Reply to D.A. Hamstra et al and A.P. Sandhu

We appreciate the thoughtful comments made by Hamstra et al and Sandhu about our recently published analysis of cancer-specific and metastasis-free survival after radical prostatectomy (RP) and external-beam radiation therapy (EBRT) for clinically localized prostate cancer.

Both letters point out that patients in our cohort who received radiotherapy (RT) were generally higher risk than those undergoing surgery. We recognize that our analysis was retrospective, and we took great pains to point out the imbalances in the treatment groups. Indeed, our RT cohort had a higher percentage of high-grade cancers, and the selected patients with T3 tumors operated on in the surgery group were likely harboring less bulky disease than were the T3 patients who underwent EBRT. We also carefully pointed out the differences in the proportion of patients with biochemical recurrences who were treated with salvage therapy, as well as the timing of therapy between the two groups.

Several factors, however, caution against explaining away the differences in metastatic and cancer-specific mortality rates between the treatment groups on the grounds of the imbalances in prognostic factors. It does not follow that because two groups differ in terms of risk, then differences in outcome are necessarily attributable only to confounding; for example, smokers tend to eat less healthily than nonsmokers, but that should not imply that smoking does not cause cancer. To adjust for baseline imbalances, we used established prognostic factors as covariates, using several alternative methods to analyze the data with similar results. Our multivariable analyses demonstrated that among the patients we treated, the treatment mode was an independent variable associated with a higher distant metastases rate, regardless of the Gleason score and other variables.

We do agree with Hamstra et al and clearly point out in the article, that the different frequency and timing of salvage therapy could explain, to some degree, the higher rate of metastasis observed in the EBRT group. However, as stated in the article, a time-dependent covariate analysis that accounted for the use of salvage or adjuvant therapy still found a significant increased metastatic risk after EBRT. We also recognize that differences in the timing and frequency of salvage therapy reflect inherent differences in the two treatments studied. After RP, prostate-specific antigen (PSA) is expected to become undetectable within 4 to 6 weeks. If it does not or if it becomes measurable later, cancer recurrence is apparent (median time of 13 months in our study) and salvage RT can be administered with relative safety. Both adjuvant and salvage RT after RP have been shown to reduce the risk of subsequent metastases and death from cancer. In contrast, because the prostate remains in situ after EBRT, PSA fluctuations are not infrequently observed during the post-treatment follow-up period, and recurrences are not detected as early. Indeed, given the uncertainty of the significance of biopsy findings until 2 years after treatment and the fact that biochemical relapse is not considered established until the PSA is elevated more than 2 ng/mL from nadir, local recurrence may not be documented for several years after EBRT. Case series of salvage RP or cryotherapy have not documented reductions in metastases or death from cancer after initial RT, perhaps because such therapies are being delivered when it may be clinically too late.

In summary, we have not concluded nor did we state in the article that EBRT should be abandoned for patients with high-risk prostate cancer. However, we were impressed with the low rate of metastases after RP for high-risk cancers in our series, a treatment previously thought to be inadequate for such patients and never tested against EBRT in a randomized trial.

Both letters suggest that the EBRT used at Memorial Sloan-Kettering Cancer Center was inadequate and imply that, if adequate treatment had been given, results would have been superior. Interestingly, the two groups advocate different reasons why our EBRT was inferior, with Hamstra et al suggesting that long-term androgen-deprivation therapy (ADT) should have been used but Sandhu arguing that image-guided RT would lead to superior outcomes. With respect to the former, although we recognize that long-term ADT is a standard of care as an adjuvant to low-dose EBRT, no randomized trials have demonstrated a benefit of long-term versus short-term ADT in the setting of modern, high-dose RT. With respect to image-guided RT, although this enhancement of treatment delivery provides greater accuracy and we have been using this approach for the last several years, there are no published studies that report improved tumor control using image-guided RT.

There is still a great deal of improvement needed in the management of high-risk prostate cancer, and many questions remain unanswered. The randomized RT trials using ADT and EBRT cited by Hamstra et al are far from home runs. A relatively high percentage of patients develop local and distant recurrence and die of their disease even with EBRT to the prostate and pelvis and long-term ADT. We need better systemic therapies to integrate with optimal local treatments. Fortunately, cooperative group studies are exploring the role of chemotherapy and hormonal therapy in conjunction with RT for high-risk patients, and another study is evaluating similar multimodal therapy before RP. In the meantime, among patients with high-risk cancer treated at our institution with EBRT, our current recommendation is to use high-dose RT to the prostate and pelvic lymph nodes along with long-term ADT. And we prefer to combine brachytherapy with EBRT, when possible, in these patients in an attempt to improve local control. For our patients who choose a surgical approach, our data and those of others suggest that RP provides cancer control comparable to other approaches for high-risk cancers. Because RP can so readily be combined with salvage RT when necessary, it can be an effective option. As with other preferences, the relative benefits and risks of these options can only be established in randomized trials.
Although our retrospective study has limitations, as described in our article and in the letters by Hamstra et al\(^1\) and Sandhu,\(^2\) the data do suggest there may be a benefit to improved local control with RP combined with adjuvant or salvage RT. It would be a mistake to dismiss these data, accepting the null hypothesis of no effect, unless randomized trials contradict these findings. Before such randomized trials, we would in the meantime encourage other institutions to analyze their own clinical experiences to confirm or refute these findings.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES

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