Form I: BTI Internship Program Mentor Application

A.1: Mentor information		
Name Zhihui (Amy) Liu Principal Biostatistician, Clinician Investigator, Assistant Professor	Institution Princess Margaret Cancer Centre	Department Biostatistics

A.2: Co-mentor information		
Name Olli Saarela Associate Professor	Institution University of Toronto	Department Dalla Lana School of Public Health

A.3: Research proposal (maximum two pages)

Title

Discovering the causal pathways leading to normal tissue toxicity in radiotherapy

Background

The goal of radiotherapy for cancer is to deliver the prescribed dose of radiation to the tumor while minimizing the amount of radiation delivered to surrounding normal tissue. While treatment related severe toxicities are uncommon, they can lead to treatment interruptions that may compromise tumor control and impact patient's quality of life. Various normal tissue complication probability models have been developed in the last two decades to determine acceptable toxicity risks. However, there is relatively limited evidence of the causal mechanisms for toxicity and quality of life outcomes. With the availability of data from multiple clinical trials and large cohort studies, 3D volumetric data, tumor radiomics features, as well as prospectively collected physician-assessed and patient-reported outcomes, we have an opportunity to develop and apply causal inference methods to discover and validate hypothesized causal pathways. This research may inform future treatment planning, offer individualized predictions of toxicity, and help develop strategies for improving patient's quality of life.

Aims and methodology

Aim 1. Adapt existing causal mediation analysis methods to incorporate high-dimensional and correlated mediators in the radiotherapy setting. Rationale: dosimetry data are multi-dimensional and highly correlated, with further methodological challenges arising when multiple organs at risk are considered simultaneously.

Aim 2. Extend these methods to incorporate longitudinal mediators. Rationale: as radiation therapy is often given over a few weeks of time, the delivered dose can be different from the planned dose. Utilizing daily dosimetry can reflect the actual dose more accurately.

Aim 3. Extend these methods for multivariate longitudinal outcomes. Rationale: physician-assessed toxicities and patient-reported outcomes in part capture difference aspects but are correlated; analyzing them as a bivariate longitudinal outcome may potentially capture more accurate information.

Aim 4. Apply the methods to study the hypothesized causal pathways of (a) prescription dose → normal tissue dosimetry → acute toxicity, (b) normal tissue dosimetry → acute toxicity → long term toxicity, and (c) normal tissue dosimetry → toxicities → quality of life.

Rationale: (a) Acute skin toxicity is a common reason for treatment interruptions in anal canal cancer; identifying modifiable dosimetry features may help reduce treatment interruptions and improve tumor control. (b) Acute and late toxicities are thought to have different causal mechanisms, but there is limited understanding if short term tissue damage contributes to long term side effects. Understanding the

pathway(s) will help develop strategies to prevent late toxicities. (c) Quantifying and understanding different contributing factors will help develop strategies to improve patient's quality of life.

Data source
The data sources will include (i) 300 anal canal cancer patients treated at Princess Margaret Cancer Centre (PM) between 1995-2017, (ii) 5,500 prostate cancer patients treated between years 2001-2017, and (iii) a series of clinical trials including the TARGET trial and ART study for localized prostate cancer, the MARGIN trial for low-intermediate risk prostate cancer, and the IMRT Pelvic Nodes Prostate trial for high-risk prostate cancer, and (iv) 300 intermediate-risk prostate cancer patients treated between 2006-2011, as part of a 27-center randomized trial (PROFIT) which allows us to further investigate in the hypo-fractionated setting.

Patient and clinical information, tumor factors (e.g. radiomics features), treatment (dosimetry data), survival outcomes, physician assessed toxicities, patient report outcomes are available. Causal mediation analysis methods will be developed and applied to quantify the contribution of different hypothesized pathways, involving statistically controlling for confounding due to various patient and tumor factors. Some of the methods will need to be extended and adapted to accommodate high dimensional and correlated mediators.

Training objectives
The trainee will be working as part of a multidisciplinary research group including radiation oncologists, medical physicists, radiation therapists, biostatisticians and bioinformaticians. S/he will develop skills in statistical methodologies, communicating statistics with clinician investigators and research groups, and proposing and developing solutions to emerging statistical problems. The trainee will gain expertise in analysis of clinical and randomized trial data using causal inference methods such as the mediation formula and inverse probability weighted estimation of marginal structural models, and dimension reduction methods such as principal component regression and partial least squares regression. The trainee will also gain knowledge of the content area of safety and effectiveness of radiation therapy and the different types of data being collected to study this.

Training environment
The Biostatistics Department at Princess Margaret Cancer Centre provides statistical design and analysis expertise and collaborates with clinical and basic scientists in a broad spectrum of oncology studies, as well as statistics teaching to medical residents and fellows. The Department provides an excellent environment for training statistics and biostatistics students to carry out methodological research that is motivated by emerging research in oncology and contributes to producing evidence that can directly impact treatment decisions. The Department currently employs 14 biostatisticians (principal, senior and junior) and 2 senior analysts, and trains postdoctoral fellows, PhD and MSc students. It has the ambitions to become one of the leading biostatistics departments in North American cancer centres.

The primary supervisor, Dr. Liu is a Principal Biostatistician, and has a Clinician Investigator appointment at PM Research Institute and Assistant Professor at Dalla Lana School of Public Health (DLSPH), University of Toronto. She has a PhD in Biostatistics from McGill University and has extensive experience in statistics for oncology studies. She will lead the planning and implementation of the statistical analyses. Of the co-supervisors, Dr. Olli Saarela is an Associate Professor in Biostatistics at DLSPH and is an expert in causal inference. Dr. Ali Hosni is a radiation oncologist and the GI site leader. Dr. Peter Chung is a radiation oncologist and the GU site leader. Drs. Hosni and Chung will provide clinical expertise during model development and validation. All will contribute to the supervision of the BTI intern.

Alignment with OICR Strategic Plan
The goal of the proposed research is to help gain a better understanding of the contributions of various

patient, tumor and treatment factors to normal tissue toxicities following radiation therapy, through statistical methods development and producing evidence to support personalized treatment planning. This is aligned with OICR's second translational research priority of *clinical impact in optimizing cancer patient management and treatment decisions.*

Requirements
We are looking for a trainee who is genuinely interested in pursuing a career as a biostatistician working in a multidisciplinary and collaborative environment, and motivated to develop communication and problem-solving skills. Prior statistical training and experience with R programming are a requirement. Intellectual curiosity and independence are assets.