Response to Letter to the Editor by Greg Shaw, Monique Roobol and John Kelly: EURUROL-D-23-01005

We thank the authors for their comments. Their concerns about the ProtecT trial are unfounded, largely due to misunderstandings about the trial design and published data.

ProtecT is a trial of treatment effectiveness for screen-detected localized prostate cancer[1] - not a trial of screening. Patients included in ProtecT had to be diagnosed with clinically localised prostate cancer and be eligible for prostatectomy, radiotherapy, or active monitoring – not just AM as Shaw et al suggest.

The authors claim that men with locally advanced cancers were ”unaccounted for”, but this is incorrect as we reported separately on this group.[2] In fact, because ProtecT was designed as a comprehensive cohort study, characteristics of all patients diagnosed with prostate cancer, including those excluded or not randomised, were reported on.[3] Further, ProtecT represents the intervention arm of the Cluster Randomised Trial of Prostate Cancer screening (CAP), in which the characteristics of all men invited to PSA testing were documented, irrespective of their inclusion into ProtecT.[4] The CAP prostate cancer screening trial published its median 10-year outcomes in 2018,[5] and publication of the median 15-year analysis is imminent. Unlike most screening and treatment trials, ProtecT and CAP have transparently published data on all men invited to and attending PSA testing, as well as those subsequently diagnosed with prostate cancer and receiving treatment.

The authors expressed concern about selection bias related to patients who underwent a treatment different to the one they were assigned to. However, changes of management do not introduce selection biases. The intention-to-treat analysis avoids such biases and reflects what happens in real life - that some men may not take up their treatment allocation. We have reported in detail on the patients who declined randomisation and changed management. In ProtecT, acceptance of allocation was 84% for active monitoring, 72% for surgery, and 77% for radiotherapy. In a trial comparing such different interventions, it is inevitable that some participants will not agree to be randomised, and we kept this to a minimum.[6] We also showed that men who changed management were very similar to those who accepted their allocation.[7]

The authors suggest that the active monitoring approach used in ProtecT was not contemporary and novel protocols are safer. However, this is not substantiated by evidence. Despite our perceived “outdated” active monitoring protocol, we have not demonstrated differences in disease-specific or overall mortality, and the reduction in metastases in favour of radical treatments was from 10% with active monitoring to 5% with radical treatment. We do agree with the authors that the remarkable long survival observed in ProtecT is at least partly due to recent advances with novel hormonal chemotherapeutic regimens.

The authors request a ‘treatment received’ analysis. This was published with a 10-year median follow-up and did not differ from the main trial result.[8]

Finally, although ProtecT is not a trial of screening, put together, the ProtecT and CAP findings do not support the principle of population screening for prostate cancer, which we know at present will cause more harm than benefit.

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Letter in word

"We read with interest the outcomes from the ProtecT study observed 15 yr after population-based prostate-specific antigen (PSA) screening for 1643 men diagnosed with prostate cancer (PC) and randomised to active monitoring (AM; n = 545), surgery (n = 553), or radiotherapy (n = 545) [1].

We are concerned that an unaccounted cohort of 492 men who were excluded from the randomisation because they were deemed unsuitable for AM (locally advanced PC, PSA >20 ng/ml, metastases, or other factors) have been ignored [2]. The 10-yr survival rate for this group is 75%, so the data presented do not describe outcomes for patients diagnosed with PC via population-based PSA screening; instead, they describe outcomes for patients diagnosed via-population based PSA screening who were deemed suitable for AM at diagnosis.

Population-based PSA screening results in early PC detection. The long natural history of slow-growing tumours results in disproportionate diagnosis of low-risk PC via screening. Draisma and De Koning [3] modelled a mean lead-time estimates with PSA screening in the ERSPC study of 11–12 yr (longer for those aged <70 yr with low-/intermediate-risk disease). If cases with disease unsuitable for AM are excluded, the lead time is so long that very low PC mortality levels should hardly come as a surprise at 15-yr follow-up.

In addition, significant numbers of patients underwent treatments other than the one to which they were assigned; for example 20% of those assigned to surgery had AM, and 15% of those assigned to AM had radical treatment. Results for per-treatment analysis are not presented.

Despite the clear selection bias described, AM does seem to result in higher rates of clinical progression and systemic treatment. Some 21.4% of men in the AM arm developed clinical progression, compared to 8.0% in the surgery arm and 8.4% in the radiotherapy arm. Corresponding metastasis rates were 9.4%, 4.7%, and 5.0%, with long-term androgen deprivation therapy initiated in 12.7%, 7.2%, and 7.7%. It is possible that these risks are lower with modern active surveillance protocols, which would support conservative treatment for these men.

That these men are not dying from PC is probably due in part to novel hormonal and chemotherapeutic regimens. Male life expectancy is increasing; according to UK government data, the average male life expectancy at age 65 is 18.5 yr [4]. Quality of life (QOL) for patients is impaired by systemic therapy, including novel agents [5]. With patients living longer on systemic treatment with impaired QOL, the aspiration to help men avoid systemic treatment while treating significant disease remains an honourable one to which the urological and oncological communities continue to respond.

In conclusion, there is a danger in extrapolating findings beyond men diagnosed with PC via PSA screening deemed suitable for AM. AM for these patients, which does not reflect modern active surveillance practice, does not carry a substantial risk of death, but entails a substantial

risk of progression requiring chemical castration over 15 yr. The published data do not support any statement regarding the futility of the use of population-based PSA screening; for such a statement, all patients found to have PC via the ProtecT PSA screening programme would need to be included in the analysis. “