

IN RESPONSE TO DR. LEE

To the Editor: Several independent analyses have all come to the conclusion that the α/β ratio for prostate cancer is probably low (1–5); however, it is important to point out that these are not just the results of data analysis exercises, but were originally suggested (1, 6) on the basis of a well-established radiobiologic principle: Specifically, tissues with low proportions of dividing cells (such as melanomas and most late-responding normal tissues) are very sensitive to changes in fractionation (i.e., show low α/β ratios), so it is hardly a surprise that prostate tumors, with their low proportion of dividing cells, seem to have a low α/β ratio.

With regard to the particular estimate of α/β for prostate to which Dr. Lee refers (5), he is certainly right to point out that randomized trials are the way to go. In fact, our analysis was about as near to being randomized as a retrospective study of a nonrandomized trial could be, in that patients from each arm of the study were retrospectively matched (5) on the basis of the “classic” prognostic indicators: pretreatment PSA, T stage, Gleason score, and age (hereafter PTGA). Dr. Lee’s interesting point is that, because the two-fraction treatments were done, on average, later than the three-fraction treatments, some other independent prognostic indicator that depends on the year of treatment might result in bias. The possibility suggested by the Cleveland group (7–9) is that extracapsular extension risk (rECE) has decreased with year of treatment and is a prognosticator of outcome that is independent of PTGA. This is an interesting suggestion, though others have not seen such a change in rECE with time (10), and several studies have suggested that rECE is not an independent prognosticator, but is predictably related to PTGA (11–13). In this light, any differences in rECE between the two- and the three-fraction groups that are independent of PTGA are likely to be small, and so matching groups based on the “classic” prognostic indicators (PTGA) are likely to be adequate in the current context.

We certainly endorse Dr. Lee’s call for caution regarding clinical trials for hypofractionation or high-dose-rate prostate radiotherapy. Apart from the fraction size to which Dr. Lee refers, the overall time needs to be carefully considered. We are, in fact, in the process of designing suggested “low-risk/high-potential-gain” hypofractionation protocols for clinical trials for prostate radiotherapy (14), which are specifically designed with a cautious eye to the possibility that the relevant α/β value might not be as low as the evidence currently indicates.

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IN REGARD TO REGINE ET AL., *IJROBP* 2002;52:333–338

To the Editor: We read with great interest the article by Regine et al. on “Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastases: Results and implications” (1). Their article is certainly a fine addition to the growing body of literature of patients treated for brain metastases without the addition of whole brain radiation treatment. Retrospective data have shown that in patients who received radiosurgery alone (Whole brain was frequently used for salvage), there was no significant decrement in survival or ultimate overall brain control vs. similar patients treated with initial radiosurgery and whole brain radiation (2). A small, single-institution prospective randomized three-arm trial of patients treated with radiosurgery alone, with radiosurgery + whole brain radiation, and with whole brain radiation only did not reveal a survival difference in any of the arms (3).

Regine et al. should also be commended for the addition of information on symptomatic brain recurrence and neurologic deficit (1). This is particularly important, because there is growing use of radiosurgery without whole brain treatment, with the assumption that this will offer superior neurocognitive function and improved quality of life.

As their final conclusion, Regine et al. note that radiosurgery alone vs. radiosurgery plus whole brain radiation treatment should be evaluated in a prospective randomized trial (1). They also conclude that neurocognitive function and quality of life should be measured, as well.

Since their article has gone to press, a multicenter randomized trial has been approved by the NCI and, at the time of this writing, has just opened for the accrual of patients. The study is the first neurosurgery trial being conducted through the American College of Surgeons Oncology Group (ACOSOG). ACOSOG is a new cooperative group and is committed to advancing Phase III trials. The group is intended to be inclusive of both academic physicians and private practitioners, and both are encouraged to participate in the available trials.

In the new trial (ACOSOG Z0300), all patients will receive radiosurgery and then be randomized to whole brain radiation or observation. The primary end point of the study is overall survival. The secondary end points include time to local failure, quality of life, duration of functional independence, long-term neurocognitive status, and posttreatment toxicity.

The important question of the superiority of whole brain radiation plus radiosurgery vs. radiosurgery alone remains unresolved. We would encour-