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IMPROVE: Improving Cancer Care by Incorporating the Patient's Voice into On-treatment Symptom Management

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IMPROVE: Improving Cancer Care by Incorporating the Patient's Voice into On-treatment Symptom Management

1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Physician-reported measures are known to under report important symptoms and toxicities from therapy and their associated level of burden on patients[1], leading to missed opportunities for clinicians to intervene and improve treatment-related outcomes. With the advances in systemic therapy and in radiotherapy, definitive-intent radiation is increasingly being offered in concert with systemic therapy for patients with locally-advanced and for limited metastatic disease.[3-9] however, these therapies are not without risk. In a systematic review of 19 randomized trials of patients with non-small cell lung cancer (NSCLC) receiving chemoradiation (chemoRT) compared to radiation alone, chemoRT improved survival but at a cost of greater toxicity (esophagitis: RR 1.8, 95% CI: 1.3-2.3; neutropenia: RR 3.53, 95% CI: 1.8-6.7; grade 3 to 4 anemia: RR 3.5, 95% CI: 1.8-6.8).[10] Given the competing medical comorbidities and frailty of cancer patients at presentation, the potential risks with aggressive radiation, the ability to optimally understand, monitor, and manage cancer treatment toxicity is critical.

Patient-reported outcome measures (PROMs) is an umbrella term that refers to any report on a health status measure that is reported directly by the patient, without the influence of clinicians or anyone else.[11] PROMs have been shown to more closely reflect a patient's daily health status when compared to physician-reported measures.[1] Given the disconnect between patient and provider-assessed toxicity, PROMs can be used to more accurately and consistently characterize the detrimental impact of treatment on a patient's symptom-specific outcomes, functional well-being, and overall quality of life. For example, a French randomized trial in stage IV NSCLC patients showed a survival benefit (22.5 vs 14.9 months) when using web-based PROMs to guide follow-up vs. standard follow-up with imaging every 3 to 6 months.[12] However, research is needed to evaluate if patient symptom reporting during treatment allows earlier and improved detection of treatment toxicity, and leads to individualized interventions which may improve the toxicity outcomes for locally-advanced and oligometastatic patients receiving definitive chemoRT.

2. Objectives (include all primary and secondary objectives)

a. Primary objective: Describe the proportion of patients with changes in physician-perception of treatment-related toxicity that result from routine physician review of PROMs reported during definitive radiotherapy.

b. Secondary Objectives: Describe (1) the proportion of patients with changes in the management of treatment-related symptoms and (2) the type of management changes that result from routine physician review of PROMs reported during definitive radiotherapy.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

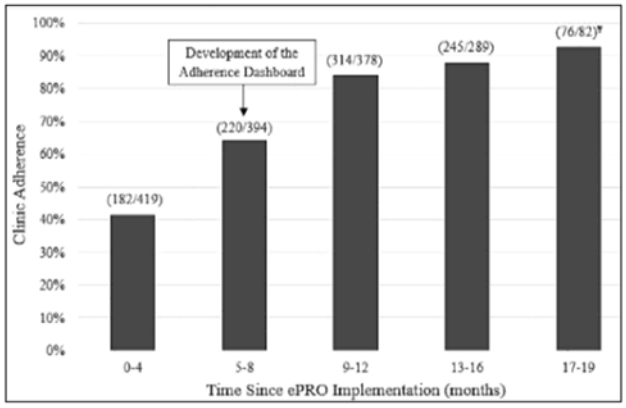
Interest is growing in using PROMs as a tool for improving assessment of patients and to guide physician decision making. Historically, PROMs were used for collecting data on patients in clinical trials but such data was not shared with the physicians involved in earlier trials to guide decision making in the care of patients. Patient-physician discordance in the rating and perception of symptom burden in patients has been demonstrated in studies of cancer patients undergoing treatment.[13] Use of PROMs by physicians may reduce this discordance and help improve overall assessment of the symptomatic burden for patients on-treatment. Recent studies have shown the feasibility and usability of PROMs in routine clinical care for cancer patients.[14-19]

Snyder et al. randomized patients receiving oncological care to three different questionnaires assessing quality of life. Patients reported that utilization of PROMs improved the quality of care, improved communication with their physicians, and patients felt more in control of their care. Although not powered for this purpose, the trial also showed that participants from minority racial groups, with lower education levels, and less computer usage were more likely to rate the PROM intervention more favorably than their peers, suggesting a benefit for this intervention in addressing the needs of vulnerable populations.[18] PROMs can also help physicians identify the symptoms that patients report as most bothersome,[19] which can help clinicians tailor decision making approaches to create more beneficial outcomes for patients. There is less evidence to suggest that these assessments can lead to changes in management of symptoms and improved symptom burden as a result of treatment, though there have been some recent examples.[12, 17, 20-21]

Lung cancer patients treated at Johns Hopkins currently report individual adverse on-treatment symptoms using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE, version 1).[22] Our group has demonstrated the feasibility of routine real-time collection of PROMs in our clinic for lung cancer patients receiving radiation. Over time, we have been able to increase patient PROM completion rates to above 80 % (Figure 1).[23]

This study builds on that clinical collection and review of PROMs by nurses. We propose a prospective pilot study to describe the proportion of patients with a change in their physician's assessment of their overall toxicity burden that result from routine physician review of PROMs during radiotherapy. We hypothesize that routine physician review of PROMs during on-treatment visits will (1) increase proportion of patients with an increased in their physician' s assessment of their overall toxicity burden during definitive radiotherapy, and (2) correspondingly increase the proportion of patients receiving physician-directed interventions for treatment-related symptoms.

Figure 1: Patient PROM completion rates in the thoracic radiation oncology clinic



4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Patient Recruitment:
We will recruit eligible cancer patients who are about to begin conventional-fractionated (chemo-) radiotherapy. Patients will be informed of the study by their physician, clinic staff or research staff prior to the day of their first on-treatment visit. For patients who decide to participate, research staff or treating physicians will obtain an informed and written consent before or on the first on-treatment visit.

Clinician Recruitment:
The treating radiation oncologists have expressed a willingness to participate in the study and will help with patient recruitment. The radiation oncologists will be recruited at Johns Hopkins and at WellSpan Health through emails and will have differing levels of experience. Once we have received IRB approval, we will go through a formal consenting process. Physicians will have the option to decide not to participate. If a physician is willing to participate, she/he will be asked to provide written informed consent.

A participating physician may be included a co-investigator in this study. No physician co-investigator may analyze their own patient's PROM data included as a part of the study. There is no requirement that to be a co-investigator physician must also be a research participant.

Study Procedures:
In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

As part of patients' routine on-treatment evaluation, patients will report: (1) their symptoms using PRO-CTCAE measures for cancer-specific symptoms during on-treatment visits, (2) the most bothersome symptom, and (3) effect of their symptoms on their perception of bother and role function in terms of interference with daily activities (**Appendix A**.) These measures should take only 5-10 minutes to complete.

** After signing informed consents - Patients will be asked to complete the measures prior to seeing their physician, during each on-treatment visit. Patient Care Technicians (PCT), Clinical Ancillary Staff, or Research Staff will provide the PROM forms to the patients and assess the forms for completion of questions. If the first three options are not available, a nurse may provide the patients the form and confirm with the patients that the PROMs have been completed without reviewing the content of the forms. PROM forms will be completed on an electronic tablet. A hard-copy will be used as a back-up measure for patients if electronic devices or wireless functioning capabilities are not available at the time.

As a part of the study, treating physicians over-seeing the care of their patients will be asked to provide a global burden score. Lee et al. demonstrated the feasibility of using a global burden score to capture the provider's overall perception of the combined burden of *all* assessed symptoms, using a visual analogue scale demarcating an aggregate score from 0 to 10. This scale uses anchors at 0, 2, 4, 6, 8, and 10 for no, mild, moderate, severe, life-threatening adverse events, and death, respectively.[24]

** During weekly on-treatment visits and prior to reviewing their patient's PROMs, physicians will rate the symptom burden for each of their patients from 0 to 10 using available clinical data. Routine available clinical data include: vital signs, laboratory work, physical exam, nursing assessment, physician's clinical judgement. Then after reviewing the patient's PROMs, physicians will re-rate the patient's symptom burden and report any change in recommended interventions due to review of the PROMs. Management changes include (1) additional counseling, (2) medications/interventions changed, (3) referrals to other services, and (4) further testing/evaluation (**Appendix B**). At the end of each patient's course of radiotherapy, providers will complete a Clinician Feedback Form to answer questions regarding the impact of PROM review on overall symptom perception and management during treatment (**Appendix C**). These forms were designed to be easy to complete and will take an estimated 5 minutes per patient.

At the time of enrollment, research staff will collect pertinent patient baseline and characteristics through clinical chart review. During each on-treatment visit, research staff collect pertinent clinical and treatment variables through chart review (Appendix D**). The research staff, if available on site, will also be available to assist patients in completing the questionnaires during scheduled visits and to address any issues or concerns patients have in completing the questionnaires.

** Marks demarcates interventions that will/may require research staff availability and assistance.

b. If your study involves data/biospecimens from participants enrolled under other research studies with a written consent or under a waiver of consent, please list the IRB application numbers for those studies. Please note: Certificate of Confidentiality (CoC) protections applied to the data in source studies funded by NIH or CDC will extend to this new study if the funding was active in 2016. If this situation applies, Section 36, question 4 in the application will need to be answered "Yes" and "Hopkins Faculty" should be selected in question 7. No other documents are required.

Not applicable.

c. Study duration and number of study visits required of research participants.

Patients will be enrolled in the study prior to or on their first radiotherapy on-treatment visit and will continue through the course of their radiotherapy. Data will be collected at routine weekly on-treatment visits; no study-specific visits are required

d. Blinding, including justification for blinding or not blinding the trial, if applicable.

Blinding will not be possible as the treating physician will need to provide routine care to the patients enrolled on this study. In addition, the treating physician will need to appropriately assign burden scores, and to report on whether there was a change in management for each of their patients who enroll on this study.

e. Justification of why participants will not receive routine care or will have current therapy stopped.

Patients will continue to receive their routine care. This study will not alter nor stop the planned radiotherapy treatments. All patients enrolled will undergo routine weekly on-treatment evaluation and toxicity management by the treating physician.

f. Justification for inclusion of a placebo or non-treatment group.

There is NO placebo group. This is a pilot study to evaluate whether physician review of PROMs during radiotherapy changes the physician's assessment of a cancer patient's overall toxicity burden and management of treatment-related symptoms. There is insufficient sample size to include a placebo group. In future studies building on this, where we have a greater sample size, we can randomize patients to 2 arms: with and without routine PROM review.

g. Definition of treatment failure or participant removal criteria.

Patients will be removed if they desire to refrain from answering the PROM questionnaire.

h. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

There will be no change in the patient's routine care or treatment.

5. Inclusion/Exclusion Criteria

Our study population will be treating radiation oncologists and their primary cancer patients requiring definitive treatment with radiation with or without concurrent chemotherapy as per the inclusion criteria below. Cancer patients receiving stereotactic body radiation therapy or hypo-fractionated definitive radiation will not be recruited as these patients represent a different treatment population with a much lower overall treatment toxicity burden.

Patients:

Inclusion Criteria:

- Men and women over 18 years of age
- Able to read and write in English or able to understand/answer questions with the aid of an interpreter
- Histologically confirmed loco-regional to advanced primary cancer, including but not limited to lung cancer, esophageal, or gastro-intestinal cancers at risk of developing radiotherapy-related toxicity.

- Receiving definitive conventionally-fractionated radiation treatment with or without chemotherapy

Exclusion Criteria:

- Patients receiving radiation for palliative intent
- Patients who do not provide informed consent
- Patients who chose to withdraw from the study

Radiation Oncologists

Inclusion criteria:

- Must be the physician overseeing the care of the patient who answers the PROMS

Exclusion criteria:

- Have not provided informed consent

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
Not applicable.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
Not applicable.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.
Not applicable.

7. Study Statistics

This is s prospective pilot study.

a. Primary outcome variable(s).

The primary outcome is the proportion of patients with any change in their physicians-assessed burden scores for at least one on-treatment visit, along with their exact binomial 95% confidence interval.

b. Secondary outcome variables

The secondary outcome is the proportion of patients with a change in their on-treatment management for at least one on-treatment visit, along with the exact binomial 95% confidence interval.

c. Exploratory outcome variables:

We will also summarize the mean change in the physician-assessed burden score across on-treatment-visits, and across patients, using mean, standard deviation, median and ranges. We will report the distribution of changes (an increase, decrease or no change) in physician burden score after PROM review across all visits.

We will also summarize the mean change in the physician interventions across on-treatment-visits, and across patients, using mean, standard deviation, median and range of cumulative changes in interventions made. We will explore the average cumulative number of management interventions based on each specified numerical change in burden score.

Additionally, we will describe differences in mean physician burden score between first half and second half of treatment. To describe changes in the physician perception of treatment-related toxicity resulting from routine physician review of PROMs, we also will compare the mean change in burden scores for on-treatment visits 4 to 7 to the mean change in burden scores for visits 1 to 3. Treatment-related toxicities are expected to worsen over time. If PROM review does not change physician perception of treatment-related symptoms, there would no difference between the mean change in burden score across patients in the first half of treatment compared to the second half of treatments. Using paired t-tests, we will examine the differences between mean physician burden score across patients in the second compared to the first half of the treatments. We would expect the changes in burden scores to be greater in later visits since treatment-related toxicities and corresponding PROMS are expected to worsen over time.

Depending on the proportion of patients with a change in physician burden assessment, we will also explore potential variables associated with a change in burden assessment by the physician.
We will evaluate associations between variables of interest and development of any point as well ≥2 absolute point change in their physician's assessed burden scores for at least one on-treatment visit using Fisher's exact test. Variables may include but are not limited to: PROM question type from the corresponding on-treatment visit (symptom type, symptom severity, most bothersome symptom, interference on activity of daily living), baseline clinical or demographic information, and/or treatment information including treating-physician or disease-site. We will not adjust for multiple comparison due to the exploratory nature of this study.

d. Statistical plan including sample size justification and interim data analysis.

The analyses will be descriptive. The statistical plan is written by study objective above. Exploratory plots will be made (line graph, bar plots) and used to visualize the distribution of data of interest. These plots may include but are not limited to cumulative number of additional interventions recommended with time and the distribution of type of additional interventions (counseling, medications/interventions, referrals, testing/evaluation). Exploratory tables will compare the average burden score change with the average cumulative number of management interventions per week. Secondary analysis will explore ratings on the Clinician Feedback Form.

Annually, 60-80 lung and esophageal cancer patients and 20 gastrointestinal tumors are treated with definitive RT over the course of 5-7 weeks at Johns Hopkins. On average >80% of on-treatment visits have PROMs completed for lung cancer patients. A sample size of at least 50 patients yields a two-sided 95% confidence interval with a width of less than 30% for descriptive analyses. Thus, we would be able to estimate the proportion of patients with a change in their physician assessed burden score and change in management with a margin of error of 15 % (+/- 15 %).

There will be no interim data analysis.

e. Early stopping rules.

Not applicable.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

There are minimal risks to patients associated with participation in this study. PROs will be collected as a part of routine clinical care. Patients may become fatigued by completing the PRO questionnaire or the study forms and they may be upset by some of the questions (although the nature of the items is not generally upsetting). Patients will be instructed that completion of the PRO questionnaire is voluntary and they may decide to stop completing the PRO questionnaire at any time. They will be informed of the approximate length of time it takes to complete the questionnaire. The data collection from clinicians is brief and should not be fatiguing or upsetting.

b. Steps taken to minimize the risks.

Because of the nature of this study, we do not anticipate any adverse events. However, if a patient is upset by completing the study forms or becomes fatigued by completing them, the patient is free to stop completing the questionnaire at any time.

c. Plan for reporting unanticipated problems or study deviations.

The principal investigator and Co-investigators at all sites will notify the appropriate regulatory agencies of any serious adverse event due to any cause during the course of this investigation. These include the Johns Hopkins Cancer Center Data and Safety Monitoring Committee, and the Johns Hopkins Medical Institutional Review Board (JHM-IRB) of The Johns Hopkins Medical Institutions. We do not expect any fatal events as a result of this study but will notify within 14 days regarding unanticipated problems or deviations.

d. Legal risks such as the risks that would be associated with breach of confidentiality:

While data will be stored data in securely locked files (computer files will be password protected and any paper records will be stored in the research office at Johns Hopkins and all respective sites under lock and key) in which only the research team has access, there is always the risk that confidentiality will be lost. Following data analysis, all clinical information will be de-identified. Data management strategies will take full consideration of regulations on the security and confidentiality of electronic data. Summary data reports will not contain any identifying information. Upon completion of the study and data retention period, patient identifiers will be deleted in compliance with the Health Insurance Portability and Accountability Act.

e. **Financial risks to the participants:**

There will be no costs accrued to the patient as a result of completing the PROM questionnaire. We will attempt to eliminate additional logistical burdens by scheduling the assessments on days patients already have other scheduled clinical appointments.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Participants will answer PROMs which may improve patient-provider communication, management of patient symptoms, and the patient's experience and satisfaction with treatment.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

A $10 dollar gift card will be offered to patients enrolled on the protocol.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

None.

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