Presenting Treatment Options to Men with Clinically Localized Prostate Cancer: The Acceptability of Active Surveillance/Monitoring

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Presenting treatment options to men with localized prostate cancer is difficult because of the lack of definitive evidence and the range of treatment options available. Active surveillance and monitoring programs are now a recognized treatment option for men with low-risk localized prostate cancer, but many patients are not fully aware of the details of such programs, and most still opt for immediate radical (surgery or radiotherapy) treatment. The provision of high-quality information with decision aids has been shown to increase the acceptability of active surveillance/monitoring programs. This chapter outlines techniques for providing high-quality information about active surveillance/monitoring, based on the findings of a randomized controlled trial of treatments for localized prostate cancer. The ProtecT (Prostate testing for cancer and Treatment) trial has randomized over 1500 men between active monitoring, radical surgery, and radical radiotherapy by ensuring that information was tailored to men’s existing knowledge and views. Care was taken with the content, order, and enthusiasm of the presentation of treatments by recruitment staff, and clinicians and other health professionals were supported to feel comfortable with being open about the uncertainties in the evidence and helped to rephrase terminology likely to be misinterpreted by patients. These techniques of information provision should be added to the use of decision aids to enable patients diagnosed with clinically localized prostate cancer in routine practice to reach well-informed and reasoned decisions about their treatment, including full consideration of active surveillance and monitoring programs.

Treatment options for men diagnosed with clinically localized prostate cancer were transformed after the introduction of prostate-specific antigen (PSA) testing in the mid-1980s. As the incidence of prostate cancer rose steeply, so did rates of radical treatment, with radical prostatectomy rising to be the treatment of choice for 30% of incident cases in the United States by 1990 (1). During these two decades, clinicians in the United States and the United Kingdom increasingly recommended radical interventions to patients: Urologists favored radical surgery, and radiation oncologists preferred radiotherapy (2–4). Watchful waiting was recommended mainly for older men and those with shorter life expectancies. By the turn of the century, however, concerns began to be raised about whether the strategy of intensive detection and immediate radical intervention was leading to overdiagnosis of prostate cancer were transformed after the introduction of prostate-specific antigen (PSA) testing in the mid-1980s. As the incidence of prostate cancer rose steeply, so did rates of radical treatment, with radical prostatectomy rising to be the treatment of choice for 30% of incident cases in the United States by 1990 (1). During these two decades, clinicians in the United States and the United Kingdom increasingly recommended radical interventions to patients: Urologists favored radical surgery, and radiation oncologists preferred radiotherapy (2–4). Watchful waiting was recommended mainly for older men and those with shorter life expectancies. By the turn of the century, however, concerns began to be raised about whether the strategy of intensive detection and immediate radical intervention was leading to overdiagnosis of prostate cancer could itself be stratified into different levels of risk (11), with the implication that treatment intensity might also be stratified or individualized. Around the mid-2000s, interest focused on opportunities to avoid immediate radical treatment, and several definitions of “no immediate intervention” emerged, ranging from “watchful waiting” (symptomatic management for those unsuitable for more radical treatment) to a range of active monitoring or surveillance programs with varying degrees of delayed radical intervention and/or intensity of follow-up (12,13). As there was little evidence to guide them, several groups across the world developed a range of different protocols for monitoring and triggering treatment, which differ markedly according to initial inclusion/exclusion criteria, methods and intensity of follow-up, and triggers for intervention (12,14–16).

Inclusion criteria for surveillance and monitoring programs range from men simply defined with clinically localized disease to those with no evidence of Gleason pattern 4 or 5 disease, cancer only in a specified number of biopsy cores, or with a specified percentage of cancer involvement in any core—based on diagnostic biopsies ranging from six to 10 or 12 cores, applied once or more frequently. The surveillance schemes range from those just with regular PSA tests to repeated biopsy protocols and sometimes digital rectal examinations. The triggers for intervention range from unfavorable findings from rebiopsy to prespecified changes in PSA kinetics or patient request for radical treatment (12–14). Although there is evidence from findings based on over 2000 patients, 200 with...
over 10 years of follow-up, that prostate cancer mortality rates are extremely low under active surveillance programs (10,15,16), there remains little consensus about the content and process of the most effective active surveillance or monitoring program. Further research with large cohorts of patients is needed.

Considerable evidence has also been accumulating from randomized controlled trials (RCTs) of screening to support the use and further development of active surveillance and monitoring strategies. The publications from the Scandinavian SPCG-4 treatment trial (17), European Randomised study of Screening for Prostate Cancer (ERSPC) (18), and US Prostate, Lung, Colorectal, and Ovarian Cancer screening trial (PLCO) (19) added important information about screening for prostate cancer, but they did not resolve the key dilemma of how to balance detecting and treating life-threatening prostate cancer while avoiding overdiagnosis and unnecessary, potentially harmful treatment. A recent systematic review and meta-analysis confirmed that the combined evidence from these RCTs and other studies did not support routine prostate cancer screening (20), and the US Preventive Services Task Force systematic review further concluded that PSA-based screening resulted in no or only a small reduction in prostate cancer–specific mortality and is associated with harms related to evaluation and treatments, some of which may be unnecessary (21).

The ERSPC and PLCO trials were not designed to provide robust data about treatments following screening. The best-quality evidence available about the most appropriate treatment for localized prostate cancer diagnosed mostly without PSA testing comes from the Scandinavian SPCG-4 trial that compared radical open prostatectomy and watchful waiting and found a clear benefit in terms of mortality and metastases from radical surgery but with considerable impact on quality of life (17,22). However, the relevance of the findings of SPCG-4 for patients now diagnosed with much smaller PSA-detected localized prostate tumors and those contemplating to undergo today’s much more “active” surveillance and monitoring protocols or minimally invasive surgery is difficult to determine.

RCTs of treatments for prostate cancer have proved difficult to mount in the PSA era, but two have now completed recruitment. The US Prostate Cancer Intervention Versus Observation (PIVOT) trial compared radical prostatectomy with a passive watchful waiting strategy for men with PSA-detected clinically localized prostate cancer (23). Although the trial has not yet been formally published, it has been reported that with a median follow-up of 10 years, there were no statistically significant differences in prostate cancer mortality or all-cause mortality between the arms (24). The PIVOT trial did not include an active surveillance program; patients were randomized to a watchful waiting strategy that discouraged review of PSA results, rebiopsy, or the use of radical interventions. The PIVOT trial will thus provide a comparison between radical surgery and no intervention, not active surveillance or monitoring.

There is one RCT currently underway that has included an active monitoring arm for men with clinically localized prostate cancer detected exclusively through population-based PSA testing. The Prostate testing for Cancer and Treatment (ProtecT) trial has enrolled over 3000 men aged 50–69 years with PSA-detected, standardized 10-core biopsy-confirmed, clinically localized prostate cancer, and it compares radical prostatectomy, radical conformal radiotherapy, and active monitoring (25). At the outset, it was anticipated that it would be a difficult trial for recruitment, and so the ProtecT trial included an integrated program of research to explore the feasibility of mounting such a trial, focusing particularly on the presentation and interpretation of treatments by clinicians (urologists, oncologists, and nurses) and patients involved in it (26). The findings of the research about the presentation of these diverse treatments are described below as they illustrate a number of factors that can influence the acceptability of treatment options such as active monitoring or surveillance within RCTs and routine clinical practice.

The Presentation of Treatment Options in the ProtecT Trial: Methods and Results

When the ProtecT trial was initiated in 1999, there were few who believed that men with PSA-detected prostate cancer (and their clinicians) would agree to randomization between radical surgery, radical conformal radiotherapy, and a conservative (no immediate intervention, active monitoring) arm. As a consequence, a feasibility study was undertaken with a nested RCT to investigate recruitment strategies and qualitative research to explore the recruitment process and the acceptability of the proposed three-arm RCT design (27). The nested RCT of recruitment strategies was based on 167 men aged 50–69 years with clinically localized prostate cancer detected following population-based PSA testing. One-hundred fifty (90%) agreed to be randomized to see either a nurse or urologist for an appointment during which they were given information about the ProtecT treatment trial and asked if they would consent to participate. Overall, 103 (69%) agreed to be randomized between treatments, the vast majority in the three-arm comparison (26). There was a minimal (4%) difference between nurses and urologists in recruitment rates to the ProtecT treatment trial (nurses 67%, urologists 71%, 95% CI = 10.8 to 18.8, P = .60) (27). The nested RCT showed that nurses were as effective at recruiting eligible participants as urologists, and an economic evaluation indicated that they were less expensive to employ (27).

The qualitative research used research methods from the social sciences and embedded these within the feasibility study and nested RCT of recruitment strategies (28). Interviews were conducted with 1) patients who were potential and actual participants in the ProtecT RCT and 2) clinical staff undertaking recruitment (urologists, oncologists, and nurses).

These interviews were analyzed using standard qualitative techniques including content and thematic approaches (29,30). Interviews were fully transcribed, and the content was scrutinized and coded, identifying similarities and differences, and the findings were summarized into themes. These thematic data were combined with findings from a more innovative methodological approach using techniques drawn from conversation analysis, a qualitative method to investigate interactions between patients and health-care professionals (31). These techniques were used in a targeted way to analyze particular sections of the recruitment appointments to investigate the acceptability of the information presented about the ProtecT RCT and reasons for any problematic communication (28).
The qualitative investigation provided evidence about participating clinicians’ views about the design and conduct of the RCT, the acceptability of the study information by urologists and nurses, and the interpretation of written and verbal study information by patient participants. The study information (written patient information sheets and a checklist of topics to be presented verbally by recruiters) was approved by the ProtecT trial management group and ethics committees. In the first few months of recruitment, most patients rejected randomization and opted for radical surgery (28). Detailed scrutiny of the audio recordings of recruitment appointments showed that surgery was usually presented first and in considerably greater detail and with more enthusiasm than radiotherapy (which was usually presented second); the arm that should have been described as “conservative management with regular PSA tests” was usually called “watchful waiting” and was usually described without detail or enthusiasm, and also as being most appropriate for men with short life expectancies (28). In their interviews, many men made it clear that they greatly feared cancer, and as asymptomatic and fit men aged 50–69 years, they felt that the way “watchful waiting” was described made it sound like a passive “no treatment” option, which seemed rather negligent compared with the radical interventions. One patient stated dramatically, “Watchful waiting? That’s not a treatment...it’s where you watch and I die” (28).

It was also clear that these men had not gained a detailed understanding of the rationale for the treatment trial or the purpose of the randomized design. In their interviews, they explained that they were confused about terms such as “trial” and “random” that had particular “lay” meanings. The term “random,” for example, was interpreted as “haphazard” or “chaotic,” and thus unscientific—the very opposite of the image that an RCT is attempting to convey (28). In these early appointments, as the recruiters talked most clearly and enthusiastically about surgery, patients tended to respond, not surprisingly, by expressing a preference for surgery and rejecting randomization (28).

The ProtecT trial management group (including urologists, oncologists, and trialists) responded quickly. The protocol for the conservative arm was refined and renamed “active monitoring” to reflect the regular PSA tests and review appointments that were undertaken (30).

PSA tests were to be undertaken 3–6 monthly in the first year, extending to 6-monthly or annually thereafter. The trigger for reevaluation of disease status was defined, according to best practice at the time (2000–2001), as an increase in PSA level of 50% or more over 12 months, with that rise confirmed by a subsequent PSA test, or symptoms or other clinical findings of concern to patient or clinician (26). Routine rebiopsy was not recommended, although its use in active surveillance programs was explained, alongside the difficulties of interpreting sampling errors and possible adverse effects. It was decided that the active monitoring option should be presented first so that it was fully explained. In addition, the findings from the qualitative analysis were presented to recruiters with clear suggestions about how to 1) avoid terminology that was misunderstood by patients, 2) provide balanced information about each of the treatments, and 3) describe the purpose of randomization and rationale for the ProtecT RCT (32).

The changes had a rapid and consistent impact on the order and content of the verbal information presented in the appointments and the outcome in terms of randomization. Active monitoring was presented first in most cases, the need for the RCT was described more clearly, the treatments were presented more equivalently, and problematic terminology was avoided or explained. Over the next 9 months, the numbers of men agreeing to randomization rose from 40% to 70% of eligible participants (28). The three-arm RCT including both radical treatments and active monitoring became the design for the full-scale ProtecT trial, with nurse-led recruitment. With continued support from the qualitative research, recruitment to the full-scale three-arm treatment trial was completed with over 60% of eligible participants consenting to randomization (32). The ProtecT trial will report its primary outcomes in 2015 or 2016, based on over 1500 randomized participants (25).

**Presenting Treatment Options in Routine Clinical Practice**

The recent National Institutes of Health Active Surveillance State-of-the-Science draft report stated that “Active Surveillance is a viable option that should be offered to patients with low-risk prostate cancer” (24). The completion of recruitment to the ProtecT trial and the increasing numbers of men joining contemporary active surveillance/monitoring cohorts show that this option is acceptable to patients and clinicians if they are informed about it. But there is little guidance about how treatment options for localized prostate cancer are best presented to patients. It is most commonly advocated that decision making should be shared by patients and clinicians (33,34). However, there is considerable evidence that men are poorly informed about the issues inherent in screening and treatment for prostate cancer. For example, the DECISIONS study systematically assessed medical decision making for prostate cancer screening in a survey of a random sample of over 3000 US adults and showed that the majority of prostate cancer decisions were not shared because participants did not receive balanced information, had limited knowledge, and were not routinely asked about their own preferences (35). There is evidence that levels of information can be improved and that decisions about treatments can be made more effective through the use of decision aids. A systematic review of trials of decision aids for prostate cancer screening, including 18 eligible trials involving over 6000 participants, showed that patient knowledge was enhanced, decisional conflict was reduced, and informed decision making was promoted in the presence of such aids (36). This study also showed that the decision aids reduced interest in PSA testing and encouraged preferences for watchful waiting as a treatment option (RR = 1.53, CI = 1.31 to 1.77, P < .001). This suggests that the provision of good-quality information can enable men to consider nonradical options.

Although there is much research advocating shared decision making and a great deal of patient-directed information about prostate cancer screening and treatment, little is known about how men develop preferences for particular treatments or how such treatments should be presented to achieve high levels of understanding. Various nomograms and algorithms can indicate probabilities of the occurrence of some of the risks, and decision aids may provide detailed information, but for any single patient the
essential dilemma of having to make a choice between treatments without robust evidence remains, often causing considerable anxiety (37,38).

In the ProtecT trial, it was possible to study in detail how men's preferences for prostate cancer treatments were expressed and the role they played in recruitment (39). The theoretical literature divides into two opposite views: either that preferences are complex and multifaceted psychological phenomena that are difficult to measure (40) or that they are a simple indication of a patient's view, easily captured by very simple single-item measures (41). We set out to investigate treatment preferences in consecutive recruitment appointments in eight ProtecT RCT clinical centers over a 3-month period (n = 93). Appointments were audiorecorded, and an experienced qualitative researcher documented when treatment preferences were expressed, their content, and how they were justified (39). Most men (69%) expressed views about treatments, ranging from clear requests to have a particular treatment to rather hesitant and more general views about fears related to cancer or side effects of surgery or radiotherapy. Their preferences and views were informed by the information they had available to them from friends, relatives, media of various sorts including the Internet, and the recommendation of health professionals (particularly general practitioners), and their own specific concerns emerging from their or others' experiences (39).

It is often stated that patients' preferences are a clear (and usually insurmountable) barrier to RCT recruitment because once patients have indicated their view, they should be enabled to receive it outside the trial (41). In this study, 29 of 93 men (31%) did not express a treatment preference, and 28 of them agreed to be randomized. In many RCTs, the remaining 64 (69%) could have been encouraged to receive their initial treatment preference. However, the ProtecT trial recruiters were trained to acknowledge the men's initial views but then to go on to explore the reasons underlying their treatment preferences. They then provided the men with details about the treatments and the rationale for the ProtecT RCT. They only sought consent for randomization when a man expressed ambivalence (42). Of the 64 men who expressed an initial treatment preference, 16 (25%) opted to have treatment outside the RCT (39). The other 48 became ambivalent during the appointment, and 38 (59%) consented to randomization, often accepting a treatment different from their original "preference." The remaining 10 men declined randomization, but only two opted for the treatment they had initially preferred. In summary, of the 93 men included in the substudy, 24 (26%) chose a treatment outside the RCT and 69 (74%) consented to be randomized (39).

This first empirical study of the definition and basis of treatment preferences has shown that patients' initially expressed treatment preferences may not in many cases be fully informed and that further discussion and provision of information may enable greater levels of participation in RCTs (39). It suggests that patients' views should always be acknowledged and respected, and those with well-informed views should receive the treatment of their choice, but that it is also essential to inform patients fully about details of treatments to ensure that they have the opportunity to participate in RCTs and consider all available treatments in routine clinical practice. This finding is likely to be particularly important for active surveillance/monitoring programs for several reasons. Active monitoring and surveillance programs are much less well known to the public and are advertised less aggressively than radical treatments, so they have a limited Web and media presence. Individuals may need more detailed explanations to counter prevalent lay fears about cancer that tend to encourage surgical removal. It is also likely, from evidence from the ProtecT study and elsewhere (3,4,28,34) that some (perhaps many) surgeons and oncologists will find it difficult to present active monitoring or surveillance in terms equivalent to those of the radical treatments they have previously recommended.

The key to enabling ProtecT trial participants to agree to be randomized between such different treatment options was the careful presentation of the evidence and the participants' engagement with the design of the trial (29,30). In the early stages of the RCT, recruiters found it difficult not to favor the surgical treatment that they had been recommending to patients for many years, but they gradually became better able to acknowledge that each of the treatments had advantages and disadvantages and that the RCT provided the best way to avoid patients struggling with the treatment dilemma in future (32). With discussion and support, recruiters (clinicians and nurses) became more comfortable with explaining other treatments and their own uncertainty. One urologist midway through the ProtecT RCT said, “It used to be not the thing for a surgeon in the beginning to say, uncertainty, and in fact I had a phase where I was very uncomfortable... But increasingly I have now become much more open...I say, ‘I do not know. I wish I had the answers, but no, I don’t.’ So being undecided used to be an uncomfortable feeling, but now, yes, it's become part and parcel of it.”

Learning to present treatments in an unbiased manner can be difficult for clinicians, particularly when they are committed to their specialties. It is well documented and not surprising that specialists tend to recommend their preferred treatments to patients in clinical practice (2–4). In many cases, the clinicians involved in the ProtecT RCT were unaware of the impact that their presentation of treatments could have, and it is likely that many clinicians in routine practice unwittingly influence patients' treatment decisions. For example, as noted by a urologist early in the ProtecT RCT, it would seem difficult for the patient not to agree to have surgery, “There's a proportion of patients who will say to me, 'What do you think, Doctor?' And in that situation, I think my gut feeling is important. I always tell them I wouldn't have become a surgeon if I thought another form of therapy was the best form of therapy.”

**Conclusion**

There remain very many uncertainties about the optimal treatment for men with low-risk PSA-detected prostate cancer. The evidence so far from cohorts of men undergoing active monitoring or surveillance programs is that they are at very low risk of dying from prostate cancer (15). A major limitation of current programs of active monitoring or surveillance is that they lack validation and standardization of their methods to select, monitor, and trigger change of treatment (24). The wide diversity of programs will yield important data about these aspects, but until diagnostic and monitoring tools or new biomarkers provide greater discriminatory power between stable and aggressively progressing disease, only time and further research will tell which of the strategies will
deliver the greatest levels of patient and population benefit. Until this urgently needed research is completed, patients will have to continue to face the very real and difficult dilemma of having to weigh up the risks of immediate radical intervention with the potential for cure but also adverse events versus the opportunity through active monitoring or surveillance to avoid the risks of immediate radical intervention but undergo regular tests that may or may not lead to more treatment in older age. In the meantime, it is important to provide the best possible information for men considering PSA testing or diagnosed with localized prostate cancer. Those providing the information need to be aware that it should be tailored to men’s knowledge and views and presented with care because of the influence of the order and enthusiasm of presentation by health professionals, use of terminology, and openness about areas and levels of uncertainty.

References


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