Editorial

Impact on quality of life of different treatments for localised prostate cancer: insights from the PROTECT trial

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Men who are diagnosed with localised prostate cancer are often faced with difficult treatment decisions. If they have a good life expectancy, they will generally need to choose between surgery, radiotherapy, and surveillance. Studies on prostate cancer therapy have to date not shown clear superiority of any of these treatment approaches in appropriately selected patients, with all being effective and safe. Men with low risk disease have less than 2% 10-year cancer-specific mortality, whichever approach they choose (1-3). The risk profile of the tumour and the co-morbidities of the patient have often been used to help make the choice, based on likelihood of cure with each approach. A patient who is given balanced counselling on management options for their prostate cancer usually has to choose between the different options based more on the expected adverse effects of each of the treatments, rather than overall cancer controlling efficacy of those treatments. While the oncological efficacy of radical prostatectomy, external beam radiotherapy, active surveillance, and other treatment modalities are well documented in randomised trials and long running case series, the adverse effects of these treatments are not as well characterised. For one, these adverse effects are usually listed as symptoms and complications that the participants had experienced. Reported rates and severity of adverse effects vary considerably between studies, and the impact on quality of life and overall functioning is rarely well studied. Studies that have examined these, such as the European Randomised Study on Screening for Prostate Cancer (ERSPC), have generally relied on retrospective recall of baseline functioning and subjective estimation of changes (4). Active surveillance is an approach that is advocated by many as a way of reducing negative impact of radical treatment on a man's quality of life. However, surveillance can also reduce quality of life due to anxiety, more intensive follow-up, and repeated investigations. AS has also not been directly compared with the other main treatment modalities in a large clinical trial. Furthermore, comparing adverse effects and quality of life outcomes between studies is not valid because of differences in study populations, outcome measures used, and multiple potential sources of bias within each study. It has therefore been difficult for patients and clinicians to fully understand what impact each of the treatment options has on a man's overall quality of life. The strong push against screening for prostate cancer by various groups around the world has stemmed largely from the assumption that the average man who is diagnosed with prostate cancer and undergoes treatment suffers a drop in quality of life that is not compensated for by his small reduction in mortality. This assumption is also not based on the highest level of evidence. To date, radical prostatectomy and external beam radiotherapy have never been successfully compared in a randomised controlled trial, despite both treatments having been performed on millions of men worldwide. Active surveillance, while shown to be safe in numerous large, long-running case series has also never been directly compared to radical treatment in a clinical trial.

The PROTECT trial, conducted in the United Kingdom, randomised 1643 men with screen-detected low and intermediate risk localised prostate cancer between 1999 and 2009 to receive radical prostatectomy (553 men),

external beam radiotherapy (545 men), or active surveillance (545 men). Early results were recently published in the *New England Journal* of Medicine by Hamdy *et al.* (5). The majority had Gleason 6 tumours (77%) and clinical stage T1c disease (76%). The number of men who received their assigned treatment within 9 months was 71%, 74%, and 88%, in the surgery, radiotherapy, and surveillance groups, respectively. After 10-year follow-up, there were 17 deaths due to prostate cancer (1% of the cohort), with no significant differences between the groups. There was, however, a significantly higher incidence of metastatic disease among patients in the active monitoring group compared to the surgery and radiotherapy groups (33, 13, and 16 cases, respectively; P=0.004).

PROTECT is the first trial to successfully compare two radical treatments for prostate cancer, and the first to compare active surveillance to radical treatment. Another unique aspect of this trial is in the design. The designers' intention was to fully document the impact that the treatments had on these men. This meant that not only were disease-related outcomes to be reported, but also careful documentation of the men's side effects, as well as their overall impact on general well-being and quality of life. Since the majority of the men enrolled in the trial had low risk prostate cancer and because follow-up is still relatively early, it is hardly surprising that there has not yet been any significant difference in mortality. It could be argued that the companion article by Donovan *et al.* (6) that was published in the same issue is at this point a more important contribution to the literature. The article reported the adverse effects and quality of life impact experienced by the men enrolled on the trial. These were broken down into four domains, namely urinary function, sexual function, bowel function, and health-related quality of life. Importantly, the investigators used validated questionnaires that not only quantified morbidity, but also assessed the impact of those symptoms on quality of life. Scores were obtained at baseline before randomisation and repeated at six months, twelve months, then annually throughout follow-up. Perhaps not surprisingly, men who underwent radical prostatectomy had the highest rates of erectile dysfunction and urinary incontinence, while the men who underwent radiotherapy had higher rates of bowel dysfunction. Active surveillance showed some protection against these side-effects, but most of this protection was within the first 3 years after diagnosis. Men initially assigned to the active surveillance group developed increasing rates of impotence (and other symptoms) as more of them received radical surgery or radiotherapy prompted by disease progression. There were no differences between the groups in overall physical health, mental health, anxiety, or depression scores.

Clinical trials in prostate cancer treatment are by necessity of long duration. This means that significant new developments in therapy are often not reflected in the trials. The authors acknowledge in their discussion that technologies such as intensity modulated radiotherapy and robotic-assisted radical prostatectomy might have had different side-effect profiles. The protocol used for active surveillance in this study differs in many ways to what is currently recommended. Follow-up was with digital rectal examination and PSA measurement, with no routine repeat biopsy. Men managed in such a manner could plausibly have different anxiety, depression, or other quality of life scores compared to men managed in a more contemporary way. Perhaps what this study lacks is an indication of the participants' overall perception of their prostate cancer treatment. A final qualitative question such as whether these men would choose to undergo the same treatment again, or if they would recommend it to a friend, would have been helpful.

Ultimately, clinical trials should be performed for our patients. The questions that we answer should be pertinent to our patients' needs. This study will assist men to understand the impact of the respective treatments for prostate cancer in a more holistic way, and to choose the one that most suits them.

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Footnote

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