The greatest problem for the correct evaluation of sensitivity of mediastinoscopy lies in the small sizes of the series reported in the literature. Small sample size determines wide confidence intervals, which reflect a lack of precision in the inference of the diagnostic value to the general population.

Furthermore, discussion about confidence intervals is needed to correct some confusing statements of Drs Lim and Dusmet. Because the confidence level represents the likelihood that another sample will provide the same results (in our case, diagnostic sensitivity), a confidence level of 95% means that 95 out of 100 times, the sample percentages will fall within the confidence intervals. When applied to our study, this means that sensitivity of mediastinoscopy in 95 out of 100 measurements will have a value between 42% and 77%. In our measurement—that is, mediastinoscopy done by our surgical team and pathologic examinations done by our pathologists—sensitivity was exactly 61%. To say that this value “crosses 50%” makes no sense at all. The confidence interval is a way of putting a probability on what future samples (or repeats of the earlier sampling procedure with different users) would yield. In other words, it is a way of saying how repeatable the results are. It does not state the definitive value of the result (sensitivity) in the general population (patients with non-small cell lung cancer after induction therapy).

Throughout the phases of design, data collection, analysis, and report of the study we kept in mind all STARD items and checked the appropriateness of our statements against the STARD guidelines. Including “not biopsied nodal stations” in the formula to calculate the diagnostic accuracy is obvious, compliant with the STARD guidelines, and consistent with the methods of previous literature.³ For example, Drs Lim and Dusmet cited the article of De Leyn and colleagues,² in which sensitivity was calculated by including a considerable number of cases with inadequate

exploration of the subcarinal station (“no biopsy”) in which residual metastases were discovered at further thoracotomy (“false-negative” result of mediastinoscopy). In the evaluation of diagnostic yield of mediastinoscopy, inadequate biopsy of a metastatic lymph node station with a false-negative finding and no biopsy of the station are two faces of the same coin, the inability of the method to rule in disease, regardless of what factor leads to the false-negative result (fibrotic alteration of nodal tissue after previous mediastinoscopy, dense adhesions with anatomic inaccessibility, and so on).

Finally, we remind the readers that the accuracy value of mediastinoscopy was as high as 88%. The ability to rule in residual disease (specificity) was present in 100% of cases. The ability to rule out residual disease (sensitivity) was present in 61%; that is, unnecessary thoracotomy could be avoided for about two thirds of patients.

On the basis of these considerations, we reaffirm our conclusion that mediastinoscopy provides histologic proof of mediastinal staging with high diagnostic accuracy.

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REFERENT VALUES AND EQUIPOISE: EDITORS' NOTES To the Editor:

Lim and Dusmet,¹ in a letter to the editors critiquing an article by Marra and colleagues,² make 4 statements about referent values (accuracy, sensitivity, specificity, positive predictive value, and negative predictive value)³ that require clarification.

Statement 1: “Specificity (ability to rule in disease) is not the major focus for surgeons.”

Referent value specificity is the measure of the ability of a test to rule out disease. It is defined as the number of patients without the disease who are identified by the test (true-negative results) divided by total number of patients without disease (true-negative plus false-positive results).

Statement 2: “What is critical is sensitivity (the ability to rule out disease).”

Referent value sensitivity is a measure of the ability of a test to rule in disease. It is defined as the number of patients with disease who are identified by the test (true-positive results) divided by the total number of patients with the disease (true-positive and false-negative results).

Statement 3: “Mediastinoscopy is associated with 100% specificity. That in itself is expected ... when tumor is seen in a biopsy it is invariably seen on the reference test.”

We believe these statements indicate the authors are confusing specificity with sensitivity. In general, screening tests have low sensitivity but high specificity. As work-up continues and the population is increasingly “enriched” with disease, sensitivity increases and specificity decreases.

However, for the surgeon dealing with this “enriched” population and

who should not operate if there is persistent N2 disease after induction therapy, the referent value, negative predictive value, is most important. It is defined as the number of patients without N2 disease who are identified by the test (true-negative results) divided by the total number of patients identified by the test to be without N2 disease (true-negative plus false-negative results). A high negative predictive value (few false-negative results) permits the surgeon to confidently use the results of remediastinoscopy to plan further surgical intervention.

Statement 4: "Sensitivity truly starts at 50% (a test of no sensitivity or equipoise), not 0%."

A referent value has merit throughout its range. A test with 0% sensitivity is unable to identify any patient with disease; one with 100% sensitivity identifies every patient with disease. Equipoise is equality of distribution, equilibrium, or counterbalance. Although we cannot verify this, we believe the writers might be confusing the referent value sensitivity with the area beneath the receiver operator characteristic, expressed as the C statistic, which is a graph of sensitivity versus 1 minus specificity. An area of 0.5 ($C = 0.5$) might be interpreted as "equipoise" because this is the expected relationship between groups whose testing has produced completely random results.

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SPIRONOLACTONE ALLEVIATES LATE CARDIAC REMODELING AFTER LEFT VENTRICULAR RESTORATION To the Editor:

Tsukashita et al¹ have performed an excellent experimental study to show that spironolactone alleviates remodeling after left ventricular restoration.

When experimental studies are translated into clinical practice, great caution should be maintained. Previous clinical studies on spironolactone showed a major impact on the prescribing patterns of the doctors. After the publication of the RALES study, there was an enormous increase in the prescription and usage of spironolactone in the late 1990s, leading to increased hospitalizations mostly due to hyperkalemia.² This was attributed to lack of clinical and laboratory monitoring, increased doses in patients with diabetes mellitus, renal dysfunction, left ventricular ejection fraction < 20%, and elderly patients.² Approximately 7.5 million of the elderly patients in the United States have a glomerular filtration rate < 60 mL/min, and in these patients, spironolactone causes increased adverse reactions.³ Microalbuminuria is a risk factor for heart failure with previous myocardial ischemia, and spironolactone has been demonstrated to reduce microalbuminuria when added to angiotensin-converting enzyme inhibitors.^{4,5}

Although spironolactone improves heart failure symptoms and decreases microalbuminuria, it should be used in a selected group of patients. We need further clinical studies that evaluate the side effect profile to show the same benefit in humans for alleviating remodeling following the success of the experimental study by Tsukashita et al.¹

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Reply to the Editor:

We appreciate the interest that Ramaraj has shown in our article, and we are deeply honored by his comments.¹ He possesses expertise in a broad area of medical science, not only in ischemic cardiomyopathy, the subject for our study.

As Ramaraj points out, hyperkalemia induced by spironolactone is a life-threatening side effect clinicians should look out for. On the other hand, as cardiovascular surgeons involved in clinical practice, we have focused on redilatation of the left ventricle in the chronic stage of left ventricular restoration (LVR) surgery, searching for any treatment to prevent it. Although the precise mechanism of redilatation has not been elucidated, fibrosis occurred both in border zone and remote area of plicated infarcted area in our study, and it was alleviated by spironolactone. It is well known that activation of renin-angiotensin-aldosterone system (RAAS) induces cardiac fibrosis in autocrine/paracrine manner. We thought it is possible that RAAS is one mechanism of redilatation. Angiotensin-converting