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LETTERS TO THE EDITOR

If subclinical turns into suboptimal

To the Editor: We read with interest the paper by Kundel *et al.* dealing with sequential chemoradiotherapy as an adjuvant approach after complete macroscopic resection for resectable, locally advanced gastric adenocarcinoma[1]. The chemotherapy (CT) regimen consisted of 6 cycles of 5-fluorouracil, 1000 mg/m^2/day administered as a 96-hour continuous infusion on day 1, and cisplatin, 100 mg/m^2 on day 2, every 21 days. Radiotherapy (RT) was delivered 3 weeks after completion of the CT protocol as a single-fraction dose of 6 Gy, using an anterior-posterior parallel-opposed field arrangement, with an irradiated volume consisting of the whole abdomen. Despite all efforts, the outcome data sound dismal and substantially inferior to those of other reported regimens[2,3], even if compared to adjuvantless surgical series[4]. Several hypotheses were put forward to explain this uneffectiveness, such as the small sample size, the type of chemotherapy, the timing of adjuvant treatment, or the radiation schedule delivered. We would like to focus our attention on the last item. A total dose of 6 Gy given in a single fraction might be easily transformed into a conventionally fractionated isoeffective dose using the so-called Withers formula[5]; hence, considering an $\alpha/ß$ ratio ranging between 6 and 10 Gy, which might be considered appropriate for gastric adenocarcinoma, the equivalent dose in 2 Gy fractions (EQD_2) ranges from 7.9 to 9 Gy. If we consider the *in vitro* cell survival data, analyzing the surviving fraction at 2 Gy (SF_2) as a measure of the steepness of the cell survival curves, we get an idea of the clinical response of tumor cells to radiation. Gastric adenocarcinoma might be allocated to the cluster of tumors having an average SF_2 value of roughly 0.5[6]. This means, practically, that it takes up to a total of 60 Gy to reduce an initial number of 10^9 clonogenic cells (which is usually considered the threshold for clinically detectable disease) to a single neoplastic cell. Therefore, a biologically equivalent dose of almost 10 Gy (considering the same slope as above) would lead to a rather ineffective decrease in clonogens to 10^7 cells. Nevertheless, it has been widely postulated that the dose-response relationship for subclinical disease might be slightly different from that of macroscopic disease, leading to the possibility of tumor control even at low doses[7], with a lower threshold and a shallower slope of the dose-response curve in microscopic disease[8]. However, the result is only a more favorable steepness for the correlation between a delivered dose and a biological endpoint, so this scenario should not be overestimated. The fractionation used in the work by Kundel *et al.* has been inspired by similar schedules delivered to different tumor types such as lymphoma, ovarian cancer and small cell lung cancer[9-11]. These tumors are considerably more radiosensitive than adenocarcinoma of the stomach with a SF_2 of roughly 0.2-0.3[5,6]; gastric cancer is much more radioresistant. This would significantly flatten the dose-response curve, erasing the steepness advantage of being in a microscopic context. Hence, the histological type should be carefully considered when choosing a radiation schedule and a total dose to be delivered. As a matter of fact, there is no better way to render a neoplastic cell radioresistant than giving it an inappropriate dose.

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IN REPLY: We appreciate the thorough theoretical review presented by Franco *et al.* in their commentary letter regarding our paper. Moreover, we fully agree with the facts depicted in their letter and with their conclusion that the dose used in our study was suboptimal. However, this is indeed the schedule that was used in our institute between 1996 and 1999, when not all the scientific details concerning the optimal radiotherapy dose and schedule in the adjuvant treatment of gastric adenocarcinoma were available; more importantly, the actual perspective of these details was clearly incomplete at that time. We can just emphasize the concern that directed us in the selection of the dose used in the study. We speculated that administration of whole-abdomen irradiation using a non-fractionated dose of more than 600 cGy to patients who have just recovered from radical gastrectomy and have just completed 6 courses of aggressive chemotherapy such as the combination of cisplatin and protracted infusion of 5-fluorouracil may be associated with unreasonable toxicity. Moreover, this concern was augmented by the adjuvant setting in which our treatment was given and the fact that there were absolutely no pre-exising efficacy data to support the potential risk using higher doses. The cumulative impact of all these facts led us to choose a more conservative approach and a dose that can now clearly be defined as inadequate. Nonetheless, this was indeed the regimen used in our institute during the study period and we think that the theoretical background provided by Franco *et al.* does not necessarily lessen the importance of the clinical data we reported. In fact, the combination of preclinical findings and clinical correlates is the key to real progress in medicine.

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Radiochemotherapy with cisplatin and oral tegafur in advanced head and neck cancer: long-term results of a phase II study

To the Editor: We read with interest this important study from the Department of Radiation Oncology in Spain. The authors concluded that the regimen of simultaneous radiochemotherapy consisting of 2 courses of continuous infusional cisplatin and oral tegafur together with conventional radiation therapy up to a total dose of 70-75 Gy over 9 weeks offers the advantage of its tolerance and toxicity profile. In this paper the authors graded acute and late reactions according to RTOG/EORTC criteria[1]. Being involved in the active management of patients with head and neck cancer we regularly come across cases treated with chemoradiation which have had extensive and severe short- and long-term unwanted effects. We do not provide the initial treatment, this being the province of the clinical oncologist; so the tendency is for us to have a potentially distorted feel for the actual incidence of such significant complications. We would like to draw the attention of the authors to the article by Trotti *et al.*[2] and the development of a new reporting system for summarizing the toxicity burden of cancer treatment. By using this new method the deficiencies and, indeed, serious underestimates made when assessing toxicity by previous methods have been reassessed. Therefore we believe that it is time to reassess the impact of chemoradiotherapy regimes using methods that incorporate validated quality of life assessments and preferably by external objective examiners using these methods. The use of traditional methods, such as those used in this study, that may systematically exclude a large proportion of high-grade adverse outcomes should be avoided. Only then will we be able to see the true figures, both in terms of potential benefits and any potential disadvantages to patients.

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IN REPLY: There is nowadays general agreement that concomitant radiochemotherapy should be offered to patients with inoperable locally advanced head and neck cancer or to those who desire to conserve the organ and its function. Unfortunately, most of the trials addressing this issue have been limited to selected groups of patients not representing the majority of head and neck cancer patients. The risk of unaccept-

able treatment-related toxicity is undoubtedly the main limitation to the inclusion of patients in these trials. The availability of a concurrent radiochemotherapy schedule as proposed by us, with a relatively low toxicity profile, could be of great interest in this setting[1]. Summarizing adequately the treatment-related adverse effects is essential in the conservative management of head and neck cancer. Different scales have been proposed to assess the toxicity related to cancer treatment (RTOG/EORTC, CTCAE v3.0). TAME, a new reporting system proposed by Trotti *et al.*[2], is a promising method that could offer some advantages in the estimation of the risk of treatment complications in head and neck cancer. Nevertheless, and as pointed out by the authors, this method still has limitations and requires standardization in the collection and reporting of adverse effect data. TAME emerges as a very interesting alternative for recording, reporting and comparing toxicities between different treatment schemes; however, its general acceptance and routine use might require some time and the method can not yet be considered as the gold standard for toxicity assessment.

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