

ing regulatory requirements necessary to obtain approval of BG-12 for general clinical use.

The study design was based on phase 2 results that showed a 32% reduction in the annualized relapse rate associated with the 240-mg thrice-daily dose.¹ Because this efficacy was similar to that of approved first-line injectable therapies, a phase 3 study to test the superiority of BG-12 over first-line therapies was not considered feasible, and a noninferiority design did not have an accepted regulatory pathway for treatments for multiple sclerosis. Nevertheless, the point estimates and 95% confidence intervals for the relative efficacy of BG-12 as compared with glatiramer acetate provide valuable information on the benefit–risk profile that allows physicians to make an informed comparison.

This concurrent evaluation of two drugs is stronger than the typical practice of cross-trial comparisons, although heterogeneity in treatment response among patients needs to be recognized.

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

1. Kappos L, Gold R, Miller DH, et al. Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study. *Lancet* 2008;372:1463-72. [Erratum, *Lancet* 2009; 373:1340.]

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Functional Outcomes after Treatment for Prostate Cancer

TO THE EDITOR: Resnick et al. (Jan. 31 issue)¹ compare prostatectomy with radiotherapy with respect to long-term function, and they raise several matters of concern. Better functional outcomes were associated with radiotherapy at 2 and 5 years after diagnosis, but these improvements disappeared at 15 years. This finding was probably biased by the dramatic reduction in the sample size (by up to 75% in the radiotherapy group, with fewer than 150 patients who could be evaluated) that rendered the “long-term response” inconclusive. This reduction in sample size was partially due to the lack of a long-term survey response rate but also to overall mortality that was much higher in the radiotherapy group. Treatment details on the radiation dose and fields and on the nerve-sparing technique were not reported. What accounts for the higher overall mortality in the radiotherapy group? Finally, unlike the previous Prostate Cancer Outcomes Study (PCOS) articles,^{2,3} in the domain of voiding function, relevant questions on urinary urgency, which is more often associated with radiotherapy, are missing.

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1. Resnick MJ, Koyama T, Kang-Hsien F, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368:436-45.

2. Potosky AL, Harlan LC, Stanford JL, et al. Prostate cancer practice patterns and quality of life: the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 1999;91:1719-24.

3. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 2004; 96:1358-67.

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TO THE EDITOR: In their article about long-term urinary, bowel, and sexual function after radical prostatectomy or external-beam radiation therapy in men with a diagnosis of prostate cancer, Resnick et al. conclude that there were no significant relative differences in disease-specific functional outcomes at 15 years of follow-up, although an increased risk of erectile dysfunction and urinary incontinence at 2 and 5 years was observed among men treated with prostatectomy as compared with radiotherapy, and an increased risk of bowel urgency at 2 and 5 years was observed among men treated with radiotherapy as compared with prostatectomy.

However, the patients involved in this study had received a diagnosis between the ages of 55 and 74 years. The authors have included the age

at diagnosis as a covariate in the logistic-regression models. Although they note that the long-term decline in functional outcomes was possibly due to age, they did not present results stratified according to age.

We think that testing the interaction of age at diagnosis with the type of treatment, and possibly stratifying according to age, might help to clarify the role of aging in this long-term decline.

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THE AUTHORS REPLY: Rocco et al. note the lack of significant differences in functional outcomes between the surgery and radiotherapy cohorts at 15 years. We agree that the observed absolute differences arouse concern over differential attrition according to treatment group and overall reduction in sample size, and we specifically discuss this in our article. Any long-term observational study involving an older cohort is limited by attrition, and there are few, if any, options to adequately control for this phenomenon. It was this very issue of sample size that prevented us from performing age-stratified analyses, as rightly suggested by Mesrine et al.

Rocco et al. also note the differential overall mortality with respect to treatment. Given the observational design of our study, the prostatectomy and radiotherapy cohorts were not balanced with regard to age or coexisting conditions. Accordingly, the finding of differential survival among treatment groups in our study is not surprising and probably reflects differences in baseline characteristics, treatment effectiveness, or some combination thereof. A detailed analysis of these survival differences is under way.

Although Rocco et al. question the lack of information on radiation dose or use of the nerve-sparing surgical technique, the original purpose of the PCOS was to “[provide] data on the impact of interventions in ‘real-world’ community practice settings.”¹ It is our strong belief that the results are reflective of general community practice and that, although stratification according to technique might be of interest to physicians, it is of less concern to patients at the point of care. In addition, surgical and radiotherapy techniques have evolved considerably since the enrollment of our cohort in 1994 through 1995.

Finally, Rocco and colleagues note that we provided no information on urinary urgency. We used the more comprehensive and validated Expanded Prostate Cancer Index Composite (EPIC)² in the 15-year survey, which precluded direct comparison with the item on urinary urgency that was used in earlier surveys conducted before EPIC existed.

In summary, observational data remain an essential resource to help inform decision making among men with newly diagnosed localized prostate cancer, particularly without adequate level I evidence. We trust that, with our presentation of appropriate and valid data and acknowledgment of the limitations of the analysis, readers can draw their own conclusions.

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

1. Potosky AL, Harlan LC, Stanford JL, et al. Prostate cancer practice patterns and quality of life: the Prostate Cancer Outcomes Study. *J Natl Cancer Inst* 1999;91:1719-24.

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Alcohol Use in Adults

TO THE EDITOR: In his Clinical Practice article, Friedmann (Jan. 24 issue)¹ mentions some medications that are approved by the Food and Drug Administration (FDA) and some drugs that are used on an off-label basis for treating alcohol

dependence. We think that sodium oxybate, which has an off-label use, also warrants mention. Sodium oxybate is approved by the FDA to manage narcolepsy. In some European countries, since it is as effective as benzodiazepines, sodium oxy-