nighttime arterial oxygen saturation and PaCO₂ until they had obtained an appropriate response to treatment, defined as compensation for nocturnal hypoventilation. Finally, it is important to emphasize the low ventilatory assistance levels (inspiratory pressure) used in the studies reporting poor response to NIV. Again, only Meecham Jones et al. used inspiratory pressures that seem to be sufficient to compensate for nocturnal hypoventilation in end-stage COPD patients. In this sense, the ventilatory parameters chosen by Casanova et al. may also be too low. Ventilatory parameters must be selected considering changes of gas exchange parameters in response to nighttime NIV together with effects seen during the day. Thus, the poor results of the trial carried out by Casanova et al. may simply be attributable to failure to achieve effective ventilation.

NIV should not be used as a blanket treatment for all patients with COPD, even when disease is severe, as Casanova et al. rightly suggest in their conclusion. However, a selected group of patients may well benefit from domiciliary mechanical ventilation, and we need to be able to identify who they are. It has been suggested that good candidates for such treatment may be those patients who have developed significant hypercapnic respiratory failure and poor response to long-term oxygen therapy, in whom nocturnal hypoventilation has been shown to be corrected by NIV, and who are motivated to comply with therapy and willing to be trained. Such patients should be enrolled by researchers carrying out the next wave of randomized, controlled trials if we are to answer the question of whether or not to administer ventilation to patients with COPD.

Antonio Antón, MD
Rosa Güell, MD
Barcelona, Spain

Drs. Antón and Güell are from the Department of Respiratory Medicine, Hospital de la Santa Creu I Sant Pau, Universitat Autònoma de Barcelona. Correspondence to: Antonio Antón, MD, Department of Respiratory Medicine, Hospital de la Santa Creu i Sant Pau, St Antoni Ma Claret 167, 08025 Barcelona, Spain; e-mail: panton@hsp.santpau.es

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Lightning Can Strike Twice
Second Primary Lung Cancers

Most patients with non-small cell lung cancer (NSCLC) present at an advanced stage and are incurable by current treatment modalities. A smaller group, 20 to 25% of cases, in whom cancer is detected while it is still localized, have a reasonable chance of long-term survival. A majority of patients with stage I and a significant minority of those with stage II NSCLC achieve cancer-free survival for > 5 years after complete resection. Recurrence of the primary tumor is rarely amenable to curative therapy. In contrast, patients with localized second primary lung cancers who are physiologically able to undergo complete resection may benefit from reoperation.

In this issue of CHEST (see page 1621), Asaphe and associates detail their experiences with the surgical
treatment of patients who have developed a meta-
chronous NSCLC. The authors identified 37 such
cases from a database of about 800 patients who had
undergone resection over the past 2 decades. Four of
the patients had initial small cell cancers. The ma-
jority of initial cancers were stage IA lesions (78%),
but 57% of second cancers were more advanced.
Anatomic resections, including 10 completion pneu-
monectomies, were carried out in the majority of
second operations (86%) and were associated with a
low operative mortality (5.4%). The complication
rates and postoperative lengths of hospitalization
were likewise low. Including death from all causes,
the 5-year and 10-year survival rates following resec-
tion of the second tumors were 33% and 10%,
respectively. The majority of both first (45%) and
second (60%) cancers were adenocarcinomas. Also,
reflective of the changing epidemiology of lung
cancer is that the report is unique in that the
majority (60%) of the patients were women. Al-
though the report is otherwise similar to other
studies and is limited in that the total number of
second lesions is unknown, since only operated cases
were identifiable, it focuses our attention on this
important clinical area. Among the many issues
relevant to second lung cancers are their differenti-
ation from metastasis, their incidence and changing
histology, optimal therapy and prognosis, and the
approach to surveillance following presumed cura-
tive treatment of the lung cancer patient.

The current authors, most previous reports, and
clinicians in daily practice apply the criteria deline-
eted by Martini and Melamed1 for defining meta-
chronous lung cancers. Although some have sug-
gested that a disease-free interval of 3 years or 4
years be required,2,3 most accept the 2-year stan-
dard. It must be stressed, however, that confident
differentiation of a new primary from a metastasis is
often impossible. Even a difference in histology is
not an absolute indicator, since many tumors are
comprised of variable cellular elements, whether
defined by degree of differentiation or by actual cell
type, and a metastasis may consist of only one of the
clones present in the initial lesion. Compounding the
dilemma is the common finding of identical histology
in the first and subsequent cancers, 35% in the
present series, and from 50 to 75% in other re-
ports.2–4 The same problem relates to synchronous
lesions. In some sense, the designations synchronous
and metachronous are arbitrary, especially in cases
with short intervals, since calculation of tumor dou-
bling times indicates that most cancers are present
for a number of years before becoming clinically
detectable. Although not commonly used, additional
evidence can be gleaned from genetic studies. In
small series, applying DNA flow cytometry5 or anal-
ysis of p53 gene mutations,4 most lesions diagnosed
by clinical criteria as separate primaries are found to
be discordant from the original tumor. Although this
suggests that the clinical criteria are largely accurate,
it must be kept in mind that the polyclonality of
many tumors indicates that some will inevitably be
misclassified. Although given our current therapeu-
tic options, the treatment plan is not altered in most
cases. Results reporting and clarification of natural
history would clearly benefit from more definitive
data.

Operations for second lung cancers made up about
4.5% of pulmonary resections for cancer in the
present series. In other series, this rate varies from
0.8% to as much as 10%.4–8 Since it is limited to surgi-
cal patients, the present series does not allow
calculation of the more important rate of develop-
ment of NSCLC after an index cancer. It has been
clear, however, ever since long-term data on suffi-
cient numbers of treated patients became available
> 2 decades ago,1,9 that these patients are at high
risk for multiple types of aerodigestive second tu-
mors, especially second lung cancers. This risk has
been confirmed in later cooperative and large insti-
tutional studies6,10,11 and by updates of the original
reports.12 The approximate rate of a second primary
lung cancer for a curatively resected NSCLC patient
is about 1 to 2% per patient per year,13 has remained
steady over time, and does not appear to decrease
significantly with the passage of time. The histology
of second lung cancers, however, has changed from
overwhelmingly squamous cancers to adenocarcino-
mas. This change is reflected in the present series, as
well as other recent reports.14–16 A particularly high
rate of 5 to 6% per patient per year has been noted
in two smaller groups of patients. As many as 45% of
surgically treated cases of “occult” lung cancer de-
velop second primaries during follow-up,17 but this
entity is rarely encountered currently. More likely to
become an increasing problem are patients success-
fully treated for limited stage small cell carcinoma, in
whom the risk of a metachronous NSCLC may be as
high as 69% 16 years after treatment.18
As for initial lung cancers, the optimal treatment
for second tumors is complete resection. Five-year
survival in about a third of cases, as noted in the
present series, is in line with most reported expe-
rience, with some reporting > 40% in stage I
cases.2,8,11,18 Operative mortality is low and re-
mains low in the small group treated by resection
for third primary lung cancers. It is obvious that
compulsive evaluation is mandatory to ensure ade-
quate pulmonary reserve and the absence of
metastatic disease. It is also clear from the current
report and others that, when necessary, comple-
tion pneumonectomy can be performed with ac-
ceptable results. Of necessity, second operations must sometimes be limited to segmental or wedge resection, but they should always be accompanied by interlobar and mediastinal nodal staging. The major prognostic factors for second cancers are the same as for index cancers, namely disease stage and completeness of resection.\textsuperscript{2,11,19,20} The late survival for second cancers, however, is lower than that for similar stage first tumors. The reason for this discordance is unknown and is likely multifactorial. In addition to the fact that patients with second lesions are older, one may speculate that the occurrence of a second primary represents an unfavorable biologic indicator or that resections are limited by technical and physiologic factors. It is also likely that the lower survival may be due to the currently unavoidable problem of admixing metastatic disease with true second primaries. In this regard, it is noteworthy that several authors have determined that a longer disease-free interval between the index and second cancer is associated with an improved prognosis.\textsuperscript{6,19,21} It is likely that more of these tumors are true second primaries. Survival is not influenced by cell type or whether the first and second cancers are of similar or different histology.\textsuperscript{11,16}

The persistent risk of second cancers and the success of their surgical treatment, as well as the significant rate of recurrent disease, suggest that careful follow-up of the curatively treated lung cancer patient should be a worthwhile, lifelong endeavor. The conventional wisdom is that, for the first 2 or 3 years, we are looking for recurrence, while later new cancers are the issue. However, there exists no consensus as to how best to structure follow-up. It is disturbing that Asaph and colleagues are excluded from long-term follow-up of their patients because of managed care. This may explain the fact that all patients with second cancers in this series underwent surgery, in contrast to the 60 to 70\% operability rate reported by others.\textsuperscript{1,6,8,11} One fears that, when medical and surgical thoracic oncologists are kept out of the surveillance and decision-making loop with respect to defining second primaries and how best to treat them, some patients may be denied a chance for cure. Although the efficacy of postoperative surveillance has been questioned,\textsuperscript{22,23} cogent counterarguments have been presented\textsuperscript{24–26} based on both clinical and humanistic benefits to the patient and the knowledge base and skills of the following physicians. Although a 1 to 2\% risk of second cancer may be interpreted as small by a health-care administrator, the cumulative risk should be alarming to both patients and physicians— alarming in a positive way, causing the former group to abandon tobacco and the latter group to strive for better means of identification, definition, and treatment. If surveillance has been found wanting, it is likely the method that is at fault, rather than the theory. Although routine imaging other than chest radiography traditionally has been discouraged, the authors correctly point out that it may be time to reassess this belief. In light of the recently reported clinical and economic utility of low-dose CT scan for identifying early-stage cancers in smokers, it is logical to apply this approach in the posttreatment patient population, a group at 10 times the risk of smokers in general. Finally, the most desirable approach would be prevention. There is evidence that smoking cessation reduces the risk. Chemoprevention data are as yet inconclusive.

\textit{Ronald B. Ponn, MD, FCCP}

Yale-New Haven Hospital
New Haven, CT

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