Response

To the Editor:

We are responding to the concerns raised by Rice and colleagues regarding the Lung Cancer Guidelines related to the treatment for patients with potentially resectable stage IIIA lung cancer, in which N2 nodal metastases were histologically proven prior to surgery, our stage IIIA. Our recommendations were based primarily on the randomized trials listed in Table 6.1 The two largest and most recent multicenter trials2,3 provided the most convincing data.

In the European Organisation for Research and Treatment of Cancer (EORTC) 08941 trial,2 patients with histologically proven stage IIA-N2 non-small cell lung cancer were administered induction chemotherapy. Only responders were randomized to either surgical resection with or without postoperative radiotherapy vs sequential radiotherapy without surgery. Rice et al note the fact that this trial accrued patients with "unresectable N2 disease" and question whether results would be applicable to patients with resectable stage IIA. In the “Methods” section of their publication,2 the EORTC definition of “unresectable” was as follows: “(1) any N2 involvement by a nonsquamous carcinoma; (2) in the case of squamous cell carcinoma any N2 involvement exceeding level 4R in a right-sided tumor and level 5 and 6 for a left sided tumor.” Essentially the EORTC considered unresectable all stage IIA-N2 patients with single or multistation N2 metastases, which is exactly the focus of the stage IIA chapter. The progression-free survival and the overall survival of the chemotherapy/surgery and chemoradiotherapy groups were not statistically different. The conclusion of the EORTC was “in view of its low morbidity and mortality, radiotherapy should be considered the preferred locoregional treatment for these [Stage IIA-N2] patients.”2

The other large randomized, multicenter trial3 was Intergroup 0139, in which stage IIA-N2 patients received induction chemoradiotherapy. Responders were randomized to surgical resection followed by chemotherapy vs completion of radiotherapy plus more chemotherapy. In this trial,3 the 30-day operative mortality was high overall at 7.9% and especially elevated in pneumonectomy patients (25.9%). Although the progression-free survival favored the surgical arm (median survival, 12.8 months in the surgical arm vs 10.5 months in the chemoradiotherapy arm, p = 0.017), overall survival rates at 2 years and 5 years were not significantly different in the two treatment groups. Unfortunately, full data from this study have not been published, so we are unable to comment on questions raised about any post hoc subgroup analysis. Of the earlier two small induction therapy studies in Table 6, the trial by Taylor et al4 was indeed retrospective and was included in error.

The final study was the earlier, small Radiation Therapy Oncology Group 89-01, a randomized phase III trial3 of stage IIIA patients with histologically proven N2 disease. After induction chemotherapy, patients were randomized to surgery vs sequential radiotherapy followed by additional chemotherapy. There was no significant difference between the two treatment groups in progression-free survival or overall survival. Unfortunately, this study closed prematurely due to poor patient accrual, making the results inconclusive.

Intuitively, surgical resection of the cancer seems ideal, particularly to thoracic surgeons (including one of the authors, L.A.R.). The occasional patient with complete N2 node clearing from induction chemotherapy (occurring in perhaps 20% of patients) may truly benefit from surgical resection, although it is likely concurrent radiotherapy in this subgroup would have an equally effective role. This may be the reason that the randomized trials show no superior survival benefit with surgery. After an exhaustive discussion of this controversial subset of stage IIIA reviewing primarily the two large randomized induction therapy trials,3,4 the Lung Cancer Guidelines Panel concluded that employing surgery for locoregional control did not provide a superior survival advantage. Therefore, the less morbid modality of radiotherapy added to chemotherapy delivered concurrently, when possible, is the preferred treatment regimen for stage IIIA.

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Complete Mediastinal and Hilar Lymph Node Staging of Primary Lung Cancer by Endobronchial Ultrasound

Moderate Sedation or General Anesthesia?

To the Editor:

Herth et al1 have reemphasized the superiority of endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) in staging non-small cell lung cancer in comparison to CT and positron emission tomography and pushed the boundary to stage I patients. In this group of patients, under general anesthesia, complete mediastinal and hilar node screening was performed with biopsy of lymph nodes (mean, 1.6 per patient) between 5 mm and 10 mm (mean, 7.9 ± 0.7 mm). In reference to their previous report,2 the authors comment that “there is no known difference in yield or patient tolerance if the procedure is
performed under moderate sedation or general anesthesia." However, the patient population studied in this previous report is different. These were patients with adenopathy not limited by size (mean size of lymph nodes sampled, 16 ± 3.6 mm; range, 8 to 32 mm), complete mediastinal and hilar lymph node screening was not performed, and fewer nodes were sampled (mean, 1.14 per patient). These three differences would lead to reduced time and increased simplicity of the procedure, making it more amenable to moderate sedation.

As more and more centers begin EBUS-TBNA programs, it is important that the procedure is performed in the correct environment and with realistic expectations of patients, operators, and equipment performance characteristics. If a consensus is reached that complete nodal staging is feasible and accurate with EBUS-TBNA, it may be more optimally performed under general anesthesia until the bronchoscopist feels comfortable in targeting these smaller lymph nodes in multiple stations in a conscious patient. We have recently described a safe option using propofol sedation with a laryngeal mask airway ventilation in the bronchoscopy suite that allows full access to the mediastinal lymph node stations. In contrast, EBUS-TBNA may be safely performed under conscious sedation in those patients with larger nodes without the requirement for complete lymph node staging.

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Response

To the Editor:

We thank Dr. Kennedy and his colleagues1 for their comments regarding the level of sedation during endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA).2 The use of propofol and a laryngeal mask airway is certainly an additional option available to the bronchoscopist. It is important to remember, though, that there is currently no proof that any level of anesthesia deeper than moderate sedation is required for performing the procedure. This applies for the goal of the procedure (full staging vs targeted biopsy) as much as for the level of experience. Even though we agree that general anesthesia may make it easier especially for the relatively inexperienced operator, some issues require consideration before asking the anesthesiologist to provide deep sedation or general anesthesia for a patient.

Part of the advantage of EBUS-TBNA is the ease and minimal patient impact compared with surgical staging, as well as the potential economic advantage. Deeper levels of sedation may partially negate these advantages by adding additional personnel and requiring operating room-type facilities in some institutions. An additional drawback to adding more resources that really are probably not required is the recent severe reimbursement cutback on the facility-based reimbursement (Hospital Outpatient Prospective Payment System) for EBUS TBNA procedures by the Centers for Medicare and Medicaid Services in January 2008.3 We need to choose the best approach for our patients but need to manage and minimize the resource use at the same time.

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3 Centers for Medicare and Medicaid Services. Federal Register 2007; 72

Does Central Venous Pressure Predict Fluid Responsiveness?

To the Editor:

Marik and colleagues1 argue that the poor correlation between right atrial or central venous pressure (CVP) and indexes of fluid responsiveness after fluid administration limit the value of CVP measurement and conclude that CVP should not be a factor in fluid administration decisions. This appears to be at odds with the classic principles of circulatory physiology by Guyton and Hall,2 in which right atrial pressure is a key independent variable influencing both systemic venous return and right ventricular output.3–5 In these constructs, venous return may be independent of right atrial pressure at low pressures while right ventricular output may be independent of right atrial pressure at high pressures, in agreement with the review, but not in the middle