

bowel in eradicating the septic focus, which is consistent with the LOLA trial.<sup>1</sup> Furthermore, the reoperation rate was significantly higher in the laparoscopic lavage group (20.3%) than in the resection group (5.7%).

Dr Roberts questions the classification of reoperation as a severe complication. We would like to clarify that it was the event leading to reoperation that was considered a complication. In many cases, these were septic complications. Prolonged sepsis and repeated general anesthesia in severely ill patients is hazardous. The study did not include some of the most seriously ill patients, in whom it may have been even more important to get immediate control of the infective focus.

Laparoscopic lavage carries the danger of recurrence because the diseased colon is left in-situ. Previous trials have shown that a delayed resection was necessary in several patients treated with laparoscopic lavage.<sup>1,2</sup> Not resecting a perforated tumor, as in 4 patients in our study, is another major concern. We agree that a Hartmann procedure carries morbidity and perhaps primary anastomosis could be an option in more patients.<sup>3</sup> In selected patients, laparoscopic lavage or nonoperative management may still be an option.<sup>4</sup> However, further research is needed to find the right selection criteria. The long-term results of our trial are currently being collected and will hopefully enlighten these issues.

Dr Mandrioli and colleagues question whether the preoperative randomization leading to the inclusion of some Hinchey grade I and II patients (n = 10 144) in this trial might have favored the resection group. We emphasize that 1 inclusion criterion was clinical indication for surgery. Furthermore, Hinchey grade I or II patients would probably have more benefit than harm from laparoscopic lavage compared with resection. This notion is supported by a study by Myers et al<sup>5</sup> in which a higher proportion of Hinchey grade II patients were included and considerably better results were obtained with laparoscopic lavage. We consider intraoperative randomization to be more susceptible to bias because Hinchey grading is not always straightforward.

Mandrioli and colleagues also question the choice of procedure for patients randomized to resection. Our aim was to compare laparoscopic lavage with common practice, which is why we chose a pragmatic design. The distribution of resection procedures was quite similar in included patients and patients treated outside the SCANDIV trial. Additionally, Mandrioli and colleagues are concerned regarding the technical skills of the surgeons in the laparoscopic lavage group. We included analysis of the variable "most experienced surgeon on the team" and it had no effect on the primary outcome. The frequency of secondary peritonitis, abdominal abscesses, and reoperations was similar in our trial and another recently published trial.<sup>1</sup>

Johannes Kurt Schultz, MD  
Sheraz Yaqub, MD, PhD  
Tom Øresland, MD, PhD

**Author Affiliations:** Department of Gastrointestinal Surgery, Akershus University Hospital, Lørenskog, Norway (Schultz); Department of

Gastrointestinal Surgery, Oslo University Hospital, Oslo, Norway (Yaqub); University of Oslo, Oslo, Norway (Øresland).

**Corresponding Author:** Johannes Kurt Schultz, MD, Department of Gastrointestinal Surgery, Akershus University Hospital, PB 1000, 1478 Lørenskog, Norway (josc@ahus.no).

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

1. Vennix S, Musters GD, Mulder IM, et al; Ladies trial collaborators. Laparoscopic peritoneal lavage or sigmoidectomy for perforated diverticulitis with purulent peritonitis: a multicentre, parallel-group, randomised, open-label trial. *Lancet*. 2015;386(10000):1269-1277.
2. Cirocchi R, Trastulli S, Vettoretto N, et al. Laparoscopic peritoneal lavage: a definitive treatment for diverticular peritonitis or a "bridge" to elective laparoscopic sigmoidectomy?: a systematic review. *Medicine (Baltimore)*. 2015; 94(1):e334.
3. Feingold D, Steele SR, Lee S, et al. Practice parameters for the treatment of sigmoid diverticulitis. *Dis Colon Rectum*. 2014;57(3):284-294.
4. Sallinen VJ, Mentula PJ, Leppäniemi AK. Nonoperative management of perforated diverticulitis with extraluminal air is safe and effective in selected patients. *Dis Colon Rectum*. 2014;57(7):875-881.
5. Myers E, Hurley M, O'Sullivan GC, Kavanagh D, Wilson I, Winter DC. Laparoscopic peritoneal lavage for generalized peritonitis due to perforated diverticulitis. *Br J Surg*. 2008;95(1):97-101.

## Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer

**To the Editor** In an update of their randomized clinical trial, Dr D'Amico and colleagues<sup>1</sup> reported that combined radiation therapy (RT) and androgen deprivation therapy (ADT) was no longer associated with an overall survival benefit among 206 men with unfavorable localized prostate cancer after a median of 16.6 years.

These observations are inconsistent with 2 prior reports of this trial and with the results of multiple randomized trials (involving >8000 men) that have consistently demonstrated a survival benefit with the addition of ADT for men receiving RT with intermediate, high-risk, and locally advanced prostate cancer.<sup>2</sup>

In addition, D'Amico and colleagues performed an unplanned exploratory analysis of patients with moderate or severe comorbidity and reported that these men had a statistically significantly increased risk of overall and cardiac mortality associated with RT and ADT. Although the authors acknowledged study limitations including low event rates (only 3 prostate cancer deaths and 6 cardiac-related deaths among the 25 men with moderate or severe comorbidity that received RT alone), alternative contributing factors including underpowered end points or a late wave in other causes of death may account for the observations.

In contrast to the study by D'Amico and colleagues, a large randomized clinical trial of men with localized prostate cancer demonstrated that the addition of ADT to RT improved overall and disease-specific survival with no significantly increased risk of cardiovascular mortality.<sup>3</sup> This study analyzed more than 1900 patients and included more than 400 men deemed at greater risk for cardiovascular mortality based on age and history of cardiovascular disease or diabetes. These data are consistent with a meta-analysis that included more than 4000 men treated with RT with or without ADT and more than 500 cardiac-related deaths that

demonstrated no increased risk of cardiovascular mortality associated with ADT.<sup>4</sup>

Based on the best available and most consistent level 1 evidence, RT and ADT remain the standard of care for patients with intermediate and high-risk prostate cancer. In addition, most available data show that treatment including ADT does not increase cardiovascular mortality risk, including in patients with cardiac risk factors.<sup>3,5</sup> Nevertheless, toxicity of therapy and competing causes of mortality should be considered within the context of appropriate prostate cancer management options during informed decision-making discussions with patients.

**Justin C. Voog, MD, PhD**  
**Matthew R. Smith, MD, PhD**  
**Jason A. Efstathiou, MD, DPhil**

**Author Affiliations:** Harvard Radiation Oncology Program, Boston, Massachusetts (Voog); Genitourinary Malignancies Program, Massachusetts General Hospital, Boston (Smith); Department of Radiation Oncology, Massachusetts General Hospital, Boston (Efstathiou).

**Corresponding Author:** Jason A. Efstathiou, MD, DPhil, Department of Radiation Oncology, 100 Blossom St, Cox 3, Massachusetts General Hospital, Boston, MA 02114 (jefstathiou@partners.org).

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

1. D'Amico AV, Chen M-H, Renshaw A, Loffredo M, Kantoff PW. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA*. 2015;314(12):1291-1293.

2. Pagliarulo V, Bracarda S, Eisenberger MA, et al. Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol*. 2012;61(1):11-25.

3. Voog JC, Paulus R, Shipley WU, et al. Cardiovascular mortality following short-term androgen deprivation in clinically localized prostate cancer: an analysis of RTOG 94-08. *Eur Urol*. 2016;69(2):204-210.

4. Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA*. 2011;306(21):2359-2366.

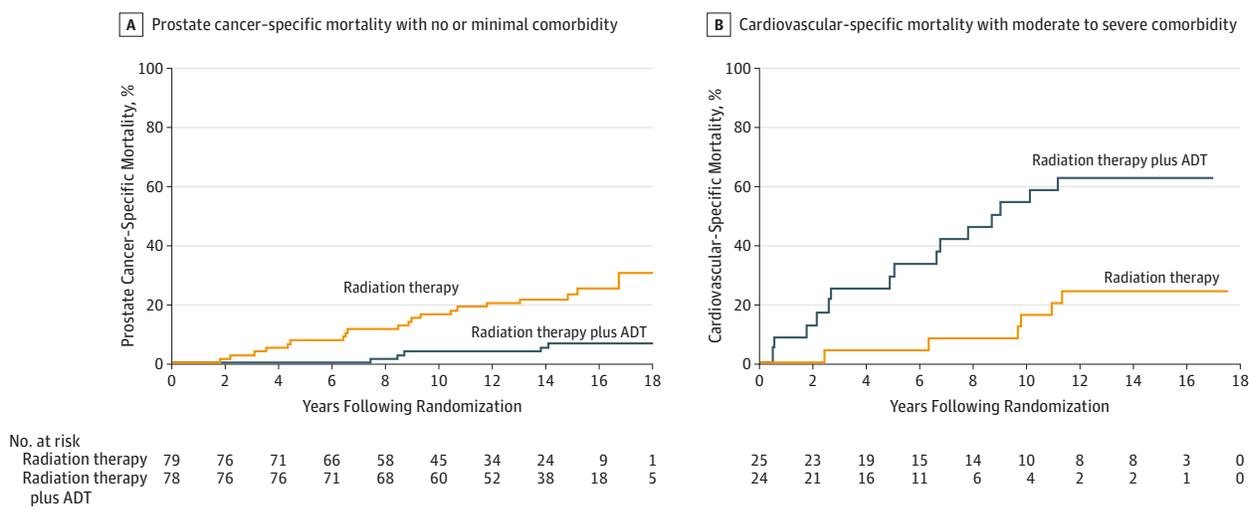
5. Efstathiou JA, Bae K, Shipley WU, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol*. 2009;27(1):92-99.

**In Reply** We agree with Dr Voog and colleagues that combining external beam RT with ADT remains the standard of care for men with intermediate or high-risk<sup>1</sup> prostate cancer. We also wish to highlight that across our entire study cohort there was no increase in the risk of cardiac death in men randomized to receive RT compared with RT and ADT (hazard ratio, 0.74 [95% CI, 0.40-1.39]; *P* = .36). This result is consistent with the study of more than 1900 men<sup>2</sup> mentioned by Voog and colleagues and the meta-analysis<sup>3</sup> evaluating this association.

However, the long-term results of our study raise the possibility that a deleterious interaction between ADT use and survival exists in men who have moderate or severe comorbidity as defined using the Adult Comorbidity Evaluation 27 metric, which has been validated in patients with cancer.<sup>4</sup> This deleterious interaction compounded over the median follow-up time of 16.6 years was enough to offset the previously noted significant survival benefit of adding ADT to RT in the overall study cohort. Specifically, the **Figure** shows that although only 24% of men had moderate or severe comorbidity, the increase in cardiac death in these men randomized to ADT exceeded the reduction in death from prostate cancer in the 76% of men with no or minimal comorbidity randomized to ADT.

The evidence provided by our study in which a validated metric for comorbidity<sup>4</sup> was used could be considered more robust than the evidence provided by studies attempting to define comorbidity subgroups without using a validated metric.<sup>2</sup> In addition, we reported in Table footnote “e” in the Research Letter that the power to detect the observed and significant interaction between ADT use and comorbidity for the end point of cardiac death was 86.5%, which is adequately powered by standard statistical practice guidelines.

**Figure. Prostate Cancer-Specific and Cardiovascular-Specific Mortality Among Men by Randomized Treatment Group**



ADT indicates androgen deprivation therapy.

We look forward to the results of the Radiation Therapy Oncology Group 0815 randomized trial, which is using the same randomized treatment groups as our trial but with higher dose RT and including men with intermediate-risk prostate cancer who have moderate to severe comorbidity. It includes a prerandomization stratification by comorbidity using the validated comorbidity metric.<sup>4</sup>

Therefore, an answer to whether men with intermediate-risk<sup>1</sup> prostate cancer and moderate to severe comorbidity experience prolonged, shortened, or no significant change in survival when ADT is added to RT will be forthcoming.

**Anthony V. D'Amico, MD, PhD**

**Ming-Hui Chen, PhD**

**Philip W. Kantoff, MD**

**Author Affiliations:** Department of Radiation Oncology, Dana Farber Cancer Institute, Boston, Massachusetts (D'Amico); Department of Statistics, University of Connecticut, Storrs (Chen); Department of Medicine, Dana Farber Cancer Institute, Boston, Massachusetts (Kantoff).

**Corresponding Author:** Anthony V. D'Amico, MD, PhD, Department of Radiation Oncology, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 ([adamico@partners.org](mailto:adamico@partners.org)).

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

- Mohler JL, Kantoff PW, Armstrong AJ, et al; National Comprehensive Cancer Network. Prostate cancer, version 2.2014. *J Natl Compr Canc Netw*. 2014;12(5):686-718.
- Voog JC, Paulus R, Shipley WU, et al. Cardiovascular mortality following short-term androgen deprivation in clinically localized prostate cancer: an analysis of RTOG 94-08. *Eur Urol*. 2016;69(2):204-210.
- Nguyen PL, Je Y, Schutz FA, et al. Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. *JAMA*. 2011;306(21):2359-2366.
- Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA*. 2004;291(20):2441-2447.

### Targeted Text Messaging Support for Patients With Coronary Heart Disease

**To the Editor** Dr Chow and colleagues<sup>1</sup> reported the results of a randomized clinical trial, the Tobacco, Exercise, and Diet Messages (TEXT ME) trial, in which large effects on cardiovascular risk factors were found for a modest text message intervention in a sample of patients with coronary heart disease. The authors conveyed the impression that they analyzed changes over time in risk factors, as when they reported “concurrent reductions” in risk factors or “change” in low-density lipoprotein cholesterol (LDL-C) level, systolic blood pressure, or body mass index. This language is misleading, as the data analyses focused on differences between intervention and control groups in 6-month risk factor levels rather than on treatment-related changes over time. For example, the “change in systolic blood pressure” of  $-7.6$  mm Hg was not a change over time but a difference between the mean blood pressure readings taken between the intervention and control groups at 6 months. The only change over time in blood pressure was an increase in blood pressure in the control group. Comparing the data in Tables 1 and 2 in the article, the control group appeared to have a

mean increase in systolic blood pressure of 7.3 mm Hg, whereas the experimental group showed a decrease of about 0.8 mm Hg. Targeted text message interventions may have a promising future, but it will be difficult to make progress unless findings are accurately depicted in the scientific literature.

**Tom Kamarck, PhD**

**Author Affiliation:** Department of Psychology, University of Pittsburgh, Pittsburgh, Pennsylvania.

**Corresponding Author:** Tom Kamarck, PhD, Department of Psychology, University of Pittsburgh, 210 S Bouquet St, Pittsburgh, PA 15213 ([tkam@pitt.edu](mailto:tkam@pitt.edu)).

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

- Chow CK, Redfern J, Hillis GS, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. *JAMA*. 2015;314(12):1255-1263.

**In Reply** The TEXT ME study was a randomized clinical trial designed to evaluate the effects of a mobile phone text messaging support program in addition to the standard secondary preventive care offered to patients with coronary heart disease. The primary outcome of the study was level of plasma LDL-C at 6 months, and the trial was designed to study the mean difference between the intervention and control group at that point. We used analysis of covariance to analyze outcomes with the baseline values as covariates<sup>1</sup>; analysis of variance of change from baseline was not used in any of the analyses. This is explained in footnote 2 of the end points table (Table 2 in the article), and the statistical comparisons in this table refer to the differences between the 2 randomized groups at 6 months, rather than change within a particular group from baseline.

We acknowledge that some of the language used in describing the results may have confused readers. For example, in the fourth and fifth line after the heading “Effect on Objective Measures of Risk Factors,” the word “change” should have been “difference,” and this sentence should have read “LDL-C level, systolic blood pressure, and BMI at 6-month follow-up were all significantly lower in the intervention group compared with the control group (difference in LDL-C level,  $-5$  mg/dL [95% CI,  $-9$  to  $0$ ]; difference in systolic blood pressure,  $-7.6$  mm Hg [95% CI,  $-9.8$  to  $-5.4$ ]; difference in BMI,  $-1.3$  [95% CI,  $-1.6$  to  $-0.9$ ])....” The article has been corrected online, and a correction accompanies this letter.

**Jay Thakkar, MBBS**

**Julie Redfern, PhD**

**Clara K. Chow, MBBS, PhD**

**For the TEXT ME Investigators**

**Author Affiliations:** Westmead Hospital, Sydney, Australia (Thakkar); The George Institute for Global Health, Sydney Australia (Redfern); University of Sydney, Sydney, Australia (Chow).

**Corresponding Author:** Clara K. Chow, MBBS, PhD, Cardiovascular Division, The George Institute for Global Health, Missenden Rd, PO Box M201, Camperdown, NSW 2050, Australia ([cchow@georgeinstitute.org.au](mailto:cchow@georgeinstitute.org.au)).