Survival after resection of synchronous non–small cell lung cancer

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Objectives: Our objective was to determine the long-term survival of patients with resected synchronous multiple pulmonary malignant tumors.

Methods: This is a multi-institutional retrospective study of patients who underwent surgical resection of synchronous (nonbronchioloalveolar) non–small cell lung cancer.

Results: Between March 1996 and December 2009, 67 patients (30 men) underwent 121 operations. Forty-four patients had bilateral tumors. Positron emission tomographic scans were performed in 58 (87%) patients, computed tomographic scans and magnetic resonance imaging of the brain in 53 (79%), and mediastinoscopy in 56 (84%). N2 lymph nodes were benign in all patients before undergoing resection of bilateral tumors of the same histologic type. Types of resection were lobectomy in 62, sublobar in 73, and pneumonectomy in 1. Eleven patients (16%) had postoperative morbidities. Cancer-specific 3- and 5-year survivals were 73% and 69%, respectively, and overall 3- and 5-year survivals were 64% and 53%, respectively. Subgroup analysis demonstrated no difference in overall survival at 5 years between bilateral tumors of the same histologic type (M1a) (49%) versus different histologic types 42% ($P = .88$), or between bilateral tumors (50%) and ipsilateral tumors (54%) ($P = .83$).

Conclusions: The 5-year survival of surgically resected, synchronous, N2-negative, nonbronchioloalveolar, non–small cell lung cancer is excellent, even in patients who have bilateral lung lesions that harbor the same histologic features. Although the new TNM classification system labels this disease as clinical stage IV M1a, survival acts more like a separate T1 lesion after surgical resection. Thus, surgical resection should be considered in appropriately selected patients who have multiple pulmonary malignant tumors that are N2 negative. (J Thorac Cardiovasc Surg 2011;142:547-53)

GTS

With improved imaging studies, particularly high-resolution computed tomography (CT) and positron emission tomography (PET), patients with lung cancer frequently have more than 1 suspicious lung nodule. In many instances, these tumors represent metastatic disease from a single original tumor and are classified correctly by current TNM classification as T3, T4, or M1a.[1] Still other possibilities include nonrelated synchronous multiple primary lung cancers (SMPLC). Stedman's Medical Dictionary[2] defines synchronous as ''occurring simultaneously'' and metachronous as ''not synchronous; multiple separate occurrences such as multiple primary cancers developing at intervals.'' Few studies accurately or consistently describe patients with synchronous lung cancer, their evaluation, treatment, or long-term outcomes. This limits the understanding of this clinical scenario. Past[3] and present[1] international systems for the staging of lung cancer have added little to this issue, further leading to confusion among physicians who care for such patients. Although it can be inferred that different histologic features would be classified independently, this is not true of tumors of the same histologic classification. Presently, these disease states are defined as T3 (same lobe), T4 (ipsilateral different lobe), or contralateral lung (M1a). However, some of these multiple tumors are in fact synchronous and unrelated even when histologically similar. When current guidelines are implemented and dictate patient care, this frequently results in undertreatment of potentially curable SMPLC.

The primary objective of this study was to determine long-term survival in patients who underwent complete surgical resection of truly SMPLC in the hopes of clarifying optimal treatment and to serve as a reference for future study in this group of patients.

METHODS

This is a multi-institutional retrospective cohort study of patients who underwent surgical resection of synchronous lung cancer (non-BAC) between March 1996 and September 2009. The study received institutional review board approval at all 3 participating institutions: Albany Medical

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Abbreviations and Acronyms

CT = computed tomography
BAC = bronchioloalveolar cancer
MRI = magnetic resonance imaging
PET = positron emission tomography
SMPLC = synchronous multiple primary lung cancer

Center, Albany, New York, Hospital of St Raphael, New Haven, Connecticut, and University of Alabama at Birmingham, Birmingham, Alabama. Waiver of individual patient consent was granted.

All patients who underwent surgical resection of more than 1 non–small cell lung cancer (NSCLC) were reviewed for possible inclusion. Patient demographics, preoperative evaluation, surgical treatment, pathologic stage, mortality, cancer-free survival, site of recurrence, overall survival, and cause of death were primary end points and were identified by multiple sources including medical records, follow-up radiographic studies, hospital computer information systems, tumor registry, Social Security Death Index, and, when necessary, telephone contact with patients or surviving family members. Patients who did not meet the inclusion criteria were excluded from further evaluation. Patients with SMPLC, by our inclusion criteria, received 2 separate staging designations.

Inclusion/Exclusion Criteria

Patients who were admitted with or were identified intraoperatively or pathologically as having more than 1 tumor and who underwent surgical resections with the intent of cure were eligible for inclusion in this study. Patients with typical carcinoid tumors, BAC, or nonmalignant nodules were excluded. Patients in whom metachronous pulmonary nodules developed were also excluded. Multiple ipsilateral tumors were included only if the tumor had different histologic features. Ipsilateral tumors of the same histologic type but different subtypes were excluded. Bilateral tumors of the same histologic type were included in this study, provided mediastinal evaluation proved N2 lymph node stations were benign. Bilateral tumors of different histologic types with positive N2 lymph nodes were included in this study.

Stages of disease were recorded according to the seventh edition of the TNM classification. We reported a stage for each of the 136 tumors as if it were a separate cancer and the other nodules were not present. If a patient had a T2 and a T1 lesion in the same side of the chest, of different histologic type, and 1 of the N1 lymph nodes was positive, both lesions were listed as N1 if the specific histologic type of the N1 lymph node could not be determined, that is, T2 N1 M0 and the other T1 N1 M0.

Statistical analysis was completed using SAS 9.1 (SAS Institute, Inc, Cary, NC). Continuous data are presented as means and categorical data are presented as percentages. Fisher's exact test or the Pearson χ^2 test was used to assess categorical data and the Wilcoxon rank sum was used for continuous data. Actuarial survival of patients was estimated by Kaplan-Meier analysis, with P values calculated by log-rank statistics. For the multivariable survival analysis, variables with a univariate P value $< .08$ were entered into a Cox stepwise proportional hazards model. Patients alive at the end of the study period were censored for purposes of survival analysis, and time-related events were calculated from the time of the initial procedure. Death from any cause was used to determine the overall survival, and only cancer-related deaths were included in the cancer-specific mortality. Recurrence of cancer was used to determine the disease-free survival. Local recurrence was defined as recurrence of tumor within the same lobe, regional recurrence was defined as the involvement of mediastinal lymph nodes ipsilateral to the side of surgery, and distant recurrence was defined as recurrence in the contralateral lung or in the remaining lung on the same side but in a different lobe from the one on which the operation was performed or tumor recurrence elsewhere in the body. Operative deaths were included in the survival analyses. Follow-up consisted of chest and abdominal CT every 6 months for the first 2 years and yearly afterward. The final data acquisition was December 2009.

RESULTS

Between March 1996 and September 2009, a total of 67 patients (30 men) underwent 121 surgical procedures to resect 136 lung cancers. Patient characteristics are shown in Table 1. Forty-four patients had bilateral tumors and 23 had ipsilateral tumor locations as shown in Figure 1. PET scans were performed in 58 (87%) patients and CT/magnetic resonance imaging (MRI) of the brain in 53 (79%) patients. N2 lymph nodes were determined to be to be negative for metastatic disease in all patients before resection of same-histology tumors. Tumor details and pathologic stage are shown in Table 2. Mediastinal (N2) lymph nodes were positive in 2 patients before resection of bilateral tumors of different histologic cell type. Surgical resections included lobectomy in 62, sublobar resection in 73, and pneumonectomy in 1 patient. Median interval between operations for those with bilateral tumors was 2.0 months. Of the 67 patients, 11 (16.4%) had major postoperative morbidities and 2 (2.9%) died after their second operative procedure. Operative mortality occurred in 2 (1.7%) of 121 surgical resections.

Overall survival and cancer-specific survival are shown in Figure 2. Cancer-specific 3- and 5-year Kaplan-Meier survival was 73% and 69%, respectively, and overall 3- and 5-year survival was 64% and 53%, respectively. Univariate analysis demonstrated no difference in overall survival at 5 years between bilateral tumors of the same histologic type (M1a) (49%) versus different histologic types (42%) ($P = .88$) or between bilateral tumors (50%) and ipsilateral tumors (54%) ($P = .83$). Mean follow-up was 45.5 months.

Table 3 shows the results of the univariate analysis that was performed to identify variables associated with survival. Analysis was performed both for overall survival and for cancer-specific survival. There was a significant difference based on highest pathologic stage for both overall survival ($P = .001$) analysis and cancer-specific survival analysis ($P = .009$). Additionally, there was a trend toward significantly greater cancer-free survival in patients who had all 3 preoperative staging tests (5-year cancer-free survival 75% in patients who had all 3 preoperative tests and 57% in those that did not), but these differences did not achieve statistical significance ($P = .160$). There were no significant differences in survival between men and women by age, histologic type, or tumor location.

TABLE 1. Patient characteristics for the 67 patients in this study

Age (mean years) ± SD	70.9 ± 8.7
Gender	
Male	30 (45%)
Female	37 (55%)
FEV_1% (mean) ± SD	81% ± 19%
Neoadjuvant chemotherapy	8 (12%)
Adjuvant chemotherapy	9 (13%)
Preoperative staging	
Mediastinoscopy	56 (84%)
Brain MRI	53 (79%)
FDG-PET scan	58 (87%)

SD, Standard deviation; *FEV_1%,* percent forced expiratory volume in 1 second; *MRI,* magnetic resonance imaging; *FDG-PET,* fluorodeoxyglucose positron emission tomography.

The disease-free survival is shown in Figure 3. Tumor recurrence occurred in 16 (24%) patients and was local in 3 (19%), regional in 1 (6%), and distant in 12 (75%). Local recurrence occurred in 3 (4%) of 73 sublobar resections. Two of these 3 patients underwent completion lobectomy. Metachronous multiple primary lung cancers developed in 3 (4%) patients, 2 of whom underwent surgical resection with curative intent.

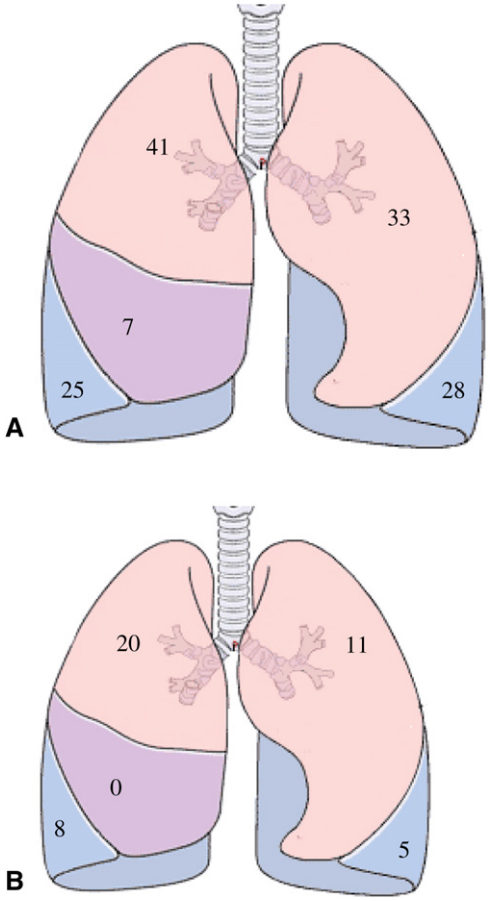

FIGURE 1. Location of non–small cell lung cancer: A, all tumors; B, bilateral tumors.

TABLE 2. Tumor characteristics

No. of patients	67
Albany Medical Center	8
Hospital of St Raphael	32
University of Alabama, Birmingham	27
No. of tumors	136
Median number of tumors (range)	2 (2-3)
Histology	23
Ipsilateral tumors	
Adenocarcinoma + squamous	8
Adenocarcinoma + neuroendocrine	8
Adenosquamous + adenocarcinoma	3
Squamous + neuroendocrine	4
Bilateral tumors	44
Adenocarcinoma (multiple)	21
Squamous (multiple)	6
Adenocarcinoma + squamous	8
Squamous + neuroendocrine	1
Adenosquamous + adenocarcinoma	2
Adenosquamous + squamous	1
Adenocarcinoma + neuroendocrine	4
Adenosquamous (multiple)	1
Pathologic stage using 7th edition for all 136 tumors	
IA	89
IB	32
IIA	2
IIB	11
IIIA	1
IIIB	2

DISCUSSION

Patients with multiple suspicious lung nodules are not uncommon. In many patients these tumors represent metastatic lung cancer from a single original tumor and are appropriately staged as T3 (same lobe), T4 (ipsilateral different lobe), or M1a (contralateral lung) disease according to the most recent staging classification.[1] Some of these patients, however, have SMPLCs, which are separate, distinct,

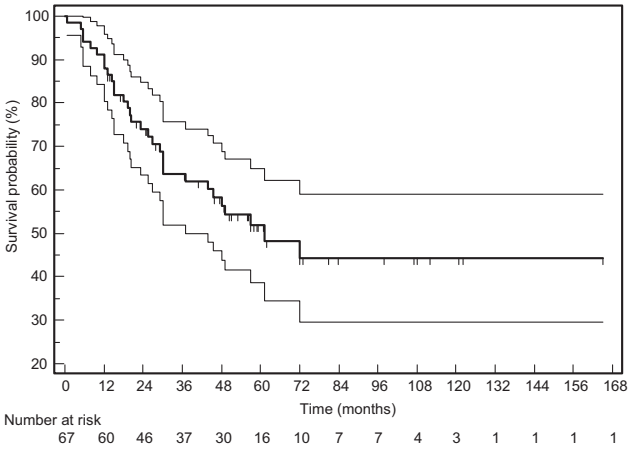

FIGURE 2. Kaplan-Meier survival curve depicting actual overall survival (N = 67) and 5-year survival (52%). *Lighter lines* indicate 95% confidence intervals.

TABLE 3. Kaplan-Meier 5-year overall survival and cancer-specific survival based on patient factors

	Five-year overall survival	*P* value	Five-year cancer-specific survival	*P* value
Gender		.438		.340
Male	53% (N = 30)		76% (N= 23)	
Female	50% (N = 37)		64% (N = 27)	
Had all 3 preop staging tests (med, brain MRI, PET)		.576		.160
Yes	56% (N = 42)		75% (N = 31)	
No	44% (N = 8)		57% (N = 19)	
Histology				
Adenocarcinoma (multiple)	72% (N = 22)	.630	87% (N = 17)	.204
Squamous (multiple)	50% (N = 6)		75% (N = 4)	
Adenocarcinoma + squamous	39% (N = 15)		61% (N = 9)	
Adenocarcinoma + other	55% (N = 17)		68% (N = 14)	
Squamous + other	22% (N = 6)		34% (N = 6)	
Adenosquamous (multiple)	(N = 1)*			
Tumor location		.831		.696
Ipsilateral	50% (N = 23)		67%	
Bilateral	54% (N = 44)		71%	
Highest clinical stage, 7th edition				
IIB (T3 N0, T4 N0)	12% (N = 6)	.002	(N = 1)*	.024
IIIA (T3-4, N1-2, M0)	18% (N = 16)		22% (N = 4)	
IIIB (T4 N2, Tx N3)	(N = 1)*		(N = 1)*	
IV (bilateral)	72% (N = 44)		72% (N = 44)	
Highest pathologic stage, 7th edition				
IA	44% (N = 81)	.297	66% (N = 51)	.869
IB	70% (N = 36)		78% (N = 33)	
IIA	(N = 3)*		(N = 2)*	
IIB	64% (N = 6)		63% (N = 6)	
IIIA	55% (N = 7)		54% (N = 7)	
IIIB, IV	(N = 3)*		(N = 1)*	

*Insufficient survival data to compute a meaningful result.

and unrelated. Patients with SMPLCs are at risk of being clinically overstaged and subsequently undertreated using the sixth and even the current seventh TNM staging systems. In this study we sought to evaluate the long-term survival of patients undergoing resection of SMPLCs avoiding pitfalls common to other recent studies.

The incidence of SMPLC is unknown but has been reported to occur in 4.5%[4] of patients with newly diagnosed lung cancer and may be increasing.[5] A better understanding of these patients, their treatment options, and outcomes is a critical part of providing the optimal treatment of this not so uncommon clinical scenario. A lack of consistency in definitions applied to overlapping clinical scenarios leads to further confusion. This explains the wide range of published results and confusion among physicians regarding appropriate treatment of patients with SMPLC.

Martini and Melamed[6] were the first to describe and categorize nuances associated with patients with multiple lung cancers. Recent publications on the subject of SMPLC have been inclusive rather than exclusive, often including

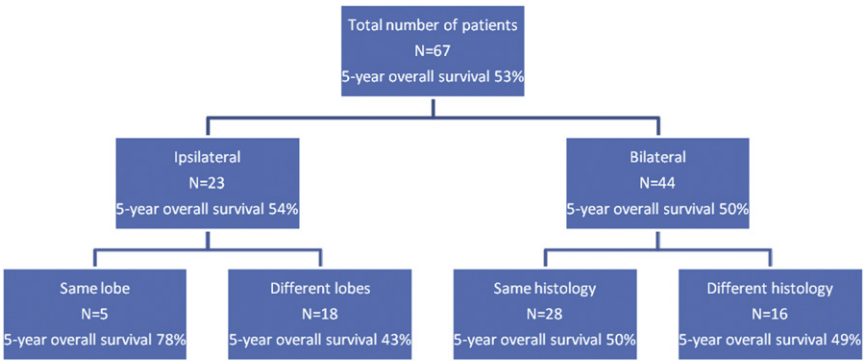

FIGURE 3. The Kaplan-Meier overall 5-year survival by side of resection and histologic type.

typical carcinoid tumors, BACs, and ipsilateral tumors of the same histologic type.[7] Finley and associates[7] recently reported the largest series to date. In that retrospective study, of 175 cases reviewed, most were ipsilateral (59%) and only 34 (19%) were of a different histologic type. This differs from our series by including what most would describe as T3 and T4 tumors as SMPLC based on retrospective histologic subtyping. Using retrospective histologic subtyping, only 7 patients with same lobe (T3) lesions were thought to be related and 27 (T3) lesions were considered different and thus included in their analysis. Other studies[4] reporting on SMPLC include patients who have second tumors develop within 2 years. These patients were considered to have metachronous multiple primary lung cancers and were excluded from our series. Varying definitions of SMPLC have limited our understanding and explain the wide range of published results. Published 5-year survival for SMPLC over the past 10 years typically ranges between 10%[8] and 35%[9] and is often cited as 30%.[10] When BAC tumors are included, the 5-year survival has been reported to be nearly 70%.[11] Using our preoperative assessment and surgical strategies, our overall 5-year survival was 53% and cancer-specific survival was 69%. Our strict inclusion and exclusion criteria were designed to minimize the risk of including metastatic secondary nodules that might influence the understanding of outcomes related to SMPLC. Our criteria appear to be validated by subgroup analysis, which shows no survival difference between bilateral and ipsilateral tumors, 50% and 54%, respectively ($P = .83$), or tumors of same or different histologic types, 49% and 42%, respectively ($P = .88$). By design, our study was more exclusive than others. Having done so, we believe this report reflects the true expected outcomes for patients undergoing resection of SMPLC who are N2 negative. Our results also support using these criteria as the basis for future study in SMPLC.

Patients who have more than 1 suspicious pulmonary nodule should undergo thorough evaluation by a thoracic surgeon. Appropriate preoperative assessment is critical in patient selection and includes routine pulmonary function testing, CT scan of chest and upper abdomen, selective cardiac and pulmonary assessment, and evaluation of other comorbidities just as in any other patient being evaluated for pulmonary resection. Although the merits of additional routine testing including PET/CT, brain imaging, and surgical staging can be argued regarding many patients with suspected lung cancer, we believe that in patients with potential SMPLC every attempt should be made to exclude metastatic disease and that routine use of these additional studies is indicated before surgical intervention. Even in the case of CT-negative and PET/CT-negative mediastinal lymph nodes, these patients should still undergo formal surgical staging with mediastinoscopy inasmuch as the possibility of false-negative rates of PET/CT are reported as 15%.[12] Endobronchial ultrasound is an alternative to mediastinoscopy, but this too may result in unacceptably high false-negative rates,[13] which have been reported by us as high as 28%.[14]

Once selected for surgical resection, planning must take into account location of tumor, pulmonary reserve, and type of surgical resection planned. What constitutes an appropriate surgical resection is influenced as much by what the patient will tolerate as by what may be considered standard of care. We believe in using sublobar resections when appropriate, especially for tumors less than 2 cm for these patients. This approach was used in the resection of more than half of the tumors presented here. The desired therapy is a segmentectomy with margins that are at least equal to the diameter the tumor, but for lesions that have visceral pleural invasion or are greater than 2 cm we prefer lobectomy. With emerging data on the cancer survival with anatomic segmentectomy[15] and our survival curves, this would appear to be the prudent choice. Local recurrence is higher with sublobar resection[16] and occurred in 3 (4%) patients in this series, 2 of whom underwent completion lobectomy. All patients with bilateral tumors in this study were treated by a staged surgical approach. We concede there are no data to support staged approaches over simultaneous resection in the treatment of bilateral SMPLC.

Despite being a multi-institutional study, shortcomings still exist. No data were evaluated regarding possible SMPLC that did not undergo surgical resection. We concede the importance of BAC SMPLC; however, it encompasses a wide spectrum of disease and we chose to exclude these patients to define outcomes in non-BAC non–small cell lung cancer. Another weakness is the potentially different surgical approaches between the different institutions and the different surgeons in the treatment of these patients. As a result, no conclusions can be drawn regarding ideal surgical treatments.

Surgical resection of SMPLC is associated with better than expected long-term survival and cure. Appropriate evaluation is essential to identify these patients and to avoid incorrectly assigning them to a more advanced disease stage. After curative resection, these patients require close surveillance for recurrent and new tumors that may be treatable. Adherence to a strict definition of SMPLC and modifications in our present TNM classification regarding tumors of the same histologic type is imperative to make further inroads in the treatment of this all too common situation.

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Discussion

Dr Steven R. DeMeester *(Los Angeles, Calif).* I congratulate Dr Fabian and coauthors on an excellent manuscript and presentation.

In this study, the authors address a clinically important issue—what to do with SMPLC by assessing the survival after resection of these simultaneous lesions. Although the title indicates that the patients were N2 node negative, there were in fact 2 patients who had positive N2 nodes. Why were these patients included in your analysis? Were these patients who did not have mediastinoscopy? Should mediastinoscopy be essential in all of these patients?

Dr Fabian. That is a good point. We elected to include them because they cover the gamut of the disease that we deal with. Both patients had bilateral tumors. Both had mediastinoscopy preoperatively, which discovered single-station N2 disease. Both patients underwent neoadjuvant therapy preoperatively, subsequent restaging, and then resection.

Dr DeMeester. Second, you mentioned that the synchronous cancers were detected preoperatively, intraoperatively, or on final pathologic examination. Did you evaluate survival on the basis of how the lesion was found? In other words, if it was found pathologically, did that imply a different survival than if it was known preoperatively? Did the number of lesions affect survival in these patients?

Dr Fabian. That is a very good point. We did not look at it. We do know that in the overwhelming majority of our patients in this series, we had the knowledge of preoperative diagnosis, particularly 44 with bilateral tumors. As well as the majority of the 18 ipsilateral lesions in different lobes. There were only 5 ipsilateral same lobe so I don't think we could determine much from these data. But I do think it is a good point and worth considering.

Dr DeMeester. The data presented by your group as well as from previous publications all show that the histologic type of the lesions does not significantly affect survival. Do you recommend making any attempt to identify the histologic type preoperatively, and why exclude patients with ipsilateral same-histology lesions?

Dr Fabian. The reason for excluding ipsilateral same-histology lesions is that the current surgical recommendations are widely established in both T3 and T4 lesions. The purpose of excluding those patients here was to confirm as best we were able what the true survival was for synchronous and avoid falsely including satellite nodules and metastatic nodules.

Dr DeMeester. From a mechanistic standpoint, it is logical that most patients with synchronous lung cancers that are indeed second primary tumors should be cigarette smokers, whereas in patients who are not cigarette smokers, you may suspect these other lesions represent metastatic lesions. How many patients in this series were cigarette smokers and did you analyze the outcome in nonsmokers to see whether indeed we should not be resecting multiple lesions in nonsmokers?

Dr Fabian. That is a very interesting point. The patients from St Raphael's and Albany Medical Center all were smokers. I cannot comment on the University of Alabama smoking percentage and we did not look at that specifically. Although if we accept radon as being the largest risk factor for nonsmoker development of non-small cell lung cancer, I believe that they may also have the risk for the development of synchronous tumors. The primary difference is the distribution, which I understand to be the lower lobe lung fields.

Dr DeMeester. Last, could you describe your operative strategy for patients with preoperatively detected synchronous bilateral lesions? Was median sternotomy and simultaneous resection used, or were these all staged procedures? How did the characteristics of the lesions affect the surgical approach? How did you choose to do lobectomy or bilobectomies versus lesser resections in these patients?

Dr Fabian. All of the bilateral lesions were approached as staged procedures. No sternotomies were performed. As far as preoperative planning, there are 2 approaches. My personal method is to approach the tumor that is most likely to increase the stage of disease and therefore obviate the need for the second operation. Having said that, the majority of the other surgeons who included their patients in this series took the opposite approach, which was to deal with the smaller lesion that would most likely get the patient through the second operation: if it was a planned sublobar or superior segementectomy on one side in a lobe, they would approach the smaller tumor first. We actually looked at whether or not the lower pathologic stage versus the higher pathologic stage

influenced the interval between operations, and although there was a trend, it did not meet statistical significance.

Dr Douglas E. Wood *(Seattle, Wash).* Dr Fabian, this was a great presentation on a very important topic. I only wish you were presenting it to a group of pulmonologists or medical oncologists rather than to this audience, which I think understands the principles fairly well.

I agree with Dr DeMeester's question about your exclusion of ipsilateral same-histology tumors, which obviously are just as likely to be synchronous tumors rather than satellite lesions. I think you may have lost some numbers and some additional ability to evaluate those. I guess I encourage you and Dr Cerfolio to potentially reconsider that decision and to include those patients.

In our own practice, we have used the lack of N2 disease and the lack of other metastatic disease as strong surrogates for synchronous rather than metastatic cancers. That is similar to the conclusion you have reached here; yet only a majority, but not every patient, had a PET scan, mediastinoscopy, and brain MRI, which would be the main criterion for eliminating the possibility that these patients actually have metastatic disease. I think you addressed that in your conclusions, but can you reaffirm for me what your principle is now for managing these patients? Would they all receive each of those 3 modalities for lymph node and distant disease staging?

Dr Fabian. That is a valid point and thank you for your comments. Specifically with regard to preoperative staging, it is critical that patients have both an integrated PET/CT scan as well as mediastinoscopy and brain imaging, as you have pointed out. Mediastinoscopy is probably the most critical component. In my practice, I am not willing to substitute endobronchial ultrasound because of potential false-positive results. In the setting of a PET scan that shows no evidence of mediastinal adenopathy, I think those patients also need mediastinoscopy. My approach is for all 3. However, I will give you an example of a patient. In a patient with bilateral suspicious nodules, it wouldn't be unreasonable to pursue a right side diagnostic thoracoscopy and perform a lymphadenectomy if, in fact, it proves to be a malignant nodule. I think for me in that patient it suffices to supplant the mediastinoscopy in that particular scenario. As far as simple procedures preoperatively, I think mediastinoscopy should be used routinely.

Dr Wood. I guess I would still argue that if you had done a mediastinoscopy and there was a node positive, you could have forgone the minimally invasive but still more invasive video-assisted thoracic surgical approach to pulmonary resection, which that patient would not have benefited from, so you learned it retrospectively rather than prospectively.

The last point I would make is to consider simultaneous procedures in at least in some of these patients. Some patients can have simultaneous rather than staged procedures even if they have bilateral disease, without even a median sternotomy but with bilateral approach. I would encourage you and Dr Cerfolio to add that into your consideration for managing these patients.

Dr Fabian. I agree and again thank you for the comments. One of the limitations of this study was in data supporting recommendations regarding surgical approaches. I have no argument or data to argue against simultaneous procedures and believe it is a perfectly acceptable way to treat these patients.

Dr Paul Schipper *(Portland, Ore).* My question is along the same lines as Dr Wood's and Dr DeMeester's in thinking about systemic versus localized disease. Suppose you have a patient who has bilateral primaries and you think they are synchronous. The N2 nodes are negative, and you have done the mediastinoscopy and endobronchial ultrasound. When you resect the first one, you find that there are in fact N1 nodes that are positive at level 11 or level 12, or you find a third nodule that is of the same histologic type, now an ipsilateral nodule. With this new evidence of metastatic disease but no N2 disease, something considered less ominous in the staging system, would you continue on with that second side at a later time or would you stop? Would you say, this is systemic disease; maybe they need some chemotherapy and no more surgery?

Dr Fabian. I think that question runs the gamut. During the bronchoscopy and mediastinoscopy, I try to establish the histologic type of both lesions, whether with biopsy, brushings, or washings this can be very helpful.

I think that, if a patient presented with T3 right upper lobe disease with the same histologic type, the indication is still for surgical resection of the contralateral side and we had patients in this series like that. Of course, there are other considerations but when falsely labeling someone with systemic or metastatic disease ensures a poor outcome I think resection after prudent consideration is still appropriate.

Dr Schipper. If the N1 node is positive at the time of your resection, would you resect the second lesion on the other side?

Dr Fabian. I would.

Dr Joseph Shrager *(Stanford, Calif).* You really went to great pains to describe the tumors studied here as non-BAC, whereas to me BAC is maybe even the more interesting group and certainly the group we see more often. I am wondering how sure you are they are actually non-BAC. Did you go back and have the pathologist look at the periphery of the tumors for a BAC component, or did you reexamine the CT scans to see whether there was any ground glass in the lesions?

Dr Fabian. We did, and I think that is a valuable question. There are patients here whose pathology was reviewed, particularly in the cases that were interpreted as adenocarcinoma with BAC features but no BACs.

Dr Schrager. No pure BACs?

Dr Fabian. No pure BACs.