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Randomised Controlled Trials Remain the Key to Progress in Localised Prostate Cancer

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Over the last 2 yr, there has been an unprecedented wealth of randomised controlled trials (RCTs) illuminating outcomes in localised prostate cancer (PCa). Several thousand patients have been included, spanning low-risk to advanced localised disease. The ProtecT trial [1] is the only substantial study comparing management options in screen-detected, predominantly low-risk disease. Favourable 10-yr survival was demonstrated whether using active monitoring, prostatectomy, or conventionally fractionated external-beam radiotherapy (EBRT) with a short course of androgen deprivation therapy (ADT). The excess risk of metastasis developing in the active monitoring group is a concern but may be mitigated by improvements in the surveillance pathway using, for example, magnetic resonance imaging (MRI) to identify disease progression, and by exploration of biomarkers to better select patients. The ProtecT study also gives important information on patient-reported outcomes; no intervention can be distinguished on overall health-related quality of life, but unbiased observers may note some advantage for nonsurgical intervention. In a second group of studies, more than 5000 patients have been included in radiotherapy (RT) studies of modest hypofractionation [2]. The patients included had predominantly intermediate- or high-risk disease. Treatment using fractions of 3 Gy/d to a total dose of 60 Gy over 4 wk was as effective and with similar late side effects as conventional 2-Gy daily fractions delivered to doses of 74–78 Gy, whether or not short-course ADT was used. Very importantly, treatment techniques using intensity-modulated RT (IMRT), with or without image guidance (IGRT) and with mandated normal tissue dose constraints, have reduced gastrointestinal side effects by approximately 50%. The shorter schedule is expected to become the new standard of care, with considerable benefits in terms of patient convenience and use of health care resources. Results of more extreme (eg, 5 fractions) hypofractionation studies in Sweden (HYPRO trial ISRCTN85138529) and UK/Canada (PACE ISRCTN17627211) are awaited.
The improved outcome using ADT observed in the CHHiP trial (with ADT) compared to the PROFIT study (without ADT) mirrors the advantage shown for ADT in the recent EORTC trial report [3] using high-dose EBRT. It appears that short-course ADT impacts on micro-metastases as well as local tumour control. The results of "super-ADT" have just been reported for the Medical Research Council STAMPEDE trial. Standard of care (SOC) in patients with locally advanced or metastatic prostate cancer was compared with SOC plus abiraterone acetate and prednisolone (AAP) [4]. An overall survival advantage was shown, but, very strikingly, the hazard ratio (HR) for failure-free survival, was 0.29 ($p < 0.4 \times 10^{-61}$) in favour of SOC + AAP, with an even lower HR of 0.21 in the M0 group. This will probably translate into a long-term survival advantage and opens up a new era in the successful treatment of advanced, high-grade localised disease.

Despite these large trials and their practice-changing results, we remain left with the quandary of which patients are best treated with primary surgical or RT options. In this issue of *European Urology*, Wallis and colleagues [5] address this issue in their international review of surgery or RT. They appropriately conclude that we just do not have the evidence from RCTs to reach a sound judgement. They comment that it has been shown that surgery prolongs survival compared to watchful waiting in clinically localised disease in the SPCG-4 trial, at least for younger age groups. The firming up of this conclusion with >10-yr long-term follow-up is instructive. However, there has been no similar RT RCT for this group. Similarly, RT with long-course ADT prolongs survival in advanced localised disease [6,7], but there are no surgical RCTs in this group. The key issue to appreciate is that both local modalities produce good efficacy, and differences in survival outcomes are likely to be small at most. It is questionable whether large enough phase 3 trials will be ever be performed in appropriate patient subgroups. Therefore, the temptation is to turn to observational data. As Wallis et al [5] point out in their review, such data are confounded by both known and unknown variables. Statistical tools attempt to correct the known imbalances; propensity score analysis is frequently used. However, it is salutary to note that it has been shown that these techniques are ineffective in localised PCa [8] and we believe the resulting comparative data are flawed and certainly unsuitable for making decisions on health care delivery.
Globally, it has been reported that PCa is the major cause of "years lived with disability" among men [9]. This emphasises the importance of reducing treatment-related effects as far as possible. Treatment should be avoided when not needed, and focal therapies need to be studied and their efficacy and side effect profiles more rigorously assessed. RT techniques continue to evolve and improve, with IMRT and IGRT becoming widely available. Focal boost treatments directed using high-quality MRI can be given to maximise local control, and randomised trials are under way using both standard and moderately hypofractionated schedules (FLAME trial NCT01168479, PIVOTALboost CRUK/16/018). ADT should not be used unless shown to improve outcome. We need better imaging, tissue, and plasma biomarkers to separate patients with intermediate risk into appropriate favourable and unfavourable groups, which can then be assessed prospectively to validate biomarker-led hypotheses. Which men really need long-course hormone treatment and which subgroups would benefit from the addition of "super-ADT" with abiraterone or the new generations of potent anti-androgens are relevant questions.
Another way of looking at the choice between prostatectomy and RT is to ask the question "After RT, which patients will develop life-shortening or symptomatic local recurrence?" With modern, high-quality RT techniques, the proportion will be small, but prospective collection of potentially predictive biomarkers including genetic heterogeneity [10] may be of assistance. The use of patient-reported outcomes, particularly using the EPIC instrument, as noted by Wallis et al [5], may help us to advise patients of the likely outcomes for different treatment modalities. Patient choice after appropriate counselling remains central to decision-making. We believe that this is best performed in well-functioning, multidisciplinary teams that can deliver both high-quality surgery and RT.

Conflicts of interest: David Dearnaley has received advisory board/consultancy fees from Takeda, Amgen, Astellas, Sandoz, and Janssen; is an employee of the Institute of Cancer Research, where abiraterone acetate was developed; has an intellectual property in a pending patent (EP1933709B1); and is the recipient of a Cancer Research UK Programme Grant and an NIHR Royal Marsden Hospital/Institute of Cancer Research Biomedical Research Centre quinquennial grants (2007-2012 and 2012-2017). Alison Tree has received research and

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