Chemotherapy in non-small cell lung cancer: An update of an individual patient data-based meta-analysis

To the Editor:

In the September 2004 issue of the *Journal*, Sedrakyan and associates¹ reported a systematic review and meta-analysis of postoperative chemotherapy versus surgery alone in non-small cell lung cancer. This meta-analysis is based on abstracted data from 15 randomized controlled trials (RCTs). This included 7200 patients and builds on results of our individual patient data-based (IPD) meta-analysis,² published in 1995.

The Non-Small Cell Lung Cancer Collaborative Group, which was responsible for the IPD meta-analysis published in 1995, welcomes the meta-analysis provided by Sedrakyan and associates,¹ which added summary data from 7 trials and approximately 5000 patients to information from the 1995 meta-analysis. However, the interpretation of the results is limited by the absence of trial description and quality evaluation. Furthermore, the results of any systematic review performed with data extracted from publications of trials should be viewed with a degree of caution.³

IPD meta-analyses, which involve the central collection, validation, and analysis of the original trial data, are the gold standard of systematic review and have many advantages over literature-based approaches. They allow the reviewer to check the data, ensure the randomization process was adequate, investigate heterogeneity, and report longer follow-up, and can limit many biases.⁴ They also permit subgroup analysis of patient level characteristics such as age or tumor stage. Of course, it is also well documented that this type of review takes longer to carry out.

The 1995 meta-analysis included more than 9000 patients from 52 RCTs and assessed the effect of chemotherapy in 4 different settings.

An updated and extended IPD meta-analysis is currently under way, and data collection is ongoing. New agents and timings have been investigated in all settings. The update consists of adding trials published since the 1995 analyses and additional follow-up data from trials already included, and investigating additional outcomes in certain settings. Seven different

therapeutic questions will be addressed, and the total number of patients randomized has increased to approximately 23,000 patients. The corresponding protocols are available at the following websites: <http://www.ctu.mrc.ac.uk/download.asp> or http://www.igr.fr/php/index.php?ids_path=2.51.70.127.567.

In a setting equivalent to that described by Sedrakyan and associates,¹ we identified 22 new RCTs with more than 8000 new patients, bringing the total number of trials to 38. If we can include these patients, it would bring the total number of patients in this comparison alone to more than 10,500 patients or 23% more patients than are included in the review by Sedrakyan and associates.¹

Although the meta-analyses by Sedrakyan and associates¹ and a recent similar review by Hotta and associates⁵ are a valuable resource in the absence of other evidence, the results should be considered with caution until they can be compared with the updated IPD meta-analysis. We anticipate that the results of our IPD meta-analyses will be available in 2006.

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doi:10.1016/j.jtcvs.2004.12.032

Reply to the Editor:

We support and applaud the efforts of Ms Burdett and her team in conducting an individual patient data-based (IPD) meta-analysis of postoperative chemotherapy trials. Although there are controversies regarding the conduct of IPD meta-analyses, such as the inclusion of data from unpublished studies and potential investigator bias in terms of data submitted,^{1,2} such studies may be particularly useful in conducting subgroup analyses to identify those patients most likely to benefit from therapy and the optimal treatment regimen to be used.

The non-IPD nature of our meta-analysis does not, however, take away from the validity of the findings that clearly demonstrate a survival advantage for patients treated with adjuvant chemotherapy over those treated with surgery alone.³ This is also underpinned by a recent presentation on adjuvant UFT (uracil and tegafur), the oral 5-fluorouracil derivative, at the 2004 annual meeting of the American Society of Clinical Oncology. In this work, individual patient data from 2003 patients recruited to 6 randomized controlled trials were systematically reviewed. The overall survival benefit for treated patients is 5.3% (hazard ratio = 0.77; $P = .011$) at 5 years and 7.7% (hazard ratio = 0.74; $P = .001$) at 7 years. This is similar to our reported survival benefit for UFT. In addition, continued divergence of the survival curves over time is similar to those commonly seen in breast cancer adjuvant trials.⁴

The authors are correct that since our publication, further randomized controlled trials have been presented. The 2 largest and principal new studies presented at the 2004 meeting of the American Society of Clinical Oncology for platinum-based chemotherapy, however, reported substantial benefits associated with adjuvant chemotherapy.^{5,6} Combining the results of these trials with the previous randomized controlled trials evaluating platinum-based regimens has demonstrated a further overall benefit for platinum-based postoperative chemotherapy (relative risk, 0.86; 95% confidence interval, 0.80-0.93). Moreover, sensitivity analyses determined that even if there were unreported or future studies enrolling more than 2000 patients that showed a statistically significant 20% higher

risk of mortality for platinum-based chemotherapy (the very unlikely scenario), the overall estimate would still significantly favor chemotherapy.

In the past there have been many instances in which the failure to adapt significant advances in treatment has led to delays in passing on the benefits to the patient in the clinic. Examples include thrombolytic therapy or beta-blocker therapy after myocardial infarctions.^{7,8} These non-IPD-based systematic reviews highlighted that each year of delay may cost thousands of lives worldwide and were influential for the development of evidence-based medicine. We believe that delay in the case of postoperative chemotherapy may have the same consequences and be interpreted as reflecting clinician uncertainty and potentially lead to the design and conduct of further clinical trials in which the question has been clearly answered.^{9,10} As Sir Austin Bradford Hill pointed out in his presidential address at the Royal Society of Medicine (January 14, 1965), "All scientific work is incomplete—whether it be observational or experimental. It is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that appears to demand at a given time." In this regard the evidence is very strong that adjuvant chemotherapy improves patient survival postresection. Optimizing therapy and targeting those patients most likely to benefit from treatment are clinically important questions that the IPD study may address. Further trials in the already studied population randomizing patients to a "no chemotherapy" arm are, however, unlikely to contribute to existing knowledge and are ethically questionable.

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Single-stage repair of extensive thoracic aortic aneurysms

To the Editor:

I congratulate Dr Kouchoukos and colleagues¹ for their excellent results with the single-stage repair technique of extended thoracic aortic aneurysms. We originally introduced this technique² in 1994 with a limited series of 16 patients and a hospital mortality of 12.5%. Ten years ago axillary artery cannulation, branched arterial grafts, and antegrade cerebral perfusion were not routinely used. As a consequence, cerebral ischemia was longer than today, and pa-

tients had to undergo operation with deep hypothermia and circulatory arrest. In our first series cerebral ischemia averaged 55.7 minutes. A further consequence of deep hypothermia was more frequent respiratory complications than observed today. During recent years, we also improved our technique by adding antegrade cerebral perfusion, either through retrograde axillary artery perfusion or the "aortic arch (or branch) first" technique, as suggested by Dr Kouchoukos and colleagues.¹ Body temperature is generally decreased to no more than 25°C. Our series now includes approximately 53 patients with an overall hospital mortality of 9.4%. Among the last 30 patients, hospital mortality was 6.7%; neurologic and respiratory complications accounted for 3.3% and 6.7%, respectively. In regard to the "clamshell" access, we still use an approach through a limited right anterior thoracotomy through the third intercostal space and an anterolateral left thoracotomy through the fourth intercostal space with the patient banked 45 degrees on the right side. In our opinion, this access gives an easier approach to the aortic root along with the arch branches and to the most distal portion of the thoracic aorta. Reimplantation of lower intercostal arteries is not a problem in this way. Contrary to some of Dr Kouchoukos' discussants, I fully agree with the author on the strategy of the single-stage approach in complex cases of thoracic aortic aneurysms. This often is the case in patients who have undergone operation for acute type A aortic dissection, in whom the aortic valve had been repaired and the ascending aorta had been replaced by a tube graft, even though it was extended in some cases to a proximal hemiarch. In such acute instances, the Bentall or equivalent techniques will not be used universally, and the elephant-trunk technique will be used even less. A common late observation in such cases is aneurysm development in the aortic root, often associated with valve incompetence, and distal part of the arch and descending aorta. Conventionally, the treatment of these patients would include a repeat sternotomy with Bentall or valve-sparing procedures, arch replacement with the elephant-trunk technique, and followed later by a second procedure with replacement or endostenting of the descending portion of the aorta whenever possible. Actually, endovascular stenting of the descending aorta is not always a