Only six patients without previous AFib were given antiarrhythmic drugs (AADs), and interaction between AADs and CPAP did not influence the incidence of AFib during follow-up among them ($P = 1$) (our unpublished data, 2013). CPAP did not add any clinical benefit to AADs in patients with previous AFib documentation ($P = .53$, unpublished data). Compliance and duration of CPAP use was not higher in patients who did not have AFib during follow-up, and lack of “antiarrhythmic” efficacy of CPAP in patients with previous AFib cannot be attributed to a lower use of this therapy in this subgroup.

A prior history of AFib is the strongest risk factor for recurrent AFib after AF ablation. It would appear by our results that other therapy in this subgroup. with previous AFib cannot be attributed to a lower use of this therapy in this subgroup.

A prior history of AFib is the strongest risk factor for recurrent AFib after AF ablation. It would appear by our results that other therapy in this subgroup. with previous AFib cannot be attributed to a lower use of this therapy in this subgroup.

We may conclude that documentation of AF sets for the identification of a subset of patients in whom underlying OSA is highly likely. This fact has notable implications in terms of cardiovascular morbidity and mortality. This also appears to include a lower incidence of AFib after CPAP initiation if this arrhythmia has never been documented. Further investigation will be needed to assess the etiopathogenic relationship between OSA and AF and the physiologic changes induced by CPAP that prevent AFib in some patients with AF.

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N2 Nodal Involvement in Multiple Primary Lung Cancer
Really an Exclusion Criterion?

To the Editor:

Girard et al reported in CHEST (January 2010) a comparison analysis of seven patients with multiple lung adenocarcinomas benchmarked on the epidermal growth factor receptor (EGFR) and Kirsten-rat sarcoma 2 viral oncogene homolog clonality status, which we read with interest and has instigated some reflections. Martini-Melamed (MM) criteria outlined a clinical and diagnostic classification of multiple primary lung cancers (MPLCs); today, American College of Chest Physicians (ACCP) guidelines provided a new MPLC classification. Both MM and ACCP criteria are used to classify an MPLC case as primary metastatic or true synchronous/metachronous multiple. Furthermore, none of these criteria incorporate information on molecular status to distinguish multiple primary from metastatic disease. The new diagnostic algorithm described by Takamochi and colleagues is based on the assessment of EGFR-Kirsten-rat sarcoma 2 viral oncogene homolog to achieve a correct definition of the clonality status among multiple lung adenocarcinomas and, in turn, is used as a differential diagnosis criterion. With this algorithm, Takamochi and colleagues could easily detect significant discrepancies in existing clinical criteria in 36 patients they thoroughly examined to assess the difference between true primary and metastatic disease. Similar evidence was reported in Girard et al; thus, confirming the inherent limitations of the MM/ACCP criteria. Moreover, Takowa et al advocated for molecular-based stratification criteria by detailing a case of multiple synchronous lung adenocarcinomas harboring an L858R mutation within exon 21 of EGFR in the middle-lobe tumor and subcarinal nodes but not in the upper-lobe tumor. In the setting where MM/ACCP criteria are taken into account, the diagnosis of N2 nodal involvement defines synchronous multiple tumors as metastatic lesions; however, these data might suggest that the number of multiple primary adenocarcinomas could be higher than what is observed if only MM/ACCP criteria are taken into account. On the other hand, very few reports compare the clonality status of primary tumors and lymph node metastases of 56 non-small cell lung cancers, the molecular appearance in the primary cancer and its lymph node metastasis were discordant in 92.9% and 69.6% by p53 and EGFR status, respectively.

According to the high concordance between the clonality of primary tumors with metastatic spread to the lymph nodes, it could be suggested that, in the case of multiple adenocarcinomas, a clonality status evaluation in the mediastinal lymph node metastasis should also be performed. We would appreciate the authors’ opinion about whether the assessment of the clonal lymph node status of their series of seven patients would be a valuable piece of information.

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Response

To the Editor:

I thank Dr Leuzzi and colleagues for their insightful comment on our article in CHEST.1 Based on the study of seven patients with multiple lung adenocarcinomas harboring distinct EGFR and KRAS mutations, we demonstrated the limits of the Martini-Melamed and American College of Chest Physicians criteria to distinguish multiple primary tumors from metastases. Nevertheless, in our article, only one of the three patients with synchronous multiple tumors presented with nodal involvement; all four metachronous tumors were N0 at the time of recurrence, precluding us to answer Dr Leuzzi and colleagues about the potential interest of mutation genotyping on tumor lymph node specimens to assess clonality. Of note, another published surgical series stressed the low frequency of nodal involvement in synchronous multiple lung cancers.2

Contrary to Takamochi and colleagues,3 we actually believe that EGFR and KRAS genotyping is not sufficiently informative to assess clonality in multiple lung cancers, considering both the variable probability of a match in independent tumors that may be high for frequent mutations (eg, 5.2% for KRAS G12D) and, conversely, the infrequency of the occurrences of each specific mutation overall.4 Thus, in a subsequent study from our group on 20 patients with 42 multiple lung cancers, no mutations were observed in either tumor for seven patients (35%), despite the sequencing (using mass spectrometry-based genotyping) of nine genes frequently harboring oncogenic mutations.5 In this study, we reported the use of array-based comparative genomic hybridization to assess clonality.6 By identifying precise regions of allelic gains and losses, this technique has a far higher potential to establish whether tumors are independent (ie, lack matching gains/losses) or clonal (ie, contain matching gains/losses) as compared with mutation profiling. Again, none of the 42 multiple lung tumors included in this analysis presented with nodal involvement.

Ultimately, a major issue when interpreting reported data on intratumor or intertumor or tumor node molecular heterogeneity is the variable technical sensitivity of genotyping techniques, which may explain most reported discrepancies. Next-generation sequencing technology may then be of great interest to further explore clonality of multiple lung cancers. A recent study showed that pyrosequencing of multiple tumor specimens from metastatic renal carcinomas leads to the identification of mutations not detectable across every tumor region or metastatic lymph nodes in >60% of cases.7 Another avenue is genotyping of circulating tumor cells that may allow the identification of different tumor clones in single or multiple tumors; EGFR T790M mutant circulating cells may then be identified in EGFR-mutant lung adenocarcinomas at time of diagnosis, before the occurrence of acquired resistance to epidermal growth factor receptor inhibitors.8 At this level of analysis, unexpected biologic mechanisms have to be considered. Dissemination of cancer cells is conventionally viewed as a unidirectional process that leads to metastatic colonization of distant organs, but circulating tumor cells have been reported in mice to be able to colonize back their tumors of origin, in a process called “tumor self-seeding.”9 Such a process remains to be explored in multiple lung cancers and, besides clonal relationships, may play a major role in the clinical outcome of patients.

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