CORRESPONDENCE

Radical Surgery or Watchful Waiting in Prostate Cancer

TO THE EDITOR: Bill-Axelson et al. (Dec. 13 issue)[1] report that at a median follow-up of 23.6 years, radical prostatectomy prolonged overall survival among men with localized prostate cancer, as compared with "watchful waiting." Using a Cox proportional-hazards model, the investigators calculated a hazard ratio for death for prostatectomy versus watchful waiting of 0.55 (95% confidence interval [CI], 0.41 to 0.74]), which they reported as a relative risk. At 23 years, they found that prostatectomy extended the men's lives by a mean of 2.9 years. However, the 23-year residual mean survival time was defined as the average remaining survival time beyond 23 years, which is different from the restricted mean survival time (i.e., the average survival time during 23 years of follow-up).[2,3] In our analysis, the difference in the 23-year restricted mean survival time was 1.4 years (95% CI, 0.5 to 2.3) in favor of prostatectomy (Table 1).[4] In addition, the 23-year survival rate from prostate cancer was 80.4% in the radical prostatectomy group and 68.7% in the watchful-waiting group, which suggests that a mixture cure model[2,5] may be more suitable for this study, since there was a large proportion of long-term event-free survivors. In our analysis, the cure rates for men with prostate cancer were 80.4% in the radical prostatectomy group and 69.0% in the watchful-waiting group, whereas no benefit was observed in terms of hazard ratios. Our findings, which were calculated with more accurate and interpretable statistics, support the conclusion that prostatectomy improved long-term survival over that for watchful waiting.

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Table 1. Comparisons of Estimates from a Mixture Cure Model and a Restricted Mean Survival Time, Based on Reconstructed Trial Data.*

End Point	Radical Prostatectomy vs. Watchful Waiting	P Value
Death from any cause		
Mixture cure model†		
Cure rate — %	24.0 vs. 12.3	<0.001
Hazard ratio (95% CI)	0.91 (0.77–1.12)	0.37
Difference in restricted mean survival time (95% CI) — yr‡	1.5 (0.6–2.5)	0.002
Death from prostate cancer		
Mixture cure model†		
Cure rate — %	80.4 vs. 69.0	<0.001
Hazard ratio (95% CI)	0.90 (0.53–1.53)	0.71
Difference in restricted mean survival time (95% CI) — yr‡	1.4 (0.5–2.3)	0.002

* The cumulative incidence of causes of death were extracted and reconstructed[4] from Figure 1 in the article by Bill-Axelson et al. with the use of the "digitize" package in R software, version 3.5.1 (R Project for Statistical Computing).
† The mixture cure model in the "smcure" package was used to perform this analysis.
‡ The "survRM2" package was used to calculate the area under the Kaplan–Meier curve to estimate the restricted mean survival times.

THIS WEEK'S LETTERS

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No potential conflict of interest relevant to this letter was reported.

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2. Yin G. Clinical trial design: Bayesian and frequentist adaptive methods. Hoboken, NJ: Wiley, 2012:151-153.
3. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol 2014;32:2380-5.
4. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
5. Yilmaz YE, Lawless JF, Andrulis IL, Bull SB. Insights from mixture cure modeling of molecular markers for prognosis in breast cancer. J Clin Oncol 2013;31:2047-54.

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TO THE EDITOR: Bill-Axelson et al. report the number of deaths from prostate cancer among men with Gleason scores of 3 to 6 who underwent radical prostatectomy (3 of 88 [3.4%]) but not the numbers in the watchful-waiting group. What were those numbers, and were the between-group differences significant? If not, the Abstract and Conclusion should have stated that radical prostatectomy is not an option in men with a Gleason score of less than 7, a prostate-specific antigen level of less than 13, and no evidence of local or regional spread. Combining patients who have minimal, moderate, and advanced disease is inappropriate in determining whether a surgical treatment should be used.

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THE AUTHORS REPLY: Yang et al. provide an interesting methodologic comment on our analyses. With a plethora of methods for analyzing survival data, we do not know which one would most closely estimate the real-world situation in our trial. All statistical models contain assumptions that are more or less difficult to validate. The analysis of Yang et al. adds to the understanding of life-years gained in our trial. We have prioritized the use of methods that are well tried and that are consistent with the methods we have used in previous articles[1-3] so that readers can critically review the long-term development of the trial results. Since the main conclusion of Yang et al. is the same as ours (despite a lack of evidence that mixture cure models are applicable to prostate cancer), their comments confirm that our main results are not sensitive to the choice of statistical model.

The analysis that Charkes describes was performed in the radical-prostatectomy group only. As stated in our article, the biopsy strategy during the recruitment to the trial differs widely from the extensive diagnostic workup that is performed today. Thus, the classification of the Gleason score in the watchful-waiting group is far less accurate than in the prostatectomy group, although on the whole the prognostic groups were well balanced because of the strict randomized design of the trial. Charkes asks us to address a hypothesis for the outcome in a particular subgroup that the trial was not designed to determine. We have repeatedly cautioned[1-3] (including in the current article) that our subgroup analyses are exploratory and thus may be subject to chance findings with low statistical precision.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352:1977-84.
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