

The ProtecT study: what have we learnt?

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The recent publication of two articles on clinical and patient reported outcomes from the ProtecT study at an average 10-year follow up has provided new information for clinicians and patients, and a continuing challenge for researchers.^{1,2} With over three decades of prostate-specific antigen (PSA) testing leading to over-detection, over-treatment as well as under-treatment of prostate cancer, it has taken over twenty years from the late Geoff Chisholm's wise words in an editorial debating PSA in this very journal, to the delivery of the first results from this study – I quote:

*"So there is concern that while aggressive screening will find more prostate cancers, many of these early cancers are destined never to become clinically evident... Indeed until randomized trials are performed, we will not know if early detection with or without radical treatment improves cancer-specific survival... Other questions such as ... the difficulty in balancing benefits with adverse effects must be considered."*³

Such a trial was deemed impossible to conduct, particularly following the inability of the Medical Research Council prostate cancer randomized controlled trial PR06 to recruit in the early nineties, resulting in its closure in 1996. The conduct and success of ProtecT is a testimony of multidisciplinary teamwork, perseverance, and a privileged environment in the United Kingdom, with an extraordinary contribution from so many participants in the community, and support from the National Institute for Health Research Health Technology Assessment (HTA) Programme.

The interpretation of the ProtecT data in the medical community and public media has varied. The overarching news from ProtecT is good: men with PSA-detected clinically localized prostate cancer do well over a median of 10 years from diagnosis, with 99% survival rates irrespective of the treatment assigned; radical treatment of the disease is effective, reducing risk of progressing and metastases by half; and for the first time, a direct comparison between surgery and radiotherapy shows that both treatments are equally effective. The findings are complemented by a report on men with advanced prostate cancer excluded from ProtecT, and analysed separately, demonstrating also a low rate of prostate cancer-specific mortality with radical and non-radical treatments in men with PSA-detected cancers.⁴

But treatment of prostate cancer is not only about oncological outcomes. The publication in this issue of the British Journal of Urology International by Lane *et al* describes the baseline quality-of-life data and methodology used on the study cohort, with remarkable follow-up compliance.⁵ To collect rigorously and analyse outcomes reported by patients is no small task, and the full 6-year patient reported outcomes reported by Donovan *et al*², illustrates the powerful contribution of quality-of-life research in ProtecT. Patients and clinicians now have new high quality information to act on and use in making difficult decisions about treatment options, and in estimating the trade-off between reduction in disease progression and adverse events of treatments received.

And what about the question of screening and its effects, described by Chisholm in his editorial? ProtecT alone will not resolve the controversies.

Results from the Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP) will report in 2017 its outcomes on the effectiveness of a single PSA-testing programme in reducing prostate cancer-specific mortality. CAP, larger than the European Randomised Study of Prostate Cancer screening (ERSPC) and Prostate, Lung, Ovary and Colorectal (PLCO) screening studies combined, has been running in parallel with ProtecT. Primary care practices in the UK were randomly assigned to enroll participants in the intervention group (ProtecT), or to follow usual NHS care as the control group, receiving no formal PSA testing. The results will complement ProtecT findings on treatment effectiveness of PSA-testing.⁶

But the recent publications form only the first ‘chapter’ of the ProtecT story.

For treatment effectiveness, two major questions remain: 1] What is the ‘trade-off’ between *survival* gained from radical treatments, and the side-effects encountered by patients? – whilst the effectiveness of radical treatments has indeed demonstrated a reduction in metastases and disease progression, this has not translated at 10 years into a survival benefit. Longer follow-up of our cohorts will be essential for the next 5 to 10 years; and 2] Can we distinguish ‘lethal’ from ‘non-lethal’ prostate cancer by targeting men at risk, using a combination of sophisticated ‘liquid’ biopsy and other non-invasive tests such as imaging, to determine who needs tissue sampling, and post-biopsy by determining relevant molecular and genomic signatures in the prostate samples taken?

The ProtecT team will endeavour to produce and disseminate systematic analyses of our maturing data in the future, and to undertake a large-scale related translational research programme. Resolving these two remaining issues will produce a paradigm shift in the management of prostate cancer, and allow clinicians to deliver precision medicine to men at risk of harbouring this common and ubiquitous malignancy.

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2. Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med* 2016.
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4. Johnston TJ, Shaw GL, Lamb AD, et al. Mortality Among Men with Advanced Prostate Cancer Excluded from the ProtecT Trial. *Eur Urol* 2016.
5. Lane A, Metcalfe C, Young GJ, et al. Patient-reported outcomes in the ProtecT randomized trial of clinically localized prostate cancer treatments: study design, and baseline urinary, bowel and sexual function and quality of life. *BJU Int* 2016.
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