patients [6]. Moreover, only a proportion of patients with MIBC benefit from NAC, and patients who progress to MIBC after treatment for prior noninvasive disease (secondary MIBC) treated with NAC have worse clinical outcomes than similarly treated patients with primary MIBC [7].

To pool the available evidence and move forward, we need to change from prognostication to prediction and elaborate modern classification systems taking into account the nature of bladder cancer from a biological rather than histopathological perspective. Biomarkers are urgently needed to select the patients who are most likely to benefit from upfront active surveillance after TURB and NAC or immunotherapy [8]. We believe that while waiting for such biomarker-driven management of bladder cancer, the current standard treatment for most patients with MIBC should still be NAC followed by RC. Patients who elect for bladder preservation strategies should be treated at high-volume institutions by multidisciplinary bladder cancer teams and should be enrolled in prospective studies with appropriate patient-centered endpoints.

Conflicts of interest: The authors have nothing to disclose.

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Re: Evaluation of Cancer Specific Mortality with Surgery versus Radiation as Primary Therapy for Localized High Grade Prostate Cancer in Men Younger than 60 Years

Huang H, Muscatelli S, Naslund M, Badiyan SN, Kaiser A, Siddiqui MM

J Urol 2019;201:120–8

Experts' summary:

This study is a classic retrospective cohort study using the Surveillance, Epidemiology and End-Results (SEER) database to compare survival rates between primary surgery and radiation as treatment options for patients with high-grade (Gleason score $\geq$8) prostate cancer (PC). The study restricted the cohort to men younger than 60 yr to minimize competing risks of mortality. Among a total of 2228 men, 1459 (65.5%) had primary surgery and 769 (34.5%) had primary radiation. PC-specific and overall mortality rates were lower among patients who underwent surgery than among patients who had radiation (hazard ratios ranging from 0.28 to 0.57 in favor of surgery). Baseline covariates included age, Gleason score, stage, and prostate-specific antigen (PSA) level at diagnosis. Inverse-probability, treatment-weighted, multivariate Cox modeling was performed to account for selection bias.

Experts' comments:

The debate continues on whether surgery or radiation provides better cancer control for patients with nonmetastatic PC. Indeed, the largest meta-analysis and systematic review of studies comparing surgery versus radiation in *European Urology* [1] was one of the most downloaded articles in its publication year. The widely anticipated results from the ProtecT trial comparing survival rates among patients with screen-detected PC treated with surveillance, surgery, or radiation [2] were disappointing owing to the lack of study power and over-representation of patients with low-risk PC [3]. No further clinical trials are expected and the research community will continue to have to rely on nonexperimental methods in evaluating this issue.

Selection bias and the inability to account for unmeasured confounding variables are key limitations in conducting these studies (which randomized studies obviate). Opponents to such studies argue that it is impossible to properly address these problems and that therefore these

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 ≤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.

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

Bill-Axelson 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 overdetection 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-Axelson 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 ≤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