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Title
Treatment Trends for Prostate Cancer—Reply

Permalink
https://escholarship.org/uc/item/8q58x0d6

Journal
JAMA, 314(18)

ISSN
0098-7484

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Publication Date
2015-11-10

DOI
10.1001/jama.2015.12607

Peer reviewed

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply Dr Rhinehart and colleagues raise an important and controversial issue concerning the effect of thrombophilia on the risk of recurrent venous thromboembolism. They were concerned that the results of the PADIS-PE trial may be biased due to the inclusion of patients with identified and unidentified thrombophilia.

First, misclassification bias was avoided because thrombophilia testing was performed at the end of the study on stored frozen blood samples taken on the day of randomization using the same standardized laboratory techniques for all included patients by technicians blinded to the study treatment allocation.

Second, the frequency of thrombophilias was equally distributed between the 2 randomized groups and, as reported in the article supplement, we found no heterogeneity of the study treatment effect in subgroups of patients with and without thrombophilia at 18 months (relative risk reduction of the primary outcome, 90% in the 94 patients with thrombophilia, 70% in 255 patients without thrombophilia, and 77% in all 371 patients). Therefore, our observation that an additional 18 months of warfarin therapy produced a major benefit during the study treatment period is unlikely to be driven by patients with thrombophilia.

We agree that thrombophilia screening in our study was not exhaustive. Because blood samples were collected at inclusion of patients while taking warfarin, we could not measure protein C and protein S levels and lupus anticoagulant. However, the prevalence of such abnormalities is expected to be low (1% to 3% for each)[1] and equally distributed between the 2 groups so that the treatment effect observed at 18 months and at 42 months is unlikely to be substantially affected.

We did not require systematic thrombophilia screening before inclusion in the study. Systematic screening for thrombophilias in patients with unprovoked venous thromboembolism is questionable because most thrombophilias are not associated with a demonstrated independent increased risk of recurrent venous thromboembolism in randomized trials.[2,3] This is particularly true for common thrombophilias (eg, heterozygous factor V Leiden or prothrombin gene variant).[2,3] The available relative risk estimates of recurrence associated with major thrombophilias appear to be weak (relative risks of about 2).[4]

Clinical guidelines[5,6] do not recommend systematic extensive thrombophilia screening for all patients with unprovoked venous thromboembolism, and, consistent with these guidelines, some patients in the PADIS-PE trial did not have previous extensive thrombophilia testing.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Couturaud reported receiving a grant from Pfizer; personal fees from AstraZeneca and Bayer; and travel expenses from Bayer, Daiichi Sankyo, Leo Pharma, Intermune, and Actelion. Dr Meyer reported receiving a grant and travel support from Bayer; receiving grants and serving on boards (uncompensated) for Boehringer Ingelheim, Leo Pharma, and Sanofi; serving as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Leo Pharma, and Pfizer; serving on boards (uncompensated) for Bayer, Bristol-Myers Squibb and Pfizer; and receiving travel support from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Leo Pharma, and Sanofi. No other disclosures were reported.

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Treatment Trends for Prostate Cancer

To the Editor Drs Cooperberg and Carroll highlighted a recent increase in active surveillance for patients with low-risk prostate cancer enrolled in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry.[1] However, the study also demonstrated that radical prostatectomy continues to be the primary management strategy in patients with low-, intermediate-, and high-risk disease during 2010-2013 and that the use of radical prostatectomy increased between 2005-2009 and 2010-2013 (with a concomitant decline in radiation therapy) in patients with intermediate- and high-risk disease.

These changes in management may be consistent with the concept of treatment migration, in which the increase in radical prostatectomies in patients with higher-risk disease corresponds to the lower use of radical prostatectomy in patients with low-risk disease due to the increase in surveillance. This raises the question whether the net number of prostatectomies has declined.

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The increase in the use of radical prostatectomy for patients with high-risk disease was seen despite the National Comprehensive Cancer Network guideline recommendations and mature randomized trial data demonstrating overall survival benefit for combination radiation and androgen deprivation therapy vs androgen deprivation alone.[2] In contrast, surgery has not been directly compared in the contemporary era with another treatment modality in patients with high-risk disease in a prospective randomized fashion.

The spectra of CaPSURE trends reflect the rapidly evolving state of prostate cancer management and suggest that practice patterns are not always driven by new level 1 evidence but may be subject to clinical intuition, conventional wisdom, potential bias, and market forces. A wide variation in management strategies based on physician specialty was shown for patients with low-risk prostate cancer in a recent Surveillance, Epidemiology, and End Results analysis.[3]

Collectively, these findings highlight the importance of evidence-based practice, including multidisciplinary models of care that support consensus guideline-directed management and provide a forum for shared and informed patient decision making.

Although multidisciplinary clinics may not be feasible or cost-effective in many health care settings, they are effective at shifting management strategies, including increased enrollment in active surveillance.[4] In the future, studies such as the Prostate testing for cancer and Treatment (ProtecT) trial will further inform the appropriateness of trends in management for patients with localized prostate cancer.[5]

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply The goal of our study was not to determine or imply the optimal treatment for patients with high-risk prostate cancer, but rather to document changes in practice patterns, which appear to be driven increasingly by cancer risk. This is good news for patients who for years have faced well-documented overtreatment and undertreatment.

We agree the overall rate of prostatectomy has remained relatively constant, but stress that surgery is now being offered more often to men more likely to benefit. Our data do not allow inferences regarding the specific reasons driving decisions between surgery and radiation therapy.

Drs Voog and Efstathiou cite a trial of androgen deprivation therapy alone vs androgen deprivation therapy plus radiation therapy[1] as the best evidence supporting a role for local therapy, rather than systemic therapy alone, for management of patients with high-risk disease. We support this approach.

The trial, however, was uninformative with respect to the question of radical prostatectomy vs radiation therapy. Furthermore, the National Comprehensive Cancer Network guideline endorses both radiation therapy with androgen deprivation therapy and radical prostatectomy with lymphadenectomy for patients with high-risk disease.

The lack of contemporary trials randomizing men to radical prostatectomy compared with radiation therapy does not imply that radiation therapy can be assumed superior. On the contrary, multiple studies (recently reviewed[2,3]) performed in a wide range of contexts have found cancer-specific and overall survival advantages (up to 3 fold) favoring radical prostatectomy over radiation therapy as initial management. Although these studies are of variable quality and not without limitations, some reported prospective cohorts and used careful risk adjustment procedures and thus cannot be rejected out of hand.

With Voog and Efstathiou, we anticipate the results of the ProtecT trial. However, the initial reports have indicated that of the 1099 men randomized to radical prostatectomy or radiation therapy, only 10% have prostate-specific antigen levels of 10 ng/mL or higher, and just 2% have Gleason tumor scores of 8 to 10.[4] Therefore, the risk exists that, as with the PIVOT trial,[5] a null overall result may mask a true survival difference among an underpowered high-risk subset of patients.

Ultimately the debate between radical prostatectomy and radiation therapy for high-risk prostate cancer may be a false one. Historically, much of the evidence base and debate around prostate cancer management has focused on low-risk disease, which, according to a growing consensus should be managed preferentially with active surveillance rather than either radical prostatectomy or radiation therapy. The result of this skewed literature, together with the greater incidence of low-risk disease, is that important truths regarding high-risk disease may have been obscured.

For high-risk prostate cancer, as for other aggressive malignancies, the best outcomes might be obtained through multimodal treatment, and the questions should focus not on which modality is best, but rather on optimizing sequences, intensities, and timing and tailoring these to individual situations for patients.[6]

We agree with Voog and Efstathiou that men with high-risk prostate cancer are best served in referral centers offering multidisciplinary care and, where applicable, given the op-

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portunity to participate in clinical research (both randomized trials and high-quality cohort studies).

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Cooperberg and Carroll reported receiving institutional research grants from Myriad Genetics, Genomic Health, and Genome Dx. Dr Cooperberg also reported receiving personal fees from Myriad Genetics, Dendreon, Astellas, Bayer, and Janssen.

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CORRECTION

Incorrect References and Figure Caption Wording: In the Review entitled "Evaluation and Treatment of Pericarditis: A Systematic Review,"[1] published in the October 13, 2015, issue of *JAMA*, there were incorrect references and figure caption wording. On page 1502, in the first full paragraph, sixth line, reference 22 should be reference 23. On page 1503, in the Figure 4 caption, 13th line, the word "increased" should not be included, and in the fifth line from the bottom, "interventricular independence" should read "ventricular interdependence." On page 1504, in the last paragraph, first line, the citation to reference 23 should be reference 51. In Table 2, the citations to references in column 1 should be as follows: for aspirin/nonsteroidal anti-inflammatory drugs, references 11 and 37; for colchicine, references 1, 2, 13-18, and 37-40; for azathioprine, reference 41; for intravenous immunoglobulins, references 42 and 43; and for subcutaneous anakinra, references 44 and 45. On page 1506, reference 54 should be deleted; current reference 53 should be reference 54, and the new reference 53 is Imazio M, Brucato A, Maestroni S, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis. *Circulation*. 2011;123(10):1092-1097. This article was corrected online.

1. Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. *JAMA*. 2015;314(14):1498-1506.

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