Editorial

Editorial on: multidisciplinary therapy of marginally operable stage IIIA non-small cell lung cancer

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Yang and colleagues report on a multidisciplinary management strategy for marginally operable stage IIIA non-small cell lung cancer (NSCLC) (1). The authors used a very broad definition of "marginally operable," as tumors with bulky or multistation N2 disease, invasion of a rib or diaphragm, atelectasis, or superior sulcus tumors. From 2006 to 2013, a treatment strategy termed "phased concurrent chemoradiotherapy" (CCRT) was employed, followed by assessment 4 weeks after CCRT to assess operability (Group A, N=16). If the patient was deemed to be inoperable, the patient received more chemotherapy and a boost of up to 30 Gy of radiation (Group B, N=12). The authors then compared these two groups to patients who underwent definitive CCRT (Group C, N=19). Per the authors, the purported rationale for this phased approach in the "marginally operable" patient is "to decrease the toxicities associated with CCRT and to maximize resectability".

Although the authors state that this phased CCRT protocol was established prospectively, it should be clear that this is not a clinical trial but a retrospective analysis of a group of patients treated with a nonstandard of care protocol. This raises a serious concern as to whether the patients truly had informed consent regarding this protocol and what alternative options were offered to them. The results show the median overall survival of Group A (not reached) was significantly better than that of Group B (34 months) and Group C (15 months). Multivariate analysis showed a performance status of 0–1, adenocarcinoma histologic subtype, and Group A were independent prognostic factors. The authors conclude that this treatment schema maximizes the probability for surgery and also provides a noninferior prognosis for unresectable patients with better tolerance of the therapy.

There are several limitations to this study. First, the definition of "marginally operable" is not standardized, and most of the criteria used in this study are not used in other studies or in clinical practice. Second, in general, decisions regarding operability and/or resectability should be made before beginning induction therapy, not after it is partly completed. Third, there are limited explanations of inclusion or exclusion criteria for entry into this protocol. There is no CONSORT diagram to guide the reader on the number of patients evaluated and why they were excluded. Fourth, in both North America and Europe, invasive mediastinal staging (EBUS, mediastinoscopy) is recommended for patients with suspected N2 disease by imaging (2,3). There is no discussion of invasive staging of the mediastinum, and there are numerous studies showing a stark difference between clinical and pathologic assessment of cN2 disease noted on CT scan. Therefore, we really do not know whether patients had pN2 disease and whether

it was single or multistation. Fifth, it is surprising that pre- and/or posttreatment PET/CT imaging was not used or even referenced in this study. In addition, there is no discussion of RECIST criteria, which could have been used to assess response to the induction CCRT. What criteria did the authors use to determine response to induction therapy and whether to proceed to surgery? Sixth, as written, we have concerns that the radiation doses used in Group C are inferior to a suggested standard of care dose of 60 Gy, which has been established by several randomized clinical trials (RTOG 9410, EORTC 08972) as well as the NCCN consensus guidelines (4-6).

Additional limitations of this study are that the majority of patients with adenocarcinoma (12/21, 57%) underwent surgery, whereas 82% (18/22) of patients with squamous cell cancer were managed nonoperatively; this introduces a potential bias. The study size is very small, and there is no power analysis to assess differences between groups; failure to employ statistical rigor limits confidence in the conclusions of the study. It is imperative that R0 resection rates, N2 nodal sterilization rates, final ypTNM stages, and postoperative complication rates are shared with the reader. We have no idea how many patients were downstaged in Group A, because apparently there was no pretreatment invasive staging of the mediastinum, and no ypstage is given.

In summary, although the authors are to be congratulated for pursuing alternative treatment approaches in this group of complicated patients, there are several concerns regarding the inclusion criteria, informed consent, methodologies, and confidence in the results. The current study does show that the majority of patients (>60%) with c-stage IIIA NSCLC relapse, especially with distant metastasis, within 2 years. Therefore, incorporation of newer systemic therapies (i.e., targeted therapy, immunotherapy) into existing multidisciplinary protocols will be the next generation of clinical trials for locoregionally advanced NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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