Study Protocol

The histologic effects of neoadjuvant stereotactic body radiation therapy (SBRT) followed by pulmonary metastasectomy—rationale and protocol design for the Post SBRT Pulmonary Metastasectomy (PSPM) trial

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Background: For the local management of pulmonary malignancies, surgical resection and stereotactic body radiation therapy (SBRT) are mutually exclusive treatments. This study aims to assess the effectiveness of SBRT on reducing tumor viability at a histologic level in the context of pulmonary metastases.

Methods: This protocol describes an open-label unblinded single-arm prospective Phase 2 trial to determine the effects of dual treatment of pulmonary metastasis amenable to curative resection using neoadjuvant SBRT followed by surgical resection, the Post SBRT Pulmonary Metastasectomy (PSPM) trial. Sample size require 39 patients, with an anticipated study duration of 30–36 months. Following completion of SBRT, eligible patients will be assessed at the 4–6-week mark by the treating radiation oncologist and thoracic surgeon with a post-treatment computed tomography (CT) of the chest. Patients with no disease progression will undergo scheduled surgical resection of all metastatic tumors at 8–12 weeks post SBRT. Patients will then be evaluated postoperatively at 30 days, and every 6 months for a total of 36 months with surveillance CT scans. Patients will also undergo sequential serologic evaluation of circulating tumor DNA (ctDNA) levels throughout their respective treatment pathway. The primary outcome of this study is the rate of complete pathologic response (pCR) following SBRT, assess using the International Association for the Study of Lung Cancer (IASLC) multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. Secondary outcomes include overall survival (OS), disease free survival (DFS), local recurrence rates, cancer histology effects on pCR and treatment related complications, and treatment effect on ctDNA levels. Primary and secondary outcomes will be analyzed using Fisher's Exact test and Student's *t*-test based on data type. Cox-proportional hazard ratios will be used to evaluate OS and DFS, using the log rank test.

Discussion: In evaluating the effect of SBRT on pulmonary metastasis at a histologic level, this trial may increase the use of this modality in selected patients who would otherwise only undergo surgery for disease that has already metastasized. Also, the trial provides secondary benefits of evaluating the abscopal effects of radiation on pulmonary metastatic disease, and serves as a platform for more comprehensive large-scale research in this field.

Trial Registration: ClinicalTrials.gov identifier: NCT04160143 (HiREB: 7925).

Keywords: Neoadjuvant stereotactic body radiation therapy (SBRT); pulmonary metastasectomy; complete pathologic response (pCR); overall survival (OS); disease free survival (DFS)

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Introduction

Background and rationale

The use of non-surgical techniques for local control of primary and secondary lung tumors continues to garner increasing attention and adoption. The most widely researched non-surgical local modality as applies to lung malignancies is stereotactic body radiation therapy (SBRT) (1-3). While surgery remains the standard of care in the management of resectable primary and with pulmonary metastases, the prevalence of SBRT has increased, particularly in patients deemed to be non-operative candidates, and in those refusing to undergo surgery (4). The majority of research comparing surgery to SBRT has focused on post-treatment oncologic outcomes (survival and recurrence) in the context of non-small cell lung cancer (NSCLC). Using post-treatment imaging surveillance only, several trials have demonstrated 3-year local control rates of up to 90% (5). The use of radiographic surveillance post-SBRT is however limited by radiation induced lung injury leading to persistent radiologic abnormalities in the treatment field that can therefore misrepresent local control rates (6). There have been few efforts assessing the effectiveness of SBRT in tumor eradication at a histologic level. However, there were a few cases undergoing salvage surgery after SBRT for pulmonary metastases and viable cells were confirmed (7,8). In addition, little comparative research has evaluated SBRT *vs.* surgery in the treatment of pulmonary metastases for metastatic tumors deposited in the lung. In contrast, the role of pulmonary metastasectomy has been well researched and is supported by several retrospective reports demonstrating a survival advantage (9,10). In evaluating the histologic effect of SBRT on pulmonary metastasis, there may be rationale to consider this modality in select patients who would otherwise undergo surgery for disease that has already metastasized.

Objectives

For the local management of pulmonary malignancies, surgical resection and SBRT are considered as mutually exclusive treatment options. The primary objective of this study is to examine the effectiveness of SBRT on reducing tumor viability at a pathologic level, in hopes of concluding this information to both primary and pulmonary metastases. In surgical specimens post SBRT, rates of complete pathologic response (pCR) will be measured by a specialized lung pathologist using the International Association for the Study of Lung Cancer (IASLC) multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy (11). Also following secondary outcomes will be assessed: overall survival (OS) at 3 years, disease free survival (DFS) at 3 years, local recurrence rates, radiation related toxicity, postoperative pulmonary complication rate (including prolonged air leak, need for invasive or noninvasive mechanical ventilation, postop pneumonia and empyema), the effect on time-to-resection and tumour histology on pCR, and treatment effect on circulating tumor DNA (ctDNA) levels measured both after SBRT and surgery and compared to index level measured at the time of initial presentation.

Trial design

It is an open-label unblinded single-arm prospective trial evaluating induction SBRT followed by pulmonary metastasectomy. A phase 2 prospective trial which is a collaborative effort between Thoracic Surgery and Radiation Oncology to determine the effects of dual treatment of pulmonary metastasis amenable to curative resection with neoadjuvant SBRT followed by surgical resection, the Post SBRT Pulmonary Metastasectomy (PSPM) trial. We present this protocol in accordance with

the SPIRIT reporting checklist (12) (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-232/rc).

Methods: participants, interventions, and outcomes

Study setting/participants eligibility criteria

This study will take place in an academic tertiary hospital, as a combined effort between two highly specialised divisions of Thoracic Surgery and Radiation Oncology. Recruitment will commence and continue until 39 patients are enrolled in the study via consecutive convenience sampling.

Patients inclusion criteria will be as follows: patient age ≥18 years; resectable pulmonary metastases without more effective systemic therapy option (regardless of type of primary malignancy, excluding hematologic malignancies) with the primary malignancy already having been treated without evidence of local recurrence; single-organ metastasis to lung only (except for colorectal cancer with synchronous hepatic metastasis); there should not be any evidence of nodal disease on pre-treatment CT scan; adequate pulmonary function to tolerate lung resection (post-operative predictive FEV1 ≥40% and DLCO ≥40%); and tumor(s) ≤5 cm. We set a number of no more than 5 metastases per lung based on restrictions from an SBRT standpoint. While it is true that number of mets is a prognostic indicator, data supports being able to completely resect these lesions as a more telling prognostic factor—hence our rational. Also, in consultation with our lung SBRT expert, we restricted treatment to lesions less than 5 cm in size—lesions with greater size would not be candidate for this trial and have traditionally been the upper limit for SBRT in other trials of oligometastatic disease. Patient having comorbidities not amenable to surgery; uncontrolled primary malignancy; hematologic malignancies (leukemia or lymphoma); >5 tumors in one lung; prior history of thoracic radiation; and history of lung cancer diagnosis within 5 years of assessment will be excluded.

Treatment & interventions

Preoperative intervention

Eligible patients will be initially evaluated by a thoracic surgeon. Consenting patients meeting inclusion criteria will be carefully evaluated for SBRT by the treating radiation oncologist with treatment commencing within 2 weeks, with planning and delivery parameters following the guidelines developed through the Canadian LUSTRE randomized SBRT lung trial for medically inoperable NSCLC (13). Specifically, SBRT will be delivered according to a risk-adjusted dose fractionation contingent on tumor size and location (48 Gy in 4 fractions for peripheral lesions, 60 Gy in 8 fractions for central or apical lesions). These doses are based on previously published data in the context of lung malignancies and are considered definitive SBRT doses given that we are evaluating the pCR of SBRT from a curative perspective. Following completion of SBRT, patients will be assessed at the 6-week mark by the treating radiation oncologist and thoracic surgeon with a post-treatment computed tomography (CT) of the chest.

Operative intervention

If no disease progression is identified, patients will undergo scheduled surgical resection of all metastatic tumors at 8–12 weeks post SBRT. The choice of lobar *vs.* sublobar resection will be determined by the participating surgeon, based on tumor size and location. Guidelines for pulmonary metastasectomy recommend lung-sparing surgical resection, with wedge resections being preferred if feasible. The majority of pulmonary metastasectomies are performed using minimally invasive (MIS) techniques via thoracoscopic or robotic assistance. The choice of surgical approach will be left to the discretion of the operating surgeon. In so doing, this methodology increases external validity. In the case of patients with bilateral metastatic nodules, SBRT will be administered to all sites of disease followed by staged resection of all malignant lesions. Only completely resectable tumors will be included in the study.

Clinical follow-up procedures

Patients will be seen post-SBRT and post-surgery between radiation and surgery 8 to 12 weeks and post-operative at 30 days for the initial postop visit, and then every 6 months for a total of 36 months after surgery with surveillance CT scans.

Outcome assessment

All patients will undergo radiographic and biochemical evaluation at baseline, post SBRT and postoperatively. The initial CT scan will be instrumental in determining patient eligibility and suitability to both SBRT and surgery. Surveillance imaging will be used to determine the initial and latent, incidence of local and distant recurrence, and to evaluate any associated post SBRT related parenchymal

and mediastinal changes. These will be performed at 6 weeks post SBRT, and then at 6 months intervals post lung resection for a total of 3 years. In addition, we also specifically aim to explore whether cancer specific tumor biomarkers correlate with treatment effects at different treatment intervals (pre SBRT, post SBRT and postoperatively). For this purpose serum ctDNA levels will be measured using specialty assays at different time frames: baseline/pre-SBRT; 6 weeks post SBRT, and 6 weeks post-surgery. As small fragments of tumor DNA that usually comprise fewer than 200 building blocks (nucleotides) in length, the quantity ctDNA can help detect treatment effectiveness and prognostication.

Primary outcome

IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy will be used to assess the rates of complete pCR in surgical specimens post SBRT (11). The IASLC outlined the detailed recommendations on how to process lung cancer resection specimens and to define pCR, including major pCR or complete pCR after neoadjuvant therapy. A standardized approach was recommended to assess the percentages of viable tumor, necrosis, and stroma (including inflammation and fibrosis) (11). As such, a thoracic pathologist will perform the detailed pathologic review of surgical specimens according to these outlined criteria in order to assess the primary outcome of interest.

Secondary outcomes

Secondary outcomes to be assessed include: OS at 3 years, DFS and local recurrence rates at 3 years based on clinical and CT scan results, radiation-related toxicity evaluated using the RTOG Common Toxicity Criteria (14), 30-day postoperative pulmonary complication rate assessed using the Society of Thoracic Surgery (STS) post lung resection complication nomenclature, and the effect of treatment on ctDNA level.

Participant timeline

Figure 1 describes the time schedule of enrolment, interventions, assessments, and visits for participants. Briefly, eligible consenting patient will be evaluated for SBRT and receive treatment within 2 weeks of initial evaluation. Post-SBRT CT scan and ctDNA will be assessed at 6-week, with surgical resection planned at 8–12 weeks post SBRT. Following routine post-operative care, patients will have repeated levels of ctDNA drawn at 6-week postoperatively, and will undergo surveillance CT scans of the chest at 6-month intervals for a total of 3 years, or until disease recurrence is identified.

Sample size

The effect size estimate of pCR is the most important metric in determining the necessary sample size. The MISSILE study which evaluated SBRT prior to surgery in NSCLC, demonstrated a pCR of 60% (15). This is the only representative value available in the literature, even though the PSPM trial evaluates SBRT and surgery for metastatic disease and not primary lung cancer. On the other hand, the SBRT literature (using post-treatment CT scans only) reports local control rates of nearly 90%. The calculated sample size requirement is 39 patients, using the Fleming procedure, in order to measure the true pCR with a 95% confidence interval ± 10% using an estimated true pCR of 70%, estimated dropout rate of 20%, and 80% power.

Recruitment

From Institutional data, the Division of Thoracic Surgery at McMaster University performs an average of 450 pulmonary resections per year with approximately 10–15% being pulmonary metastasectomies for a spectrum of malignancies (including colorectal carcinoma, renal cell carcinoma and soft tissue sarcoma). It is estimated that the recruitment will be approximately 1–2 patients per month. In addition, the principal investigator is part of other disease-site multidisciplinary cancer conference groups and has presented this trial in order to promote collaboration and increase patient identification and recruitment. Regarding long-term follow-up, all patients undergoing pulmonary metastasectomies require cancer surveillance with dedicated CT scans of the chest. As such, there is no anticipation of any significant challenges to retention or significant loss to follow-up.

Data collection/analysis, management and monitoring

As a single-arm trial, all eligible study participants will undergo the same intervention and evaluation on a per-protocol basis. Subgroup analysis will be used to explore different prognostic related features associated with improved pCR post SBRT. Typical of Phase 2 trials, this is an unblinded study. Patients, investigators and outcome

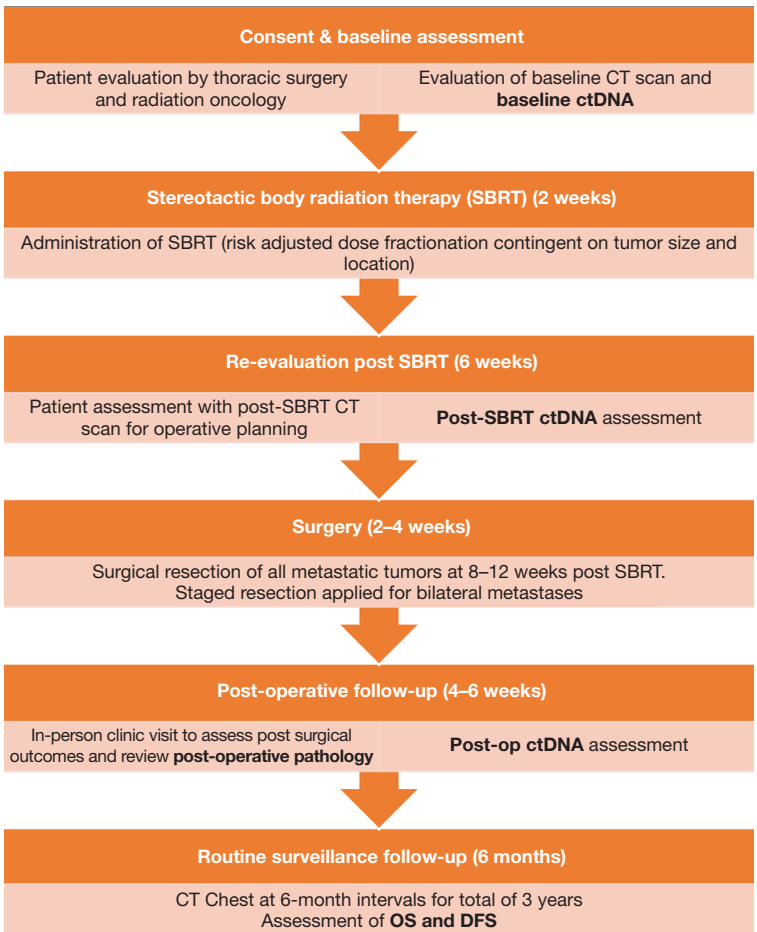

Figure 1 Participant timeline & study flow diagram. CT, computed tomography; ctDNA, circulating tumor DNA; SBRT, stereotactic body radiation therapy; OS, overall survival; DFS, disease free survival.

assessors will be aware of study protocol. It is important for radiologists and pathologists to know of prior SBRT in order to be able to assess radiographic and pCR rates on post treatment CT scans and in the final surgical specimen respectively. We do not believe that the unblinded nature of this Phase 2 trial will promote bias, given that there is no comparator group. In fact, treatment information may promote more detailed assessments by radiology and pathology.

Long-term patient data will be assessed as part of standard post malignant lung resection surveillance guidelines, given that all these patients undergo follow-up CT scan post resection to rule out disease recurrence. Survival data will be collected at the time of surveillance postop visits. Regarding descriptive statistics, continuous variables will be reported as means (standard deviation) and medians (range), while categorical data will be reported using rates and proportions. Primary and secondary outcomes will be analyzed using Fisher's Exact test for categorical data and Student's *t*-test for continuous data. Linear regression analysis will be used to assess differences in time to surgery post-SBRT on pCR rates. As part of the pre hoc secondary analysis, Cox-proportional hazard ratios will be used to evaluate OS and DFS. Survival analysis will be conducted using the log rank test.

The co-principal investigators of the trial will oversee all aspects of the study including management and training of study personnel, ensuring data integrity, overseeing data collection; assembly of a data-safety monitoring committee (DSMC), and analysis and dissemination of research findings. The DSMC will comprise a thoracic surgeon, radiation oncologist, molecular medicine specialist

and statistician. The primary objective of the DSMC is to evaluate any significant adverse events related to treatment and ensure that the conduct of the trial does not pose increased risk to participants or lead to harm. The risks to participants in this study are pain, vomiting and weakness, which will be minimized and managed by continuous observation, appropriate medication by physicians. Interim analysis of the DSMC will take place once n=7 patients are treated per-protocol (8–12 months), concurrent with recruitment.

Ethics and dissemination

Current trial progress

This study has received local institutional approval from the local research ethics board, Hamilton Integrated Research Ethics Board (HiREB) (#7925; PSPM Trial Protocol v1.1 08May2020) and has successfully received funding by three local institutional grant committees. The study is registered with clinicaltrials.gov (NCT04160143). In addition, three additional Canadian centers have expressed interest in participation in hopes of rendering this a multicenter endeavor. Contract and data-sharing agreements have yet to be in place. Participant assessment and enrollment is soon to being in hopes of study completion by the end of study duration in 2 years.

We certify that this study will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki (as revised in 2013) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations. Patients or their legally acceptable representative must be consented. If allowable per local regulations, exceptions may be granted in cases where the patient is unable to provide informed consent.

Patients are typically evaluated preoperatively with several radiologic and functional tests to ensure that they meet surgical indications. After initial assessment, patients meeting inclusion criteria will be cross-referred for evaluation by a radiation oncologist to assess candidacy for SBRT. Eligible patients will then be approached (in-person or by phone) by a research assistant to consent to trial participation. The participants will have the option to withdraw at any point in time and will inform their respective treating physician and the study coordinator, who will notify the principal investigator. Participant baseline demographic information and outcome data will be recorded using Case Report Form (CRF) (Appendix 1) with data entered into REDCap, a web-based secure system that collects and stores the data behind secure institutional firewall. A tracking log of on-study patients will also be maintained on a secure institutional drive. The paper files and code will also be stored under lock-and-key. Participant data will be anonymized after follow-up is completed.

Given the set precedent and routine clinical use, we do not believe that the combination of SBRT and surgery would prove to be an ethical challenge. Most importantly, the combination treatment approach in the context of secondary metastases is distinctly different than primary malignancies, where delays in surgical resection may potentially compromise care. In the setting of pulmonary metastasectomies, the necessary wait time to surgery (as patients receive induction SBRT) actually provides several potential benefits: (I) induction radiation may increase the probability of negative resection margins (particularly in the context of multiple metastatic tumors), (II) demonstrating disease stability over 2–3 months (longer disease free-interval) with no new metastatic nodules validates surgical intervention and is an important prognostic factors, and (III) for patients undergoing chemotherapy, a lag period to surgical intervention may be necessary—receiving SBRT in the mean time would provide these patients with a form of treatment as they await surgery.

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland (October 2008). Informed written consent will be obtained from the patients prior to any study specific procedures. The right of a patient to refuse participation without giving reasons will be respected (Appendix 2). All members of the research team have received good clinical practice (GCP) training, honorary National Health Service (NHS) contracts, and adhere to NHS confidentiality guidelines and codes of conduct. In addition, this study has access to a number of private rooms in the outpatient and ward areas in which to consent patients and carry out the study processes.

Publication & dissemination policy

The project is registered with an authorised registry. The project's success depends on the cooperation of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contribution. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. So, the authorship credit should be based only on substantial contribution to: conception and design, acquisition of data, analysis, interpretation of data, drafting the article or revising it critically for important intellectual content, and/or final approval of the version to be published. Considering this, the principal investigator and relevant research staff, will be named as authors in any publication. Additionally, all collaborators will be listed as contributors for the main publication, giving details of roles in planning, conducting, and reporting. To maintain the scientific integrity of the project, data will not be released prior to the first publication of the analysis of the primary endpoint, either for publication or oral presentation purposes, without the permission of the research team and the DSMC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the project until the first publication of the analysis of the primary endpoint.

Discussion & study impact

Much of the literature supporting pulmonary SBRT focuses on the treatment of NSCLC. The most widely reported study demonstrating the effectiveness of SBRT in the treatment of primary lung lesions is a pooled analysis of two randomized trials (STARS and ROSEL—both closed early due to poor recruitment). The unpowered analysis of 58 patients randomly assigned to lobectomy *vs.* SBRT demonstrated no difference in overall and recurrence-free survival at 3 years (OS: 79% *vs.* 95%, and 80% *vs.* 86%) (15). Surgery was associated with a 4% mortality rate and 44% high-grade complication rate. In contrast, 10% of SBRT patients had grade 3 adverse events, with no reported grade 4 events (15). This study is generally criticized for its lack of methodologic rigor and post hoc analysis. A recent meta-analysis of 19 trials spanning 2005–2018 of 1,434 patients demonstrated good local and regional control using SBRT, with similar complication rates to surgery. Three-year OS ranged from 43–95% with loco-reginal control rates as high as 98%. Up to 33% of patients, however, demonstrated distant recurrence at 3 years (1). This high distant recurrence rate could be secondary to low pCR as compared to complete surgical resection, an association that has yet to be evaluated.

Ibrahim *et al.* (16) evaluated the comparative effectiveness of surgery *vs.* other local control measures in the management of colorectal cancer pulmonary metastasis. The authors concluded that the highest level of evidence supported the use of surgery as the primary treatment modality. Although some patients underwent repeated surgical resection, no patients underwent combination treatment of surgery and SBRT. Generally, surgery was associated with low procedure-related mortality (0–2.4%) and an average 5-year OS rate of approximately 50%, while SBRT was associated with similar survival but only at 2-year (17). In addition, the surgical and non-surgical management of sarcoma pulmonary metastases can be more complex particularly with repeat thoracotomy (18), however given the relative lower incidence of sarcoma compared to other cancer subtypes, the effect of this on a Phase 2 trial is unlikely to be significant. Only one retrospective cohort study directly compared surgery *vs.* SBRT in colorectal cancer oligometastases, with most patients being offered surgery as first line treatment. The results demonstrated no difference in survival or local control comparing both modalities, but DFS was only 17% at 3 years in the entire cohort (19). Similarly, a recently conducted exploratory analysis demonstrated that OS after SBRT is similar to surgery for the first 2 years (20). Moreover, recent research has demonstrated the abscopal effect of SBRT, where radiation induced activation of the immune system can elicit immune-mediated anti-tumor responses (21). These results highlight the important principle that in the setting of pulmonary metastasis, distant recurrence remains a challenge. Despite the survival equivalence, patients tend to be treated surgically as the first option without addressing the risk of distant disease (22).

There only exists one trial evaluating the effects of combined modality pulmonary SBRT and surgery. The MISSILE trial evaluated the pCR rate of SBRT on primary lung cancer undergoing surgical resection for definitive cure. The pCR was 60% on histologic analysis, and the regional control rate was 56% at 2 years (17). The rationale behind this is unclear and may suggest worsening nodal spread of disease between the intervals of SBRT and surgical resection. This is less likely to be of concern in the setting of metastasectomy given that nodal disease control is not typically part of the management of pulmonary

metastatic disease. It is possible that secondary malignancies represent a different local disease burden compared to primary lesions and accordingly a potentially different pCR following SBRT. This trial is therefore valuable in assessing the pCR in SBRT for metastatic disease, and in explaining the unexpectedly high regional recurrence rates of MISSILE.

Taken together, the literature supports the pursuit of this novel trial given the knowledge gaps that exist. The principles used in the management of primary *vs.* secondary lung malignancies differ, potentially creating greater equipoise between surgery and SBRT in the setting of metastatic disease. The SBRT plays a role as a potentially non-invasive treatment for small-volume tumors in the lung is well established, however the effectiveness of tumor eradication has yet to be determined (13,23,24). This trial (prospective Phase 2) will provide several novel contributions to the literature: (I) the SBRT effectiveness assessment in metastatic tumor control (radiotherapeutic metastasectomy), (II) by surgical resection, the evaluation of pCR to SBRT, (III) identification of histologic predictors of radiation effect and toxicity (i.e., what are the effects of SBRT on different type of metastatic disease), (IV) the effect of combined modality SBRT and surgery on survival and local recurrence as compared to either modality alone, and (V) assessing the association of SBRT and surgical resection on the levels of ctDNA and the burden of systemic disease at a biochemical level. This trial will exclusively evaluate whether surgery as an adjunct to radiotherapy offers better tumor control as compared to SBRT alone (compared to historical controls from previously published reports), and whether it decreases locoregional recurrence. By evaluating the pCR following SBRT, this study lays the groundwork for further research to evaluate if SBRT could be considered first line treatment in pulmonary metastasis. Most importantly, evaluation of pCR following SBRT is an important concept that has not been fully evaluated in the literature, and this trial will add to the results of the MISSILE study to determine the pCR of SBRT across different malignancies, and potentially identify prognostic features outlining which patients are best treated by SBRT and/or surgery.

In evaluating the effect of SBRT on pulmonary metastasis at a histologic level, this trial may increase the use of this modality in selected patients who would otherwise only undergo surgery for disease that has already metastasized. We believe this study to be innovative for several reasons. Firstly, to date there are limited published reports on the rates of pCR response following SBRT, with only one pilot study assessing this phenomenon in the setting of NSCLC. Secondly, this study will be able to accurately quantify the effects of SBRT on tumor eradication—and accordingly will provide a large contribution to the literature which is drastically lacking. Thirdly, no study has evaluated the role of induction SBRT in the treatment of pulmonary metastasis. Finally, SBRT may have a greater role in pulmonary metastases (as compared to primary lung cancer) given a theoretical lower burden of local disease, the fact that the majority of patients would have already received adjunctive chemotherapy, and that regional lymph node metastasis is less likely (with most disease spread being a consequence of a hematogenous phenomenon and not secondary to locoregional spread).

Moreover, at a local level, this study protocol has had the added impact improved communication and multidisciplinary care of patients with stage IV malignancies. Essentially, the promotion of the PSPM trial has facilitated multimodal care of patients and promoted the use of surgical intervention and radiotherapy in the treatment of patients with oligometastatic disease. As such, one of the unintended consequences has been the promotion of more aggressive local therapy for patients receiving chemotherapy only under the care or medical oncologists.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-232/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-232/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-232/coif). The authors

have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has received local institutional approval from the local research ethics board, Hamilton Integrated Research Ethics Board (HiREB) (#7925; PSPM Trial Protocol v1.1 08May2020). The study is registered with clinicaltrials.gov (NCT04160143). We certify that this study will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki (as revised in 2013) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations. Patients or their legally acceptable representative must be consented. If allowable per local regulations, exceptions may be granted in cases where the patient is unable to provide informed consent.

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Cite this article as: Begum H, Swaminath A, Lee Y, Fahim C, Bramson J, Naqvi A, Shargall Y, Finley C, Hanna W, Agzarian J. The histologic effects of neoadjuvant stereotactic body radiation therapy (SBRT) followed by pulmonary metastasectomy—rationale and protocol design for the Post SBRT Pulmonary Metastasectomy (PSPM) trial. Transl Cancer Res 2022;11(4): 918-927. doi: 10.21037/tcr-22-232

Supplementary

Appendix 1

Case Report Form (CRF)

Screening Visit

Patient study code: _____
Gender: male/female
Year of birth: _____
Date of visit (DD/MM/YYYY): _____

Eligibility Criteria
Inclusion Criteria

Yes	No	
□	□	Patient age >18, resectable pulmonary metastases without a more effective systemic therapy option (regardless of type of primary malignancy, excluding hematologic malignancies) with the primary malignancy already having been treated without evidence of local recurrence
□	□	Patient having single-organ metastasis to lung only (with the exception of colorectal CA with synchronous hepatic metastasis)
□	□	Tumors <5cm
□	□	Patient with no evidence of nodal disease on pre-treatment CT scan
□	□	Patient having adequate pulmonary function to tolerate lung resection (post-operative predictive FEV1≥40%).

Exclusion Criteria

Yes	No	
□	□	Patient having comorbidities not amenable to surgery
□	□	Patient with uncontrolled primary malignancy
□	□	Patient with hematologic malignancies (leukemia or lymphoma)
□	□	Patient having more than 5 tumors in one lung
□	□	Patient with prior history of thoracic radiation

Informed Consent

Yes	No	
□	□	The patient does meet the inclusion criteria
□	□	A signed informed consent form has been obtained

Informed Consent Signature Date (DD / MM / YYYY) : _____

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Baseline Visit

Patient study code: _____
Date of visit (DD / MM / YYYY): _____

Radiology:

CT chest _____ (DD / MM / YYYY)	□ No evidence of disease progression □ Evidence of disease progression. Please specify: _____

Circulating tumour cells

Date of blood work collected _____ (DD / MM / YYYY)	Results:

Primary Cancer

□	Soft tissue sarcoma	□	Melanoma	□	Gastric cancer
□	Colorectal cancer	□	Head and neck cancer Specify:	□	Other:
□	Renal cell carcinoma	□	Osteosarcoma		
□	Germ cell cancer	□	Breast cancer		
□	Gynecologic cancer Specify:	□	Hepatocellular cancer		

Date of resection of primary cancer (DD / MM / YYYY):
Final pathology of primary cancer: T _____ N _____ Margin: clear / positive

Pulmonary Metastases

Number of Nodules

□	Right upper lobe_____	□	Right middle lobe _____	□	Right lower lobe _____
□	Left upper lobe _____	□	Left lower lobe _____		

Biopsy performed?
□ No
□ Yes Location of nodule: _____ Date of biopsy: _____ Pathology: _____

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Medical History

Significant Medical History? □ Yes □ No	
System	Comments
Ear, Nose, Or Throat	
Ophthalmologic	
Cardiovascular	□ CHF Class. I □ II □ III □ IV □ □ Angina Class. I □ II □ III □ IV □ □ MI □ CABG □ Coronary Artery Disease □ Hypertension □ Hypercholesterolemia □ Other:
Respiratory	□ COPD Class. I □ II □ III □ IV □ Other: FEV 1: DLCO:
Gastrointestinal	
Neurological	
Genitourinary	
Musculoskeletal	□ Osteoarthritis □ Other:
Endocrine	□ Diabetes Insulin dependant Yes □ No □ □ Other:
Dermatologic	
Blood disorders	
Lymph Nodes	
Mental	
Pre-op Chemo/Radiation	Pre-op chemo Yes □ No □ Pre-op rad. Yes □ No □ Body site:
Other:	

Smoking Status		Smoking history
Never Smoked	Patient quit smoking? Yes □ No □	
Past Smoker		
Current Smoker	How long ago did patient quit smoking?	
No Information	# of □ years □ months □ days	# Pack years

CHF, Angina, and COPD Classification. Symptoms only with: Class I: severe or strenuous activity. Class II: moderate activity. Class III: light activity. Class IV: at rest

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Baseline

Patient study code: _____
Date of visit (DD / MM / YYYY): _____

Study Information:

Date of surgical resection (DD / MM / YYYY)	
Date of discharge (DD / MM / YYYY)	
Date Trial intervention commencement (DD / MM / YYYY)	
Research Coordinator Signature:	

Stereotactic Body Radiation Therapy (SBRT)

Patient undergoes SBRT delivered according to a risk-adjusted dose fractionation contingent on tumor size and location.

Study Information:

Date of SBRT (DD / MM / YYYY)	
Date of discharge (DD / MM / YYYY)	
Tumor characteristics	Size Location
Doses of Trial intervention (DD / MM / YYYY)	Dose other
Research Coordinator Signature:	

Post-Radiation Follow-up Clinic Visit (Re-evaluation post SBRT)

Patient study code: _____
Date of visit (DD / MM / YYYY): _____

A) Radiology:

CT chest _____ (DD / MM / YYYY)	□ No evidence of disease progression □ Evidence of disease progression. Please specify: _____

B) Circulating tumour cells

Date of blood work collected _____ (DD / MM / YYYY)	Results:

C) Surgical Resection

Proceed with surgical resection? □ Yes □ No. Please specify reason: _____

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Operation/Clinical Stage (Pre-Surgery)

Patient study code: _____
Date of operative procedure (DD / MM / YYYY): _____
Surgeon: □ Y. Shargall □ C. Finley □ W. Hanna □ J. Agzarian

Incision:
□ Open
□ MIS
□ VATS converted to open

If open:
□ Thoracotomy:
□ right □ left
□ post-lateral □ antero-lateral □ axillary
□ Sternotomy
□ Rib resection _____ (rib #)

If MIS:
□ right □ left
# of ports: _____

Lung resection:
□ Lobectomy: □ RUL □ RML □ RLL □ LUL □ LLL
□ Pneumonectomy: □ right □ left
□ Segmental resection _____ (segment #)
□ Wedge: □ RUL □ RML □ RLL □ LUL □ LLL _____ (# of wedges)

Lymph node stations: _____

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First Post-operative Follow-up Clinic Visit (6 week follow up)

Patient study code: _____
Date of visit (DD / MM / YYYY): _____

A) Pathologic Report (Complete pathologic response - pCR):

□ Soft tissue sarcoma	□ Melanoma	□ Gastric cancer
□ Colorectal cancer	□ Head and neck cancer Specify:	□ Other:
□ Renal cell carcinoma	□ Osteosarcoma	
□ Germ cell cancer	□ Breast cancer	
□ Gynecologic cancer Specify:	□ Hepatocellular cancer	
Margin: clear / positive		

B) Radiology:

CXR - Post-op _____ (DD / MM / YYYY)	□ Normal □ Abnormal. Please specify: _____

C) Circulating tumour cells

Date of blood work collected _____ (DD / MM / YYYY)	Results:

D) Adjuvant Therapy:

Is this patient on chemotherapy or radiation? □ Yes □ No If yes, please fill out the chemotherapy/radiation Case Report Form

E) Overall Assessment:

□ No evidence of recurrence & clinically well □ No evidence of recurrence. Problem identified : □ Intervention to problem identified: □ Recurrence □ Other:	
Follow up Plan	□ 3 months □ 6 months □ 12 months □ PRN

https://dx.doi.org/10.21037/tcr-22-232

Late Follow-up Clinic Visit (Routine follow up for 3 years)

Patient study code: _____
Date of visit (DD / MM / YYYY): _____

A) Radiology:

CXR - Post-op _____ (DD / MM / YYYY)	□ Normal □ Abnormal _____ (details)
CT chest (if performed) _____ (DD / MM / YYYY)	□ No evidence of recurrence or complication □ Evidence of recurrence. Please specify: _____

B) Adjuvant Therapy:

Is this patient on chemotherapy or radiation? □ Yes No If yes, please fill out the chemotherapy/radiation Case Report Form

C) Overall Assessment:

□ No evidence of recurrence & clinically well □ No evidence of recurrence. Problem identified : □ Intervention to problem identified: □ Recurrence □ Other:	
Follow up Plan	□ 3 months □ 6 months □ 12 months □ PRN

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Concomitant Medications

Patient study code: ___________________

Is the patient taken any concomitant medications? If Yes, please provide details below	□ Yes □ No

Medication	Indication	Other Information
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes
		Started medication at: □ Baseline Other:_________________ Discontinued this medication? □ Yes

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Adverse Events

Patient study code: ___________________

Adverse Event *	Severity **	Attribution ***	Date Started (DD/MM/YYYY)	Date Ended (DD/MM/YYYY)	Patient Outcome
		□ Surgery □ Chemotherapy □ Radiation □ Other:		□ Ongoing	□ Remains in study □ Withdrawn from study □ Lost to follow-up □ Death
		□ Surgery □ Chemotherapy □ Radiation □ Other:		□ Ongoing	□ Remains in study □ Withdrawn from study □ Lost to follow-up □ Death
		□ Surgery □ Chemotherapy □ Radiation □ Other:		□ Ongoing	□ Remains in study □ Withdrawn from study □ Lost to follow-up □ Death
		□ Surgery □ Chemotherapy □ Radiation □ Other:		□ Ongoing	□ Remains in study □ Withdrawn from study □ Lost to follow-up □ Death

* Adverse Event: Event not considered an SAE, but an event that was identified through patient reports (diaries, interviews). Examples might include fragmented sleep, appetite issues etc.

** Severity: Please use the Common Terminology Criteria of Adverse Events (CTCAE) V.5 to assign grading

***Attribution Description: 1. Unrelated 2. Unlikely 3. Possible 4. Probable 5. Definite

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Serious Adverse Events

Patient study code: _____

*** If an SAE has occurred please report to your local REB and notify the coordinating center within 48 hours of the identification of the event. Please see the AMPLCaRe Procedures Manual for more instruction, or call the coordinating center. ***

Serious Adverse Event*	Severity **	Attribution ***	Date Started (DD/MM/YYYY)	Date Ended (DD/MM/YYYY)	Date Reported (DD/MM/YYYY)	Patient Outcome
		□ Surgery □ Chemotherapy □ Radiation □ Other:		□ Ongoing		□ Remains in study □ Withdrawn from study □ Lost to follow-up □ Death

I am aware of this serious adverse event, and have verified the details above: _____
Site Principle Investigator Date

* Serious Adverse Event: Death; life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Please see AMPLCaRe Procedures Manual for more instruction, or call the coordinating center.
** Severity: Please use the Common Terminology Criteria of Adverse Events (CTCAE) V.5 to assign grading
***Attribution Description: 1. Unrelated 2. Unlikely 3. Possible 4. Probable 5. Definite

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Documentation Record Log

Patient study code: _____

Date of visit (DD / MM / YYYY): _____

Tests to be completed from baseline to follow up appointments:

Baseline/pre-RT Week- 0	Post RT Follow-up Week -6	1st Pre-op Follow-up Week 8-12	3-month Follow-up	6-month Follow-up	9-month Follow-up	12-month Follow-up	18-month Follow-up	24-month Follow-up	30-month Follow-up	36-month Follow-up
□ CT chest □ CTC	□ CT chest □ CTC	□ Chest x-ray □ CTC	□ CT chest	□ CT chest	□ CT chest	□ CT chest	□ CT chest	□ CT chest	□ CT chest	□ CT chest

*Please include the results of these tests on the Case Report Forms.

CRFs to be completed by Research Coordinator:

Baseline Date:	Post RT Follow-up Date:	Operatory/ Clinical Stage Date	1st Post-op Follow-up Date:	3-month Follow-up Date:	6-month Follow-up Date:	9-month Follow-up Date:
□ Screening visit □ Medical history □ Study info □ Medication log	□ Post RT form	□ Operation form	□ 1st FU form	□ Late FU form	□ Late FU form	□ Late FU form

12-month Follow-up Date:	18-month Follow-up Date:	24-month Follow-up Date:	30-month Follow-up Date:	36-month Follow-up Date:	End of Study Date:
□ Screening visit □ Medical history □ Study info □ Medication log	□ Post RT form	□ Operation form	□ 1st FU form	□ Late FU form	□ End of Study form

* At any stage, please be sure to fill out an AE/SAE form if needed.

** If patient withdraws please fill out the 'End of Study' report

End of Study

Patient study code: _____

Year of birth: _____

Date (DD / MM / YYYY): _____

Date of final follow up: (DD / MM / YYYY)	
Reason to End Study:	□ Normal Completion □ Recurrence, patient decides to stop study drug □ Serious Adverse Event □ Death □ Patient withdrawal, reason: _____ □ Lost to follow up □ Principal Investigator Decision, Specify: _____ □ Other: _____
Comments:	

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Adjuvant Chemotherapy/Radiation

Patient study code: _____

Cycles of Chemotherapy:

Drug(s)	Dose(s)	Date Started (DD / MM / YYYY)	Date ended (DD / MM / YYYY)	Adverse Events
				Y □ N □
				Y □ N □
				Y □ N □
				Y □ N □
				Y □ N □
				Y □ N □

Courses of Radiation:

Daily Dose	Total Dose	Date Started (DD / MM / YYYY)	Date ended (DD / MM / YYYY)	Adverse Events
				Y □ N □
				Y □ N □
				Y □ N □
				Y □ N □
				Y □ N □
				Y □ N □

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Appendix 2

Consent Form

Study Information and Informed Consent Form
Post SBRT Pulmonary Metastasectomy (PSPM) Trial

Post SBRT Pulmonary Metastasectomy: Evaluating the effects of SBRT on pulmonary metastasis using post-surgical histologic evaluation.

Study ID: SJHH_PSPM 7925

Lead Investigator:	Dr. John Agzarian, BHSc, MD, MSc Division of Thoracic Surgery St. Joseph's Healthcare Hamilton T2105-50 Charlton Ave E. Hamilton ON Tel: 905-522-1155 x 32701
Co-Investigators:	Dr. Anand Swaminath, MD, MSc (*Radiation Oncology*), Dr. Christine Fahim, PhD, MSc (*HRM & Implementation Science*), Dr. Asghar Naqvi, MD (*Anatomic Pathology*), Dr. Yaron Shargall, MD (*Thoracic Surgery*), Dr. Christian Finley, MD, MPH (*Thoracic Surgery*), Dr. Wael Hanna, MD, MBA (*Thoracic Surgery*)
Research Coordinator	Housne Begum, MSc, PhD Division of Thoracic Surgery T2105-50 Charlton Ave E. Hamilton ON Tel: 905-522-1155 x 35338 Email: begumh@mcmaster.ca
Funding Source	MSA Grant, JHCCF Grant, Firestone

Emergency Contact Number (24 hours/7 days a week): 905-870-2647 (pager)
Non-Emergency contact numbers are at the end of this document under Contacts.

You are being invited to take part in a study called Post SBRT Pulmonary Metastasectomy (PSPM) Trial, because you are a patient will having surgery to remove metastatic lung nodules. Participating in this study is optional, and will not affect your any usual treatment.

In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits. This form gives detailed information about the research study. Please take your time to fully understand what comprises participation. After you have read this form, you will be asked to sign it if you wish to participate.

Introduction
The role of SBRT as a treatment for small-volume tumors in the lung is well established, but the effectiveness of tumor eradication has yet to be determined. Surgery and stereotactic body radiation therapy (SBRT) are both acceptable treatment options for the local management of lung tumors where the cancer has originated elsewhere in the body. This trial will assess whether the addition of SBRT to surgery offeres better tumor control, and whether it decreases recurrence of the cancer. This is a collaborative effort between the divisions of Thoracic Surgery and Radiation Oncology to evaluate the effects of dual treatment of pulmonary metastasis amenable to curative resection with upfront SBRT followed by surgical resection.
Study recruitment and analysis will be conducted at St. Joseph Healthcare Hamilton and the Juravinski Cancer Center. The Primary Outcome will be measured as the rates of complete pathologic response (pCR) in surgical specimens post SBRT-this

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means that the removed tumor will be evaluated under the microscope to determine how effective SBRT was in eradicating the cancer. Other outcomes that will be assessed include: overall survival (OS) at 3 years, disease free survival (DFS) at 3 years, local recurrence rates, radiation related toxicity, postoperative complications.

What is the purpose of the study?
The goal of this study is to determine the effectiveness of SBRT on reducing tumor viability at a pathologic level. We hope to extrapolate this information to both primary and secondary lung cancer.

What will happen during the study?
If you choose to participate in this study, treatment will be delivered within 2 weeks, with planning and delivery parameters following the standard guidelines. Following completion of SBRT, you will be assessed at the 4–6-week mark by the treating radiation oncologist and thoracic surgeon with a post-treatment computed tomography (CT) of the chest.
If no disease progression is identified, you will undergo scheduled surgical resection of all metastatic tumors at 8–12 weeks post SBRT. The choice of lobar *vs.* sublobar resection (type of surgery) will be determined by the participating surgeon, based on tumor size and location. The choice of surgical approach (MIS *vs.* thoracotomy) will be left to the discretion of the operating surgeon.
You will be seen Post SBRT and Post Surgery between Radiation and Surgery 8 to 12 weeks and post-operative at 30 days for 36 months after surgery. Routine post lung cancer resection required interval surveillance CT scan to be performed at internals of 6 months for at least 3 years. You will be typically followed by both Thoracic Surgery and medical oncology.

What are the possible risks of participating in the study?
Both SBRT and surgical wedge resection are well established as safe and effective modalities in the treatment of pulmonary malignancies. This trial utilized well established treatment protocols that are currently routinely applied to day-to-day clinical practice. So we do not anticipate that there will be any harm or discomfort from taking part in this study. Radiation prior to surgery can increase scarring during surgery and made surgery more challenging. This is less likely to affect your type of operation given the decreased amount of lung tissue being removed, and the fact that SBRT if focal radiation with less spread and less effects to the local area. In addition, we routinely operate on patients after they had radiation treatment.
You should know that the addition of SBRT to surgery will necessitate a delay to surgery, but we do not anticipate this delay to be of any significance, and some research has shown that radiation may have benefits in cancer treatment throughout the body (abscopal effect). Our own research has already shown, that delays ins patients with lung cancer who are completing necessary work-up is not associated with worsened outcomes.

Will I be paid to Participate in this study?
You will not be paid or compensated in any way for participation.

Will there be any costs to me in this study?
There will be no costs associated with taking part in this study.

What will happen to my personal information?
Your data that is collected will not be shared with anyone except with your consent or as required by law. All personal information such as your name or phone number will be removed from the data by research staff and be replaced with a study identification (ID) number (de-identified) before the data is analyzed by research staff. A password protected document is kept by the research team linking your study ID with your name on a password protected computer. This linking of your name to your study ID number is needed to link information from the study.
Once the study is complete and the data analyzed, all identifying information will be permanently removed and destroyed, and the remaining study records will be kept confidential and secure for 10 years. Following this, all study records will be destroyed in a confidential manner.
For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Hamilton

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Integrated Research Ethics Board and this institution and affiliated sites may consult your research data for quality assurance purposes. However, no records that identify you by name or initials will be allowed to leave the research office. By signing this consent form, you authorize such access.

What happens if I choose not to participate?

Your participation in this study is entirely voluntary. You may refuse to take part in the study, or you may stop participation at any time, without affecting future treatment. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities. If during the course of the study, information becomes available that might affect whether you choose to continue your participation in the study, the research staff will give this information to you.

Can participation in the study end early?

You can stop taking part at any time and your doctor will continue to treat you with the best means available. If you decide to stop participating in the study, we encourage you to talk to your doctor first. If you do choose to stop your participation in the study, we ask that we have your permission to retain the data collected to date and to continue to follow you via your medical records for survival and hospital readmissions.

What if I have questions about the study?

If you have any questions or concerns about this study, please feel free to contact the Principal Investigator, Dr. John Agzarian at 905-522-1155 x32701 or the study coordinator Housne Begum at 905-522-1155 x35338.

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Post SBRT Pulmonary Metastasectomy (PSPM) Trial

Lead investigator: Dr. John Agzarian
Division of Thoracic Surgery
St. Joseph's Healthcare Hamilton
T2105-50 Charlton Ave E. Hamilton ON Tel: 905-522-1155 x 32701

CONSENT STATEMENT

Participant:

I have read the preceding information thoroughly. I have had an opportunity to ask questions and all of my questions have been answered to my satisfaction. I agree to participate in this study as stated in the above information. I understand that I will receive a signed copy of this form.

Name (printed)	*Signature*	*Date*

Person obtaining consent:

I have discussed this study in detail with the participant. I believe the participant understands what is involved in this study.

Name (printed)	*Signature*	*Date*

Investigator:

In my judgment, this participant has the capacity to give consent, and has done so voluntarily.

Name (printed)	*Signature*	*Date*

Witness: *(required if participants are unable to read, or if translation is necessary)*

I was present when the information in this form was explained and discussed with the participant. I believe the participant understands what is involved in this study.

Name (printed)	*Signature*	*Date*

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, Hamilton Integrated Research Ethics Board at 905.521.2100 x 42013.

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