

Understanding participation in a trial comparing cryotherapy and radiation treatment

Michael Eng, MD,¹ Liam Taylor, MA,² Marja Verhoef, PhD,² Scott Ernst, MD,³ Bryan Donnelly, MD⁴

¹Division of Urology, University of British Columbia, Vancouver, British Columbia, Canada

²Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

³London Regional Cancer Centre, London, Ontario, Canada

⁴Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

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Background: To date, few two-arm active treatment randomized control trials (RCTs) have compared prostate cancer therapies.

Objective: To examine the difference and similarities between the reasons for accepting and declining participation in a two-arm active treatment RCT comparing external beam radiation therapy (EBRT) versus cryotherapy.

Methods: Eleven men with prostate cancer, selected purposively, participated in a 30-minute post-treatment semi-structured interview. Interviews were transcribed verbatim, coded and analyzed for patterns with the assistance of the text management (TM) software (NVivo).

Results: RCT accepters participated principally with

the hope of being randomized into the cryotherapy treatment arm. Consequently, randomization into the EBRT arm was often perceived as receiving the consolation prize. RCT "decliners" were either pushed away from cryotherapy and/or pulled towards another treatment (surgery, EBRT, brachytherapy). Factors influencing accepters'/decliners' treatment decisions include (1) personal factors such as patient research and treatment preference, cancer survivors, family/friends, and altruism, and (2) physician, trial, and treatment factors such as patient-physician rapport, RCT awareness and understanding, therapy convenience, expected outcome and perceived side effects.

Conclusions: By better understanding patients' views about RCT participation, recruitment rates for prostate cancer RCTs can be improved.

Key Words: prostate cancer, randomized controlled trial, trial participation, cryotherapy, decision-making

Introduction

Prostate cancer accounts for almost 25% of male cancer diagnoses. Currently numerous prostate cancer treatments exist, but no single one predominates as

the gold standard.^{1,2} RCTs are considered the pre-eminent manner of validating new therapeutic approaches. However, only a small proportion of new cancer patients participate in RCTs (3%).³ RCTs have tended to include one active treatment such as radical prostatectomy versus "watchful waiting".⁴ One of the first ever two-arm active treatment trials comparing cryotherapy^{5,6} versus EBRT is taking place in Calgary, Alberta. In Alberta, cryosurgery is available on an elective basis for those patients having had a local recurrence of cancer subsequent to EBRT or surgery. However, as a primary treatment, cryotherapy is only obtainable through RCT enrolment at the Tom Baker Cancer Centre (TBCC).⁷

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Address correspondence to Marja Verhoef, PhD, Professor, Department of Community Health Sciences, 3330 Hospital Drive NW, Calgary, AB T2N 4N1 Canada

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Due to low accrual, the trial was stopped in 2003. Follow-up is still ongoing. Preliminary results are not available at this time pending the completion of the trial and the final analyses of remission rates and overall survival.

A variety of factors determines whether a patient agrees to participate in a RCT including design characteristics,⁸ health care team characteristics and patient related factors including pre-existing treatment preferences.⁹⁻¹⁴ The current RCT speaks both to cancer patients' perceptions of cryotherapy as a research treatment for prostate cancer and highlights prominent factors considered in the decision to participate in the RCT. The objective of this study is to explore factors considered by patients in their decision to participate in the RCT.

Sample and methods

Influenced by the uniqueness of this RCT, this project is an exploratory qualitative study added to the main study. Qualitative research methods are an appropriate way of assessing and understanding meanings, concepts, and descriptions of phenomena.^{15,16}

RCT recruitment consisted of (1) attending a forum delivered by the radiation oncologist, cryosurgeon, clinical psychologist/sex counselor and research nurse, and if further interested (2) a one on one meeting with the oncologist and nurse. Participants

were recruited from among those attending (at minimum) the cryotherapy information session and included individuals who accepted RCT participation and some who declined participation. Purposive sampling was employed to select patients having given considerable thought to their treatment decision.¹⁷ Individuals were selected by the first author and research nurse who were intimately knowledgeable of the sample population. The purpose in qualitative research is not to generalize to a wider population but to achieve conceptual clarification which means that no new themes will emerge by adding more participants to the sample.

Eleven English-speaking participants agreed to being interviewed post-treatment about their decision to participate or not in the RCT: six participants accepted RCT participation and five declined RCT participation. Of the six who accepted RCT participation, two were randomized for EBRT and four for cryotherapy. Of the five who declined RCT participation, four elected to undergo EBRT and one surgery.

After obtaining written consent, data were collected via semi-structured open-ended interviews conducted by the first author (see Table 1 for interview guide). Semi-structured interviews follow a pre-determined set of questions, but allow flexibility to explore issues raised by the informant. Interviews were conducted in 2000 at the TBCC, lasted approximately thirty minutes, and were audio taped

TABLE 1. Interview guide

1. Could you please describe to me the consultation(s) when you were asked about participating in this research trial?
2. Please describe your thoughts and feelings when you were first asked about participating in a treatment research project?
3. How do you think a treatment decision should be made?
4. Could you tell me what you wanted to know about this research project?
5. When you decided whether or not to participate in the suggested research project, what influenced your decision?
6. Could you tell me how you reached a decision?
7. All in all, what do you feel were the most important factors in your decision?
8. If you had the choice, which treatment would you have preferred?
9. What do you think in general about patients participating in research?
10. Why do you think you were asked to participate in a research project?
11. Is there any other information you would like to share that could help us with this study?

Trial decliners only:

1. In different circumstances, could you imagine to have agreed to participate?
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and transcribed verbatim to preserve informants' accounts. Pseudonyms have been assigned to protect patient anonymity.

Initial analysis involved reviewing transcripts to gain an understanding of emerging results. Second, the use of the text management (TM) software program NVivo was employed to group text by emerging themes. This is accomplished, much like "copy and paste" functions in word processing software, by selecting text and assigning it to "nodes" or themes. As new themes emerged these were repeatedly revisited, split, and/or merged to 'make sense of the data' (constant comparison). Coding was completed by authors M.E. and L.T., and co-authors assisted with data analysis and interpretation.

This study was approved by the Conjoint Health Research Ethics Board, The University of Calgary.

Results

Two themes comprising nine sub-categories were identified as playing a role in RCT accepters' and decliners' decision to participate.

Theme I: personal factors

Patient research

Information gathering and its assessment were a vital component in most patients' treatment choice. "No one ever really thinks about it (collecting and reviewing information) until you have it yourself. Then all of a sudden you're quickly digging into all this information that you never paid any attention to before" (Mr. Burns – Acceptor). Information needs

varied by patient. Some did extensive research on their own while others relied on physician-supplied information. Patients wanted to know the success rates, side effects and time commitment for each type of treatment. In addition to physicians, patients obtained information from a wide array of sources such as books, the Prostate Cancer Institute, the Internet, family members/friends and cancer patients. Table 2, quote 1.

Both accepters and decliners reported they received the quantity and quality of information they needed to make a decision. Accepters did more research about cryotherapy than did decliners who reported feeling strongly about the successes of EBRT or surgery. Other decliners reported feeling overwhelmed with the total amount of treatment information and consequently leaned toward traditional treatments (EBRT or surgery). Accepters also did extensive information gathering, and felt comfortable with reported side effects and expected outcomes of both cryotherapy and EBRT although they shared a strong preference for cryotherapy.

Cancer survivors

Cancer survivors' influence on decliners ranged from being very important to having no significance whatsoever Table 2, quote 2. One decliner explained his treatment choice as the "proven and accepted method and the one his friends had had". Findings indicate that decliners may have spoken less with cancer survivors than accepters who also had more interaction with previously treated cryotherapy recipients. Based on interactions with both cryotherapy and EBRT recipients, accepters either

TABLE 2. Personal factors impacting RCT participation

1. **Patient research:** Answer: "I got it [information] from books and off the Internet and the Canadian Cancer Institute and down in the States and so on and so forth. My daughter had some good references too". (Mr. Peters – Acceptor)
 2. **Cancer survivors:** "I talked to people and relatives who had prostate cancer, had surgery, had radiation. I talked to them and they gave me names of other people that I phoned and I talked to. There was a lady at the church who was a nurse here and she put me in touch with somebody else in the parish that had prostate cancer. Prostate cancer was in his family. He had the radiation because he was older and his brother had surgery and he was down in Toronto so I talked to him. I managed to talk to quite a large group of people in various areas in the province as well as outside the province". (Mr. Wright - Decliner)
 3. **Family/friends:** "Yeah. I discussed it with two members of my family that were there at the time when he (cryosurgeon) explained it to us and then we all felt the same way". (Mr. Hickey – Acceptor)
 4. **Altruism:** "Down the road, for people in the future generations it would be better if they didn't have to get into a research program hoping to get one or the other that they choose. That's another reason, I felt we had a chance of getting cryo and that we could help the future down the road". (Mr. Burns - Acceptor)
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gravitated towards cryotherapy after speaking with successful recipients and/or were pushed away from EBRT towards cryotherapy. For example, two accepters had friends already involved in the trial and a third spoke by telephone with an individual who went to a private clinic in the United States for cryotherapy and who spoke very highly of the results. One accepter entered the trial hoping to get randomized into the cryotherapy arm as a means to potentially avoid EBRT as he had heard stories about patients suffering from EBRT burns.

Family/friends

The influence of family members (wives, children, brother-in-laws, etc) was comparable between RCT participants and non-participants. No major influence on treatment choice was observed among study informants. In all 11 cases, the patient was the one who made the final choice to enter the RCT or not.

Accepters' and decliners' family members acted in supportive roles by attending information sessions, acting as proxy informants by compiling information, and participating in family discussions Table 2, quote 3. Friends were much less active in attending information sessions, but proved useful as proxy informants.

Altruism

The notion of participating for altruistic reasons was presented at the forums and while it did not prove to be a primary reason for RCT enrolment it did play a more prominent role among accepters. Several accepters had family members who previously experienced prostate cancer and acknowledged their participation was in part a contribution for the benefit of other relatives Table 2, quote 4. In addition to supporting medical research they also hoped that cryotherapy, if proven to be effective, would become a standard option for future patients.

Among decliners participating for altruistic reasons did not hold as high a priority. For several, choosing to participate meant sacrificing what they believed to be their most effective treatment and consequently the treatment they felt offered them the best chances at recovery.

Theme II: physician, trial, and treatment factors

In addition to personal factors patients considered, to varying degrees, influences of patient-physician rapport, the trial process itself, and treatment factors such as expected outcome and side effects.

Patient-physician rapport

Patient-physician rapport can be a strong factor in treatment choice. Patients with positive physician rapport tended to value their opinions more than those with less positive or negative relations. Patient-physician rapport was also influenced by physician willingness to assist with treatment choice. Participants can be grouped as active, collaborative, or passive in terms of their RCT decision-making process. Most of the participants showed a desire for the collaborative approach in which decisions were a joint responsibility with their physician. Physician reluctance to advocate one treatment over another compelled some to become active decision makers. On occasions when physicians expressed an opinion about treatment choice this became a stronger influence than friends or family: e.g. one patient cited an EBRT oncologist's recommendation to decline trial participation as a major influence in his decision.

The RCT physicians' reputation, impressions of honesty, "friendly" demeanor, and good "communicator image" were important factors in accepters' participation. Accepters cited the knowledgeable manner in which cryotherapy and the RCT were explained and questions answered as the confidence booster they needed to participate Table 3, quote 1. Accepters noted that they did not feel pressured to participate and that the cryosurgeon even took time to explore treatment options available outside of the RCT with them.

RCT awareness and understanding

RCT awareness and understanding played a factor in trial acceptance. Interview participants had heard little about the RCT forum until physician referral. Those who did hear about it did so through the local newspaper or via acquaintances. All spoke very highly of the educational nature of the forum including one-on-one time with surgeon and nurse, and brochures outlining the RCT. The majority had previous knowledge of the use of RCTs for medical purposes and all felt RCTs were important for the advancement of health services. However, post-treatment some still did not understand how RCTs work Table 3, quote 2.

Several decliners commented that the RCT was to prove cryotherapy was only "as good as" EBRT so "why settle for anything less". Some felt they were taking a chance with cryotherapy due to a lack of long-term data as is available for surgery and EBRT. Accepters identified the stringent RCT follow-up as a consideration for participation as this would ensure thorough monitoring and improved their confidence

TABLE 3. Physician, trial, and treatment factors impacting RCT participation

1. **Patient-physician rapport:** "..., Dr. X went into it very thoroughly. He never sort of left a stone unturned. He was very thorough and I was very impressed with the way he gave the presentation" (Mr. Jones – Acceptor).
2. **RCT awareness and understanding:** "Well, yah, that would be nice to know why I was not accepted [for cryosurgery] and how they pull it out of the hat. What does the computer decide on, age, how bad your cancer is? This is kind of a mystery to me. I wouldn't mind knowing why I was rejected" (Mr. Edwards – Acceptor).
3. **Therapy convenience:** "I'm retired but my thinking at the time was that I do have time. To go to the hospital every day [for radiation] is a nuisance, but there really is no serious impediment. I'm not missing time at work. It would be a disaster if I was still working, but since I'm retired there was no problem" (Mr. Boswell – Decliner).
4. **Expected outcome:** "But I looked at the recuperative part and I thought 'God, if I take the radiation am I going to feel like this for two years?' I don't think I want that. So I was looking basically at the effectiveness from what I had seen anywhere from 95 to 98% success with cryotherapy on prostate cancer. Recuperative within two to three weeks people back on their feet, going. When you really think about that you've gone in, solved a problem with a 95% chance of getting it all" (Mr. Sampson – Acceptor).
5. **Perceived side effects:** "Yes, they told me it [EBRT] took seven weeks plus the side effects versus a very short time [cryotherapy]. Even if the side effects were as serious with cryogenics they would be short lived anyway and there would be recovery from it very quickly" (Mr. Boswell – Decliner).

in cryotherapy. Several decliners viewed the strict follow-up as more of an inconvenience.

Therapy convenience

Therapy convenience includes aspects of the actual treatment itself and the varying travel requirements of each treatment. Cryosurgery was commonly referred to as "quick" and "convenient" for it was perceived as a treatment requiring less healing time and a shorter hospital stay. Patients were keen to avoid a "long drawn out procedure" of six months hormone therapy and seven to eight weeks of daily EBRT treatment. Disparity existed among those still engaged in a working career. Workers felt that EBRT would "dominate your whole day" whereas cryotherapy was a quicker procedure with shorter recovery time. Retired persons did not consider the daily trek to a hospital for treatment to be as much of a burden Table 3, quote 3.

Expected outcome

At the core of the decision process for both groups was the weighing of success rate versus side effects Table 3, quote 4. Accepters and decliners both pointed to the lack of long-term results for cryotherapy as a concern. Some RCT accepters remained apprehensive about being randomized into the EBRT arm because subsequent treatment sessions, if necessary, are not medically feasible as with cryotherapy. Accepters also pointed to the additional follow-up they would

receive - from participating in the trial - irrespective of whether they received cryotherapy or EBRT. Furthermore, accepters noted reduced side effects from cryotherapy as a primary advantage.

Conversely, at the forefront of decliners' concerns about cryotherapy was the lack of success rate evidence and less well known history of side effects. Decliners emphasized if you are trying to prove that the new technique is "as good as" the standard treatments there has to be another reason for participating. While these men liked cryotherapy for its short treatment time, they dismissed it due to a lack of long-term success rate data.

Perceived side effects

Irrespective of treatment choice, a shared goal of accepters and decliners was to "kill the cancer" and minimize the side effects. Both short and long-term side effects were considered by both accepters and decliners. Accepters perceived cryotherapy to be less invasive, more localized, having a quicker recovery, and resulting in fewer side effects (burns, scarring) than EBRT Table 3, quote 5. Decliners also acknowledged the belief that cryotherapy involved fewer and shorter-lived side effects than EBRT. EBRT, accessible via non RCT participation, was desired for being the "proven and accepted method", the method friends had chosen, the method they felt most comfortable with, and accepted side effects of EBRT as being nothing more than a nuisance.

TABLE 4. Discussion: patient comments about cryotherapy

Accepters

1. Mr. Edwards: "Yes, I would have picked that [cryotherapy if available outside RCT]. It would have been my first choice"
2. Mr. Peters: "I could have lived with the radiation side too although I felt better ending up with the cryosurgery because that seemed to be just the best of all worlds and it works really well"
3. Mr. Sampson: "But like I say I became very adamant about having the cryosurgery ... because like I said before I had read so much about it, talked to my brother-in-law, talked to other people who had, had it done and I figured that was the way"

Decliners

4. Mr. Davis: "The cryo I wasn't sure of it. It somehow didn't appeal to me"
5. Mr. Galbraith: "I think actually what made my decision first of all I decided that I was not going to do the cryo. I can't really tell you why I just didn't like it that much"
6. Mr. Wright: "The one thing that maybe was questionable was the fact that the long term results and evidence set up for cryosurgery wasn't there so therefore you were trying something new and there was risk involved in it that maybe you wouldn't have with surgery and even radiation"

While cryotherapy may have shorter lived and fewer side effects it does have one major shortcoming raised by our patient sample as a legitimate concern - the near universal side effect of impotence. For one decliner this was the primary reason for choosing EBRT outside the RCT while for one accepter, a married informant, this was not perceived as the end of the world as he and his wife had enjoyed many years of intimacy. However, if cryotherapy had the same side effect profile as EBRT, including increased erectile function maintenance rates, then he would have preferred cryotherapy because of its speed.

Discussion

RCTs are a necessary part of the objective evaluation of different treatments and serve to improve patient care. The decision to participate in RCTs can be difficult and involves personal, physician, trial and treatment considerations. Personal reflection involved time collecting and reviewing information about prostate cancer treatments; talking with family, friends, cancer patients, and their physician(s); and reflecting on RCT participation for altruistic reasons. Physician, trial and treatment considerations factoring into the decision included the patient-physician rapport, understanding of RCT process, convenience of RCT participation, and perceived side effects and expected outcome.

All accepters reported their predilection for receiving cryotherapy as the primary reason for RCT participation Table 4, quote 1. Had cryotherapy been

available off study, RCT participation would most likely have been compromised. Subsequent randomization into the EBRT arm was perceived as a consolation prize. Some accepters used the RCT as a means of avoiding other treatments such as chemotherapy and surgery Table 4, quote 2. Inclination for cryotherapy included short treatment and recovery time, therapy convenience, increased post-op follow-up, success of cryotherapy to date, and altruistic reasons Table 4, quote 3.

Conversely, decliners cited they were not comfortable undergoing experimental therapy and held the belief that a treatment other than cryotherapy was preferable Table 4, quote 4. Known and unknown side effects of cryotherapy (including the high incidence of erectile dysfunction) and the lack of long-term data to support cryotherapy deterred several men from RCT participation. The concern existed among decliners that if the RCT is a means for showing that cryotherapy is "only as good as" a tried and tested treatment such as EBRT or surgery then there has to be other benefits in order for them to participate.

The depth and breadth of information that patients required to make their decision varied greatly. Some patients formed an opinion based on minimal knowledge while others researched treatments thoroughly. In general, those patients who collected minimal information tended to decline participation in the clinical trial, basing their decision primarily on instinctive feelings Table 4, quote 5. It may be hypothesized that these patients were more

comfortable with traditional treatments on the basis that experimental treatments equate to reduced efficacy and safety. Decliners were content receiving traditional therapies they felt were proven, and therefore superior Table 4, quote 6. Consequently, they tended to develop bias by focusing on the benefits of conventional therapies and negative effects of experimental treatments. This is one of the largest barriers that research trial accrual must overcome.

Ultimately, both accepters and decliners shared the same primary concern - to select a treatment that would "cure the problem" and allow them to "walk and talk". Health care providers can improve patient accrual by providing concise information about trial treatment options in common language. This should include treatment benefits, (inconvenience, potential side effects and long-term results of trial treatment. They may also encourage patients to talk with others who have taken part in RCTs. Finally, the significance of physician rapport with patients should not be underestimated. Spending time with potential patients, making their acquaintance and answering their questions may prove invaluable at increasing recruitment rates. □

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