



European Association of Urology



Platinum Opinion

Prostate Cancer and the John West Effect

EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel

Every specialist wants to know the best treatment for localised prostate cancer; or do they? Maybe some want to know, but on the condition that their own favoured modality—surgery, radiation therapy, or another modality—comes out on top. If so, and in the absence of any reliable data from well-designed randomised controlled trials, they have been well supported in their quest by calling on any number of nonrandomised retrospective studies as the underpinning evidence for whatever conclusion they wished for. And why not, if the said studies were well constructed and carefully reported?

In the 1960s, the food company John West began an advertising campaign with the slogan “It’s the fish John West reject that make John West the best!” [1]. What does this have to do with prostate cancer? Everything! In the case of early prostate cancer, nonrandomised studies (the “bread and butter” of the “outcomes after surgery or radiotherapy” genre of paper) were the ingredients of a systematic review and meta-analysis of treatments that concluded that the “best” treatment for early prostate cancer was surgery [2]. Better ingredients were not possible because there have been very few attempts at randomised trials and those done were either pitifully small in size or abysmally poor in quality. Despite this, the authors concluded that “The results ... would be an important consideration for patients and physicians...”; in other words, clinicians should use these results as a basis for advising patients.

Why has this view not been adopted in the European Association of Urology (EAU) prostate cancer guidelines? First and foremost, the guidelines, which are evidence-based, take into account the quality of evidence available and make graded recommendations accordingly. The systematic review by Wallis et al [2] is a priori wide open for bias—despite the authors’ view that the studies included were of only low or moderate risk of bias—because of the inherent biases invariably present in nonrandomised studies. Randomisation is one of the most powerful

protections against bias; this is its principal *raison d’être*. It is a recognised fact that the majority of randomised trials, especially those conducted in accordance with Consolidated Standards of Reporting Trials (CONSORT) criteria, make painstaking efforts to minimise biases and to ensure that known and unknown confounders are balanced across all groups. Bias can be conscious or unconscious; it can be selection bias, performance bias, detection bias, or bias arising from a host of other sources. Nonrandomised studies with apparently dramatic results are always impressive. Population-based studies, no matter how large, are subject to the underlying and inescapable fact that some patients who are advised by their physicians to have radiotherapy and not surgery are fundamentally different to some patients who are encouraged to have surgery. Are impressive results really due to excellent treatment, or to conscious or unconscious patient selection? Remember, it’s the fish John West reject ...

We now have the first results from the UK ProtecT study [3,4]. In this multicentre randomised controlled trial, 1643 men with localised prostate cancer were randomised between active monitoring, radical prostatectomy, and external-beam radiotherapy. The first, most striking outcome is the rarity with which men in this category die of their disease, with only approximately 1% dying of prostate cancer at 10 yr. But the all-important comparisons between treatments showed no differences between surgery and radiotherapy in terms of cancer-specific survival and overall survival. Moreover, the patient-reported outcomes indicate that although (as is well known) the patterns of treatment-related side-effects differ markedly according to the modality, neither surgery nor radiotherapy appears to be “kinder” overall. Intriguingly, more men in the active monitoring group developed progressive disease (both local and metastatic), but so far without a detriment in terms of either cancer-specific or overall survival, which was the same as for patients treated with surgery or radiotherapy.

* Corresponding author. Department of Urology, University Hospital, St. Etienne, France. Tel. +33 477828331; Fax: +33 477517179. E-mail address: nicolas.mottet@chu-st-etienne.fr (N. Mottet).

As yet, we cannot say what this disease trajectory might mean in terms of quality of life in the long term, but we now have level 1 data to help patients navigate the choice between active monitoring and treatment, and to balance the risks and the benefits of each. More men managed by active monitoring developed metastases, but this was still only seen in 33 out of 545 men, compared to 13 after surgery and 16 after radiotherapy.

Assuredly, there are caveats. For a disease such as low- to intermediate-risk prostate cancer, these are early days, and longer follow-up from ProtecT is very likely to clarify the picture still further. Critics will assert that the trial cannot be extrapolated to “modern” techniques such as robot-assisted prostatectomy or intensity-modulated, image-guided radiotherapy. The protocol for “active monitoring” is different to that used in many of today’s active surveillance programmes; there was no routine re-biopsy, for example. Neither brachytherapy nor experimental therapies such as high-frequency ultrasound or cryotherapy were included. The acceptance of their allocated treatment by 70–88% of patients was extraordinary for such a “difficult” randomisation, but nonetheless the lower end is less than ideal from a purely scientific standpoint. Outcomes for men with—mainly—lower-risk disease in ProtecT cannot necessarily be extrapolated to patients with high-risk or locally advanced disease (reports on the outcomes for such patients excluded from the randomised ProtecT study are currently in press). Ultimately, though, ProtecT is what it is: a pragmatic, randomised comparison of three major modalities using the—then—gold standards of treatment. At this stage, it is fair to say that the outcomes could hardly be bettered by today’s techniques for surgery or radiotherapy. Although it has been widely assumed that early postoperative outcomes following robot-assisted prostatectomy will be superior to those after open prostatectomy, recent randomised trial data suggest that this is not necessarily the case [5], and there are no level 1 data to show survival benefits when compared to open prostatectomy. People often read into randomised trials what they want to read, and no doubt this will be the case with ProtecT.

The EAU guidelines are implacably evidence-based, with a randomised trial as the highest form of evidence, second only to a meta-analysis of high-quality randomised trials. Clinicians must question the veracity of data from nonrandomised studies, even though in some circumstances such studies are not without merit, provided the investigators have taken adequate precautions to minimise the risks of bias and confounding. In some circumstances, nonrandomised studies might even be the only practical route, for example, where very large effect sizes are seen (chemotherapy for testicular cancer in the 1970s being one example). Sometimes it might be unethical or overly burdensome to randomise. Usually, though, for questions on the efficacy of interventions it must be clearly and unequivocally stated that nothing is as good as a high-quality randomised trial; there are abundant examples of utterly reasonable propositions that have been found

wanting after randomised controlled trials failed to support them [5]. A treatment should be judged on its true merits, but not on the basis of the patients who were rejected during its nonrandomised evaluation. Our guidelines will continue to highlight the strengths and the gaps in our knowledge as we make recommendations for the management of our patients based on evidence. In the case of early prostate cancer, the evidence still justifies equipoise in the choice of surgery versus radiotherapy for early prostate cancer, plus nuanced equipoise in the additional choice of active monitoring.

Conflicts of interest: Members of the EAU-ESTRO-ESUR-SIOG Prostate Cancer Guidelines Panel: Nicolas Mottet has received grant and research support from Takeda Pharmaceutical, Millenium, Astellas, Pierre Fabre, Sanofi, and Pasteur, and has received honoraria or consultation fees from Takeda Pharmaceutical, Millenium, Jansen, Astellas, BMS, Bayer, Ipsen, Ferring, Novartis, Nuclétron, Pierre Fabre, Sanofi, and Zeneca. Joaquim Bellmunt is a company consultant for Janssen, Astellas, Pierre Fabre, Genentech, Merck, Ipsen, Pfizer, Novartis, and Sanofi Aventis, and has received research support from Takeda, Novartis, and Sanofi, and travel grants from Pfizer and Pierre Fabre. Michel Bolla has received company speaker honoraria from Ipsen and Astellas, honoraria or consultation fees from Janssen, and fellowship and travel grants from Janssen, AstraZeneca and Astellas. Erik Briers has received grant and research support from the European Association of Urology; is an ex officio board member for Europa UOMO; is an ethics committee and advisory group member for REQUITE; is a patient advisory board member for PAGMI; and is a member of SCA and EMA PCWP. Philip Cornford is a company consultant for Astellas, Ipsen, and Ferring. He receives company speaker honoraria from Astellas, Janssen, Ipsen, and Pfizer; participates in trials from Ferring; and receives fellowships and travel grants from Astellas and Janssen. Maria De Santis is a company consultant for GlaxoSmithKline, Janssen, Bayer, Novartis, Pierre Fabre, Astellas, Amgen, Eisai, ESSA, Merck, and Synthon; has received company speaker honoraria from Pfizer, Takeda, Sanofi Aventis, Shionogi, Celgene, and Teva OncoGenex; has participated in trials for Pierre Fabre, Astellas, Exelixis, Bayer, and Roche; has received fellowship and travel grants from Bayer, Novartis, Ferring, Astellas, Sanofi Aventis, and Janssen; has received grant and research support from Pierre Fabre; has received honoraria from AstraZeneca; and is associated with Amgen. Malcolm D. Mason is a company consultant for Bristol-Myers Squibb, Janssen, Bayer, Sanofi, and Dendreon, and receives company speaker honoraria from Takeda and Bayer. Steven Joniau is a company consultant for Astellas, Ipsen, Bayer, Sanofi, and Janssen; has received company speaker honoraria from Astellas, Amgen, Bayer, Sanofi, Janssen, and Ipsen; has participated in trials for Astellas, Janssen, and Bayer; has received fellowship and travel grants from Astellas, Amgen, Bayer, Sanofi, Janssen, Ipsen, and Pfizer; and has received grant and research support from Astellas, Bayer, and Janssen. Thomas B. Lam is a company consultant for and has received company speaker honoraria from Pfizer, GSK, Astellas, and Ipsen. Henk G. van der Poel is a company consultant for Intuitive Surgical, has participated in trials for Astellas and Steba Biotech, and has received grant and research support from Astellas. Olivier Rouvière is a company consultant for EDAP-TMS, Bracco, and Philips, has received company speaker honoraria from EDAP-TMS, Bracco, and Philips, and has participated in trials for EDAP-TMS and Bracco. Thomas Wiegel has received company speaker honoraria from Astellas, Takeda, Hexal, Ipsen, Janssen-Cilag, and Ferring. Roderick C.N. van den Bergh, Liam Bourke, Thomas Van den Broeck, Marcus G. Cumberbatch, Nicola Fossati, Tobias Gross, Ann M. Henry, Michael Lardas, Matthew Liew, Theo H. van der Kwast, Ivo G. Schoots, and Peter-Paul M. Willems have nothing to disclose.

References

- [1] John West UK. www.john-west.co.uk/advert/1966-red-salmon.
- [2] Wallis CJD, Saskin R, Choo R, et al. Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2016;70:21–30. <http://dx.doi.org/10.1016/j.eururo.2015.11.010>.
- [3] Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;375:1415–24. <http://dx.doi.org/10.1056/NEJMoa1606220>.
- [4] Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375:1425–37. <http://dx.doi.org/10.1056/NEJMoa1606221>.
- [5] Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet* 2016;388:1057–66. [http://dx.doi.org/10.1016/S0140-6736\(16\)30592-X](http://dx.doi.org/10.1016/S0140-6736(16)30592-X).



Apply for your EAU membership online!

Would you like to receive all the benefits of EAU membership, but have no time for tedious paperwork?

Becoming a member is now fast and easy!

Go to uroweb.org/membership to apply online. It will only take you a couple of minutes to submit your application, the rest is for you to enjoy!