Letter of Intent

The Department of Radiation Oncology at London Health Sciences Centre is seeking Give a Breath Research Award funding to support a landmark clinical trial that will expand second- and third-line treatment options via reirradiation for people with recurrent lung cancers. We request $25,000 to support the per-patient costs for enrollment of 10 Canadians to this trial.

For almost all people with non-small cell lung cancer, their disease will eventually progress after first-line treatment. Systemic treatments, such as chemotherapy, immunotherapy, and targeted drugs, are used as maintenance or second/third-line therapies to control disease burden. In this setting, incorporation of salvage radiotherapy is sought when limited lesions progress despite excellent response elsewhere; this improves local control and supports continuation of the preferred second/third-line therapy. Unfortunately, the feasibility of salvage radiotherapy is limited if it overlaps with previous radiation. Concerns for normal tissue toxicity often restrict how much dose is delivered, resulting in treatments that deliver less dose than what people could benefit from, or denying further radiation altogether. Importantly, not treating or underdosing malignancies permits continued growth, which could cause morbidity and mortality that could be more severe than possible radiation-induced toxicities.

There is increasing clinical demand for 'reirradiation' – i.e. radiotherapy to areas that previously received radiation – and the practice is endorsed by international experts and professional societies. Still, significant uncertainty remains regarding safe implementation due to a lack of prospective clinical evidence needed to predict reirradiation toxicity. There is an unmet need for trials to determine safe dose limits for reirradiation, particularly in lung cancer.

We are proposing a phase I clinical trial design that will evaluate dose escalation via previous dose forgiveness ('recovery factors'). This enables an approach that is universal to different combinations of dose, fractionation, and treatment interval; thereby making it widely applicable to people treated with different radiation protocols over time and across Canada. Previous dose forgiveness is in alignment with presumed normal tissue recovery and can make reirradiation within known dose constraints feasible. Clinical practice varies widely on the application of this principle, and without clinical trial evidence, implementation has become more art than science.

The trial has been presented to European (ESTRO) and American/international (ReCOG) audiences, including experts in reirradiation, and both groups have expressed enthusiasm for the study design. This work is a Canadian-led effort by early- and mid-career investigators, with international collaborations and world-leading expertise in clinical trial design/implementation, radiation plan evaluation/delivery, and patient care. The trial is not yet open but is approved by the Ontario Cancer Research Ethics Board and has substantial clinical interest in Canada; we have commitments for activation at additional sites across the country, pending complete funding, including: BC Cancer Agency (Vancouver), Sunnybrook (Toronto), and QEII Cancer Centre (Halifax).

The trial will provide critical information on the relationship between dose and toxicity in the reirradiation setting to inform safe dose limits. In addition to providing the foundation for future reirradiation trials, the results will be immediately relevant for patient care to support shared-decision making and ensure the risk-benefit trade-offs of reirradiation align with each patient's wishes. Thank you for considering this project for the Give a Breath Research Award.

Donna Murrell, PhD MSc MCCPM and David Palma, MD PhD MSc FRCPC

Summary of Proposed Research

This **phase I dose-escalation study** aims to determine the maximal safe dose of radiation that can be used in the reirradiation setting, to maximize tumor control while minimizing treatment-related toxicity. Patients with recurrent metastatic, or new primary, thoracic malignancies requiring radiation and who have previously received radiation to the thorax will be recruited, if reirradiation is expected to exceed the dose constraints used for *de novo* treatments. This trial design requires a sample size equal to the number of dose levels in the study multiplied by 6; with 8 dose levels in this trial, the **sample size is 48** [1]. We estimate accruing 12-16 patients per year (multiple sites) and completing recruitment over 36-48 months.

The trial escalates dose by "forgiving" increasing percentages of previous radiation at each level (via 'recovery factors') as a surrogate for normal tissue healing post-radiation. This allows more radiation to be given for retreatment. Accrual will start at level 1 (recovery factor=10% at 6 months + 0.75%/month thereafter). This was selected as the equation works out to approximately 10%/year, which is used at many Canadian sites, and a lower starting dose may compromise local control for patients enrolled initially. The maximum dose level (Level 6, 100% recovery at 5 years) was chosen as there are small reports of full-dose thoracic reirradiation. Further dose escalation beyond level 6 may be investigated in a follow-up study when more is known about recovery time dynamics and organ-specific tissue responses.

Patients will be assigned to recovery factors using the **time-to-event continual reassessment method (TITE-CRM)** (Appendix, Fig 1), which was used in previous successful thoracic dose escalation trials: RTOG 0813 and SUNSET [2,3]. The model uses all available information from previously accrued patients to assign the highest level with a predicted risk of grade 3 toxicity ≤35% (similar allowable toxicity level to phase I trials using 3+3 designs). In the TITE-CRM design, to allow the trial to remain open to accrual without interruption despite long observation time before toxicity manifestation, and to use the maximum information from patients already accrued when assigning dose levels, data from patients who have not completed the 1-year follow-up period are weighted according to the proportion of follow-up completed. Weights run from 0 to 1, with zero denoting no follow-up and 1 denoting 12 months of follow-up (e.g. a patient with 6 months of follow-up will be weighted as 0.5). Any patient with a grade 3-5 toxicity will be weighted as 1, regardless of length of follow-up. The following restrictions on dose escalation will also be employed: (i) Dose levels may only increase one level between consecutive patients; (ii) A patient may not be assigned to a higher recovery factor level unless there is at least 2 years of cumulative observations on patients at the current recovery factor level. This cumulative observation may be divided among several patients (e.g. four patients treated on level 1 and followed for 6 months each would be 24 months cumulative observation).

Primary endpoint: The maximally tolerated dose (MTD) of thoracic reirradiation implemented by sequentially increasing the normal tissue recovery factors applied to previously delivered dose. The MTD is the recovery factor equation associated with a ≤35% rate of grade 3-5 pre-specified treatment-related toxicity occurring within 1 year of treatment.
Secondary endpoints: toxicity, progression of treated disease, distant metastases, progression-free survival, overall survival, patient reported outcomes and quality of life.

Patients will undergo planning CT simulation with a 4D-CT and motion assessment. Any prescription dose and fractionation may be included. Prescription de-escalation and/or target

volume compromise is allowed at the discretion of the treating physician to meet organ-at-risk dose constraints. Further details on radiation administration can be found in the Appendix. Dose constraints in Appendix, Table 2 may not be exceeded. Dose accumulation must be performed using rigid or deformable image registration and conversion of physical dose to equieffective dose (EQD2). Recovery factors are applied to each dose distribution after conversion to EQD2. Time since previous treatment is calculated from the last day of each previous radiation course. Multiple prior courses of radiation are allowed, but each dose distribution must be scaled by the appropriate recovery factor based on the interval between treatments.

Patients will be seen in follow-up every 3 months in year 1, every 6 months in year 2 then annually to 5 years. Toxicity will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading scale. Pre-specified treatment-related toxicities are listed in the Appendix, Table 1. At each visit, a history and physical examination will be conducted by the oncologist, CTCAE V5.0 study treatment related toxicities recorded, and the quality-of-life questionnaire (FACT-L) completed. CT chest will be repeated at 3, 6, 12, 18 and 24 months then annually to 5 years. Pulmonary function tests and ECG's will be repeated at 6, 12 and 24 months then annually. Additional investigations may be carried out at the discretion of the oncologist.

DATA ANALYSIS: Descriptive statistics will be used to report on the cohort studied. The MTD and estimates for the probability of dose-limiting toxicity at 1-year (±95% confidence interval) will be obtained from the TITE-CRM. During the trial, the data safety monitoring committee will monitor toxicity rates, including the rate of grade 5 toxicity which is not specifically evaluated by the TITE-CRM model. All grade 3-5 toxicities will be reported and described. Kaplan-Meier analysis will be used to compute rates of progression of treated disease, distant metastases, progression-free survival, and overall survival. FACT-L data over time will be analyzed using linear mixed modeling. Sex will be collected as a variable and included in analysis to determine if a participant's sex has any impact on their treatment outcomes. This is the first study of its kind, therefore further social determinants of health are outside the scope and are not being investigated; however, these may be included in future studies.

EXPECTED RESULTS: This trial is designed to determine the MTD for thoracic reirradiation. It will also provide information on the relationship between reirradiation dose and toxicity to support development of safe dose constraints. This trial is the first of its kind to investigate previous dose forgiveness and using this concept to enable dose-escalation for reirradiation would provide opportunities for long-term survival in otherwise incurable disease.

LIMITATIONS: As the first trial to test the concept of dose escalation via recovery, several assumptions were required in trial design (e.g. dose limits, shape of recovery curves) due to lack of data in this emerging field. We mitigated this limitation by collaborating with international experts, such that these decisions have been vetted by leaders in the field. There is a risk we have not escalated dose enough to determine the MTD; in this case, the protocol could be amended to add further escalation levels. Further, with a modest sample size, there is potential we may have limited toxicity data for some organs; this is a known limitation of this trial design and will be addressed in follow up phase 2/3 studies. Finally, we assume all organs recover and do so at the same rate, which may not be true. Regardless, this trial will take the first step in understanding thoracic normal tissue recovery in the clinical context and future trials will be designed based off the results – positive or negative – to take the next steps in building the field of reirradiation.

Impact Statement

This trial will provide critically needed prospective clinical evidence to support safe reirradiation for people with advanced and metastatic lung cancers. The results of this trial will benchmark the standard for safe use of recovery factors, which in turn will enable dose escalation for reirradiation. This will increase the options for reirradiation, which could extend survival for patients, and/or allow them to remain on a preferred systemic therapy after oligoprogression. If the top escalation levels in this trial are safely reached, this would cause a profound break with previous patterns of practice and introduce a new paradigm that enables curative cancer treatments in what is usually considered a palliative situation.

Reirradiation is an emerging field catalyzed by significant clinical demand, but without robust clinical trial data for evidence-based decision making. This trial will be foundational in our understanding of the relationship between reirradiation dose, time interval, and organ recovery with outcomes such as toxicity, disease progression, survival, patient-reported outcomes, and quality of life. In the medium-long term, further research, including phase 2/3 trials, will be developed based on knowledge gained in this work. In the short-term, the results from this study can be directly used for patient care.

Consider this example:

A person received standard chemoradiation for their stage III lung cancer 5 years ago. This would have included a radiation dose, for example: 60 Gy in 30 fractions (60 EQD2), and it overlapped with the bronchus due to the location of the tumour. Cancer recurs near the bronchus and partial dose overlap with the first treatment is expected.

Due to the overlap with prior radiation, the cumulative dose to the bronchus limits how much dose can be given to the recurrence. If no forgiveness of the prior dose is considered, then standardly a dose of 20 Gy in 5 fractions would be allowed; however, that is quite low and would not provide durable local control. In this trial, we could go higher with the reirradiation dose, perhaps to 50 Gy, and improve local control. If Level 6 is reached and shows safety, then this person's previous dose could be fully discounted (100% recovery). This enables stereotactic ablative techniques, which treat to the full bronchus dose limit, to be used for re-treatment. Stereotactic ablative treatment has been shown to improve survival in metastatic settings where overlapping dose was not a concern and would be transformative if applied for people with recurrent cancers.

Public Summary

This clinical trial is for people who have lung cancer requiring radiation treatment and have already received radiotherapy to the same part of their body. For some patients, radiation can be used to try to cure a lung cancer, and for others, radiation is used to treat symptoms from the lung cancer (such as shortness of breath). Traditionally, it was considered that radiation can only be delivered once to a certain area of the body, but recent research suggests that for many patients, the normal tissues can heal after radiation, allowing doctors to safely give more radiation. The objective is to find out what the maximum safe dose of repeat radiotherapy is when people have already received radiotherapy before.

Repeat radiotherapy is called reirradiation. As people live longer after initial cancer treatment, there is a growing unmet need for this type of treatment because cancers may return near locations that were previously treated with radiotherapy. The problem is that doctors do not have enough information to predict how toxic reirradiation is and so they aren't sure how much dose to give. If they give too much dose, it may cause side effects; but if they don't give enough, then it allows the cancer to grow, potentially resulting in worse problems than the side effects from treatment, including even dying from the cancer. Without safety information from clinical trials, the current approach is to limit reirradiation to low doses. This avoids bad side effects, but it also means some people get less radiotherapy than what they could benefit from, and for others it means no further radiotherapy is given at all. Previous research has suggested that reirradiation might be safe, but the data has not been strong enough to make this widely accepted.

The method used in this research is called a 'phase 1 dose escalation clinical trial' and it will evaluate reirradiation to the chest. The first people who participate get the starting dose of reirradiation, and if it does not cause serious side effects, then the next person will get a higher dose. Doses are escalated or deescalated based on side effects. The maximum safe dose is determined when serious side effects happen that require the dose to be lower. We will collect information about toxicity and how well the reirradiation works. Participants will complete questionnaires about their physical and emotional well-being and how bad their symptoms are so we can learn more about how reirradiation affects their quality of life.

This research will provide important information that doctors need to deliver reirradiation safely. If dose escalation is successful, it will change the way we approach repeat treatment with radiotherapy. This clinical trial could have game-changing impacts in lung cancer treatment and provide opportunities for curative treatment and long-term survival in what is usually considered a palliative situation.

Budget

The full budget is being requested to support the per-patient costs of running the clinical trial through the Clinical Research Unit at London Health Sciences Centre.

The $25,000 offered in the Give a Breath funding award would make a direct and meaningful impact for 10 Canadians living with recurrent or metastatic lung cancer by supporting the costs of their enrollment in this dose escalation trial, where higher doses of radiation could optimize their care. We are actively seeking additional funding to support the remaining patients needed to complete recruitment for this trial.

Clinical Research Unit support:
$2,500 per patient recruited at any participating Canadian centre X 10 patients = $25,000

Clinical Research Unit support includes procedure costs for enrolled patients as well as the data/project management tasks related to their participation in the study.

Other sources of funding:
We received 1-year pilot funding from our institution to support development of this clinical trial. See Donna Murrell CCV “Internal Research Fund (IRF) Award”. There is no budgetary overlap between these awards.

Names of Investigators

Principal Investigators

Dr. Donna Murrell, MSc PhD MCCPM
London Health Sciences Centre

Dr. David Palma, MD, MSc PhD, FRCPC
London Health Sciences Centre

Trial Committee

Dr. Nicolaus Andratschke MD (ESTRO ReCare reirradiation project lead, EORTC 2011-RP)
University Hospital Zurich

Dr. Alanah Bergman, PhD FCCPM
BC Cancer Agency – Vancouver

Dr. Kristy Brock, PhD (expert in human deformable modeling applied to dose accumulation)
MD Anderson Cancer Center

Dr. Emma Dunne, MD PhD MBBS, FRCPC
BC Cancer Agency – Vancouver

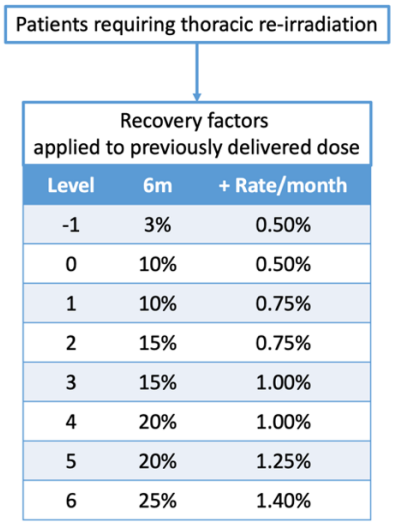
Dr. Mitchell Liu, MDCM FRCPC
BC Cancer Agency - Vancouver

Dr. Alexander Louie, MD, PhD MSc, FRCPC
Sunnybrook Health Sciences Centre

Dr. Humza Nusrat, PhD MCCPM
Sunnybrook Health Sciences Centre

Mr. Andrew Warner, MSc (Statistics Lead)
London Health Sciences Centre

Appendix



Level	6m	+ Rate/month
-1	3%	0.50%
0	10%	0.50%
1	10%	0.75%
2	15%	0.75%
3	15%	1.00%
4	20%	1.00%
5	20%	1.25%
6	25%	1.40%

Figure 1: Study schema and recovery factor equations to be applied against previous dose.

Table 1: Examples of treatment related adverse events.

Structure	Adverse Event
Cardiac and Pericardial	Constrictive pericarditis
	Symptomatic pericardial effusion
	Pericardial tamponade
	Pericarditis
Gastrointestinal	Esophageal fistula
	Esophageal hemorrhage
	Esophageal necrosis
	Esophageal obstruction
	Esophageal stenosis
	Esophageal perforation
Pulmonary/ mediastinal	Atelectasis - symptomatic
	Bronchial fistula
	Bronchial obstruction
	Bronchopleural fistula
	Bronchopulmonary hemorrhage
	Dyspnea
	Pneumonitis
	Tracheal/Pulmonary fistula
	Tracheal stenosis
	Mediastinal hemorrhage

Table 2 lists near-maximum dose limits for several critical organs and volume constraints for lung. These are absolute limits, and PTV coverage or prescription dose must be adjusted to meet them, if needed. These are mostly based on equivalent dose in 2Gy fraction (EQD2) conversions of the UK 2022 Consensus on Normal Tissue Dose-Volume Constraints for 5 fraction treatments [4]. The lung constraint is from RTOG 0617 (14.7 Gy EQD2 is equivalent to V20 in physical dose) [5]. There is no clear mandatory constraint for chest wall in the literature. This trial will use a chest wall constraint of 180 Gy EQD2; this is the equivalent of 60 Gy in 5 fractions, which is often allowed in lung SABR where PTV is not compromised for chest wall dose. The focus of this trial is on lung and mediastinal structure doses and escalation based on chest wall alone is not the goal of this protocol. Near-maximum point dose in undefined normal tissue should be kept as low as reasonably achievable, with a recommended limit of 200 Gy EQD2.

Table 2: Organ at risk dose constraints in EQD2. D0.1cc is the maximum dose in EQD2 allowable to the hottest 0.1cc. V14.7EQD2 refers to the percent of lung_eval (total lung minus all GTVs) receiving 14.7 Gy EQD2 or more (and is equivalent to a standard V20 using physical dose).

Organ	α/β	Metric	Dose Limit
Spinal cord*	2	D0.035cc	60 Gy EQD2
Brachial plexus	3	D0.1cc	60 Gy EQD2
Esophagus	3	D0.1cc	70 Gy EQD2
Heart	3	D0.1cc	80 Gy EQD2
Trachea	3	D0.1cc	80 Gy EQD2
Proximal Bronchial Tree	3	D0.1cc	80 Gy EQD2
Great Vessels	3	D0.1cc	144 Gy EQD2
Chest wall	3	D0.1cc	180 Gy EQD2
Lung_eval	3	V14.7EQD2	37%

*Note: recovery factors determined by the dose level in this trial do not apply to spinal cord. 60 Gy EQD2 is allowed irrespective of dose level assigned by the trial. This limit may include up to 20% recovery of previous dose, at the discretion of the treating oncologist [6–8].

Cumulative dose constraints listed in Table 2 may not be exceeded; these include both the current dose and the previous dose(s) scaled by the assigned recovery factor(s).

Table 3: Example calculations

EXAMPLE: RECOVERY FACTOR		
Assigned Level	Time since previous treatment	Recovery factor calculation
Level 1	6 months	10 + 0 = 10%
Level 1	1 year	10 + [0.75% * (6 months)= 14.5%†
Level 1	10 years	No further repair after 5 years; apply 5 years for calculation. 10 + [0.75% * ({5 years * 12 months/year} – 6 months)]= 50.5%†
Level 3	Two prior courses: Course 1 = 3 years ago Course 2 = 2 years ago	For course 1: 15 + [1% * ({3 years * 12 months/year} – 6 months)]= 45% For course 2: 15 + [1% * ({2 years * 12 months/year} – 6 months)]= 33%

EXAMPLE: PROXIMAL BRONCHIAL TREE DOSE					
Course	Physical Dose	EQD2	Recovery	Calculation	EQD2 applied to cumulative plan
1 (previous course 1 year ago)	60Gy/30	60	15%	60*0.85	51
2 (current course)	30Gy/10	36	0%	N/A	36
Total					87 < 88 EQD2

†in practice, recovery values will be rounded to the nearest whole number so 14.5→15% and 50.5→51%.

*note point dose calculations are not sufficient for this trial; full EQD2 dose evaluation based on dose distribution is required; this is for illustrative purposes of the dose scaling and dose constraint only.

References

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[2] NRG Oncology. RTOG 0813 Seamless phase I/II study of stereotactic lung radiotherapy (SBRT) for early stage, centrally located, non-small cell lung cancer (NSCLC) in medically inoperable patients. 2015.

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[7] Nieder C, Grosu AL, Andratschke NH, Molls M. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 2006;66:1446–9. https://doi.org/10.1016/j.ijrobp.2006.07.1383.

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Schulich MEDICINE & DENTISTRY

Department of Oncology

January 17, 2025

Lung Cancer Canada
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RE: Letter of Institutional Support for Dr. Donna Murrell

To Whom it May Concern,

On behalf of the department of Oncology, within Schulich School of Medicine & Dentistry at Western University, I want to express my enthusiastic support for Dr. Donna Murrell's proposal entitled *"A Safety and Efficacy Trial of Reirradiation Dose Escalation in Thoracic Cancers: Re-evaluating previous dose and allowing increasing recovery (REPAIR)"* being submitted to the Give a Breath Research Award competition. The proposed work addresses a priority health need within our society. The proposed work addresses a critical health priority and aligns closely with Western University's Strategic Areas of Research Activity, particularly our focus on "A Healthy Future." Additionally, it is in harmony with the Faculty's strategic vision, "Leading in Health…with our region for the world," and our commitment to advancing research excellence.

Dr. Murrell joined Western University in December 2018 as an Assistant Professor, with a primary appointment in the Department of Oncology and a cross-appointment in the Department of Medical Biophysics. During her tenure at Western, she has taken two leaves of absence: a medical leave of six months starting in January of 2019 and a parental leave of eleven months from October 2022 to September 2023. These leaves warrant maintenance of early career investigator status. Dr. Murrell will be mentored for this trial by Professor David Palma, a radiation oncologist whose research focuses on conducting pragmatic trials in radiation oncology. Dr. Palma has a strong track record of mentoring young investigators in completing their first clinical trials.

Dr. Murrell workload includes 15% of her time dedicated to research, with the remainder allocated to clinical service, teaching and administrative duties. As Chair of the department of Oncology, I confirm that Dr. Murrell has the necessary space, facilities, equipment and administrative support to ensure the successful completion of the proposed research. Dr. Murrell will be supported by the Cancer Clinical Research Unit (CCRU), which has extensive experience in running multi-centre investigator-initiated trials, ranging from phase I to phase III. The CCRU supports all trial aspects, including protocol completion, ethics and regulatory submission and approval, database design and data collection, patient consent, monitoring during treatment and follow-up, and statistical analysis. In addition, the CCRU has successfully conducted a trial in lung cancer radiotherapy using the TITE-CRM methodology, as is proposed for the REPAIR trial.

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Department of Oncology

It is with great enthusiasm that we support Dr. Murrell's application for the inaugural Give a Breath Research Award. We are confident in her ability to make significant contributions to the field of reirradiation research and advance our understanding and treatment of lung cancer.

Sincerely,

Michael C. Ott, MD, MSc, MHPE, FRCSC, FACS, FASCRS
General and Colorectal Surgery
Professor, Schulich School of Medicine & Dentistry
Department of Surgery & Surgical Oncology
Chair Department of Oncology
Physician Executive Oncology LHSC
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