CORRESPONDENCE

Re: Five-Year Update of a Randomized Trial of Alternating Radiotherapy and Chemotherapy Compared With Radiotherapy Alone in Treatment of Unresectable Squamous Cell Carcinoma of the Head and Neck

We wish to comment on the recent report by Merlano et al. (1), from the National Institute for Cancer Research in Genoa, Italy, regarding the use of alternating radiotherapy and chemotherapy for advanced head and neck cancer. An important observation made by the authors is that their findings should be considered with caution. We will limit our comments solely to the results of the radiotherapy-alone arm. Although the authors state that these were unresectable cancers, the stages listed in their Table 1 show that many of the tumors were not extraordinarily advanced. Forty-two of the 77 patients had T1, T2, or T3 cancers. By our staging classification, 18 patients would be classified as stage III, eight patients as stage IVA, and 51 patients as stage IVB.

We have compared our results using radiotherapy alone (with or without the addition of a neck dissection after irradiation) to the results reported by Merlano et al. for radiotherapy alone for equivalent-stage patients. Our data used for this analysis were reported elsewhere (2). Our results have been scaled so that our patient numbers reflect the numbers of patients in each disease stage as were reported by Merlano et al. The observed 5-year results for similar-stage patients were as follows: local-regional control (48% at the University of Florida versus 7% in the Merlano article [as calculated from the authors’ Fig. 1, A, in which the local-regional relapse-free survival rate was 32% of the 22% who completely responded]); 5-year overall survival (33% at the University of Florida versus 10% in the Merlano data); and 5-year relapse-free survival (40% at the University of Florida versus 9% in the Merlano report). We contend that the radiotherapy-alone results reported by Merlano et al. are inexplicably poor and not at all representative of modern-day radiotherapy on the North American continent.

It is extraordinary that 32% of the radiotherapy-alone patients reported by Merlano et al. required split-course irradiation. The total doses of radiotherapy were not particularly high (average, 65.6 Gy). Perhaps the combination of underdosage and the liberal use of treatment interruptions resulted in the poor rates of tumor control. Other factors that may have played a role cannot be evaluated. Of note, in our own data (2), using twice-a-day radiation therapy with a more aggressive radiation scheme (74.4-81.6 Gy at 1.2 Gy twice a day over 6-6.5 weeks) than that used by Merlano et al., an unplanned treatment interruption was necessary in only five (1.2%) of 419 patients.

Certainly, the trial reported by Merlano et al. would have to be more rigorously tested by others because the conventional arm has yielded unprecedentedly low rates of tumor control and survival.

JAMES T. PARSONS
WILLIAM M. MENDENHALL

References


Notes

Affiliation of authors: Department of Radiation Oncology, UF Shands Cancer Center, University of Florida, Gainesville.

Correspondence to: James T. Parsons, M.D., Department of Radiation Oncology, UF Shands Cancer Center, University of Florida, P. O. Box 100385, Gainesville, FL 32610-0385.

Response

Drs. Parsons and Mendenhall state their concern about the behavior of the radiotherapy-alone arm that they deem inexplicably poor. We have already answered a similar comment in 1993 (1). Moreover, we have shown in the report published in the Journal of the National Cancer Institute (Fig. 2) that similar behavior has been reported in other clinical trials performed both in Europe and in the United States.

However, some points must be emphasized: 1) the comparison between series of patients from different studies is fraught with hazard because selection factors going into treatment decisions may differ among treatment centers and with time. 2) Drs. Parsons and Mendenhall report data from their nonrandomized experience with twice-a-day radiotherapy and compare these data with the results of our control arm on the basis of a single daily fraction radiotherapy. Making such a comparison, they implicitly suggest that these two radiotherapy regimens are equivalent and can be compared. We do not hold the same view. 3) However, with regard to the interesting data from the University of Florida mentioned by Drs. Parsons and Mendenhall, the usually favorable behavior of nonrandomized experiences (phase II trials) has been well-known for many years. We agree with Simon (2) that in most situations, such as head and neck cancer, randomized trials are necessary for identifying major advances in treatment: "False innovations are much more numerous than real breakthroughs and it is difficult to distinguish one from the other." 4) Drs. Parsons and Mendenhall suggest that our trial would have to be more rigorously tested by others. Confirmatory trials are always desirable because the possibility of false-positive or false-negative results is never zero. Confirmatory trials are therefore a fundamental step in scientific methodology. One reason why any paper reports a Materials and Methods section is to facilitate replication in confirmatory trials. Science requires reproducibility of data. Nonetheless, we believe that our trial that was randomized and by design avoided some of the pitfalls inherent in