

CORRESPONDENCE



10-Year Outcomes in Localized Prostate Cancer

TO THE EDITOR: The primary survival analysis in the Prostate Testing for Cancer and Treatment (ProtecT) trial by Hamdy et al. (Oct. 13 issue)¹ tested for equality across all three interventions (active monitoring, surgery, and radiotherapy). Because there was no significant difference among treatments, comparing pairs of interventions directly is not possible. In addition, treatment of low-risk prostate cancer has minimal effects on survival within the first 10 years after diagnosis. There were only 108 to 120 men with intermediate-risk cancer in each group. Therefore, the trial was underpowered to show treatment-related differences. Suggestions that the study shows a benefit of surgery over radiation, or of either intervention as compared with active monitoring, are not justified.

The difference in the rate of metastases between men assigned to active monitoring and those assigned to radical treatment (surgery or radiotherapy) is not surprising, given that 23% of the participants had intermediate-grade or high-grade disease. The fact that disease grade was not a predictor of death is probably a reflection of the small number of events. Furthermore, men undergoing active surveillance require careful follow-up and periodic rebiopsy, imaging, or both; neither mandated rebiopsy nor imaging was part of the protocol. Therefore, these results should not be interpreted as a case against conservative management of low-risk disease.

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

1. 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.

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THIS WEEK'S LETTERS

- 178 10-Year Outcomes in Localized Prostate Cancer
- 181 Adjunctive Azithromycin Prophylaxis for Cesarean Delivery
- 183 Chronic Cough
- 184 Graves' Disease
- 186 Hepatic Encephalopathy
- 187 Mental Illness and the Criminal Justice System
- 188 Improving the Accuracy of Prenatal Screening with DNA Copy-Number Analysis
- 189 TARGT Gene Therapy Platform for Correction of Anemia in End-Stage Renal Disease
- 191 Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab

TO THE EDITOR: The randomized trial by Hamdy and colleagues compared the effectiveness of different treatments for localized prostate cancer. Although randomized trials represent the highest level of evidence, their generalizability might be limited by their cohort selection. To test the generalizability of the results of this trial to the U.S. population, we identified men in the National Cancer Database (NCDB) for the period 2010–2013 who met the inclusion criteria of the ProtecT trial (we excluded men with a Gleason score ≥ 8 [on a

scale from 6 to 10, with higher scores indicating a worse prognosis] because they represented 2% of the trial cohort) and compared them with the ProtecT cohort. Interestingly, although prostate-specific antigen (PSA) level and clinical stage were similar in the NCDB population and the ProtecT cohort, approximately half of the NCDB population had a Gleason score of 7, as compared with only 21% in the ProtecT trial. Moreover, 14% of the men in the NCDB population were black, as compared with less than 1% in the ProtecT trial. Black men often harbor a more aggressive form of prostate cancer than their white counterparts,¹ and thus the natural history of their disease might be different from that documented in the trial. These points should be considered carefully when the trial results are used to counsel U.S. men.

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Dr. Abdollah reports having received consulting fees from GenomeDx Biosciences. No other potential conflict of interest relevant to this letter was reported.

1. Kelly SP, Rosenberg PS, Anderson WF, et al. Trends in the incidence of fatal prostate cancer in the United States by race. *Bur Urol* 2016 July 27 (Epub ahead of print).

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TO THE EDITOR: A striking feature of the report by Hamdy et al. is that nearly one third of men who had radical surgery were found to have extracapsular tumor extension when their excised prostates were examined histologically. All trial participants were assessed as having intracapsular disease by clinical assessment, imaging, and histologic analysis. In the men who underwent surgery, postoperative histologic analysis revealed pathologic extracapsular (pT3) disease in 114 (29%) of the 391 men and positive surgical margins in 93 (24%).

“Unexpected” extracapsular tumor was also reported in studies from Queensland, Australia,^{1,2} and Chicago³ that compared robot-assisted radical prostatectomy with open surgery, after similar procedures to identify men with intracapsular disease. This marked underestimation of tumor extent is a cause for concern. If explained by limitations of imaging techniques, then improvement

should be expected from multiparametric magnetic resonance imaging (MRI). A more worrying possibility is that current biopsy methods, involving multiple samplings and associated bleeding and capsular injury, might facilitate tumor spread in men with intracapsular disease. Until the safety of biopsy has been properly evaluated in a prospective trial, a repeat multiparametric MRI scan after biopsy would seem an essential precaution before management decisions are made.

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

1. Gardiner RA, Yaxley J, Coughlin G, et al. A randomised trial of robotic and open prostatectomy in men with localised prostate cancer. *BMC Cancer* 2012;12:189.
2. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet* 2016;388:1057-66.
3. Pearce SM, Pariser JJ, Karrison T, Patel SG, Eggener SE. Comparison of perioperative and early oncologic outcomes between open and robotic assisted laparoscopic prostatectomy in a contemporary population based cohort. *J Urol* 2016;196:76-81.

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TO THE EDITOR: D’Amico¹ comments on the ProtecT trial by Hamdy et al. and by Donovan et al.² (Oct. 13 issue), “[I]f a man wishes to avoid metastatic prostate cancer . . . monitoring should be considered only if he has life-shortening coexisting disease.” All men wish to avoid metastases but should still be guided by the hazards of their disease-management options.

In the ProtecT trial, the incremental risk of metastases was 3 to 4 percentage points with monitoring versus surgery or radiotherapy over a period of 10 years. At 6 years, the surgical group had an incremental risk (vs. monitoring) of 13 percentage points for impotence and 9 percentage points for incontinence, but those numbers are understated because 55% of the patients crossed over from monitoring to active treatment. The similar Prostate Cancer Intervention versus Observation Trial (PIVOT),³ with a crossover rate of only 10%, showed a 2-year impotence rate of 81% with prostatectomy versus 44% with monitoring and an incontinence rate of 17% versus 6%.

So informed consent for prostatectomy for early cancer would appropriately disclose that

monitoring is associated with an increased risk of metastases of 3 to 4 percentage points, whereas surgery is associated with an increased risk of impotence of approximately 37 percentage points, an increased risk of incontinence of approximately 11 percentage points, and a rate of perioperative complications of approximately 21%. Men can then choose the option that is most compatible with their personal values.

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

1. D'Amico AV. Treatment or monitoring for early prostate cancer. *N Engl J Med* 2016;375:1482-3.
2. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375:1425-37.
3. Wilt TJ, Brar MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367:203-13.

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THE AUTHORS REPLY: We agree with Klotz and Kibel that the lack of significant differences in survival among the three treatments makes a comparison between radiotherapy and surgery unwise. The predetermined power calculation for the ProtecT trial estimated a prostate-cancer mortality rate of 10% at a median of 10 years, and because the observed rate was 1%, longer follow-up is required to evaluate differences. We agree that the ProtecT findings should not be interpreted as a case against active surveillance. The similar rates of survival in the three groups, the lower rate of symptoms in the active-monitoring group than in the radical-treatment groups, and the finding that 80% of the men in the active-monitoring group remained progression-free provide evidence to support this option.

Nocera et al. raise important issues about the generalizability of the ProtecT results by comparing patients reported in the NCDB. We have acknowledged the limitation of the ProtecT trial regarding numbers of ethnic minorities. The ProtecT cohort was assessed at baseline by means of a 10-core biopsy after an initial measurement of the PSA level. This produced a similar pattern of cancer stage and grade as in other trials.¹ In the ProtecT trial, 29% of the men who underwent

surgery had pT3 disease, indicating that the baseline clinical assessment was inaccurate — as raised by Stainsby. The ProtecT findings are most directly generalizable to men with low-risk and intermediate-risk disease. However, all men who received a diagnosis of prostate cancer were followed, and an observational analysis of outcomes in those excluded with advanced or high-risk disease has been published.²

Stainsby mentions that new techniques have been introduced. We agree that multiparametric MRI before biopsy should identify and stage high-risk tumors more accurately. We are not aware of an association between tumor spread and biopsy but agree that the use of multiparametric MRI to target or reduce biopsies would be helpful. Advances such as robot-assisted radical prostatectomy and intensity-modulated radiotherapy should improve side-effect profiles, although a recent trial showed similar short-term outcomes after robotic and open prostatectomy.³

Longer follow-up is required to elucidate the full trade-off between risks seen in these 10-year data and longer-term mortality, disease progression, and quality of life. Clinicians need to consider the robustness of the ProtecT findings in relation to contemporary patients and encourage them to weigh the advantages and disadvantages of each option in their decision making.

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

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2. Johnston TJ, Shaw GL, Lamb AD, et al. Mortality among men with advanced prostate cancer excluded from the ProtecT trial. *Eur Urol* 2016 October 6 (Epub ahead of print).
3. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. *Lancet* 2016;388:1057-66.

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THE EDITORIALIST REPLIES: In response to Kelleher: at 10 years in the ProtecT trial, the absolute increases in the rates of erectile and urinary dysfunction among men assigned to radical prostatectomy versus active monitoring were greater than the absolute increase in the rate of metastatic prostate cancer. However, with time the absolute difference in the rate of metastatic prostate cancer between these randomized treatment groups is expected to increase, as illustrated in PIVOT.¹ Therefore, for a man with a long life expectancy, the increasing difference in the rate of metastatic prostate cancer among men selecting active monitoring versus radical prostatectomy could exceed the fixed difference in the rate of treatment-related side effects between these two randomized treatment groups. Moreover, although erectile dysfunction and urinary incontinence have effective treatments,² sequelae³ after lifelong treatment for metastatic prostate cancer — including decreased libido, impotence, hot

flashes, increased risks of fracture and nonfatal cardiac events, metabolic alterations, and changes in cognition — may not be reversible. Therefore, when selecting management for early prostate cancer, careful consideration should be given to what may happen during the remaining life expectancy, which for a healthy man in his 50s exceeds three decades.

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Since publication of his editorial, the author reports no further potential conflict of interest.

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Adjunctive Azithromycin Prophylaxis for Cesarean Delivery

TO THE EDITOR: In reporting on the results of the Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) trial, Tita and colleagues (Sept. 29 issue)¹ describe an absolute reduction of 5.9 percentage points in the rate of the primary composite outcome of endometritis, wound infection, or other infection occurring within 6 weeks after nonelective cesarean section with the use of adjunctive azithromycin prophylaxis. The absolute reduction in maternal postpartum use of antibiotics was 4.3 percentage points. The study drug was administered after the first incision in 12.4% of the patients who received azithromycin and in 12.3% of those who received placebo. The authors did not indicate when the standard prophylaxis (mainly cefazolin) was delivered.

Twenty-five years ago, Classen et al.² showed that administration of short-acting beta-lactams well before or any time after the first incision, rather than within 2 hours before surgery, leads to increased rates of postoperative wound infection. This finding is supported by more recent data.³ If the administration of the study drug had been prioritized over other activities in the C/SOAP trial, the standard prophylaxis may have

been administered outside of this vital time period, compromising its effect. Any such delay, even if equivalent in the two study groups, would have favored the azithromycin recipients because of the broad spectrum of activity of azithromycin over many common pathogens in obstetrical wounds.

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

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2. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992; 326:281-6.
3. Koch CG, Li L, Hixson E, et al. Is it time to refine? An exploration and simulation of optimal antibiotic timing in general surgery. *J Am Coll Surg* 2013;217:628-35.

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TO THE EDITOR: Tita et al. conducted a multicenter trial and concluded that among women