Local Control of Brain Metastasis with Post-Surgical Cavity-Directed Adjuvant Radiation Utilizing Stereotactic Radiosurgery: A Scoping Literature Review and Institutional Retrospective Study

by

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List of Abbreviations

ALK – Anaplastic Lymphoma Kinase
ARE – Adverse Radiation Effects
BAX – bcl-2-associated X protein
BBB – Blood Brain Barrier
BRAF – v-raf murine sarcoma viral oncogene homolog B1
CNS – Central Nervous System
CI – Confidence Interval
CI – Conformity Index
CK – Cyber Knife
cm3 – centimeter cubic
DC – Distant Control
DNA – Dexoyribonucleic Acid
DP – Distant Progression
ECOG – Eastern European Cooperative Group
EGFR – Epidermal Growth Factor Receptor
ER/PR/HER – Estrogen Receptor/Progesterone Receptor/Human Epidermal Growth Factor 2
et al. – et alia
FSR – Fractionated Stereotactic Radiation
GK – Gamma Knife
GKRS – Gamma Knife Radiosurgery
GPA – Graded Prognostic Assessment
GTR – Gross Total Resection
Gy – Gray
HER2Neu – Human Epidermal Growth Factor Receptor 2, ERBB2 amplification, HER2 overexpression
HR – Hazards Ratio
IBM SPSS – International Business Machines Statistical Package for the Social Sciences
KPS – Karnofsky Performance Scale
LC – Local Control
LMD – Leptomeningeal Disease
LINAC – Linear Accelerator
MVA – Multivariable Analysis
mm – millimeters
MRI – Magnetic Resonance Imaging
NR – Not Reported
NSCLC – Non-Small Cell Cancer
PIV/TVC – Prescription Isodose Volume/Target Volume Ratio
PRISMA – Preferred Reporting in Systematic Reviews and Meta-Analyses
PTV – Planning Target Volume
ROC – Receive Operating Characteristics
RPA – Recursive Partitioning Analysis
RCC – Renal Cell Cancer
RT – Radiotherapy
RTOG – Radiation Therapy Oncology Group
SCC – Squamous Cell Carcinoma
SCLC – Small Cell Lung Cancer
SRS – Stereotactic Radiosurgery
SRT – Stereotactic Radiotherapy
STR – Subtotal Resection
TKI – Tyrosine Kinase Inhibitor
TTT – Time to Treatment
UVA – Univariate Analysis
WBRT – Whole Brain Radiotherapy
T1/T2 – Tesla 1/Tesla 2

ABSTRACT

Objective: To investigate potential factors influencing local control in metastatic brain disease patients undergoing adjuvant stereotactic radiosurgery (SRS) to surgical cavities.

Methods: A scoping review of the literature and retrospective analysis were conducted. The scoping review encompassed multiple databases, to determine relevant studies that identified factors impacting local control in metastatic tumor surgical cavities. The retrospective analysis involved a 17-year cohort of patients who underwent adjuvant SRS for metastatic surgical cavities. Data regarding factors influencing control rates were collected and analyzed.

Results: The scoping review yielded 10,633 articles, with 22 included in the final analysis. Factors such as histology, radiation dose, tumor size, extent of resection, treatment timing, tumor depth, and dural or pial attachment demonstrated impacts on local control. However, primary disease status, surgical corridor coverage, and tumor location did not significantly affect control. In the retrospective study of 63 patients with 63 surgical cavities, the 12-month local control rate was 66.7%, and the 24-month rate was 57.1%. Distant progression occurred in 58.7% of cases. Overall development of leptomeningeal disease, and treated cavity adverse radiation effects were observed in 15.9% and 20.6% of cases, respectively. None of the examined factors significantly influenced local control. Local progression within the first year of treatment was associated with a 5.0-fold increased risk of death at 24 months, while distant intracranial progression showed a 6.0-fold increased risk at 12 months and an 8.2-fold increased risk at 24 months.

Conclusion: Prospective studies are necessary to identify predictive factors for achieving local control following cavity-directed SRS. These findings have implications for developing future treatment guidelines and optimizing outcomes in the management of metastatic brain disease.

Chapter 1: Introduction

Metastatic brain disease is a health-care challenge associated with limited survival and quality of life (Brem & Panattil, 2005). Metastases are the leading cause of central nervous system neoplasms (Brem & Panattil, 2005). While there have been some improvements in survival rates, the outcomes for patients with metastatic brain disease are still generally poor.

Therapeutic success of brain metastases is hindered by several factors, including high rates of recurrence and progression (Brem & Panattil, 2005). The optimal treatment strategy minimizes the risk of recurrence and progression while maintaining a good quality of life for the patient.

Current armamentarium for management of metastatic brain disease

The current pillars of anti-cancer therapies, including surgery, chemotherapy, and radiation therapy are employed in the treatment of metastatic brain disease (Brem & Panattil, 2005). Surgery, which is the mainstay treatment for mass effect producing metastases has a local recurrence rate as high as 50% (Patchell et al., 1990). Standard chemotherapy has limited success due to the pharmaceutical sanctuary that is the blood brain barrier (Soffietti et al., 2017). Newer targeted therapies have shown promising outcomes (Niranjan et al., 2019). Some have demonstrated good penetrance to the CNS environment (Niranjan et al., 2019; Sharma et al., 2021); however, the responses are not sustained with reports of tumor recurrence following discontinuation of treatment (Sharma et al., 2021). Immunotherapy, when implemented in the

appropriate context of receptor expression, has shown impressive results in terms of tumor response, albeit accompanied by adverse treatment effects that occur in approximately 50% of cases (Topalian et al., 2012). Radiotherapy in its multiple forms, plays a crucial role in disease control (Andrews et al., 2004). Whole brain radiotherapy as monotherapy or adjuvant therapy provides significant control of the metastatic deposits and surgical cavities (Patchell et al., 1998), although it has been linked to poor cognitive outcomes (Brown et al., 2017). Radiosurgery allows better cognitive outcomes, however, most studies (Brown et al., 2017; Patel et al., 2014), including a randomized controlled trial (Brown et al., 2017), showed it to lower local control compared to WBRT. In fact, the annual cavity control rates for WBRT is reported to be as high as 80% vs. 60% for SRS (Brown et al., 2017). Interestingly, despite WBRT having better annual control rates than SRS, it did not confer a survival benefit in comparison (Brown et al., 2017; Patel et al., 2014). It also worth noting that some evidence suggest comparable, if not superior, local control outcomes in favor of SRS when compared to WBRT (Vlachos et al., 2023).

Role of stereotactic radiosurgery

Stereotactic radiosurgery (SRS) has emerged as a versatile treatment modality, with utility as both an adjuvant and primary approach, depending on patient and tumor characteristics, including symptomatology, number of metastases, location, and size. It is currently being utilized as standard of care in many instances (Akanda et al., 2020; Brem & Panattil, 2005).

When comparing the adjuvant radiotherapeutic modalities, the primary focus is to examine their capacity to achieve robust control for both, the treated cavity and distant disease, their toxicity profile, and their impact of survival outcomes.

The control aspect has the noteworthy finding that SRS has potentially comparable cavity control results to WBRT as previously highlighted (Brown et al., 2017; Vlachos et al., 2023), as well as good distant disease control when the number and size of the additional metastatic deposits fall within the feasibility of SRS (Brown et al., 2016; Kocher et al., 2011). WBRT serves as the modality of choice when the number of metastatic deposits surpasses safe treatment with SRS (Ramos et al., 2022).

In terms of toxicity, it is important to highlight that SRS has significantly fewer neurocognitive toxicities compared to WBRT (Brown et al., 2016). This disparity has particular significance when selecting the optimal modality for patients with limited intracranial metastatic burden, wherein SRS becomes the superior choice given its lower negative impact on neurocognitive function.

Regarding survival outcomes, both modalities have not shown survival advantage, reinforcing the similarity in efficacy between SRS and WRBT (Akanda et al., 2020; Brown et al., 2017; Vlachos et al., 2023). In that comparison, particularly considering the reduced neurocognitive toxicities associated with SRS, it becomes evident that SRS stands as the preferred option for treating surgical cavities in patients with limited intracranial metastatic burden (Ramos et al., 2022).

SRS, however, can be delivered in numerous different ways that can potentially influence its efficacy. Moreover, treatment related factors such as extent of surgical resection, the specifics of radio-surgical treatment, and the timing of adjuvant therapy are still being studied with inconsistent results (Akanda et al., 2020; C. Y. H. Choi et al., 2012; Gui et al., 2020; O'Brien et al., 2021; Ramos et al., 2022).

The goal of this thesis is to identify factors that will refine the role of stereotactic radiosurgery as an adjuvant therapy to resected metastatic tumor cavities. Identifying potential patient, tumor, and modifiable treatment characteristics with significant association to tumor control, will allow optimization of patient selection, treatment planning, and delivery.

1.1 Aims and Hypotheses

1.1.1 Overriding Hypothesis

The overriding hypothesis of this thesis is: Several patient, tumor, and radiosurgical technique factors have a significant effect on cavity control rates following adjuvant cavity-directed stereotactic radiosurgery.

To explore this hypothesis, this thesis will aim to analyze patient selection, treatment planning, including several different patient, tumor, and treatment related characteristics in terms of tumor control and survival outcomes.

1.1.2 Variation of SRS Treatment Related Parameters:

Multiple retrospective studies have demonstrated the significant impact of specific stereotactic radiosurgery (SRS) treatment parameters on recurrence rates following adjuvant treatment in resected brain metastases (Akanda et al., 2020; Auchter et al., 1996; C. Y. H. Choi et al., 2012; Gui et al., 2020; O'Brien et al., 2021; Soltys et al., 2008). However, there is a lack of studies focusing on crucial parameters such as plan conformity, treatment margin, coverage of surgical tract and dural attachment, and treatment timing. This thesis aims to address the following question for this domain:

1) Are there specific treatment planning parameters that would lead to better local tumor control following adjuvant SRS to the surgical cavities of brain metastases?

To investigate this question, the thesis will employ a two-fold approach. First, a concise scoping review of published studies will be conducted, systematically exploring the available literature on the aforementioned treatment-related factors and their impact on local control in resected brain metastases treated with adjuvant Gamma Knife radiosurgery. Second, a local retrospective database study will be performed to analyze these treatment parameters and their association with local control outcomes. The study will focus on a specific cohort of patients who underwent adjuvant SRS for resected brain metastases, and relevant data regarding the treatment-related factors will be collected and analyzed.

Hypothesis 1: Modifiable treatment related parameters, including marginal dose, maximum delivered dose (D100%), plan conformity, time to treatment, dural-tail and surgical corridor coverage will influence local control rates at 12 and 24 months. Larger

doses, expanded margins, shorter time to treatment, and coverage of dural-tail and surgical corridors will result in better control rates.

1.1.3 Tumor and Histopathological Variations:

Limited research has been conducted on the influence of histopathological variations (e.g., breast, lung, renal, melanoma, etc.) (Brennan et al., 2014; C. Y. H. Choi et al., 2012), and other characteristics of metastatic tumors (such as multiple lesions, pre-operative tumor size, degree of resection, and surgical cavity volume) (Auchter et al., 1996; Jensen et al., 2011; Mahajan et al., 2017), radiosensitivity (Ahmed et al., 2014), and its impact on local control. The existing literature is notably scarce and characterized by heterogeneity in outcome reporting, often combining the different primary histopathologies when analyzing the outcomes of adjuvant-treated metastatic cavities. This prompts the following research question:

2) To what extent do variations in the histopathological, morphological, and molecular profiles of primary diseases impact tumor control and patient survival after adjuvant SRS in the surgical cavities of brain metastases?

The two-fold approach adopted by this thesis will address this research question by conducting an in-depth analysis of the existing literature, focusing on histopathology-specific studies and their reported outcomes. This comprehensive review will systematically examine the available evidence and identify control and survival patterns across the various primary pathologies. Secondly, by

analyzing the local data, this thesis will further investigate the influence of histopathological variations on tumor control and patient survival following adjuvant SRS.

Hypothesis 2: Histopathology will predict local control rates, with higher dosing required for radioresistant histopathologies (e.g. melanoma, and renal cell) (McPherson et al., 2010). Larger post-operative cavities, subtotal resection, eloquent and dural based location, cystic lesions and irregular appearance will confer worse local control.

1.1.4 Patient and Primary Disease Parameters:

Insufficient attention has been given in the existing literature to the influence of specific patient and disease characteristics (Sankey et al., 2019; Stark et al., 2005). These include factors such as patient age, the presence of microvascular damage-inducing comorbidities like diabetes mellitus (LeCompte et al., 2018), hypertension (Sneed et al., 2015), and smoking (Shenker et al., 2017), as well as having active systemic disease, higher systemic metastatic burden, undergoing active treatment for systemic disease concurrently. Additionally, emerging evidence suggests that older age, performance status (Sperduto et al., 2008), radioresistance (Brown et al., 2002), and intracranial progression (Noteware et al., 2023), may play a role in survival outcomes. Consequently, the following research question arises:

3) To what extent do patient and disease-specific characteristics, including age, comorbidities, functional status, and intracranial metastatic burden, influence cavity

control and survival outcomes in patients who have undergone SRS to the surgical cavities of brain metastases?

The two-fold approach will address this question comprehensively. The scoping review will analyze the current body of literature and investigate the reported impact of these factors on survival outcomes following adjuvant SRS. This systematic examination of existing studies will help identify trends, gaps, and inconsistencies in the literature, thereby establishing a foundation for further analysis. The outcomes within the local cohort will then be analyzed to further explore the influence of patient and disease-specific characteristics on treated cavity control and survival outcomes. By examining a dataset specific to patients that received adjuvant SRS for brain metastases, relevant information pertaining to patient age, comorbidities, functional status, and intracranial metastatic burden will be collected and analyzed. This local analysis will provide valuable insights into the specific impact of these factors on the cohort's outcomes, complementing the findings from the scoping review.

Hypothesis 3: Older age, and multiple metastases will result in worse control rates.

Hypothesis 4: Age, performance status, radioresistance, and intracranial progression will have worse survival rates.

1.2 Overview of Thesis

Chapter 2 will present an overview of existing literature on the current management strategies for cerebral metastases. It will cover surgical options and the different methods for cavity boost, such as whole brain radiotherapy, stereotactic radiosurgery, and stereotactic radiotherapy. The chapter will summarize key predictive factors for local control found in the literature and highlight potential knowledge gap areas to be addressed by this thesis.

Chapter 3 provides the findings of a systematic scoping review of the literature analyzing the effect of treatment and pathological factors on local control of brain metastases after adjuvant treatment with single-fraction, cavity-directed stereotactic radiosurgery, further delineating the current knowledge gaps.

Chapter 4 presents the results of a retrospective analysis of a prospectively maintained local Gamma Knife database, which attempts to bridge existing knowledge gaps by examining the factors that affect local control and patient survival of brain metastases following cavity-directed adjuvant Gamma-Knife Radiosurgery.

Chapter 5 summarizes the main findings in relation to the original research questions and hypotheses, providing a conclusion to the thesis-related research.

Chapter 6 discusses future directions.

Chapter 2: Review of the Literature

2.1 Management of Metastatic Brain Disease

The management of patients with brain metastasis is a complex, multidisciplinary, and requires careful consideration of various factors (Ramos et al., 2022).

The primary objective is to maximize survival while ensuring the preservation of neurocognitive function, and quality of life (Brem & Panattil, 2005). This includes a thorough assessment of the patient's clinical status, medical history, performance status, and primary tumor characteristics, as well as the number, size, and location of brain metastases (Soffietti et al., 2017).

The treatment approach can be monotherapy, or often involves a combination of surgical resection, and adjuvant radiation therapy, along with systemic therapies (Brem & Panattil, 2005; McPherson et al., 2010; Sharma et al., 2021; Soffietti et al., 2017).

2.1.1 Patient Assessment and Prognostication Tools

In aiding patient selection, and prognostication, different assessment tools have been introduced including the Karnofsky performance status KPS (KARNOFSKY & D. A, 1949; Schag et al., 1984), the Eastern European Cooperative Group ECOG score (Oken et al., 1982), and the Recursive Partitioning Analysis (RPA) class (Sperduto et al., 2008). KPS and ECOG are

performance evaluators that proved to be significant predictors of survival (Oken et al., 1982; Schag et al., 1984).

RPA is a tool that combines the different significant predictors and classifies patients into groups with different survival outcomes. RPA has been the most remarkable prognostication tool for patient selection (Sperduto et al., 2008). Gasper et al (Gaspar et al., 1997) retrospectively analyzed one of the Radiation Therapy Oncology Group (RTOG) databases consisting of 1200 patients, for a clinical trial looking at the effectiveness of radiation and radiation sensitizers on brain metastases. They found that the most important prognostic factor was the KPS score, other factors included control of systemic disease and age less than 65 (Gaspar et al., 1997). Patients having a KPS of 70 or higher, with controlled systemic disease and age of <65 were given a class 1 allocation which predicted the best survival outcomes following intervention (Gaspar et al., 1997). Patients with a KPS less than 70 were automatically assigned a class 3 which predicted the poorest survival outcomes with median survival of 2.3 months. Class 2 patients with KPS greater than 70 but with uncontrolled systemic disease or age greater than 65 and extra-cranial metastases had a median survival of 4.2 months. Ultimately theses prognostication tools aid in selecting the appropriate intervention and patient's tolerance of the potential toxicities of delivered therapies (Gaspar et al., 1997; KARNOFSKY & D. A, 1949; Oken et al., 1982; Schag et al., 1984; Sperduto et al., 2008).

For example, in selecting patients for surgical resection, their functional status and disease prognosis are strongly considered (Soffietti et al., 2017). For example, surgical resection of a large metastases is indicated when the extra-cranial disease is controlled or expected to respond to treatment, and the intracranial metastasis becomes the rate-limiting step for improved survival and

quality of life (Brem & Panattil, 2005). Traditionally, patients with good functional status, with single or few surgically accessible metastases and a stable extra-cranial disease are deemed ideal surgical candidates (Brem & Panattil, 2005; Soffietti et al., 2017).

2.1.2 Surgical Resection

Surgery is a viable option for treating brain metastasis, and often times is the initial management strategy, particularly when there is a single metastasis that is large in size, more superficial with symptomatic mass effect. In such cases, surgery can be beneficial in increasing survival and functional independence of the patient (Stark et al., 2005). The goal in surgical resection is to obtain gross total resection, ensuring clear tumor cavity margins, while avoiding injury to functional brain (Sills, 2005). Surgery also provides histological diagnosis in case of uncertainty. This is particularly important when the metastatic brain disease is the initial presentation (Stark et al., 2005).

Significant evidence supporting the survival benefit of surgical resection has been observed since the 1980s, as reflected in various retrospective studies (Patchell et al., 1998, 1990). Notably, the pioneering 1990 Patchel study (Patchell et al., 1990) marked a pivotal milestone by providing compelling evidence through a randomized controlled trial, demonstrating a substantial improvement in survival outcomes with surgical resection (Patchell et al., 1990). The surgical group exhibited a median survival of 40 weeks, in stark contrast to the control group's mere 15 weeks (Patchell et al., 1990). Moreover, surgical resection offers the added advantage of

alleviating symptoms caused by lesions exerting significant mass effect and hydrocephalus (Patchell et al., 1990; Sills, 2005).

However, it is important to note that surgery alone also carries a significant risk of local recurrence, with rates as high as 50% (Patchell et al., 1998, 1990). It is also important to note that surgery does not address distal or systemic disease, including smaller brain metastases or other metastases that have spread to areas of the brain that are difficult to safely reach surgically. This could include tumors located deep within the brain or in areas that are not easily accessible through traditional surgical methods. Additionally, surgery may also have risks like infection, bleeding, or neurological injury (Ene & Ferguson, 2022).

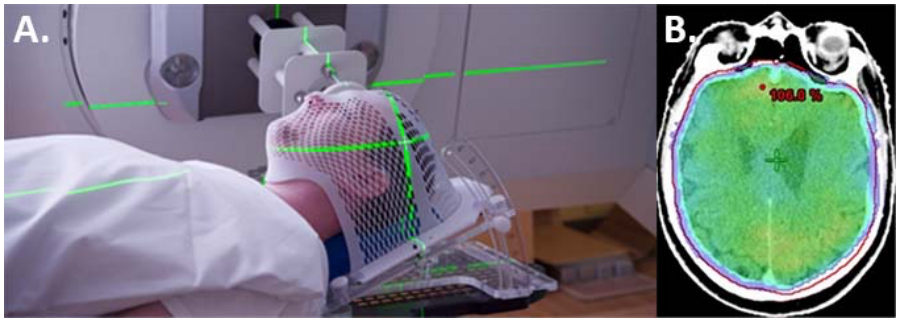
2.1.3 Adjuvant Therapy

Radiotherapy can be delivered in different forms such as whole brain radiation (WBRT), stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS). These have been shown to provide disease control when utilized as either monotherapy, or adjuvant treatment (Ramos et al., 2022). Stereotactic radiation as an adjuvant option to the surgical bed, reduces the risk of local recurrence and minimizes the negative effects on cognitive function associated with WBRT (Brown et al., 2016). The following sub-sections address both WBRT and SRS in the treatment of cerebral metastasis in more detail.

1. Adjuvant Whole Brain Radiotherapy

Whole Brain Radiotherapy (WBRT) typically involves the use of a linear accelerator, which generates high-energy X-rays, to administer radiation to the entire brain in a series of treatment sessions (Halperin et al., 2013). The process begins with a comprehensive treatment planning phase, where imaging techniques such as magnetic resonance imaging (MRI), and computed tomography (CT) are employed to delineate the target volume (Halperin et al., 2013). The patient is placed in a fitted mask to help immobilize and avoid inadvertently radiating critical structures outside of the planned treatment volumes (Halperin et al., 2013) (Figure 1). The session typically lasts for half an hour or longer, following which the patient is observed for any potential adverse effects. The number of treatment sessions and the total radiation dose are determined based on individual factors and treatment goals (Halperin et al., 2013).

Figure 1. Whole Brain Radiotherapy Process



A. Patient with fitted mask undergoing WBRT treatment. B. Dose distribution on a planning CT scan (whole brain coverage).

Images sources: A) Istock (Model(s) used for illustrative purposes only), B) Zindler, J.D., Bruynzeel, A.M.E., Eekers, D.B.P. et al. Whole brain radiotherapy versus stereotactic radiosurgery for 4–10 brain metastases: a phase III randomised multicentre trial. BMC Cancer 17, 500 (2017). https://doi.org/10.1186/s12885-017-3494-z

In reviewing the timeline of introducing WBRT in managing brain metastases, it was first studied in the 1950s as an option for treating metastatic brain disease (Minesh P. Mehta & Khuntia, 2005).

Prior to that, survival following development of brain metastases was extremely grim, limited to 2 months from detection (Minesh P. Mehta & Khuntia, 2005). As an adjuvant option, Patchell et al in 1990 looked at 48 patients randomized to surgical resection followed by adjuvant WBRT vs stereotactic biopsy only followed by WBRT (Patchell et al., 1990). The surgical resection group with adjuvant WBRT group had better local control (20% compared to 52% in the WBRT alone group) (Patchell et al., 1990). This also conferred a survival benefit of 10 months in the surgical resection group compared to 4 months in the WBRT alone group (Patchell et al., 1998). Another study showed that surgical resection followed by WBRT provided longer functional independence compared to WBRT alone (7.5 months versus 3.5 months; p=0.06) respectively (Vecht et al., 1993). The survival benefit of surgical resection with adjuvant WBRT has not been observed in all trials. Mintz et al randomized 84 patients with a single metastasis to resection followed by WBRT versus WBRT alone and were unable to detect a significant survival difference between the two groups (6.3 months compared to 5.6 months; p=0.24) (Mintz et al., 1996). However, in interpreting the survival result of that trial, it's important to note that more than half of the cohort had other confounders that might have affected their survival outcomes, including uncontrolled extra-cranial disease and functional Karnofsky Performance score KPS of less than 70 (Mintz et al., 1996).

Patchell et al 1998 proceeded with a Phase III randomized trial that included 95 patients with oligometastases and randomized to surgery alone versus surgical resection with adjuvant WBRT (Patchell et al., 1998). Local recurrence was significantly less in the group receiving adjuvant WBRT (10% compared to 46%; $p < 0.001$) (Patchell et al., 1998). That trial also showed a lower rate of neurological death in the adjuvant WBRT group (14% compared to 44%; p=0.003).

However, the trial was not powered for survival analysis and there was no survival benefit between the two groups (10.8 months compared to 12.0 months) (Patchell et al., 1998). Also, patients who had recurrences in the observation group received WBRT, which improved their survival confounding the results. Essentially, this trial provided a comparison between upfront adjuvant WBRT and WBRT at recurrence (Patchell et al., 1998).

Ultimately, there is significant evidence that the addition of adjuvant radiation provides improved local control rates, with actuarial recurrence rates without adjuvant radiation as high as 50-70% within six months (Patchell et al., 1998).

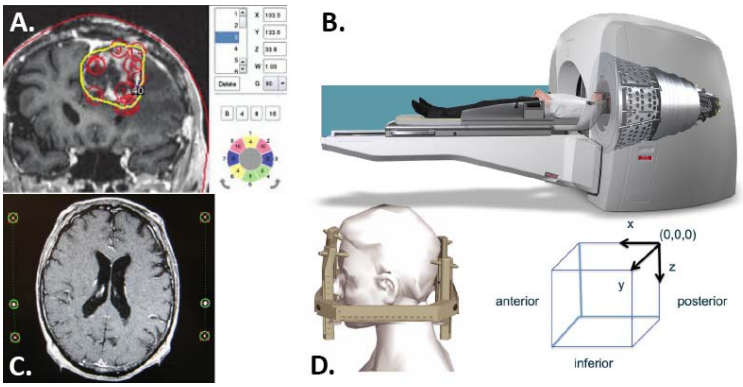
2. Adjuvant Stereotactic Radiosurgery

Using the principles of stereotaxy, SRS provides focal radiation using photons or charged particles to the selected lesion, resulting in tumoral DNA and endothelial damage with subsequent ablation (Semwal, 2020). Different systems are used to deliver SRS, the most common being the Gamma Knife delivery systems (Leksell Gamma Knife, Elekta Intsrtument AB, Inc., Stockholm, Sweden), the linear accelerator (LINAC), and the more accurate LINAC-based system, CyberKnife (Hall & Giaccia, 2012).

Gamma Knife systems utilize a stereotactic head frame that immobilizes the head with fiducial points creating a localizing box on imaging that provides localization of lesions using a Cartesian coordinate system. It uses a cobalt-60 source, decay of which results production of gamma rays

(Jung et al., 2015). It has a head collimator unit featuring circular openings of varying sizes (4, 8, 14, and 18 mm), through which radiation beams from 201 cobalt-60 sources converge to form the desired target at each planned isocenter. To ensure complete coverage of the target volume and create a conformal treatment plan, multiple isocenters are utilized (Jung et al., 2015). The use of different sized collimators, beam blocking, and multiple isocenters alter the isodose distribution (Jung et al., 2015) (Figure 2).

Figure 2. Gamma Knife Process



A. Planning software with collimator size, shot distribution, and isodose-line delination, B. The Gamma Knife Perfexion Machine with Collimator Visualized, C. MRI with fiducial sets for target coordinates on image slice, D. Indicator box attaches to frame providing fuidical marking

Images sources: A) Sahgal, A., (2009).Technology in cancer research & treatment, B) ©2019 Elekta C) Descovich. AAPM (2014, June 22). D) Descovich. (2014,June22). GammaKnife&CyberKnifeImaging [PowerPoint].AAPM. https://www.aapm.org/meetings/2014SS/documents/Descovich_Final_REVISED_ToPost.pdf

LINAC systems on the other hand deliver photon particles using a stereotactic frame with or without fixation. LINAC systems use a variety of techniques to create focal conformal plan, including arc angle manipulation, the use of numerous isocenters, differential weighting of the isocenters, and the use of blocks, collimators, and multileaf collimators, to tune the radiation beam to the target (Foote et al., 1999; Hall & Giaccia, 2012; Semwal, 2020). Additionally, the beam aperture in multileaf collimator devices can be dynamically changed while the gantry revolves around an isocenter (Semwal, 2020). Robotically operated accelerators with static collimators may

focus beams in a variety of non-coplanar directions and adjust each beam's dwell period, enabling efficient dosage modulation throughout the target volume. The LINAC system can be utilized for fractionated stereotactic radiation as well as for treating other body areas (FSR) (Levy et al., 2012).

Although there are advantages and disadvantages to each system, the differences between the two systems do not seem to provide a significant difference in clinical outcomes (Andrews et al., 2004; Becker et al., 1999; Sanghavi et al., 2001).

The high local dose of radiation delivered in single fraction, in theory, should provide better tumor control, translating into better survival. Radioresistant tumors like sarcomas, renal cell cancers, and melanoma have shown good responses to radiosurgery (Hall & Giaccia, 2012; Halperin et al., 2013). The radiobiological effect of radiosurgery works in different ways, including DNA damaged and an early direct effect by inducing apoptotic or mitotic death through the sphingomyelin pathway, and release of ceramides, leading to activation of apoptotic proteins (e.g BAX, bcl-2 family of pro-apoptotic regulators). This leads to endothelial damage and fibrosis, which eventually disrupts tumor perfusion (Balagamwala et al., 2012; Ch'ang et al., 2005). Stimulation of immune response induces further tumoral damage (Kondziolka et al., 1999).

Theoretical caveats of conformal dose delivery include underdosage of margins and incomplete ablation of cells. Overdosage on the other hand increases risk of complications such as radiation necrosis (Halperin et al., 2013; Shaw et al., 1993, 2000). Increasing number of targets also increases the irradiated volume and dose received by normal brain (Halperin et al., 2013; Shaw et al., 1993, 2000). The radiation therapy oncology group RTOG conducted a dose escalation study

and found that tumor size influences the therapeutic ratio, with tumor size having a direct correlation to the maximum tolerated radiosurgery dose (Shaw et al., 2000). They stratified tumors into 3 ordinal groups, tumors less than 20mm in size, tumors between 21 and 30mm, and tumors between 31 and 40mm. A radiosurgical dose of 18Gy was found to cause neurotoxicity in 8% of tumors less than 20mm, 20% in tumors between 21 and 30mm and up to 50% in tumors between 31 and 40mm. Given that, and using a 20% toxicity rate as the cut-off, maximum tolerable doses were selected based on tumor size. Doses of 24Gy, 18Gy, and 15Gy were the recommended maximum doses for tumors <20mm, 21-30mm, and 31-40mm respectively (Shaw et al., 2000). Moreover, in addition to risk of neurotoxicity, tumor size was also found to influence control rates. Mehta et al (M. P. Mehta et al., 1992) found that patients having tumors <2cm3 had complete response rates of 61% compared to tumors >10cm3 having a complete response rate of 10% (M. P. Mehta et al., 1992).

The new treatment paradigm following the accumulating evidence has introduced SRS as a viable option to boost the surgical resection cavity (Brown et al., 2017; Mahajan et al., 2017). Two recent randomized trials have concluded SRS to provide significantly better tumor bed control rates compared to observation alone and also decreased the risk of cognitive decline associated with WBRT (Brown et al., 2017; Mahajan et al., 2017).

The utilization of SRS as an adjuvant therapy needs refining to achieve an optimal outcome. This includes but not limited to determining the appropriate timing for postoperative SRS treatment, prescribing the optimal radiation dose and fractionation, and defining the surgical bed's target delineation.

2.2 Local Control and Survival Following Adjuvant Cavity Directed SRS

2.2.1 Local Control

The sturdiest evidence available to date is the randomized phase III trial conducted at MD Anderson in 2017 (Mahajan et al., 2017). Prior to that, only retrospective studies were reporting their control rates using SRS as an adjuvant modality. The MD Anderson trial randomized patients into groups undergoing Gamma Knife SRS within 30-days of surgical resection of their metastatic tumors and an observation group. All participants had a KPS of greater than 70 (Mahajan et al., 2017). Their trial analyzed the results of 128 patients, with 64 patients in the upfront SRS group (Mahajan et al., 2017). The 12-months freedom from local recurrence was 72% for the SRS group compared to 43% for the observation group (P=0.015) (Mahajan et al., 2017). It is notable that despite improved control, the study did not detect a significant difference in survival, with a median overall survival of 18 months in the observation group compared to 17 months in the SRS group (P=0.24) (Mahajan et al., 2017). A systematic review conduced in 2019, included fifty studies and 3458 patients that received single and fractionated SRS as surgical cavity boost, reported an overall local control rate of 83.7% at 1-year across all studies (Akanda et al., 2020).

Factors that may potentially influence local control have been explored by several retrospective studies. In terms of treatment related parameters, radiation dose has been flagged as a potential predictor of control by several other studies (Gui et al., 2020; Luther et al., 2013). Other studies

have identified longer interval times between surgical resection and SRS treatment as a predictor of worsening control (Iorio-Morin et al., 2014; O'Brien et al., 2021). The MD Anderson trial had a time to delivery within 30 days of surgical resection. A tumor treatment margin of 1mm was added (Mahajan et al., 2017). They followed a dosing scheme based on cavity volumes with 16Gy for cavities less than 10cc, 14Gy for cavities between 10.1-15cc, and 12Gy for cavities >15 cc (Mahajan et al., 2017). Tumor attachments and surgical tracts were not included within the treatment (Mahajan et al., 2017). Thus, it's difficult to draw conclusions from this trial with regards to the impact of aforementioned parameters given the standard delivery technique that was employed.

In terms of treatment margins, the most recent consensus contouring guideline published in 2018 suggests planning a target volume based on the contouring of the surgical cavity and addition of a margin up to 5mm along the bone flap and meninges. The recommendation for tumors with pre-operative dural attachment, is to add a margin of up to 10mm along the bone flap beyond the noted pre-operative attachment (Soliman et al., 2018). That recommendation comes from retrospective evidence showing increased recurrence rates for tumors with pre-operative dural contact (Susko et al., 2019). In terms of tract coverage, there has not been any strong evidence to support that practice (Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020).

Looking at potential tumor and primary disease related factors that have been reviewed to date, tumor specific factors such as tumor size, extent of resection, histopathology, and tumor attachments would be considered. Many studies have detected a significance for tumor size and

control, with larger tumors and cavity volumes having worse control rates (Brown et al., 2017; Minniti et al., 2011, 2016).

Unfortunately, there has not been any strong evidence to support specific patient selection, delivery technique, and timing practices. It is unclear whether a different dosing scheme, or larger margins, and tract coverage would have resulted in better tumor control rates.

The evidence that exists to date is scattered between retrospective studies with several limitations and contradicting results. Moreover, consensus guidelines created recommendations for delivery technique and timing based on expert opinions and the available retrospective evidence.

2.2.2 Survival

In terms of survival, the constant significant predictor is patient's recursive portioning analysis class (RPA), with patients of RPA class 1 having better survival (Brown et al., 2002; Gaspar et al., 1997; Sperduto et al., 2008). In reviewing the randomized trails that have compared cavity boosting and observation (Mahajan et al., 2017), and cavity boosting with different modalities (Brown et al., 2017), reduced recurrence rates did not translate into improved survival. One main limitation across these trials is the heterogeneity of the pathologies included, with several systemic cancers enrolled into one study which makes it difficult to have meaningful interpretation of the survival outcomes.

2.2.3 Knowledge Gap

There is insufficient strong evidence to support specific patient selection, delivery technique, and timing practices. Consensus guidelines have provided recommendations based on expert opinions and retrospective evidence, but these guidelines lack robust supporting data. Tumor-specific factors such as size, extent of resection, histopathology, and tumor attachments have been identified as potential factors affecting control rates. However, contradictory findings and limited evidence make it difficult to draw definitive conclusions. Moreover, studies comparing cavity boosting and different modalities have not shown improved survival despite reduced recurrence rates. The heterogeneity of pathologies included in these trials further complicates the interpretation of survival outcomes. Overall, there is a need for further research to address these gaps and provide more concrete evidence for optimizing treatment planning parameters, understanding the impact of primary disease characteristics on tumor control and patient survival, and identifying the specific patient and disease factors that influence survival outcomes. Such knowledge gaps are to be bridged through Chapter 3, a formal systematically conducted review of the literature on the topic, and Chapter 4, a local retrospective observational cohort study on patients undergoing GK SRS.

Chapter 3: The Influence of Treatment and Pathological Variations on Local Control of Resected Brain Metastases Following Adjuvant Treatment with Single-Fraction, Cavity-Directed Stereotactic Radiosurgery: A Concise Systematic Scoping Review of the Available Literature

3.1 Introduction:

Adjuvant radiosurgery has been shown to be effective in reducing the risk of cancer recurrence at the site of the surgical resection cavity and minimizing the potential adverse effects of whole brain radiotherapy (WBRT) on cognitive function (Brown et al., 2016; Patchell et al., 1998).

However, the specific details of the radiosurgical technique are still being studied with inconsistent results (Brennan et al., 2014; Soliman et al., 2018; Susko et al., 2019). As shown in Chapter 2, a significant knowledge gap exists in the field regarding specific patient selection, delivery techniques, and timing practices for the treatment of tumors. Although consensus guidelines have offered recommendations based on expert opinions and retrospective evidence, the lack of robust supporting data undermines their reliability. Various tumor-specific factors, including size, extent of resection, histopathology, and dural attachments, have been identified to have potential influences on control rates (Brennan et al., 2014; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Mahajan et al., 2017; Ojerholm et al., 2014; Susko et al., 2019). However, conflicting findings and limited evidence hinder the ability to draw definitive conclusions.

To optimize the use of SRS and guide patient selection and treatment planning, further research is needed to identify the patient, tumor, and modifiable treatment characteristics that may influence the control of tumors at the surgical site.

In this concise, systematically conducted scoping review, the is aim to gather the existing evidence of the potential factors influencing local control to help inform future studies and trials, preliminarily addressing Hypothesis #1 through #4 of this thesis, and further highlighting the current knowledge gaps.

3.2 Methods:

A systematic review was conducted in accordance with the methodologies outlined in the Cochrane Handbook for Systematic Reviews and reported in line with the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

3.2.1 Search Questions

This systematically conducted scoping review aimed to answer the following questions:

a) Do the variations in histopathology, molecular profiles, and treatment planning, including dose delivered, and timing have an influence over local control rates within the metastatic disease surgical cavity at 12 and 24 months after adjuvant single fraction stereotactic radiosurgery?

b) What are the reported local control rates within the metastatic disease surgical cavity at 12- and 24-months following treatment with adjuvant single fraction stereotactic radiosurgery?

3.2.2 Inclusion and Exclusion Criteria

To meet the inclusion criteria, the studies had to be fully published in peer-reviewed journals, in the English language. Patients had to be adults over 18 years of age with metastatic brain disease that had undergone post-operative stereotactic radiosurgery to the surgical cavity. Patients with prior history of receiving intracranial radiation were excluded. The SRS treatment had to be delivered in a single fraction. Studies describing hypo-fractionated regimens were excluded. The studies also had to describe the histopathology of the treated metastasis. Studies not providing SRS treatment details, and not reporting local control rates at 12 or 24 months were excluded. Studies describing intraoperative delivery of radiotherapy were also excluded. Abstracts without full-length manuscripts were excluded as-well.

3.2.3 Search Strategy

Seven databases were searched, including: Ovid Medline, PubMed, Web of Science, EMBASE, BIOSIS, Scopus, Global Health, and Cochrane with date ranges from inception to date of search on August 2nd, 2021. The following Boolean term was employed:
"(((Radiosurgery) OR (Gamma Knife)) AND ((Brain Metastasis) OR (Intracranial Metastasis)) AND ((Resection) OR (Surgical) OR (Cavity)))". The relevant studies reference lists were also screened (See Appendix 1 for search sample).

3.2.4 Study Selection and Filtering Process

The search yielded a total of 10633 results. The results were uploaded into Covidence, a web-based tool for conducting systematic reviews (Covidence, 2017). Automatic identification and removal of duplicates resulted in 7687 results for screening. Researchers (N.A., and A.A.) conducted a level 1 screening of the titles and abstracts for their eligibility as “Yes”, “Maybe”, or “No”. A level 2 screening in the form of a full-text review of the articles assessed as “Yes”, or “Maybe” was conducted and studies meeting the criteria were included into the final review. The reference lists of those articles were also be screened for relevant studies. Disputes regarding eligibility of studies were resolved through discussion between the investigators. A.A. served only as the second filtered for the purpose of managing database search results. N.A. was the primary filterer and responsible for research question design, data abstraction and data analysis.

3.2.5 Data Extraction and Summarization

Data were extracted and recorded using a standard extraction form with study details including study type, population, demographics, SRS treatment details, and outcome. The relevant variables including the histopathology, degree of resection, number of metastases, platform utilized, Isodose %, median dose in Gy, median cavity volume, addition of margin, median time to SRS, local control at 12 and 24 months, median overall survival and progression free survival were recorded. Reported significant predictors of control were recoded if available.

3.2.6 Assessment of Risk of Bias

As this is a systematically conducted scoping review of the literature, the goal was to provide a comprehensive overview of available literature pertaining to the topic. Subsequently, a formal grading/assessment of risk of bias within the final included articles was not conducted.

3.2.7 Statistical Considerations

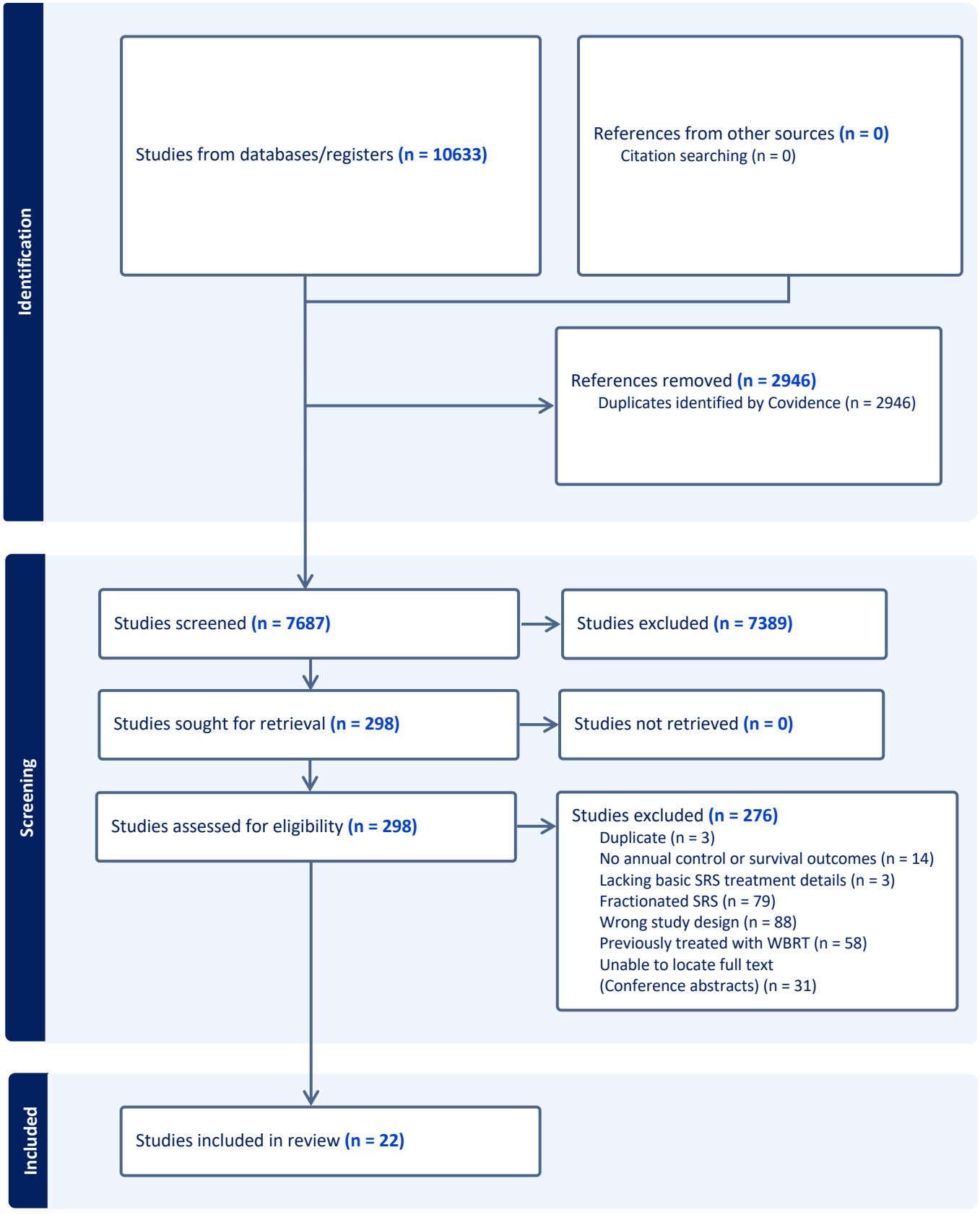
As this was a systematically conducted scoping overview of the available literature, a formal meta-analysis was not conducted.

3.3 Results:

3.3.1 Study Selection

The search resulted in 10633 articles, following removal of duplicated 7687 articles remained. The 7687 studies were screened, and 7389 studies did not meet the inclusion criteria. A total of 298 studies were reviewed in full-text, and 276 were excluded for reasons including wrong design, multi-fractionated regimens, conference abstracts without full text publication, and not providing SRS treatment details. A total of 22 articles were selected for the final review and data extraction. Three studies were prospective trials, and the remaining 19 studies were retrospective reviews (Figure 1).

Figure 3. – PRISMA Flow Diagram



3.3.2 Study Characteristics

The median age across all studies was 59, ranging from 45.1 to 66. The number of treated cavities within the individual studies ranged from 16 to 150 cavities treated with single fraction SRS session with a total of 1749 treated cavities across all studies. Primary tumor type was reported in all of the selected studies, with the most common pathology being NSCLC, with reported frequencies ranging from 14-60% of primary reported pathologies, followed by Breast (10-26%), and Melanoma (4.2-39%). Notably, the molecular status was reported in only one study (Abel 2019), reporting the Her2Neu status, which was positive in half of the breast cancers in their study. There was no sub-analysis for the molecular status in that study. Median follow-up was reported in 18 of the 22 studies and ranged from a median of 7.1-24 months. Resection rates were reported in all studies, with gross-total-resection (GTR) rates ranging from 54-100% with median= 89% (Interquartile Range [IQR], 82% - 96.4%), whereas reported rates of sub-total resection ranged from 0-46%, median= 8%; (IQR, 0% - 19%). (Table 1).

Table 1 – Scoping Review Study Characteristics

Author (year)	Study Type	# of Cavities	Median Age	Primary Type	Tumor Location	Molecular Status reported	Median Follow-up (Months)	% GTR	%STR	Primary Type Sub-analysis
Abel (2019)	Retrospective	85	57	Melanoma=33 (39%) Sarcoma=1 (1%) Renal=6 (7%) NSCLC=12 (14%) Breast =16 (19%) GI=7 (8%) SCLC=1 (1%) Other=9 (11%)	Frontal Lobe most common	No	NR	54%	46%	No
Brenann (2014)	Prospective	50	59	NSCLC= 28 (57%) Breast= 9 (18%) GI= 4 (8%) Melanoma=4 (8%) other=4 (8%)	Supratentorial= 82% Infratentorial= 8%	No	12	92%	8%	No
Brown (2017)	Prospective	98	61	Lung 58 (59%) Other 29 (30%) Radioresistant 11 (11%)	NR	No	11.1	55%	44%	No
Choi (2015)	Retrospective	25	57	NSCLC = 10 (41.7) Breast = 2 (20.8)	NR	No	16.5	100%	0%	No

				RCC = 1 (4.2) Melanoma = 1 (4.2) Other = 20.8						
Hartford (2013)	Retrospective	49	64	NSCLC = 23 (47%) Breast = 5 (10%) Melanoma=7 (14%)	Frontal (35%) Parietal (20%) Cerebellar (18%)	No	9.3	76%	24%	No
Hwang (2010)	Retrospective	25	59	NSCLC = 15 (60%) Breast = 4 (16%) Other = 4 (16%)	NR	No	NR	95%	5%	No
Iorio-Morin (2014)	Retrospective	113	58	NSCLC = 57 (50%) Breast = 15 (13%) RCC = 5 (5%) Melanoma=11 (10%) Other = 25 (23%)	NR	No	10	81%	19%	No
Iwai (2008)	Retrospective	21	61	NSCLC = 5 (24%) Breast = 2 (10%) RCC = 1 (5%) Other = 12 (59%)	NR	No	21.6	86%	14%	No
Jensen (2011)	Retrospective	112	56	NSCLC = 50 (47%) Breast = 15 (14%) RCC = 6 (5%) Melanoma = 11 (10%) Other = 20 (19%)	Infratentorial: 31 (27.7%) Supratentorial 81 (72.3%)	No	NR	96.4%	3.6%	No
Johnson (2016)	Retrospective	112	NR 73% <65	NSCLC = 65 (58%) Breast = 18 (16%) Other = 29 (26%)	NR	No	NR	82%	18%	No
Shi (Mar 2020)*	Retrospective	76 single fraction	NR for single fraction subgroup	Breast = 78 (18%) Lung = 152 (34%) Melanoma = 50 (11%) RCC = 27 (6%) GI = 53 (12%) Other/Unkn = 82 (19%)	Supratentorial= 76% Infratentorial = 24% *entire cohort	Yes	10.1	90% *entire cohort	10% *entire cohort	Yes
Shi (Oct 2020)*										
Rava (2016)	Retrospective	87	59	NSCLC = 51% Melanoma = 9% Breast = 10% Ovarian = 8% Other = 22%	Supratentorial = 77%	No	7.1	62%	38%	No
Smith (2014)	Retrospective	150	46.1	NSCLC = 65 (43%) Breast = 32 (21%) RCC = 10 (6.7%) Melanoma = 15 (10%) Other = 28 (19%)	NR	No	NR	100%	0	No
Smith (2020)	Retrospective	16	61	NSCLC = 12 (52%) Breast = 6 (26%) Renal = 2 (9%) Melanoma = 2 (9%) Oral = 1 (4%)	Frontal = 11 (48%) Parietal = 6 (26%) Occipital = 3 (13%) Temporal = 1 (4%) Cerebellum = 2 (9%)	No	12.3	100%	0	No
Strauss (2015)	Retrospective	102	62.3	Lung = 41 Breast = 13 GI = 16 Melanoma = 14 Renal = 3 Sarcoma = 7 Gyne = 5 Thymus = 1	NR	No	16.3	100%	0	No
Susko (2019)	Retrospective	60	59	NSCLC = 21 Breast = 12 Melanoma = 10 Colorectal = 3 RCC = 5 Other = 9	Supratentorial = 54 (90%) Infratentorial = 6 (10%)	No	19.8	90%	10%	No
Teyateeti (2020)	Retrospective	62	66	NSCLC = 34 (55%) Melanoma = 9 (15%) Breast = 9 (15%) Renal = 5 (8%) Other = 5 (8%)	Supratentorial = 44 (71%) Infratentorial = 18 (29%)	No	15.1	89%	11%	No

Patel (2018)	Retrospective	83	59	NSCLC = 34 (41%) Breast = 17 (20%) RCC = 9 (11%) Melanoma = 15 (18%) Other = 8 (9%)	NR	No	12.3	100%	0	No
Ojerholm (2014)	Retrospective	96	96	NSCLC = 39 (43%) Melanoma=3 (14%) Breast=12 (13%) Colorectal= 8 (9%) Renal= 6 (7%) Others	Supratentorial= 74 (77%) Infratentorial= 22 (23%)	No	15.3	82%	18%	Yes
McDermott (2019)	Retrospective	43	61	NSCLC = 18 (42%) Melanoma= 11 (25%) Breast= 5 (12%) Renal= 4 (9%) Other = 5 (12%)	Supratentorial= 31 (72%) Infratentorial= 12 (28%)	No	11.1	93%	7%	No
Mahajan (2017)	Prospective	66	58	NSCLC = 13 (21%) Breast = 9 (14%) RCC = -- (---) Melanoma = 14 (22%) Other = 27 (43%)	NR	No	11.1	100%	0	No

*GTR= Gross Total Resection, STR= Subtotal Resection, NR = Not reported, NSCLC=Non-small cell lung cancer, RCC= Renal Cell Carcinoma, GI= Gastrointestinal , Gyne= Gynecological , *Same cohort, with different analysis*

3.3.3 Radiosurgery Technique

Leksell Gamma Knife platform was used in fifteen studies (Abel et al., 2015; J. W. Choi et al., 2015; Hwang et al., 2010; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Johnson et al., 2016; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; T. R. Smith et al., 2014; Susko et al., 2019; Teyateeti et al., 2020), four studies used LINAC based systems (Brennan et al., 2014; Hartford et al., 2013; Z. T. Smith et al., 2020; Strauss et al., 2015), two studies reported using Cyberknife (Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020), and one was a multicenter study with a mixture of LINAC based and Gamma knife platforms (Brown et al., 2017). A single fraction of treatment was used in all studies. The median marginal dose delivered ranged between 15-20 Gy, median =18 Gy across studies (IQR, 16-19 Gy) with a median isodose range 40-80% for the Gamma Knife based treatments (Abel et al., 2015; J. W. Choi et al., 2015; Hwang et al., 2010; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Johnson et al., 2016; Mahajan et al., 2017; McDermott

et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; T. R. Smith et al., 2014; Susko et al., 2019; Teyateeti et al., 2020). In the LINAC studies, 10-20 Gy, median= 17Gy (IQR, 13-19 Gy), were delivered to isodose lines 80-95% (Brennan et al., 2014; Hartford et al., 2013; Z. T. Smith et al., 2020; Strauss et al., 2015), and 18 Gy to 80% isodose in the Cyberknife studies (Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020). The reported median times to treatment ranged from 7 – 32 days, median=25.8 days (IQR, 19.7-30.5 days). Twelve studies reported adding margins to the treatment plans, those ranged from 1-3mm with average of 2mm as standard practice (Abel et al., 2015; Brennan et al., 2014; Brown et al., 2017; J. W. Choi et al., 2015; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Z. T. Smith et al., 2020; Teyateeti et al., 2020). One study described a single outlier case where a 4mm margin was added due to anatomic uncertainty (Z. T. Smith et al., 2020). Median target volumes reported ranged from 4 – 13.3 cm^3 , median=8cm^3 , (IQR, 6-11.5cm^3) (Table 2).

Table 2 – Scoping Review Radiosurgery Technique Details

Author (year)	Platform (GK, LINAC, CyberKnife)	Isodose (%)	Median marginal dose (Gy)	Time to SRS (days)	Margin (mm)	Target volume (cm3)	Median Cavity Diameter
Abel (2019)	GK	50%	17.3 (14-20)	25 (1-97)	CI 1.68 (1.28-3.92)	12 (0.3-83)	2.7 x 2.9 x 2.6
Brenann (2014)	LINAC	80%	18 (15-22)	31 (7-56)	2mm PTV	NR	2.8 (1.7-5.4)
Brown (2017)	Multicenter (all)	NR	Volume-based: <4.2ml: 20Gy 4.2-7.9: 18Gy 8.0-14.3: 17Gy 14.4-19.9: 15 Gy 20-29.9: 14 Gy >30: 12 Gy	NR	2mm	11.1	< or =3 cm (60%) >3cm (40%)
Choi (2015)	GK	50%	15	14.5	"few mm"	10.5	NR
Hartford (2013)	LINAC	80-95%	10	23	NR	11.1	NR
Hwang (2010)	GK	50%	15-20	27.6	NR	NR	NR
Iorio-Morin (2014)	GK	50%	18	NR	NR	12	NR
Iwai (2008)	GK	50%	17	14-31	NR	10.7	0.3

Jensen (2011)	GK	50%	17	24	NR	12.6	3.2
Johnson (2016)	GK	NR	16	NR	NR	10.6	NR
Shi (Mar 2020)*	Cyberknife	80%	16-18	19 (14-27)	0-2mm	6.4 (3.6-10.2)	3 (2.2-4)
Shi (Oct 2020)*							
Rava (2016)	GK (Model C)	40-60%	18 (14-22)	30 (5-56)	1-2mm	NR	13.4 (3.0-40.8)
Smith (2014)	GK	50%	17.8	22.4	NR	NR	NR
Smith (2020)	LINAC	NR	16 (16-18)	41.3	1-2mm *one case = 4mm due to anatomic uncertainty	4.6 (7.7-33.3)	7.0 (1.3-52.1)
Strauss (2015)	LINAC	80%	20 (15-24)	36	0	4 (0.9-7.1)	NR
Susko (2019)	GK	50-80%	17 (16-18)	28	0	5.7 (3.5-8.8)	NR
Teyateeti (2020)	GK	50%	18-20	11 (1-49)	2-3mm	8.0 (1.4-37.7)	NR
Patel (2018)	GK	50%	16	20.5	1mm	8.2	NR
Ojerholm (2014)	GK	50%	16	42	0	9.2	NR
McDermott (2019)	GK	50%	18	30 (25-43)	1-2mm	6.9	NR
Mahajan (2017)	GK	50%	16	NR	2mm	8.9	NR

*NR = Not reported, GK= Gamma Knife, LINAC= Linear Accelerator, CI= Confidence Interval, mm= milimeters cm3= centimeter cubic, *Same cohort, with different analysis*

3.3.4 Outcomes

3.3.4.1 Control Rates

Local control rates at 12-months ranged from 50 - 100%, median= 82%, (IQR, 73%-84.4%). One study reported its local failure rate at 15.6% over the follow-up duration of 2-15.5 months (Johnson et al., 2016) (Table 3). The 24-months local control rates ranged between 16 – 89%, median=78%, (IQR, 67-82%). (Table 3).

Distant Progression rates were reported in fourteen studies and ranged from 36 – 64 % at 12-months, median=45.5%, (IQR, 38-51%) (Abel et al., 2015; Brennan et al., 2014; Brown et al., 2017; Hartford et al., 2013; Jensen et al., 2011; Mahajan et al., 2017; Rava et al., 2016; Shi,

Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; T. R. Smith et al., 2014; Z. T. Smith et al., 2020; Strauss et al., 2015; Teyateeti et al., 2020), and 39 – 76%, median=53%, (IQR, 46-55%) at 24-months (Abel et al., 2015; Hartford et al., 2013; Iwai et al., 2008; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; T. R. Smith et al., 2014; Strauss et al., 2015; Teyateeti et al., 2020) (Table 3).

3.3.4.2 Time to Progression

The time to progression, defined as time from treatment to time of treated tumor cavity recurrence or progression based on imaging findings of new or increasing T1-Gadolinum enhancement within the treated cavity was reported in fifteen studies (Abel et al., 2015; Brennan et al., 2014; Brown et al., 2017; J. W. Choi et al., 2015; Hartford et al., 2013; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Johnson et al., 2016; Mahajan et al., 2017; McDermott et al., 2019; Rava et al., 2016; T. R. Smith et al., 2014; Z. T. Smith et al., 2020; Strauss et al., 2015). The shortest time to progression was 4.1 months (T. R. Smith et al., 2014), and longest was not reached in one study, median=6.4 months, (IQR, 5.8-7.2 month) (Mahajan et al., 2017).

3.3.4.3 Survival

11 out of the 22 studies reported their survival rates at 12 months, which ranged from 46.8 – 76%, median=54.7%, (IQR, 52-63%) (J. W. Choi et al., 2015; Hartford et al., 2013; Iorio-Morin et al., 2014; Jensen et al., 2011; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; T. R. Smith et al., 2014; Z. T. Smith et al., 2020; Strauss et

al., 2015; Teyateeti et al., 2020) (Table 3). Eight studies reported survival at 24 months, ranging from 28.7 – 53%, median=33%, (IQR, 32-39%) (J. W. Choi et al., 2015; Iorio-Morin et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; T. R. Smith et al., 2014; Strauss et al., 2015; Teyateeti et al., 2020). Median overall survival across studies ranged from 11.1 – 25 months, median=14.3 months, (IQR, 11.1-19.8 months). (Table 3).

Table 3 – Scoping Review Control and Survival Outcomes

Author (year)	Median Follow-up	Local Control at 12 months	Local Control at 24 months	Distant Progression at 12 months	Distant Progression at 24 months	Overall Survival at 12 months	Overall Survival at 24 months	Median Overall Survival (months)
Abel (2019)	NR	88%	88%	50%	55%	NR	NR	20
Brenann (2014)	12 (1.0-94.1)	78%	NR	44%	NR	NR	NR	14.7
Brown (2017)	11.1	60.5%	NR	35.3%	NR	NR	NR	12.2
Choi (2015)	16.5	71%	NR	NR	NR	43.1%	28.7%	11
Hartford (2013)	9.3	86%	67%	56%	76%	53%	32%	NR
Hwang (2010)	NR	100%	NR	NR	NR	NR	NR	15
Iorio-Morin (2014)	10	73%	64%	NR	NR	63%	38%	11
Iwai (2008)	21.6	82%	76%	NR	52%	NR	NR	20
Jensen (2011)	NR	80.3%	NR	64.6%	NR	46.8%	NR	10.9
Johnson (2016)	9	84.4% *at 15 months	NR	NR	NR	NR	NR	12.9
Shi (Mar 2020)*	10.1	93.5%	91.2%	36.9%	43.4%	54.7%	31.3%	13.9
Shi (Oct 2020)*								
Rava (2016)	7.1	82%	75%	56%	39%	54%	39%	14.3
Smith (2014)	34	77%	16%	38%	53%	52%	33%	13.2
Smith (2020)	12.3	50%	NR	50%	NR	67%	NR	11.1
Strauss (2015)	16.3	84%	79%	42%	53%	63.5%	44%	18.9
Susko (2019)	19.8	85%	82%	72% *over entire follow-up		68.3% *over entire follow-up		19.8
Teyateeti (2020)	15.1	88%	78%	36%	46%	76%	53%	25
Patel (2018)	12.3	92.1%	89%	NR	NR	NR	NR	NR
Ojerholm (2014)	9.8	81%	NR	64% * at median of 7.3 months		NR	NR	22.3
McDermott (2019)	11.1	82%	NR	NR	NR	NR	NR	NR
Mahajan (2017)	11.1	72%	NR	58%	NR	NR	NR	17

NR = Not reported

3.3.4.5 Imaging Related Adverse Radiation Effects

12 out of 22 studies utilized the term radiation necrosis describing the range of imaging and clinical adverse radiation effects (Abel et al., 2015; Brennan et al., 2014; Brown et al., 2017; J. W. Choi et al., 2015; Iwai et al., 2008; Jensen et al., 2011; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude,

et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Z. T. Smith et al., 2020; Strauss et al., 2015; Susko et al., 2019). The reported rates of which ranged from 0 – 17.5%, median=5.5%, (IQR, 2.8-10.9%). (Table 4).

3.3.4.6 Leptomeningeal Disease

12 out of the 22 studies reported rates of leptomeningeal disease following SRS treatment, which ranged from 1.7 – 28%, median=10%, (IQR, 4.3-21%) (Brown et al., 2017; J. W. Choi et al., 2015; Hartford et al., 2013; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Johnson et al., 2016; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Strauss et al., 2015; Susko et al., 2019). (Table 4).

Table 4 – Scoping Review Additional Outcomes

Author (year)	Time to Progression (months)	Adverse Radiation Effects %	Leptomeningeal disease %
Abel (2019)	24	7%	NR
Brenann (2014)	14.7	17.5%	NR
Brown (2017)	12.2	4%	7.2%
Choi (2015)	11	0%	4.2%
Hartford (2013)	10.2	NR	4.3%
Hwang (2010)	NR	NR	NR
Iorio-Morin (2014)	6	1%	11%
Iwai (2008)	7	0%	24%
Jensen (2011)	6	2.8%	7.5%
Johnson (2016)	10.6	NR	21%
Shi (Mar 2020)*	NR	10.9%	13.2%
Shi (Oct 2020)*			
Rava (2016)	5.8	10.3%	9.2%
Smith (2014)	4	NR	NR
Smith (2020)	7.2	6.3%	NR
Strauss (2015)	11.6	5%	10%
Susko (2019)	NR	12%	1.7%

Teyateeti (2020)	NR	2%	19%
Patel (2018)	NR	5.5%%	NR
Ojerholm (2014)	NR	6.6%	14%
McDermott (2019)	6.2	NR	NR
Mahajan (2017)	15.6	0%	28%

NR = Not reported

3.3.4.7 Predictive Factors of Local Control

Of the 22 studies, only 15 assessed the association between potential predictive factors and local control following cavity-directed SRS (Abel et al., 2015; Brennan et al., 2014; Hartford et al., 2013; Iorio-Morin et al., 2014; Jensen et al., 2011; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Strauss et al., 2015; Susko et al., 2019; Teyateeti et al., 2020). Factors assessed included primary histology and radiosensitivity(Abel et al., 2015; Brennan et al., 2014; Iorio-Morin et al., 2014; Jensen et al., 2011; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Z. T. Smith et al., 2020; Strauss et al., 2015; Teyateeti et al., 2020), pre-operative tumor diameter (Brennan et al., 2014; Hartford et al., 2013; Jensen et al., 2011; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; Teyateeti et al., 2020), completeness of resection (Abel et al., 2015; Hartford et al., 2013; Iorio-Morin et al., 2014; Jensen et al., 2011; Ojerholm et al., 2014), target volume (Iorio-Morin et al., 2014; Jensen et al., 2011; McDermott et al., 2019; Patel et al., 2014; Rava et al., 2016; Strauss et al., 2015; Susko et al., 2019; Teyateeti et al., 2020), treatment dose (Brennan et al., 2014; Hartford et al., 2013; Iorio-Morin et al., 2014; Iwai et al.,

2008; Jensen et al., 2011; McDermott et al., 2019; Patel et al., 2014; Rava et al., 2016; Strauss et al., 2015; Susko et al., 2019; Teyateeti et al., 2020), isocenters (Iorio-Morin et al., 2014), treatment margin (Shi, Sandhu, Jin, Wang, Liu, et al., 2020), conformity indices (Abel et al., 2015; Jensen et al., 2011; Rava et al., 2016; Susko et al., 2019), time to treatment (Brennan et al., 2014; Iorio-Morin et al., 2014; McDermott et al., 2019; Ojerholm et al., 2014; Strauss et al., 2015; Teyateeti et al., 2020), tumor location in terms of supra-tentorial or infratentorial compartment (Brennan et al., 2014; Iorio-Morin et al., 2014; Jensen et al., 2011; McDermott et al., 2019; Ojerholm et al., 2014; Rava et al., 2016), Pial and Dural attachment (Brennan et al., 2014; McDermott et al., 2019; Susko et al., 2019; Teyateeti et al., 2020), and surgical corridor coverage (Shi, Sandhu, Jin, Wang, Liu, et al., 2020). Some studies even assessed factors including KPS (Iorio-Morin et al., 2014), disease related graded prognostic assessment GPA (Mahajan et al., 2017; Strauss et al., 2015), recursive partitioning analysis score RPA (Iorio-Morin et al., 2014), sex (Iorio-Morin et al., 2014; Z. T. Smith et al., 2020), age (McDermott et al., 2019; Z. T. Smith et al., 2020), extra-cranial disease (Mahajan et al., 2017), including progression of primary disease, and focal neurological deficits (Iorio-Morin et al., 2014). Notably, only one study had described the molecular and receptor status of the primary histology (EGFR, ER/PR, and HER2) and assessed the effect of hormonal therapy on local control (Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020). Of note, some studies only commented on the variables that were significant and neglected to mention the other tested factors that were not significant (Table 5).

1. *Histology*

Primary histology was concluded to have significant association with local control in only 1 out of the 13 studies that assessed the association (Brennan et al., 2014). In that study, NSCLC

histology was found to have better local control (Brennan et al., 2014). One study found breast cancer histology to have significantly higher local failure rates on UVA, but that association lost its significance with MVA (Ojerholm et al., 2014). Like-wise, another study found a significant association between radiosensitive histologies and progression-free survival on UVA, the significance of which was lost when controlling for other variables (Abel et al., 2015) (Table 5).

2. Diameters and Volumes

Tumor diameter, including pre-op diameter, maximum cavity diameter, and post-surgical cavity volumes were assessed as potential predictors of local control in 13 studies (Abel et al., 2015; Brennan et al., 2014; Hartford et al., 2013; Iorio-Morin et al., 2014; Jensen et al., 2011; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; Strauss et al., 2015; Susko et al., 2019; Teyateeti et al., 2020). Tumor and cavity diameters were found to be significant in 5 studies (Brennan et al., 2014; Jensen et al., 2011; Mahajan et al., 2017; Ojerholm et al., 2014; Susko et al., 2019). Jensen et al (Jensen et al., 2011) and Brennan et al (Brennan et al., 2014) both concluded that larger tumors with pre-operative diameters > 3cm, had worse control rates. Hartford et al (Hartford et al., 2013) also reported tumors with pre-operative diameter > 3 cm to have shorter times to local recurrence, however, that association was not significant on multivariate testing. Mahajan et al (Mahajan et al., 2017) found that metastases less than 2.5cm in diameter, had up to 90% freedom from local recurrence. Patel et al (Patel et al., 2014) also found an association between pre-op lesion diameter and increased risk of local recurrence. Moreover, Jensen et al (Jensen et al., 2011) also looked at post-surgical cavity volumes, and found volumes < 8 cm^3 to be predictive of need for salvage WBRT (Table 5).

3. Extent of Resection

A total of 5 studies analyzed the relationship between the extent of resection and risk of recurrence (Abel et al., 2015; Hartford et al., 2013; Iorio-Morin et al., 2014; Jensen et al., 2011; Ojerholm et al., 2014). Only one study, Ojerholm et al (Ojerholm et al., 2014), found that residual tumor at the time of SRS increased risk for local failure (Table 5).

4. Dosing

11 studies assessed the effect of dosing parameters on local control including maximum dose, isodose line, and number of isocenters (Brennan et al., 2014; Hartford et al., 2013; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; McDermott et al., 2019; Patel et al., 2014; Rava et al., 2016; Strauss et al., 2015; Susko et al., 2019; Teyateeti et al., 2020). Ioro-Morin et al (Iorio-Morin et al., 2014) concluded that a lower maximum dose to the cavity increased risk of recurrence, however, none of the other dosing parameters they tested including marginal dose, and number of isocenters achieved statistical significance. Iwai et al (Iwai et al., 2008) found significantly increased rates of local recurrence with marginal doses <18 Gy. Likewise, Pate let al (Patel et al., 2014), found that 18 Gy to be a cut-off for improved local control rates. Furthermore, Jensen et al (Jensen et al., 2011) found an association between maximum cavity dose of >35 Gy and need for salvage WBRT (Table 5).

5. Location

There were six studies in this review that analyzed the association of tumor location and risk of recurrence (Brennan et al., 2014; Iorio-Morin et al., 2014; Jensen et al., 2011; McDermott et al., 2019; Ojerholm et al., 2014; Rava et al., 2016). The location was stratified into a binary variable

of supra-tentorial and infratentorial location. Brennan et al (Brennan et al., 2014) did not find an association with location and local control, however, they found worse distant control rates in cases with infratentorial resection cavities. None of the other studies found a significant association (Iorio-Morin et al., 2014; Jensen et al., 2011; McDermott et al., 2019; Ojerholm et al., 2014; Rava et al., 2016) (Table 5).

6. Pial and Dural Involvement

Involvement of pia and dura was explored as a potential risk of recurrence in four of the studies included in this review (Brennan et al., 2014; McDermott et al., 2019; Susko et al., 2019; Teyateeti et al., 2020). Brennan et al (Brennan et al., 2014) found that tumors that were superficial with pial and or dural attachments had worse local control rates. Susko et al (Susko et al., 2019), also found dural contact to increase the rate of local recurrence and suggested need for adding dural margin during treatment. Intriguingly, although out of the scope of this review, Smith Z et al (Z. T. Smith et al., 2020) found that employing stereotactic radiotherapy SRT, to lesions with pial and or dural involvement to have worse local control rates compared to single-fraction SRS (Table 5).

7. Time to Treatment

The time from surgical resection to radiation was assessed in six studies (Brennan et al., 2014; Iorio-Morin et al., 2014; McDermott et al., 2019; Ojerholm et al., 2014; Strauss et al., 2015; Teyateeti et al., 2020). Ioro-Morin et al (Iorio-Morin et al., 2014) found that longer time to SRS conferred significantly increased risk for local recurrence. Likewise, Strauss et al (Strauss et al., 2015) found increased risk for local failure with increased lag time between surgery and SRS, however, that was only significant on univariate testing (Table 5).

8. Margin and Conformity

A total of seven studies looked at cavity coverage parameters (Abel et al., 2015; Hartford et al., 2013; Jensen et al., 2011; McDermott et al., 2019; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Susko et al., 2019), one study assessed adding a margin outside the resection cavity (Shi, Sandhu, Jin, Wang, Liu, et al., 2020), and four studies looked at conformity index (Abel et al., 2015; Jensen et al., 2011; Rava et al., 2016; Susko et al., 2019), which is a metric used to evaluate how closely a radiosurgical dose distribution matches the size and shape of a target volume (Paddick, 2000), with one study also looking at modified conformity index (Susko et al., 2019). In terms of assessing the addition of a margin, only Shi et al (Shi, Sandhu, Jin, Wang, Liu, et al., 2020) were able to assess its significance, while the remaining studies either had addition of margin as standard of practice or had no cases where a margin was added. Shi et al (Shi, Sandhu, Jin, Wang, Liu, et al., 2020) had 76% of their cases with 1-3mm margin added to their target volume, and 24% with no margin, and they did not find a significant correlation to control with addition of margin (Table 5). There were 10 articles that reported addition of margin as a standard practice (Brennan et al., 2014; Brown et al., 2017; C. Y. H. Choi et al., 2012; Iorio-Morin et al., 2014; Mahajan et al., 2017; Patel et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Z. T. Smith et al., 2020; Teyateeti et al., 2020), within these, local control rates at 12-months ranged between 72-88% (Table 6). One of those studies fell as an outlier with 50% local control rate at 12-months, that study had only 16 cases in their analysis (Z. T. Smith et al., 2020). There were six studies that did not add a margin (Jensen et al., 2011; Johnson et al., 2016; McDermott et al., 2019; Ojerholm et al., 2014; Strauss et al., 2015; Susko et al., 2019), and their reported control rates at 12-months ranged between 80.3-84% (Table 6).

In terms of the evidence behind adding a margin to the cavity, there is one study by Soltys et al (Soltys et al., 2008) that found significance to adding a treatment margin to improve local control rates, similarly, lower conformity index showed worse control rates. However, this study was excluded from the review as it included multi-session SRS cases in their analysis without doing a subgroup analysis for single-session cases.

9. Primary Disease Status

Mahajan et al (Mahajan et al., 2017) and Iorio-Morin et al (Iorio-Morin et al., 2014) both looked at the status of primary disease and found no correlation between it and local control (Table 5).

10. Surgical Corridor Coverage

Shi et al (Shi, Sandhu, Jin, Wang, Liu, et al., 2020) assessed the need for surgical corridor coverage in deep resected metastasis and failed to find a significant association to local recurrence rates nor recurrence patterns (Table 5).

Table 5 - Scoping Review Factors Associated with Local Control

Factors	**Studies**	
Tumor Related Characteristics		
	Significant on MVA	**Not Significant on MVA**
Histology	Brennan	Abel, Iorio-Morin, Jensen, Mahajan, Mcdermott, Ojerholm*, Rava, Shi, Smith, Strauss, Teyateeti, Patel
Dimensions:		
Pre-op Diameter	Brennan, Jensen	Harford*, Ojerholm, Rava, Teyateeti, Patel
Cavity Diameter	Mahajan	Abel, Brennan, Jensen, Mcdermott, Rava
Cavity Volume	Jensen	Ioro, McDermott, Rava, Strauss, Susko, Teyateeti, Patel
Extent of Resection	Ojerholm	Abel, Hartford, Iorio-Morin, Jensen
Attachments (Pial, Dural)	Brennan, Susko	McDermott, Teyateeti
Location (Supra, Infratentorial)	Nil	Brennan, Iorio-Morin, Jensen, McDermott, Ojerholm, Rava
Treatment Related Characteristics		
Dose	Iorio-Morin, Iwai, Patel, Jensen	Brennan, Hartford, McDermott, Rava, Strauss, Susko, Teyateeti
Isodose line	Nil	Iorio-Morin, Susko
Number of Isocenters	Nil	Iorio-Morin
Time to Treatment	Iorio-Morin	Brennan, McDermott, Ojerholm, Strauss*, Teyateeti

Margin**	Nil	Shi
PTV	Nil	Hartford, McDermott, Shi
CI	Nil	Jensen, Rava, Susko, Abel
Modified CI	Nil	Susko
Corridor Coverage	Nil	Shi
Patient Related Characteristics		
Sex	Nil	Iorio-Morin, Smith
Age	Nil	McDermott, Smith
KPS/RTOG	Nil	Iorio-Morin
Focal Neurological Deficits	Nil	Iorio-Morin
Primary Disease Related Characteristics		
Extracranial RT	Nil	Iorio-Morin
Progression of Primary	Nil	Iorio-Morin
GPA	Nil	Mahajan, Strauss
Systemic Disease Status	Nil	Mahajan
Hormonal Therapy	Nil	Shi

MVA= Multivariate Analysis, PTV=Planning Target Volume, CI=Confidence Interval
**Significant on UVA not MVA*
***Standard of practice in some studies, see Table # for details*

Table 6 – Scoping Review Margin as a Standard Practice and Control Rates

Margin as Standard Practice	**Control Rate at 12 Months**
Brennan	78%
Brown	80.4%
Choi	84.9%
Iorio-Morin	73%
Mahajan	72%
Rava	82%
Shi (0-2 mm to CTV)	93.5%
ZT Smith (16 patients)	50%
Teyateeti	88%
Patel	92.1%
Margin Not Applied	
Jensen	80.3%
Johnson	84.4% * at 15 months
McDermott	82%
Ojerholm	81%
Strauss	84%
Susko	85%

CTV = Clinical Target Volume

3.4 Discussion

In this comprehensive review, 22 articles investigating the use of single-fraction metastasis cavity-directed stereotactic radiosurgery (SRS) as adjuvant therapy were analyzed. The findings suggest that SRS is a promising alternative to whole brain radiotherapy (WBRT) for boosting local control at the surgical site due to its lower risk of neurocognitive decline and reduced treatment visits. Most of the studies reviewed reported favorable local control rates exceeding 80% at 12 months (Abel et al., 2015; Hartford et al., 2013; Hwang et al., 2010; Iwai et al., 2008; Jensen et al., 2011;

Johnson et al., 2016; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Shi, Sandhu, Jin, Wang, Liu, et al., 2020; Strauss et al., 2015; Susko et al., 2019; Teyateeti et al., 2020).

To gain a deeper understanding of the impact of various parameters on local control in cavity-directed SRS, the available evidence was compiled and analyzed. Factors such as histology, radiation dose, tumor size, extent of resection, treatment timing, tumor depth, and dural or pial attachment were found to potentially influence local control (Brennan et al., 2014; Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Mahajan et al., 2017; Ojerholm et al., 2014; Patel et al., 2014; Susko et al., 2019). However, factors like primary disease status, corridor coverage, and lobar location did not show a significant effect (Brennan et al., 2014; Iorio-Morin et al., 2014; Jensen et al., 2011; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Liu, et al., 2020). Notably, the significance of treatment margins could not be directly compared as no studies in this review specifically addressed this aspect.

It is important to acknowledge that the quality of evidence in the reviewed studies was not formally assessed, as the aim with this scoping review was to compile all available evidence on cavity-directed SRS and its associated factors. The majority of the studies were retrospective and nonrandomized, with limited sample sizes, making it challenging to draw definitive conclusions and control for confounding variables. Additionally, the heterogeneity of pathologies across the studies further complicates the interpretation of control and survival outcomes and given the limited sample sizes, conducting a pathology-specific analysis is understandably challenging.

The results of this review highlight areas of agreement among the studies and provide valuable insights for designing future randomized trials. However, certain factors such as margin and conformity indices, surgical tract and dural attachment coverage, comorbidities, and primary disease characteristics were not extensively analyzed and warrant further investigation, which is aimed to be addressed through the local database study in Chapter 4.

3.5 Conclusion

The findings of this review underscore the importance of identifying areas of consensus among the studies and offer valuable insights to guide the design of future randomized trials, while preliminarily addressing Hypotheses #1 through #4 of this thesis. Nevertheless, several modifiable SRS-treatment and patient selection factors, including margin and conformity indices, surgical tract and dural attachment coverage, comorbidities, and primary disease characteristics, have not received comprehensive analysis and necessitate further investigation. To address these gaps, the local database study in Chapter 4 will shed light on these factors and contribute to the existing body of knowledge. This review emphasizes the need for prospective studies to evaluate predictive factors for achieving optimal local control in the context of cavity-directed SRS. Additionally, it underscores the need for minimizing pathology heterogeneity in future research to accurately assess the impact of different treatment variables. Single-fraction SRS has emerged as an effective and convenient approach for boosting the metastatic surgical cavity, with promising local control rates, better cognitive outcomes, and minimal disruption to systemic therapies.

Chapter 4: Factors Influencing Local Control of Brain Metastasis and Patient Survival Following Cavity-Directed Adjuvant Gamma-Knife Radiosurgery: A Single-Center Retrospective Cohort Study

4.1 Introduction:

Recent evidence supports the use of adjuvant radiosurgery to the surgical bed following resection to reduce risk of local recurrence and to minimize the neurocognitive toxicities associated with WBRT.(Andrews et al., 2004; Auchter et al., 1996) SRS, however, can be delivered in numerous different ways that can influence its efficacy. Moreover, treatment related factors such as extent of surgical resection, the specifics of radio-surgical treatment, and the timing of adjuvant therapy are still being studied with inconsistent results. A recent retrospective review identified the time to treatment as a significant predictor of local recurrence and suggested a cut-off of 4 weeks after which the risk of recurrence is significantly increased.(O'Brien et al., 2021) Meanwhile, another review that looked at 106 patients treated with adjuvant Gamma Knife radiosurgery failed to establish the same correlation.(Jensen et al., 2011) Other studies suggest a less conformal plan was associated with better control and recommended allowing for a 2mm margin when treating a surgical cavity.(C. Y. H. Choi et al., 2012; Soltys et al., 2008) In terms of tumor-related factors, some studies have found a significant risk of recurrence for larger surgical cavities.(Gui et al., 2020) Others have reported a pre-operative tumor diameter of > 3cm as predictor of failure of local control.(Jensen et al., 2011) Tumor histology is also identified as a significant factor, with tumor-resistant histology requiring higher doses to improve local control.(Gui et al., 2020) A recent systematic review and meta-analysis assessed local control following SRS boost to the surgical

cavity and identified a local control rate of 83.7% at 12 months. In their analysis they identified fractionation to be associated with better control compared to single fraction therapy and increasing the treatment margin had no effect.(Akanda et al., 2020)

Furthermore, the scoping review in Chapter 3 revealed a noticeable gap in the literature regarding the investigation of several factors including margin and conformity indices, surgical tract and dural attachment coverage, comorbidities, and primary disease characteristics. These factors, and their potential impact on cavity control rates, have not received sufficient attention in previous studies, highlighting the need for further investigation. Therefore, this local database study is designed to specifically address these gaps and provide a comprehensive analysis of these factors, with the goal of more comprehensively addressing Hypotheses #1 through #4 of this thesis. Through this study, the aim is to contribute valuable insights that will enhance the current understanding of the subject matter and expand the existing body of knowledge.

4.2 Methods

4.2.1 Patient selection:

Patient cohort was selected from the Winnipeg Center for Gamma Knife Radiosurgery, which is a prospectively kept database for patients undergoing Gamma Knife Radiosurgery, with data including demographics, diagnosis, treatment details, and follow-up. The cohort included patients treated since inception of the Winnipeg Center for Gamma Knife Radiosurgery in 2003, till the date of the database query on March 31st, 2021.

The study included all adult patients, 18 years of age and older, with confirmed metastatic brain disease, that have undergone surgical resection and received adjuvant SRS to the surgical cavity.

The initial database query resulted in 237 potential cases. Patients who did not have at least 3 months of follow-up, including those who were deceased prior to their follow-up or those who were lost to follow-up, those who have received prior intracranial radiation and patients without histopathological confirmation of metastatic disease were excluded.

Following removal of duplicates, miscoded cases, cases with missing plans, and those with delayed SRS treatment (TTT > 135 days), a total of 63 cases were included in the final analysis.

4.2.2 Variables:

Investigated variables included patient demographics, tumor characteristics, SRS treatment details, and events and outcomes.

For tumor characteristics, the number of brain metastases was recorded and was dichotomized to single (oligometastasis) or multiple metastases and was analyzed as a categorical binary variable. Pre-operative tumor and cavity volumes were analyzed as continuous variables. The 3-dimensional measurements (maximum width, length, and height) of the enhancing tumor and the surgical cavity on T1-Gadolinum-enhanced magnetic resonance imaging (MRI) were obtained. The cavity volumes were obtained from the Gamma Knife treatment planning system. Tumor location was recorded as either deep, subcortical or dural-based and analyzed as a categorical variable. It was also recorded as either supra-tentorial or infra-tentorial in a binary format. Cavity shape was recorded as either round or irregular and analyzed as a binary variable. The pre-operative pattern of enhancement was recorded as either homogenous, heterogenous, or ring enhancement and analyzed as a nominal variable. Tumor histopathology was dichotomized to either radio-sensitive or radioresistant and analyzed as a binary variable (Appendix B). The molecular subtypes were recorded and analyzed as categorical variables. The extent of surgical resection was determined based on radiologist reporting of the post-operative (within 24-48hrs) Gadolinium-enhanced MRI findings and was recorded as either gross total resection (GTR), sub-total resection (STR), or biopsy and was analyzed as an ordinal variable.

In terms of SRS Treatment Characteristics. The marginal dose in Gray (Gy) was analyzed as a continuous variable. The maximum dose delivered (D100%) was calculated and analyzed as a continuous variable. The prescribed isodose line was recorded as a percentage and was analyzed as a continuous variable. Plan conformity was recorded based on the formula of prescription isodose volume/target volume ratio (PIV/TVC) (reference). The coverage of the surgical corridor

within the treatment field as well as the coverage of the dural tail and leptomeninges were recorded and analyzed as a binary variable with either yes or no. Timing from surgical resection to SRS was recorded in days and analyzed as a continuous variable.

Complications related to SRS treatment were stratified as mild, moderate, or severe. Mild complications did not require intervention, moderate complications required some form of intervention but not hospitalization, and severe complications required hospitalization. This stratification was similar to that used in a previous publication (Plowman, 1999). The timing of complications was also recorded as an ordinal variable, with acute complications occurring within 12-48 hours, sub-acute occurring 3-10 months following SRS, and late occurring beyond 10 months, according to a classification proposed by P. N. Plowman (Plowman, 1999; St George et al., 2002).

Recurrence was recorded as a binary variable, with either a "yes" or "no" and was further classified based on imaging progression, clinical progression, or progression requiring intervention. Local progression was defined as the development of a new area of enhancement within the treated cavity or the progression of previously observed enhancement by at least 2mm. The timing of recurrence was recorded in months from the day of SRS treatment and analyzed as a continuous variable. Distant failure/progression was defined as progression of enhancement by at least 2mm within a previously treated but non-resected lesion or a new area of enhancement, in a non-previously irradiated area. Adverse radiation effects (ARE) were analyzed as a binary variable and assessed using two methods: reviewing radiology reports and using consensus among treating physicians (which includes the conclusion made based on radiology reports, and discussion amongst radiation

oncologists, and neurosurgeons during a multidisciplinary meeting), and using a previously published method for predicting radiation effect versus tumoral growth based on radiological appearance on MRI T1/T2 mismatch (Kano et al., 2010). This was recorded and analyzed as a binary variable. Leptomeningeal spread was also recorded based on available radiology reports and analyzed as a binary variable.

4.2.3 Radiosurgery Technique:

Gamma Knife Model C (2003-2007), followed by Gamma Knife Perfexion Radiosurgical system (2007 onward) were used to deliver single fraction radiosurgical treatments. Stereotactic Leksell headframes were placed on the patient's head. T1-gadolinium-enhanced magnetic resonance (MRI) images were obtained with the frame in place. Treatment planning was done by the treating neurosurgeon and radiation oncologist and cross checked with a physicist. The target volume was defined by the treating neurosurgeon and radiation oncologist based on the contrast enhancing post-operative cavity. Typically, no treatment margins were added. Doses ranged between 15-20 Gy, with a median margin dose of 16 Gy. A 50% isodose line was used across the cohort.

4.2.4 Statistical analysis:

IBM SPSS Statistical Analysis Software (IBM Corp. Released 2021. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp) was used for statistical analysis. Continuous variables were analyzed and reported as medians and ranges, whereas categorical variables were reported as frequencies and percentages. A p-value of 0.05 was used as the threshold of statistical

significance for all of the analyses. Tumor control and survival at 12 and 24 months were analyzed using the Kaplan-Meier product-limit method and log-rank testing. Univariate regression models were used to assess the significance of the hypothesized predictors of tumor control.

4.3 Results

4.3.1 Cohort Characteristics:

The study consisted of 63 patients with a total of 63 tumor cavities treated with adjuvant GK SRS. The population included 35 females (55.6%) and 28 males (44.4%). The median age at the time of SRS treatment was 61.0 (range, 34.4-82.5). Thirty-eight (60.3%) had a single metastatic brain lesion, with remaining 25 (39.7%) having multiple intracranial metastases (Table 7). Non-small cell lung cancer was the most common pathology (n=28; 44.4%), followed by breast cancer (n= 13; 20.6%). Remaining subtypes and their frequencies are summarized in Table 8 and Figure 2. Gross-total-resection (GTR) was achieved in 77.8% of the cases, whereas sub-total resection was 22.2%. The majority of tumors were radiosensitive (n=43; 69.35%), radioresistant (n=19; 30.65%). The primary disease was deemed in remission in 24.1% of the cases at the time of brain metastasis diagnosis, whereas 75.9% of the cases were undergoing active treatment for their primary disease. More than half of the patients were placed on steroids at the time of SRS treatment (n=35; 55.6%). The majority of patients were RTOG RPA class 1 (n=48; 76.2%), with the remaining being class 2 (n=9; 14.3%) and class 3 (n=6; 9.5%). Similarly, most patients had a KPS of 90 (n=36; 57.1%), few had KPS < 70 (n=6; 8.2%), with only 3 patients having a KPS of 50

(Table 7). The median time to treatment with SRS (TTT) was 22 days, ranging from 1 – 134 days. Median follow-up was 12 months (range 3-168 months).

Figure 2 – Primary Cancer Distribution

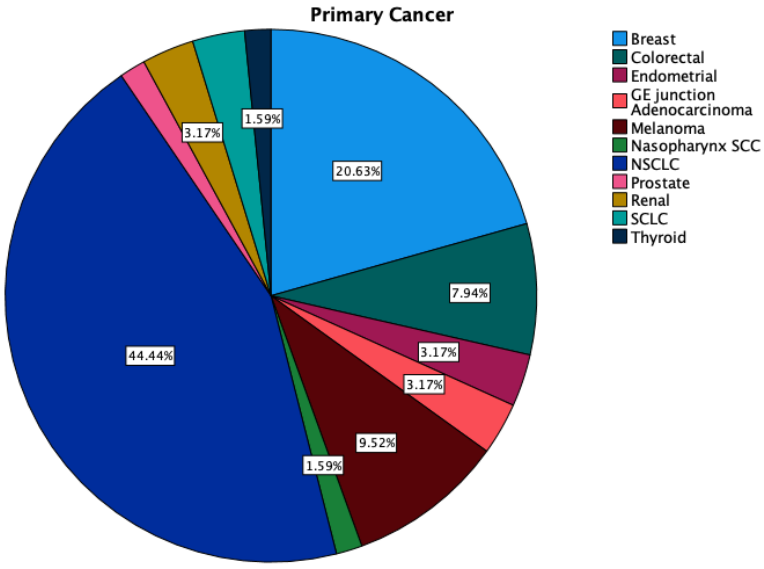


Table 7 – Retrospective Database Study Demographics

Demographic	Count	Percentage
Age		
< 50	6	9.5%
50-59	16	25.4%
60-69	19	30.2%
>= 70	22	34.9%
Sex		
Male	31	49.2%
Female	32	50.8%
Disease State		
Remission	33	52.4%
Active	26	41.3%
Missing Status	4	6.3%
Number of Metastases		
1	37	58.7%
2-3	18	28.6%
>3	8	12.7%
Diameter		
>3	16	25.4%
2-3	19	30.2%
<2	28	44.4%

Location		
Frontal	26	41.3%
Parietal	11	17.5%
Occipital	7	11.1%
Temporal	6	9.5%
Cerebellar	13	20.6%
Deep	14	22.2%
Subcortical	34	54.0%
Dural-based	15	23.8%
Performance Status		
RPA 1	41	65.1%
RPA 2	15	23.8%
RPA 3	7	11.1%
ECOG 0-1	34	53.9%
ECOG 2-3	19	30.2%
ECOG 4	10	15.9%
KPS >90	51	81.0%
KPS 70-90	10	15.9%
KPS <70	2	3.2%

Table 8 – Retrospective Database Study Primary Cancer Distribution

Primary Cancer		
	N	%
NSCLC	28	44.4%
Breast	13	20.6%
Melanoma	6	9.5%
Colorectal	5	7.9%
Renal	2	3.2%
SCLC	2	3.2%
Endometrial	2	3.2%
GE junction Adenocarcinoma	2	3.2%
Nasopharynx SCC	1	1.6%
Prostate	1	1.6%

Thyroid	1	1.6%

NSCLC=Non-small cell lung cancer, SCLC=Small Cell Lung Cancer, GE=Gastroesophageal, SCC=Squamous cell carcinoma

4.3.2 Outcomes:

This section and its subsections will present the outcomes observed within the cohort, focusing on cavity control rates, distant disease progression rates, leptomeningeal disease rates, adverse radiation effects rates, and survival rates. The subsections to follow will present the analysis results of the selected potential predictive factors for local control and survival.

4.3.2.1 Local Control

At 12 months 66.7% of the cases had no progression at the treated surgical cavity. The local control rate dropped at 24 months to 57.1%. Overall local control throughout the study period was 54%.

4.3.2.2 Distant Progression

Throughout the study period, the rate of distant progression, which refers to the development of new lesions beyond the surgical cavity or progression of enhancement in previously treated distant metastasis, was observed to be 58.7%.

4.3.2.3 Leptomeningeal disease and Imaging Related Adverse Radiation Effects

The overall rates of leptomeningeal disease development following treatment was 15.9%. Adverse radiation effects developed in 20.6% of the treated cases.

4.3.2.4 Survival

Survival rate at 12 months was 63.5% in this cohort, the rate dropped to 38.1% at 24 months. The survival duration ranged between 3-51 months, with a mean of 16.29 months (SD=12.01).

4.3.2.5 Predictive Factors for Local Control

On univariate testing, none of the hypothesized predictors of control achieved statistical significance, therefore, multivariate testing was not conducted. Results are summarized in Table 9.

Table 9 - Retrospective Database Study Predictors of Local Recurrence

Univariate Analysis LR at 12 months	HR (95% CI)	p-value
Patient Characteristics		
Age	0.94 (0.89, 1.00)	0.07
Sex	0.90 (0.31, 2.61)	0.85
ECOG grade at SRS	0.94 (0.59, 1.51)	0.81
KPS score at SRS	1.01 (0.96, 1.06)	0.55
Primary Disease		
Radiosensitivity	2.22 (0.62, 7.86)	0.21
Primary Disease State	0.55 (0.16, 1.93)	0.35
Steroid Used	1.47 (0.50, 4.30)	0.47
Tumor Characteristics		
Extent of Resection	0.87 (0.25, 3.03)	0.83
Cavity Volume	1.05 (0.94, 1.17)	0.33
Maximum Dimension		

Max Length	1.02 (0.95, 1.09)	0.49
Max Width	0.98 (0.922, 1.05)	0.71
Max Height	0.99 (0.92, 1.07)	0.87
3 cm cut-off for max diameter	2.479 (0.71, 8.58)	0.15
Tumor Location		
Depth (Superficial vs. Deep)	1.79 (0.69, 4.62)	0.22
Compartment (Supra vs Infratentorial)	1.96 (0.63, 6.10)	0.24
Pattern of Enhancement	0.76 (0.39, 1.48)	0.43
Shape (Smooth vs. Irregular)	1.77 (0.54, 5.82)	0.34
Edema (Mild vs. Moderate vs. Severe)	1.00 (0.45, 2.21)	1.00
SRS Characteristics		
Marginal dose	0.83 (0.52, 1.32)	0.44
Maximal dose	0.92 (0.73, 1.17)	0.52
Plan Conformity		
Paddick Conformity Index	0.24 (0.00, 12.01)	0.48
PIV/TVC	1.49 (0.37, 5.96)	0.57
Surgical Corridor Coverage	2.50 (0.74, 8.44)	0.14
Dural Coverage	1.32 (0.46, 3.81)	0.59
Time to SRS (TTT) in days	1.00 (0.98, 1.03)	0.39
TTT 14-days cut-off	0.75 (0.21, 2.66)	0.66

ECOG=Eastern European Cooperative Group, KPS=Karnofsky Peroformance Scale, HR= Hazard's Ration CI= Confidence Interval, LR=Local Recurrence, SRS=Stereotactic Radiosurgery, PIV/TVC=Prescription Isodose Volume/Target Volume Ratio, TTT=Time to Treatment

4.3.2.6 Predictive Factors for Survival

On univariate analysis of patient characteristics, KPS score was significantly associated with survival at 24 months (Hazards Ratio [HR]: 0.93 [95% CI: 0.87-0.92]; p=0.02. Table 10). Age, sex, ECOG score did not correlate with survival at neither 12, nor 24 months (Table 10). For primary disease characteristics, neither radiosensitivity nor disease state had a significant association (Table 10). In terms of intracranial progression, treated cavity progression within the first year of treatment was significantly associated with a 5.0-fold increase in risk of death at 24 months ([HR]: 5.00 [95% CI: 1.25-19.86]; p=0.02. Table 10). Distant intracranial progression

within the first 12 months of treatment was significantly associated with the 1-year and 2-year survival (Figure 3). In fact, distant intracranial progression within the first year of treatment showed a 6.0-fold increase in risk of death at 12 months, and an 8.2-fold increase in risk of death at 24 months ([HR]: 6.00 [95% CI: 1.52-23.62]; p=0.01), and ([HR]: 8.28 [95% CI: 2.53-27.06]; p=<0.00 respectively; Table 10). Those with early tumor progression within 12 months had a median survival of 10 months.

On multivariate analysis (MVA) for survival at 24-months, only distant intracranial progression within the first year of treatment and KPS score maintained their significance ([HR]: 12.95 [95% CI: 2.46-68.05]; p=<0.00) and ([HR]: 0.90 [95% CI: 0.84-0.97]; p=<0.00) respectively. Cavity related progression within the first year lost its significance on MVA ([HR]: 2.02 [95% CI: 0.38-10.72]; p=<0.40).

ROC curve analysis was conducted to identify a KPS score cut-off, however, it was technically categorized as a poor indicator with area under curve = 0.64, and significance of 0.052. No cut-off point with adequate sensitivity and specificity was identified (Figure #).

Figure 5 - ROC Curve for KPS cut-off

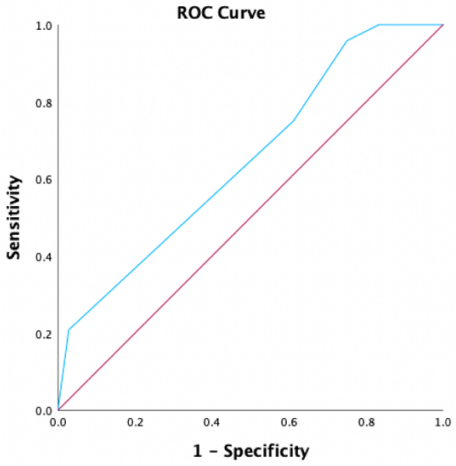
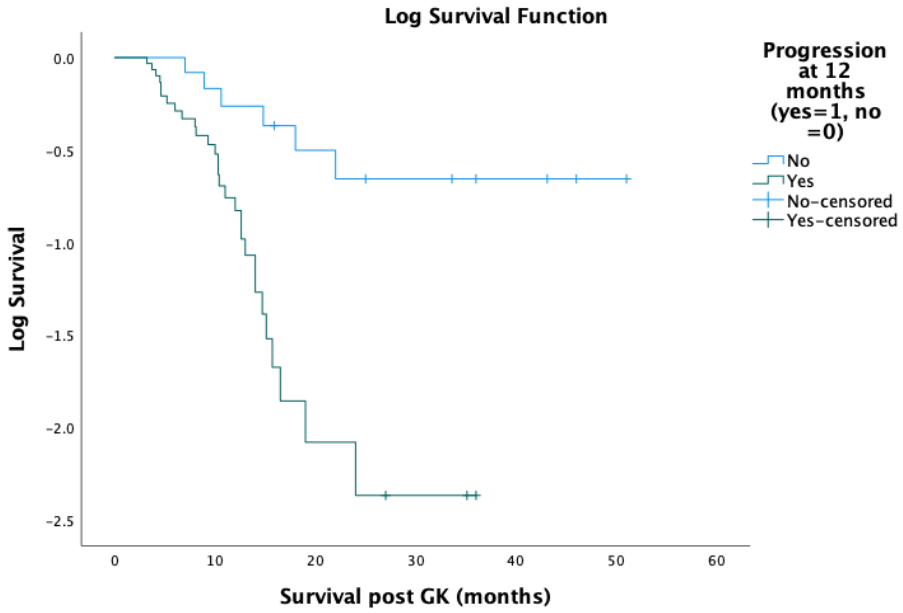


Table 10 - Retrospective Database Study Predictors of Survival

	Survival at 12 months		Survival at 24 months	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Patient Characteristics				
Age	1.01 (0.96, 1.07)	0.58	1.01 (0.96, 1.07)	0.61
Sex	0.75 (0.25, 2.21)	0.60	1.12 (0.39, 3.18)	0.83
ECOG	1.50 (0.93, 2.43)	0.09	1.63 (0.95, 2.80)	0.07
KPS	0.96 (0.092, 1.01)	0.13	0.93 (0.87, 0.92)	**0.02**
Primary Disease Characteristics				
Radiosensitivity	0.88 (0.28, 2.76)	0.83	0.62 (0.19, 1.97)	0.42
Disease state (active vs. remission)	1.97 (0.47, 8.26)	0.35	1.89 (0.54, 6.65)	0.31
Intracranial Progression				
Local at 12 months	1.16 (0.37, 3.61)	0.78	**5.00 (1.25, 19.86)**	**0.02**
Distant at 12 months	**6.00 (1.52, 23.62)**	**0.01**	**8.28 (2.53, 27.06)**	**<0.00**
Local at 24 months	NA	NA	1.78 (6.13, 5.22)	0.28
Distant at 24 months	NA	NA	3.10 (087, 11.03)	0.08

ECOG=Eastern European Cooperative Group, KPS=Karnofsky Peroformance Scale, HR= Hazard's Ration CI= Confidence Interval

Figure 6 – Intracranial Progression and Survival



4.4 Discussion

Adjuvant radiation therapy to the site of a surgical resection has been shown to be more effective than surgery alone in controlling the recurrence of tumors within the resection cavity (Patchell et al., 1998). In fact, the rates of cavity recurrence following resection alone are as high as 50% (Patchell et al., 1990). The rationale behind employing radiation to the resection cavity is to ensure destruction of all tumor cells, be it residual, or microscopic disease.

In comparing the available options for cavity boosts, the outcomes of WBRT and SRS have been compared in randomized trials with a trend supporting improved cavity control rates with WBRT, however, without a significant survival benefit. In exploring the cognitive outcomes, SRS was shown to be significantly superior to WBRT, which plays in favor of SRS as a better boost option despite WBRT having better cavity control rates (Brown et al., 2017). More recent evidence has suggested that SRS has comparable, and potentially better control rates than WBRT with proper dosing (Redmond et al., 2021). In this retrospective review, two main aspects of evaluating the effectiveness of cavity-directed SRS were explored: 1) How well SRS controls disease at the treated cavity and whether there are predictive factors for improved control. 2) The overall survival following cavity-direct treatments and whether there are factors that may influence survival.

In terms of SRS cavity control, the reported control rates in the literature range between 61-100%, with a mean of 83.7% at 1-year (Akanda et al., 2020). This cohort had a 63% local control rate at 1-year, falling into the reported range, albeit, within the lower end. As all treated patients since Gamma Knife was established at the treating center in 2003 were included, it is possible that the

changes in primary cancer management throughout the years have potentially influenced the control rates shown in this cohort.

Predictive Factors for Risk of Recurrence

In terms of factors influencing control, as highlighted in Chapter 3, numerous studies have investigated the various factors, including primary pathologies, tumor location and dimensions, and the nuances of the SRS technique, covering aspects like dose, coverage, and timing of treatment.

Work by Brennan (Brennan et al., 2014), Jensen (Jensen et al., 2011), and Mahajan et al (Mahajan et al., 2017) have underscored the potential significance of pre-operative tumor dimensions and cavity volumes as predictors of recurrence. However, several other studies, including those by Hartford (Hartford et al., 2013), Ojerholm (Ojerholm et al., 2014), Rava (Rava et al., 2016), Teyateeti (Teyateeti et al., 2020), Patel (Patel et al., 2014), Abel (Abel et al., 2015), McDermott (McDermott et al., 2019), Iorio-Morin (Iorio-Morin et al., 2014), and Strauss (Strauss et al., 2015), contrarily, have not recognized the dimensional aspects as significant. Echoing these results, this database study too could not detect a significant correlation to the dimensional aspects of the treated cavities. This poses an important question: When considering risk of recurrence, how pertinent are the published size cut-offs in determining patient selection? It is important to consider the limitations of the published studies, including this database study, as it is very plausible that the negative results were simply because these studies were not sufficiently powered to detect weak effects like minor variations in cavity dimensions.

Looking at primary histology, Brennan et al (Brennan et al., 2014) identified NSCLC metastatic tumors to have better control rates compared to the other histopathologies. This observation was not consistent with other published reports (Abel et al., 2015; Iorio-Morin et al., 2014; Jensen et al., 2011; Mahajan et al., 2017; McDermott et al., 2019; Ojerholm et al., 2014; Patel et al., 2014; Rava et al., 2016; Shi, Sandhu, Jin, Wang, Jaoude, et al., 2020; Z. T. Smith et al., 2020; Strauss et al., 2015; Teyateeti et al., 2020). This database study also had similar findings in that it did not detect a significant association between histology and local control outcomes. While it seems logical to link primary histopathological profiles with response to cavity-directed SRS, the prevailing inconsistencies in the literature challenge this assumption. Several explanations can be posited for this observation. The most straightforward rationalization might be that, unlike conventional radiation where the concept of radiosensitivity and radioresistance holds true (Hall & Giaccia, 2012), SRS at the administered doses possibly exerts equal effects across the different histologies. Additionally, the lack of significance could potentially be attributed to under-powering of the studies. Furthermore, the inconsistency in findings can also be attributed to the fact that most of the studies were not tailored to specific pathologies. Indeed, future pathology-specific studies are necessary to elucidate the true effect of histopathology on control outcomes.

In evaluating the extent of resection, we can find one study by Ojerholm et al (Ojerholm et al., 2014) showing a significant increase of local failure with sub-total resections. The majority of studies including this study found no such relationship (Abel et al., 2015; Hartford et al., 2013; Iorio-Morin et al., 2014; Jensen et al., 2011). It is possible that SRS is sufficiently effective that residual tumor is inconsequential in terms of risk of recurrence. It is also possible that this study

and the other studies were not adequately powered to detect a relationship between extent of resection and local control. Finally, it is conceivable that the categorical variable "sub-total resection" was too broadly defined as there could be a threshold of residual disease beyond which risk of recurrence becomes significant. However, due to the limited number of cases, it was not possible to stratify the extent of resection in this study. Of note, this oversight is not unique to this study.

Moreover, debating the optimal dose, several studies report a minimum cut-off of 18Gy to improve local control (Iorio-Morin et al., 2014; Iwai et al., 2008; Jensen et al., 2011; Patel et al., 2014). The findings in this database study and those of Brennan (Brennan et al., 2014), Hartford (Hartford et al., 2013), McDermott (McDermott et al., 2019), Rava (Rava et al., 2016), Strauss (Strauss et al., 2015), Susko (Susko et al., 2019), and Teyateeti (Teyateeti et al., 2020), did not reiterate this threshold's superiority, suggesting that perhaps minute dosage deviations from the standard dosing (15-25 Gy (Gui et al., 2020)) might not substantially influence local control outcomes. The possibility also remains that this study and the others were not sufficiently powered to detect an effect.

Furthermore, reports by Brennan (Brennan et al., 2014) and Susko et al (Susko et al., 2019), showed that tumors with pial and dural attachments had worse control rates. The consensus around surgical corridor coverage, despite being advocated by Soliman H et al. (Soliman et al., 2018), remains under-researched and unsupported by strong evidence. This database study also failed to detect statistical significance to local control rates. This lack of significance was also echoed by Shi et al. (Shi, Sandhu, Jin, Wang, Liu, et al., 2020) with regards to surgical corridor coverage.

The case for corridor coverage might be significant for certain histopathologies with predilection for seeding (Pinggera et al., 2017; J. S. Smith et al., 2005), in which case this study is underpowered to detect the difference.

As for the time interval between surgical resection and delivery of SRS, Iorio-Morin et al (Iorio-Morin et al., 2014) detected a significant correlation between risk of failure and prolonged durations. However, several studies including Brennan (Brennan et al., 2014), McDermott (McDermott et al., 2019), Ojerholm (Ojerholm et al., 2014), Strauss (Strauss et al., 2015), and Teyateeti (Teyateeti et al., 2020), along with this database study, did not resonate with this finding. In reconciling these differences, a few explanations could be posited, one being the possibility that a true cut-off timing does not exist as long as the treatment falls within a reasonable time range. It is also possible that this study and the other studies were simply not sufficiently powered to detect the effect of treatment delays on local control.

In regards with inclusion of a treatment margin, only one study by Soltys et al (Soltys et al., 2008) concluded that margin addition enhanced local control rate, identifying a decline with reduced conformity indices. In contrast, studies by Jensen (Jensen et al., 2011), Rava (Rava et al., 2016), Susko (Susko et al., 2019), Abel (Abel et al., 2015), Shi et al (Shi, Sandhu, Jin, Wang, Liu, et al., 2020), and this database study could not identify a significant correlation to conformity indices. This could indicate that clinical judgment plays a crucial role in determining the appropriate treatment margin on a case-to-case basis and true margin limit does not exist. It's also plausible that this cohort, having mainly tightly conformal plans, might have been unable to discern the impact of applying broader margins. Additionally, it's possible that the thresholds used for

stratification were not defined accurately compromising the chances of identifying significant differences. It is obvious that the available studies are not robustly designed to detect small but meaningful effects.

Although this study has its own set of limitation that warrant careful consideration of its results, it needs to be acknowledged that this study echoes the inconsistencies witnessed in the literature, as detailed previously. Both this study, and the other negative studies might indeed be presenting genuine results of post-operative cavity management realities, offering a more pragmatic perspective. Such results can sometimes serve as a counterbalance, prompting a better exploration of the true effects of the variables analyzed in these studies. The potential significance of reported factors by the positive studies will need to be further scrutinized with sufficiently powered study designs to elucidate their true effects.

Survival

In terms of survival following cavity boost with SRS, the literature reports median overall survival range between 8.6-28.3 months, with a median of 15.1 months (Akanda et al., 2020). The reported median rates of overall survival at 12-month is 62.0%, ranging from 35-91.3% (Akanda et al., 2020). The cohort fell within the range, exhibiting a 12-month survival rate that is slightly above the median reported rate, at 63.5%. The rates significantly drop at 24 months to 38.1%.

Interestingly, while the literature suggests that extracranial disease is typically the primary factor affecting survival (Carpenter et al., 2023; Li et al., 2023), this study's cohort showed trends of worse survival following intracranial progression. After evaluating factors that may affect survival,

intracranial progression within the first 12 months of treatment was significantly associated with survival at one and two years. In fact, those with intracranial progression within the first year of treatment had a 6.0-fold increase in the risk of death at 12 months and an 8.2-fold increase in the risk of death at 24 months. The median survival for those with early tumor progression within the first 12 months was only 10 months. This observed drop in survival rates following disease progression could be reflective of the local practice of not actively pursuing aggressive measures in treating patients with intracranial progression. This suggests a common perception that intracranial progression is an ominous sign for an end-of-life prognosis, which in many cases, is true. It is important to recognize that this particular cohort represents a real-world scenario, providing valuable insights into the challenges and realities faced by patients and healthcare professionals when managing metastatic disease within this specific context.

Nevertheless, these findings indicate that timely and effective treatment of intracranial disease progression may be critical for improving survival outcomes.

4.5 Limitations

The retrospective nature of this study imposes certain limitations that need to be taken into account when interpreting the non-significant findings. These limitations could have potentially influenced the lack of significant results. Firstly, this study included a cohort that spanned a 17-year period, during which various neurosurgeons, radiation oncologists, and treatment systems were involved. The involvement of different healthcare professionals and treatment approaches introduces potential variability and confounding factors that may impact the outcomes.

Furthermore, as with any retrospective study, inherent biases are present, including selection bias, recall bias, and other confounding biases. These biases can affect the accuracy and reliability of the results obtained.

Another aspect to consider is the heterogeneity observed in the SRS technique, primary pathologies, and advancements in systemic therapies over the study period. The SRS technique itself may vary among different institutions and treating physicians, leading to variations in treatment outcomes. Additionally, the diverse primary pathologies and the continuous development of systemic therapies introduce additional complexity in interpreting the findings. The response to treatment and the impact on local control may differ across different tumor types and treatment regimens, further contributing to the challenge of drawing definitive conclusions.

Given these limitations and the complex nature of the variables involved, caution is warranted in the interpretation of the results. Future studies should aim to address these limitations by employing prospective designs, standardized treatment protocols, and larger sample sizes to provide more robust evidence on the factors influencing local control in the context of adjuvant SRS for surgical cavities of metastatic brain disease.

4.6 Conclusion

The present study aimed to address several hypotheses related to the impact of various treatment parameters, histopathology, age, and other factors on local control rates and survival outcomes in patients undergoing cavity-directed SRS. Hypothesis 1 proposed that modifiable

treatment-related parameters, such as marginal dose, maximum delivered dose (D100%), plan conformity, time to treatment, dural-attachment and surgical corridor coverage, would influence local control rates at 12 and 24 months. The local database study conducted in this chapter, however, did not detect any significant associations between these factors and local control rates. Similarly, Hypothesis 2 suggested that histopathology would predict local control rates, with radioresistant histopathologies requiring higher doses for better control. Additionally, factors such as post-operative cavity size, extent of resection, location (eloquent and dural-based), cystic nature, and irregular appearance were hypothesized to influence local control. Nevertheless, this local database study did not find significant correlations between these parameters and local control rates. Hypotheses 3 and 4 proposed that older age and multiple metastases would result in worse control rates, while age, performance status, radioresistance, and intracranial progression would impact survival rates negatively. Although the local database study did not detect a correlation between the parameters of these hypotheses and local control, it revealed a significant association between intracranial progression and survival. Notably, patients experiencing progression within the first and second year of treatment exhibited significantly worse survival outcomes. Overall, while intracranial progression was found to be significantly associated with survival, the local database study did not identify significant factors influencing local control as reported in the literature. This could be attributed to the heterogeneity of the patient cohort and the inclusion of a wide range of treatment variables. Consequently, further research is necessary to comprehensively understand the optimal use of cavity-directed SRS and to identify patient, tumor, and modifiable treatment characteristics that can inform patient selection and treatment planning. Gaining a better understanding of these factors will allow for refinement of SRS utilization and ultimately lead to improved patient outcomes in the future.

Chapter 5: Overall Thesis Conclusion

This thesis explored the utilization of stereotactic radiosurgery (SRS) as a method for boosting metastasis cavities. The aim was to define the role and effectiveness of this approach, while also examining potential factors that might influence its efficacy. These factors fall within the categories of patient selection, planning and delivery techniques, and other adjustable confounders. The thesis involved a comprehensive literature scoping review and the evaluation of outcomes from a local database cohort study spanning 17 years of operation.

The following hypotheses of this thesis were addressed:

Hypothesis 1: Modifiable treatment related parameters, including marginal dose, maximum delivered dose (D100%), plan conformity, time to treatment, dural-tail and surgical corridor coverage will influence local control rates at 12 and 24 months. Larger doses, looser margins, shorter time to treatment, and coverage of dural-tail and surgical corridors will result in better control rates.

Chapters 3 and 4 explored this hypothesis, the scoping review in Chapter 3 revealed some evidence in the literature to consider SRS treatment dose and time to SRS treatment as significant factors. The review also revealed a lack of attention to margin, conformity indices, surgical tract, and dural coverage as potential factors. The local database study addressed these deficiencies in Chapter 4, however, it failed to detect significance to these factors. The discussion in Chapter 4 offers several possible explanations, from postulating the genuine insignificance of these factors, to the possibility of the study being

underpowered or having inappropriate stratifications that affected its ability to discern significance.

Hypothesis 2: Histopathology will predict local control rates, with higher dosing required for radioresistant histopathologies (e.g. melanoma, and renal cell). Larger post-operative cavities, subtotal resection, eloquent and dural based location, cystic lesions and irregular appearance will confer worse local control.

Chapters 3 and 4 addressed this hypothesis, histology, pre-operative tumor diameter, target volumes, extent of resection, and attachments were found to have significant impact on control rates in a number of studies, with several more studies failing to detect the same significance. In Chapter 4, the local database study looked at these parameters and was unable to detect significance. The discussion in Chapter 4 offers interpretations of these findings, from the possibility of the findings being truly insignificant, to the studies' flaws hindering the detection of subtle yet impactful effects.

Hypothesis 3: Older age, and multiple metastases will result in worse control rates.
Hypothesis 4: Age, performance status, radioresistance, and intracranial progression will have worse survival rates.

Chapters 3 and 4 addressed these hypotheses, none of the studies in the scoping review showed a significant relation between the listed patient and disease parameters in relation to intracranial progression. Similarly, no relation is detected between the parameters and survival outcomes. The local database study also did not detect a correlation between the hypotheses' parameters and local control, however, it revealed a significant association

between intracranial progression and survival, indicating that patients experiencing progression within the first and second year of treatment had notably worse survival outcomes.

Chapter 6: Future Directions

The scoping review conducted for this thesis in Chapter 3 revealed several limitations in the existing studies, such as their retrospective nature, nonrandomized design, and small sample sizes. These limitations make it challenging to draw definitive conclusions and control for confounding variables. Furthermore, the heterogeneity of pathologies across the studies adds complexity to the interpretation of control and survival outcomes, highlighting the importance of pathology-specific analysis. Additionally, the contradictory results among studies regarding the significance of different factors further highlight the need for more comprehensive investigations.

The local database study in Chapter 4 did not detect any significant relationships between the studied factors and local control. This might imply that the factors examined are truly of little significance to local control outcomes. It further suggests that by employing the current doses of SRS within the established dimensional boundaries of tumor cavities, the ablative effects of SRS are robust enough to ensure consistent control rates at the resection site. It is also important to consider the retrospective nature of this study and the other published reports, which introduces inherent biases such as selection bias, recall bias, and confounding biases that may have influenced the lack of significant findings. The involvement of various healthcare professionals, treatment approaches, and advancements in systemic therapies over the study period also contribute to the complexity of interpreting the results.

Given these limitations and complexities, caution is necessary before making conclusions from the results of this thesis. Future studies should aim to address these limitations by employing

prospective designs, standardized treatment protocols, and larger sample sizes to provide more robust evidence on the factors influencing local control in the context of adjuvant SRS for surgical cavities of metastatic brain disease.

In terms of future research directions, randomized trials comparing different delivery techniques, specifically the significance of margin addition, surgical tract coverage, and volume- and histology-specific dosage, are warranted. These investigations will provide valuable insights into optimizing treatment strategies and improving patient outcomes. Additionally, pathology-specific studies that account for disease-specific graded prognostic assessments (GPA) and systemic therapy, including targeted treatments and immunotherapy are crucial for personalized treatment approaches and enhanced patient outcomes. Furthermore, studies focusing on failure patterns can help identify other potential predictors for cavity recurrences, enabling the development of more accurate prognostic models and refined treatment guidelines.

By pursuing these future research directions, we can advance the field of SRS for metastasis cavity boost and ultimately enhance the outcomes for patients with metastatic brain disease.

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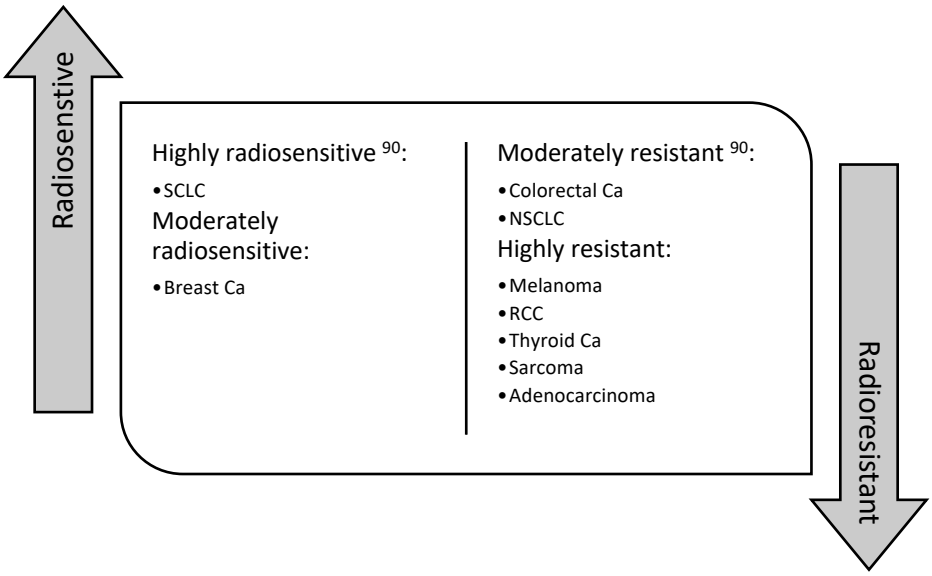
Appendix 1 – Scoping Review Search Sample

Books@Ovid <August 2, 2021>
EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2, 2021>
EBM Reviews - ACP Journal Club <1991 to May 2021>
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2016>
EBM Reviews - Cochrane Clinical Answers <July 2021>
EBM Reviews - Cochrane Central Register of Controlled Trials <August 2, 2021>
EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>
EBM Reviews - Health Technology Assessment <4th Quarter 2016>
EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>
Embase <1974 to 2021 August 02>
JBI EBP Database <Current to August 2, 2021>
Journals@Ovid Full Text and abstracts
Journals@Ovid held by WOHS
Ovid Healthstar <1966 to August 2, 2021>
Ovid MEDLINE(R) ALL <1946 to August 2, 2021>
APA PsycInfo <1806 to August Week 1 2021>
1 Radiosurgery.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 99113
2 Gamma Knife.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 28804
3 1 or 2 103167
4 Brain Metastasis.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 70933
5 Intracranial Metastasis.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 1844
6 4 or 5 72087
7 Resection.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 1681616
8 Surgical.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 6471266
9 Cavity.mp. [mp=tx, bt, ti, ot, ab, kw, sh, ct, fx, hw, tn, dm, mf, dv, kf, dq, sw, nm, ox, px, rx, an, ui, ds, on, sy, ux, mx, tc, id, tm] 904684
10 7 or 8 or 9 7876485
11 3 and 6 and 105033
12 limit 11 to english language 4835
13 limit 12 to human 4659

Appendix B – List of Radiosensitive and Radioresistant Primary Cancers (Doble & Miklos, 2018)



Appendix C – Retrospective Database Study Table of Definitions

Variable	Type	Definition
Oligometastasis	Binary	Single metastasis to the brain based on T1-Gadolinium enhanced MRI findings.
Multiple Metastases	Binary	More than one metastasis to the brain based on T1-Gadolinium enhanced MRI findings.
Pre-operative Tumor Dimensions	Continuous	T1-Gadolinium enhancing lesion on the pre-operative MRI with maximum width, length, and height recorded in centimeters.
Cavity Volume	Continuous	Tumor cavity as contoured by the treating physician on the treatment scan and measurement provided by the Gamma Knife treatment planning system.
Deep Tumor	Categorical	Tumor located within deep structures including basal ganglia, thalamus, and brainstem.
Subcortical Tumor	Categorical	Tumor located within the subcortical white matter.
Dural-based Tumor	Categorical	Tumor with mainly dural attachments outside the cerebral cortex.
Supra-tentorial Tumor	Binary	Tumor within the supra-tentorial compartment (above the tentorium cerebelli: Frontal, parietal, temporal, and occipital lobes).
Infra-tentorial Tumor	Binary	Tumor within the infratentorial compartment (below the tentorium cerebelli: Cerebellum, and brainstem).
Homogeneous	Categorical	Tumor appears to uniformly enhance on T1-Gadolinium enhanced MRI.
Heterogeneous	Categorical	Tumors having variable signal intensity on T1-Gadolinium enhanced MRI.
Ring enhancement	Categorical	Tumors with peripheral enhancement on T1-Gadolinium-enhanced MRI.
Radiosensitive	Binary	Tumors with robust responses to conventional radiation (see Appendix B).
Radioresistant	Binary	Tumors with weak responses to conventional radiation (see Appendix B).
Gross Total Resection	Ordinal	Complete resection of tumor based on absence of enhancement in the surgical cavity on post-operative Gadolinium-enhanced MRI findings.
Sub-total Resection	Ordinal	Residual enhancement in the surgical cavity on post-operative Gadolinium-enhanced MRI findings.

Biopsy	Ordinal	Small sampling of tumor with majority of enhancement persistent on Gadolinium-enhanced MRI.
Marginal Dose	Continuous	The dose delivered at the prescribed isodose line.
Maximum Dose	Continuous	The dose delivered at the center of the tumor.
Prescribed Isodose line	Continuous	A contour on a treatment planning visualization that demarcates a specific radiation dose level.
Plan Conformity	Continuous	A metric that quantifies how well the radiation dose conforms to the shaped and size of the target tumor volume.
Surgical Corridor	NA	Pathway between the pial surface and resection cavity.
Imaging Progression	Binary	New area of enhancement or progression of previously observed enhancement by at least 2mm on follow-up Gadolinium-enhanced MRI.
Local Progression	Binary	Imaging progression within the previously treated surgical cavity.
Distant Progression	Binary	Imaging progression within a previously treated but non-resected lesion, or a new 2mm or greater area of enhancement in a non-previously irradiated area.
Adverse Radiation Effects	Binary	Progressive enhancement attributed to radiation effects as opposed to tumor progression.
Leptomeningeal spread	Binary	Evidence of linear or nodular enhancement along the leptomeninges on T1-Gadolinium enhanced imaging.

Annex A:

Conformity Index:

PI = prescription isodose

PIV = PI volume

TV = target volume

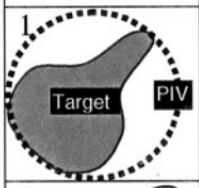
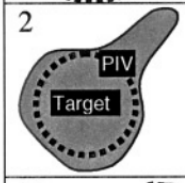
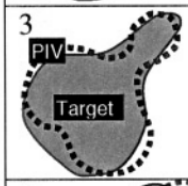
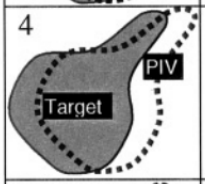
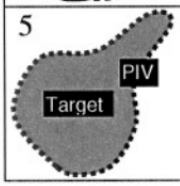
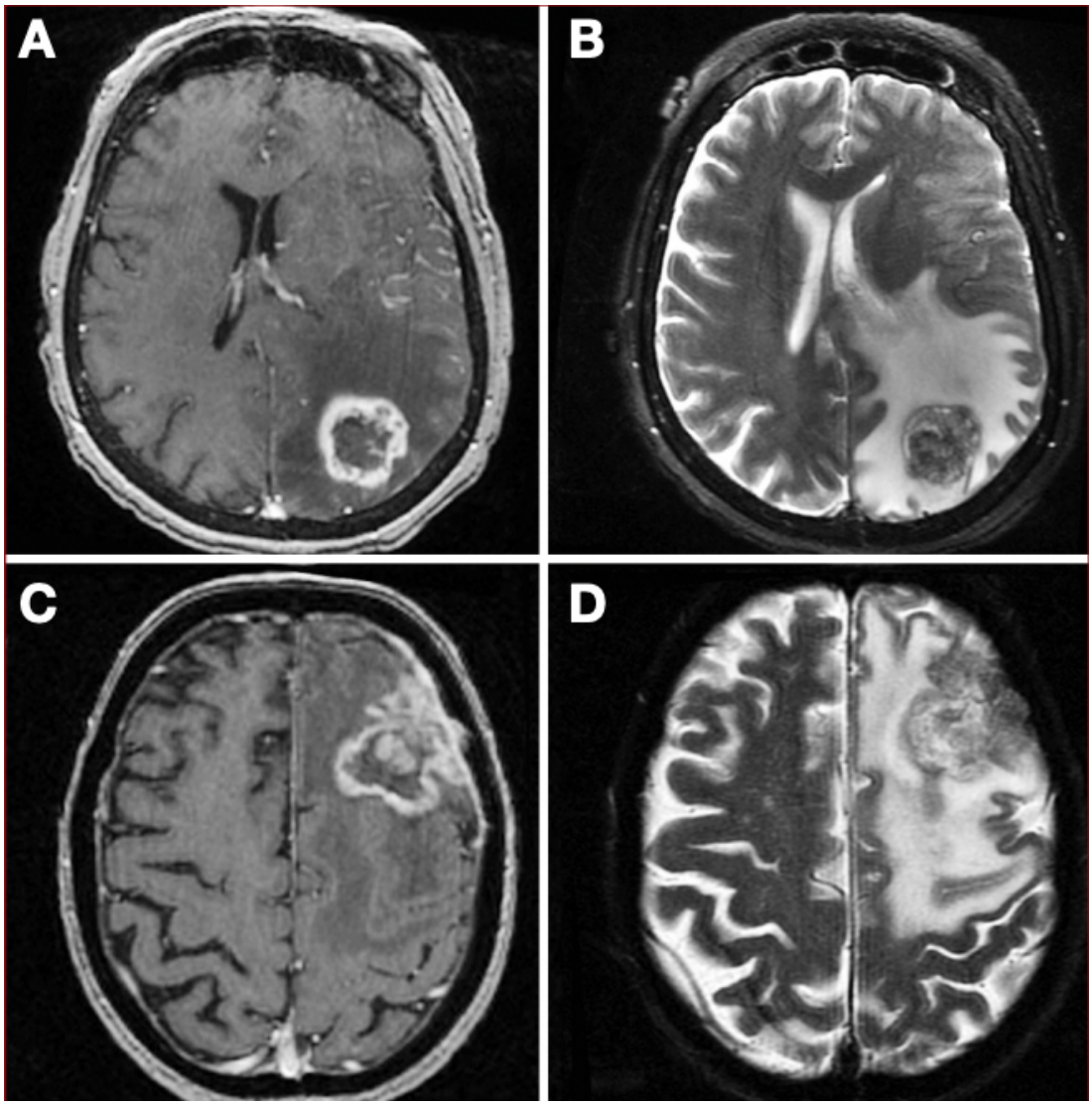
Isodose Plan	Parameters	PITV	RCI_i	Proposed Index
		$\frac{PIV}{TV}$	$\frac{TV_{PIV}}{TV}$	$\frac{TV_{PIV}^2}{TV \times PIV}$
1 	$TV = 5cm^3$ $TV_{PIV} = 5cm^3$ $PIV = 10cm^3$	2.00	**1.00**	0.50
2 	$TV = 5cm^3$ $TV_{PIV} = 3cm^3$ $PIV = 3cm^3$	0.60	0.60	0.60
3 	$TV = 5cm^3$ $TV_{PIV} = 4cm^3$ $PIV = 5cm^3$	**1.00**	0.80	0.64
4 	$TV = 5cm^3$ $TV_{PIV} = 3cm^3$ $PIV = 5cm^3$	**1.00**	0.60	0.36
5 	$TV = 5cm^3$ $TV_{PIV} = 5cm^3$ $PIV = 5cm^3$	1.00	1.00	1.00

FIG. 5. Comparison of the PITV ratio and the new conformity index for various treatment plans.

Table obtained directly from publication by: Paddick, I. (2000). A simple scoring ratio to index the conformity of radiosurgical treatment plans. *Journal of neurosurgery*, *93*(supplement_3), 219-222.

Annex B:

T1/T2 Mismatch



•A + B no mismatch = Tumor recurrence

•C + D mismatch = Radiation necrosis

Figure obtained directly from publication by: Kano, H. et al. T1/T2 matching to differentiate tumor growth from radiation effects after stereotactic radiosurgery. Neurosurgery 66, 486–91; discussion 491-2 (2010).

Annex C:

Performance Scales

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

KARNOFSKY, D. A. The clinical evaluation of chemotherapeutic agents in cancer. Evaluation of Chemotherapeutic Agents. Published online 1949:191-205. 35.

ECOG	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on selfcare. Totally confined to bed or chair
5	Dead

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.