randomized trials in high-risk patients are needed.

Hisato Takagi, MD, PhD
Hideaki Manabe, MD
Takuya Umemoto, MD, PhD
Department of Cardiovascular
Surgery
Shizuoka Medical Center
Shizuoka, Japan

References

1. Kuss O, von Salviati B, Börgermann J. Off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of propensity score analyses. *J Thorac Cardiovasc Surg.* 2010;140:829-35, 835.e1-13.
2. Wijesundera DN, Beattie WS, Djaiani G, et al. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. *J Am Coll Cardiol.* 2005;46:872-82.
3. Möller CH, Penninga L, Wetterslev J, Steinbrüchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J.* 2008;29:2601-16.
4. Feng ZZ, Shi J, Zhao XW, Xu ZF. Meta-analysis of on-pump and off-pump coronary arterial revascularization. *Ann Thorac Surg.* 2009;87:757-65.
5. Takagi H, Matsui M, Umemoto T. Off-pump coronary artery bypass may increase late mortality: a meta-analysis of randomized trials. *Ann Thorac Surg.* 2010;89:1881-8.

doi:10.1016/j.jtcvs.2010.10.059

NO MATTER HOW COMPLEX THE PROBLEM, THERE IS ALWAYS A SIMPLE SOLUTION—WHICH IS WRONG!

To the Editor:

Is it the cough that carries them off?

Asbestos-related pulmonary disease, and specifically the development of mesothelioma, continues to be a tragic health issue. There are characteristics of the whole disease entity that seem both unusual but interrelated. The inhalation of relatively long asbestos fibers is followed by their transport to the visceral pleura and subsequently to the parietal pleura and, via lymphatics, elsewhere. The fibers produce subpleural fibrosis in the lungs, but this discussion relates to the more

significant parietal pleural changes. Usually, the first and most diagnostic appearance is that of pleural plaques, with or without calcification, at chest radiograph or computed tomographic scan. There are several features of these that warrant consideration.

1. They involve the parietal pleura and not the visceral.
2. They arise in areas of greatest movement between the opposing pleural layers, with respiration, coughing, and sneezing. They do not occur over the lung apices or within the interlobar fissures where the pleural surfaces move in unison.
3. The plaques and calcifications tend to group deep to the ribs. And yes, some also form over the diaphragm and pericardium.

A simple question then arises—Is the development of pleural plaques and subsequent mesothelioma a result of chronic abrasive trauma caused by these fibers at the visceral surface abraiding the parietal pleura, akin to oral tumors resulting from “ill fitting dentures?” This would then infer a mechanical etiology rather than a chemical carcinogenesis and perhaps explain why other fibers with similar physical characteristics have also been implicated or are under suspicion. Of interest, talc had been viewed with suspicion by some because of its fiber structure, but the fact that it produces pleurodesis would negate any such effect.

If this hypothesis is worthy of consideration, several other points arise.

The negative pressure within the pleural cavity during quiet respiration, maintaining the apposition of the visceral and parietal pleural layers, is very low, and this would by inference reduce abrasive effects. However, during coughing the glottis closes while the intercostal muscles and abdominal wall muscles contract, increasing the intrathoracic and intrapleural pressure before there is an explosive release of air from the chest. The markedly increased direct pressure exerted by the ribs on the underlying pleural space may explain the

apparent predilection of pleural plaques for these regions.

If these suppositions hold weight, then an obvious question arises. Is there a place for prophylactic pleurodesis in the prevention of mesothelioma by preventing chronic abrasion between the pleural surfaces?

The risk of development of mesothelioma in those with asbestos-related disease has been quoted at 10%, a figure presumably subject to much discussion. It may be arguable whether even a procedure of low morbidity should be universally proposed as a panacea. However, other factors, possibly including plaque load, life expectancy, smoking, and chronic cough, may enable identification of higher risk groups for whom active intervention may be justified.

Vincent Acton, FRANZCR
Sydney, Australia

doi:10.1016/j.jtcvs.2011.04.016

ALICE IN WONDERLAND OF MEDIASTINAL LYMPH NODES To the Editor:

We read with great interest the results of the American College of Surgery Oncology Group (ACOSOG) Z0030 trial,¹ which was a randomized, multi-institutional, prospective trial of mediastinal lymph node dissection (MLND) versus sampling (MLNS) during pulmonary resection for patients with early-stage (N0 or nonhilar N1, T1, or T2) non-small cell lung cancer (NSCLC). At a median follow-up of 6.5 years, 44% died in the MLNS arm and 42% died in the MLND arm, and the median survival was 8.1 years in the MLNS group and 8.5 years in the MLND group ($P = .25$). Studies addressing the survival benefit of MLND, however, have been inconclusive. We herein performed a meta-analysis of randomized controlled trials of MLND versus MLNS during pulmonary resection for prevention of all-cause mortality in early-stage NSCLC.

FIGURE 1. All cause mortality (A, risk ratio; B, hazard ratio) among patients with early-stage non-small cell lung cancer randomized to mediastinal lymph node dissection (MLND) versus sampling (MLNS) during pulmonary resection. IV, Inverse variance; CI, confidence interval; ACOSOG, American College of Surgery Oncology Group; SE, standard error.

Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; the study population was patients with early-stage (stage I–IIIA) NSCLC; patients were randomly assigned to MLND versus MLNS during pulmonary resection; and main outcomes included follow-up all-cause mortality. For each study, data regarding all-cause mortality in both the MLND and MLNS groups were used to generate risk ratios (RRs) and 95% confidence intervals (CIs). Hazard ratios (HRs) for all-cause death and 95% CIs were also abstracted from each individual study. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic RRs or HRs in both fixed- and random-effects models. Where no significant statistical heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure.

Our comprehensive search (current through March 2011) identified 4 trials: median 6.5-year results of the ACOSOG Z0030 trial,¹ 10-year results of a trial by Wu and associates,² median 5.4-year results of a trial by Sugi and colleagues,³ and median 4.0-year results of a trial by Izbicki and collaborators.⁴ Pooled analysis of the 4 trials (representing

1778 patients with early-stage NSCLC) demonstrated a statistically nonsignificant reduction (but a strong trend toward a significant reduction) in all-cause mortality with MLND relative to MLNS in fixed-effects models (RR, 0.91; 95% CI, 0.82–1.00; $P = .05$; P for heterogeneity = .59 [Figure 1, A]; HR, 0.86; 95% CI, 0.73–1.01; $P = .06$; P for heterogeneity = .29 [Figure 1, B]). Exclusion of any single trial of the previous 3 trials^{2–4} from the analysis did not substantively alter the overall result of our analysis. Eliminating the ACOSOG Z0030 trial,¹ however, demonstrated a statistically significant reduction in all-cause mortality with MLND relative to MLNS (RR, 0.87; 95% CI, 0.76–0.99; $P = .04$; HR, 0.69; 95% CI, 0.51–0.93; $P = .01$).

The results of the present analysis suggest that MLND may not reduce all-cause mortality over MLNS during pulmonary resection in patients with early-stage NSCLC. The results are not robust, however, because exclusion of the ACOSOG Z0030 trial¹ substantially changed the pooled estimate. *Which way we ought to walk from here depends a good deal on where we want to get to.*

Hisato Takagi, MD, PhD
Masafumi Matsui, MD

Takuya Umemoto, MD, PhD
Department of Cardiothoracic Surgery
Shizuoka Medical Center
Shizuoka, Japan

References

1. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 trial. *J Thorac Cardiovasc Surg.* 2011;141:662–70.
2. Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer.* 2002;36:1–6.
3. Sugi K, Nawata K, Fujita N, Ueda K, Tanaka T, Matsuoka T, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. *World J Surg.* 1998;22:290–4; discussion 294–5.
4. Izbicki JR, Passlick B, Pantel K, Pichlmeier U, Hosch SB, Karg O, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Ann Surg.* 1998;227:138–44.

doi:10.1016/j.jtcvs.2011.03.032

Reply to the Editor:

We read with interest the letter of Takagi, Matsui, and Umemoto, who provided the results of their meta-analyses of randomized controlled trials of mediastinal lymph node