**1. BACKGROUND**

Gastrointestinal (GI) cancer is a group of cancers affecting the digestive system (e.g. pancreas, stomach, liver, bladder, bowel, etc.). An estimated 24,000 Canadians will die from GI cancer in 2016.1 It is the most common form of cancer and among the deadliest because it is often diagnosed at a late stage. In particular stage IV advanced GI cancers, which have metastasized or spread to other organs in the body, have high-fatality rates. For instance, the 5-year relative survival rate for pancreatic cancer is 8% and for stage IV stomach cancer is 4% compared to the general population. Yet survival times vary greatly by cancer type and patient characteristics. Therefore for advanced cancer especially, balancing anti-cancer treatment options with quality-of-life (QoL) is often a major challenge.

Palliative care is an approach to care that focuses on improving QoL and controlling physical and psychological symptoms for patients with life-limiting illnesses.2 Dozens of randomized trials on cancer patients and several systematic reviews over two decades have demonstrated the benefits of palliative care interventions compared to usual care.3-8 Palliative care interventions consisted of timely access to symptom management, psychosocial support, and care coordination. Benefits included improved QoL, reduced symptom burden, fewer hospitalizations, and lowered healthcare costs. Given the evidence of benefits, palliative care has become a priority across Canada and other countries.9-12

Since 2009, several randomized trials have demonstrated the benefits of *early* *integration* of palliative care (i.e. at diagnosis) with active cancer treatment.13-15 These trials also showed improved QoL and symptom control. This evidence led the American Society of Clinical Oncology to endorse that early palliative care be offered concurrent with standard oncologic care in 2012.16 This is in contrast to the current care model: where curative care is typically pursued fully until no other treatment options are available, after which palliative care is then introduced. (See Appendix 1) Indeed much data shows palliative care is often provided very late in the disease trajectory or not at all. In Ontario, palliative care is used in 50% of all deaths for a median of 30 days before death.17 US statistics are very similar.18

Why is palliative care introduced so late? Advances in cancer care have increased treatment options and clinical trials, thus delaying the point when no other treatment options are available. Oncologists are overly optimistic in their prognosis predictions and often struggle with knowing when to discuss palliative care, as they want to offer treatment options and not take away patient hope.19-22 Of note, existing evidence does not support the commonly held belief that most patients want to avoid discussions about death. In fact, research shows patients with advanced illnesses want to discuss “preferences for care in the event of life-threatening illness” and “prognosis”—these were rated by patients as the two most important elements to discuss with their doctors,23 and doing so was identified as best practice in the literature.24 Yet evidence shows that providers often do not discuss prognosis and palliative care with patients with advanced illness, even when very close to death,25, 26 or do so inadequately,27, 28 contributing to over-aggressive care, often in the final months of life, even when patients prefer treatments focused on comfort and QoL.29-32

To help oncologists know when to discuss palliative care, much cancer research has focused on prognostic tools to predict death. Several systematic reviews summarized the factors associated with death used in prognostic tools: they mostly identified biological and laboratory variables, such as cancer antigen levels, elevated C-reactive protein, leukocytosis, etc.33, 34 These reviews have been used in guidelines by the National Comprehensive Cancer Network, look-up tables, and nomograms.35, 36 There has been increasing interest in the use of web-based prognostic tools for cancer. A systematic review identified 22 online prognostic tools addressing 89 different cancers; 5 tools included GI cancers.37

However, this large body of research on prognostic tools has largely failed at integrating palliative care earlier in the disease trajectory for three main reasons. One, despite strong evidence that many oncologists avoid discussing prognosis with advanced cancer patients (even with many prognostic tools available),38-40 the vast majority of tools continue to be designed for oncologists, as evidenced by the heavy use of laboratory and biological data. Since patients do not know these laboratory values, they cannot use these tools. Therefore current tools empower doctors, not patients, to initiate palliative care discussions. Two, as a systematic review points out, tools focus only on predicting death, but “no tool used QoL as one of its outcomes…yet QoL outcomes are most meaningful and important to patients when making treatment decisions.”37, 41 Three, existing tools do not include data on palliative care interventions, a modifiable factor that can improve QoL. **In sum, due to the lack of QoL and palliative care data in prior research, a major knowledge gap is the creation of prognostic tools designed for patients that include how palliative care interventions affect QoL predictions.**

Our study team is uniquely positioned to address this knowledge gap because we have research expertise in palliative care and QoL-related outcomes. We have published several studies on the association of palliative care interventions—specifically physician home visits, home care services, and caregiver support—with reduced acute care use.42-48 A large body of international research has also shown that these three palliative care interventions are associated with improved QoL and patient outcomes.49-53 With respect to QoL-related outcomes, we have particular expertise investigating pain and performance status. We have examined how those two specific QoL-related outcomes are: i) associated with death;54-58 ii) associated with each other at end-of-life;59 and iii) useful quality indicators for home care.60, 61 Our team’s prior research capitalized on large and unique Ontario databases that contain these two QoL-related data: the Ontario Cancer Symptom Management (OCSM) and interRAI database. (See Methods 3.1.2). Both databases have been used separately by our study team; we propose to link them together for the first time. By doing so, **we can address the knowledge gap by creating a novel prognostic tool: the tool will be used by patients to predict survival and QoL; and also estimate how palliative care interventions will change those predictions.** This model is useful to cancer patients because we can predict their future outcomes based on outcomes from patients with the same baseline characteristics as them in the past. Last, our Knowledge Users and team have expertise in patient engagement and have developed and evaluated tools for end-of-life and cancer before.23, 40, 62-64

In this research agenda, we aim to improve care for patients with advanced GI cancer by generating evidence that will help to integrate palliative care earlier in the disease trajectory. Specifically, this study will develop an interactive web-based tool designed with and for patients with advanced GI cancer. First, we will derive and validate statistical models that will form the components of the tool: the models will predict risk of death and QoL (i.e. pain and performance status), while controlling for palliative care interventions. Second, we will co-develop the tool’s interface using input obtained from patient interviews, so that the tool’s information is presented in an acceptable way to them. Direct patient input into the design of the tool is essential to addressing concerns or potential fears about receiving information about predictions on death and palliative care. In next steps of the research agenda, we will pilot test the tool with patients, families, and providers; refine it further; and then test its efficacy via a randomized trial. The ultimate goal is to support advanced GI cancer patients to initiate palliative care earlier in their illness, which can reduce symptoms, avoid unwanted hospital visits, and greatly improve QoL. This study’s methods can also be applied to other cancers in future research.

**2. OBJECTIVES**

This study has two objectives:

1. To derive and validate statistical models to predict: i) risk of death, ii) level of pain; and iii) performance status, while controlling for use of palliative care interventions, use of anti-cancer treatment, and baseline covariates, for advanced GI cancer patients.
2. To co-develop a web-based tool with patients so that the data within the validated models is presented in an acceptable way to them.

**3. METHODS**

**3.1. OBJECTIVE 1: DERIVE AND VALIDATE PREDICTION MODELS**

***3.1.1. Design:*** We will use a population-based, retrospective cohort study of adults diagnosed with stage IV GI cancer, as confirmed by the cancer registry, in Ontario during 2008-2015.

***3.1.2. Data sources:*** We will use these administrative databases [and corresponding covariates]:

* Ontario Cancer Registry [cancer type, diagnosis date, stage (>90% complete for GI post-2009)];
* Vital Statistics [age, date of death];
* Statistics Canada [rurality, income quintile, region];
* Activity Level Reporting [chemotherapy regime, radiation treatment];
* Discharge Abstract Database [hospitalization dates, diagnoses, cancer surgery, comorbidity];
* National Acute Care Registry System [Emergency Department (ED) visits, reasons];
* Ontario Drug Benefit [narcotics];
* Ontario Health Insurance Plan physician billing [physician visits, billing codes];
* Home care database [nursing, personal support];
* OCSM Dataset [pain, performance status];
* InterRAI database [pain, performance status].

The two databases that contain QoL-related data are the OCSM and interRAI databases. The OCSM database began in 2007, when Cancer Care Ontario (CCO) mandated the systematic screening of oncology outpatients for: 9 symptoms, including pain, using the Edmonton Symptom Assessment System (ESAS) and for performance status using the Palliative Performance Scale (PPS).54 Every patient attending a cancer centre for a visit became eligible to complete the ESAS and PPS, both validated tools in cancer populations.65, 66 The ESAS asks patients to self-report the severity of 9 symptoms on a scale of 0 (symptom absent) to 10 (most severe). The current monthly provincial screening rate is 56%, with several centres at 70% each month, which is the provincial target.67 About 38,000 people are screened monthly and the dataset has 3.3 million assessments. The PPS describes a patient’s performance status based on a patient’s level of ambulation, level of activity, and ability to perform self-care. It is completed by the provider or nurse during the patient’s visit. We have over 500,000 PPS assessments in the database. The OCSM database represents one of the largest population-based cancer databases with symptom assessments in the world.54

The interRAI database began in 2002, when Ontario mandated the use of the interRAI-Home Care, a standardized tool for patients receiving publicly-funded home care services for an expected 60 days or more. 70% of cancer patients use homecare in the last year of life.68, 69 The interRAI-Home Care collects QoL-related data for nearly 300 unique items measuring domains such as cognition, mood, pain, performance status, and hours of caregiver support. It is completed by the case manager at intake and reassessed at least every six months. The assessment demonstrated strong validity and reliability70-72 and is used across Canada and internationally. The database has over 2.1 million assessments.

***3.1.3. Data Access:*** The Institute of Clinical Evaluative Sciences (ICES) holds all the databases listed above. A special request will be made to CCO for the OCSM data, which we have successfully done in two prior grants.54, 73 The work will be conducted at ICES, a not-for-profit research institute with a vast and secure array of health-related data from Ontario. It is a ‘prescribed entity’ under Ontario privacy laws which allows it to collect and use personal health information for health services research in Ontario. ICES is staffed with experienced analysts, methodologists and support staff. ICES uses de-identified data for analysis and has strict policies to ensure the privacy of personal health information. The PI (HS) and members of the research team (CE, LB, RS, JY) are ICES Scientists, are permitted to access ICES data, and have used it extensively for their research.46, 54-58, 73, 74

***3.1.4. Index Dates:*** For the primary outcome of death, the initial index date for each patient will be their date of diagnosis. As covariates and treatments may change over time, we also want to predict conditional survival probabilities; thus, the survival analysis will be re-implemented by moving the index date to the 1, 2, 3, and 4-year survival marks. Only patients who are alive at those marks will contribute to the analysis. This avoids the complications of incorporating time-varying covariates into predictive survival models.

For secondary outcomes (defined below), to ensure variation in time since diagnosis, a random number generator will be used to randomly assign an index date to each patient. The random index date will be between the diagnosis and last follow-up. This approach allows the model to predict an individual’s future outcomes when he/she uses it at any point after diagnosis until death (e.g. QoL 6 months from the date a patient uses the tool), which contrasts the survival models, which require a common time origin (e.g. survival model predicts risk of death from a common time point, such as date of diagnosis or the 2-year survival mark, etc.). For each model, baseline covariates (See Section 3.1.6) will be derived using all available databases in the year prior to the index date.

***3.1.5. Outcomes:***

1. The primary outcome is death, as per date of death in the Vital Statistics database.

Secondary outcomes are listed below

1. Moderate to severe pain (Y/N) within six months. Derived from 2 sources: i) From OCSM Database, we will use the pain symptom from the ESAS. Moderate to severe pain is defined as a score of 4-6 (moderate) or 7-10 (severe) on ESAS.75 ii) Equivalent comes from interRAI-Home Care tool, section K (health conditions), question 4B, which assesses the patient’s intensity of pain. It is scored as 0 (no pain), 1 (mild), 2 (moderate) or 3 (severe or excruciating).
2. Low performance status (Y/N) within six months. Derived from 2 sources: i) From OCSM Database, we will use PPS, which ranges from 10 to 100 (100=best) in 10-point increments. Low performance status is PPS score of <=60, meaning the patient is mainly in bed and requires considerable assistance with self-care. ii) Equivalent comes from the interRAI tool, section H (performance status), question 2, which asks about 10 Activities of Daily Living within the last 3 days. Each activity is scored from 0 (independent) to 6 (total dependence). Low performance status will be when 2 of these 4 activities—personal hygiene, toilet transfer, locomotion, and eating—have a score of 4 or more. This means extensive assistance is required based on the validated Activities of Daily Living Hierarchy Scale.76 Note: where multiple assessments are available for pain or performance status, we will use the assessment that is closest to the six month end point (for predicting outcome) and closest to the index date (for determining baseline covariate).

***3.1.6. Covariates:*** The model can produce individualized predictions because it will control for the baseline covariates listed below:

* Demographic: age at index date, sex, income quintile (based on postal codes), region, rurality;
* Clinical and prior anti-cancer treatment: diagnosis date, cancer stage, cancer type, Deyo-Charlson comorbidity score,77 prior chemotherapy and radiation treatment, prior cancer surgery;
* Health utilization in last year: hospitalizations, ED visits, physician claims, narcotics;
* QoL in last year: prior performance status, prior pain.

We will also control for palliative care interventions, for 3 months prior to index date, defined as:

* End-of-life home care services (Home Care database): average # of home care nursing visits/month.
* Caregiver support (interRAI): taken from Section G, Question 3: “hours of informal care for personal activities of daily living over the last 7 days.” We will create a pro-rated average when more than 1 assessment is available.
* Physician home visits (billing claims): # of visits with palliative care billing code/month.

***3.1.7. Analytic Plan:*** For the primary outcome of death, survival analysis will be conducted starting from diagnosis and then starting from every 1-year survivor mark after diagnosis up to 5-years. Each derived 1-year survival model will follow the below steps:

***3.1.7a. Step 1. Survival model building:*** We will randomly select half of eligible patients for model derivation and use the other half for validation. Using the derivation cohort, we will use a multivariable Cox regression model to predict the instantaneous risk of death as a function of time. As the goal is to develop a tool for patients, predictors in the Cox model need to be values that will be known by the patient (e.g. cancer stage) as well as have known clinical and statistical prognostic value.78 A priori, we will create a multivariable model consisting of all potential predictors mentioned above.79 As the Cox model assumes a linear relationship on the log hazard scale, we will also examine different transformations of continuous variables,80, 81 until we achieve maximal discriminative ability, as determined by the concordance index described below.82

***3.1.7b. Step 2. Model calibration and discrimination:*** Once the final regression model is built, the 1-year predicted probability of death will be calculated for each patient in the validation cohort using their specific covariate values, the estimates of the regression parameters, and the estimate of the baseline survival function. That is, a risk estimate will be available for each patient based on their individual covariate profile, which is a combination of the baseline characteristics described above.83

Calibration (that is, how close the model-estimated risk is to the observed risk) will be examined by grouping patients into octiles of model-estimated 1-year risk of death. We will then review the plot of the observed 1-year probabilities of death against the predicted 1-year probabilities of death from the model.84 We will measure the model’s discriminative ability (ability to distinguish between patients who have died from those who did not) via a concordance index (c-index).85, 86 Concordance for survival data is computed based on information gathered from pairs of patients within the cohort: it is calculated as the proportion of pairs in which the patient who dies has a higher predicted probability than the patient who does not die. The index is measured on a scale of 0.5 to 1, where 0.5 implies that the discriminative ability is no better than chance, whereas 1 implies perfect discrimination.

***3.1.7c. Step 3. Model Validation:*** Internal validation of the model will be assessed via bootstrap validation methods. The method consists of drawing patients randomly (with replacement) from the derivation cohort until we reach the same sample size as the derivation cohort. Once the bootstrap sample is collected, the prediction model derived from the derivation cohort will be applied to obtain the 1-year model-predicted estimate of death for each patient in the bootstrap sample, and then the concordance index will be calculated on the bootstrap sample. This process will be repeated 200 times, thereby producing 200 bootstrap sample concordance indices. The average of the 200 concordance indices provides a bias-corrected estimate of the concordance index for the prediction model.78 All analyses will be conducted using the statistical software R version 2.15 and SAS version 9.3.

***3.1.7d. Step 4. Subsequent models for secondary outcomes:*** We will follow the same model building, calibration, and validation steps as outlined in the survival model above for each of the secondary outcomes separately. We will implement logistic regression. Complete case analyses will be used to develop the regression models.

***3.1.8. Anticipated outcome:* At the end of Objective 1, we will have derived and validated a statistical model that can provide useful information to patients about death based on their baseline characteristics. We will also have models that predict future QoL (pain and performance status) with and without palliative care. Each model will become the components of the tool.**

**3.2. OBJECTIVE 2: ENGAGE PATIENTS TO CO-DEVELOP A WEB-BASED TOOL**

***3.2.1. Study Design:*** This Objective has two steps. ***Step 1. Co-design tool with patients:*** We will conduct 25 one-on-one interviews with patients and family members who have advanced GI cancersto help inform and co-develop the tool’s interface. The methods for Step 1 are described in detail below.

***Step 2. Contract out tool application development:*** To develop the online tool, we will contract out for professional services in web-based application-tool development and computer programming, so as to optimize current standards of design and technology. Moreover, we can maintain a more aggressive timeline with clear deliverables with a formal contract, rather than an in-kind partnership.

***3.2.2. Participants:*** Patients and families living with or surviving from advanced GI cancer. We are including families because while the tool is targeted primarily at patients, we recognize that families can use it too. The interviews’ purpose is to solicit advice on how to optimally introduce and interpret the information provided in the tool from a patient-family perspective. This feedback will be used to develop the web-based tool’s interface (e.g. what it will look like, how information will be organized, how concepts will be described, etc.) and is critical to ensuring the final tool is acceptable and useful to patients. We will conduct interviews until data saturation is reached and no new themes emerge.87, 88

***3.2.3. Recruitment:*** Our regional and provincial Knowledge User partners (LM and RJ) will be instrumental in recruiting patients and families. Regionally, patients and families will be recruited from the cancer clinics at the Juravinski Cancer Centre (Hamilton, Ontario) and the Odette Cancer Centre (Toronto, Ontario), where study team members work (RJ, HS, MB, LB, CE). Provincially, we will recruit from CCO’s Patient and Family Advisory Committee and the Ontario Palliative Care Network. We will use systematic non-probabilistic sampling: we will sample different GI cancer types to garner diversity among interviewees.89 Patients and family members will be paid an honorarium for their time.

***3.2.4. Data collection:*** We will collect data from one-on-one interviews, expected to last one hour. A semi-structured interview will guide discussion. Patients will be asked about how to present the information from the models in acceptable ways that are useful for decision-making. Inquiries include:

* Background experiences:
  + What is most important to you when making decisions about your goals of care?
  + What is your understanding of palliative care? Has it been discussed? Why or why not?
  + Whether their future QoL has been discussed? Why or why not?
* Preferences with how to present the data
  + How can we best present the information in the models in an acceptable and useful way?
  + How can we optimally present the various components of the tool so it is clear?
  + How can we design the tool to support your decision-making about palliative care?

***3.2.5. Data analysis:*** Each interview will be audio recorded and transcribed verbatim. A purposeful constructivist framework will be used in the content analysis of the transcripts.88, 90 This framework contextualizes respondent input in acknowledging that options elicited are formed in reflection of personal experiences and that these data are co-constructed by the participants and the researcher. Content of the transcripts will be coded by theme independently by two members of the research team using a constant comparative approach,91 discussed until agreement is reached, and member checked by participants.92 A template organizing style of data corresponding to the questions in the interview guides will be used to group emerging themes.93 A data summary table showing the common and unique themes to each question will be constructed and the data used to refine the tool.

***3.2.6. Anticipated outcome:* At the end of Objective 2, we will have engaged patients to help co-design a web-based tool for patients that accurately predicts how palliative care interventions will impact a patient’s future QoL. The tool will have been co-designed with patients to ensure we present its information in an acceptable way and will support their decision-making about initiating palliative care. The tool will then be ready for the next steps of the research agenda: for formal small-scale pilot testing, and then large-scale testing via a randomized trial.**

**3.3. ADDRESSING ANTICIPATED CHALLENGES**

With respect to model validation, there are no anticipated challenges with data linkage or time lag, as ICES already holds data up to March 31, 2015. Linkage of data up to March 31, 2016 is expected to occur in fall 2016. Should delays arise, we will begin analysis using existing data, which will still yield an incredibly large cohort size. Moreover, since we are using existing QoL-related data in new ways, we do not know how many assessments exist for each person over the course of their dying trajectory. Despite the fact that we are using multiple data sources to determine pain and performance status respectively, it is possible that some patients will have no assessments during our outcome period. This potential limitation will be addressed by having a very large sample size because this will increase the likelihood that there are large numbers of patients who have identical covariates, and a sufficient number of whom that do not have missing data. This will minimize issues of generalizability that may arise from complete case analysis. Additionally, we will explore imputation methods, if required.

To address the fact that existing prognostic tools are not widely used, we will employ a robust patient engagement strategy throughout the study process. As a key first step to facilitating uptake, we are designing the tool for patients as the primary user (all existing tools are designed for clinicians). We are also including predicted QoL data in the tool (which is extremely relevant to patients for decision-making and has never been done before). We will engage patients via interviews to help co-design the tool and plan to do further patient engagement during pilot testing. This will ensure that the final tool will be acceptable, useful, and widely used by patients. (See Section 5. Knowledge Translation)

**4. RESEARCH TEAM**

We have assembled an interprofessional research team with expertise in palliative and end-of-life care, health services and cancer research, administrative data, QoL data, statistical modeling, tool development, and patient engagement. The PI, **Dr. Seow**, PhD, is a health services researcher; Associate Professor, McMaster University; and Canada Research Chair in Palliative Care, Cancer and Health System Innovation. His expertise is in developing and evaluating interventions to improving palliative care and using large administrative databases. The coI’s include: **Dr. Barbera**, MD, MPA, is a radiation oncologist; Clinician Scientist at Sunnybrook Odette Cancer Center; Associate Professor, University of Toronto; and CCO Clinical Lead for Patient Reported Outcomes. She has expertise using administrative data for palliative care, particularly patient-reported outcome data, such as ESAS and PPS. **Dr. Earle**, MD, MSc, is a medical oncologist; Professor, University of Toronto; and Director of the Health Services Research Program at CCO/Ontario Institute for Cancer Research. He has expertise using administrative data for defining quality indicators in palliative care. **Dr. Sutradhar**, PhD, is a biostatistician; and Associate Professor, University of Toronto. Her area of expertise is analytic methods for longitudinal data, including predictive risk modeling for death. **Dr. Guthrie**, PhD, is a health services researcher; Professor, Wilfred Laurier University; and interRAI fellow. She has expertise in risk-adjusted quality indicators from interRAI’s QoL items, with a focus on palliative care. **Dr. Brouwers**, PhD, is a KT researcher and Professor, McMaster University. She is the Provincial Director of the CCO Program in Evidence-Based Care and is an international leader in the gold standard of guideline and tool development, reporting, implementation, and evaluation. **Dr. Moody**,PhD, is our provincial Knowledge User and CCO’s Clinical Program Director of Person-Centred Care. She will use her roles leading the patient-family advisory council and patient engagement strategy, and measuring patient experience and patient-reported outcomes, to advise the research plan and engage patients effectively. **Dr. Juergens**, MD, PhD, is our regional Knowledge User, a medical oncologist and Associate Professor, McMaster University. She is the Director of Clinical Trials at Juravinski Cancer Centre and oversees recruitment of participants to studies at the Centre. Her expertise will help to recruit patients and families to our study.

**5. KNOWLEDGE TRANSLATION (KT) STRATEGY**

This study has optimized an integrated KT approach by collaborating with Knowledge Users and clinicians as part of the study team and engaging patients throughout the study. Knowledge Users have identified integration of early palliative care as a strategic priority, helped devise the research objectives and study design, and will help to advise and implement our patient engagement strategy throughout the research study. We have aligned our patient engagement plans with CCO’s provincial strategy and guidelines.94, 95 Patients will be engaged throughout the tool’s development, allowing them to provide input into the design of the tool itself and the strategies to present the information. This is critical to ensuring that the final tool will be acceptable and useful to patients, address concerns or potential fears they may have about the tool’s death predictions, and empower them to discuss palliative care earlier in their disease trajectory. As our intended primary user, engaging patients regularly allows them to co-design the web-based tool and ensure that it is valuable to them and widely used. We will be strategic to recruit patients from multiple cancer centres and also from provincial patient and family committees so as to represent the diverse patient needs. Note our engagement strategy will also include family members since they can be secondary users of the tool.

We have partnered with Knowledge Users who have experience engaging and recruiting patients and families in research. Our provincial Knowledge User (CCO) also has experience developing web-based applications designed for cancer patients, such as symptom management guidelines. Staff from CCO’s clinical programs will advise us on how to optimally engage and recruit patients, and create and disseminate web-based tools. Our team’s clinical experience will support the tool being developed in a way that is acceptable to providers, which will be formally tested in next steps. We will have bi-weekly calls with the analyst and biostatistician and monthly calls with the entire study team.

Our end-of-grant KT activities include publishing our results in peer-reviewed journals and presenting at academic conferences to share our results broadly. Our provincial Knowledge User, as the provincial cancer agency, is ideally positioned to disseminate knowledge at end-of-grant to patients and providers. Our regional Knowledge User leads the Clinical Trials Department at a major academic cancer centre and is ideally positioned to support the next steps of the research agenda, which includes pilot testing and a randomized trial. We will hold a large meeting with a broader network of provincial and national stakeholders, such as Provincial Cancer Care Agencies, Canadian Hospice Palliative Care Association, etc.

**6. SIGNIFICANCE**

This research can have a significant impact on the treatment and QoL of patients with advanced GI cancer by supporting earlier access to palliative care. We will develop a unique and novel prognostic tool: a patient using the tool will input their baseline covariates and receive their individualized predictions about likelihood of death within a year, and likelihood of moderate-severe pain and low performance status in the next six months. The tool will also predict how these likelihoods will change if palliative care interventions are received. In sum, the tool will predict a patient’s future disease course, and how this prediction may change by initiating palliative care interventions. To create this tool we will combine QoL databases that have never been linked before and advance the science of prognostic tools.

The resulting tool is significant in several ways. First existing tools solely predict time to death; our tool will provide much richer information: it will predict death and QoL outcomes (pain and performance status); and also predict how these outcomes are modified by palliative care. Second, the tool is innovative because it is designed for use by patients, whereas the vast majority of tools are designed for providers. We will engage patients throughout the study so their input can be used to design and test the tool, which ensures the final tool will be acceptable, useful, and widely used by patients. Third, the tool can change the dynamic of such conversations because it provides novel information: a prediction of their QoL in the future with and without palliative care. Patients can also use the tool outside of busy clinic schedules, spend more time contemplating their preferences about treatment and QoL, and gather information about options. Then they will be much more prepared to have a discussion with their providers about how palliative care interventions can help them achieve their goals. In turn, this will create a fundamental shift in how and when palliative care is discussed: the tool empowers patients with information to initiate the discussion about palliative care with their clinicians when it is right for them, without solely relying on the oncologist to initiate the discussion, which is often the case now. Providers and families can also use it to support the patient in the decision-making process.

Ultimately, our web-based tool can have a significant impact: it can support GI cancer patients to initiate palliative care discussions with their oncologists earlier in their illness, even during active treatment. This can increase access to palliative care interventions, which can reduce symptom burden, avoid unwanted hospitalizations, and improve QoL for thousands of Canadians with advanced GI cancer each year. Moreover the methods can be applied to other cancers in future research extending its impact.

**7. TIMELINE**

This is a 1 year project. See Appendix 2.

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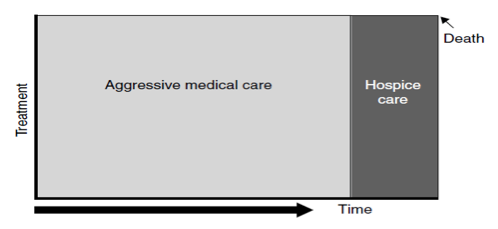
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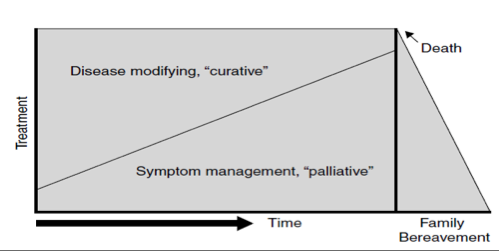
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**APPENDIX 1**

1. **Current Model of Palliative Care**

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1. **Model of Early Integration of Palliative Care**

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Citation: Canadian Hospice Palliative Care Association. A Model to Guide Hospice Palliative Care. Ottawa: ON. 2013. A revision of Ferris F, Balfour H, et al. A Model to Guide Hospice Palliative Care. 2002.

**APPENDIX 2. Timeline**

This is a 1 year project.\* The GANTT chart is below.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Month** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| Hire and Assign staff | X |  |  |  |  |  |  |  |  |  |  |  |
| Privacy Impact Approval | X |  |  |  |  |  |  |  |  |  |  |  |
| Data linkage | X |  |  |  |  |  |  |  |  |  |  |  |
| Define and explore baseline covariates |  | X |  |  |  |  |  |  |  |  |  |  |
| Outcome 1. Survival Analyses: Derive and validate |  |  | X | X | X |  |  |  |  |  |  |  |
| Outcome 2. QoL-pain: Derive and validate model |  |  |  |  |  | X | X |  |  |  |  |  |
| Outcome 3. QoL-performance status: Derive and validate model |  |  |  |  |  |  | X | X |  |  |  |  |
| Engage patients-families to co-design web-based tool |  |  |  |  |  |  |  |  | X | X | X |  |
| Develop web-based beta-tool |  |  |  |  |  |  |  |  | X | X | X |  |
| End of grant KT with stakeholders and patients |  |  |  |  |  |  |  |  |  |  |  | X |

* In months 1-2, we will hire staff, link databases, and explore baseline covariates. In months 3-5, we will derive and validate the survival models of death (primary outcome). In months 6-8, we will build and validate models for the QoL-related outcomes of pain and performance status. In months 9-11, we will engage patients during pre-tool development and contract out the development of a beta web-based tool. In month 12, we conduct end-of-grant KT activities to share findings and prepare for next stages of the agenda: pilot testing and evaluation via randomized trial.

**$100K for one year**

**Title: Deriving and validating a prediction tool for advanced gastrointestinal cancer patients to support early integration of palliative care**

**Lay title: A tool to support early palliative care for gastrointestinal cancer patients**

**Co-I’s:**

Hsien Seow, Lisa Barbera, Rinku Sutradhar, Dawn Guthrie, Craig Earle, Melissa Brouwers

Lesley Moody, Ros Juergens.

**Lay abstract. 1922 characters. Max 2000 characters.**

The goal of this research is to develop a tool for patients with advanced cancer of the digestive system that will help them start palliative care earlier in their illness. Cancer of the digestive system, also known as gastrointestinal cancer, is the most common type of cancer and one of deadliest. Palliative care is care that focuses on making quality of life and symptoms better for patients with life-limiting illness. Research has shown that starting palliative care early (such as at diagnosis) improves quality of life in cancer patients. Thus our tool’s ultimate purpose is to support earlier palliative care and to enhance quality of life for the thousands of Canadians living with advanced gastrointestinal cancer.

Researchers have created tools that predict when death will occur to help doctors, as they often do not know when to start palliative care. Many tools already exist. One recent review found 22 online tools for 89 different cancers. Yet still palliative care is often started very close to death or not at all. Our tool will be different from other tools in a few important ways. Existing tools only predict when you will die. But our tool will also predict what your quality of life, such as pain level, is likely to be in the future. It will also predict how that quality of life will change as a result of starting palliative care services, such as homecare. Our tool is also designed for patients, whereas existing tools are designed for doctors.

This study has two steps. First we will create the prediction models for death and quality of life using healthcare data from a large group of gastrointestinal cancer patients from 2008-2015 in Ontario. Second, we will co-design the online tool with patients and families by interviewing them for input on how to present the data in an acceptable way. After this study, the tool will be ready for pilot testing and evaluation via randomized trial.

**SUMMARY. Max one page.**

**CONTEXT:** Gastrointestinal (GI) cancers are the most common cancer and among the most deadly. Early integration of palliative care has been shown to improve quality of life (QoL) and reduce symptom burden in cancer patients, yet it is often introduced very close to death or not at all. While existing prognostic tools are designed for providers to help them know when to introduce palliative care, tools are poorly used by them and limited by only predicting time to death. A major knowledge gap is the development of a prognostic tool designed for patients that provides information on how palliative care interventions affect QoL.

**OBJECTIVE:** The broad goal of this research is to help patients with advanced GI cancer to receive early integration of palliative care and improve their QoL. The specific research aim is to develop a web-based tool for that predicts risk of death and QoL based on a patient’s baseline covariates, and shows how initiating palliative care interventions will change QoL predictions.

**METHODS:** The study has 2 steps:

**1. Derive and Validate Models.** Wewill use a retrospective cohort study of adult cancer patients diagnosed with stage IV cancer between 2008-2015 in Ontario to derive prediction models. The primary outcome is death. Secondary outcomes are QoL-domains of moderate-severe pain and low performance status in the next six months. We will control for baseline covariates and palliative care interventions (e.g. home care). We will link several administrative databases: Ontario Cancer Registry for cancer type and diagnosis date; Vital Statistics for death date; Discharge Abstract Databases for hospitalizations; and InterRAI Database and Cancer Symptoms Database for pain and performance status; etc. We will randomly select half of eligible patients for model derivation and use the other half for validation. Using the derivation cohort, a multivariable Cox regression model with baseline characteristics will be developed for the prediction of death. Using the model from the derivation cohort, the probability of death will be calculated for each patient in the validation cohort. Then we will measure the model’s discriminative ability via a concordance index (c-index) and examine calibration by comparing observed versus predicted probabilities in octiles. For each of the secondary outcomes separately, we will follow the same model building, calibration, and validation steps as outlined in the survival model above. We will use logistic regression to predict QoL outcomes.

**2. Co-Design Tool with Patients and Families:** We will conduct 25 patient and family interviews to solicit input on how to introduce and interpret the information in the prediction models in an acceptable and useful way. Interviews will be recorded, transcribed, and analyzed using a constant comparative approach. Based on patient feedback, we will hire professional web-application designers to develop the web-based tool.

**STUDY TEAM:** Our team has expertise in palliative and end-of-life care, health services and cancer research, administrative data, QoL data, statistical modeling, tool development, and patient engagement.

**SIGNIFICANCE:** This study will advance the science of cancer prognostic tools by including QoL outcomes and controlling for palliative care interventions, which has never been done before. The expected outcome is a web-based tool that accurately predicts a GI cancer patient’s time to death and how palliative care interventions will impact his/her future QoL. As such, this interactive predictive tool could support GI cancer patients to initiate palliative care discussions with their oncologists earlier, even during active treatment. This will improve care for thousands of Canadians living with GI cancer by increasing access to palliative care, improving QoL, and reducing symptom burden for patients. Moreover, the methods can be applied to other cancers in future research to improve care for tens of thousands more cancer patients.