2. Okubo K, Okamoto T, Isobe J, Ueno Y. Rupture of a chronic expanding hematoma of the thorax into lung parenchyma. *J Thorac Cardiovasc Surg.* 2004;127:1838-40.
doi:10.1016/j.jtcvs.2004.08.008

Isolated mediastinal skip metastasis in lung cancer: Is it real N2 disease? To the Editor:

I read with great interest the study by Keller and colleagues¹ for the Eastern Cooperative Oncology Group titled "Prolonged Survival in Patients With Resected Non-Small Lung Cancer and Single-Level N2 Disease," published in the July 2004 issue of the *Journal*. The better prognosis for single-level N2 disease than for multiple N2 station involvement is a relatively old concept. Keller and colleagues¹ correctly reported that several previous studies showed a better clinical outcome of patients with mediastinal skip metastasis than for patients with metastases also in the hilar nodes. The results of the Eastern Cooperative Oncology Group's trial indicated that this advantage is limited to upper lobe tumors, especially to the left upper lobe. The authors stated that "the reason for improved survival remains unclear, although patients with skip metastases may have true regional disease."¹

I would suggest that the scientific explanation of such results may be found in the recent studies on the sentinel node in non-small cell lung cancer. The sentinel node should be the first site of metastatic involvement, because it is the first lymph node that receives afferent lymphatic drainage from a primary tumor. The sentinel lymph node is located in the mediastinum in as many as 35% of patients; mediastinal sentinel nodes are generally found from upper lobe tumors, with the highest incidence in the left upper lobe.²⁻⁶ Furthermore, such data are not new. An excellent anatomic French study published in the *Journal* in 1989 demonstrated that the direct lymphatic drainage of lung segments to the mediastinal nodes is quite common for the upper lobes.⁷ All such reports indicate that isolated involvement of mediastinal sentinel nodes could be considered in the group of N1 disease. It is not surprising that a large, cooperative, randomized, prospective trial led to such conclusions.

In conclusion, I think that the current knowledge on the anatomic pathway of the pulmonary lymphatic drainage indicates

that the TNM classification regarding N status is quite rough. The Eastern Cooperative Oncology Group's trial is another important confirmation that stage IIIa non-small cell lung cancer represents an extremely heterogeneous disease stage, open to future staging revision.

Francesco Puma, MD,
Chief of General Thoracic Surgery
Azienda Ospedaliera S. Maria
University of Perugia Medical School
Terme, Italy

References

1. Keller SM, Vangel MG, Wagner H, Schiller JH, Herskovic A, Komaki R, et al. Prolonged survival in patients with resected non-small lung cancer and single-level N2 disease. *J Thorac Cardiovasc Surg.* 2004;128:130-7.
2. Little AG, DeHoyos A, Kirgan DM, Arcomano TR, Murray KD. Intraoperative lymphatic mapping for non-small cell lung cancer: the sentinel node technique. *J Thorac Cardiovasc Surg.* 1999;117:220-4.
3. Liptay MJ, Grondin SC, Fry WA, Pozdol C, Carson D, Knop C, et al. Intraoperative sentinel lymph node mapping in non-small-cell lung cancer improves detection of micrometastases. *J Clin Oncol.* 2002;20:1984-8.
4. Nomori H, Horio H, Naruke T, Orikasa H, Yamazaki K, Suemasu K. Use of technetium-99m tin colloid for sentinel node identification in non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2002;124:486-92.
5. Schmidt FE, Woltering EA, Webb WR, Garcia OM, Cohen JE, Rozans MH. Sentinel nodal assessment in patients with carcinoma of the lung. *Ann Thorac Surg.* 2002;74:870-5.
6. Sugi K, Kaneda Y, Sudoh M, Sakano H, Hamano K. Effect of radioisotope sentinel node mapping in patients with cT1 N0 M0 lung cancer. *J Thorac Cardiovasc Surg.* 2003;126:568-73.
7. Riquet M, Hidden G, Debesse B. Direct lymphatic drainage of lung segments to the mediastinal nodes: an anatomic study on 260 adults. *J Thorac Cardiovasc Surg.* 1989;97:623-32.

doi:10.1016/j.jtcvs.2004.08.029

Studies of fetal cardiac bypass

To the Editor:

In their elegant studies of fetal cardiopulmonary bypass (CPB), Carotti and colleagues¹ use time-dated pregnant sheep of 120 to 130 days' gestation. Indeed, in all published studies, the preferred animals for studying fetal CPB have been near-term fetal sheep (mean, approximately 126 days' gestation; term, 148 days' gestation). However, this age does not agree with the now-accepted window for effective fetal therapy in the clinical setting: 21 to 29

weeks' human gestation. Therefore we propose that all investigators conduct future fetal CPB studies at clinically relevant gestational ages (83-112 days' gestation in sheep; see below).

This is of great import when considering the vast changes taking place in the uteroplacental and umbilical-placental vascular beds during pregnancy. For example, the uterine weight, uterine blood flow (UBF), and UBF per gram of uterine weight increase significantly from 90 days onward. Indeed, this final phase in the growth of UBF is exponential and associated with a 3-fold increase in fetal weight that occurs after 110 days in sheep and beyond 30 weeks in human subjects.² Similarly, blood flow distribution during this period changes substantially; nearly half the UBF is diverted away from endometrium-myometrium to the placenta. These changes reflect significant alterations in placental vascular resistance, which affect studies of fetal CPB. Finally, similar gestational differences in physiology affect other experimental features, such as fetal responses to steroids.³

We would like to caution investigators, however, against using direct gestational equivalence (human 280 days = sheep 148 days). Differences in fetal growth rates between species can lead to large errors when assuming direct equivalence, as we discovered during our research involving early-gestation lambs. Therefore, we developed an equation to successfully translate gestational equivalence between species on the basis of previous studies of sheep⁴ and human⁵ embryos that have established the gestational age for completion of specific Carnegie stages of development. We translated these stages into developmental equivalence at specific times during gestation. Using the age for each species at equivalent Carnegie stages and assuming full-term pregnancy, we derived a second-degree polynomial equation:

$$\text{Sheep gestation day} = -0.003 \times \text{Human gestation day}^2 + 0.6296 \times \text{Human gestation day},$$

with a correlation coefficient (R^2) equal to 0.9973.

Comparing our developmentally based gestational age with that determined by direct equivalence reveals a difference as large as 14%, which can significantly affect experimental design. For example, a 5-day