Guideline 21-4

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario

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An assessment conducted in January 2023 deferred review of Guideline 21-4. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 21-5 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/60751

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Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To provide the optimal organizational guidelines for facilities performing stereotactic radiosurgery (SRS) on patients with brain metastasis in Ontario.

TARGET POPULATION

Adult patients with brain metastasis eligible for SRS at centres in Ontario.

INTENDED USERS

This guideline is targeted for:

1. Clinicians involved in the organization and delivery of care for patients with brain metastases who are eligible to receive SRS in Ontario.
2. Administrators involved in the organization and delivery of care for patients with brain metastases who are eligible to receive SRS in Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1: Practice Team
The following members should be part of the multidisciplinary case conference (MCC) evaluating patient eligibility and performing SRS for patients with brain metastasis in Ontario • Radiation oncologist • Neurosurgeon • Medical physicist • Radiation therapist • Medical dosimetrist • Neuroradiologist
Qualifying Statements for Recommendation 1
• It is possible that one individual could fulfill both the responsibilities of the radiation therapist and medical dosimetrist, if the appropriate qualifications are obtained. • The clinical and imaging details of each SRS case must be discussed in an MCC. The MCC should be comprised ideally of a radiation oncologist, neurosurgeon, medical physicist, radiation therapist/medical dosimetrist, and a neuroradiologist. At a minimum, the radiation oncologist, neuroradiologist and, if available, a neurosurgeon and neuro-oncologist should be involved when discussing possible radiation necrosis versus tumour progression. • The members of the MCC listed above are in addition to the nurses and administrative staff who provide general support for all patients in the radiation oncology department

Recommendation 2: Qualifications and Responsibilities of the Multidisciplinary Team Members

The following are recommendations for the qualifications of the practitioners of the MCC and their associated responsibilities.

Radiation Oncologist

- Qualifications:
  - The radiation oncologist is accredited by a nationally or internationally recognized program or licensing board
  - Participation in a dedicated fellowship or course that provides technology-specific training is strongly recommended
  - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
  - Team leader, responsible for the selection of members of the SRS team
  - Oversee treatment of patient and sign off on treatment plan
  - Verification of target volume and normal tissues
  - Selection of patient positioning and immobilization
  - Participate in the monitoring and follow-up of patients post-SRS

Neurosurgeon

- Qualifications:
  - The neurosurgeon is accredited by a nationally or internationally recognized program or licensing board
  - Participation in a dedicated fellowship or course that provides technology-specific training is strongly recommended
  - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
  - It is recognized that a neurosurgeon may not be present at each SRS centre within Ontario; however, participation in the treatment decision-making team through an MCC is strongly recommended
  - In an ideal setting, the neurosurgeon would be involved in determining target volume and normal tissues, in particular for benign indications, functional indications, and complex metastasis including postoperative radiosurgery. It is recognized that this is not achievable at smaller centers without neurosurgery and in this situation at least one radiation oncologist must have sub-speciality training in SRS and lead that team.
  - Participation in the monitoring and follow-up of patients post-SRS

Neuroradiologist

- Qualifications:
  - The neuroradiologist is accredited by a nationally or internationally recognized program or licensing board
  - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
  - Participation in the development of imaging protocols required for SRS cases

- Reviewing pre- and post-procedure imaging
- Participation in the MCC

Medical Physicist

- Qualifications:
  - The qualified medical physicist is certified by the Canadian College of Physicists in Medicine or an equivalent national or international certification agency
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
- Responsibilities include:
  - Being knowledgeable of all technical aspects of an SRS program, which includes simulation, imaging, planning, equipment, treatment delivery, and verification of output calibration
  - Development of the technical quality assurance (QA) program including continual monitoring and associated documentation
  - Working with the radiation oncologists, radiation therapists, and medical dosimetrists to develop the optimal application of SRS and optimal treatment plan for a given patient
  - Being available for consultation for patient set-up and treatment delivery on the day of the treatment
  - Participating in the peer review process
  - Being knowledgeable of the radiation safety procedures
  - Ensure members of the SRS team have the necessary training to ensure the safe operation of the SRS program
  - Working with the information technology staff to ensure network connectivity and data backup procedures are in place
  - Being aware of all sources of uncertainty in SRS, including mechanical and dosimetric, and be able to provide mitigation strategies
  - Participating in continual education activities to maintain expertise and awareness of best practices and guidelines
  - Note: in some centres the medical physicist may also be responsible for SRS planning

Radiation Therapist

- Qualifications:
  - Medical Radiation Technologist (MRT[T]) graduate of a recognized radiation therapy program with registration with the appropriate provincial college
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
- Responsibilities of the radiation therapist must be clearly defined and may include the following:
  - Appropriate fabrication of effective patient immobilization devices
  - Patient treatment preparation for the SRS procedure, which includes patient positioning/immobilization
  - Performing and assessing pre-treatment imaging for treatment verification
  - Monitoring the patient during treatment
  - Delivering accurate SRS treatment after appropriate approvals
  - Patient care and side effect management
  - Organizing daily workflow of patients and staff
  - Performing daily QA and ensuring safe operation of the technology unit

- Performing emergency procedures adhering to protocols if necessary

Medical Dosimetrist

- Qualifications:
  - MRT(T) graduate of a recognized radiation therapy program with registration with the appropriate provincial college
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
  - Considered beneficial if experienced in treatment planning
- Responsibilities of the medical dosimetrist must be clearly defined and may include the following:
  - Working with the radiation oncologist and medical physicist in developing an effective SRS treatment plan for the patient
  - Ensuring all relevant volumetric patient image data are included in the treatment planning system (TPS)
  - Generate all appropriate technical documentation required to implement the treatment plan
  - Be available for the first treatment and assist with verification for subsequent treatments as necessary
  - Note: It is possible that one individual could fulfil both the responsibilities of the radiation therapist and medical dosimetrist, if the appropriate qualifications are obtained

Recommendation 3: Minimum applicable technologies

Predominant technologies that are employed in Ontario for the delivery of SRS include:

- Gamma Knife (GK),
- CyberKnife (CK) and
- Linear Accelerator (linac)

Qualifying Statements for Recommendation 3

- Other units may be available; however, in Ontario these are the most common units used for SRS delivery within the province.
- In addition, the recommendations and guidelines presented apply to any technology that a centre would use for SRS

Recommendation 4: Simulation

The following are recommendations for imaging needed both pre (i.e., simulation) and post (i.e., follow-up) SRS to ensure safe practice and patient safety.

- Simulation
  - Simulation (magnetic resonance imaging [MRI]) to treatment should be performed as close as possible to the treatment delivery date and optimally no longer than seven and certainly no more than 14 days (including weekend days and statutory holidays)
- MRI
  - Thin-slice volumetric MRI is recommended
  - Slice thickness no greater than 1 mm is recommended with in-plane resolution of no more than 1 mm × 1 mm. If 2 mm slice thickness is used then interpolation to 1 mm, and this is acknowledged to be dependent on the type of MRI scanner and image reconstruction
  - Spatial resolution should be sufficiently high for the brain metastases to be adequately visualized and contoured. This may differ according to the device used and, therefore, documents made available by the treatment unit manufacturer should be consulted
  - Signal-to-noise ratios and contrast-to-noise ratios should be sufficiently high for the brain metastases to be adequately visualized and contoured. This may differ according to the device used and, therefore, documents made available by the treatment unit manufacturer should be consulted
  - Minimal geometric distortion. This may differ according to the device used and, therefore, documents made available by the treatment unit manufacturer should be consulted
  - Head coil to accommodate head frame is recommended
  - Independent QA by the SRS medical physicist to ensure compliance with radiotherapy needs as they are independent of those per medical imaging
  - All aspects of image quality should be thoroughly investigated prior to use for SRS including (but not limited to): partial volume averaging, spatial distortion, motion artifacts, magnetic susceptibility artifacts, image reformatting, etc
- Computed tomography (CT)
  - Slice thickness of no greater than 1 mm is recommended
  - With or without contrast
  - In-plane pixel size of 1 mm × 1 mm or finer is recommended
  - All aspects of image quality should be thoroughly investigated prior to use for SRS including (but not limited to): partial volume averaging, spatial distortion, motion artifacts, image reformatting, etc
- Immobilization
  - Invasive head frame or dedicated frameless system manufactured for radiosurgery for all single fraction delivery. Hypofractionated SRS is a distinct entity regarding immobilization
  - Margins considered based on technology

Qualifying Statements for Recommendation 4

- The Working Group members recognize that the MRI recommendations are dependent on the scanner at the SRS centre; however, the recommendations for MRI imaging in this guideline should be viewed as the minimum achievable requirements for safe practice and patient safety
- Guidelines and recommendations for MRI in radiation oncology should be strictly followed to minimize the risks associated with geometric distortion especially if using a 3T scanner [1,2]
- In some instances, images may come from diagnostic departments that are not a part of the dedicated SRS centre. In these cases, special consideration should be given to those scans as they may not meet the minimum recommendation parameters for simulation
- In certain cases, patients may have MRI without any head frame or localization device and then MRI is co-registered to a stereotactic image set later in the process. In such cases, care should be taken to keep the patient as still as possible (minimize motion artifacts) and have their head as close to treatment orientation as possible
- For CT, sufficiently high spatial resolution and signal must be used in accordance with guidelines and recommendations [3,4]

Recommendation 5: Quality Assurance Systems

The following are recommendations for a QA system required for the safe operation of a SRS treatment unit in Ontario.

- The responsible medical physicist should determine that the appropriate testing procedure is used, and documentation is maintained
- Spatial accuracy: The accuracy and precision of delivery should be well-characterized and routinely tested for sub-millimetre targeting accuracy. For multileaf collimator-based delivery of multiple metastases, in particular when treating off-axis, specialized QA devices may be needed to verify the accuracy of radiation field placement throughout the angular range of gantry, collimator, and couch angles [5,6]. A positional end-to-end test for delivery accuracy is recommended that encompasses as much as the workflow as possible, from MRI, through to target delineation and treatment delivery
- Small field dosimetry: For reference dosimetry in linacs, standard protocols TG-51 and IAEA TRS-398 apply [7,8]. For GK, CK, tomotherapy, and cone-based treatments, recommendations as per TRS-483 using machine-specific reference (MSR) fields apply [9]. The differential detector response at small fields relative to the MSR field must be taken into account using Monte Carlo calculated corrections. Additionally, proper alignment and orientation of the detector with respect to the field are also important to consider in relative small field dosimetry

Qualifying Statements for Recommendation 5

- These recommendations are specific to SRS and are in addition to existing guidance documents made available by the treatment unit manufacturer and international and national guidelines [10-14]
- It is recommended that a medical physicist on the SRS team have dedicated small-field dosimetry training, whether through a certified medical physics training program, or by a combination of continuing education courses and direct training by experienced physicists with small-field dosimetry expertise.

Recommendation 6: Patient Follow-up
The following are strongly recommended for a follow-up program for SRS patients in Ontario: • Follow-up of SRS patients should consist of routine clinical visits for the first year (every 2-3 months); second and third year (every 3-4 months); and, thereafter, as determined by the MCC
Qualifying Statements for Recommendation 6
• A routine clinical visit incorporates a standard imaging examination – MRI and preferably with volumetric axial sequences • Interpretation of follow-up imaging should occur based on input from the radiation oncologist, neurosurgeon, and neuroradiologist when it is unclear that progression has occurred, i.e., presented at MCC prior to any further radiation decision • The follow-up treatment plan may be changed at the discretion of the MCC

Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To provide the optimal organizational guidelines for facilities performing stereotactic radiosurgery (SRS) on patients with brain metastasis in Ontario. This guideline document is not intended to present the evidence base for dose prescribing practices in the delivery of SRS for brain metastases. This literature should be reviewed separately and used to guide clinical management upon meeting the institutional guidelines set out in this document for the delivery of this treatment modality.

TARGET POPULATION

Adult patients with brain metastasis eligible for SRS at centres in Ontario.

INTENDED USERS

This guideline is targeted for:

1. Clinicians involved in the organization and delivery of care for patients with brain metastases who are eligible to receive SRS in Ontario.
2. Administrators involved in the organization and delivery of care for patients with brain metastases who are eligible to receive SRS in Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1: Practice Team
The following members should be part of the multidisciplinary case conference (MCC) evaluating patient eligibility and performing SRS for patients with brain metastasis in Ontario • Radiation oncologist • Neurosurgeon • Medical physicist • Radiation therapist • Medical dosimetrist • Neuroradiologist
Qualifying Statements for Recommendation 1
• It is possible that one individual could fulfill both the responsibilities of the radiation therapist and medical dosimetrist, if the appropriate qualifications are obtained • The clinical and imaging details of each SRS case must be discussed in an MCC. The MCC should be comprised ideally of a radiation oncologist, neurosurgeon, medical physicist, radiation therapist/medical dosimetrist, and a neuroradiologist. At a minimum, the radiation oncologist, neuroradiologist and, if available, a neurosurgeon and neuro-oncologist should be involved when discussing possible radiation necrosis versus tumour progression. • The members of the MCC listed above are in addition to the nurses and administrative staff who provide general support for all patients in the radiation oncology department
Key Evidence and Justification for Recommendation 1

The detailed requirements for human resources are the opinion of the Guideline Development Group (GDG), based on the resources that the group determined would be necessary to support the treatment of patients with SRS in Ontario oncology centres.

Interpretation of Evidence for Recommendation 1

The application of SRS requires the coordinated effort of an MCC of professionals who assume roles during the patient selection and treatment procedure. The MCC performing SRS should include the following individuals who have the credentials and responsibilities listed below. These are in addition to the nurses and administrative staff who provide general support for all patients in the radiology department.

Recommendation 2: Qualifications and Responsibilities of the Multidisciplinary Team Members

The following are recommendations for the qualifications of the practitioners of the MCC and their associated responsibilities.

Radiation Oncologist

- Qualifications:
    - The radiation oncologist is accredited by a nationally or internationally recognized program or licensing board
    - Participation in a dedicated fellowship or course that provides technology-specific training is strongly recommended
    - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
    - Team leader, responsible for the selection of members of the SRS team
    - Oversee treatment of patient and sign off on treatment plan
    - Verification of target volume and normal tissues
    - Selection of patient positioning and immobilization
    - Participate in the monitoring and follow-up of patients post-SRS

Neurosurgeon

- Qualifications:
    - The neurosurgeon is accredited by a nationally or internationally recognized program or licensing board
    - Participation in a dedicated fellowship or course that provides technology-specific training is strongly recommended
    - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
    - It is recognized that a neurosurgeon may not be present at each SRS centre within Ontario; however, participation in the treatment decision-making team through an MCC is strongly recommended
    - In an ideal setting, the neurosurgeon would be involved in determining target volume and normal tissues, in particular for benign indications, functional indications, and complex metastasis including post-operative radiosurgery. It is recognized that this is not achievable at smaller centers without neurosurgery and in this situation at least one radiation oncologist must have sub-speciality training in SRS and lead that team.
    - Participation in the monitoring and follow-up of patients post-SRS

Neuroradiologist

- Qualifications:
  - The neuroradiologist is accredited by a nationally or internationally recognized program or licensing board
  - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
  - Participation in the development of imaging protocols required for SRS cases
  - Reviewing pre- and post-procedure imaging
  - Participation in the MCC

Medical Physicist

- Qualifications:
  - The qualified medical physicist is certified by the Canadian College of Physicists in Medicine (CCPM) or an equivalent national or international certification agency
  - Considered beneficial if trained in an SRS specific setting (within an SRS program or by a supervised vendor)
- Responsibilities include:
  - Being knowledgeable of all technical aspects of an SRS program, which includes simulation, imaging, planning, equipment, treatment delivery, and verification of output calibration
  - Development of the technical quality assurance (QA) program including continual monitoring and associated documentation
  - Working with the radiation oncologists, radiation therapists, and medical dosimetrists to develop the optimal application of SRS and optimal treatment plan for a given patient
  - Being available for consultation for patient set-up and treatment delivery on the day of the treatment
  - Participating in the peer review process
  - Being knowledgeable of the radiation safety procedures
  - Ensure members of the SRS team have the necessary training to ensure the safe operation of the SRS program
  - Working with the information technology staff to ensure network connectivity and data backup procedures are in place
  - Being aware of all sources of uncertainty in SRS, including mechanical and dosimetric, and be able to provide mitigation strategies
  - Participating in continual education activities to maintain expertise and awareness of best practices and guidelines
  - Note: in some centres the medical physicist may also be responsible for SRS planning

Radiation Therapist

- Qualifications:
  - Medical Radiation Technologist (MRT[T]) graduate of a recognized radiation therapy program with registration with the appropriate provincial college
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
- Responsibilities of the radiation therapist must be clearly defined and may include the following:

- Appropriate fabrication of effective patient immobilization devices
- Patient treatment preparation for the SRS procedure, which includes patient positioning/immobilization
- Performing and assessing pre-treatment imaging for treatment verification
- Monitoring the patient during treatment
- Delivering accurate SRS treatment after appropriate approvals
- Patient care and side effect management
- Organizing daily workflow of patients and staff
- Performing daily QA and ensuring safe operation of the technology unit
- Performing emergency procedures adhering to protocols if necessary

Medical Dosimetrist

- Qualifications:
  - MRT(T) graduate of a recognized radiation therapy program with registration with the appropriate provincial college
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
  - Considered beneficial if experienced in treatment planning
- Responsibilities of the medical dosimetrist must be clearly defined and may include the following:
  - Working with the radiation oncologist and medical physicist in developing an effective SRS treatment plan for the patient
  - Ensuring all relevant volumetric patient image data are included in the treatment planning system (TPS)
  - Generate all appropriate technical documentation required to implement the treatment plan
  - Be available for the first treatment and assist with verification for subsequent treatments as necessary
  - Note: It is possible that one individual could fulfil both the responsibilities of the radiation therapist and medical dosimetrist, if the appropriate qualifications are obtained

Qualifying Statements for Recommendation 2

- Responsibilities may be reassigned where appropriate supposing all qualifications and training standards are met
- Support for continuing education for personnel may also be beneficial

Key Evidence and Justification for Recommendation 2

Recommendations for the minimum skill set and experience for SRS team members that perform SRS in Ontario was the consensus of the GDG, based on currently accepted definitions for these specialities in Ontario. These recommendations are also in keeping with other North American standards for SRS facilities [15].

Recommendation 3: Minimum applicable technologies

Predominant technologies that are employed in Ontario for the delivery of SRS include:

- Gamma Knife (GK),
- CyberKnife (CK) and
- Linear Accelerator (linac)

Qualifying Statements for Recommendation 3

- Other units may be available; however, in Ontario these are the most common units used for SRS delivery within the province.
- In addition, the recommendations and guidelines presented apply to any technology that a centre would use for SRS

Key Evidence and Justification for Recommendation 3

These recommendations are the consensus of the Working Group members based on the current technologies that are available in Ontario.

Recommendation 4: Simulation

The following are recommendations for imaging needed both pre (i.e., simulation) and post (i.e., follow-up) SRS to ensure safe practice and patient safety.

- Simulation
    - Simulation (magnetic resonance imaging [MRI]) to treatment should be performed as close as possible to the treatment delivery date and optimally no longer than seven and certainly no more than 14 days (including weekend days and statutory holidays)
- MRI
    - Thin slice volumetric MRI is recommended
    - Slice thickness no greater than 1 mm is recommended with in-plane resolution of no more than 1 mm × 1 mm. If 2 mm slice thickness is used then interpolation to 1 mm, and this is acknowledged to be dependent on the type of MRI scanner and image reconstruction
    - Spatial resolution should be sufficiently high for the brain metastases to be adequately visualized and contoured. This may differ according to the device used and, therefore, documents made available by the treatment unit manufacturer should be consulted
    - Signal-to-noise ratios and contrast-to-noise ratios should be sufficiently high for the brain metastases to be adequately visualized and contoured. This may differ according to the device used and, therefore, documents made available by the treatment unit manufacturer should be consulted
    - Minimal geometric distortion. This may differ according to the device used and, therefore, documents made available by the treatment unit manufacturer should be consulted
    - Head coil to accommodate head frame is recommended
    - Independent QA by the SRS medical physicist to ensure compliance with radiotherapy needs as they are independent of those per medical imaging
    - All aspects of image quality should be thoroughly investigated prior to use for SRS including (but not limited to): partial volume averaging, spatial

distortion, motion artifacts, magnetic susceptibility artifacts, image reformatting, etc
- Computed Tomography (CT)
  - Slice thickness of no greater than 1 mm is recommended
  - With or without contrast
  - In-plane pixel size of 1 mm × 1 mm or finer is recommended
  - All aspects of image quality should be thoroughly investigated prior to use for SRS including (but not limited to): partial volume averaging, spatial distortion, motion artifacts, image reformatting, etc
- Immobilization
  - Invasive head frame or dedicated frameless system manufactured for radiosurgery for all single fraction delivery. Hypofractionated SRS is a distinct entity regarding immobilization
  - Margins considered based on technology

Qualifying Statements for Recommendation 4

- The Working Group members recognize that the MRI recommendations are dependent on the scanner at the SRS centre; however, the recommendations for MRI imaging in this guideline should be viewed as the minimum achievable requirements for safe practice and patient safety
- Guidelines and recommendations for MRI in radiation oncology should be strictly followed to minimize the risks associated with geometric distortion especially if using a 3T scanner [1,2]
- In some instances, images may come from diagnostic departments that are not a part of the dedicated SRS centre. In these cases, special consideration should be given to those scans as they may not meet the minimum recommendation parameters for simulation
- In certain cases, patients may have MRI without any head frame or localization device and then MRI is co-registered to a stereotactic image set later in the process. In such cases, care should be taken to keep the patient as still as possible (minimize motion artifacts) and have their head as close to treatment orientation as possible.
- For CT, sufficiently high spatial resolution and signal must be used in accordance with guidelines and recommendations [3,4]

Key Evidence and Justification for Recommendation 4

The time from simulation to treatment interval recommendation was based on the combined experience of the Working Group members as well as accepted practice within the SRS community. The evidence presented below was not systematically searched, but was 'indirect' evidence provided by the Working Group to justify Recommendation 4. Two studies, provided by the Working Group, evaluated the optimal time interval between simulation and treatment [16,17]. In a study by Seymour et al [16], 82 patients with 151 brain metastasis treated with SRS were evaluated. The median time from MRI to treatment was 11 days (range, 6-23 days). Local freedom from progression (LFFP) was longer in metastases with an MRI performed less than 14 days before treatment (p=0.0003). The six- and 12-month LFFP rates were 95% and 75% for metastasis with an interval of less than 14 days from MRI to treatment compared with 56% and 34% for metastases with an MRI greater than 14 days before treatment, respectively. On multivariate analysis, LFFP remained significantly shorter for metastases with an MRI ≥14 days from the time of SRS (p=0.002, Cox proportional hazards; hazard ratio, 3.4; 95% confidence interval, 1.6 to 7.3) [16].The second study by Salkeld et al. [17] aimed to determine if there were changes in brain metastasis or resection cavity volumes according to the time interval between MRI imaging and the SRS treatment, and whether these changes led to a change in patient management. Thirty-four patients with 59

lesions had a planning MRI and a second MRI within 24 hours prior to SRS. The intent was to determine if a change in management was required based on the results of the second MRI. The median time between the first MRI and second MRI was seven days. In the per patient analysis, 41% (9 of 22) of patients with a seven days or less time interval between scans required a change in management; among those patients with a time interval of eight days or more between scans, 78% (7 of 9) required a change in management [17].

Brain metastases SRS relies completely on MRI for target delineation and localization. Depending on how small a lesion a centre is willing to treat, the MRI scanning parameters must be set accordingly with sufficiently high spatial resolution and signal for the brain metastases to be adequately visualized and contoured. In addition, there should be discussion with the neuroradiologist as to the amount of Gadolinium contrast, type of Gadolinium, and timing of administration to ensure optimal visualization of metastases. Of particular concern for MRI is the potential for geometric distortion, which could lead to an erroneous localization of a brain metastasis if present and unaccounted for [18]. High field strengths (1.5T or 3T) are typically required to detect small brain metastases with sufficient detail for delineation. Guidelines and recommendations for MRI in radiation oncology should be strictly followed to minimize the risks associated with geometric distortion especially if using a 3T scanner [1,2]. Imaging considerations include, but are not limited to, partial volume averaging, two-dimensional versus three-dimensional (3D) acquisition, pixel size, slice thickness, distance between slices, image reformatting for the TPS, spatial distortion and image warping, motion artifacts, and magnetic susceptibility artifacts. As an example, a radiation oncology department in Toronto uses a full 3D T1-weighted acquisition sequence (post-gadolinium injection) with interleaved 2 mm slice thickness (reformatted to 1 mm) and 0.5 mm in-plane pixel size using a 1.5T MRI. A specific QA process by medical physics is required to determine suitability of the MR images as the QA measures are distinct from medical imaging. The MRI to treatment time interval should be as short as possible, ideally no more than seven and certainly no more than 14 days as a maximum [16,39]. The head coil used on MRI should accommodate whatever immobilization/localization device is being used [19]. In certain cases, patients may have MRI without any head frame or localization device and then MRI is co-registered to a stereotactic image set later in the process. In such cases, care should be taken to keep patient as still as possible (minimize motion artifacts) and have their head as close to treatment orientation as possible. Most SRS systems require that the scan volume spans the entire head, extending one to two axial slices beyond the top of the head, and down to the level of C1 or C2 depending on the system.

The use of CT alone for brain metastases SRS is not common. As with MRI, sufficiently high spatial resolution and signal must be used in accordance with guidelines and recommendations [3,4]. CT is typically geometrically robust but adhering to guidelines and reports on CT QA is required. As an example, a radiation oncology department in Toronto uses a 1 mm slice thickness and 0.6-0.7 mm in-plane pixel size.

Recommendation 5: Quality Assurance Systems

The following are recommendations for a QA system required for the safe operation of a SRS treatment unit in Ontario:

- The responsible medical physicist should determine that the appropriate testing procedure is used, and documentation is maintained
- Spatial accuracy: The accuracy and precision of delivery should be well-characterized and routinely tested for sub-millimeter targeting accuracy. For multileaf collimator (MLC)-based delivery of multiple metastases, in particular when treating off-axis, specialized QA devices may be needed to verify the accuracy of radiation field placement throughout the angular range of gantry, collimator, and couch angles [5,6]. A positional end-to-end test for delivery accuracy is recommended that encompasses as much as the workflow as possible, from MRI, through to target delineation and treatment delivery
- Small field dosimetry: For reference dosimetry in linacs, standard protocols TG-51 and IAEA TRS-398 apply [7,8]. For GK, CK, tomotherapy, and cone-based treatments, recommendations as per TRS-483 using machine-specific reference (MSR) fields apply [9]. The differential detector response at small fields relative to the MSR field must be taken into account using Monte Carlo calculated corrections. Additionally, proper alignment and orientation of the detector with respect to the field are also important to consider in relative small field dosimetry

Qualifying Statements for Recommendation 5

- These recommendations are specific to SRS and are in addition to existing guidance documents made available by the treatment unit manufacturer and international and national guidelines [10-14]
- It is recommended that a medical physicist on the SRS team have dedicated small-field dosimetry training, whether through a certified medical physics training program, or by a combination of continuing education courses and direct training by experienced physicists with small-field dosimetry expertise.

Key Evidence and Justification for Recommendation 5

These recommendations are the consensus of the Working Group and are specific to SRS centres in Ontario. Regardless of technology, the success of an SRS program hinges on a thorough and ongoing QA program to ensure that the treatment unit is in compliance with the recommendations of the treatment unit manufacturer and within specified clinical tolerances based on international and national guidelines and recommendations [10-14].

Recommendation 6: Patient Follow-up

The following are strongly recommended for a follow-up program for SRS patients in Ontario:

- Follow-up of SRS patients should consist of routine clinical visits for the first year (every 2-3 months); second and third year (every 3-4 months); and, thereafter, as determined by the MCC

Qualifying Statements for Recommendation 6

- A routine clinical visit incorporates a standard imaging examination – MRI and preferably with volumetric axial sequences
- Interpretation of follow-up imaging should occur based on input from the radiation oncologist, neurosurgeon, and neuroradiologist when it is unclear that progression has occurred, i.e., presented at MCC prior to any further radiation decision
- The follow-up treatment plan may be changed at the discretion of the MCC

Key Evidence and Justification for Recommendation 6

The surveillance recommendation was the consensus of the Working Group members and further supported by a systematic review of the evidence detailing the incidence and onset of radiation necrosis (RN) in SRS patients. The evidence available did not specifically evaluate the optimal follow-up imaging interval; however, detail on MRI surveillance program post-SRS as well as the onset and incidence of RN were evaluated to aid in determining the optimal follow-up regimen. The incidence of adverse radiation effects (ARE), including RN, varied between studies, ranging from 0-64.5%. Onset of RN ranged from 3-33.2 months post-SRS, with most occurring after three months post-SRS. Close clinical and radiographic surveillance is required following SRS due to the risk of treatment failure as well as the development of symptomatic RN, which can occur in 5-10% of patients [20]. Distinguishing between recurrence and post-treatment changes including RN may often be difficult requiring specialized MRI such as MR spectroscopy and MR perfusion imaging. The Working Group members weighed the available evidence as well as their clinical experience and determined that the optimal follow-up SRS program should consist of routine clinical visits for the first year (every 2-3 months); second and third year (every 3-4 months); and, thereafter, as determined by the MCC. Based on the incidence and onset of RN in the evidence above as well as the combined clinical experience of the Working Group members, the Working Group hypothesizes that this program would lead to better patient outcomes in the absence of a randomized controlled trial (RCT) to determine the optimal follow-up intervals.

KEY EVIDENCE AND JUSTIFICATION FOR RECOMMENDATIONS

The detailed requirements for human resources are the opinion of the guideline development group, based on the resources that the group determined would be necessary to support the treatment of patients with SRS in Ontario oncology centres**.**

Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of GDGs in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and the Radiation Treatment Program is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

It has been demonstrated in the literature that SRS is a viable option for the management of patients with limited (1-4) brain metastasis [21,22]. At present, high-level care is being provided at several centres within Ontario. As a result, the Radiation Treatment Program sponsored this topic based on an identified need for guidance to inform the process and to address safety issues related to the delivery of radiotherapeutic services for patients with brain metastases in Ontario.

GUIDELINE DEVELOPERS

This guideline was developed by the SRS for Brain Metastasis GDG (Appendix 1), which was convened at the request of the Radiation Treatment Program.

The project was led by a small Working Group of the SRS for Brain Metastasis GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in neuro-oncology, radiation oncology, radiation therapy, medical physics, and health research methodology. Other members of the SRS for Brain Metastasis GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [23,24]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [25] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigor and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

Patient and Caregiver-Specific Consultation Group

Four patients/survivors/caregivers participated as Consultation Group members for the SRS for the brain metastasis Working Group. They reviewed copies of the project plan/draft recommendations and provided feedback on its/their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The SRS for Brain Metastasis GDG would like to thank the following individuals for their assistance in developing this report:

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- Sara Miller for copy editing.

Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario

Section 4: Evidentiary Base

INTRODUCTION

Approximately 10-30% of cancer patients will develop brain metastases. As metastatic patients are living longer due to novel systemic targeted therapies and immunotherapy, the incidence of brain metastases will only continue to increase while the extracranial disease burden remains controlled. As a result, the intent of therapy for patients with brain metastases is no longer short-term palliative gain associated with whole brain radiotherapy (WBRT), but definitive treatment with SRS with the intent to maximize local control and minimize adverse effects on patient neurocognition and quality of life.

In 2019, the evidence supports SRS, and not WBRT, as first-line therapy for patients presenting with up to four brain metastases, good performance status, and control of extracranial disease [21,26-28]. The randomized trials and meta-analyses conclude that patients have superior neurocognitive function, quality of life, and local tumour control when treated with SRS alone. Furthermore, there is no survival detriment associated with reserving WBRT as a salvage therapy as needed [21]. However, SRS alone is associated with an increased risk of distant brain failure (30-50% with SRS alone as opposed to approximately 20% with WBRT) and, as a result, treatment with SRS alone demands vigilant follow-up with serial MRIs to diagnose new metastases and offer salvage treatments as indicated. Lastly, although SRS is effective in tumour control, it can cause symptomatic RN in approximately 5-10% of patients. Therefore, vigilant clinical and MRI follow-up is required in addition to multidisciplinary management to avoid the life-threatening consequences of mismanaged RN [29].

As a result of the clinical comparative evidence and patient awareness/preference favouring SRS alone, there are increasing demands on cancer centres across the province to offer SRS [30]. There is also evidence that availability of SRS on site influences the patterns of care and, therefore, a provincial need exists to improve access to SRS at regional cancer centres to ensure equitable care [31]. The technical challenge lies in the complexity of delivering SRS, and adherence to stringent requirements with respect to delivery standards. As a result, a significant investment by radiotherapy departments is needed to ensure appropriate equipment and training. Clinical challenges include access to specialized technical and clinical training; hospital resources to ensure appropriate care for these patients as admissions and neurosurgical evaluation are not infrequent; access to specialized MRI within a suitable time period from the time the treatment decision is made and for post-SRS surveillance; and creating an MCC to evaluate not only eligibility for SRS but review of follow-up imaging to ensure appropriate diagnoses if radiation necrosis versus tumour progression is suspected. Ultimately, the care pathway has changed from a more passive management approach with WBRT and palliative care, to an active management approach requiring a significant commitment of specialized care.

This report, created by the SRS for Brain Metastasis GDG, presents organizational standards for the delivery of SRS in a Canadian Cancer Program. These standards apply to all institutions and hospitals delivering SRS within the province of Ontario, and address the following domains: the planning of new SRS programs, practice setting requirements, tools, devices and equipment requirements; professional training requirements; the role of personnel; requirements for QA and safety; and the follow-up of patients.

RESEARCH QUESTIONS

1. Who are the medical professionals who ideally should be part of the MCC evaluating patient eligibility and performing SRS?
2. What are the training and/or certification requirements for members of the MCC performing SRS?
3. What are the minimum applicable technologies required for the safe performance of SRS?
4. What imaging is needed both pre (i.e., simulation) and post (i.e., follow-up) SRS to ensure safe practice and patient safety?
5. What is the appropriate level of QA for: (a) treatment-delivery unit/machine quality control; (b) imaging; and (c) treatment planning
6. What are the minimum requirements for patient follow-up after the SRS procedure (i.e., MRI timing and frequency)?

METHODS

As with all PEBC guidelines, a search for existing guidelines was completed. The methods and results of the search for existing guidelines are presented below. The standards presented below embody recommendations for the organization of the delivery of SRS in Ontario. With the exception of Research Question 6, the recommendations are based on the consensus opinion of the SRS for Brain Metastasis GDG. Primary consideration was given to the perceived benefits for patients and the small likelihood of harm arising from recommendation implementation. For the research questions that preceded this section, with the exception of Research Question 6, it was determined that there would be no evidence available, and therefore a systematic review of the primary literature was not required. All evidence cited in the key evidence section following these research questions is considered indirect and was provided by the Working Group in conjunction with their collective expertise in the field of SRS.

Guideline Review

This Organizational Guideline was developed by the SRS for Brain Metastasis GDG, a collaboration of CCO's PEBC and Radiation Treatment Program. The standards were written in accordance with a methodology adapted from the PEBC's practice guideline development process and reporting format. The report was designed to address professional and organizational standards around the delivery of SRS in Ontario.

Prior to the development of the recommendations it was known that the American College of Radiology (ACR) practice parameter for the performance of brain stereotactic radiosurgery [15] existed. The websites for Canadian Associated of Radiation Oncology (CARO) and the Canadian Partnership for Quality radiation Therapy (CPQR) were also searched as these are the relevant radiology organizations providing guidance for the use of radiology equipment in Canada.

Evidence was selected by the PEBC methodologist (SK) and reviewed by members of the SRS for Brain Metastasis Working Group, which included representation from neuro-oncology, radiation oncology, radiation therapy, medical physics, neuroradiology, CCO's Radiation Treatment Program, and the PEBC. The Panel met through teleconference and in-person meetings and used e-mail as the main vehicle of communication. Differences were resolved through consensus and the use of evidence that informed the standards document.

Two organisational guidelines (ACR and CPQR) in addition to the ACR practice parameter contained relevant information regarding the optimal organization for a SRS program. The CPQR has several technical Quality Control Guidelines which outlined QA procedures for some parts of the SRS procedure.

1) ACR Practice Parameter for the Performance of Brain Stereotactic Radiosurgery (2016)

2) Solberg et al. ASTRO Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. Practical Radiation Oncology 2012 Jan; 2(1): 2–9.
    - Supplementary Material: Quality and Safety Considerations in Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy. Practical Radiation Oncology August 2011
3) Canadian Partnership for Quality Radiotherapy Technical Quality Control Guidelines for Canadian Radiation Treatment Centres http://www.cpqr.ca/wp-content/uploads/2017/01/TQC-2016-05-01.pdf

Table 4-1. Domains Assessed by Pre-existing Organizational Guidelines

Guideline	SRS Program Domains Assessed in the PEBC Guideline						
	MCC Team	MCC Team Qualifications	Minimum Applicable Technologies	Image Guidance Systems	Simulation	QA Assurance Programs	Post SRS Follow-up
ACR (2016)	X	X				X	
ASTRO (2011)	X	X	X	X	X	X	
CPQR (2016)						X	

Abbreviations: ACR, American College of Radiology; ASTRO, American Society for Radiation Oncology; CPQR, Canadian Partnership for Quality radiation Therapy; MCC, multidisciplinary case conference; QA, quality assurance; SRS, stereotactic radiosurgery

Due to the nature of this PEBC Guideline, the Guidelines listed in Table 4-1 were unable to be endorsed directly by the SRS for Brain Metastasis GDG. While the ACR practice parameter contained information on a number of relevant domains, it could not be endorsed because of geographical differences between the American and Canadian SRS centres. The same was the case with the ASTRO guideline. The CPQR guideline, while geographically relevant to Canadian SRS centres, was not detailed enough to be endorsed in this PEBC Guideline. In all cases there was no detail on how recommendations were concluded or supported.

Primary Literature Review

For Research Question 6, a systematic literature search was conducted to find studies with details on MRI follow-up programs. The gold standard would be an RCT comparing follow-up MRI to clinical observation only, and its effect on patient management and survival; however, it was hypothesized in the systematic review planning stage that there would be no studies that evaluated this and, therefore, data on the incidence of RN in the study population and the onset of RN were prioritized as this would provide valuable information as to the frequency of RN in SRS patients and the need for a specialized follow-up program. Studies were included if they contained the following information:

- Had greater than 12 patients
- Were available in full text
- Were available in English
- Included patients that were treated with an SRS technology available in Canada (linac equipped with a subcentimeter MLC, CK, or GK)
- Had details on the patient MRI follow-up program
- Included information on the incidence of RN in the patient population

- Included information on the onset of RN in the patient population
- If available, details on how the MRI follow-up program negatively or positively impacted survival.

The literature search was conducted on OVID MEDLINE and Embase from 1980 to September 10, 2018. A total of 812 records were retrieved and were reviewed by one research methodologist (SK). After title and abstract screening, 88 records remained. Upon full-text review of the remaining studies, 20 were included in the guideline [15,16,42-59]. A final study was identified by a Working Group member (AS) that dealt with adverse radiation effects and was subsequently added to the literature included in this Guideline [60]. Details on these 21 studies can be found in Table 4-3 and details on the literature search can be found in Appendices 2 and 3.

Recommendation Development Process

Due to the lack of relevant guidelines and high-quality primary evidence to support the recommendations, the SRS for Brain Metastasis Working Group relied on their combined expertise to develop recommendations that would be acceptable for use within Ontario SRS treatment centres. The Working Group drafted and confirmed a preliminary set of recommendations related to the organizational requirements for programs performing SRS within Ontario. Discussions were conducted through teleconference and e-mail communication and were informed by the existing guidance documents, and the clinical experience of members.

KEY EVIDENCE FOR RECOMMENDATIONS

1. **Who are the medical professionals who ideally should be part of the MCC evaluating patient eligibility and performing SRS?**
2. **What are the training and/or certification requirements for members of the MCC performing SRS?**

The application of SRS requires the coordinated effort of an MCC of professionals who assume roles during the patient selection and treatment procedure. The MCC performing SRS should include the following individuals who have the credentials and responsibilities listed below. These are in addition to the nurses and administrative staff who provide general support for all patients in the radiology department. The evidence for this research question is indirect and is based on the expert consensus of the SRS for Brain Metastasis GDG.

Radiation Oncologist

- Qualifications:
    - The radiation oncologist is accredited by a nationally or internationally recognized program or licensing board
    - Participation in a dedicated fellowship or course that provides technology-specific training is strongly recommended
    - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
    - Team leader, responsible for the selection of members of the SRS team
    - Oversee treatment of patient and sign off on treatment plan
    - Verification of target volume and normal tissues
    - Oversee patient positioning and immobilization

- Participate in the monitoring and follow-up of patients post-SRS

Neurosurgeon

- Qualifications:
  - The neurosurgeon is accredited by a nationally or internationally recognized program or licensing board
  - Participation in a dedicated fellowship or course that provides technology-specific training is strongly recommended
  - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
  - It is recognized that a neurosurgeon may not be present at each SRS centre within Ontario; however, participation in the treatment decision-making team through a multidisciplinary case-conference is strongly recommended
  - In an ideal setting, the neurosurgeon would be involved in determining target volume and normal tissues, in particular for benign indications, functional indications, and complex metastasis including post-operative radiosurgery. It is recognized that this is not achievable at smaller centers without neurosurgery and in this situation at least one radiation oncologist must have sub-speciality training in SRS and lead that team.
  - Participation in the monitoring and follow-up of patients post-SRS

Neuroradiologist

- Qualifications
  - The neuroradiologist is accredited by a nationally or internationally recognized program or board
  - Mentoring or training in a supervised setting within an SRS program is strongly recommended
- Responsibilities include:
  - Participation in the MCC
  - Participation in developing imaging protocols required for stereotactic radiosurgical cases
  - Reviewing pre- and post-procedure imaging

Medical Physicist

- Qualifications:
  - The qualified medical physicist is certified by the CCPM or an equivalent national or international certification agency
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
- Responsibilities include:
  - Being knowledgeable of all technical aspects of an SRS program, which includes simulation, imaging, planning, equipment, treatment delivery, and verification of output calibration
  - Development of the technical QA program including continual monitoring and associated documentation
  - Working with the radiation oncologists, radiation therapists, and medical dosimetrists to develop the optimal application of SRS and optimal treatment plan for a given patient

- Being available for consultation for patient set-up and treatment delivery on the day of the treatment
- Participating in the peer review process
- Being knowledgeable of the radiation safety procedures
- Ensure members of the SRS team have the necessary training to ensure the safe operation of the SRS program
- Working with the information technology staff to ensure network connectivity and data backup procedures are in place
- Being aware of all sources of uncertainty in SRS, including mechanical and dosimetric, and be able to provide mitigation strategies
- Participating in continuing education activities to maintain expertise and awareness of best practices and guidelines
- Note: In some centres, the medical physicist may also be responsible for SRS planning

Radiation Therapist

- Qualifications:
  - MRT(T) graduate of a recognized radiation therapy program with registration with the appropriate provincial college
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
- Responsibilities of the radiation therapy must be clearly defined and may include the following:
  - Appropriate fabrication of effective patient immobilization devices
  - Patient treatment preparation for the SRS procedure that includes patient positioning/immobilization
  - Performing and assessing pre-treatment imaging for treatment verification
  - Monitoring the patient during treatment
  - Delivering accurate SRS treatment after appropriate approvals
  - Patient care and side effect management
  - Organizing daily workflow of patients and staff
  - Performing daily QA and ensuring safe operation of the technology unit
  - Performing emergency procedures adhering to protocols if necessary

Medical Dosimetrist

- Qualifications:
  - MRT(T) graduate of a recognized radiation therapy program with registration with the appropriate provincial college
  - Considered beneficial if trained in an SRS-specific setting (within an SRS program or by a supervised vendor)
  - Considered beneficial if experienced in planning
- Responsibilities of the medical dosimetrist must be clearly defined and may include the following:
  - Working with the radiation oncologist and medical physicist in developing an effective SRS treatment plan for the patient
  - Ensuring all relevant volumetric patient image data are included in the treatment planning system (TPS)
  - Generate all appropriate technical documentation required to implement the treatment plan

- Be available for the first treatment and assist with verification for subsequent treatments as necessary
- Note: It is possible that one individual could fulfil both the responsibilities of the radiation therapist and medical dosimetrist, if the appropriate qualifications are obtained.

In addition to the members listed above an administrative team is required to support the SRS program. These duties may include ensuring there are adequate resources, time, and personnel required for performing SRS. Support for continuing education for personnel should also be considered.

These recommendations for team members and their minimum skill set and experience for SRS team members that perform SRS in Ontario was the consensus of the GDG, based on currently accepted definitions for these specialities in Ontario.

3. What are the minimum applicable technologies required for the safe performance of SRS?

Minimum SRS Technologies

SRS is a technologically intensive program that requires the use of resources that are above what would be considered traditional for radiotherapy treatment. Regardless of the SRS technology being used, the potential for errors in SRS is a major concern due to the highly conformal nature of SRS, steep dose gradients beyond the tumour edge, high dose per fraction radiation, lack of planning target volume (PTV) margin (or a very small PTV margin in the order of 1-2 mm), sensitivity of the surrounding normal brain tissue that surrounds the tumour in three dimensions, and risk of RN that can result in serious impairment of the patient and even cause death [19]. Having a strict QA program in place is essential for mitigating those risks. The next section outlines the typical types of technology used for SRS, followed by recommendations for QA guidelines for SRS TPSs, imaging and simulation procedures, and treatment delivery.

The following technical guidelines were provided by Working Group members for their applicability to the technical considerations for SRS treatment (Table 4-2). While these technical documents were beyond the current scope of this Guideline, they were deemed by the Working Group members to be informative to clinicians performing SRS in Ontario and thus have been listed below (Table 4-2); however, they will not be discussed further in this Guideline.

Table 4-2: Technical Guidelines Provided by the Working Group

Area	Report
General SRS	AAPM Report No. 54: Schell MC, Bova FJ, Larson DA, Leavitt DD, Lutz WR, Podgorsak EB, Wu A. "Stereotactic Radiosurgery", Report of TG 42 Radiation Therapy Committee. 1995.
General SRS	ICRU REPORT 91 Prescribing, Recording, and Reporting of Stereotactic Treatments with Small Photon Beams, 2014
Imaging	AAPM TG-117, "Use of MRI in Treatment Planning and Stereotactic Procedures". *In press*
Imaging	Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG, Jr., Froelich JW, et al. ACR guidance document on MR safe practices: 2013. J Magn Reson Imaging. 2013;37(3):501-30.

Imaging	Paulson ES, Erickson B, Schultz C, Allen Li X. Comprehensive MRI simulation methodology using a dedicated MRI scanner in radiation oncology for external beam radiation treatment planning. Med Phys. 2015;42(1):28-39.
Imaging	AAPM Report No. 100: Jackson JF, Bronskill MJ, Drost DJ, Och J, Pooley RA, Sobol WT, Clarke GD. "Acceptance Testing and Quality Assurance Procedures for Magnetic Resonance Imaging Facilities" Report of MR Subcommittee Task Group I. 2010
Imaging	AAPM Report No. 83: Mutic S, Palta JR, Butker EK, Das IJ, Huq MS, Loo LN, Salter BJ, McCollough CH, Van Dyk J AAPM Report No. 083 (TG-66): "Quality assurance for computed-tomography simulators and the computed-tomography-simulation process". Report of Radiation Therapy Committee TG NO. 66. 2003.
General Machine QA	AAPM TG-101: Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. Medical Physics. 2010;37(8):4078-101.
General Machine QA	AAPM TG-142: Klein EE, Hanley J, Bayouth J, Yin F-F, Simon W, Dresser S, et al. Task Group 142 report: Quality assurance of medical accelerators). Medical Physics. 2009;36(9Part1):4197-212.
Small Field Dosimetry	AAPM TG-155, "Small fields and non-equilibrium condition photon beam dosimetry", *In press*.
Small Field Dosimetry	IAEA Report: "Dosimetry of Small Static Fields Used in External Beam Radiotherapy". *In press*.

Abbreviations: QA, quality assurance; SRS, stereotactic radiosurgery

Treatment Delivery Units

Regardless of technology, SRS employs multiple narrow beams that accurately place high doses of radiation within the brain with a steep dose gradient/penumbra to spare normal tissue. Technologies that are employed in Ontario to accomplish SRS include GK, CK, and linac. The radiation units, including beam-shaping apertures, beam-arrangement, isocentre, and immobilization/positioning devices are well characterized in the literature [21]. Positioning and immobilization can be performed using surgically placed frames, or with non-surgically placed frames such as bite blocks, or with completely frameless workflows such as thermoplastic masks.

GK is a dedicated SRS unit, which since 2007 consists of 192 cobalt-60 sources cylindrically arranged that yield radiation beams that intersect at the focus, and robotically driven to align with fixed collimator sizes: 4 mm, 8 mm, or 16 mm. Dedicated treatment planning software and QA tools are provided by the vendor. More recently, cone-beam CT-based image guidance has been incorporated into the technology and both frameless and frame-based approaches are supported [32,33]. Real-time monitoring with an optical camera can be used.

CK is robotically mounted linac that sequentially delivers large numbers of non-isocentric beams through the target [34]. Until recently, circular collimators(5 mm to 60 mm) were used together with an iris collimator (fixed or dynamically controlled) but currently, a high-definition MLC system is attached that can facilitate larger treated volumes and off-axis delivery, with a total field size 120 mm × 102.5 mm. X-ray-based image guidance is used to ensure accurate patient positioning, and real-time monitoring can be used during treatment.

Linacs are isocentric devices that often employ tertiary collimators (MLCs) to finely shape the radiation beams. Intensity-modulated radiotherapy and Volumetric Arc Therapy can be used as a means of creating inversely planned complex dose distributions, including off-axis irradiation that can treat multiple targets with a single isocentre. Alternatively, a multi-isocentric approach can be used in conjunction with static or dynamically conformal arcs or beams. In either case, it is common practice to rotate the couch to yield oblique beams/arcs mimicking the trajectory of beam arrangements from GK or CK. Using flattening-filter-free technology, high dose rates are achievable, which has the potential to minimize treatment

time. QA recommendations for linacs include AAPM Task Group Reports 142 and 101 [10,11] and COMP technical quality control guidelines [13]. Specifically, linacs that are designated for SRS should be carefully tested for: (1) targeting accuracy at all combinations of couch, gantry, and collimator angles used clinically; and (2) dosimetric accuracy for small (<2 cm) MLC-defined fields at the location of the target, which includes off-axis locations.

Treatment Planning Systems

Commissioning and QA of the TPS following international guidelines [35-37] applies to SRS systems. Of specific relevance to SRS is the support of multimodality imaging, specifically multiple MRI and CT scans. MRI acquired from a diagnostic department may have attributes uncommon to SRS, or radiation oncology planning systems, such as oblique (or non-axial) images, non-square arrays or voxels, and non-uniform slice spacing. Of particular relevance for SRS and brain metastases is the ability of the TPS to accommodate the treatment of multiple metastases, both in a single session as well as over time, as patients may return multiple times for SRS to new lesions or to salvage failures. The image co-registration method used by the TPS also requires special consideration, especially when acquiring non-stereotactic MRI and co-registering to a stereotactic image set (CT or cone beam CT) as even small misalignments could lead to geographical misses of the target. The AAPM Task Group Report 132 specifically addresses image registration and fusion algorithms for radiotherapy [38].

4. What imaging is needed both pre (i.e., simulation) and post (i.e., follow-up) SRS to ensure safe practice and patient safety?

Imaging and Simulation

Brain metastases SRS relies completely on MRI for target delineation and localization. Depending on how small a lesion a centre is willing to treat, the MRI scanning parameters must be set accordingly with sufficiently high spatial resolution and signal for the brain metastases to be adequately visualized and contoured. In addition, there should be discussion with the neuroradiologist as to the amount of Gadolinium contrast, type of Gadolinium, and timing of administration to ensure optimal visualization of metastases. Of particular concern for MRI is the potential for geometric distortion, which could lead to an erroneous localization of a brain metastasis if present and unaccounted for [18]. High field strengths (1.5T or 3T) are typically required to detect small brain metastases with sufficient detail for delineation. Guidelines and recommendations for MRI in radiation oncology should be strictly followed to minimize the risks associated with geometric distortion, especially for 3T MRI [1,2]. Imaging considerations include, but are not limited to, partial volume averaging, two-dimensional versus three-dimensional (3D) acquisition, pixel size, slice thickness, distance between slices, image reformatting for the TPS, spatial distortion and image warping, motion artifacts, magnetic susceptibility artifacts, etc. As an example, a radiation oncology department in Toronto uses a full 3D T1-weighted acquisition sequence (post-gadolinium injection) with interleaved 2 mm slice thickness (reformatted to 1 mm) and 0.5 mm in-plane pixel size using a 1.5T MRI. A specific QA process by medical physics is required to determine suitability of the MR images as the QA measures are distinct from medical imaging. The MRI to treatment time interval should be as short as possible, ideally no more than seven and certainly no more than 14 days as a maximum [16,39]. Finally, the head coil used on MRI should accommodate whatever immobilization/localization device is being used. In certain cases, patients may have MRI without any head frame or localization device, which is then co-registered to a stereotactic image set later in the process. In such cases, care should be taken to keep the patient as still as possible (minimize motion artifacts) and have their head as close to treatment orientation as possible. Most SRS systems require that the scan volume spans the entire head, extending

one to two axial slices beyond the top of the head, and down to the level of C1 or C2 depending on the system.

The use of CT alone for brain metastases SRS is not common and represents an exception to standard recommended practice. As with MRI, sufficiently high spatial resolution and signal must be used in accordance with guidelines and recommendations [3,4]. CT is typically geometrically robust but adhering to guidelines and reports on CT QA is required. As an example, a radiation oncology department in Toronto uses a 1 mm slice thickness and 0.6-0.7 mm in-plane pixel size.

5. What is the appropriate level of quality assurance for: (a) treatment-delivery unit/machine quality control; (b) imaging; and (c) treatment planning?

Regardless of technology, the success of an SRS program hinges on a thorough and ongoing QA program to ensure that the treatment unit is in compliance with the recommendations of the treatment unit manufacturer and within specified clinical tolerances based on international and national guidelines and recommendations [10-14]. The responsible medical physicist should determine that the appropriate testing procedure is used, and documentation is maintained. Specific to SRS, the most essential elements of treatment delivery QA are:

(1) Spatial accuracy. The accuracy and precision of delivery should be well-characterized and routinely tested for sub-millimeter targeting accuracy. For MLC-based delivery of multiple metastases, in particular when treating off-axis, specialized QA devices may be needed to verify the accuracy of radiation field placement throughout the angular range of gantry, collimator, and couch angles [5,6]. A positional end-to-end test for delivery accuracy is recommended that encompasses as much of the workflow as possible, from MRI, through to target delineation and treatment delivery.

(2) Small field dosimetry. For reference dosimetry in linacs, standard protocols TG-51 and IAEA TRS-398 apply [7,8]. For GK, CK, tomotherapy, and cone-based treatments, recommendations as per TRS-483 using MSR fields apply [9]. The differential detector response at small fields relative to the MSR field must be taken into account using Monte Carlo calculated corrections. Additionally, proper alignment and orientation of the detector with respect to the field are also important to consider in relative small field dosimetry. It is recommended that a medical physicist on the SRS team have some dedicated small-field dosimetry training, whether through a certified medical physics training program, or by experienced physicists with small-field dosimetry expertise.

6. What are the minimum requirements for patient follow-up after the SRS procedure (i.e., MRI timing and frequency)?

Close clinical and radiographic surveillance is recommended following SRS due to the risk of treatment failure, and symptomatic RN that can occur in 5-10% of patients [20]. Distinguishing between recurrence and post-treatment changes including RN, may often be difficult requiring specialized MR imaging such as MR spectroscopy and perfusion imaging. Upon questionable progression versus necrosis, the case must be discussed in MCC. Management options include observation if the patient is asymptomatic, short-course corticosteroid administration with a short-interval repeat MRI, and surgery/biopsy as indicated. For symptomatic patients, initial considerations consist of corticosteroid use and surgery/biopsy. If there is progression on steroids, imaging consistent with RN or

biopsy/resection-confirmed necrosis, there is evidence to support bevacizumab as a rescue agent [40]. If tumour progression is confirmed, typical options include surgery followed by fractionated cavity SRS or WBRT, repeat SRS that is typically delivered with a more fractionated approach as opposed to repeat single fraction SRS, and WBRT. This recommendation is also in keeping with a survey by Stockham et al., who polled physicians from ASTRO and the Society for Neurologic Oncology, and generally practitioners responded such that they follow their patients every three months with imaging (47%) [41].

The clinical and radiological follow-up of SRS patients varied among the studies, but generally consisted of clinical and radiological evaluations within one month post-SRS procedure. MRI scans were then required every three months for the first year and every four to six months the second year. Clinical evaluations frequently occurred at the same time as the MRI scans. The clinical and radiological follow-up programs were able to be modified at the discretion of the clinician at the onset of either symptomatic or asymptomatic signs of neurotoxicity or tumour recurrence. The incidence of ARE including RN varied between studies, ranged from 0-64.5%. Onset of RN ranged from three to 33.2 months post-SRS, with most occurring after three months post-SRS. In some cohorts of SRS patients, WBRT was performed prior to SRS and this is a risk factor for a higher rate of RN [42-45]. In the cohort of Kohutek et al [43], 14.4% of the patients received prior WBRT. After a median follow-up of 17.2 months, RN was noted in 25.8% of the lesions including 17.3% of asymptomatic cases. In univariate analysis, prior WBRT was significantly associated with RN ($p=0.004$), maximum tumour diameter ($p<0.001$), prescription dose ($p=0.02$), and histology ($p=0.04$). In a similar study, Sneed et al evaluated incidence, onset, and risk factors of ARE in patients who had undergone SRS [46]. In this study, 435 patients with 2200 brain metastases were treated with GK SRS. The procedure for follow-up was a brain MRI every three months. The median patient survival time was 17.4 months and the median lesion imaging follow-up was 9.9 months. ARE was determined in 118 cases. Of those, approximately 60% were symptomatic and 85% occurred three to 18 months after SRS, with a median onset of 7.2 months. The risk factors for ARE were determined to be prior SRS to the same lesion (20% 1-year risk of symptomatic ARE vs. 3%, 4%, and 8% for no prior treatment, prior WBRT, or concurrent WBRT, respectively) and any of the following volume parameters: target, prescription isodose, 12-Gy, or 10-Gy volume [46].

Based on the literature identified, as well as the combined clinical experience of the Working Group members, a dedicated radiosurgery program needs to follow the patients that they treat. This includes routine clinical visits for the first year (every 2-3 months); second and third year (every 3-4 months), and thereafter as determined by the MCC. Follow-up incorporates a standard brain MRI and preferably with a volumetric axial T1 post-gadolinium sequence and interpretation should occur by the radiation oncologist, surgeon, and neuroradiologist in an MCC when it is unclear that progression has occurred. Acknowledgment of ancillary imaging sequences such as spectroscopy and perfusion is strongly recommended to inform diagnosis and management. Before a decision is made to re-irradiate it is mandatory to consult the MCC and surgical input is recommended.

Table 4-3: Studies with details on SRS follow-up programs and RN incidence

Study	Population	SRS Procedure	Follow-up Protocol	RN	RN onset
[42]	132 patients with 1 to 4 brain metastases, each with a maximum diameter of no more than 3 cm, histologically confirmed systemic cancer	No details on SRS technology Metastases up to 2 cm: 22-25 Gy; if larger than 2 cm: 18-20 Gy	Clinical evaluations and MRI scans 1 and 3 months after SRS and every 3 months thereafter	RN: SRS alone: 1/67 case (1.5%) of Grade 4 RN WBRT+SRS: 3/65 cases (4.6%) (1 Grade 1 and 2 Grade 4)	NS
[47]	A total of 103 tumours treated with SRS in 54 patients. Median number of tumours treated was 1 (range: 1-6).	CyberKnife-based SRS	Follow up neurologic exam and MRI scanning (or CT if ineligible for MRI) 2 months after SRS, every 2-3 months for the first year, and 3-6 monthly intervals thereafter	RN: 1/54 case (1.9%) New Mets: 81%	RN: NS New Mets: 2 months (median)
[48]	141 consecutive patients with 305 brain metastases treated with SRS at a single center	Linear Accelerator-based SRS The dose prescribed to the PTV margin, the prescription isodose curve ranged from 90–95%.	Follow-up MRI every 1–3 months during the first year after SRS. Thereafter, additional imaging done if neurologic symptoms or as part of a routine clinical follow-up	RN: 10/305 lesions (3.3%) (5 had previous WBRT)	NS
[45]	60 patients with 1 to 3 brain metastases: 21 patients received WBRT+SRS, 21 patients received WBRT-only and 18 patients received SRS alone	Brown-Roberts-Wells CT stereotactic (BRW) localization system frame	Neurologic examinations and MRI 3 months after start SRS and in 3 month intervals	RN: WBRT+SRS: 1/21 (4.7%) WBRT: 0/21 SRS: 1/18 (5.5%)	NS
[49]	16 patients with 19 tumour volumes. Intact metastases and resection cavities treated with SRS if new MRI contrast enhancement within the treatment field > 18 months after SRS	CyberKnife-based SRS	After SRS, follow-up imaging every 3 months for the first year, every 4 months the second year, then every 6 months. This schedule reset in the event of a new distant brain metastases	NOTE: patients were selected for this study because they had contrast enhancement on MRI. RN rates not reflective of general SRS populations RN: 12/19 Local Failure: 7/19	RN: median 33.2 months Failure: 23.6 months

Study	Population	SRS Procedure	Follow-up Protocol	RN	RN onset
[50]	117 patients	CyberKnife or hypo-fractionated SRT	MRI follow-up at least once within 3 months and possibly at 6 months post-treatment.	RN: 2/117 cases (1.7%) (1 subacute, 1 chronic)	NS
[43]	327 patients with 583 metastases treated with single-fraction SRS	Single fraction linear accelerator-based SRS	MRI 2 months post SRS and every 3 months thereafter.	Asymptomatic radiographic treatment change in 25.8 % (n = 70) Incidence of RN at 6 Months: 5.2% (95%CI, 2.5–7.8 %), 12 Months: 17.2% (95%CI, 12.1–22.0%), 18 Months: 23.0% (95%CI, 17.0–28.6%), 24 Months: 34.0% (95%CI, 26.4–40.7 %)	The median time RN: 10.7 months (range, 2.7–47.7) *on univariate analysis RN was associated with: Max tumour diameter (p<0.001), prior WBRT (p=0.004), prescription dose (p=0.02), histology (p=0.04)
[51]	109 patients with 119 large MBTs	GammaKnife SRS	MRI and clinical evaluation at 2- to 3-month intervals.	RN: 0 cases	NS
[44]	28 patients with 1 to 3 brain metastases from melanoma primary (43 lesions) treated with SRS	Gamma Knife SRS	Repeat MRI every 3–4 months for follow-up	RN: 1 case	10 months after SRS and was treated with surgery
[52]	1939 patients (5747 lesions)	Gamma Knife SRS	MRI 4 to 6 weeks after SRS and every 3 months thereafter	RN: 285/1939 (15%)	Median time to RN: 7.6 Months Incidence of RN: 6 Month - 3.2%, 12 Month – 5.6%, 18 Month - 6.7%
[20]	206 consecutive patients with 1-3 metastases less than 3.5 cm, histologically confirmed systemic cancer, treatment with SRS	Linac-based SRS		RN: 75/206 (24%); symptomatic in 31 (10%) and asymptomatic in 44 (14%) per lesion	Median time to symptomatic and asymptomatic RN were 11 months (range, 2-32 months) and 10 months (range, 2-30 months), respectively
[53]	27 patients evaluated with perfusion MR when they had a progressive enhancing lesion on follow- up MRI after SRS	Linac-based SRS and Gamma Knife SRS	Routine MRI and clinical evaluation every 1–3 months	NOTE: patients were already determined to have either RN or progressive disease RN: 21/27 (75%) Recurrence: 7 (25%)	Median interval between SRS and enlargement was 11.8 months (range: 2– 35)

Study	Population	SRS Procedure	Follow-up Protocol	RN	RN onset
[54]	Salvaged patients: n=132; Never salvaged patients: n=152 284 patients with 677 brain metastases treated with SRS alone	Gamma Knife SRS	Clinical and MRI follow-up 1 month after SRS and every 3 months thereafter	The highest rate of RN in those that had both salvage SRS and salvage WBRT (6/28 or 21.42%). RN in this group was also significantly more frequent than those receiving no salvage therapy (3/152, p<0.001), salvage SRS alone (0/31, p<0.001), and salvage WBRT alone (0/58, p<0.001). RN was not significantly greater than in patients salvaged with surgery alone (0/7, p=0.311) or salvage surgery with radiation (0/8, p=0.302)	NS
[55]	21 patients were analyzed (11 RS+WBRT,10 S+WBRT) *trial stopped due to slow accrual	Linear Accelerator	Clinical evaluation weekly during protocol treatment, at 2 and 3 months after the SRS, then 3 monthly, and MRI brain at 3 and 6 months and/or when clinically indicated.	RN: 0 cases No grade 3-4 late radiation effects and no significant difference between the arms with respect to grade 0-2 toxicities for the nine patients who were assessable more than 90 days after starting either treatment	NA
[56]	340 patients with 1-3 Mets	Modified Linear Accelerator-based SRS (Mevatron M/Fa. Siemens)	No information	RN: 21/340 cases (6.1%) In 5 pts clinically relevant radiation necrosis was confirmed by PET imaging	NS
[57]	1555 brain metastases in 1126 patients	Gamma Knife SRS	Clinical examinations and MRIs at 4-6 weeks after SRS and 3 months thereafter.	RN: 245/1555 lesions (5.7%)	NS
[58]	43 lesions in 37 patients	Linear accelerator	No details; however patients were excluded if they had no follow-up MRI after second round of SRS	RN: 7/43 lesions (16%)	11.6% at 6 months and 16.5% at 12 months Median months from the 2nd SRS to the

Study	Population	SRS Procedure	Follow-up Protocol	RN	RN onset
					diagnosis of RN was 2.8 months
[59]	60 patients. Mean number of brain metastases per patient was 3.7 ± 2.7	Linear Accelerator	MRI every 3 months until 1 year and then imaging every 6 months, with the same patient assessments as at baseline, plus scoring of events that were possibly, probably, or definitely related to treatment using the Common Terminology Criteria for Adverse Events, version 4	Acute Necrosis: Grade 2 – 1 *One unexplained death at 4 weeks that could have been grade 5 necrosis* Late Necrosis: Grade 1- 2 Grade 2– 2 Grade 3– 3 Grade 4– 2 Grade 5– 0	NS
[60]	27 patients/30 metastases	Gamma Knife	Follow-up MR imaging in intervals of ≤3 months once post-SRS MRI indicates progressively enhancing regions	RN: 10/30 lesions (33%) Recurrence: 20 lesions	Mean time to RN 353 days (SD: 171d)
[46]	435 patients and 2200 brain metastases	Gamma Knife	MRI was obtained every 3 months post-SRS	Among 118 cases of ARE were determined	85% occurred 3-18 months after SRS (median 7.2 months)
[61]	243 patients who underwent gamma knife SRS; 17 patients with RN	Gamma Knife	Clinical and MR follow up was obtained every 2 or 3 months in patients with radiation necrosis until symptoms had resolved	17 patients identified as having RN	median time to symptomatic radiation necrosis was 4 months (range 2–14 months)

Abbreviations: ARE, adverse radiation effects; CI, confidence interval; CT, computed tomography; Max, maximum; Mets, metastases; MRI, magnetic resonance imaging; NS, not stated; PET, positron emission tomography; PTV, planning target volume, RN, radionecrosis; SRS, stereotactic radiosurgery; WBRT, whole body radiotherapy

DISCUSSION

The purpose of this organizational guideline was to provide a framework of the minimum clinical and technical standards for facilities performing SRS on patients with brain metastasis in Ontario. This guideline was created due to the increasing demands on provincial centres to offer SRS to patients within their region by both patients and medical professionals. SRS is an effective treatment for brain metastases; however, it carries significant risks associated with RN, management of in-field treatment failures, and distant brain failure. It was recognized by CCO that there was a strong need for consistency among the centres with respect to training standards, and robust QA processes to ensure patient safety. Guideline developers relied heavily on their consensus-based opinion when formulating recommendations as the intent was not to provide clinical guidelines for patient selection.

The first recommendation stipulates the development of an MCC when determining patient eligibility for SRS, and in evaluating follow-up imaging when there is a question as to tumour progression given the confounding factor of RN. The MCC should be comprised ideally of a radiation oncologist, neurosurgeon, medical physicist, radiation therapist/medical dosimetrist, and a neuroradiologist. At a minimum, the MCC should include the radiation oncologist, neuroradiologist and, if available, the neurosurgeon and a neuro-oncologist. The second recommendation outlines the qualifications and responsibilities of each of these medical professionals in the MCC.Traditionally, SRS required a specialized delivery unit such as the GK, CK, or significant adaption to an existing linac that prohibited smaller regional centres from delivering SRS. This impacted patterns of care in Ontario as reported by Hodgson et al [31]. In that study, it was clear that the availability of on-site SRS significantly impacted patient care as SRS was provided to only 8% of the cohort at any time during the course of their disease. Even in the most ideal patient, where the evidence at that time supported an SRS boost following WBRT rather than WBRT alone, only 4% of patients had SRS as compared to 33% if SRS facilities were on-site (p=0.015) [31,62]. Currently, SRS is delivered with GK, CK, and linac-based technologies in Ontario. Certainly, linac-based technology has evolved significantly with the advent of frameless immobilization, image-guidance, and sub-centimetre MLCs such that regional centres can offer SRS with existing equipment. This also prompted the current organizational guideline to ensure consistency among the centres in the province with respect to training standards and robust QA processes to ensure patient safety. Recommendations 3, 4, and 5 are technical in nature to ensure those minimum standards with respect to technology, imaging, and quality assurance.

The committee also deliberated on the issue of post-SRS follow-up. It was recognized that this is an area where clear guidelines are not stipulated in the literature. The critical issue in terms of a policy for follow-up assessment, that includes MR imaging, is the diagnosis and management of RN versus tumour progression. RN can be symptomatic in 5-10% of patients and managed medically, with neurosurgery (which includes minimally invasive ablative procedures) reserved for medical failures. Medical management has traditionally been based on use of corticosteroids and sometimes hyperbaric oxygen, and now there is evidence to support the use of bevacizumab, which would require medical and neuro-oncology input. RN poses a major diagnostic challenge as it is most often determined based on specialized MRI sequences that still lack sensitivity and specificity as compared to tissue diagnoses. Ultimately, a neurosurgical biopsy is invasive and the patient population is palliative; therefore, unless management would be informed in an appropriately selected patient, then biopsy is typically deferred and patients managed medically.

In order to inform the recommendation as to appropriate follow-up intervals, a literature search was conducted to find studies with details on MRI follow-up programs, data on the incidence of radiation necrosis and, if available, time of onset. The results of the

literature review as summarized in Table 4-3, as well as the combined clinical experience of the Working Group members, informed Recommendation 6. The committee endorsed follow-up of patients undergoing SRS, which should consist of routine clinical visits with an MRI for the first year (every 2-3 months); second and third year (every 3-4 months) and thereafter as determined by the MCC. Follow-up incorporates a standard brain MRI, preferably with a volumetric axial T1 post-gadolinium sequence, and interpretation by the radiation oncologist, surgeon, and neuroradiologist when it is unclear that progression has occurred. Acknowledgment of ancillary imaging sequences such as spectroscopy and perfusion is strongly recommended to inform diagnosis and management. Before a decision is made to re-irradiate, it is strongly recommended to consult the MCC and surgical input is recommended.

CONCLUSIONS

The recommendations in this organizational Guideline were developed by the CCO PEBC and SRS for Brain Metastasis GDG. Limited evidence exists with respect to technical and organization parameters for program development in SRS and, as such, the committee relied heavily on expert opinion based on their experience in creating this guideline. The recommendations provide a framework for the minimum requirements for a cancer centre in Ontario, Canada, to offer SRS for brain metastases and serve to inform provincial radiotherapy departments and the hospital administration.

Organizational Guideline for the Delivery of Stereotactic Radiosurgery for Brain Metastasis in Ontario

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the four members of the GDG Expert Panel, four members cast votes and none abstained, for a total of 100% response in May 2019. Of those that cast votes, all approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. For recommended MRI protocol (see Page 6): "Signal intensity should be sufficiently high…" should change to "Signal-to-noise ratio should be sufficiently high…"	Thank you, we have made the requested change.
2. Follow-up imaging (see Page 8): first year (every 3 months); second and third year (every 3-4 months)	We respectfully request we leave a range for the first year as there is variation based on risk to have more frequent follow-up. We have changed the second and third year to every three to four months.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in May 2019. The RAP approved the document May 2019. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Regarding the "Simulation to Treatment" timeline recommendation: I would change that recommendation to be closer to the follow-up recommendations. This simulation to treatment interval is not how to technically carry out the simulation (as the other areas of the recommendation box reflect) but rather, it is part of the SRS regimen – interval to start, so you target the correct spot before the lesions in the brain shift, and then frequency of follow-up so you can balance seeing disease progress quickly enough versus parts of the brain tissue dying. So I would keep those things closer together.	Respectfully, we have gone through the document and we believe the information is accurately presented as currently written.

2. Interval between simulation to treatment should have had a systematic review to search for evidence regarding the optimal timing.	This is currently standard practice within Ontario and we respectfully do not think that a systematic review was needed. The recommended interval from simulation to treatment is also in line with the CCO quality indicator of two weeks.
3. Are there any patients on this panel?	Four patients/survivors/caregivers participated as Consultation Group members for the SRS for Brain Metastasis Working Group. They reviewed copies of the project plan/draft recommendations and provided feedback on its/their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

Table 5-3. Summary of the Working Group's responses to comments from the Patient Consultation Group.

Comments	Responses
1. Do the clinicians on the MCC make the patients aware of the outcomes and potential side effects of the SRS treatment?	That is standard medical practice where consent requires discussion of outcomes and adverse effects.
2. What happens to patients with <4 brain metastases?	Typically, the treatment would be SRS; however, we did not get into treatment recommendations as that is beyond the scope of the guideline.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario who are considered to be clinical experts on the topic were identified by the Working Group members. Three agreed to be the reviewers (Appendix 1). Two responses were received (AN, KS). Results of the feedback survey are summarized in Table 5-4. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					2
2. Rate the guideline presentation.					2
3. Rate the guideline recommendations.				1	1
4. Rate the completeness of reporting.					2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	1
6. Rate the overall quality of the guideline report.				1	1

	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					2
8. I would recommend this guideline for use in practice.					2
9. What are the barriers or enablers to the implementation of this guideline report?	Enablers: 1) Access to CCO Website-PEBC Disease Site Guidelines; and 2) E-mail distribution to Radiation Program Lead for discussion and dissemination within their respective Programs				

Table 5-5. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. Recommendation 4: Although the MRIs may be permitted to have 2 mm slice thickness, they should be reconstructed on 1 mm centres, not 2 mm centres. One millimetre margins are often used for SRS. Requiring 0.6–0.7 mm resolution in the axial plane and permitting 2 mm resolution in the craniocaudal direction is illogical. SRS planning with this kind of non-isotropic imaging resolution causes targets to be too large in the craniocaudal direction due to volume averaging, which would increase the risk of RN. The additional information on page 25 clarifies what is done in Toronto, but this should be the guideline recommendation for the entire province. In my opinion, no MRI with craniocaudal imaging resolution of >1 mm should be used for SRS. Centres should not be using an MRI scanner for SRS that cannot achieve this quality of imaging (AN).	We agree with the reviewer in principle; however, there are many issues with MRI and SRS and these recommendations are in par with AAPM and a minimum for the community. There are pixel size, bandwidth, field of view, etc., that all are important aspects of MRI and different scanners allow for different options including interpolation, no skip, etc., specific to the MRI scanner brand. Therefore, the intent of this paper is not to be so prescriptive as to not address different options per scanner. We provide the example of what is done in Toronto as a reference. We have amended the recommendation as follows: *Slice thickness no greater than 1 mm is recommended with in-plane resolution of no more than 1 × 1 mm. If 2 mm slice thickness is used then interpolation to 1 mm, and this is acknowledged to be dependent on the type of MRI scanner and image reconstruction.*
2. Recommendation 6: Imaging every two months would substantially increase the cost of follow-up imaging and the cost of retreatments for no clinical advantage over imaging every three months, as was done in the majority of clinical trials of SRS. The decision to recommend follow-up imaging every two months is out of keeping with most other guidelines and is not supported by any evidence. In my years of following hundreds of patients after SRS, I have never had a patient develop clinical symptoms from a new metastasis that appeared during a three-month time interval. There is no value of MRIs four to six weeks after SRS (AN).	We state every two to three months, and this is in keeping with current practice in Ontario.
3. "Upon questionable progression versus necrosis, the case must be discussed in MCC" page 26. This recommendation is excessively prescriptive. Enlargement of treated brain metastases is so common that it should be	This is for the community to ensure that these cases are not mistakenly judged to be progression versus necrosis. This is a safety issue and one we believed is appropriate for Ontario.

regarded as normal. Most cases do not require any specialized imaging or any discussion. I think it makes sense to mandate that every case of an enlarging, symptomatic treated lesion be discussed in MCC if the symptoms do not settle with a finite course of corticosteroids (AN).	
4. This guideline discusses advanced imaging, biopsy, and surgery, etc., for enlarging treated lesions. However, I am not sure that this document is meant to provide advice about how to manage enlarging treated lesions. If it is, it should make clear that observation without any special imaging or biopsy is the preferred management, unless the lesion causes symptoms that do not settle with a finite course of corticosteroids (AN).	We need to provide guidance but this guidance is not meant to be prescriptive; hence, we state these cases should be discussed in an MCC as there are many options.
5. Page 31 "At a minimum, the MCC should include the radiation oncologist, neuroradiologist and, if available, the neurosurgeon and a neuro-oncologist." This is unclear. What is the minimum membership of an MCC? Does there need to be another clinician apart from the treating radiation oncologist, or is the treating radiation oncologist and a neuro-radiologist sufficient? I question the value of neuro-oncologists, who specialize in the care of primary brain malignancies as members of an SRS MCC (AN).	We disagree, especially as we use Avastin more and more. A neuro-oncologist needs to prescribe this and it is highly useful for symptomatic necroses.
6. Another relevant guideline: Stereotactic radiosurgery for treatment of brain metastases: A report of the DEGRO Working Group on Stereotactic Radiotherapy. Strahlenther Onkol 2014;190:521–532 (AN).	Thank you for bringing this to our attention. It was not captured in the guideline review as it was not one of the North American organizations we reviewed; however, upon review, this guideline supports our recommendations for the organizational aspects of SRS.
7. As the document is an Institutional Guideline Policy, it would not be expected to provide a detailed background and recommendation based on clinical practice/evidence base. However, in reviewing the document it may be useful within the introduction to include a statement: This guideline document is not intended to present the evidence base for dose prescribing practices in the delivery of SRS for brain metastases. This literature should be reviewed separately and used to guide clinical management upon meeting the institutional guidelines set out in this document for the delivery of this treatment modality (AN).	We agree and have amended the Guideline to add in this statement.
8. This is a really minor issue. There is an error in Table 4-3 about my clinical trial, which is reference 59. There was one unexplained death at four weeks that could have been grade 5 necrosis and there was no late grade 5 necrosis (AN).	Thank you. We have corrected the table.

Excellent document: well researched, designed, and presented (AN).	Thank you.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All neuro-oncologists, radiation oncologists and medical oncologists in the PEBC database were contacted by e-mail to inform them of the survey. In total, 245 experts were contacted. All were located in Ontario. Thirty-five (14.2%) responses were received. Seventeen stated that they did not have interest in this area or were unavailable to review this guideline at the time and one did not fill out the professional consultation form. The results of the feedback survey from 17 people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	Number 17 (7%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	o	1	3	8	5
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1	3	3	7	3
3. I would recommend this guideline for use in practice.	0	2	4	4	7
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Human resources (especially at smaller cancer centres) • Access to SRS technology (especially at smaller cancer centres • Availability of MRIs • MCC team member availability • Getting widespread distribution - and overturning the separate guidelines most Ontario centres have already created (largely similar but with some key differences) • Constitution of the MCC as recommended may be difficult for some centres.				

Table 5-7. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. This document is very good in several respects but there are some non-evidence-based recommendations that will not improve patient safety or quality of care but WILL compromise access to care for patients at mid-sized cancer centres. Most importantly, there is no	The recommendation for the MCC is clearly stated: "The clinical and imaging details of each SRS case must be discussed in a multi-disciplinary case conference (MCC). The MCC should be comprised ideally of a radiation oncologist, neurosurgeon, medical physicist, radiation therapist/medical

	evidence to support MCC assessment including neurosurgery and neuroradiology for all patients. The indications for treatment in the majority of patients are clear and decision making is straightforward. At our cancer centre we have deliberately recruited several radiation oncologists who have completed formal fellowship training in precision neuroradiation oncology in order to promote devolved regional access to this important modality for brain metastases and they are perfectly capable of making these decisions. We have access to rapid neurosurgical consultation as needed. It would not be difficult to agree provincial guidelines for neurosurgical referral (e.g., mass effect, complex/large lesions, uncertain diagnosis etc.) to further strengthen this aspect of care.	dosimetrist, and a neuroradiologist. At a minimum, the radiation oncologist, neuroradiologist and, if available, a neurosurgeon and neuro-oncologist should be involved when discussing possible radiation necrosis versus tumour progression." It should not be underscored that a neuroradiologist is of high importance to the MCC. A radiation oncologist may not have the understanding of the surgical indications and it is important to have neurosurgery in the MCC *when possible*, as cases that are better served with surgery or vice versa is the issue at hand. Neuromedical oncologists are in need for the evaluation of necroses, as more and more Avastin will be prescribed. There are too many variations to stipulate which patient should be discussed at MCC; it is safer to state that all patients where SRS is decided need to be brought to the MCC and that is what is done at centres globally that perform this technique safely. CCO and safety warrants that all patients should be discussed and is the current standard of care at most institutions in Ontario. This guideline has input from J Perry, who is a neuro-oncologist. We do acknowledge that the availability of neurosurgery may be a barrier to the implementation of this guideline. If possible, smaller centres should link up with larger centres to provide that expertise. Additionally, we have amended the recommendation to include radiation oncologists who have completed formal fellowship training in precision neuroradiation to help fill this resource gap.
2.	I disagree with the recommendation to have neurosurgeons routinely involved in target selection, except for post-operative cases. Radiation oncologists with the help of neuro-radiologists are fully capable of doing this.	
3.	There is over-emphasis on the role of neurosurgery and neuroradiology in upfront decision making, while the diagnosis and management of the majority of cases with a known cancer diagnosis should be straightforward. It would be helpful to define criteria when their expertise are required	
4.	Smaller centres with the intention of providing SRS, may not have access to a specific fellowship-trained neuroradiologist. I suggest that a general radiologist with an interest or focus in neuroradiology may also be allowed. Similarly, the neurosurgeons in such centres may have less SRS experience, which may not preclude radiation oncologists treating oncology patients.	
5.	Many of the issues are highly technical and outside of the scope of many medical oncologists. I wonder whether an expert systemic therapy specialist (neuro-oncologist or medical oncologist) should take part in a centre's SRS committee or if this input is considered in the referral process for SRS?	
6.	This is a very consensus-based report and therefore it is difficult to know the strength of the recommendations. There	A systemic review was not performed for the simulation interval as this is currently standard practice within Ontario and we respectfully do not

was one comment around Recommendation 4 that this was not based on a systemic review but evidence provided by the team. Why was a systemic review not performed? I also think this is missing a systematic review of the evidence for SRS. There are some brief statements in the introduction that SRS is the standard of care. I would have thought the logical order to approach this was a systemic review of the evidence for SRS followed by a document of recommendations on how/what is needed to implement this.	think that a systematic review was needed. The recommended interval from simulation to treatment is also in line with the CCO quality indicator of two weeks. Due to the presence of pre-existing guidelines regarding the utility of SRS in patients with brain metastasis, CCO's Radiation Treatment Program may consider endorsing one of these guidance documents in the future. The need for an organizational guideline was based on the current use of SRS in Ontario and the need to standardize practice among centres currently using the technology.
7. The CCO mandate has always been providing timely access to cancer care closer to home. As new technologies become more available to smaller cancer centres, recommendations should be supportive of such a model. Quality criteria need to be realistically attainable for this model to be adopted in smaller cancer centres.	We are confident that the recommendations outlined in this Guideline are the minimum applicable recommendations for the safe delivery of SRS in Ontario. CCO mandates safe delivery and if that cannot be afforded then the centre should not be doing this technique.
8. It is worth mentioning that the few other PEBC guidance documents I have been involved in (for potentially curative treatments) have not even been as restrictive.	The GDG is confident that the recommendations outlined in this Guideline are the minimum applicable recommendations for the safe delivery of SRS in Ontario.
9. Please detail what type of immobilization device should be used. List the currently available research protocols.	This is beyond the scope of this guideline. Additionally, these immobilization devices are also specific to the technology.
10. No nurse on the team?	In our interpretation of evidence for Recommendation 1, we state that "These are in addition to the nurses and administrative staff who provide general support for all patients in the radiation oncology department". However, we have moved this statement into the qualifying statements as well for clarification.
11. Under Recommendation 4, Simulation, it is unclear under the CT heading why "image quality" is left hanging at the end. It's not really clear what the authors are trying to say here.	We have amended this bullet to read: *"All aspects of image quality should be thoroughly investigated prior to use for SRS including (but not limited to): partial volume averaging, spatial distortion, motion artifacts, magnetic susceptibility artifacts, image reformatting, etc."*
12. Much of the recommendations already exist or are not be able to exist at a given centre (e.g., qualifications, type of scanner). Follow-up frequency is not data driven and is contingent on scanning resources.	The GDG believe that the recommendations outlined in this Guideline for patient follow-up are the minimum applicable recommendations for the safe delivery of SRS in Ontario. The Working Group does recognise that the availability of MRI may be a barrier to implementation; however, we believe that clinical follow-up alone is not appropriate and not in keeping with global practice. This section has been reviewed by the GDG and is appropriate for Ontario.
13. The strong recommendations for MRI as a required element of follow-up are not justified by the data provided nor do they represent an appropriate use of limited	

funds in this population. Individuals followed clinically with MRIs triggered by clinical finding had similar outcomes.	
14. The follow-up section of this report should be amended or additional feedback sought from other clinician groups as the authors do not appear to consider alternative data in their recommendations.	
15. The very frequent follow-up schedule may duplicate work being done by the medical/neuro-oncologist and perhaps could be shared? With these palliative patients, frequent appointments for imaging and medical visits interfere with quality of life.	This should be handled internally by the centre as imaging follow-up by the Central Nervous System team is imperative to the safe delivery of SRS.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table 1. Members of the SRS for Brain Metastasis Working Group.

Name	Affiliation	Declarations of interest
Arjun Sahgal Working Group Chair Radiation Oncologist	Sunnybrook Hospital Toronto, ON	Dr. Arjun Sahgal has received honorarium for past educational seminars from Elekta AB, Accuray Inc, and Varian Medical Systems and research grants from Elekta AB. Dr. Sahgal also belongs to the Elekta MR Linac Research Consortium.
Jeffery Greenspoon Radiation Oncologist	Juravinski Cancer Centre Hamilton, ON	Dr. Greenspoon has been PI on some studies related to radiosurgery and brain metastases at McMaster. CEC.3, involved in CE.7. in house smaller studies Involved in the Accuray Fellowship at McMaster, fellowship focus is SRS/SBRT
Matthew Follwell Radiation Oncologist	Royal Victoria Regional Health Centre Barrie, ON	No conflicts declared
John Sinclair Neurosurgeon	The Ottawa Hospital Ottawa, ON	No conflicts declared
James Perry Systemic Therapy Neuro-Oncologist	Cancer Care Ontario Toronto, ON	No conflicts declared
Mark Ruschin Medical Physicist	Sunnybrook Hospital Toronto, ON	Dr. Ruschin is the co-inventor of and owns associated intellectual property specific to the image-guidance system on the Gamma Knife Icon. Co-investigator on Elekta-sponsored technical grants (statements of work)
Omar Islam Radiologist	Kingston General Hospital Kingston, ON	No conflicts declared
Sarah Kellett Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	No conflicts declared

Table 2: Members of the SRS for Brain Metastasis Expert Panel

Name	Affiliation	Declarations of Interest
Dr. Eric Marmor Neurosurgeon	Trillium Health Partners Toronto, ON	No conflicts declared
Dr. Normand Laperriere Radiation Oncologist	Radiation Medicine Program at the Princess Margaret Toronto, ON	Abbvie Corporation Completion of an online survey Merck Sponsored travel and honorarium for speaking at a meeting Merck Sponsored travel
Dr. Luluel Khan Radiation Oncologist	Trillium Health Partners Toronto, ON	No conflicts declared
Dr. Chinthaka (Chris) Heyn Neuroradiologist	Sunnybrook Hospital Toronto, ON	No conflicts declared

Table 3: **Members of the Report Approval Panel**

Name	Affiliation	Declarations of Interest
Dr. Laurie Elit Surgeon	McMaster University Hamilton, ON	No conflicts declared
Dr. Melissa Brouwers Public Health and Epidemiology	University of Ottawa Ottawa, ON	No conflicts declared
Dr. Jonathan Sussman PEBC, Director	McMaster University Hamilton, ON	No conflicts declared

Table 4: Members of the Targeted Peer Review Panel

Name	Affiliation	Declarations of Interest
Dr. Alan Nichol Radiation Oncologist	University of British Columbia, Department of Surgery Vancouver, BC	Was a PI in clinical trials: NCT01046123 NCT02220491
Dr. Kenneth Schneider Radiation Oncologist	Windsor Cancer Centre Windsor, Ontario	No conflicts declared

Table 5: Members of the Patient Consultation Panel

Name	Declarations of Interest
Lauri Petz	No conflicts declared
Bob Tuck	No conflicts declared
Marissa Myers	No conflicts declared
Lise Craig	No conflicts declared

Appendix 2: Literature Search Strategy

1. Radiosurgery/
2. (radiosurg* or stereotactic or linear accelerator or cyberknife or gamma knife or linac).mp.
3. 1 or 2
4. exp Brain Neoplasms/
5. ((brain or cerebral or cerebellum) adj5 (tumor* or tumour* or neoplas* or cancer* or carcinoma* or malignan* or metast*)).mp.
6. 4 or 5
7. exp Magnetic Resonance Imaging/
8. (magnetic resonance Imaging or MRI).mp.
9. 7 or 8
10. (radiation necrosis or radiation injury or radionecrosis).mp.
11. 3 and 6 and 9 and 10

Appendix 3: PRISMA Flow Diagram