Project Title: A pilot study of prostate cancer-specific anxiety in active surveillance
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I RESEARCH OBJECTIVES AND PURPOSE OF THE STUDY

The purpose of this study is to identify patients undergoing active holistic surveillance (AHS) for prostate cancer who have anxiety associated with their diagnosis, to implement a 12-week licensed psychologist-facilitated group intervention in this patient population to determine if treating disease-related anxiety improves quality of life, delays radical, elective treatment of prostate cancer, and to monitor symptom progression and remission during and after therapy.

Our goal is to further our understanding of anxiety in men who are diagnosed with prostate cancer, and to determine if effectively treating disease-related anxiety can improve patients' quality of life, delay radical, elective treatment, and potentially improve disease progression.

II BACKGROUND AND RATIONALE

Previous research suggests that the prevalence of anxiety in prostate cancer (PCa) patients undergoing active surveillance (AS) may be two to three times greater than anxiety levels of similarly aged men in the general population who have not been diagnosed with prostate cancer[1]. There is concern that substantial feelings of anxiety in men undergoing AS may be enough to divert PCa patients from AS to pursue definitive treatment[2].

To date, there is no consensus with regard to the optimal active surveillance protocol. Most active surveillance regimens consist of regular prostate-specific antigen (PSA) tests, digital rectal exams (DREs), and serial biopsies to assess for signs of progression.

Although numerous studies have assessed the psychological impact active surveillance may have on men, no study has examined the role that a holistic regimen may have on these men's health-related quality of life (HRQoL). The aim of this study is to determine the extent to which disease-related anxiety in patients undergoing our institution's AS protocol may alter their course of treatment. It is possible that the psychosocial concern of living with cancer may have adverse effects on PCa patients, and the anxiety related to living with cancer may be enough to divert PCa patients from participating in AS to pursue definitive treatment[2]. Previously, it has

been demonstrated that, at the moment of treatment choice, fear of disease progression is the main reason patients reject AS for a more radical treatment approach[4].

Clinical studies have investigated the claim that men who choose AS as a treatment option may be at higher risk of psychological distress than men who choose a more radical approach[1]. Patients with PCa undergoing AS experienced substantially higher rates of depression and anxiety, when compared to a control population[1]. This may be due in part to the passive nature of AS, but studies have also shown that the adverse side effects of PCa may also contribute to an increase in anxiety and depression levels for men undergoing AS[1].

Some data suggest PCa patients undergoing AS may benefit from psychological interventions such as behavioral therapy, group therapy, or mindfulness-based stress reduction[5]. In one study, AS PCa patients who participated in a mindfulness training program for 8-weeks demonstrated significant decrease in PCa-related anxiety. These patients also reported significant increases in global mental health, posttraumatic growth, and mindfulness[5]. Other studies have yielded similar results, demonstrating that educating patients about PCa and how to manage the adverse side effects through cognitive-behavioral interventions may also reduce disease-related anxiety in patients undergoing AS[3].

III STUDY DESIGN

Patients who are diagnosed with PCa will be given the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) which is a highly internally consistent, and concurrently and discriminately valid questionnaire used to identify levels of anxiety related to prostate cancer[6,7] as well as the Generalized Anxiety Disorder-7 (GAD-7) scale, which is a valid, reliable, and efficient 7 item scale used to identify patients with generalized anxiety disorder and has also been effectively used in a population of men with prostate cancer[8,9].

Those PCa patients who have elected AS, obtain a score of ≥16 on the MAX-PC, and who meet other inclusion criteria, will be randomly assigned to the treatment or control group. Patients assigned to the treatment group will receive 12 weekly 1-hour sessions of structured group therapy intervention led by a licensed psychologist, in addition to AS educational material. Patients assigned to the control group will receive the standard AS educational material only. The research coordinator, who will be responsible for disseminating the educational material and answering patient questions regarding AS, will be blinded to the randomization outcome the the study subjects.

Patients in both the treatment group and control group will be monitored using MAX-PC, GAD-7, and Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires at various time points, as described below. We hypothesize that those patients who undergo group therapy will have a significant reduction in their disease-related anxiety, as reflected by a reduction in their MAX-PC score by the end of their 12-week group therapy intervention. Furthermore, we expect to see an improvement in their quality of life, as measured by the scores obtained on the FACT-P. In addition, results of the program intervention will be correlated with PSA level changes.

<u>Interventions</u>

- 12 1-hour group therapy sessions, occurring once a week
- Facilitated by licensed psychologist
- Group therapy will be conducted using a manualized CBT treatment for anxiety, modified to focus on disease-related anxiety, and incorporating mindfulness-based stress reduction exercises.
- Participants will complete the MAX-PC, GAD, and FACT-P during the 4th and 12th weeks of therapy. Those who are absent during the 4th week and/or 12th week will be given the questionnaires to fill out during the next session or within 7 days.
- Any participant in the study who presents with suicidal/homicidal ideations will be assessed for suicidality/homicidality and referred to Winthrop-University Hospital's ED for treatment if he is deemed to be at imminent risk of harm to himself or others.
- Participants will be asked to consult with the psychologist or treating physician before taking psychotropic medications as they may affect the results of the study.

IV RESEARCH METHODS

1. Method of Subject Identification and Recruitment. Subjects will be identified by their physicians based on their primary diagnosis of prostate cancer. No advertising or outside recruitment will be employed.

2. Process of Consent. Physicians treating the patient for prostate cancer at WUH will be responsible for obtaining consent from potential participants. The consent form and the process will be fully explained, and patients will have a chance to review the form before signing. This will allow the process to be conducive to rational and thoughtful decision making by the subject or the subject's legally authorized representative.

   The following details are directly from the Institutional Review Board policies at WUH and slightly edited to fit the format of this research: The individual who signs the informed consent form as the "person obtaining consent" is responsible for conducting the entire consent process. This means:

   a. All aspects of the study, as described in the informed consent form, are first discussed with the potential participant.

   b. The informed consent form is thoroughly reviewed with the potential participant answers to the potential participant's questions are provided.

   c. While reviewing the informed consent form, the person obtaining consent asks questions designed to assess the potential participant's understanding of the material. The person will specifically state this intent to the potential participant (i.e., the person is making sure the potential participant appreciates what the participant is being asked to do, and why).

   d. The potential participant is given ample opportunity to decide, without coercion or undue influence, whether or not the participant wants to be in the study.

   e. The consent process does not end with the formal signing of the consent document. Rather, it is an ongoing process that continues throughout the participant's participation in the research study. The Principal Investigator is responsible for continued assessments of the participant's understanding of what

is happening to the participant, his/her willingness to continue participating and for providing the participant with any new information that may affect the willingness to participate.

3. Subject Capacity. All subjects to be included in this study must possess the capacity to sign a consent form independently.

4. Subject/Representative Comprehension. The investigator is responsible for ensuring that the subject participating in this research is fully aware of the nature of the study.

5. Debriefing Procedures. No debriefing procedures are deemed necessary in support of this research.

6. Consent Forms. A consent form must be signed by every subject participating in this study.

7. Documentation of Consent. The Principal Investigator is responsible for ensuring that valid consent is obtained and documented for all subjects.

8. Costs to the Subject. There are no foreseen additional costs to the patients who choose to participate in this research aside from the time that it takes to complete the questionnaires.

9. Payment for Participation. There will be no payment offered as compensation for participation in this study.

10. Data Analysis and Data Monitoring. We will compare the baseline and outcome MAX-PC and FACT-P scores by the end of the group therapy intervention (week 12). Monitoring and reporting unanticipated problems will be handled by the lead investigator and/or the head of the Urology Department. If a patient wishes to be withdrawn from the study, they may opt out at any time. Considering the minimal invasiveness of our approach, we predict this situation to be unlikely.

11. Data Storage and Confidentiality. Subjects' names and any personal identifying data will be excluded from any public access and protected based on the privacy standards at WUH. Data will be stored in a secure computer in the office of the lead investigator, Dr. Aaron Pinkhasov. Access to this information will only be allowed to authorized investigators participating in the study. There is no expected expiration date to this study as it is intended to be an ongoing database.

V SUBJECT SELECTION AND STUDY ENTRY

1. Number of subjects: 48

2. Gender of Subjects: All subjects to be included in this study will be male.

3. Age of Subjects: The subjects of this study will be over the age of 40.

4. Racial and Ethnic Origin: No discrimination will be made based on race or ethnic origin of subjects.

5. Inclusion Criteria: Inclusion requirements for this study are men above the age of 40 with a primary diagnosis of Prostate Cancer, and initial MAX-PC score of ≥16. In order to participate, patients must sign a consent form allowing related information to be included in this research. This form will be written in simple terms clearly stating the voluntary nature of their participation.

6. Exclusion Criteria: Subjects will be excluded from the study if prostate cancer is not their primary diagnosis. Subjects who, in the judgment of the investigator, cannot appropriately fill out the questionnaires will also be excluded from the study. Subjects will be excluded if they have pre-existing diagnosed psychiatric conditions, are currently taking psychotropic medications (e.g., antidepressants, anxiolytics, mood stabilizers), or have been diagnosed with cancer other than prostate cancer (and non-melanoma skin cancer), and/or evidence of active substance abuse. Participants in the treatment group who are absent from more than 3 therapy sessions will be excluded.

7. Vulnerable Subjects: Elderly subjects being treated for prostate cancer may have diminished decisional capacity. Subjects deemed in the judgment of the investigator to be unable to sign consent will be excluded from the study.

VI RISKS AND BENEFITS

1. The risks to the patient are:

    a. The potential for unforeseen exposure of information and breach of confidentiality.
    b. The possibility that a patient may feel uncomfortable answering certain questions regarding sexual and urinary function.

2. Protection against Risks.

    a. In order to protect private patient information and confidentiality, the data will be password protected and encrypted.
    b. If a subject feels uncomfortable with answering questions, they will be allowed to opt out of responding to those questions.

3. Potential Benefits to the Subjects. Potential benefits include patient treatment for anxiety and therefore possible quality of life improvement.

VII STATISTICAL ANALYSIS

Statistical methods: The investigators will perform all data analysis. Two groups, the experimental (recipients of group therapy) and the control (literature only) will be compared for anxiety based on their MAX-PC and FACT-P questionnaire scores. PSA anxiety scores will be summarized via descriptive statistics (mean, median, standard deviation, range) at baseline, 4 weeks, and 12 weeks for each treatment arm. Average pre/post changes (12 weeks – baseline) will also be computed for each treatment arm, along with 95% confidence intervals. Analysis of covariance will be used to examine our primary hypothesis that 12-week anxiety scores will be lower in patients receiving group therapy by regressing 12-week PSA anxiety scores onto baseline PSA scores and an indicator variable for treatment arm (12 weeks of group therapy vs.

standard follow-up). The estimate, 95% confidence interval and statistical significance of the treatment effect are the main statistics of interest. In secondary analysis, a mixed effects model will be used when the outcome vector consists of all three measurements (baseline, 4 and 12 weeks) and via statistical contrasts will examine whether the relationship between PSA anxiety scores and time is linear or if the effect of intervention on anxiety scores is fully observed by week 4. Two-sided p-values ≤ 0.05 will be considered statistically significant. All analyses will be conducted using SAS/STAT version 9.4 (SAS Institute, Cary, NC).

Power and Sample size: Power and sample size will be computed via simulation. Normally distributed anxiety scores were assumed such that pre-intervention scores are distributed with mean of 18 (SD=4.0); post-intervention (at 12 weeks) distributed with a mean of 14 (SD=4.0) for a 20% reduction. Pre/post score correlation (rho) was assumed to be 0.40. The final analysis set in each simulated data set consisted of n patients with baseline (score >= 16) and 12-week PSA anxiety score data, where n corresponds to the specified sample size per arm. **A total of n=48 patients will be recruited for the study, for a total of 24 in each study arm. Assuming an attrition rate of 25% (n=18 per treatment arm at 12 weeks for analysis), we will have >85% power at the 0.05 level of significance to detect a 20% reduction in PSA anxiety scores from baseline**.

VIII ANTICIPATED RESULTS AND POTENTIAL PITFALLS

We anticipate that our study will reveal important characteristics of patients with the diagnosis of prostate cancer, and test a CBT therapeutic approach to reducing the anxiety in these patients. We predict that an anxiety reduction in prostate cancer patients undergoing AHS will improve quality of life, delay radical, elective treatment, and potentially improve disease progression.

We have carefully designed our study so as to minimize the potential for pitfalls. For example, based on the current literature and our clinical experience, the chosen MAX-PC cutoff of 16 will identify a sufficient number of patients from our AHS cohort to enroll in group therapy. In an ongoing study, approximately 50% of our AHS patients exhibited a MAX-PC score of 16+. The risk of patient attrition due to lack of interest in the group-therapy intervention remains, but because we are fully implementing the group therapy into the AHS protocol, we anticipate that the attrition rate will be low, as this has been our experience in our ongoing AHS cohort.

We do not foresee any potential pitfalls that would alter or increase the risk level of the study subjects. The appropriate confidentiality safeguards are already implemented.

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