRS arm did not receive any treatment. A further 20 patients in the intervention arm underwent multiple SRS sessions (including 11.9% who underwent 2 SRS sessions). In addition, 37.3% of the SRS arm received additional WBRT during the course of the study. Little information was found on the procedure of SRS: While performance of the procedure was generally allowed via gamma knife, cyberknife, or linear accelerator depending on availability, in particular the SRS dose level remained unclear. In addition, it was not explained whether only single-session SRS was planned a priori or whether in principle multiple-session SRS was also possible. In contrast, in the control group, a total of 97.8% of the randomized patients were treated with WBRT as assigned, with the dose strength set in advance at 37.5 Gy with 15 fractions of 2.5 Gy each. 29.2% later received additional SRS or other focal radiotherapy. The exact patient flow (including the exact number of dropouts per treatment arm) cannot be clearly followed due to partly contradictory data.

In the multicentre Polish Kepka 2016 study [21], conducted between 2011 and 2015, SRS or WBRT was also performed following total or subtotal resection of a single brain metastasis. About half of the patients included had primary lung cancer. With a median age of 59.5 years, the 60 randomized patients had to be in good general physical health (KPS ≥ 70) at baseline and have a remaining life expectancy of more than 6 months. A subtotally resected brain metastasis was reported for 17% (SRS arm) and 10% (WBRT arm) of these patients. Both study interventions, which had to be started no later than 6 weeks after performing the resection, were applied using linear accelerators and primarily aimed to irradiate the postoperative resection cavity. In the control group, the radiation dose of 30 Gy was spread over 10 sessions over 2 weeks. In contrast, the actual radiation dose of single-session SRS varied between 15 and 24 Gy, depending on the size of the resection cavity. In 6 of the 30 SRS-allocated patients, SRS was delivered as a hypofractionated treatment with 25 Gy distributed over 5 sessions because of the size (> 50 mm), location, or shape of the resection cavity. Contrary to the study protocol, 5 further patients switched to WBRT before the assigned SRS was performed (3 of them because of newly identified brain metastases). Two further patients in the SRS arm received only single-session SRS for treatment of newly identified brain metastases, and 1 patient in the SRS arm did not receive either study intervention due to extracranial progression. For patients who did not die during the course of the study, the median duration of follow-up was 29 months. Details of systemic adjunctive therapies or prespecified treatment algorithms for treatment of progression or recurrence were not provided.

In the 3 other studies comparing single-session SRS versus WBRT, the study interventions were applied as primary therapy without prior resection or other pretreatment of brain metastases.

In the Egyptian single-centre El Gantery 2014 study [14], conducted between 2008 and 2011, 3 intervention arms were compared: SRS alone, WBRT alone, and combined SRS and WBRT. The latter study arm was not considered for the present assessment. The 60 patients included in the study had 1 to 3 brain metastases, each with a maximum diameter of 4 cm. The upper age limit at inclusion in the study was 70 years. In addition, patients had to be in good general physical health (KPS ≥ 70). No other characteristics or information regarding the health status of the patients included were presented in the publication on the study results. Likewise, it was not reported whether or what concomitant interventions or salvage therapies were provided to treat the primary disease, progression or recurrence. The type of SRS was not mentioned. The radiation dose of single-session SRS varied between 18 and 20 Gy (median: 20 Gy). The dose of WBRT distributed over 10 fractions totalled 30 Gy. The subsequent follow-up duration was a median of 8.5 months across groups, with a range of 0 to 34 months.

The Dutch study Hartgerink 2021 [16] recruited adult patients with 4 to 10 previously untreated brain metastases, with a median of 6 brain metastases. The cumulative GTV was not allowed to exceed the limit of 30 cm^3 (or brainstem metastases were not allowed to exceed a planning target volume [PTV] of 20 cm^3). The patients to be included also had to be in good general condition (KPS ≥ 70) at baseline in this study. On average, randomized patients were 60 (SRS arm) or 65 (WBRT arm) years of age. More than 80% had primary lung cancer. The dose of

single-session SRS treatment via cyberknife or linear accelerator was set at 15 to a maximum of 24 Gy prior to the start of treatment, depending on the PTV of the largest brain metastasis. In individual cases (e.g., brainstem metastases), treatment with 24 Gy over 3 sessions was possible. This hypofractionated SRS was received by 2 of the 15 (13.3%) SRS-randomized patients. WBRT in the control arm was 20 Gy distributed over 5 fractions of 4 Gy each for 5 consecutive days. Concomitant systemic therapies were allowed up to 1 week before or from 1 week after the study intervention, according to the inclusion criteria. It was planned to conduct the study with 230 patients. However, due to recruitment difficulties, only 29 patients were included after the recruitment period between 2016 and 2018 (15 patients were randomized to the SRS arm and 14 to the WBRT arm). The median follow-up duration was 26 months.

Similar to this study, the multicentre Canadian feasibility study Raman 2020 [24] randomized a total of 20 adult patients with 1 to 10 brain metastases from 2015 to 2017. The prerequisites were that the diameter of the metastases did not exceed 4 cm, the remaining life expectancy was 3 to 6 months, and the patients – in addition to being in good general health (KPS ≥ 70 or Barthel index ≥ 90) – had no severe cognitive impairment, i.e., had a least 20 points in the Montreal Cognitive Assessment (MoCA). A radiation dose of 15 Gy was chosen for single-session SRS by linear accelerator, and a radiation dose of 20 Gy distributed over 5 sessions of 4 Gy each was chosen for the WBRT. With regard to permitted co-interventions or a treatment algorithm for the treatment of progression or recurrence, the only information that was provided was that concomitant corticosteroid therapy was possible in both study arms. The median duration of follow-up was 7 months.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes could be extracted from all 7 studies included. Table 2 shows the overview of available data on patient-relevant outcomes.

In the study comparing SRS versus resection (Muacevic 2008), usable results on all-cause mortality, AEs and treatment-related complications, and length of hospital stay were reported. Data on activities of daily living and health-related quality of life (HRQoL) outcomes, which were also collected, could not be used for the present assessment because of insufficient response criteria. Data on neurological function or cognitive function were not reported.

For the comparison of SRS versus WBRT, results on all-cause mortality, as well as AEs and treatment-related complications, were reported in all 6 studies. For Raman 2020, however, the reported AE data were not usable, as they were exclusively reported across groups or without specification of the respective severity grades. With regard to cognitive function (recorded in 4 of the 6 studies), Brown 2017 in particular reported multiple operationalizations or instruments, examining different components of cognitive function (including memory performance, speech fluency or executive functions). However, the reported results were only partially usable, as the selected response criteria were insufficient or the results were only reported as part of a combined outcome (Kepka 2016). Similarly, data on activities of daily living and HRQoL (each reported in 4 of the 6 studies) could not be fully used. For these two outcomes, an inadequate

response criterion was selected for the analysis in Brown 2017 and only across-group results on HRQoL were reported in Raman 2020. For the outcomes of neurological function and length of hospital stay, no (usable) data were found for the comparison of SRS versus WBRT.

Due to the lack of patient relevance, outcomes reported in the studies, such as the frequency of recurrences or progression (including the occurrence of leptomeningeal metastases) or the response to treatment, were not used for the present assessment. This is particularly due to the fact that relevant events were primarily defined by radiological imaging, without a validated surrogate association of these events with patient-relevant outcomes. Furthermore, the study interventions SRS or WBRT were not performed with primarily curative intent, so the patients considered had no expectation of cure in the palliative context. Data reported in Kepka 2016 on the combined outcome of deterioration of neurological or cognitive function (Cumulative Incidence of Neurological / Cognitive Failure [CINCF]) were excluded because no separate outcomes were reported for the individual components included in the combined outcome. Results for neurological mortality (Cumulative Incidence of Neurological Death [CIND]), which included progression- and toxicity-related deaths as well as those of undetermined cause, were also excluded, as they had already been considered in the report via all-cause mortality.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes						
	Mortality	Morbidity					
	All-cause mortality	Neurological function	Cognitive function	Activities of daily living	Adverse events and treatment-related complications	Health-related quality of life	Length of hospital stay
SRS versus resection							
Muacevic 2008	●	-	-	○[a]	●	○[a]	●
SRS versus WBRT							
Brown 2017[b]	●	-	●	○[a]	●	○[a]	-
El Gantery 2014[c]	●	-	-	-	●	-	-
Hartgerink 2021	●	-	-	●	●	●	-
Kayama 2018[b]	●	-	●	●	●	-	-
Kepka 2016[b]	●	○[d]	○[a, d]	-	●	●	-
Raman 2020	●	-	○[e]	○[e]	○[f, g]	○[f]	-

●: Data were reported and were usable.
○: Data were reported but were not usable for the benefit assessment.
-: No data were reported (no further information) or the outcome was not recorded.
a. Insufficient response criterion or no response criterion mentioned.
b. In this study, SRS or WBRT was adjuvant following resection of brain metastases.
c. For the present assessment, only the data comparing SRS versus WBRT were used from this 3-arm study.
d. Results not usable because only the first event of neurological or cognitive deterioration was reported.
e. Results not usable because the number of patients analysed per study arm is unclear.
f. Results were reported across groups only.
g. In the response to the query to the authors, the number of patients with fatigue, nausea, and headache was reported, but without information on the severity of the events.

AE: adverse event, SAE: serious adverse event; SRS: stereotatic radiosurgery; WBRT: whole brain radiotherapy

4.4 Assessment of the risk of bias of the results

The risk of bias across outcomes was rated as low for only 1 of the 7 studies included (Brown 2017). Only this study provided information on a possible treatment algorithm for the treatment of recurrences or progression of brain metastases and transparent information on the respective subsequent treatments. Regarding the choice of the appropriate salvage therapy, it seems plausible in principle that the decision (besides e.g. size and location of the lesion to be treated) depends considerably on the previous study intervention. For example, recurrences in patients with WBRT as a study intervention are usually not treated with renewed WBRT, but with SRS or surgical resection. In contrast, patients who initially received SRS alone have all 3 options

available as salvage therapy. A predefined pathway for subsequent treatment in case of progression or recurrence or for concomitant treatment of the underlying disease can ensure that patients with comparable disease status, e.g. with a comparable recurrence situation and status of the primary disease, are treated according to a predefined treatment algorithm both within and between the study groups. Only in this way can the risk be reduced of influencing the treatment decision and of a possible co-intervention bias, which could impair the comparability of the study groups investigated and thus the validity of the results reported. Of course, this does not affect a justified deviation from the specified treatment paths.

If reported at all in the other studies, the decision on the necessity and choice of follow-up therapy, as well as systemic adjunctive therapy, was made by the respective medical staff. In addition, information was missing on the generation of the randomization sequence (Muacevic 2008, El Gantery 2014, Hartgerink 2021, Kayama 2018, and Kepka 2016) and on how group allocation concealment was ensured (El Gantery 2014, Hartgerink 2021, and Kayama 2018). Moreover, selective reporting was suspected in 4 studies (Muacevic 2008, El Gantery 2014, Hartgerink 2021, and Kepka 2016). Blinding, particularly of the outcome assessors, was only performed in Brown 2017 (assessment of cognitive function).

4.5 Outcomes on patient-relevant outcomes

For Comparison 1 (SRS versus resection), 1 completed study (NCT00460395 [9]) with no reported results was identified from the study registry search. As stated in Section 4.1, the sponsor of the study declined to submit study results to IQWiG, so no results are available for 50% of the total study population of the 2 completed studies (NCT00460395 and Muacevic 2008). Because there is thus a risk of publication bias of a relevant magnitude, the results available from Muacevic 2008 comparing SRS versus resection are presented only descriptively in the following sections. A conclusion on benefit (proof, indication, hint of a (greater) benefit or harm) for individual outcomes and an (overall) conclusion on benefit across outcomes cannot be drawn for this comparison.

4.5.1 Results on mortality

SRS versus resection

For the outcome of all-cause mortality, Muacevic 2008 reported median survival in the intervention and control groups of 10.3 and 9.5 months, respectively. There was no statistically significant difference in terms of a treatment effect.

Irrespective of these data, due to the risk of publication bias for the comparison of SRS versus resection, no conclusion can be drawn with regard to a greater or comparable benefit or harm of either treatment option for mortality.

SRS versus WBRT

Also for this comparison, usable results on mortality were reported for all studies included. Only Brown 2017 showed a low risk of bias for this outcome. The median survival in the control

groups of the studies varied between 4 and 16 months. For the respective HR, with partly very wide 95% confidence intervals (CIs), only Kepka 2016 showed a statistically significant difference to the disadvantage of SRS (HR: 1.8; 95% CI: [0.99; 3.30]; p = 0.046).

In the only study with an outcome-specific low risk of bias (Brown 2017), there was no statistically significant difference between treatment groups, with an HR of 1.07 (95% CI: [0.76; 1.50]). In the meta-analytic summary of data from all 6 studies comparing SRS versus WBRT, the pooled HR was 1.18 (95% CI: [0.78; 1.80]). Thus, based on both the results of the 1 study with an outcome-specific low risk of bias (Brown 2017) and the overall estimate of all 6 studies with respect to all-cause mortality, no statistically significant effect and thus no hint of a greater benefit or harm of either treatment option can be inferred.

Furthermore, for this outcome, with a 90% CI of [0.80; 1.42] from Brown 2017 and a 90% CI of [0.83; 1.68] of the calculated overall HR estimate, non-inferiority of SRS versus WBRT cannot be inferred for any of the thresholds reported in Brown 2017 or Kayama 2018 (upper limit of 90% CI ≤ 1.3 or ≤ 1.385).

4.5.2 Results on neurological function

SRS versus resection

No data were reported on the outcome of neurological function in Muacevic 2008.

SRS versus WBRT

For the comparison of SRS versus WBRT, only 1 study (Kepka 2016) reported results on neurological function. However, these were not usable because they were reported exclusively as part of a combined outcome of relevant deterioration of neurological function (using the Medical Research Council [MRC] neurological scale) and/or cognitive function (using the Mini-Mental State Examination [MMSE]). Complete separate results on neurological function were not available.

Therefore, for the outcome of neurological function, no hint of greater benefit or harm of either treatment option can be derived for the comparison of SRS versus WBRT.

4.5.3 Results on cognitive function

SRS versus resection

No data were reported on the outcome of cognitive function in Muacevic 2008.

SRS versus WBRT

For the comparison of SRS versus WBRT, results on the outcome of cognitive function were reported in 4 of the 6 studies included. In Brown 2017, usable results were reported after 6 months for the Controlled Oral Word Association Test (COWAT), as well as for the multi-part Hopkins Verbal Learning Test - Revised Version (HVLT-R) and the Trail Making Test (parts A and B [TMT-A / -B]). A statistically significant difference in favour of the SRS arm was

shown exclusively for HVLT-R Delayed Recall (odds ratio [OR]: 0.22; 95% CI: [0.06; 0.86]; p = 0.023) and HVLT-R Recognition (OR: 0.14; 95% CI: [0.03; 0.67]; p = 0.006) and thus for (longer-term) memory performance as a component of cognitive function. In contrast, the results for short-term memory performance using HVLT-R Immediate Recall were not statistically significantly different (OR: 0.29; 95% CI: [0.07; 1.15]; p = 0.074). Nor were results for other components of cognitive function statistically significantly different between groups, neither in COWAT (speech fluency; p > 0.999) nor in TMT-A or TMT B (including executive functions and cognitive processing speed; p = 0.107 and p = 0.170). Survival without deterioration of cognitive function as a further operationalization of the outcome in this study was not usable due to an insufficient response criterion (deterioration of scores at baseline by at least 1 standard deviation).

In Kayama 2018, the results of the multidimensional MMSE, which, among other things, examines temporal and spatial orientation and numeracy, showed no statistically significant difference in terms of deterioration in cognitive function since baseline at 6 (OR: 1.11; 95% CI: [0.68; 1.78]; p = 0.769) or 12 months (OR: 1.12; 95% CI: [0.69; 1.80]; p = 0.711) between treatment groups. In contrast, as with the data on neurological function, the MMSE results from Kepka 2016 were not usable, as they were reported only as part of a combined outcome of relevant neurological and/or cognitive deterioration. Complete separate results on cognitive function were not available. Similarly, data from Raman 2020 on the MoCA test, which is also multidimensional, could not be used because the number of patients analysed for this per study arm is unclear.

The different subcomponents of cognitive function were recorded and analysed separately in Brown 2017. In contrast, in Kayama 2018 only results of the multidimensional MMSE were reported. No meta-analytical summary of the results on cognitive function was performed. However, based on the statistically significant effects regarding memory performance, a hint of a greater benefit of SRS versus WBRT can be inferred for this subcomponent of cognitive function.

4.5.4 Results on activities of daily living

SRS versus resection

The results reported in Muacevic 2008 for the outcome of activities of daily living were not usable due to an insufficient response criterion.

Irrespective of these data, due to the risk of publication bias of a relevant magnitude for the comparison of SRS versus resection, no conclusion can be drawn with regard to a greater benefit or harm of either treatment option for activities of daily living.

SRS versus WBRT

For the comparison of SRS versus WBRT, the results from 2 studies could be considered for the outcome of activities of daily living. In this context, neither the KPS at 3 months (Hartgerink

2021; p = 0.34) nor the Eastern Cooperative Oncology Group Performance Status (ECOG-PS) at 6 or at 12 months (Kayama 2018; p = 0.933 and p > 0.999, respectively) showed a statistically significant difference between the treatment groups.

The Barthel index data reported in Brown 2017 were not usable due to an insufficient response criterion (deterioration of the baseline value by at least 10%). Similarly, the KPS data reported separately for Raman 2020 could not be used because the number of patients analysed per study group was unclear. Furthermore, no group-specific results on the Modified Barthel Index of Activities of Daily Living were reported in this study, which used an insufficient response criterion.

Due to the different operationalizations and analysis times of the results from Hartgerink 2021 and Kayama 2018, a meta-analytic summary of the reported data was not possible for the outcome of activities of daily living.

In terms of usable data, no hint of greater benefit or harm of either treatment option could be derived for this outcome for the comparison of SRS versus WBRT.

4.5.5 Results on adverse events and treatment-related complications

For the evaluation of AEs and treatment-related complications, only the results of the first data collection period, i.e. from the start of treatment, were used for the comparisons examined. Because of the high mortality within a few weeks due to the underlying disease, a structural imbalance of the treatment groups may occur. Therefore, the data on late AEs and treatment-related complications from data collection periods and separate analyses after > 30 days after initial treatment were not considered for the present assessment.

SRS versus resection

In the included study Muacevic 2008, there was no statistically significant difference between the treatment groups for treatment- or radiation-related toxicities of Grade 3 or 4 (according to Common Toxicity Criteria, version 2.0) for the follow-up period up to 90 days after the start of treatment.

Irrespective of these data, due to the risk of publication bias of a relevant magnitude for the comparison of SRS versus resection, no conclusion can be drawn with regard to a greater benefit or harm of either treatment option for AEs and treatment-related complications.

SRS versus WBRT

For the comparison of SRS versus WBRT, with regard to severe AEs (Grade 3 to 4 of the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0), there was no statistically significant difference between treatment groups for the overall rate of ≥ Grade 3 toxicities (Brown 2017; OR: 0.94; 95% CI: [0.52; 1.69]; p = 0.884), Grade 3 to 4 non-haematologic toxicities (Kayama 2018; OR: 0.78; 95% CI: [0.33; 1.84]; p = 0.60), or ≥ Grade 3 radiotherapy-related toxicities (Kepka 2016; no events). Haematologic toxicities (Grade 3 to

4) occurred in less than 5% of all patients regardless of the assigned intervention (Kayama 2018). There was also no statistically significant difference in the number of deaths due to an AE (Grade 5) (Brown 2017; OR: 0.67; 95% CI: [0.24; 1.84]; p = 0.532).

With regard to central nervous system necrosis (≥ Grade 2), the 95% CI of the relative effect in Brown 2017 showed such an imprecise result (OR: 9.30; 95% CI: [0.49; 175.27]; p = 0.046) that neither a halving nor a doubling of the effect can be excluded. In Kayama 2018, no events of severe radiation necrosis (Grade 3 to 4) were observed at up to 30 days after the start of treatment.

In the meta-analytic summary of reported overall rates of ≥ Grade 3 toxicities, the pooled estimate of the overall effect from 3 studies (Brown 2017, Kayama 2018, and Kepka 2016) was found to be uninformative when calculated using the Knapp-Hartung method, and the overall estimate using the DerSimonian-Laird method was not statistically significant. There was no statistically significant difference between the intervention groups being compared. Thus, based on the higher severity grades (Grade 3 to 4) for the comparison of SRS versus WBRT, no hint of greater benefit or harm from either treatment option can be inferred.

With regard to AEs of Grade 1 to 2, Kayama 2018 showed a statistically significant advantage in favour of the SRS group after up to 30 days after the start of treatment, especially for the AEs radiation dermatitis (OR: 0.01; 95% CI: [0.00, 0.09]; p < 0.001) and nausea (OR: 0.05; 95% CI: [0.02, 0.15]; p < 0.001). Although the observed difference is very large, since the vast majority of events were of the mildest severity grade, Grade 1 (according to CTCAE without need for intervention and partly without clinical symptoms), no advantage in terms of a hint of a greater benefit of SRS versus WBRT can be derived from this.

4.5.6 Results on health-related quality of life

SRS versus resection

In the included study Muacevic 2008, data on HRQoL were collected using the Quality of Life Core Questionnaire (QLQ-C30) and the associated module for malignancies of the brain (Quality of Life Questionnaire - Brain Cancer Module [QLQ-BN20]; former designation: QLQ-BCM20) of the European Organisation for Research and Treatment of Cancer (EORTC). Because these results were reported in a very limited manner, no conclusion on the comparison of treatment groups with each other was possible for this study.

Irrespective of these data, due to the risk of publication bias of a relevant magnitude for the comparison of SRS versus resection, no conclusion can be drawn with regard to a greater benefit or harm of either treatment option for HRQoL.

SRS versus WBRT

For the SRS versus WBRT comparison, HRQoL results were reported in 4 of the 6 studies included. Usable data were found in Kepka 2016 on the EORTC QLQ-C30 and EORTC QLQ-BN20. Here, a statistically significant difference in favour of the SRS-treated patients was

found only for the domains loss of appetite (as subscale of the QLQ-C30) and sleepiness (as subscale of the QLQ-BN20). However, neither difference was clinically relevant (Hedges' g: -0.78 [-1.46; -0.09] and -0.61 [-1.28; 0.06]).

The data on the generic instrument EuroQol 5 Dimensions (EQ-5D) Visual Analogue Scale (VAS) score on the health state of patients were not statistically significantly different in Hartgerink 2021. The results of the EQ-5D Health State as a descriptive health profile were not used because the reported sum score of the 5 dimensions recorded (or its change from baseline) does not allow a quantitative comparison of the treatment groups due to the lack of arithmetic properties of the response options. No data were reported for the optional collection of HRQoL data using EORTC QLQ-C30 planned in Hartgerink 2021, the associated module for brain tumours (QLQ-BN20), and the module for cancer-related fatigue (QLQ-FA13 [currently QLQ-FA12 with only 12 items]). In addition, the results of a post-hoc analysis of HRQoL recorded using the Linear Analogue Self-Assessment (LASA) and Functional Assessment of Cancer Therapy - Brain (FACT-Br) reported in Brown 2017 were not usable due to an insufficient response criterion (change of at least 10% from baseline values). Similarly, the EORTC QLQ-BN20 and Quality of Life Core Questionnaire in Palliative Cancer Care Patients (QLQ-15PAL) data reported in Raman 2020 could not be used because these results were reported exclusively across groups.

Because the usable HRQoL data in Hartgerink 2021 and Kepka 2016 were collected with different questionnaires with deviating domains and ranges of the scales, and because in Hartgerink 2021 only the mean change in HRQoL after 3 months compared with baseline was reported (with an unclear number of patients analysed) no meta-analytic summary of the results was performed for HRQoL.

With regard to the usable results of the two studies, no hint of greater benefit or harm of either treatment option could be derived for HRQoL for the comparison of SRS versus WBRT.

4.5.7 Results on length of hospital stay

SRS versus resection

In Muacevic 2008, the median length of hospital stay of the control group after resection was 18 days, whereas SRS in the intervention group was performed exclusively on an outpatient basis.

For this outcome, there is an obvious patient-relevant advantage of SRS (which can generally be performed in an outpatient setting) over resection (which requires hospitalization). Thus, irrespective of the risk of publication bias for the other outcomes, an indication of a greater benefit of SRS versus resection with regard to the length of hospital stay can be derived.

SRS versus WBRT

It can be assumed that both SRS and WBRT can generally be performed on an outpatient basis, but no data on length of hospital stay were reported for this comparison in any of the studies

included. Therefore, no hint of a greater benefit or harm of either treatment option can be derived for the length of hospital stay for the comparison of SRS versus WBRT.

4.6 Summarized assessment of results

Evidence map

The following Table 3 shows the evidence map in relation to patient-relevant outcomes.

Table 3: Evidence map in relation to patient-relevant outcomes

	Mortality	Morbidity				Health-related quality of life	Length of hospital stay
	All-cause mortality	Neuro-logical function	Cognitive function	Activities of daily living	Adverse events and treatment-related complications		
SRS vs. resection	No outcome-specific conclusion possible[a]						⇑[b]
SRS vs. WBRT[c]	⇔	–	⇗[d]	⇔	⇔	⇔	–[e]

⇑: indication of greater benefit or indication of lesser harm
⇗: hint of greater benefit or hint of lesser harm
⇔: no hint, indication, or proof; homogeneous result
-: no (usable) data reported.
a. Due to risk of publication bias of a relevant magnitude
b. Outcome-specific indication of greater benefit in favour of SRS exists independent of the risk of publication bias of the comparison.
c. The evidence presented refers equally to primary as well as postoperative treatment after prior resection of brain metastases.
d. The hint of a greater benefit of SRS versus WBRT was shown for memory performance as a subcomponent of cognitive function.
e. Both interventions can generally be delivered on an outpatient basis. The intervention-related burden on patients is much lower for single-session SRS than for WBRT with 5 to 15 sessions.

SRS: stereotactic radiosurgery; vs.: versus; WBRT: whole brain radiotherapy

Evaluation of the extent of unpublished data

As discussed in Sections 4.1 and 4.4, for Comparison 1 (SRS versus resection), there is 1 completed study with no reported results (NCT00460395 [9]) identified from the study registry search. Feedback from the sponsor suggests that the study was completed as reported in the study registry entry. However, transmission of the study results was declined. With 64 patients recruited, this study has an identical sample size as the included study with published results (Muacevic 2008); there is thus a risk of publication bias of a relevant magnitude. Therefore, irrespective of the basic advantage of outpatient SRS, it remains unclear what the evidence map would look like if all study data were available.

Weighing of benefits and harms

For the comparison of SRS versus resection, due to the completed study without reported results and the associated risk of publication bias of a relevant magnitude, no conclusive conclusion

across outcomes could be made regarding a greater or comparable benefit or harm of either treatment option. Because the modes of action of SRS and resection differ markedly in their invasiveness and the available study data also show a marked difference with respect to treatment duration, an outcome-specific indication exists of a greater benefit of SRS with respect to length of hospital stay, independent of the risk of publication bias. However, as it seems possible that these apparent advantages may be outweighed by disadvantages in other patient-relevant outcomes – especially with regard to mortality – no weighing of benefits and harms across outcomes is possible for this comparison without knowledge of the missing study data.

For the comparison of SRS versus WBRT in patients with one or a few brain metastases, neither a greater nor an at least comparable benefit of SRS could be demonstrated with regard to all-cause mortality. However, for memory performance as a subcomponent of cognitive function, there was a hint of a greater benefit in favour of SRS. In addition, compared with WBRT, single-session SRS has other patient-relevant treatment-inherent advantages: On the one hand, due to the routine single-session application, the treatment-related burden for the patients concerned is considerably lower than with fractionated WBRT, which comprises about 10 to 20 sessions. On the other hand, SRS can be applied again (especially in case of recurrences or newly emerging brain metastases), whereas WBRT should only be applied once due to its greater neurotoxicity [3]. Since there was no statistically significant difference in favour of either treatment option in the other outcomes, a hint of a greater benefit of single-session SRS versus WBRT is also derived in the overall evaluation across outcomes.

Evaluation of the potential of SRS as a necessary treatment alternative to resection

For the comparison of SRS versus resection, due to the risk of publication bias of a relevant magnitude, a conclusion regarding a greater benefit or harm can only be derived for the outcome of length of hospital stay (see “Evaluation of the extent of unpublished data”). Assuming a comparable effect with regard to overall survival, a potential of a necessary treatment alternative can be derived for SRS versus resection in patients with one or a few brain metastases due to the intervention-related lower invasiveness of SRS and the basic advantage of an outpatient setting (see weighing of benefit and harms).

4.7 Key points of a testing study comparing SRS versus resection

Since there is a potential of a necessary treatment alternative in the comparison of single-session SRS versus resection for patients with one or a few brain metastases, the following section outlines key points for a testing study.

The goal of the testing study is to demonstrate the noninferiority of SRS versus microsurgical resection in terms of overall survival in patients with one or a few brain metastases. In doing so, the existing evidence gap created by the completed RCT without reported results and the associated risk of publication bias can be closed by 1 testing study with a correspondingly large sample size. The following key points and assumptions are outlined for this testing study:

Study type

An RCT with a blinded outcome assessment of the secondary outcomes should be conducted. Blinding of patients and medical staff is not possible.

Target population

Patients with one or a few brain metastases who have a medical indication for both single-session SRS and microsurgical resection are to be included in the study. Several other factors should be considered (in particular, type of primary tumour, size or volume and intracranial location of the metastases, recurrence status, and presence of extracranial metastases).

Test intervention

In the test group, treatment of all brain metastases, if possible, using single-session SRS.

Appropriate control interventions

In the control group, microsurgical resection of all resectable brain metastases is performed. If clinically indicated, the resection may be followed by adjuvant WBRT.

Study design

The study objective is to demonstrate that in patients with one or a few brain metastases, single-session SRS is non-inferior to resection (possibly with adjuvant WBRT) in terms of all-cause mortality (non-inferiority question). Because SRS has a greater benefit in other outcomes because of its considerably lower invasiveness, overall survival shown to be comparable between SRS and resection would be sufficient to conclude a greater benefit of SRS across outcomes.

Thus, the primary outcome is all-cause mortality. The duration of follow-up should cover a period of at least 12 months from randomization or from the start of treatment.

Secondary outcomes to be recorded include, in particular:

- Morbidity outcomes (especially cognitive and neurological function; to be measured using disease-specific, validated instruments).
- HrQoL (to be measured using a disease-specific, validated instrument).
- AEs and treatment-related complications
- Unplanned hospitalization or hospital stay

The type and number of other treatment interventions related to the underlying disease (including systemic therapies for treatment of the primary tumour and treatments for progression and recurrence of brain metastases) or with potential impact on the outcomes to be recorded should be documented.

If a median survival of 10 months is assumed for both study groups (HR = 1.0), following the thresholds of known studies (Brown 2017 [12]: HR = 1.3; Kayama 2018 [18]: HR = 1.385; Roos 2011 [26]: HR = 1.25), an HR of 1.3 is suggested as a threshold for non-inferiority. To demonstrate this, about 600 patients (approximate estimate for the demonstration of non-inferiority by the testing study alone) would be needed, although under certain conditions, a smaller sample size could be sufficient or a testing study could even be completely omitted (see under "Prospects of success of a testing study").

The study should be a multicentre study. Since Muacevic et al [11] found strong treatment preferences on the part of both patients and physicians, study inclusion should ideally be carried out by centres or locally cooperating hospitals that offer both treatment methods. Currently, there are about 8 to 10 centres available in Germany that can provide both interventions (possibly in cooperation with other hospitals).

The study must be conducted in compliance with the rules of Good Clinical Practice (GCP).

Before the start of the testing study, the sample size must be calculated, taking into account the data available at that time.

On the basis of the assumed sample size of 600 patients and the number of possible study centres, it follows that a testing study can only produce meaningful results after clearly more than 10 years.

Study costs

For studies with a large sample size (in this case approx. 600 patients to be recruited) and high study-related additional expenses, study-specific expenses of approx. €4000 per participant can be estimated. Based on these assumptions, estimated study costs of about €2.4 million can be calculated. The figures for the cost estimate are of an exploratory nature and are not suitable as a basis for contractual cost agreements.

Prospects of success of a testing study

The conduct of a testing study appears to be difficult for 2 reasons: On the one hand, a very long study duration has to be expected due to considerable recruitment difficulties caused by preferences on all sides, which, among other things, led to study termination with a markedly reduced sample size in Muacevic 2008 [11]. Further studies were not able to recruit patients for this reason (e.g., NCT01295970 [27]). Second, the intersection of those patients who have both a medical indication for SRS and one for microsurgical resection seems to be small [8,26]. Therefore, the prospects of success of such a testing study with 600 patients to be included are considered to be very low.

Feedback from the sponsor of the study identified for the preliminary report without reported results suggests that this study (NCT00460395 [9]) was conducted and completed corresponding to the information in the study registry entry. To resolve the associated risk of publication bias,

complete submission of the data collected in this study is required, especially since, to the best of our knowledge, no other studies are ongoing for this comparison. Should the study sponsor in future – contrary to its previous statements – make the previously unpublished results available, this could possibly considerably reduce the sample size required for the testing study, depending on the characteristics of the results. Should a meta-analysis of the submitted mortality data together with the results from Muacevic 2008 even yield an overall estimate that, compared with the threshold proposed for the testing study (HR = 1.3), shows non-inferiority of SRS versus WBRT with regard to mortality, a testing study could be dispensed with completely.

Similarly, the need for and the size of a testing study depend on the choice of noninferiority threshold (see Chapter 5), so it would be useful to review the appropriateness of a threshold before or during the testing study.

5 Classification of the assessment result

SRS versus resection

For this comparison, 2 major difficulties arose that prevented a conclusive assessment: the risk of publication bias of a relevant magnitude and the fact that only discontinued studies were available (partly discontinued even before inclusion of the first patient), with consequently only few available data.

The completed but unpublished study conducted between 1998 and 2005 (NCT00460395 [9]) means that data for an assessment are only available for 50% of the total patients included in the two studies for this comparison. Due to the non-submission of data for NCT00460395, an assessment of the data available from Muacevic 2008 alone does not appear to be meaningful.

With regard to study data to be expected in the future, it should be added that the field of application of SRS seems to have shifted over the years. Whereas around the 2000s, SRS appeared to be investigated as a replacement for microsurgical resection, more current studies tend to focus on whether SRS can replace WBRT, which may explain why, to the best of our knowledge, there are currently no ongoing studies comparing SRS versus resection. Current guideline recommendations suggest that the intersection of patients with one or a few brain metastases who can be treated equally using SRS and resection should be considered small. Rather, the two procedures now complement each other, depending in particular on the size, location and symptoms of the brain metastases, as well as the general physical condition of the patients (e.g., KPS $\geq$ 60) and status or radiosensitivity of the respective primary tumour. Whereas single-session SRS is primarily indicated for a limited number of smaller brain metastases with a diameter of up to 3.5 cm and/or in the direct vicinity of critical brain structures (such as the brain stem) and for patients with a high risk of complications during anaesthesia, resection should be used primarily for larger brain metastases, i.e., 3 cm or more in diameter, and for necrotic or cystic changes or oedema-related effects of the tumour mass and associated neurological deficits [8]. For those patients who appear to be equally suitable for both procedures, the lower invasiveness and the much shorter treatment duration of SRS during the

limited remaining life expectancy in particular are likely to have a decisive influence on the personal preference of the choice of treatment. It is precisely this aspect that is repeatedly cited in the literature as a decisive hurdle in patient recruitment and thus as a major cause of premature discontinuation of studies (e.g. in Muacevic 2008).

The strong patient preference in favour of SRS can also be seen as an indication that many patients accept a possibly much shorter survival period after SRS compared with resection. Overall, this would mean that the non-inferiority threshold (HR of 1.3) set in Roos 2011 might be too strict. Overall, more liberal thresholds are quite common in medicine: In a systematic analysis of 111 non-inferiority studies on drugs, the median threshold for all-cause mortality was an HR of 1.5 [28]. In the present case, it would therefore be helpful to have preference measurements on the question as to whether, for example, a survival shortened by a maximum of 5 months (corresponding to a threshold value of about HR = 2 with an estimated 10-month survival time) appears justifiable, if one takes into account the lower invasiveness and the resulting avoidance of hospitalization and / or surgery-associated side effects. Smaller studies show at least that from the perspective of many patients, neurological and cognitive function are similarly important treatment goals as survival [29,30].

SRS versus WBRT

For the comparison of SRS versus WBRT, overall, the studies are heterogeneous. In addition to the permissible number of brain metastases and the sometimes unclear treatment of primary diseases or recurrences or progression, in particular the treatment approaches for SRS varied between the studies. Whereas in Kepka 2016 for example, in patients with relatively minor impairments, only the resection cavity of a pretreated single brain metastasis was irradiated postoperatively to prevent local recurrence, in Kayama 2018 only residuals of up to 4 resected brain metastases or additional unresected or newly appeared lesions were treated postoperatively and prophylactic irradiation of the resection cavity was omitted. Since in the second largest study of the comparison SRS versus WBRT (Brown 2017 with 194 patients) both treatment approaches were followed, a separate presentation of the results according to the respective postoperative treatment approach of SRS was not meaningful. Nor did separate analysis of the data according to pretreatment (status after resection versus no pretreatment) seem to be meaningful, because for Raman 2020 it remained unclear to what extent the patients had been pretreated, and the two studies without pretreatment of metastases (El Gantery 2014 and Hartgerink 2021) had very different inclusion criteria regarding the number of brain metastases allowed. Rather, it can be assumed that these different therapeutic indications and treatment regimens reflect the diversity of SRS use in current clinical practice and therefore no further specification of the results is meaningful or necessary.

Across studies, it can be assumed that all treatment approaches investigated in the studies included primarily pursue the goal of symptom control with preservation of cognitive or neurological function, as well as HRQoL, and less the goal of lower mortality. The results in Kepka 2016 narrowly show a statistically significant difference in favour of WBRT in direct comparison with SRS. However, the reasons for this study-specific effect, observed only in

Kepka 2016, remain unclear. One possible explanation could be that no information regarding concomitant systemic therapy of the underlying primary disease was available for this study. Thus, it remains unclear to what extent equal treatment between groups was ensured with this open study design. Furthermore, the proportion of patients with (prognostically worse) subtotal resection of the brain metastasis is higher in the SRS group (17%) than in the WBRT group (10%). The study authors themselves point out that the observed difference in survival for the patients included cannot be explained by a worse local effect of SRS in the tumour bed. Rather, the recurrence-preventing effect of WBRT in the other brain regions could be the primary cause of the clear effect.

Considering all 6 studies included, the upper limit of the 90% CI for the overall HR estimate was 1.68. Thus, the non-inferiority of SRS with respect to all-cause mortality could not be shown using the non-inferiority thresholds proposed in the literature for this comparison (e.g., upper limit of the 90% CI ≤ 1.385 [Kayama 2018]). For this reason, it is not possible to reliably conclude a comparable benefit between the two treatment options based on the study data alone. Therefore, to reduce this uncertainty, the results of the study with a high qualitative certainty of results (Brown 2017) were primarily considered to assess the outcome-specific evidence. Here, a point estimate in the range of zero effect was shown for all-cause mortality, as with the data from the largest study (Kayama 2018). The results of these two studies cannot resolve the uncertainty regarding a possible disadvantage in all-cause mortality. Nevertheless, this possible disadvantage must be contrasted with 2 important treatment-inherent advantages: On the one hand, the treatment-related burden for patients, who have limited remaining life expectancy, is considerably lower with single-session SRS than with fractionated WBRT. On the other hand, SRS can be applied again (especially in case of recurrences or newly emerging brain metastases), whereas WBRT should only be performed once due to its greater neurotoxicity. Overall, the available data are considered sufficiently reliable to derive a hint of a greater benefit of SRS versus WBRT across outcomes.

This approach is supported by the opinions from the hearing on the preliminary report that in all likelihood neither a testing study nor the currently ongoing studies will be able to resolve the above-mentioned uncertainty in the mortality data with regard to a comparable benefit of the two interventions in the future. Since single-session SRS has already become widely established in clinical practice as the standard of care for patients with ≤ 4 brain metastases in recent years [31-33], it is likely that preferences on all sides have further strengthened and thus recruitment difficulties in a testing study would be even more pronounced than in previous studies. In addition, it is unclear to what extent the results of the currently ongoing studies, which primarily include patients with ≥ 5 to up to 20 brain metastases and where in part SRS is performed both single and multiple times, can actually be applied to the present research question and contribute to the elimination of the aforementioned uncertainty.

Studies on the combined use of SRS and WBRT

In the course of study selection, Kondziolka 1999 [34-36] and the study RTOG 9508 [37,38], first published in 2004, were identified as further studies investigating SRS versus WBRT.

Contrary to the present commission, the study intervention (as with the third study arm from El Gantery 2014 [14]) was a combined therapy of SRS and WBRT. For patients with 1 to 3 (RTOG 9508) or 2 to 4 brain metastases (Kondziolka 1999), there was no statistically significant difference in terms of all-cause mortality (El Gantery 2014, Kondziolka 1999 [with imprecise data], and RTOG 9508) and in terms of acute toxicities (El Gantery 2014 [from Grade 2]) RTOG 9508 (from Grade 1 to 2), with very few patient-relevant data reported overall. However, in the RTOG 9508 study, despite identical WBRT radiation dose across groups (37.5 Gy distributed over 15 fractions), statistically significantly more patients in the intervention group (SRS plus WBRT) were affected by severe toxicities (Grade 3 to 4) than in the control group with WBRT alone.

In studies in which the combined use of SRS and WBRT was investigated in patients with 1 to 3 brain metastases in comparison to SRS alone, a relevant disadvantage of the combined use was shown, particularly with regard to cognitive function and partly also toxicity. In addition, for other patient-relevant outcomes such as all-cause mortality, there was no advantage of combined use (Aoyama 2006 [39], Chang 2009 [40], Brown 2016 [41]).

According to current recommendations (e.g., Congress of Neurological Surgeons [CNS] Guidelines 2019 [7] or National Comprehensive Cancer Network [NCCN] Guidelines 2021 [33]), the combination of the two procedures SRS + WBRT should only be used in isolated cases on the basis of these studies and is thus to be classified as clinically irrelevant.

For this reason, Roos 2011 [26] was not included in the present assessment. Here, the combined use of SRS + WBRT versus resection + WBRT was investigated. This showed non-inferiority with respect to mortality (HR threshold: 1.25) for the intention-to-treat population of the SRS test group versus the control group. With regard to HrQoL, a clinically relevant lower rate for loss of appetite was found using the QLQ-C30 than in the resection group. Due to the lack of relevance of the combined therapy of SRS + WBRT, these results were not used for the present report.

6 Conclusion

A total of 7 randomized controlled trials (RCTs) were included in the present assessment. These were assigned to 2 different comparisons, depending on the control intervention investigated.

For the comparison of single-session SRS versus microsurgical resection (Comparison 1), a treatment-inherent advantage of SRS with regard to length of hospital stay was found. However, due to the risk of publication bias of a relevant magnitude, no conclusion regarding a greater benefit or harm of either treatment option could be drawn for this comparison across outcomes. Nor could valid conclusions be drawn regarding a comparable benefit of SRS.

Due to the intervention-specific differences in invasiveness and length of hospital stay, the present results suggest that single-session SRS in patients with one or a few brain metastases may have the potential to be a necessary treatment alternative to resection. The prospects of

success of a testing study for this comparison must be considered very low due to the known recruitment problems.

For the comparison of single-session SRS versus WBRT (Comparison 2), data from a total of 6 randomized trials could be used, of which 1 had a high and 5 had a moderate qualitative certainty of results across outcomes. In terms of all-cause mortality, across studies, overall the data provide no hint of a greater benefit or harm of any of the treatment options. In addition, the available results do not suggest with sufficient certainty that SRS provides at least comparable overall survival versus WBRT. With regard to memory performance as a subcomponent of cognitive function, there was a hint of a greater benefit of SRS, but not for other components of cognitive function, such as speech fluency or executive functions. For the outcomes of activities of daily living, adverse events and treatment-related complications, and health-related quality of life, there was no hint of a greater benefit or harm of any of the treatment options. For the outcome of neurological function, no usable data were identified. Beyond the results reported in the studies, single-session SRS has treatment-inherent advantages over WBRT in terms of repeatable application of the intervention and in terms of treatment-related burden. Thus, a hint of a greater benefit of SRS can be also be derived for the comparison of single-session SRS versus WBRT in the overall assessment across outcomes.

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Please see full final report for full reference list.

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The full report (German version) is published under

https://www.iqwig.de/en/projects/n20-04.html

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April Week 2 2021,
- Ovid MEDLINE(R) Daily Update April 14, 2021

The following filters were adopted:

- RCT: Lefebvre [42] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)
- Systematic review: Wong [43] – High specificity strategy

#	**Searches**
1	Brain Neoplasms/sc [Secondary]
2	((brain* or cerebral*) adj3 metastas*).ti,ab.
3	(cavit* adj3 resection).ab,ti.
4	or/1-3
5	Radiosurgery/
6	(gamma* adj1 knife*).ti,ab.
7	(linac* or (linear* adj1 accelerator*)).ab,ti.
8	(cyber knife* or cyberknife*).ab,ti.
9	(stereotactic* adj1 radiosurg*).ti,ab.
10	or/5-9
11	and/4,10
12	Randomized Controlled Trial.pt.
13	Controlled Clinical Trial.pt.
14	(randomized or placebo or randomly or trial or groups).ab.
15	drug therapy.fs.
16	or/12-15
17	exp animals/ not humans/
18	16 not 17
19	cochrane database of systematic reviews.jn.
20	(search or MEDLINE or systematic review).tw.
21	meta analysis.pt.
22	or/19-21
23	11 and (18 or 22)
24	23 not (comment or editorial).pt.
25	24 and (english or german).lg.

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations April 14, 2021

#	**Searches**
1	((brain* or cerebral*) and metastas*).ti,ab.
2	(cavit* adj3 resection).ab,ti.
3	or/1-2
4	(gamma* adj1 knife*).ti,ab.
5	(linac* or (linear* adj1 accelerator*)).ab,ti.
6	(cyber knife* or cyberknife*).ab,ti.
7	radiosurg*.ti,ab.
8	or/4-7
9	and/3,8
10	(clinical trial* or random* or placebo).ti,ab.
11	trial.ti.
12	(search or meta analysis or medline or systematic review).ti,ab.
13	or/10-12
14	and/9,13
15	14 not (comment or editorial).pt.
16	15 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2021 April 14

The following filters were adopted:

- RCT: Wong [43] – Strategy minimizing difference between sensitivity and specificity
- Systematic review: Wong [43] – High specificity strategy

#	**Searches**
1	brain metastasis/
2	brain tumour/
3	metastasis/
4	and/2-3
5	((brain* or cerebral*) adj3 metastas*).ti,ab.
6	(cavit* adj3 resection).ab,ti.
7	or/1,4-6
8	exp radiosurgery/
9	gamma knife/
10	(gamma* adj1 knife*).ti,ab.
11	(linac* or (linear* adj1 accelerator*)).mp.
12	(cyber knife* or cyberknife*).mp.
13	(stereotactic* adj1 radiosurg*).ti,ab.
14	or/8-13
15	and/7,14
16	(random* or double-blind*).tw.
17	placebo*.mp.
18	or/16-17
19	(meta analysis or systematic review or MEDLINE).tw.
20	15 and (18 or 19)
21	20 not medline.cr.
22	21 not (exp animal/ not exp humans/)
23	22 not (Conference Abstract or Conference Review or Editorial).pt.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2021
- Cochrane Database of Systematic Reviews Issue 4 of 12, April 2021

#	Searches
#1	MeSH descriptor: [Brain Neoplasms] this term only and with qualifier(s): [secondary - SC]
#2	((brain* or cerebral*) near/3 metastas*):ti,ab
#3	(cavit* near/3 resection):ti,ab
#4	#1 or #2 or #3
#5	MeSH descriptor: [Radiosurgery] this term only
#6	(gamma* near/1 knife*):ti,ab
#7	(linac* or (linear* near/1 accelerator*)):ti,ab
#8	(cyber knife* or cyberknife*):ti,ab
#9	(stereotactic* near/1 radiosurg*):ti,ab
#10	#5 or #6 or #7 or #8 or #9
#11	#4 and #10
#12	#11 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#13	#12 not (*clinicaltrial*gov* or *who*trialsearch* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#14	#13 in Cochrane Reviews, Cochrane Protocols
#15	#13 in Trials

4. Health Technology Assessment Database

Search interface: INAHTA

#	Searches
1	((brain* OR cerebral*) AND metastas*) OR cavit*) AND (gamma OR knife OR linac* OR accelerator* OR cyberknife* or radiosurg*

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
(gamma knife OR cyber knife OR linear accelerator OR stereotactic radiosurgery OR single-fraction radiotherapy) AND (brain metastasis OR cerebral metastasis OR cavity resection OR acoustic neuroma)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
gamma knife OR cyber knife OR cyberknife OR linear accelerator OR linac OR stereotactic OR single-fraction radiotherapy (without Synonyms)