stations and 90% had 10 or more nodes removed from 3 mediastinal lymph node stations.

Dr Zielinski. My second question is, do you know how many patients were positive on the initial sampling with frozen-section?

Dr Darling. We don't have that data because they were not eligible to be randomized.

Dr Paul De Leyn (Leuven, Belgium). That was a nice presentation. When you read the article in 2005, which describes morbidity and mortality, you indeed think that the sampling is already extensive, and this is important. Can you describe from a technical point of view when you sample, let's say, station 7, is this just picking out a few nodes or is this removing this whole station? What is the difference between sampling and dissection in your study?

Dr Darling. The sampling protocol specified that you were simply directed to sample one node from each station. If there were any suspicious-looking nodes, obviously they were also required to be sampled as opposed to doing a formal clean-out of the area. So the protocol did specify to sample 1 node. Occasionally the surgeons would take more than 1 node, but, as I mentioned, if they took a whole lot of nodes (eg, 5–7 nodes from station 7), we disqualified those as being a dissection rather than a sampling. For the lymph node dissection, the protocol specified removing all lymph node-bearing tissues between anatomic boundaries. For example, for stations 2R and 4R all tissue between the superior vena cava, trachea, right innominate artery, and the right bronchus was removed, not just the visible lymph nodes.

COMMENTARY

Less is more... (more or less...)

Sudish C. Murthy, MD, PhD

In this month's issue, Dr Darling and colleagues present the results of a long-awaited multicenter, prospective, randomized trial comparing efficacy of mediastinal lymph node sampling (MLNS) and mediastinal lymph node dissection (MLND) for localized non-small cell lung cancer (NSCLC). This study was one of the many "brain-children" of the late Dr Robert J. Ginsberg, and its organization, attention to detail, and insight speak to the lasting legacy of this pioneer. In addition, the group of distinguished authors who carried this trial to its conclusion has overcome enormous obstacles to complete this ambitious enterprise, dutifully and meticulously organizing data collected from over 100 surgeons at 63 member institutions while maintaining some element of quality control throughout the process—truly a formidable task whose complexity should be appreciated.

The importance of this trial cannot be underestimated inasmuch as the role of lymphadenectomy for NSCLC, until now, has served as a point of confusion for most thoracic

surgical oncologists. Although widely heralded as an important adjunct for management of the disease, there has been little evidence to support this grandiose contention in clinical practice. In fact, a shockingly high number of lung cancer operations are performed without a single mediastinal lymph node even being sampled.¹ Yet, despite this, sophisticated and detailed guidelines of how MLND should be integrated into NSCLC management have continued to emerge.² At last, there is a well-done, randomized trial to support a position on the subject.

The findings of this trial are provocative, as surprisingly, equivalence was found between MLNS and MLND for patients with early NSCLC (N0 or nonhilar N1 cancers). This, in part, corroborates results from a similar, albeit much smaller and less well-controlled, trial from a decade ago.³ But the results appear to fly against the popular notion that MLND is a superior surgical technique with important survival benefits for patients with early-stage NSCLC.⁴⁻⁷ None of these lesser studies was randomized or as well conceived, however. Importantly, after careful review of each study, including my own, unfortunately, the authors of the latter group of manuscripts need not ready their retraction statements just yet, inasmuch as there may still be room for peaceful coexistence between studies, because slightly different questions were addressed by each.

There is a reason why such randomized studies are completed so infrequently and why this trial casts such a heroic specter. Clearly, it is difficult to have equipoise for such a trial if one believes strongly (either way) about MLND,

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Jan 13, 2011; revisions received Jan 13, 2011; accepted for publication Jan 13, 2011.

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J Thorac Cardiovasc Surg 2011;141:670-72

0022-5223/\$36.00

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doi:10.1016/j.jtcvs.2011.01.024

and that the authors were able to enlist so many qualified surgeons speaks to their diligence and perseverance, no doubt. In addition, data organization and institutional review board clearance at each institute are time and resource consumers. Perhaps most important of all is that, unlike randomized chemotherapy trials for NSCLC, where drug type, dose, mechanism of delivery, and infusion timing can be easily standardized, this trial involved the performance of two specific techniques by 102 different surgeons, hardly a model to guarantee reproducibility.

The lead investigators provided guidelines and an instructional video to the participants and have dutifully reviewed pathology reports from member institutes, but that is the extent of their standardization. They did use a reasonable surrogate as a quality index (number of lymph nodes resected), although I would challenge any pathologist to differentiate between fragments of lymph nodes and actual number, and any surgeon to extract each lymph node en bloc for his or her pathologists to faithfully count. I suspect that volumetric or mass assessment of resected lymphatic tissues might have made for a stronger surrogate from a quantitative standpoint, but those data were unavailable.

Even the lesser of these two procedures, MLNS, provides staging information perhaps of an order of magnitude greater than that which traditionally accompanies a standard lung cancer resection performed in this country.¹ The assumption that all of us must make is that MLNS is still just sampling and is distinct from MLND, which must more closely approximate an exenteration. However, one can easily imagine a vigorous sampling by one surgeon considered a passable lymphadenectomy by another, and vice versa. Consequently, the possibility is raised that the two treatment arms are similar enough to be statistically indistinguishable and hence explain the negative trial. Instead of comparing apples to oranges, the comparison becomes apples to apples, perhaps Macintosh to Red Delicious, where even the trained palate may have difficulty discerning between the two.

In their defense, the authors demonstrate that, on average, 18 more lymph nodes were resected in the MLND group. But whether this represents 18 more fragments from already well-sampled lymph nodes or 18 novel mediastinal/hilar lymph nodes is impossible to speculate. That the authors did remove some patients from the trial who they believed were too vigorously sampled or weakly dissected suggests that this limitation was not ignored, and the investigators were making every attempt to navigate safely down this slippery slope.

I, for one, believe that Dr Darling and her colleagues got it right—that MLNS was sampling and that MLND was a more complete lymphadenectomy, and that the two have an identical impact on survival and recurrence for patients with well-staged early cancers. After all, why should lung cancer behave any differently from most other solid-organ

cancers for which regional lymphadenectomy is becoming an increasingly marginalized technique?⁸⁻¹²

Moreover, these findings should ease lingering concerns that lesser operations for early-stage cancer (video-assisted thorascopic surgery) are inferior from an oncologic standpoint because fewer lymph nodes are interrogated¹³ and, instead, redirect efforts toward determining how much MLNS is sufficient for a case to be considered well staged. Are a few needle passes with ultrasound guidance through a bronchoscope enough? Algorithms are already being devised using existing complementary staging techniques to simplify care and reduce costs and morbidity, and until now, it was hard to adopt such because one had to believe without knowing that less really might be more.

The authors conclude on a bit of a curious note. Despite the compelling data that were presented and the apparent incontrovertible finding that was rendered, the article ends with the recommendation that MLND still be performed for resectable NSCLC because it does not increase morbidity or mortality and remains the most accurate way to stage the disease, points proudly made in some of those nearly retracted studies from above. It is almost as if MLND is reaching out from the grave, still refusing to go quietly into the night. Perhaps their intentions are to remind us not to put all our eggs into MLNS. Their results, though, suggest we should.

So what does MLND really offer? As demonstrated in this trial, it identifies 4% of patients who would have otherwise had unsuspected N2 disease if only treated by MLNS (stage IIIA/B). They would almost certainly have been offered adjuvant chemotherapy if properly identified, and perhaps 10% to 15% of them would have been cured. That is a 0.5% potential salvage rate, and for a study of this size, it translates into 2 patients who may have been cured if they had received MLND instead of MLNS. Is this really worth the hedge? Surely there must be more sophisticated and intelligent mechanisms (proteomics and genomics) than MLND to identify these needles in our haystacks.

Regardless, it is a terrific study performed by a group of scholarly thoracic surgeons and should immediately affect surgical management of lung cancer by relegation of MLND to highly selected instances. The finding of equivalence does not make this a negative trial. On the contrary, there is absolutely nothing negative about the trial. It was simply constructed well enough that any result, including equivalence, would be important.

To end where much of this began, we can retreat backward about a decade and a half. In his review from then, Dr Ginsberg¹⁴ wrote: “The addition of mediastinal lymph node dissection produces the best possible surgical and pathologic staging of lymph node disease but has yet to be proven more efficacious as a curative procedure.”

Finally, after these many years, I think it can be stated with more than just a modicum of courage and conviction

that MLND is *not* more efficacious and, indeed, it does appear that less is more...more or less.

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