Letter to the Editor

PET scan avidity and its role in surgical resection for IIIa N2 disease

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We appreciate Dr. Martin and Mehran's interest in our article. The primary focus of our study examined the relationship between reduction in PET scan avidity (SUVmax) in mediastinal nodes and the presence of persistent N2 disease after induction therapy as a means to provide an additional tool for risk stratifying prospective surgical patients.

Dr. Martin and Mehran expressed concern that our publication appears to advocate for the use of serial PET scanning to establish persistence of nodal disease as the sole determination of operability. This was not the intention of the article. We simply wanted to show that assessing the postinduction metabolic activities of the tumor and mediastinal nodes may help surgeons modify their management strategy to more appropriately fit their patient's risk profile.

It was also noted that our paper was done in an era where endobronchial ultrasound (EBUS) was not routinely used prior to induction therapy. As mentioned in the limitations of the article, we recognized that the vast majority of the cohort studied had preinduction mediastinoscopy, whereas the recent trend is towards the use of EBUS. Using EBUS in this setting would allow for the use of mediastinoscopy following induction therapy, theoretically removing the significant hazards and false negative rate of a redo mediastinoscopy. However, the data on the role that EBUS plays in the postinduction setting are scant. The initial results appear slightly better than the 25% false negative rate of repeat mediastinoscopy, but the number of studies is limited and it still needs be determined whether or not these results hold up when they include less cautiously selected patients and centers.

Since postinduction primary mediastinoscopy performs well in comparison to primary mediastinoscopy in general, we agree that in an ideal world, EBUS should be the initial choice in preinduction lymph node staging. Yet, this requires important forethought when patients undergo initial evaluation and staging, something that is often disregarded. Moreover, since EBUS is both operator dependent and still not universally available nationwide, we feel a non-invasive staging modality such as PET scanning could provide a gap for those institutions (1,2).

Dr. Martin and Mehran queried as to why not operate regardless of nodal status, if patients who underwent resection while not achieving mediastinal downstaging still revealed substantially better survival rates than those seen with definitive chemotherapy. This is an important question, as the utility of observing PET scan avidity lie not only in the ability to downstage patients, but the capacity to accurately upstage patients with stage IIIa NSCLC as well.

We acknowledge that many centers have adopted an approach that favors resection regardless of persistent N2 or downstaged N2 disease; however, this is not our methodology. If a patient has histologically proven single station or non-bulky multistation IIIa N2 disease, it is our preference to offer induction chemotherapy and surgical

resection. This is where the utility of PET scan is observed beyond its prognostic significance in nodal downstaging. Surgical resections more extensive than a lobectomy carry an inherently greater operative risk. The ability for PET scan to show persistent disease or upstage these patients can clearly influence therapeutic options and reduce unnecessary and futile surgeries. It was the work of the Intergroup Trial 0139 that revealed a subset of patients with IIIa disease who would be better served avoiding surgery.

Initial results of the Intergroup Trial 0139 suggested that a trimodality treatment approach integrating surgery did not improve overall survival (OS) over definitive chemoradiation alone in stage IIIA NSCLC (3). However, the post-hoc, exploratory analysis showed that when you dichotomize the INT 019 group into two subsets, induction chemoradiotherapy (CRT) plus lobectomy and induction CRT plus pneumonectomy, it was evident that the lobectomy subset fared better. The OS of the pneumonectomy subset compared to the matched CRT subset for 5-year OS was 22% to 24%, respectively (P= not significant), whereas the OS of the lobectomy subset compared to the matched CRT subset for 5-year OS was 36% to 18%, respectively (P=0.002) (3). Aggarwal *et al.* revealed similar findings in their work.

In 2014, Aggarwal *et al.* reported their outcomes of stage IIIA N2 NSCLC patients that were treated with concurrent CRT with or without surgery, and similarly showed that those undergoing pneumonectomy were not associated with a statistically significant survival benefit over CRT (median OS: 28 *vs.* 22 months, P=0.534). Likewise, they showed that the lobectomy subset yielded superior OS compared with CRT (median OS: 39 *vs.* 22 months, P=0.038). The lobectomy subset had higher 1-, 2-, and 5-year OS rates (88%, 63%, and 40%, respectively) compared with the CRT subset (75%, 45%, and 29%, respectively) (4).

While our group has previously shown that both pneumonectomy and lobectomy can be safely performed after induction therapy, preliminary evidence clearly demonstrates a benefit for patients undergoing lobectomy rather than pneumonectomy as part of trimodality therapy. It was the aim of this study to establish a non-invasive, predictive model that could assess mediastinal nodal downstaging and upstaging following induction therapy. This would optimistically provide another important prognostic tool that may help in screening out patients not suitable for resection, particularly those with marginal performance status and/or needing to undergo more extensive resections.

To best understand and define the role of surgery in stage IIIa N2 disease, a number of randomized clinical trials are needed. E.g., a formal randomized trial comparing induction chemoradiation followed by lobectomy compared to definitive chemoradiation in patients with stage IIIA N2 disease whose tumors are amenable to resection by lobectomy. This may help surgeons better tailor their management for patients with N2 disease more effectively.

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Footnote

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

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