Project Title: *Radiation Therapy for Brain Metastases: A Systematic Review*

I. Background and Objectives for the Systematic Review

The development of secondary malignant growths has particular implications when cancer metastasizes to the brain. The management of brain metastases is challenging due to the effects of the disease and treatment on patients. The planned systematic review will determine the effects of radiation therapy to treat brain metastases.

Brain metastases are a common problem in cancer care, occurring in 10 to 30 percent of adult patients.[1] The apparent incidence of brain metastases is increasing as diagnostic tools are refined and advances in systemic therapy that improve survival may also be leading to an actual increase.[2, 3] The development of brain metastases may have substantial prognostic implications by causing neurologic symptoms or death.

Historically, patients with brain metastases had a poor prognosis, and little thought was given to determining each individual's prognosis and optimal treatment.[4] However, the patient population affected by brain metastases is heterogeneous, and recent studies have shown that prognosis can vary substantially.[5-8] Brain metastases occur with a variety of cancers, which may have different subtypes or molecular profiles that respond differently to treatment.[3] Primary tumors that most commonly metastasize to the brain are lung cancer (30-60% of all brain metastases), breast cancer (5-30% of brain metastases in women), and melanoma (5-21%); this systematic review will focus on these primary cancer types.[3]

Treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), conventional surgery, and systemic therapies. WBRT is administered to the entire brain, typically over multiple treatments (although hippocampal-avoidance WBRT is more selective regarding the dose for different areas of the brain). SRS is a treatment option that delivers precisely-targeted radiation to the brain metastases. Surgery for brain metastases aims to remove the tumor. Systemic therapy includes chemotherapy and immunotherapy regimens. Each of these treatment options may be considered alone or in combination. Finally, for some patients with a very poor prognosis, supportive care alone may be appropriate.[9]

Several guidelines for the management of brain metastases have been published.[10-15] The American Society of Radiation Oncology (ASTRO) published guidelines for the radiotherapeutic and surgical management of brain metastases in 2012. The ASTRO guidelines recommended using estimated prognosis and aims of treatment to guide management decisions. The use of histology-specific indices was recommended to estimate prognosis. For patients with good prognosis (expected survival of 3 months or more), the number, size and resectability of metastases were identified as important factors to consider. For patients with a single brain metastasis and good prognosis,

management options including surgery and WBRT or SRS, SRS alone, WBRT, or WBRT and SRS were included as potential options. For patients with multiple brain metastases and a good prognosis, WBRT, SRS alone, or WBRT and SRS were recommended options for consideration. For patients with poor prognosis (expected survival less than 3 months), palliative care with or without WBRT was recommended. Regarding radiation dose fractionation for WBRT, the guideline noted that no altered dose fractionation scheme improved survival or symptom control compared with the commonly used 30 Gy in 10 daily fractions or 20 Gy in 5 daily fraction schemes. The ASTRO guidelines highlighted the limited neurocognitive outcomes data available at the time, and recommended further trials to address this shortcoming.

The focus of this review is on radiation therapies, although the effects of combining other treatments with radiation will be considered.

For each of the available radiation treatments, several important clinical questions must be considered. Regarding WBRT, an updated review may provide additional information. on the optimal dose, fractionation, and technique (e.g., hippocampal avoidance WBRT). Pressing questions include the following: Does the efficacy of WBRT depend on tumor histology, and should treatment options be adapted accordingly? What are the benefits and harms of WBRT on neurocognition and quality of life that need to be communicated to patients and caregivers? Do co-interventions such as memantine mitigate the neurocognitive effects, and if so, should they be offered in conjunction with WBRT? Is there a benefit to adding SRS to WBRT? And does the addition of systemic therapy change the efficacy of WBRT? When determining treatment choice, how does the effectiveness of SRS compare to that of WBRT? Does the effectiveness depend on tumor type or the number or volume of brain metastases, and, if so, should the treatment plan be adapted accordingly? Does the effectiveness depend on tumor size or radiation dose and fractionation and, and again, should the treatment plan be adjusted accordingly?

For SRS, does the addition of systemic therapy change the efficacy of SRS so that it should be routinely offered? Several key questions must be considered for patients who undergo surgical resection of brain metastases. How do the outcomes compare among observation, postoperative WBRT, and SRS therapy to help patients decide on the best course of action? In addition, to decide on the best treatment approach, patients and providers need to evaluate existing evidence on whether the effectiveness varies with tumor type, size, or dose and fractionation.

In addition, updated information is needed on adverse events associated with the interventions to guide policy makers, clinicians, patients, and caregivers. Critical questions include the following: What adverse cognitive effects are to be expected after radiation treatment? What adverse effects of SRS do patients and caregivers need to consider, and how do they compare with those of WBRT? Does systemic therapy change the toxicity of treatment so that patients need to carefully weigh the advantages and disadvantages? In patients undergoing surgical resection, how do adverse events compare among those who also undergo postoperative WBRT or and SRS therapy, compared with observation alone, to inform decisions? Although aspects of these questions have been addressed in published systematic reviews,[11-13, 16-73] and there is some clinical guidance on the topic,[11-13, 70] our literature searches and stakeholder input indicated the need for an up-to-date, comprehensive evidence review on radiation therapy for brain metastases.

Purpose of the Review: The Agency for Healthcare Research and Quality (AHRQ) evidence report, commissioned and funded by the Patient-Centered Outcomes Research Institute (PCORI), will synthesize the available evidence on radiation therapy for brain metastases. The synthesis aims to support an update of the American Society for Radiation Oncology (ASTRO) guidelines.

II. Key Questions

The systematic review will be guided by the following Key Questions and subquestions:

Key Question 1: What is the effectiveness of WBRT, alone or in combination with SRS or systemic therapies, as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

    KQ1a. How does effectiveness vary by dose fractionation schedule and technique?
    KQ1b. How does effectiveness differ by patient prognosis and primary tumor site?
    KQ1c. How does effectiveness differ by the addition of systemic therapies?

Key Question 2: What is the effectiveness of SRS/fractionated stereotactic radiation as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

    KQ2a. How does effectiveness vary by dose fractionation schedule and technique?
    KQ2b. How does effectiveness differ by patient prognosis and primary tumor site?
    KQ2c. How does effectiveness differ by the addition of systemic therapies?

Key Question 3: What is the effectiveness (or comparative effectiveness) of postoperative SRS compared to WBRT, observation, or preoperative SRS in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

    KQ3a. How does effectiveness vary by dose fractionation schedule?

Key Question 4: What are the adverse effects (i.e., serious harms) of WBRT, SRS, and systemic therapies for patients with brain metastases (either alone or in combination)?

    KQ4a. Do adverse effects vary by important patient characteristics (i.e., age, performance status, patient prognosis, disease status, primary tumor site) or dose fractionation schedule and technique?

The evidence review will answer the review questions, summarizing the identified evidence across studies.

The key questions were posted for public comment in July 2019, and PCORI conducted a stakeholder call to discuss the comments in August 2019. The public comments primarily addressed the subquestions. In response, we have revised the subquestions to broaden the scope (e.g., "dose fractionation schedule" was changed to "dose fractionation schedule and technique"). In addition, all subquestions for Key Question 1 were also added to Key Question 2, and vice versa.

III. Analytic Framework

The analytic framework outlines the patient population, the interventions, and the outcomes that will be addressed in the evidence synthesis.

Figure 1. Analytic framework for radiation therapy for brain metastases
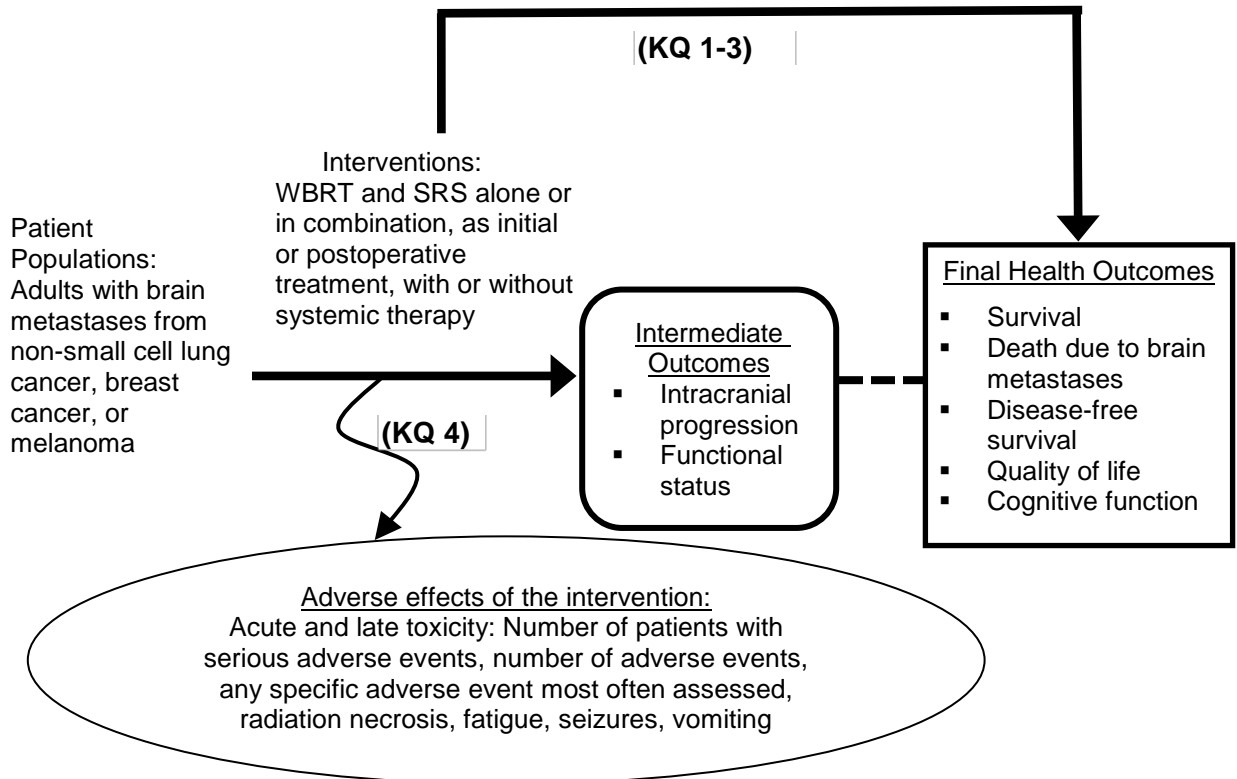
Abbreviations: KQ = Key Question, SRS = stereotactic radiosurgery, WBRT = whole brain radiation therapy

IV. Methods

The methods for this evidence review follow the Methods Guide for Evidence-based Practice Center (EPC) Program. The evidence report will be based on a systematic review that is outlined in this draft review protocol. The draft protocol is informed by key informants representing patients, care givers, patient advocates, healthcare providers, and evidence synthesis experts. Throughout, the evidence review team will be supported by a technical expert panel (TEP), a diverse panel of relevant stakeholders affected by the results of the evidence report. TEP members are not responsible for the content of the evidence report, but they provide the review team with important perspectives and advice on key components of the systematic review. The key questions, the protocol, and the draft report will be publicly posted to allow additional input.

Criteria for Inclusion/Exclusion of Studies in the Review: Table 1 describes the eligibility criteria in a PICOTSS (population, intervention, comparator, outcomes, timing, setting, and study design) framework.

Table 1: Eligibility criteria

PICOTS	Inclusion	Exclusion
Population	• Primary research studies that include a majority (50% or more) of adult patients with metastases in the brain resulting from non-small cell lung cancer, breast cancer, or melanoma	• Study samples comprising patients with cancer from other origins or primary brain tumors (e.g., glioblastomas) and pediatric samples
Interventions	• Studies evaluating radiation therapy, including WBRT and SRS alone or in combination, as initial or postoperative treatment, with or without systemic therapy (immunotherapy and chemotherapy) • Studies have to report on effects of radiation therapy in the 1990s or later	• Studies without WBRT or SRS treatment arms • Studies based exclusively on pre-1990 data
Comparators	• Studies comparing eligible interventions to other eligible interventions or other management approaches (no intervention; waitlist; delayed intervention [radiation to be given at a later time]; placebo; observation, watchful waiting, or surveillance; supportive care, palliative care, or steroid treatment; usual care; systemic therapy, immunotherapy, or chemotherapy; WBRT; SRS; surgery; different dose fractionation schedules; different radiation therapy approaches; different intervention combinations)	• Studies comparing only non-intervention features (e.g., comparing two patient subgroups)
Outcomes	• Studies reporting on patient health outcomes, such as o overall survival, progression-free survival	• Studies reporting only on therapy acceptance, provider variables (e.g., provider knowledge),

PICOTS	Inclusion	Exclusion
	recurrence/cancer control (local tumor control, intracranial control / complete response, partial response, stable response of all metastases); o symptom burden, health status or health-related quality of life; - functional status (physical, affective or neurocognition functions); o or adverse events, including acute and late toxicity (e.g., radiation necrosis, hair loss, or nausea) • Patient health outcomes may include patient- and caregiver-reported outcomes as well as clinical, physician assessed, and hospital record outcomes and measures may include quantitative as well as qualitative reports and no restrictions will be imposed regarding the specific measurement, metric, aggregation method (e.g., mean, proportion), or timepoint.	organizational measures (e.g., wait times), treatment utilization, or costs
Timing	• Studies will not be limited by the duration of the intervention or the length of follow up	• No exclusions apply
Setting(s)	• Inpatient and outpatient settings • Studies may include national and international settings	• Studies in resource-limited settings such as developing countries will be reviewed for comparability with US settings
Study design	**All KQs** • RCTs • Studies with results published in clinicaltrial.gov will be included regardless of whether a journal publication is available • English-language publications **KQ4**	• Studies without comparator (e.g., case studies) • Evaluations reported only in abbreviated format (e.g., in a conference abstract) and that are not registered in a research registry

PICOTS	Inclusion	Exclusion
	• Prospective experimental and observational studies (including non-randomized clinical trials and cohort studies comparing 2 or more intervention cohorts) of 200 patients or more or those that report a statistical power analysis for adverse events	• Studies exclusively reported in non-English publications will be retained as a resource but will not be eligible for inclusion • Systematic reviews will be retained for reference mining

Systematic reviews identified in the searches will be retained for reference mining, as an additional search strategy to identify potentially relevant studies.

The scope of the review is to evaluate radiation therapy for brain metastases in adults with melanoma, breast cancer, or non-small lung cancer. Although studies do not have to include these patients exclusively, they need to comprise the majority of patients (50% or more) for a study to be eligible for inclusion or results need to be presented for eligible cancer origin subgroups. As outlined, these cancer origins represent the most common cancer types in adults. While treatment for brain metastases from other primary cancers and in pediatric patients is equally important, it was deemed to be outside the scope of this project and should be addressed in future reviews.

In response to public comments on the posted review questions and preliminary inclusion criteria, we further restricted the studies of lung cancer brain metastases included in our review from those on all lung cancers to those including only patients with non-small cell lung cancer. This restriction will ensure a more homogeneous evidence base. A further change since the initial posting is the expansion of the eligible study designs for Key Question 4 from RCTs and observational studies to non-randomized experimental studies (e.g., clinical trials) as well. RCTs will be eligible for all key questions. The broader inclusion criteria for adverse event data take into account that rare adverse events are difficult to detect in smaller and short-term trials.

The inclusion criteria for outcomes include several categories of patient outcomes—including health, wellbeing, and side effects. Key informant input consistently emphasized the importance of patient-relevant outcomes. Patients need to weigh many aspects of treatment outcomes in addition to effectiveness and toxicity. These include effects on survival as well as quality of life during and after treatment. Functional status in general as well as retention of normal function—for example being able to care for one's child—are other key considerations for patients. Furthermore, the extent and the potential consequences of cognitive changes are very important considerations.

The TEP provided input on the restricting inclusion to studies reporting data from 1990 or later for intervention evaluations. Because of technological advances, especially in the area of imaging, results of older studies may not be relevant to current clinical decisions. We decided to exclude non-English studies, as non-English language studies may not contribute substantially to the evidence base in this research area. The inclusion of non-

English language studies can make the evidence base less transparent and ASTRO's guideline committee members may wish to use individual studies to formulate guidance.

Literature Search Strategies to Identify Studies to Answer the Key Questions: For this review we will search a variety of sources and apply a number of approaches to reduce potential reviewer errors and bias.

Sources: We will search the research databases PubMed, EMBASE, Web of Science, Scopus, and CINAHL. PubMed indexes a wide-range of biomedical literature, EMBASE emphasizes pharmacological and European journals, CINAHL includes nursing literature, and the Web of Science and Scopus index many technology journals.

We will reference-mine published systematic reviews to ensure that all relevant studies have been identified, i.e., rather than summarizing the reviews, we will use them as sources to identify available research studies. In addition, we will search the ECRI Guidelines Trust. To be included in the guideline database, guidelines have to be based on a systematic review of the evidence base. These guidelines will be helpful for placing the topic in the current policy context. We will also search the trial registry, clinicaltrials.gov. Increasingly, authors provide results in trial records, and particularly for new technology developments, trial registries are an important source of research information.

Furthermore, we will seek input from content experts on the TEP and experts serving as peer reviewers to help ensure that all relevant studies have been considered. Finally, a Supplemental Evidence And Data for Systematic review (SEADS) portal will be available and a Federal Register Notice will be posted for this review to ensure that all relevant evidence has been considered.

The draft search strategy for the databases is documented in Appendix A. The search strategies will be developed, executed, and documented by an experienced EPC librarian and peer-reviewed by an experienced methodologist. The literature search will be updated while the draft report is under peer review to ensure that the evidence included in the final report is up to date.

Screening Procedures: The citations will be screened by two independent literature reviewers. Citations deemed relevant by at least one reviewer will be obtained as full text. Full text articles and grey literature material will be screened by two independent reviewers against the explicit eligibility criteria. Any discrepancies will be discussed among the full review team.

Data Abstraction and Data Management: Data will be abstracted in an online data abstraction program for systematic reviews (DistillerSR). The abstraction forms include detailed instructions, definitions, and descriptions of categories to guide reviewers and to avoid ambiguities. The data abstraction will be checked for accuracy and consistency across studies by an experienced literature reviewer. The progress will be monitored frequently, any questions will be discussed among the review team, and additional guidance will be added to the online forms as needed.

The data abstraction process will capture all information published about the study, including information in the trial record, study protocol, interim analyses, main analysis,

or subgroup analyses. Multiple publications reporting on the same participant groups will be counted as single studies and will not enter the review analysis multiple times. Throughout the data abstraction process, publications reporting on the same participant group will be consolidated.

The data abstraction will include study-level variables that will be displayed in evidence tables and variables that will be used in the review analysis, critical appraisal of the study, or assessment of applicability:
- Study characteristics
  - Author and publication year of the main publication, country, PubMed entry link, trial registration number, additional publications reporting on the study, type of publication (journal manuscript, trial record), study status (e.g., early trial termination, preliminary data only), study design (parallel RCT, cluster RCT, clinical trial, cohort study), key question contribution (effects, adverse events, both), number of participants (study size indication), power calculation for non-inferiority analysis, and funding type (industry-funded, industry-funded but unrestricted grant, unclear, non-industry funding)
- Participant characteristics
  - Age (mean, standard deviation [SD]), gender (% female)
  - Diagnosis and cancer origin (melanoma; breast; non-small cell lung cancer; combination of melanoma, breast, and lung cancer; combination of cancer diagnoses)
  - Extent of metastases: number of metastases (mean, SD, other measures), volume of metastases (mean, SD, other measures), size of metastases (mean, SD, other measures)
  - Prognostic information (using the authors' classification, proportion of patients with poor or good prognosis, limited/favorable versus extensive brain metastases), prognosis classification for analysis (poor; unclear or mixed; good)
- Intervention arms
  - Intervention type (initial WBRS, initial SRS, post WBRS, post SRS), intervention description and technique (e.g., hippocampus-sparing), radiation dose and fractionation (e.g., 4000 cGy, 20 fractions bid), N randomized (or initially included), N analyzed
  - Co-treatment type (systemic therapy, additional WBRS or SRS, other), co-treatment description (e.g., chemotherapy, genotype-directed [yes/no], dose, duration), pre-treatment description (e.g., repeat SRS)
    - the most intense intervention will be classified as the main intervention
- Control and comparator arms
  - Type, description, dose, fractionation, and co-treatment
    - the least intense intervention will be classified as the main comparator
- Outcomes and results
  - Type (survival, quality of life, cancer-related effectiveness, functional status, cognitive effect, neurological function, adverse event, serious

adverse effects), measure description and origin (e.g. assessment scale, hospital record data), follow up calculated from start of the intervention, follow up calculated from end of the intervention, results at latest follow up comparing intervention and control arms

To facilitate comparisons across studies, we will standardize descriptions throughout (e.g., reporting intervention characteristics in a clear structure) and convert study characteristics to proportions (e.g., % female). Results will be converted to measure-independent variables such as standardized mean differences (SMDs), relative risks (RRs), and hazard ratios (HRs). All results will be presented together with the 95% confidence interval (CI).

Assessment of Methodological Risk of Bias of Individual Studies: All included studies will be assessed for key sources of bias that may have influenced the reported results. The assessments will be undertaken by one reviewer; a second reviewer will check the assessment for accuracy and consistency across studies.

Studies contributing to key question 1 through 3 will be assessed for the following sources of bias:

- Selection bias and risk of bias arising from the randomization process
- Performance bias and bias due to deviations from intended interventions
- Attrition bias and bias due to missing outcome data
- Detection bias and bias in measurement of the outcome
- Reporting bias and bias in selection of the reported results
- Other sources of bias

The risk of bias domain selection was informed by established risk of bias assessment approaches and the latest revision of the Cochrane Risk of Bias Tool (RoB 2) that is currently being applied in practice.[74] For *selection bias*, we will assess the randomization sequence and allocation concealment in RCTs as well as baseline differences and potential confounders in all studies. *Performance bias* will evaluate whether patient- or caregiver knowledge of the intervention allocation or circumstances such as the trial context may have affected the outcome, and whether any deviations from intended interventions were balanced between groups. *Attrition bias* will consider the number of dropouts, any imbalances across study arms, and whether missing values may have affected the reported outcomes. *Detection bias* will assess whether outcome assessors were aware of the intervention allocation, whether this knowledge could have influenced the outcome measurement, and whether the outcome ascertainment could differ between arms. *Reporting bias* assessment will include an evaluation of whether a pre-specified analysis plan exists (e.g., a published protocol), whether the numerical results likely have been selected on the basis of the results, and whether key outcomes were not reported (e.g., an obvious effectiveness indicator is missing) or inadequately reported (e.g., anecdotal adverse event reporting). In addition, we will assess *other potential sources of bias* such as early termination of trials, inadequate reporting of intervention details, and lack of intention-to-treat analyses. For the outcomes *functional status* and *quality of life* we will assess whether the outcome assessment used scales that have been validated for patients with brain tumors.

Given that the reliability and validity of the data are critical to answer key question 4 and adverse event reporting is often lacking in rigor, we will apply an additional critical appraisal tool for adverse event research, assessing the following:[75, 76]

- Data collection of adverse events
- Reporting of adverse events

The appraisal of the data collection method will evaluate the rigor of the adverse event assessment (e.g., use of a scale or checklist) and whether adverse events were collected actively (e.g., all participants were asked about the occurrence of specific harms) or passively (e.g., participants might have reported events at their discretion but without structured assessment or specific prompts). The reporting will also assess whether adverse events, including serious adverse events, were defined by the study authors. In addition, we will review whether the authors specified the number of participants affected by each type of adverse event (the number of adverse events per group is a problematic measure because some patients experience multiple events).

For each risk-of-bias criterion, we will assess high, moderate or unclear, and low risk of bias. In addition, literature reviewers will be asked to provide two overall summary assessments, one for the outcome domain, patient health outcomes, and one for adverse events. The assessments will determine the suitability of the study to answer key questions 1 through 3 and key question 4, respectively. The critical appraisal result will be used for sensitivity analyses where appropriate (e.g., excluding high risk of bias studies). The summary assessments will be incorporated into the strength of evidence assessment.

Data Synthesis: The results will be documented in a structured synthesis, supported by tables and figures, as well as, potentially, an online portal providing access to the included studies. The included studies will be broadly characterized based on study characteristics, participant details, intervention categories, identified comparator, and outcome categories employed in the published studies. Study details and results of all included studies will be documented in an evidence table that allows a concise overview. The included studies will likely represent a multitude of comparisons—such as SRS versus WBRT or SRS plus surgery versus surgery alone. Thus, we will map the network of available research for each of the four key questions to provide an overview of the evidence base. Figures will document the available interventions and comparators for each of the four key questions.

Analysis Plan for Key Questions 1-3: Key questions 1 through 3 aim to evaluate the effects and comparative effects of different radiation therapy interventions (WBRT, SRS, post-surgery treatment) and intervention combinations. For all studies where a similar comparator was employed (e.g., all evaluated interventions compared to surgery alone), individual and summary results will be shown in forest plots to answer the key questions (measure comparability permitted). The forest plots will provide a clear overview of the individual effects, study size, direction of effects across studies, and outliers in the study pool. The risk of bias will be integrated into the forest plots, where possible, and discussed when summarizing the forest plot results. We will present stratified forest plots that use broad categories (e.g., WBRT, WBRT plus SRS) to organize the research studies. To determine the comparative effects of interventions, we will use direct evidence from head-to-head comparisons (e.g., WBRS vs SRS). In addition, we will

explore effects through indirect comparisons across studies. Specifically, we will assess whether combination treatments of WBRT plus SRS are more effective than the individual interventions WBRT or SRS.

Given the evidence base and review questions, we will assess the suitability of the available research for network meta-analyses. A network analysis will be able to incorporate direct and indirect evidence. The suitability evaluation will assess homogeneity, transitivity, and consistency of the data. We will assess statistical heterogeneity and review the studies qualitatively for potential effect modifiers to ensure adequate homogeneity.

The subquestion section shows key study-level characteristics that will be explored in this review. To assess transitivity, we will establish the available connections for each review question and the resulting potential network, i.e., the different comparisons in the included trials. To assess the consistency assumption, we will calculate effect sizes for the direct comparisons and compare results with the indirect network comparison estimates to ensure that there are no clear violations of the assumption. If there are insufficient studies for connected networks for the outcomes of interest within key questions, we will use pairwise meta-analyses for summary effect estimates. Where only unique outcome, intervention, and comparator combinations can be found, we will list the individual study's point estimates and confidence intervals to address the key questions.

Outcome domains (e.g., survival, quality of life, functional status, metastases control, cognitive effects, neurological symptoms) for analyses were selected with input from the TEP. The TEP also provided input on outcome measures within outcome domains (e.g., disease free survival vs overall survival; see Box 1).

For eligible interventions for which no RCTs were identified, we will review the studies that met inclusion criteria for Key Question 4. However, the analysis will be interpreted with caution given the study limitations of observational and non-randomized studies.

Analysis plan for Key question 4: For Key Question 4, the synthesis will focus on key adverse events, also selected with input from the TEP. All analyses will consider the number of studies that assessed an adverse event and the observed events. The analysis will report on the presence and the absence of events.

For this key question, a number of study designs are eligible to contribute information. Given the nature of the clinical condition, we will assess the frequency of adverse events for an intervention compared to those for a similar control group, i.e., in comparison to a sample also affected by brain metastases but receiving a different or no treatment. We will aim to quantify the effects across studies, for example by calculating the number of patients with serious adverse events. We will highlight results with clear denominators (e.g., number of patients with the event) but may report on less clear denominators (e.g., number of events) as sensitivity analyses (individual patients can experience multiple adverse events).

Where studies report events for one arm, we will assume that no event occurred in the other study arm. We will use the authors' classification of serious adverse events. However, if not specified, we will apply the FDA definition of serious adverse events (death, life-threating, requiring hospitalization, disability or permanent damage,

congenital anomaly, requiring intervention to prevent permanent impairment, or other serious events).[77]

We will evaluate if RCT data for individual outcomes of interest exist that can be assessed in a network meta-analysis. In the absence of suitable data, we will aim to report pairwise comparisons for the selected outcomes to pool across studies. We anticipate that several outcomes of interest will be available only in individual studies: Even when studies report on the same outcome domain, differences in measurement may not allow us to combine studies (e.g., number of patients with fatigue reported in one study, mean differences in fatigue according to a rating scale in another study). However, throughout the report, we will use measures that facilitate comparisons between studies by converting the number of patients to proportions and using scale and measure-independent effect estimates such as relative risks.

Summary Across Studies: Throughout, where possible, study results will be synthesized in statistically pooled analyses to provide a numerical estimate of the size of the treatment effect across all available research evidence. For key question 1, the analysis will be centered around WBRT as initial treatment. For key question 2, the analysis will be centered around SRS as initial treatment. For key question 3, the analysis will focus on postoperative treatment. The analyses for key question 4 will address adverse events associated with all eligible interventions. The review will inform decisional dilemmas for patients (e.g., how do the intervention options compare, what are the effects on critical outcomes such as survival and quality of life after treatment; KQ1-3) and what adverse effects need to be expected (KQ4)? We will follow the principle of "first lumping, then splitting." While differentiation is important where studies are clinically and empirically different, given the many interventions and intervention combination, an analysis that is too granular will also not be adequate to answer the key questions. The network meta-analysis will be based on a frequentist approach using the netmeta package in R. Pair-wise meta-analyses will use random effects models with Knapp-Hartung corrections using the metafor package in R.[78] Heterogeneity will be documented using the I-squared statistic.

Initial analyses will aim to assess effects of the broad categories WBRT, SRS, WBRT plus SRS, and WBRT plus systemic therapies addressed in the key questions. More granular analyses will be based on the available comparisons reported in individual studies. The anticipated nodes across key questions are WBRT alone, hippocampal-avoidance WBRT, WBRT plus radiosensitizer, WBRT plus steroids, WBRT plus supportive care, WBRT plus memantine, hippocampal-avoidance WBRT plus memantine, WBRT plus chemotherapy, WBRT plus surgery, WBRT plus SRS, SRS alone, SRS plus immunotherapy, SRS plus surgery, surgery alone, immunotherapy alone, chemotherapy alone, and observation. Chemotherapy, immunotherapy, and radiosensitizer agents will be grouped for the analyses. The effects of different fractionations will be assessed in separate analyses to answer the subquestions. We will consult with ASTRO for interventions and groups of interventions of interest that may require additional or different nodes as the guideline plans develop. The combination of direct and indirect evidence will help with identifying the effects of the numerous treatment options.

Analyses will be conducted for the outcomes of interest identified in the strength of evidence assessment using the longest follow-up reported in the individual studies. Where outcome domains do not specify a metric or method of aggregation (e.g., mean differences or counts), we will choose the measure that allows the most studies to enter the analysis. Where heterogeneity is detected in the analyses, we will explore potential sources, for example through subgroup analyses. Specifically, we will evaluate the publication year as a potential source of heterogeneity. If a systematic effect is detected, the review needs to report sensitivity analyses (e.g., omitting older studies) or stratify the results by publication year cluster (e.g., 2010 to date). For comparisons that show statistically significant differences across studies, we will assess publication bias.[79] Where publication bias is indicated, we will use the trim and fill method to provide adjusted estimates. Sensitivity analyses will explore the robustness of key results, for example by excluding studies with high risk of bias.

Regardless of whether studies can be combined in a meta-analysis for a key question, all studies meeting inclusion criteria will be summarized in a narrative synthesis. The synthesis will be structured by interventions, comparators, and outcomes and will mirror the summary of findings table used for documenting the strength of evidence assessment. Summary results across studies will report the magnitude of the effect as well as the direction of effects.

Subquestions and subgroup analyses: Subquestions 1a-c, 2a-c, 3a, and 4a address intervention and patient characteristics. We will answer the subquestions with direct evidence whenever possible, for example where dose fractionation schedules have been compared in head-to-head comparisons. In addition, especially in the absence of direct evidence, we will compare studies indirectly. Where meta-analysis is possible, we will add variables of interest to the meta-analytic model to determine whether study findings vary systematically depending on the variable of interest (e.g., whether the addition of memantine systematically influences treatment outcomes). The meta-regressions may use qualitative categories (e.g., cancer sites) or quantitative operationalizations (e.g., number of metastases).

While we need to work with what is reported in identified studies, and studies may vary in their reporting of clinical categories (e.g., limited/favorable versus extensive brain metastases), the classifications will be clearly defined to ensure transparency.

We will aim to assess the effects of all characteristics called out in the subquestions (dose fractionation schedule and technique, patient characteristics, patient prognosis, primary tumor site, addition of systematic therapies) with the identified studies. Where analyses indicate systematic differences across studies, we will stratify studies and present data for the subgroups of interest separately. Furthermore, the TEP will provide input on important subgroups that should be differentiated. These subgroups will be established *a priori*.

Finally, we will present analyses according to how the evidence will be used. For example, if the ASTRO guideline committee plans to stratify recommendations by specific prognostic or tumor characteristics, we will provide an equivalent evidence summary for the area of interest.

Grading the Strength of Evidence for Major Comparisons and Outcomes: We will review the quality of evidence across studies for the selected outcomes, and the report will communicate the strength of evidence clearly.

For each key question, no more than seven outcomes will be considered, to ensure a concise overview. While the evidence table will report all patient outcomes and reported adverse events for the identified studies, it is critical that the strength of evidence assessment applies a concise set of evaluation criteria to describe the findings across studies. The report will include evidence statements for outcomes outlined in the box below. Outcome domains and individual outcome measures were selected for their relevance and importance, and the selection was made *a priori*—i.e., before the results of studies were known—to ensure an unbiased evidence assessment. As part of the review process, we gathered input from TEP members regarding potential outcomes of importance based on published studies and existing systematic reviews. Outcomes were ranked and checked for conceptual overlap.

Box 1: Key Outcomes

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Outcomes for Key Question 1-3
1. Overall survival (time to death, hazard ratio)
2. Quality of life as measured by validated scales
3. Cognitive function measured by any scale
4. Deaths due to brain metastases (number of patients, relative risk)
5. Disease-free survival (time to event, hazard ratio)
6. Intracranial progression/central nervous system failure (development of new or progressive metastases)
7. Functional status as measured by any scale or measure (standardized mean differences)

</td></tr>
<tr><td>

Outcomes for Key Question 4 (adverse events)
1. Number of patients with serious adverse events
2. Number of adverse events
3. Any specific adverse event most often assessed
4. Radiation necrosis
5. Fatigue
6. Seizure
7. Vomiting

</td></tr>
</table>

The outcomes will be used to compare between studies, and they will be used to answer the review questions. The summary of findings table will document the presence and the absence of evidence for each of the selected outcomes.

We will document the findings across studies as well as the quality of the evidence and our confidence in effect estimates. The strength of evidence assessment will use the AHRQ EPC program strength of evidence assessment categories. The strength of evidence assessment will take the following domains into account:
- Study limitations
- Directness

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- Consistency
- Precision
- Reporting bias

The domains are compatible with the GRADE group's criteria to downgrade the quality of evidence. Study limitations can be judged as low, medium, or high level of study limitations. Directness differentiates between direct (head-to-head) and indirect (across studies) evidence. The domain consistency differentiates among consistent, inconsistent, and unknown in the case of a result that is based on a single study and that has not been replicated yet. Precision is scored as either precise or imprecise, where precise indicates the result reflects a clinically unambiguous conclusion. Where results are primarily based on network meta-analysis findings, the strength of evidence assessment will be informed by the new Cochrane guidance on network meta-analysis.[80] The domain, reporting bias, differentiates between suspected bias (e.g., there is indication of publication bias, selective outcome reporting, or selective reporting of the analysis) and undetected bias (no bias indicated).

Each evidence statement will be assessed with these criteria to determine the overall strength of evidence. We will differentiate the following strength of evidence levels:
- High
- Medium
- Low
- Insufficient evidence

The categories communicate the confidence in the summary estimates for the findings across studies. The evidence statements will be drafted by one literature reviewer and discussed among the team to ensure quality control and consistency of interpretation.

We will highlight the direction and size of effect narratively in addition to providing the numerical point estimate and confidence interval. Throughout, results will be interpreted with caution. For comparative effectiveness assessments (Key Questions 1 through 3) that do not show a statistically significant difference between interventions, we will take evidence of statistical power to detect differences into account before making non-inferiority statements for interventions. The interpretation of Key Question 4 will take into account that frequentist approaches are problematic for rare adverse events (rare events require large samples to detect effects). Associations of adverse events with an intervention will be based on comparative evaluations, and events in the intervention group will be reported together with events documented in control groups not exposed to the intervention.

Key results that are based on measure-independent effect estimates, such as relative risks or standardized mean differences, will be translated into absolute effects or mean differences on known scales to help the interpretation of the effect. We will call out specific areas of uncertainty such as large effects that are not statistically significant (given that the number and the size of studies also affect statistical significance) and outline the range of possible effects consistent with the data. If we determine that there is 'insufficient' evidence, we will provide additional information about the specific data limitations to assist in decision-making.

The review will document available research as well as remaining research gaps. The gap presentation will be structured by key question and subquestion and will use the eligibility criteria framework PICOTSS to provide concrete recommendations for future research. The report discussion will compare our findings with those of existing reviews and guideline conclusions to place the results in context. We will highlight similarities and discrepancies for the reader.

Assessing Applicability: The applicability assessment will take the developing technology in the field of radiation therapy into account, review the samples included in the studies, and review the outcome measurement.

The review is purposefully limited to studies conducted in 1990 or later to ensure that the review can advise on current decisional dilemmas, and we will consider publication year as a potential source of heterogeneity. In addition, we will critically review the samples included in existing trials to determine how well they represent the population of patients with brain metastases. We will review the applicability of the assessment scales to the population of interest. The adverse event assessment will specifically include larger observational studies and not limit the assessment to findings in RCTs.

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VI. Definitions of Terms and Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ASTRO	American Society for Radiation Oncology
bid	twice daily
cGy	centigray
CI	confidence interval
EPC	Evidence-based Practice Center
GPA	Graded Prognostic Assessment
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
KQ	key question
N	number of participants
PCORI	Patient-Centered Outcomes Research Institute
PICOTSS	population, intervention, comparator, outcomes, timing, setting, study design
RCT	randomized controlled trial
RoB	risk of bias
RR	relative risk
SD	standard deviation
SMD	standardized mean difference
SRS	stereotactic radiosurgery
TEP	technical expert panel
US	United States
WBRT	whole brain radiation therapy

VII. Summary of Protocol Amendments

If the protocol needs to be amended, the EPC will give the date of each amendment, describe the change, and give the rationale in this section.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized the Key Questions after review of the public comments and seeking input from Key Informants and the Technical Expert Panel (TEP). This input was intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

None of the team members have any conflicts of interest to declare. EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XIII. Role of the Funder

This project was commissioned and funded by the Patient-Centered Outcomes Research Institute (PCORI) and executed under Contract No. 290-2015-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by PCORI, the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Search strategies: Radiation Therapy for Brain Metastases

PubMed
30 July 2019
((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR "gamma knife"[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
RCT filter OR systematic review filter
OR
((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR "gamma knife"[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
AND clinical trial*[tiab] OR cohort stud*[tiab] OR "case series"[tiab])
OR
((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR "gamma knife"[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
AND random[tiab] OR RCT[tiab] OR clinical trial*[tiab] OR cohort stud*[tiab] OR "case series"[tiab]
AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]))
OR
Guideline*[ti]
AND ((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR "gamma knife"[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
TOTAL: 4140

ECRI Guidelines Trust Search
"brain metastasis" = 6 = 1 unique (and relevant*)
"brain metastases" = 10 = 1 unique (and relevant)
"metastatic brain" = 8 all duplicates no unique or relevant
TOTAL = 2
*must contain something about radio/radiation or one of the specific terms from the pubmed searches.

Embase
3 September 2019
Limit: Article/Review/Article in Press
('brain'/exp OR brain:ab,ti) AND (metastasis:ab,ti OR metastatic:ab,ti OR metastases:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR carcinoma*:ab,ti OR metastasectomy:ab,ti)
AND
'radiosurgery'/exp OR radiation:ab,ti OR radiosurgery:ab,ti OR radiosurgeries:ab,ti OR radiotherapy:ab,ti OR radiotherapies:ab,ti OR irradiation:ab,ti OR wbrt:ab,ti OR 'gamma knife':ab,ti OR cyberknife:ab,ti OR linac:ab,ti
AND
([systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)
OR
('brain'/exp OR brain:ab,ti) AND (metastasis:ab,ti OR metastatic:ab,ti OR metastases:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR carcinoma*:ab,ti OR metastasectomy:ab,ti)
AND
'radiosurgery'/exp OR radiation:ab,ti OR radiosurgery:ab,ti OR radiosurgeries:ab,ti OR radiotherapy:ab,ti OR radiotherapies:ab,ti OR irradiation:ab,ti OR wbrt:ab,ti OR 'gamma knife':ab,ti OR cyberknife:ab,ti OR linac:ab,ti
AND
"clinical trial*" OR "cohort stud*"
Results: 2397
OR
Limit: Conference Abstract
('brain'/exp OR brain:ab,ti) AND (metastasis:ab,ti OR metastatic:ab,ti OR metastases:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR carcinoma*:ab,ti OR metastasectomy:ab,ti)
AND
'radiosurgery'/exp OR radiation:ab,ti OR radiosurgery:ab,ti OR radiosurgeries:ab,ti OR radiotherapy:ab,ti OR radiotherapies:ab,ti OR irradiation:ab,ti OR wbrt:ab,ti OR 'gamma knife':ab,ti OR cyberknife:ab,ti OR linac:ab,ti
AND
[randomized controlled trial]/lim
Results: 238

Scopus
Limit: Article, 1980-present, Human
TITLE-ABS((brain) AND (metastasis OR metastatic OR metastases OR cancer* OR neoplasm* OR carcinoma* OR metastasectomy)) AND (LIMIT-TO (DOCTYPE , "ar"))
AND
TITLE-ABS(radiation OR radiosurgery OR radiosurgeries OR radiotherapy OR radiotherapies OR irradiation OR wbrt OR "gamma knife" OR cyberknife OR linac)
AND (LIMIT-TO (DOCTYPE , "ar"))

AND
TITLE-ABS-KEY-AUTH("clinical trial*" OR "cohort stud*") AND (LIMIT-TO (
DOCTYPE , "ar"))
Results: 1635

Web of Science
Limit: Article, 1980-present Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI
(TS=(brain) AND TS=(metastasis OR metastatic OR metastases OR cancer* OR
neoplasm* OR carcinoma* OR metastasectomy))
AND
TS=(radiation OR radiosurgery OR radiosurgeries OR radiotherapy OR radiotherapies
OR irradiation OR wbrt OR "gamma knife" OR cyberknife OR linac)
Results: after duplicate removal: 717

CINAHL
1980-present; Academic Journals
(((MH "Brain") OR TI brain OR AB brain) AND (TI(metastasis OR metastatic OR
metastases OR cancer* OR neoplasm* OR carcinoma* OR metastasectomy) OR
AB(metastasis OR metastatic OR metastases OR cancer* OR neoplasm* OR
carcinoma* OR metastasectomy)))
AND
(MH "Radiosurgery") OR TI(radiation OR radiosurgery OR radiosurgeries OR
radiotherapy OR radiotherapies OR irradiation OR wbrt OR "gamma knife" OR
cyberknife OR linac) OR AB(radiation OR radiosurgery OR radiosurgeries OR
radiotherapy OR radiotherapies OR irradiation OR wbrt OR "gamma knife" OR
cyberknife OR linac)
AND
clinical trial* OR cohort stud*)
NOT
(SU Animal studies)
Results: 417 – after duplicate removal: 213

Results: 8,337