

studies should not even be performed. Proponents argue that many of these issues can be addressed using a variety of statistical methods, including direct matching, sensitivity analysis, and propensity score analysis. Despite these limitations, it is important to continue conducting these studies to report actual real-world data, preferably at a population level. At the very least, this approach can provide new hypotheses for future study.

In their study, Huang et al used a well characterized and validated population-based cohort from the SEER data set. What is elegant about the study is the lack of any complex attempt to adjust for selection bias and unmeasured confounding. A simple inclusion criterion was selected and patients were included between 2004 and 2012, representing a fairly contemporary time period. The decision to only study patients aged  $\leq 60$  yr was the key factor to minimize the effects of selection bias. Despite the results favoring surgery, we must acknowledge the differences in baseline characteristics, including the distributions of stage, grade, and PSA level between the surgery and radiation groups. Although the authors used a weighting multivariate analysis to better adjust for this, the differences cannot be ignored. A direct matched analysis could have been performed to better account for the differences. A previous study by Tilki et al. [4], who also compared surgery versus radiation for patients with high-grade PC, showed equivocal results. Why is there a difference? Is it because the study by Tilki et al used propensity score matching and determined plausibility indices for the calculated hazard ratios, whereas Huang et al conducted only weighted Cox modeling? No. In these studies, the importance of content expertise trumps any knowledge of advanced statistical methodology. It simply comes down to the PSA distributions. In the study by Huang et al, the PSA distribution favored patients who had surgery: a higher proportion of patients in the surgery group had PSA of  $< 20$  ng/ml. In the study by Tilki et al, median PSA was lower in the radiation (10.6 ng/ml) than in the surgery group (up to 21 ng/ml). This

translated to a high number of patients who had metastatic lymph nodes (up to 80% positive in the surgery group). It is well established that stage is the most important prognostic factor for patients with any PC. Thus, no amount of statistical adjustment could account for the fact that patients with metastasis would progress at a higher rate than patients without metastasis.

For researchers who continue to study this area, it is important to objectively evaluate nonexperimental methods and to design novel methods to address bias. Content expertise remains essential when evaluating these studies.

**Conflicts of interest:** The author has nothing to disclose.

## References

- [1] 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.
- [2] 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.
- [3] Wallis C, Nam R. The optimal treatment of patients with localized prostate cancer: the debate rages on. *BJU Int Blog* 2016 [www.bjuinternational.com/bjui-blog/the-optimal-treatment-of-patients-with-localized-prostate-cancer-the-debate-rages-on/](http://www.bjuinternational.com/bjui-blog/the-optimal-treatment-of-patients-with-localized-prostate-cancer-the-debate-rages-on/)
- [4] Tilki D, Chen MH, Wu J, et al. Surgery vs radiotherapy in the management of biopsy Gleason score 9-10 prostate cancer and the risk of mortality. *JAMA Oncol* 2019;5:213–20.

Robert K. Nam\*

\*Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.

E-mail address: [robert.nam@utoronto.ca](mailto:robert.nam@utoronto.ca).

<https://doi.org/10.1016/j.eururo.2019.03.003>

© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.



## Re: Radical Prostatectomy or Watchful Waiting in Prostate Cancer—29-Year Follow-up

Bill-Axelsson A, Holmberg L, Garmo H, et al

*N Engl J Med* 2018;379:2319–29

### Experts' summary:

Prostate cancer (PC) is the most commonly diagnosed cancer in Europe [1]. Similar data are available from the USA and other countries. Any active PC treatment may have secondary side effects and impact the quality of life for patients to variable degrees and durations [2]. Our understanding of PC overdiagnosis and overdiagnosis, as well as greater knowledge of PC biology, has led to the utilization of observational approaches, such as active surveillance (AS) and watchful waiting (WW) [3].

Bill-Axelsson et al. [4] have reported results from 29 yr of follow-up (FU) for 695 patients with PC who were randomly assigned to radical prostatectomy (RP) or WW between

October 1989 and February 1999 in the SPCG-4 study. All of the patients had clinically localized disease, but only 12% had nonpalpable tumors. They also had PC of WHO grade 1 or 2 and prostate-specific antigen (PSA) of  $\leq 50$  ng/ml; the mean age was 65 yr. The current paper reports that 80% of the patients enrolled had died by the end of 2017. Overall, 32% ( $n = 181$ ) of the deaths were due to PC, 71 in the RP group and 110 in the WW group. The longest actual FU was 28 yr, but with a maximum FU potential of 29.3 yr. The authors also point out that nearly 12% had an absolute risk reduction for PC-related death at 29 yr. The number of patients who needed treatment to avert one PC-related death was 8.4. Radical treatment resulted in a mean gain of 2.9 yr of life.

### Experts' comments:

This study can be approached from many angles. First, it is necessary to emphasize that the data reported are for an unscreened population. The present situation in PC

management is rather different: (1) opportunistic PSA testing detects a majority of PC cases; (2) stage migration is observed; and (3) life expectancy is increasing. As a result, observational management has gained in importance, and WW is reserved for selected patients only, whereas the majority (if they meet the inclusion criteria) are managed with AS. This was not the case when the SPCG-4 study was initiated, when palliative hormonal treatment was used for both groups in the case of progression. Nevertheless, the SPCG-4 study has revealed good evidence that RP (when compared to observation in an unscreened patient population) leads to better metastasis-free, PC-specific, and overall survival. The benefit for the latter two doubled between yrs 10 and 23 of the study. The greatest benefit observed was for patients aged <65 yr, for whom there was an absolute reduction of 18.6% in the risk of metastasis (relative risk 0.49) and of 15% in the risk of PC-related death (relative risk 0.50) at >23 yr. It is also important to note that the risk of death was 3.4% and only 5.4% for patients with a Gleason score (GS) of 3 + 3 and 3 + 4, respectively, although 78% had palpable tumors and/or intermediate- or high-risk PC according to their PSA (29% with PSA >10 ng/ml and 20% with PSA >20 ng/ml). Conversely, the risk of PC-related death was nearly six times higher in the group with GS 4 + 3 when compared to GS 3 + 4. These data justify nonradical management, such as AS or focal therapy, provided that appropriate patient selection (magnetic resonance imaging, good-quality biopsy, and future biomarkers or tissue markers) and counseling have been carried out. The SPCG-4 study provides, with the power of time, compelling evidence for surgical treatment if rationalized for a more selected population after screening.

The same information supports the possibility of less aggressive treatments for certain patient groups. Bill-Axelsson et al. advocate for selection and individualized treatment strategies.

**Conflicts of interest:** The authors have nothing to disclose.

## References

- [1] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618–29.
- [2] Jang JW, Drumm MR, Efsthathiou JA, et al. Long-term quality of life after definitive treatment for prostate cancer: patient-reported outcomes in the second posttreatment decade. *Cancer Med* 2017;6:1827–36.
- [3] Briganti A, Fossati N, Catto JWF, et al. Active surveillance for low-risk prostate cancer: the European Association of Urology position in 2018. *Eur Urol* 2018;74:357–68.
- [4] Bill-Axelsson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer—29-year follow-up. *N Engl J Med* 2018;379:2319–29.

Xavier Cathelineau, Petr Macek\*, Rafael Sanchez-Salas  
 Department of Urology, Institut Montsouris, Descartes University,  
 Paris, France

\*Corresponding author. Department of Urology, Institut Montsouris,  
 Descartes University, 42 Boulevard Jourdan, Paris 75014, France.  
 E-mail address: [petr.macek@imm.fr](mailto:petr.macek@imm.fr) (P. Macek).

<https://doi.org/10.1016/j.eururo.2019.03.033>

© 2019 European Association of Urology. Published by Elsevier B.V. All rights reserved.

