Project title: Patient preferences for reducing adverse events following brain irradiation

Background and Significance:

Radiation therapy (RT) side effects vary in intensity, frequency, and functional impairment, depending on the part of the body being treated. RT side effect reduction for patients undergoing cranial irradiation have been specifically identified as a patient and public health priority. As compared to radiation therapy to other parts of the body, long-term effects of cranial irradiation can lead to significant memory impairment and personality changes that can impact a patient's quality of life and patient-perceived psychosocial well-being. Multiple studies are currently underway to evaluate treatment options that may minimize radiation-induced side effects from cranial irradiation, such as proton beam therapy and hippocampal-avoidance during irradiation.

Toxicity reporting in cancer clinical trials has been traditionally performed utilizing the maximal-grade method, which reports the total cumulative incidence of any high-grade treatment toxicity, as assessed and documented by physicians. Although this provides a conceptual framework for analyzing treatment toxicities, such data has limited utility to patients because it assumes each treatment side effect is of equal significance.

A growing emphasis in healthcare studies has been placed upon accounting for patient preferences when evaluating alternative treatment interventions. Techniques for evaluating patient preferences have traditionally relied upon qualitative interview techniques.[1,2] However, use of quantitative stated-preference methods has now been developed to scientifically study and quantify what factors patients and stakeholders value most.[3]

The most commonly applied approach for evaluating patient preferences is to perform a conjoint analysis (also known as a discrete-choice experiment [DCE]).[4] Briefly, in a DCE, patients are given a series of trade-off tasks involving different hypothetical treatment attributes, such as treatment toxicity.[5] Patients are then asked to select which treatment they would prefer based upon the different attribute profiles in each scenario they are presented with. Based upon the respondents' choices, a mean preference weight for each of the different attributes studied can then be calculated.

In oncology, a DCE has been utilized to successfully evaluate and quantify patient preferences related to different chemotherapy and surgical treatment toxicities.[6-8] However, **no studies to do date have utilized a DCE to help evaluate patient preferences related to different radiation-induced side effects**.

International best-practices guidelines for proper use and evaluation of DCE have now been published.[9] In the present proposal, the study PI (Mishra) will be working directly with collaborators (Mullins and Bridges) who have helped write these best-practice guidelines to perform a DCE to determine patient preferences for side effect reduction.

The specific aims of the present study are to:

1) **To develop a discrete choice experiment tool that can be used to measure patient preferences for side effect reduction** (Phase 1). In keeping with best practice guidelines, we will conduct one-on-one patient interviews with patients who have previously undergone cranial irradiation for a primary brain malignancy to develop a tool to encompass the spectrum of side effects that patients experience as a result of brain RT (short- and long-term effects).
2) **To conduct a discrete choice experiment to determine patient preferences for side effect reduction in treatment of central nervous system malignancies (**Phase 2). The DCE tool developed in Phase 1 will be administered to new and former brain radiation patients from the University of Maryland School of Medicine's Department of Radiation Oncology, the University of Maryland Greenebaum Cancer Center (UMGCC) and affiliated community practices, to quantify the relative importance/significance of the different side effects.

The present study will be conducted in collaboration with Dr. Daniel Mullins, Professor and Chair of the Pharmaceutical Health Services Department, and Dr. John Bridges, who is an international leader in conducting DCEs. The proposal will also leverage existing resources available on campus at the University of Maryland, Baltimore through the AHRQ-funded PATient-centered Involvement in Evaluating effectiveness of Treatment (PATIENTS)program, which will provide resources for patient and stakeholder engagement in the present study that can lead to future funding opportunities through AHRQ, PCORI, and/or NCI. The results of this proposal will: (1) provide a novel method for characterizing and understanding patient preferences for side effect reduction; and (2) can be used to inform study endpoints in comparative effectiveness research (CER) studies evaluating techniques for preventing RT-induced side effects.

Research Design:

Developing a discrete choice experiment tool: (Phase 1; in collaboration with Daniel Mullins and John Bridges)

Qualitative methods with cognitive interviewing (in keeping with best practices guidelines) will be employed to develop the DCE tool. Cognitive interviews will be conducted one-on-one between a qualified study investigator and former brain tumor patients. The use of one-on-one interviews, in place of large focus groups, is recommended because this approach allows each patient to provide a full and detailed account of his/her individual perspective and experience during treatment. Moreover, this approach allows interviewers the opportunity and flexibility to explore any new or relevant topics that emerge during the interview.

Identifying potential patients (to be conducted through the Department of Radiation Oncology after obtaining IRB approval)

Inclusion Criteria
• Adult ≥18 y old • Current or previous cranial RT for a primary brain tumor • Ability to speak and read English

- Potential study participants who meet the study inclusion criteria (shown at right) will be approached by their radiation oncologist to inquire whether they wish to participate in the study
- Up to 25 patients will be enrolled for this portion of the study (see analysis of interviews below). Based upon the experience of the research team, no more than 3 months will be required to complete this portion of the study

Conducting cognitive interviews

- After providing informed consent, each patient will be interviewed either in person or via telephone (whichever is the most convenient for the patient)
- Patient will be interviewed by Dr. Mishra/Mullins/Bridges and/or another trained study staff
- Patients will be asked broad and open-ended questions about the side effects they found to be most bothersome during and immediately following completion of treatment
- Interviews will last a total of 45–60 minutes and patient participants will be paid $50 to compensate them for time and effort

Analysis of Interviews

- The endpoint of the cognitive interviews is *theoretical saturation*, defined as "the phase in which the researcher has continued sampling and analyzing data until no new data appear."[10] Based on Dr. Bridges' previous experience in qualitative work and in-depth interviews,[11] theoretical saturation requires a minimum of 10 and is usually reached after 25 interviews. To be conservative, we have planned for 25 interviews.
- A method known as interpretative phenomenological analysis (IPA) will be applied to identify common themes highlighted by patients during the one-on-one interviews.[12] This method is commonly applied during qualitative analyses, and the study's Qualitative Chair has utilized this approach in the past to identify the preferences of cancer patients.[13-16]

After the completion of the analysis of cognitive interviews, study results will be reviewed with the research team as well as the PATIENTS program staff (through collaboration with Dr. Daniel Mullins), and a preference instrument will be finalized for Phase 2 of the study.

Measuring patient preferences through DCE: (Phase 2; in collaboration with Daniel Mullins and John Bridges)

In our DCE instrument, preferences will be measured by showing respondents multiple side effect profiles that consist of various severities (measured from none to severe). For each profile, the patient will be asked to sequentially identify which feature is the most and least tolerable. By varying the side effect profile in each sample scenario presented to a patient and observing the choices that each patient makes, one can statistically deduce (through the generation of utility values or preference weights) which attributes are most important and will have the most impact on patient choice.

In this study:

- The DCE tool will be administered to current and former cranial irradiation patients . A total of 75 patients will be enrolled to this portion of the study.
- Consistent with current guidelines,[17] we will include 5 to 7 side effect profiles in the survey questionnaire, in keeping with best practices for conducting a DCE.
- Analyses will be performed to determine the effect for the entire patient cohort, as well as sub-group analyses for current versus former patients

Timeline and Milestones:

Year 1:

- Obtain IRB approval for phase 1 of study
- Identify research associate to help conduct one-on-one cognitive patient interviews
- Open Phase 1 of study at through the Department of Radiation Oncology and affiliated community practices
- Conduct 50% of Phase 1 interviews
- Send annual update to Keep Punching Board

Year 2:

- Complete accrual to phase 1 of study
- Conduct analysis for Phase 1 study portion
- Prepare findings for national presentation and publication
- Obtain IRB approval for Phase 2 of study
- Send annual update to Keep Punching Board

Years 3-4:

- Phase 2 study open to enrollment through the Department of Radiation Oncology and affiliated community centers
    - Estimated enrollment of 50% of patients each year
- Annual update to Keep Punching Board

Year 5:

- Analysis of Phase 2 study portion
- Prepare findings for national presentation and final manuscript submission to national journal
- Send final report of project findings to Keep Punching Board

References:

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Keep Punching Foundation		
5 years	$5,000/yr	
	Start date	2/1/16
	end date	1/31/21

BUDGET		
Mark Mishra, Principal Investigator	$1,335	
TBD Research Assistant, to assist with patient interviews and data processing	$2,000	
Salary and Fringe:	$3,335	
Supplies and annual computer license renewal	$665	
Statistical Support	$1,000	
	$5,000	**per year/ for 5 years**

The funds for this proposed project would be administered by the University of Maryland Baltimore Foundation, Inc. (UMBF). UMBF has operated as a Maryland nonprofit corporation since July 1, 2000. Its purpose is to facilitate fund-raising programs and contributions from private sources to further the educational, research or service mission of the University of Maryland.

Michael B. Dowdy, MBA
President & CEO

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