

## LETTER TO THE EDITOR

# The Trimodality Treatment Approach in Stage III/pN2 Non-Small Cell Lung Cancer

“Usually Appropriate”  
May Well be a Very  
Inappropriate  
Treatment Option

## To the Editor:

In a recent article, Willers et al<sup>1</sup> presented the American College of Radiology (ACR) appropriateness criteria for the induction and adjuvant therapy of patients with N2 disease of stage III non-small cell lung cancer. Our attention was drawn to a subset of patients in whom the authors have discussed the use of induction radiochemotherapy (RT-CHT) followed by surgery. On the basis of an unplanned subgroup analysis of a single study, the authors cite<sup>2</sup> that trimodality therapy is “usually appropriate” treatment option. Whereas the study in concern was negative by all statistical and scientific measures (which do not take into account a post hoc unplanned analysis or any other surrogates of efficacy), other fully published studies<sup>3,4</sup> also did not show the superiority of trimodality over exclusive concurrent RT-CHT. In addition to that, no high-level evidence exists identifying the extent of surgery (lobectomy vs. pneumonectomy) as an important predictor or even a prognosticator in this setting. Finally, although we completely agree that an experienced thoracic surgeon is always good to have at hand, what about an experienced radiation oncologist? It should be the same way, isn't it? Not to mention the seemingly outdated and, therefore, inferior RT treatment planning and execution aspects

present during INT0139,<sup>2</sup> at least with respect to the current standards, because newer RT technologies can definitely provide a better dose conformity and, hence, more effective RT.

We firmly believe that evidence-based oncology principles should be respected, enabling practicing thoracic oncologists to offer their patients the best available treatment option based on the strongest evidence existing. If so, then it would be fair to say that there is not a single piece of strong evidence supporting the use of trimodality therapy in this setting.<sup>5</sup> Although we do not exclude the possibility that there may be a subset of patients benefitting from it, it is currently unknown as to which patients we are speaking about as there is a tremendous lack of data supporting it. As a matter of fact, there are no studies attempting to identify potential predictors of the superiority of trimodality therapy, and furthermore, there is also a huge inconsistency in the findings of the poor literature addressing the issue of potential pretreatment prognostic factors in this setting. Taken altogether, what may seem to one as “Usually Appropriate” may very well be a “Very Inappropriate” option because we do not know before the treatment starts (ie, concurrent RT-CHT regardless of whether followed by surgery or not) as to which patients actually may (or may not) benefit from the trimodality approach. We ultimately believe that nobody wants to learn that on an operating table or later on, but rather before any treatment approach is advocated as the best available for a particular patient.

An obvious solution to the problem and the simplest one is the design and the performance of one or, preferably and synchronously, more clinical trials in this setting. That way, we may be able not only to learn as to which patient subgroup may potentially benefit from the trimodality approach but also to perform adequate predictive factor analyses and identify subgroups of patients that may benefit from the trimodality approach before a patient is even considered for surgery. We would then be able to save

patients from harm by not offering a poorly justified treatment approach that is of similar activity, at best, yet which may bring up to 10% of mortality in non-pneumonectomy patients, increasing to 25% in pneumonectomy patients.<sup>2-4</sup> Securing full access to and taking into account all existing evidence is what makes evidence-based principles superior to expert-based opinions, no matter how good in nature the latter is.

**Branislav Jeremic, MD, PhD\***

**Francesc Casas, MD†**

**Pavol Dubinsky, MD, PhD‡**

**Nikola Cihoric, MD§**

**Antonio Gomez-Caamano, MD||**

\*Institute of Lung Diseases, Sremska Kamenica, and BioIrc Centre for Biomedical Research, Kragujevac, Serbia

†University Clinic, Barcelona, Spain

‡University Hospital to East Slovakia Institute of Oncology, Kosice, Slovakia

§Inselspital, Bern, Switzerland

||University Hospital, Santiago de Compostela Spain

## REFERENCES

- Willers H, Stinchcombe TE, Barriger RB, et al. ACR appropriateness criteria induction and adjuvant therapy for N2 non-small-cell lung cancer. *Am J Clin Oncol*. 2015;8:197-205.
- Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374:379-386.
- van Meerbeeck JP, Kramer GW, van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst*. 2007;99:442-450.
- Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol*. 2008;9:636-648.
- Jeremic B. Standard treatment option in stage III nonsmall cell lung cancer. Case against trimodality therapy and consolidation drug therapy. *Clin Lung Cancer*. 2015;16:80-85.

The authors declare no conflicts of interest.