To the Editor:

We have read with great interest the article recently published in CHEST (March 2008) by Mathier et al., who report a case of a morbidly obese patient with idiopathic pulmonary artery hypertension (PAH). We do not agree with some aspects related to the management of the patient, and we would like to discuss them.

A morbid patient (body mass index of 46.3 kg/m²) with sleep apnea syndrome treated successfully with continuous positive airway pressure and oxygen therapy is presented. There is no comment about the functional respiratory status of the patient. We do not know if he had respiratory insufficiency. We do not know anything about the PaCO₂ level. Was he hypercapnic?

There is no comment about the sleep study. We do not know if the patient had obesity hypoventilation syndrome associated with sleep apnea syndrome. If so, the patient would have been treated with nocturnal noninvasive ventilation. In this sense, if the patient has not been treated correctly and there is respiratory insufficiency, how can the authors establish a diagnosis of idiopathic PAH? Hypoxemic stimulus would completely justify PAH.²

After bariatric surgery, the patient had a substantial decrease in weight and body mass index and a dramatic increase in 6-min walk test distance. However, once again we do not know anything about the improvement in the sleep study results of the patient. Perhaps the improvement in functional status of the patient was related to the weight loss?

We were also surprised by the treatment prescribed by authors. We think that there are insufficient data related to left ventricular diastolic dysfunction, which is commonly associated with severe obstructive sleep apnea, and can represent a contraindication for using these new vasodilators. In fact, by using bosentan, mean pulmonary artery pressure got worse initially up to 53 mm Hg.³ In addition, portal hypertension, renal failure, and thyroid disorders should be ruled out to apply the term of idiopathic PAH in this case. Finally, it seems that there are no clear criteria in terms of using combination therapy. We do not understand why a second or a third drug are added because the results obtained compared to monotherapy are probably very similar. It would be also interesting to have more data about the dosages used and decision making in the future.⁵ We think there are doubts enough to consider adequate the management of the patient and the treatment prescribed by authors.

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The authors have no conflicts of interest to disclose.

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REFERENCES


Response

To the Editor:

Díaz-Lobato et al, in addressing our recent report in CHEST (March 2008), outlined the many complexities inherent in the diagnosis and management of the morbidly obese patient with pulmonary hypertension. We appreciate their comments. They have raised a number of questions about our patient that we would like to clarify.

Regarding the question of obesity-hypoventilation syndrome, our patient underwent a single arterial blood gas analysis at the time of the initial diagnosis and was not hypercarbic. Regarding the question of sleep apnea, as stated in the report: “Obstructive sleep apnea had been diagnosed years earlier, and continued to be treated successfully with positive airway pressure.” Díaz-Lobato et al suggested that hypoxemia could completely explain the presence of pulmonary arterial hypertension (PAH) in our patient. We would stress again, however, that nocturnal hypoxemia was corrected with therapy with continuous positive airway pressure and oxygen for several years prior to the diagnosis of PAH. Furthermore, daytime hypoxemia was not present until 1 year prior to the patient undergoing bariatric surgery, and supplemental oxygen therapy was initiated at that time. Thus, it is difficult to ascribe our patient’s PAH to hypoxemia.

Díaz-Lobato et al also suggested that PAH therapy should not have been administered to our patient because of the presence of diastolic heart failure. Yet, our patient’s pulmonary artery balloon occlusion pressure was normal or minimally elevated throughout the course of his treatment, suggesting very mild, if any, diastolic heart failure. Nevertheless, we acknowledged all of these issues in the report, stating “...while a contribution of left ventricular...”
diastolic dysfunction or obesity hypoventilation syndrome could not be definitively excluded, the patient appeared to have idiopathic PAH. Following a full diagnostic evaluation, there was no evidence of hepatic, renal, or thyroid disease, or any other established cause of PAH. While our patient’s pulmonary pressures were higher while receiving bosentan therapy, this was found 3 years after therapy with the agent was initiated; it is more likely that this represented the expected progression of the disease rather than an adverse effect of bosentan.

We fully agree that there are no clear criteria for the use of combination therapy for patients with PAH. As indicated in the report, we initially recommended therapy with epoprostenol. When our patient refused this, yet wished to pursue bariatric surgery, we felt that a combination of the other available therapies was the best way to achieve sufficient hemodynamic improvement to allow for surgery. As can be seen in Table 1 in our article, there was indeed a stepwise improvement in hemodynamics (most notably cardiac output and pulmonary vascular resistance) with each added therapy leading up to surgery.

We agree that the improvement in functional status experienced by our patient following bariatric surgery was likely related to weight loss. As we stated in the original report, “the mechanism of the observed improvement is uncertain…” That it was not related to the resolution of PAH is indicated by the findings of the follow-up echocardiogram and a recent right heart catheterization that revealed ongoing severe PAH with normal pulmonary artery balloon occlusion pressure and preserved cardiac output. Despite this, the patient’s functional status remains markedly better than it had been before surgery; while mild sleep apnea persists (and treatment of it continues), daytime hypoxemia has resolved.

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Dr. Mathier received consulting fees from Actelion, Gilead, and United Therapeutics; grant support from Actelion; and speakers bureau fees from Actelion, Gilead, GlaxoSmithKline, and United Therapeutics. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

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REFERENCE


Potential Confounders in the “Influence of Gender on the Outcome of Severe Sepsis” Study

To the Editor:

In the prospective observational study on influence of gender in the outcome of severe sepsis in a recent issue of CHEST (December 2007), Adrie and colleagues failed to incorporate an adjustment for the timing of administration and appropriateness of the antibiotic to be used as potential confounders in their analysis. The early (ie, within 1 h of diagnosis) institution of broad-spectrum antibiotics has been endorsed as a strong recommendation for the management of severe sepsis with or without shock by the 2008 Surviving Sepsis Campaign guidelines. Ample evidence to support the recommendations exists.

In a 14-center, retrospective cohort study of 2,731 adult patients with septic shock, the time to the initiation of effective antimicrobial therapy was the single strongest predictor of in-hospital mortality. In the same study, it was found that each hour of delay in antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival of 7.6%. Also, the failure to initiate appropriate therapy (ie, therapy with an agent having activity against the pathogen that is subsequently identified as the causative agent) within a given time period correlates with increased morbidity and mortality.

We wonder whether the presumed differences in level of care in the form of proper and timely antibiotic use may have accounted for the discrepant outcomes between sexes due to lack of adjustment in the study. The authors have beautifully used the propensity score to match confounding factors, but there is no mention of whether they were matched for two important determinants of outcome, the timing of administration and appropriateness of antibiotic use.

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Response

To the Editor:

First, we would like to thank the authors for their interest in our article. They raised a very interesting issue about a potential gender difference in an early time to initiation of an appropriate antimicrobial therapy that is known to be a crucial therapeutic strategy for improving survival in patients with severe sepsis. Conversely to the
results of a previous Austrian study, we did not find any difference in the level of care between the sexes. However, we do agree that this particular issue could have been a potential confounder in our recently published article. Among the 1,608 men and women matched using our propensity score, 891 patients were appropriately treated right at the day of diagnosis (55%). Among them, 544 were men (54%) and 347 were women (57%). After conditional regression logistic analysis, early and appropriate antibiotherapy rate was treated right at the day of diagnosis (55%). Among them, 544 were men (54%) and 347 were women (57%). After conditional regression logistic analysis, early and appropriate antibiotherapy rate was not different between men and women (odds ratio, 1.12; 95% confidence interval, 0.91 to 1.38; p = 0.28). This clearly shows that early and appropriate therapy is not a confounder in our study and does not modify our message.

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Please Lead, But Don’t Mislead

To the Editor:

Herth and colleagues deserve much credit for leading the way in carefully establishing the role of endobronchial ultrasound (EBUS) in the staging of lung cancer. They have been part of developing the technology and clearly have established the validity of this procedure in a broader group of patients, most of which had enlarged lymph nodes. In a recent article, they have continued to lead the way in studying the role of EBUS in another cohort, those with small nodes (ie, ≤ 1 cm and negative positron emission tomography scan findings). This was an important article that further established the value of this procedure in experienced hands.

Unfortunately, some details of the study are vague and potentially misleading. Although the techniques are described in detail, the analyses are not. It is unclear whether the analysis was calculated per patient or per node. A per-node calculation would artificially elevate all of the test performance measures, and would be inappropriate because we care for patients and not individual nodes. The article implies that it addresses the value of EBUS in staging the mediastinum, but the analysis lumps stage N1 and N2 nodes together. This is not appropriate, and is not consistent with how we have approached preoperative staging for lung cancer. If I have added up the numbers correctly, the results of EBUS for mediastinal staging are even better: sensitivity, 100%; specificity, 100%; and false-negative and false-positive result rates of 0. It is not clear why the authors would choose to report on stage N1 and N2,3 nodes combined.

The incidence of positive stage N2 nodes (6%) is a little higher than has been reported in other series (average, 3%) of patients with negative CT and positron emission tomography scan findings. Nevertheless, it is fairly low. Whether 6% is high enough to justify performing this test on all patients is a matter of judgment, particularly since all of the patients went on to undergo surgical procedures. I would argue that the rate of mediastinal node involvement is low enough that invasive staging of any sort is hard to justify in this patient cohort.

There clearly are some advantages to EBUS over mediastinoscopy. However, modern mediastinoscopy, using a videomediastinoscope, provides excellent access to posterior subcarinal nodes, and in fact allows a complete lymphadenectomy to be performed. It is also not clear that EBUS performed under general anesthesia is any less costly than mediastinoscopy, which is also routinely performed on an outpatient basis, at least in North America. The advantage that EBUS allows “additional pulmonary procedures” to be performed is rather vague. What additional procedures? Are they really of value in these patients, or is this just a theoretical statement?

These issues are raised not to diminish the value of this article; in fact, I wish to enhance it. However, the authors should be careful to be fair in their assessment of EBUS and not overplay the benefits. The simple facts speak well enough.

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The author has no significant conflicts of interest with any companies/organizations whose products or services are relevant to this article.

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Response

To the Editor:

We wish to thank Dr. Detterbeck for his thoughtful comments and compliments. We obviously do agree that endobronchial
ultrasound (EBUS)-guided transbronchial needle aspirations (TBNA) have become a most valuable tool in the diagnosis and staging of lung cancer patients, especially in patients with enlarged lymph nodes.

Dr. Detterbeck’s criticisms and questions of our study that was recently published in CHEST (April 2008)2 addressing the usefulness of EBUS-guided TBNA in cancer patients with a radiologically normal mediastinum are as follows: (1) how the analysis was performed (ie, per patient or per node); (2) the issue of the inclusion of N1 nodes in our study; (3) whether invasive staging in our patients was required; (4) the role of EBUS-guided TBNA in the context of emerging video mediastinoscopy; and (5) what additional bronchoscopic procedures could be of value when performing EBUS. We will address these issues in order.

1. The analysis was conducted on a per-patient basis and was clearly reported as such.

2. We agree that there may be some confusion about why we included N1 nodes. The title of the article could suggest that only mediastinal nodes were biopsied, but it is clearly stated that the mediastinum had to be radiologically negative and that nodal biopsies were not specifically limited to those stations. It was stated in the “Material and Methods” section that N1 nodes were biopsied. We did not feel it was ethical to perform endoscopic staging without including the N1 stations with a procedure that made them easily accessible. Considering the changing criteria of the TNM classification and the realization that patients with bulky N1 stage tumors have outcomes comparable to those of patients with N2 tumors may in fact make it very important to include hilar staging in the future.

3. Whether staging is required is a valid discussion, and we respect Dr. Detterbeck’s opinion. If, on the other hand, with the help of a minimally invasive low-risk procedure these patients with positive nodes can be identified, then we think it is eminently justified and is what we would want for our family members. To quote Dr. Detterbeck: “We take care of individuals, not nodes” (or cohorts for that matter).

4. The advent of video mediastinoscopy is exciting. We are surprised, however, that Dr. Detterbeck, who cautioned readers to use restraint in technology assessment, was so quick to endorse this technology. The literature about its added benefit is very limited and has come from very few centers. Blanket statements or recommendations cannot yet be made due to a lack of good evidence. The quoted study3 is not an original investigation, and we would refer to an original study, such as, for example, the article by Witte et al.4

5. Additional procedures can certainly be indicated and beneficial, such as, for example, an attempt at biopsy of a peripheral lesion, be it a primary or secondary one. A malignancy is not always the leading potential diagnosis, and transbronchial biopsies as well as endobronchial biopsies may be performed to rule out other diseases, such as, for example, sarcoidosis.

Again, we thank Dr. Detterbeck for his thoughtful comments. It is through this kind of scientific discussion that data and opinions can be discussed and clarified.

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1 Detterbeck FC. Please lead, but don’t mislead. Chest 2008; 134:672

Non–Sized-Based Descriptors in Staging of Stage I Non–Small Cell Lung Cancer

To the Editor:

On et al1 have recently reported an excellent experience assessing non–sized-based descriptors in staging of stage I non–small cell lung cancer (NSCLC). We concur with their basic message that tumor size < 3 cm is the most important favorable prognostic factor among all descriptors for stage I NSCLC.

Nonetheless, some questions still remain. The work is based on clinically staged patients. No information is provided on whether all or part of these patients are staged pathologically, which would increase classificatory certainty. If these were clinical T1–2N0M0, certainty is more imprecise. How can it be clinically claimed that the visceral pleura is only involved in a tumoral process? Or how can it be clinically claimed that an NSCLC falls into a clinical N0 classification?

A further problem is the absence of cases with two or more stage I descriptors. In our experience2 in patients with pathologic stage I with a tumor > 3 cm in size (n = 804), there is simultaneous concurrence of 254 patients (32%) with involvement of the visceral pleura, 223 patients (28%) with atelectasis-pneumonitis, and 59 patients (7%) in whom the main bronchus is involved > 2 cm from the carina.

In the reference work,1 it is claimed that in tumors < 3 cm, some non–sized-based descriptors are indeed independent prognostic factors. Given that new proposals have come to light to
handle the “tumor size” variable, with greater prognostic discrimination using cut-off values > 2 to 3 cm. 2,3 The question is: In your largest study, would non-sized-based descriptors disappear as prognostic values if, on multivariate analysis, tumor size were to be considered in a larger number of cut-off values? Our experience suggests so. 4

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REFERENCES


Response

To the Editor:

We thank Dr. Lopez-Encuentra et al for their thoughtful and insightful comments. As described in the ‘Materials and Methods’ section, we included only stage I (T1–2N0M0) non-small cell lung cancer patients whose TNM codes were completely recorded in the California Cancer Registry. The T descriptors of all the patients in the study were coded by one of the three extent of disease (EOD) codes: 10, 20, or 40 with no overlap or missing codes indicating excellent internal consistency. The EOD codes and N descriptors were generally abstracted from pathology and/or radiology reports so they can be either pathologically or clinically staged. This limitation was discussed in the article. The Surveillance, Epidemiology, and End Results EOD codes are hierarchically arranged so if a tumor contains both EOD-20 (mainstem bronchus ≥ 2 cm from carina) and EOD-40 (visceral pleura invasion, hilar atelectasis, or obstructive pneumonitis) criteria, only EOD-40 will be coded. We agree with Dr. Lopez-Encuentra et al that we cannot separate the three criteria (visceral pleura invasion, hilar atelectasis, or obstructive pneumonitis) individually, nor can we know how many EOD-40 cases also had EOD-20 criteria, and this is a study limitation. However, we demonstrated that T descriptors coded as T2 due to EOD-20 criteria alone (mainstem bronchus ≥ 2 cm from carina) are infrequent (5.7%).

One of our major conclusions is that for tumors ≤ 3 cm but are coded as T2 due to non-sized-based criteria, the overall survival of these T2 tumors are similar to tumors ≤ 3 cm (T1). 1 The referent in the Cox analysis is T2S (tumor > 3 cm), and here T2p ≤ 3 cm has a hazard ratio of 0.8 (p = 0.0039) and T2p > 3 cm has a hazard ratio of 1.155 (p < 0.0001) (Table 3). 1 We can only conclude that for tumors > 3 cm, T2p > 3 cm is an independent poor prognostic factor. Given that we did not compare T2p ≤ 3 cm to tumors ≤ 3 cm (T1) in the Cox multivariate analysis, we cannot conclude that T2p ≤ 3 cm is an independent favorable prognostic factor for tumors ≤ 3 cm. However, we agree with Dr. Lopez-Encuentra et al that it will be important to determine whether the overall survival and prognostic significance of these non-size-based criteria diverge at tumor size 2 cm or 3 cm as the International Association for the Study of Lung Cancer has subdivided the T1 descriptor into T1a (≤ 2 cm) and T1b (> 2 cm and ≤ 3 cm) in the forthcoming lung cancer TNM staging changes. 2

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