**'Good news, Mr. Jones – your prostate biopsy is clear – your risk of dying of prostate cancer is now twice the average'.**

**Mark Emberton FMedSci**

**Professor of Interventional Oncology, UCL Division of Surgery and Interventional Science, London WC1E 6BT**

About 30 years ago, Tom Stamey persuaded urologists to abandon a diagnostic approach to prostate cancer that was predicated on measurable disease to one that was not (1). The new and 'better' approach was a semi-random interrogation of the prostate – otherwise known as the trans-rectal biopsy, most often triggered by an elevated PSA. Urologists have never been entirely comfortable with *PSA-Biopsy* as a risk-stratification tool. The number of needle deployments has increased with time in order to overcome the sampling error. The poor criterion validity of *PSA-Biopsy* has been very evident to surgeons who witness 'upgrading' in up to half of the patients they operate on compared to the risk that was predicted on *PSA-Biopsy* (2).

Assessing the true utility of *PSA-Biopsy* has proved challenging but we now have studies that span the *PSA-Biopsy* era. The SPCG-4 study recruited men before PSA was available (3); PIVOT was right in the middle with exactly half the patients presenting with T1c disease (4); ProtecT was the near perfect application of *PSA-Biopsy* at a community level (5). Prostate cancer mortality in the men randomized to conservative care within these studies was 20%, 8% and 1%, respectively. In other words, the better *PSA-Biopsy* was applied the worse it performed at identifying men

at risk. PROMIS – one of the first studies to assess the diagnostic accuracy of *TRUS-Biopsy* against an exacting reference standard – has shown what many have long felt (6). *TRUS-Biopsy* missed over half of all clinically significant prostate cancers. So, it is possible that we have been telling just over half the men with clinically significant prostate cancer that they are either 'all clear' or have insignificant disease.

So what happens to the men who are exposed to *TRUS-Biopsy* and are given the 'all clear' by their doctors? The paper by Klemann and colleagues in this issue provides some insight (7). In summary, they tracked the fate (in April 2015) of 64,430 men who were referred for TRUS-guided biopsy during the period spanning 1995-2011. Just over 27,000 of these men tested negative on their initial exposure to the biopsy. Despite a relatively short median follow-up (5.9 years), the authors reported a 1 in 20 risk of a prostate cancer death in men who were told they were 'all clear' on their first biopsy. A rate that is nearly twice as high as the average lifetime risk of a prostate cancer death for the average male. If we take the most recent data from ProtecT we have the rather difficult dilemma of telling men who test negative (by TRUS biopsy) that they are at least at five-time greater risk of dying of prostate cancer than the men with a confirmed diagnosis of prostate cancer who were followed up for longer.

How could this be possible? Well, clinical studies, by their very nature are more restrictive in terms of inclusion criteria than registries that are specifically designed to include all cases. The SPCG-4 and PIVOT studies were relatively unrestrictive with regard to PSA (≤50ug/L) but did require men to be free of metastases as determined

by bone scan. ProtecT excluded men with a PSA of 20ug/L or more, so all studies included men with a PSA of up to 20ug/L. When the analysis within the Danish registry study was restricted to men with a negative first-time biopsy that was associated with a PSA of less than 20ug/L the risk of dying of prostate cancer was preserved albeit at a slightly lower rate.

Could these data from the Denmark registry be giving us some insight into our diagnostic efficiency? The results from the PROMIS trial suggests that this might, indeed, be the case as more than half the clinically significant tumours were missed by biopsy. The Danish study suggests that these men remain at risk over a fairly short period of follow-up. Perhaps slightly more worrying is that the very men who test negative – despite harbouring significant prostate - would not make it into any of our prostate cancer clinical trials in view of their 'benign' pathology. Their prostate cancer-related deaths would occur outside the trials and registries and, as a consequence, would not be reported on. The result is a systematic under-reporting of prostate cancer related deaths in our evidence base. This might mean that the very things that are contingent of the quality of our evidence - risk calculators, shared decision making programs, tissue archives and our policy positions might carry this bias and, as a result, have got it all terribly wrong.

**Acknowledgments**

Mark Emberton is supported by the UK's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator status in 2015.

**References**

1. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol. 1989 Jul;142(1):71-4; discussion 74-5. PMID: 2659827

2. Shaw GL, Thomas BC, Dawson SN, Srivastava G, Vowler SL, Gnanapragasam VJ, Shah NC, Warren AY, Neal DE. Identification of pathologically insignificant prostate cancer is not accurate in unscreened men. Br J Cancer. 2014 May 13;110(10):2405-11. doi: 10.1038/bjc.2014.192. Epub 2014 Apr 10. PMID: 24722183

3. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, Nordling S, Häggman M, Andersson SO, Spångberg A, Andrén O, Palmgren J, Steineck G, Adami HO, Johansson JE. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med. 2014 Mar 6;370(10):932-42. doi: 10.1056/NEJMoa1311593. PMID: 24597866

4. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Gilhooly P, Grob BM, Nsouli I, Iyer P, Cartagena R, Snider G, Roehrborn C, Sharifi R, Blank W, Pandya P, Andriole GL, Culkin D, Wheeler T; Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012 Jul 19;367(3):203-13. doi: 10.1056/NEJMoa111316

5. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Neal DE;ProtecT Study Group. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016 Oct 13;375(15):1415-1424. PMID: 27626136

6. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Collaco-Moraes Y, Ward K, Hindley RG, Freeman A. Kirkham AP, Oldroyd R, Parker C, Emberton M, On behalf of the PROMIS Study Group. PROMIS: diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer. Lancet 2016, *in press.*

7. Klemann N, Røder MA, Helgstrand JT, Brasso K, Toft BG,Vainer B, Iversen P. Risk of prostatic cancer diagnosis and mortality in men with a benign initial TRUS-guided biopsy set: a population-based analysis. Lancet Oncol 2016 [full reference to be provided]