

experience of the patients from Stanford to evaluate this theory.

With regard to the method of volume estimation utilized, Dr. Wasserman implies that the prolate spheroid formula utilized for volume determination at our facilities (both VA and university) is less accurate because of the omission of the longitudinal dimension. We have established that the longitudinal dimension of the prostate measured by ultrasound correlated extremely poorly ($r = 0.37$) with the longitudinal dimension of the actual prostate gland in 150 patients undergoing ultrasound prostatic measurements followed by prostatectomy and measurement of the actual dimensions of the fresh prostate gland.¹ In contrast, the ultrasound-determined transverse and anteroposterior dimensions correlated well with that of the prostate gland (0.78 and 0.79, respectively). The omission of this longitudinal dimension actually improved the accuracy of volume estimation. We showed that in a direct comparison of the formulas for calculating prostate volume, the prolate spheroid formula utilized at our institution correlated best ($r = 0.94$) with the actual prostate volume, particularly in comparison to the prolate ellipsoid formula utilized by Dr. Wasserman ($r = 0.90$).¹

We are unconvinced of the potential regional differences in prostate size suggested in the above letter. The only scientifically sound means of prostate volume comparison is the use of the identical equipment and volume estimation techniques at the facilities to be compared, as was done in our study as well as in the comparison performed in Washington. Both sites found statistically significant differences in the prostate volumes of the VA versus university patient populations. The differences in the average biopsy-negative prostate volumes listed for the three VA centers in the above letter are not really comparable because each center utilized different equipment and techniques. In addition, these values are actually within the range of error for prostate volume determination: With the prolate ellipsoid formula utilized in the above letter, the average error (\pm SD) is 12.1 ± 8.8 g, whereas the average error (\pm SD) for the prolate spheroid formula used at our facilities is 8.8 ± 7.1 g.¹

We certainly do not claim that the statements of caution expressed in our article regarding the selection bias of scientific studies originating from the VA population are novel. Rather, we offer concrete evidence of these differences as opposed to assumptions.

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Bicalutamide Versus Flutamide in Combination Therapy

TO THE EDITOR:

Despite the fact that the study of Schellhammer *et al.*¹ does not have the statistical power to demonstrate any efficacy of bicalutamide (Casodex),² the follow-up data at 160 weeks from the same study are presented without any acknowledgment of such a limitation of the original study

design.³ Essentially, the criterion was that a 25% inferior response was required to be able to demonstrate that bicalutamide was inferior to flutamide (Eulexin).¹ However, because flutamide accounts for only 19.7% of the effect on survival in the combination of leuteinizing hormone-releasing hormone agonist (LHRH-A) plus flutamide,⁴ it becomes clear that bicalutamide could never be shown to be inferior to flutamide in such a trial. In fact, the replacement of flutamide by a placebo (instead of bicalutamide) should have given a 19.7% inferior response, this difference being within the 25% range needed to declare bicalutamide not different from flutamide and thus permitting placebo to be called a "drug" not different from flutamide. Clearly, because of its deficient design, the study of Schellhammer *et al.*¹ is not useful for assessing any activity of bicalutamide.

In addition to the above, some comments specific to the recent update of this study³ seem appropriate. Possibly after recognition of the weakness of treatment failure used as an end point in the original reports,^{1,5} a new end point, namely time to progression, is now presented. It should be mentioned that time to progression was not originally indicated as either a primary or secondary end point of the trial.^{1,5} The information required on progression was thus evaluated retrospectively in 34% of patients.³ Because the design of the Schellhammer *et al.*¹ study did not allow statistically significant differences for the major end points to be shown, it is not surprising that the results reported at a follow-up of 160 weeks still do not show significant differences either for time to progression or for survival.³

A fundamental argument, as indicated previously,² is that a drug needs to be taken by the patient to show benefits. Consequently, the fact that 34% more patients were at risk of not receiving treatment in the flutamide arm at 49 weeks¹ needs to be taken into account in all the follow-up analyses, and an appropriate correction needs to be introduced. In fact, these patients were admittedly removed from the flutamide arm for non-cancer-related reasons.¹ It is thus reasonable to assume that these patients, had they not been prematurely removed from the study, would have shown a response comparable to those who remained under treatment. This reasonable correction is illustrated in Figure 1: the hazard ratio of 0.93 for time to progression assigned in favor of bicalutamide at 160 weeks³ should thus be multiplied by 1.34 to obtain the expected hazard ratio had the patients removed from treatment in the flutamide arm for non-cancer-related reasons remained under treatment, thus leading to a hazard ratio of 1.25 in favor of the patients who received flutamide. Similarly, the hazard ratio for time to death goes from 0.87 to 1.17 in favor of the flutamide arm. The values thus obtained are close to those observed in the National Cancer Institute (NCI) 036 trial⁴ and EORTC 30853 trial.⁶

Another important argument is that 160 weeks of follow-up is too short a period in which to reach a statistically significant difference on survival in a population of patients with metastatic prostate cancer. This limitation has been well recognized by the senior author of the present study.⁷ Reference was then made to the EORTC 30853 trial, where no statistically significant advantage of the combination of goserelin acetate (Zoladex) plus flutamide versus orchiectomy was observed at 2.5 years (130 weeks), whereas a 15.1-month cancer-specific survival advantage was observed in favor of combination therapy at 5 years.⁶

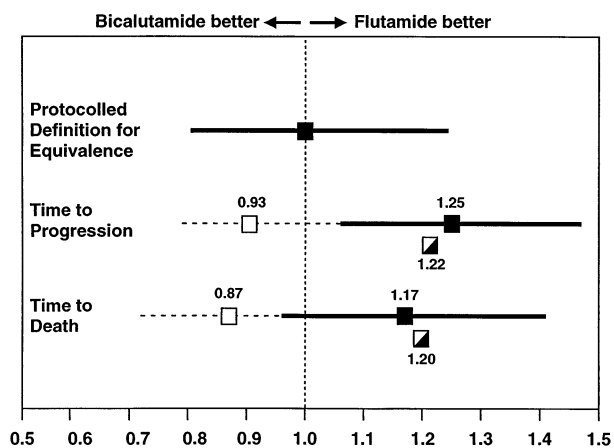


FIGURE 1. Hazard ratio and 95% confidence interval at 160 weeks' median follow-up: open squares (Schellhammer et al.³); open/solid squares, LHRH-A + flutamide versus LHRH-A + placebo (Crawford et al.⁴); and solid squares, data corrected for treatment failure (non-cancer-related).

Similarly, although the study comparing orchiectomy plus nilutamide (Nilandron) versus orchiectomy plus placebo showed no statistically significant advantage at 6 years,⁸ a statistically significant survival advantage was seen at 8.5 years of follow-up.⁹ The same limitation applies to the SWOG-INT 105 trial,¹⁰ which shows a nearly statistically significant survival advantage at 4.5 years in analogy with all other similar studies. A longer follow-up period is likely to be required before the advantage of combination therapy becomes statistically significant compared with monotherapy.

Schellhammer et al.³ suggest that the similarity observed between the relative risk of death and the risk of treatment failure supports the validity of treatment failure as an end point. As mentioned above, our interpretation is very different: patients who are removed from therapy for non-cancer-related reasons will automatically suffer earlier. Thus, it should be recognized that early removal of patients from treatment for non-cancer-related reasons will cause earlier death in these patients. This argument is based on the fact that even the best drug, if not taken by the patient, has no benefit.

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REPLY BY THE AUTHORS:

In response to the letter of Drs. Labrie and Candas, I submit the following: (1) the hazard ratios favor the study drug arm at all end points studied; (2) the study drug is convenient and well tolerated; and (3) if the trial is not good enough to believe, are imaginative alterations more believable?

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