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Re: Fifteen-year Outcomes After Monitoring, Surgery, or Radiotherapy for Prostate Cancer

Hamdy FC, Donovan JL, Lane JA, et al.

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Experts' summary:

The ProtecT randomised controlled trial examined death from prostate cancer as the primary endpoint for three arms: an active monitoring (AM) arm, a radical prostatectomy (RP) arm, and a radical radiotherapy (RT) arm. The AM protocol mandated prostate-specific antigen (PSA) measurement every 3 months for 1 year and then every 6–12 months, with a 50% rise in PSA triggering clinical review.

At 15 years, among 1610 randomised men who completed follow-up and were included in the intention-to-treat analysis, the cancer-specific mortality rate was 2.7% (no difference between arms: AM 3.1% vs RP 2.2% vs RT 2.9%) and the all-cause mortality rate was 21.7%. The metastasis rate was 9.4% in the AM arm, double the rate for the radical treatment arms (RP 4.7%, RT 5%). Some 80% of the patients received their allocated radical treatment within 6 months. The AM crossover rate to radical treatment was 10% at 6 mo and 61% at 15 yr; 24.4% of the AM patients were alive without oncological treatments. Of the men who underwent RP within 12 months regardless of treatment allocation, 29% were upstaged to T3/4 and 51% had International Society of Urological Pathology grade group (GG) 2 disease.

Experts' comments:

The headline message from ProtecT is that AM is safe for all patients with low or intermediate risk, with a very low 15-year cancer-specific mortality rate (3%) regardless of treatment allocation. This suggests that all such patients could be offered surveillance and only treated if they experience disease progression according to updated active surveillance criteria. The results also support deferred investigation, for instance after negative multiparametric magnetic resonance imaging. Perhaps this means that pathways designed to expedite prostate cancer diagnosis and treatment need to be revised, a suggestion at odds with recent publications such as the RAPID diagnostic pathway [1].

The study authors have been keen to dispel certain misconceptions about ProtecT. Although 77% of ProtecT trial men had GG 1 disease at diagnosis, 34% were classified as having intermediate or high risk on further baseline risk stratification [2], and more than half were intermediate risk at surgical pathology. A further misconception is that the trial data obviate the need for radical treatment. The rate of crossover from AM to radical treatment was 61% at 15 years, suggesting that a majority of men on surveillance defer rather than completely avoid treatment, but without any negative impact on survival. For comparison, 55% of patients in a contemporary nonrandomised cohort study remained untreated and on surveillance [3]. The reasons for AM failure in ProtecT would represent a useful future analysis.

It is noteworthy that of the 13 men who died after RP, all six with GG 1 disease at diagnosis were upgraded, and all 13 were upstaged at pathological staging. Clearly, this was an

undersampled cohort. It would be interesting to know how many of the 39% from the AM arm who did not undergo radical treatment had GG >1 disease at biopsy; we suspect that evidence showing that some higher-grade tumours do not need treatment may lie in this subgroup.

Finally, it is interesting that only 12 of the 40 patients alive with metastases at 10 years had sadly died by 15 years. A further five had died of other causes, and 23 were still alive after treatment of metastases. This does challenge the notion that the development of metastases is inevitably fatal, and we may have to reconsider our preferred surrogate for lethality in prostate cancer. That said, many have questioned whether mortality is the right metric. Individual patients' priorities need to be aligned to quality of life. By 15 years, 151 participants had required androgen deprivation therapy, with those allocated to AM 70% more likely to require hormones.

While we await a precise understanding of the biology of lethality [4], it is essential that we share both the cancer outcomes and the linked comprehensive patient-reported outcomes from ProtecT [5] with our patients during discussions regarding treatment selection.

Conflicts of interest: The authors work at the same institution as Freddie C. Hamdy, lead author on the ProtecT study. Freddie C. Hamdy had sight of this manuscript but was not directly involved in its preparation.

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Re: Pain and Health-related Quality of Life with Olaparib Versus Physician's Choice of Next-generation Hormonal Drug in Patients with Metastatic Castration-resistant Prostate Cancer with Homologous Recombination Repair Gene Alterations (PROfound): An Open-label, Randomised, Phase 3 Trial

Thiery-Vuillemin A, de Bono J, Hussain M, et al.

Lancet Oncology 2022;23(3):393-405

Experts' summary:

PROfound was an open-label phase 3 trial that randomised patients to olaparib (investigational arm) versus physician's choice of abiraterone and prednisone or enzalutamide (control arm) in the metastatic castration-resistant prostate cancer (mCRPC) setting [1]. All patients were confirmed to have a deleterious alteration in one of 15 homologous recombination repair genes [2]. A total of 152/166 patients in the olaparib arm and 77/83 in the control arm were assessed. Some of the prespecified secondary endpoints were pain, health-related quality of life (HRQOL), and symptomatic skeletal-related events (SREs). Using the Brief Pain Inventory-Short Form questionnaire, median time to pain progression was not reached (NR; 95% confidence interval [CI] NR–NR) in the olaparib arm versus 9.92 mo (95% CI 5·39–NR) in the control arm (p = 0.019). There was an improvement in Functional Assessment of Cancer Therapy-Prostate scores in 15/152 patients (9.9%) in the olaparib arm versus 1/77 (1.3%) in the control arm (p = 0.006) [1]. Olaparib recipients were therefore 8.3 times more likely to have an improvement in HRQOL. In addition, 89.5% and 77.6% patients in the olaparib arm were free from SREs at 6 and 12 months, respectively, in comparison to 77.6% and 53.6% in the control arm (p = 0.001) [1].

Experts' comments:

PROfound represents the largest series of patient-reported outcomes data in mCRPC in a phase 3 setting for a PARP inhibitor. Patient and public involvement has been a requirement by many funders and regulatory agencies in recent years [3] and this has led to increased engagement of patients and advocates in the design of trials. As patients are living longer, there is an emphasis on ensuring their ability to carry on with their activities of daily living. Some patients are also able to carry on with their day-to-day work and vocations.

mCRPC represents the final end of the disease spectrum, with 56% annual all-cause mortality, the highest among all