Concurrent Radiochemotherapy in Stage IIIA Non-Small-Cell Lung Cancer: Not Just Effectiveness But Very Low Toxicity

To the Editor:

I read with interest the article by Seder and colleagues [1] about two trimodality and one bimodality (radiochemotherapy [RT-CHT]) regimens in patients with stage IIIA non-small-cell lung cancer (NSCLC). One study finding seems to be of special importance, requiring additional consideration.

Recent metaanalysis identified exclusive concurrent RT-CHT as standard treatment in inoperable stage III NSCLC [2]. In addition, trials testing surgery versus exclusive concurrent RT-CHT in (mostly stage III) NSCLC failed to show an advantage for surgically treated patients [3,4]. Therefore, optimization of treatment approaches in locally advanced NSCLC seems to be focusing on toxicity.

A large body of data confirms the potential for increased toxicity of exclusive concurrent RT-CHT, but only when high-dose radiotherapy (RT) is combined with high-dose chemotherapy (CHT). Alternatively, the use of lower doses of daily CHT or altered fractionation (e.g., hyperfractionation), or both [5], showed much less toxicity, including stage IIIA NSCLC [6]. Acute high-grade esophageal and bronchopulmonary toxicity (7% and 8% of patients, respectively) and late high-grade toxicity (7% and 3% patients, respectively) was low, with no treatment-related deaths [6]. This observation contrasts with 2% treatment-related deaths and substantial acute esophageal toxicity reported by of Seder and colleagues [1]. The better toxicity profile we observed could indicate a sparing effect of hyperfractionation or less toxic potential of low-dose daily CHT. Importantly, median survival time of 38 months and a 5-year overall survival of 41% were achieved in our study, seemingly not different from 38% and 54% at 5 years for the preoperative CHT with Gy or 60 Gy, respectively, in the study by Seder and colleagues [1].

Although surgery will occasionally be practiced in this setting, thoracic oncologists should focus on further optimizing what is effective and low toxic. Exclusive concurrent RT and low-dose CHT offers such a scenario.

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Reply

To the Editor:

We read with interest the comments of Dr Jeremic [1] on our recent publication [2] regarding morbidity and mortality associated with multimodality treatment regimens in stage IIIA (N2) non-small cell lung cancer (NSCLC). We agree that concurrent, high-dose (>60 Gy) chemoradiation is standard treatment throughout most of the world for inoperable stage IIIA disease. The question of “operable” in the context of stage IIIA (N2), however, remains poorly defined. Many factors influencing this definition exist, including disease burden (single-station versus multi-station nodal metastases), extent of required resection (lobectomy versus pneumonectomy), the functional status of the patient, and importantly, the concept of “surgical dose” (case volume, experience, and surgical outcomes). Interpretations of the INT 0139 [3] study leave many unresolved questions.

What INT 0139 did clearly show is a cure rate of approximately 20% for concurrent chemoradiation to 60 Gy, albeit with significant morbidity and a 2% mortality rate, a better surgical outcome for those patients achieving mediastinal nodal clearance, and a worse outcome for pneumonectomy compared with lobectomy [3]. Many have interpreted this study as clear evidence for eliminating the potential role of surgery in the clinical management of IIIA NSCLC. The logical extension of this argument is that we should accept an 80% mortality rate for stage IIIA NSCLC, and resign ourselves to tinkering with radiation regimens, even in the face of clear evidence showing that higher doses up to 74 Gy have worse cancer outcomes [4]. This conclusion is nihilistic and unsatisfying to say the least.

Advancing the science for locally advanced NSCLC remains challenging. Optimal sequencing and use of surgery, chemotherapy, and radiation therapy in multimodality treatment regimens will continue to be controversial. The use of surgery for the presence of residual disease after definitive chemoradiation to 60 Gy (the treatment outcome for approximately 80% of patients) also remains controversial with a theoretical but unproven benefit. How best to assign multimodal treatment in the expanding era of targeted therapy is also a game-changing proposition. Ongoing improvements in chemotherapeutic regimens may serve to enhance the role of local therapy (surgery or radiation), such as that seen in the radical change in approach to oligometastatic disease in colorectal cancer. A myopic focus on radiation regimens alone in conjunction with historical systemic treatment is unlikely to realize the possible advances in treating this deadly disease.

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References