Comment

‘ProtecTion’ from overtreatment: does a randomized trial finally answer the key question in localized prostate cancer?

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For the first time we now have a randomized trial comparing active monitoring, surgery and radiation therapy for the management of localized prostate cancer, and the investigators are to be congratulated on their highly anticipated landmark study, the Prostate testing for cancer and Treatment (ProtecT) trial [1]. Comparing 545 patients randomized to active monitoring, 553 to radical prostatectomy and 545 to radiotherapy, at a median follow-up of 10 years, the study reports no significant difference in prostate-cancer specific or overall survival among the three groups [1]. Whilst this is being cited by some as compelling evidence that radiation offers equal treatment efficacy to surgery, it is at odds with the multitude of observational data and the recent meta-analysis by Wallis et al. [2], which suggest otherwise. It is important to recognize that it is often difficult for observational studies to account for all bias and confounders, which are better controlled for in a randomized trial, but why does this discrepancy in outcome analysis exist and can we extrapolate the ProtecT findings to contemporary cohorts undergoing treatment for prostate cancer?

As stated by the ProtecT investigators, there are several limitations in regards to recruitment for the study [1]. A key shortcoming is the fact that patients with low-risk cancer dominated the cohort (77% with Gleason score 6). Whilst it is appreciated that among the patients randomized to radical prostatectomy, 29% were subsequently upgraded or upstaged on final pathology, this finding is consistent with that regularly reported in the literature when biopsy and final pathology are compared, and the patients in ProtecT remain a largely low-risk population in an ‘intention-to-treat’ analysis. The sample size was calculated based on the estimate of 10% prostate cancer mortality in the active monitoring group, but the patient characteristics of the ProtecT trial saw fewer mortality events occur than expected (~1% and 17 in total). This is a somewhat interim analysis, therefore, and further follow-up will be needed to determine whether survival curves separate over time. Given that a similar population in the PIVOT trial [3], randomized to surgery or observation, failed to demonstrate a benefit of active treatment in such men, it is unsurprising that a comparison of active treatments in ProtecT likewise shows no difference in survival at this time interval. As a result, the study confirms the evidence supporting conservative management of low-risk prostate cancer but inadequately addresses treatment efficacy in patients with intermediate- to high-risk disease, who make up an increasingly greater proportion of treatment groups [4]. Given the significant risk of disease progression and post-treatment recurrence in patients with higher-risk disease, it is dangerous to extrapolate ProtecT’s findings to these men. We are left no better off as to whether surgery or radiation offers an advantage as the first step in the treatment algorithm of a contemporary cohort.

Furthermore, the active monitoring protocol in the study differs greatly from contemporary practice. Given the inclusion of patients with intermediate- and high-risk prostate cancers in the active monitoring arm of the study, and the relatively lax monitoring protocol, the higher rate of disease progression in the active monitoring cohort is unsurprising. This reiterates the need for accurate assessment of risk and appropriate monitoring protocols that not only include PSA checks but also regular DRE and repeat biopsies. Also of note was the fact that more accurate diagnostic tools such as transperineal biopsy and MRI were not part of the trial. One may suggest that the rate of metastasis might have been lower in the ‘active monitoring’ group if patients were selected and monitored in line with contemporary protocols.
Advances in treatment methods during the follow-up period of the trial also preclude an accurate representation of the current landscape. Radiotherapy has shifted from three-dimensional conformal radiotherapy to brachytherapy and intensity-modulated radiotherapy. The increasing use of neoadjuvant and adjuvant androgen deprivation therapy with radiotherapy adds another layer of complexity in terms of side effect comparisons, and therefore radiation therapy is compared as combination treatment with surgery as monotherapy. Radical surgery has also evolved with advances in laparoscopic and robotic techniques that were not included in the trial.

By comparison, in their recent meta-analysis, Wallis et al. [2] gathered quality observational data and concluded that radiotherapy for prostate cancer is associated with an increased risk of overall and prostate cancer-specific mortality compared with surgery. A total of 19 studies of low to moderate risk of bias involving up to 118 830 patients were pooled, and consistent outcome measures were used, incorporating time-to-event data and adjustment for known confounders. Whilst the randomized data of ProtecT present high-level evidence (albeit with low event numbers) to counsel patients with low- to intermediate-risk disease, this meta-analysis represents a comprehensive review that can be used to estimate treatment benefits in all cancer risk groups.

When comparing complication rates between the two active treatments, the accompanying manuscript reported worse voiding and bowel symptoms among patients who had undergone radiotherapy and worse urinary incontinence and erectile function in those who underwent surgery [5]. These are important findings about which patients should be made aware when considering treatment options, although the positive margin rates as a ‘key performance indicator’ of the quality of surgery in this trial are unexpectedly high when compared with current published series, including the recent randomized Brisbane trial of robot-assisted vs open radical prostatectomy [6].

Lastly, despite an ideal study design, ProtecT did not demonstrate the long-term complications seen in other observational series. In a paper published in The Lancet that examined the 5-year cumulative incidence of complications after prostate cancer treatment, Nam et al. [7] reported that patients who underwent radiotherapy were at an increased risk of hospital admission, undergoing rectal or anal procedure, requiring open surgical procedures and developing a secondary malignancy than those men who were treated with surgery. Additionally, it has been shown that complications after radiotherapy increase over time (with findings then reproduced using Surveillance Epidemiology and End Results data from the USA) and thus it is expected that longer follow-up will shed more light on whether these observational series are misleading, or whether more complications will become evident in the ProtecT population [8].

The ProtecT team are to be congratulated and acknowledged for their tremendous effort. Recruitment obstacles, along with constant advances in prostate cancer treatment and greater use of surveillance in low-risk patients, have, however, challenged the ability of long-term randomized controlled trials to assess treatment efficacy adequately. As such, the utilization of observational data continues to be important in current times.

Conflict of Interest
None declared.

References

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