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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:

In this retrospective study, the authors focused on men younger than 60 yr with high-risk, localized prostate cancer (PC) from the Surveillance, Epidemiology and End Results (SEER) database who underwent upfront radical prostatectomy (RP) or radiation therapy (RT; either external beam [EBRT] or EBRT + brachytherapy [BT]) from 2004 to 2012. The population consisted of 2228 men, of whom 65.5% underwent RP as their initial treatment.

For median follow-up of 44 mo, multivariate analysis revealed that RP was associated with better PC-specific mortality (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.19–0.74; $p = 0.005$) and overall mortality (HR 0.41, 95% CI 0.24–0.70; $p = 0.001$) compared with initial RT treatment.

Experts' comments:

Whereas active surveillance is recommended or at most single-modality treatments for low-risk and even some intermediate-risk PCs, for high- and very high-risk PCs there is more of a tendency to recommend aggressive multimodal treatments [1].

Using SEER data to analyze outcomes for young patients with high-risk localized PC, the authors try and answer an age-old question as to what constitutes the “best treatment” in this population with long life expectancy who experience high PC-specific mortality (>50% in this study) and side effects of therapy.

Unsurprisingly, there needs to be a nuanced approach in interpreting these results because of many inherent pitfalls with the population-based data, some of which were accounted for by the authors. First, SEER consists of observational data and was never designed for treatment comparisons per se. Treatment groups are obviously not randomized, and in this case multivariate analysis was performed in an attempt to minimize the influence of selection and other biases. However, there are no data on comorbidities, one of the most important factors that could influence treatment decisions.

In the group of RP patients, 18.2% received adjuvant RT and this is the only information provided on outcome after primary treatment, with no data on pathologic status, whether lymph

node dissection was performed and, if so, to what extent, or the timing of androgen deprivation therapy (ADT).

There are even potential latent confounders within SEER data such as surgical experience, and this earlier timeframe does include the “learning curve” for many robotic surgeons. In addition, radiation delivery has evolved over time, and recent data for combined EBRT + BT demonstrated a significant advantage over EBRT for Gleason 9–10 patients in a study by Kishan and colleagues [3]. Moreover, guidelines recommend long-term ADT for high-risk patients (level of evidence 1b, grade of recommendation A)[1], meaning that all patients in the RT cohort should have received ADT for appropriate comparison with the RP cohort, and this is not precisely known for this study.

Furthermore, the study had median follow-up of <5 yr (44 mo), which is too short in the natural treated history of PC, even for high-risk disease. The survival curves reveal mortality comparable with results from other observational studies for the first 4 yr[2,4]. The differences in estimated mortality at 5 and 7 yr are probably because of the small number of patients at risk after 3 yr of follow-up and the usual biases inherent to SEER. It is even challenging to guess whether the curves would become wider or even narrower with this type of data.

In summary, these results are suggestive at best that RP could be the preferred treatment for younger men. One thing known is that RP is the single most effective modality, since radiation therapy includes ADT for high-risk disease. Randomized clinical trials are being conducted in high-risk disease and perhaps subset analyses for younger males will be provided.

Conflicts of interest: The authors have nothing to disclose.

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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:

This prospective randomized study investigated the impact of radical prostatectomy (RP) versus watchful waiting (WW) on overall survival for men with clinically detected localized prostate cancer and initial prostate-specific antigen <50 ng/ml ($n = 659$, recruiting from November 1989 to February 1999) [1]. After median follow-up of 23.6 yr, the authors found lower mortality among patients undergoing prostatectomy (RP 71.9% vs WW 83.8%; $p < 0.001$) and a lower rate of metastatic disease (RP 26.5% vs WW 43.1%; $p < 0.001$).

Experts' comments:

Prostate carcinoma is the second most common tumor among men. A 10-yr survival rate of >90% suggests a low oncologic threat, but prostate cancer still has the fifth highest mortality rate among all tumors worldwide [2]. In this context, SPCG-4 is of rare and high value, especially since—not least for ethical reasons—such a trial could not be repeated today knowing the aggressiveness of the high-risk tumors included.

In 2002, after follow-up of 6.2 yr, the first results of this study showed no significant difference in terms of overall survival between RP and WW [3]. At that time, the perception by a large part of the medical community was that treatment with RP may cause more harm than good. However, even at that time a lower risk of distant metastases was observed for men undergoing RP. In 2005, the lower disease-specific mortality became significant for the RP group [4]. Today, the advantage for RP is highly significant (see above), although the procedure was not performed for patients with N+ disease, a group that would have benefited most from RP [1]. In this respect, it is

important to note that the PIVOT study also shows an advantage for RP over WW among patients with intermediate- and high-risk cancers, albeit not significant because of insufficient statistical power for relevant subgroup analysis [5].

The course of SPCG-4 shows that therapy studies for prostate cancer require sufficient long-term follow-up. It also highlights the oncologic efficacy of RP in patients with intermediate- and high-risk disease.

Conflicts of interest: The authors have nothing to disclose.

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Re: Prostate Cancer-specific Mortality Across Gleason Scores in Black vs Nonblack Men

Mahal BA, Berman RA, Taplin ME, Huang FW

JAMA 2018;320:2479–81

Experts' summary:

Mahal et al. [1] used the Surveillance, Epidemiology and End Results (SEER) prostate active surveillance (AS)/watchful waiting database from 2010 to 2015 to identify