(pN1) group of tumors involvement at the intralobar level is substantially better prognostically than that at the hilar level (as well as single versus multiple nodes or stations).

Because this strongly and comprehensively supports the idea that it is correct to stratify (classify) the pN1 cases according to the level (intralobar best, hilar worst) in addition to the number of involved lymph nodes (one better, more than one worse) we amicably invite Marra and colleagues to clarify their position regarding the possible use of such important information, especially regarding the opportunities to actually “stratify for optimization” in terms of adjuvant and neoadjuvant treatment. In fact, the discussion of their experience is mainly focused on the evaluation of such evidence in comparison to others’ similar work. Regarding adjuvant treatment, we have developed a timely consolidated experience in the adoption of postoperative radiotherapy in completely resected non-small cell lung cancers, even in the early stage.^{2,3} Moreover we have directly discussed the Post Operative Radiotherapy Trialists Group conclusions⁴ and strongly support the evidence that modern radiotherapy, accurately planned and administered, can give good results with acceptable side effects in this class of tumors.

From the report of Marra and colleagues,¹ we have taken the idea that because for the best prognostic class pN1 cases any therapeutic effort aimed at the local control could have significance, modern radiotherapy could certainly find its place, especially at the investigational level. For the worst prognostic class pN1 cases, we agree with Marra and colleagues¹ that an attempt at systemic (rather than local) control is justified. In the setting of neoadjuvant treatment, we see the point of view of the Marra and colleagues¹ when they note that it is “promising.” The core fact in managing patients with N1 disease in the clinical setting is that it is truly difficult to obtain a substantially correct diagnosis of true clinical N1 status. In their very reported experience, in fact, Marra and colleagues¹ noted a limited (24.5%) pathologic confirmation rate of clinical N1 assessment. Moreover, when a suspicion of N1 involvement is present at the clinical staging, this is rarely histologically or cytologically assessable; thus an induction treatment planned on the basis of the clin-

ical N1 status alone may still be considered hazardous. In fact, the best that is currently done in the ongoing phase III induction trials for early stage non-small cell lung cancers is to exclude, when N1 status is suspected, the involvement of N2 stations by cervical mediastinoscopy, leaving substantially uncovered the erroneously clinically upstaged to N1 cases (true N0s). We would be very grateful if Marra and colleagues could disclose and describe their point of view regarding these issues.

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Reply to the Editor:

We are glad to respond to the questions of Margaritora and colleagues, as they come from a thoracic surgical group with an established experience in the multimodality treatment of lung cancer.

The results of our study show that pN1 non-small cell lung cancer (NSCLC) could not be considered an “early stage” disease, because as many as 45% of patients at the time of diagnosis and treatment had occult disease beyond the boundaries of the lobe of origin, if we consider that even a locore-

gional recurrence develops outside the margins of “radical” surgical resection.

Another finding is that N1 NSCLC behaves heterogeneously, with two extremes: a population of patients with hilar lymph node metastases prognostically comparable to “limited” N2 disease and, on the other side, a more favorable subgroup of cases with N1 disease by direct infiltration of pulmonary lymph nodes. This difference involves also the pattern of tumor relapse. In fact, we have observed rates of cancer recurrence of 41% at distant sites and of 12% locoregionally for the hilar N1 group and of 24% and 17%, respectively, for the N1 group by direct invasion. It is therefore our opinion that the optimal treatment of all these patients mandates multimodality approaches, which should be appropriately investigated by means of randomized clinical trials.

In the adjuvant setting, in all N1 subgroups the risk of distant metastases overwhelms that of locoregional recurrence. This evidence represents a rationale to use systemic therapy (eg, chemotherapy) after surgical resection, although the role and effectiveness of adjuvant chemotherapy in early stage NSCLC are still controversial.^{1,2} Radiotherapy seems to be less mandatory, because adequate surgery is able to achieve long-term local control in as many as 85% of patients and chemotherapy may also contribute to reduce locoregional failures. Nevertheless, the cited phase III study on patients with N0 NSCLC suggests that modern radiation therapy improves local control with an acceptable toxicity.^{3,4} Further randomized trials are needed to define the role of radiotherapy in N1 NSCLC. Interesting data could be obtained from the forthcoming publication of the results of the International Adjuvant Lung Cancer Trial (EORTC Trial CT0142), which in stages I to IIIA NSCLC compares different adjuvant chemotherapy regimens (cisplatin plus VP16 or cisplatin plus vinca alkaloids) against control, with radiotherapy being optional.

In the neoadjuvant setting, preoperatively scheduled chemotherapy, alone or in combination with radiotherapy, provides survival advantages in locoregionally advanced NSCLC, as shown by many clinical trials.⁵⁻⁷ Phase II studies of patients with early-stage NSCLC treated with induction chemotherapy have had encouraging results, but randomized trials are needed to

clarify whether a multimodality approach could protect the patients against tumor recurrence.

The main problem of designing randomized trials with neoadjuvant treatment for patients with N1 NSCLC is how to obtain an accurate lymph node staging with the available diagnostic tools. Whereas cervical mediastinoscopy is highly sensitive and specific to exclude N2 as well as N3 status, computed tomographic scan of the chest does not allow detection of lymph node metastases in the stations 10 to 14 in most cases. The simultaneous combination of positron emission tomography and computed tomographic scan, as well as endoscopic ultrasonography, could afford further information about N1 nodes but are not yet considered for routine use. We agree with Margaritora and coauthors that is difficult to achieve the histologic or cytopathologic assessment of N1 disease and that more invasive diagnostic procedures (eg, video-assisted thoracoscopy or thoracotomy) are to be considered improper for routine clinical staging. Therefore, phase III studies on neoadjuvant chemotherapy or chemoradiotherapy in early stage NSCLC could actually be designed only by excluding patients with N2 and N3 disease and enrolling patients with true N1 and true N0 disease together.

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Influence of chromosome 22q11.2 microdeletion on surgical outcome after treatment of tetralogy of Fallot with pulmonary atresia

To the Editor:

We read with interest the important article by Cho and colleagues¹ recently published on the Journal. The article reported the huge surgical series of patients affected by pulmonary atresia with ventricular septal defect (PA-VSD) treated at the Mayo Clinic during the last 20 years. The analysis of follow-up data and risk factors related to surgery was extremely accurate, and the operative results were excellent. However, we noticed that the authors did not take into consideration the possible association with a genetic syndrome among the hypothetical risk factors for surgical mortality or morbidity.

The high prevalence of genetic abnormalities among patients with PA-VSD, particularly the chromosome 22q11.2 microdeletion (Di George or velocardiofacial syndrome) is well described in the literature,²⁻⁷ including important contributions from the Mayo Clinic.^{6,7} Chromosome 22q11.2 microdeletion (del22q) has been reported in about 40% of patients with PA-VSD,² particularly those with major aortopulmonary collateral arteries (MAPCAs)³ and complex loop morphology of the pulmonary arteries.^{4,5} The del22q abnormality has also been related to peculiar perioperative problems after surgery for PA-VSD, such as persistent airway hyperresponsiveness or increased prevalence of infectious complications.^{6,7}

Among the surgical series of 37 consecutive patients with PA-VSD and MAPCAs surgically treated at our institution between January 1994 and March 2002 (mean age 39 ± 48 months, range 22 days–13 years, 62% of patients 2 years old or younger), genetically diagnosed del22q (fluorescence in situ hybridization test) was present in 15 cases (40%, 95% confidence interval [CI] 24%-56%). Its occurrence did not relate to any peculiar anatomic phenotype with respect to either pulmonary vascular supply (mean number of MAPCAs 3.7 ± 1.3 for 15 patients with del22q, vs 3 ± 1.4 for 22 patients without del22q, *P* not significant), mean pulmonary arteries/collateral arteries lung segment perfusion ratio 1.5 ± 1.5 vs 2 ± 1.9 , *P* not significant) or prevalences of right aortic arch (53% [*n* = 8] among patients with del22q vs 36% [*n* = 8] among patients without del22q, *P* not significant) and infundibular atresia (53% [*n* = 8] among patients with del22q vs 50% [*n* = 11] among patients without del22q, *P* not significant).

Twenty-five patients underwent total unifocalization⁸ associated with successful either primary (*n* = 18) or secondary (*n* = 2) VSD closure in 80% of cases (20/25, 95% CI 64%-96%). The other 12 received an intermediate right ventricular outflow tract reconstruction with eventual second-stage unifocalization and repair in 11 cases, accounting for an overall reparability rate of the disease of 86% (31/36, 95% CI 74%-98%).

Mortality included 5 in-hospital deaths (15%, 95% CI 3%-27%), and 1 late death. Survival at 7-year follow-up was 81%. Two deaths occurred during the immediate postoperative course in 2 patients with del22q; pulmonary vascular disease was the cause in 1 case and no apparent cause was found at autopsy in the other. Postoperative hospital infections, including 2 fungal pneumonias, 1 fungal endocarditis, and 1 *Pseudomonas* pneumonia, occurred in 4 patients with del22q. Fungal infections were always related to a decreased CD4 lymphocyte count on peripheral blood samples and were responsible for 2 of 3 further in-hospital deaths. The last in-hospital death was that of a patient with del22q whose VSD was left open because of airway bleeding. Late death finally occurred in the case of a patient with del22q who had sudden airway bleeding early after successful second-stage closure of VSD. In