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High-risk prostate cancer: treat the prostate

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Hundreds of thousands of men are diagnosed with clinically localised prostate cancer every year, and each faces a complex treatment decision with little high-quality evidence to help choose among treatments. Successfully completed, randomised trials of active treatments for localised prostate cancer are, unfortunately, scarce; a large systematic review commissioned by the US Agency for Healthcare Research and Quality noted that insufficient evidence exists to make conclusions about the relative benefits and harms of treatments.¹ The US Institute of Medicine has identified prostate cancer as among the USA's top 25 priorities for future comparative effectiveness research.²

In *The Lancet*, Pdraig Warde and colleagues³ report a successfully accrued randomised trial comparing androgen deprivation therapy alone with androgen deprivation therapy plus radiation therapy. In a planned interim analysis of more than 1200 men with locally advanced or otherwise high-risk disease, combination treatment improved survival by an amount both statistically significant and clinically meaningful. After a median follow-up of 6 years, in the radiation plus androgen deprivation therapy group, cancer-specific survival improved by 10% in absolute terms and by 46% (hazard ratio [HR] 0.54 [95% CI 0.22–0.73, $p=0.0001$]) in relative terms, compared with androgen deprivation therapy alone. For overall survival, the primary endpoint, the corresponding improvements were 8% and 23% (HR 0.77 [95% CI 0.61–0.98], $p=0.033$), respectively. Almost 10%

of the androgen deprivation therapy only group received delayed radiation for local progression, so these results underestimate, if anything, the benefit of radiation.

Other-cause mortality did not differ between treatment groups. Warde and colleagues' assertion, however, that the benefit of radiation comes at no expense to long-term urinary or bowel effects challenges clinical experience and many other studies.⁴ The findings are probably affected by the relative insensitivity to the effects of radiation of the Functional Assessment of Cancer Therapy—Prostate and the European Organisation for Research and Treatment of Cancer QLQ-C30 quality-of-life instruments used in this trial, compared with newer measures.⁵ Furthermore, the Functional Assessment of Cancer Therapy—Prostate instrument, completed by the large majority of patients in the trial, does not capture bowel symptoms. Only 120 patients—about 10% of the overall cohort—completed the European Organisation for Research and Treatment of Cancer questions about bowel symptoms during follow-up.

This study improves on the SPCG-7 study,⁶ which had a similar design and recorded an even larger treatment effect. The SPCG-7 study, however, used antiandrogens—which would not be considered adequate androgen deprivation therapy by contemporary standards—rather than medical or surgical castration.⁶ These trials are both commendable, although the results are not particularly surprising. Androgen deprivation therapy alone does not constitute curative therapy, and is not endorsed by clinical practice guidelines as a standard option for localised prostate cancer, high-risk or otherwise.^{7,8} Indeed, only men with aggressive tumours receive the survival benefit from androgen deprivation therapy even compared with observation alone, and the effect is small at best.⁹ Androgen deprivation therapy is, however, frequently used in clinical practice, particularly for older men and those with high-risk disease,¹⁰ who are most at risk for adverse effects from androgen deprivation therapy and for cancer-specific mortality, respectively. Indeed, overuse of androgen deprivation monotherapy might partly explain the notably high rates of cancer-specific mortality among men diagnosed with high-risk prostate cancer even in their late 70s and 80s.¹¹

No randomised trial comparing surgery and radiation has yet been successfully completed. However, two

large comparative studies, one reporting data from two academic institutions¹² and one from a multicentre community-based cohort,¹³ both noted—after many adjustments for case-mix and disease risk—substantially improved outcomes after surgery compared with radiation. The community-based analysis also recorded, as did Warde and colleagues, better outcomes after either surgery or radiation than after androgen deprivation monotherapy. In both studies, differences between treatments were small for men with low-risk disease, and increased progressively as risk rose.

Warde and colleagues have provided the strongest evidence to date that androgen deprivation therapy alone for men with high-risk prostate cancer is not adequate. These patients require an aggressive, multimodal approach incorporating prostate-directed local therapy. However, the crucial question—whether the optimum initial strategy should include radiation combined with androgen deprivation therapy, or surgery followed by selective radiation on the basis of pathological findings and early biochemical outcomes—is still open. The definitive answer will only come through trials of men with high-risk disease randomly assigned to receive surgery or radiation as an initial treatment.

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I declare that I have no conflicts of interest.

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No evidence that patient choice in the NHS saves lives

The Health and Social Care Bill 2011 has been framed to abolish direct parliamentary control and public accountability for the National Health Service (NHS) in England. In the face of enormous public opposition to the Bill, the UK Government stood down the legislative process between April and June, 2011. Prime Minister David Cameron used the temporary pause to advance the case for the Bill and argued “Put simply: competition is one way we can make things work better for patients. This isn’t ideological theory. A study published by the London School of Economics found hospitals in areas with more choice had lower death rates.”¹

The study to which Cameron referred was a working paper by Zack Cooper and colleagues.² However, contrary to Cooper and colleagues’ claims, their study did not

show a causal inverse relation between patient choice and death rates.² A statistical association is not the same as causation. As set out by Bradford Hill in his seminal paper,³ certain factors must be considered when determining whether a statistical association is likely to be causal: “experiment” or study design, plausibility of intervention and outcomes, strength, consistency, specificity, coherence, temporality, and quality of data. Cooper and colleagues’ study does not meet scientific standards. In the absence of evidence proving that competition improves health, Cooper and colleagues’ work should not be cited as scientific evidence in support of choice, competition, or the current market-oriented Health and Social Care Bill 2011. A revised version of the study, published in *The Economic Journal*, clarified points of detail, but Cooper

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For the **Health and Social Care Bill 2011** see <http://services.parliament.uk/bills/2010-11/healthandsocialcare.html>