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Outcomes after Contralateral Anatomic Surgical Resection in Multiple Lung Cancer

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Abstract

Background Patients treated surgically for lung cancer may present synchronous or metachronous lung cancers. The aim of this study was to evaluate outcomes after a second contralateral anatomic surgical resection for lung cancer.

Methods We performed a retrospective two-center study, based on a prospective indexed database. Included patients were treated surgically by bilateral anatomic surgical resection for a second primary lung cancer. We excluded nonanatomic resections, benign lesions, and ipsilateral second surgical resections.

Results Between January 2011 and September 2018, 55 patients underwent contralateral anatomic surgical resections for lung cancer, mostly for metachronous cancers. The first surgical resection was a lobectomy in most cases (45 lobectomies: 81.8%, 9 segmentectomies: 16.4%, and 1 bilobectomy: 1.8%), and a video-assisted thoracic surgery (VATS) procedure was used in 23 cases (41.8%). The mean interval between the operations was 38 months, and lobectomy was less frequent for the second surgical resection (35 lobectomies: 63.6% and 20 segmentectomies: 36.4%), with VATS procedures performed in 41 cases (74.5%). Ninety-day mortality was 10.9% ($n = 6$), and 3-year survival was 77%. Risk factor analysis identified the number of resected segments during the second intervention or the total number of resected segments, extent of resection (lobectomy vs. segmentectomy), surgical approach (thoracotomy vs. VATS), tumor stage, and nodal involvement as potential prognostic factors for long-term survival.

Conclusion A second contralateral anatomic surgical resection for multiple primary lung cancer is possible, with a higher early mortality rate, but acceptable long-term survival, and should be indicated for carefully selected patients.

Keywords
- lung cancer
- lobectomy
- multiple primary
- mortality
- survival

Introduction

Surgical anatomic lung resection with systematic lymph node dissection is the recommended treatment for early-stage non-small cell lung cancer, with an estimated postoperative mortality of ~2.8% at 30 days and 5.4% at 90 days.[1] Second or multiple primary lung cancer was first described in 1924 by Beyreuther,[2] and its current incidence is estimated at 0.2 to 20% of cases.[3] Martini and Melamed proposed a spatiotemporal pathology-based classification in 1975 to

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distinguish between synchronous and metachronous multiple primary lung cancers and between these cancers and metastasis.[4] Based on these criteria, recent studies have suggested that the incidence of a second synchronous lung cancer is 4.5% of cases,[5] whereas the incidence of a second metachronous lung cancer is 5 to 10% of cases.[6] There are currently no well-defined guidelines concerning the care strategy for these patients, and the type of treatment may differ according to the specialty of the consultant,[7] although repeat surgery seems to be the best option in eligible patients.[8] In this study, we evaluated early postoperative morbidity and mortality, and long-term survival outcomes in patients treated for multiple primary lung cancer by sequential bilateral anatomic surgical resection.

Patients and Methods

Patients

We performed a retrospective study at two centers in our country, over an 8-year period, from January 2011 to September 2018. We included all consecutive cases of patients treated surgically by anatomic resection for bilateral multiple lung cancer (synchronous or metachronous) identified by analysis of the multidisciplinary meeting decision in our institutional indexed database. We excluded patients treated by nonanatomic sublobar resection, patients treated for indications other than primary lung cancer (benign tumors, secondary cancer lesions), and patients with multiple primary tumors on the same side as the initial intervention. As an observational retrospective study based on an indexed prospective database (ref. DRCI-T38), patients' data were already anonymized and were used in accordance with our Institutional Review Board policy, without requirement for a supplemental ethic committee consent. A signed informed consent was obtained from every patient registered in this database.

Open approach procedures were performed with posterolateral thoracotomy in the fifth intercostal space, with half section of the posterior part of the latissimus dorsi muscle and preservation of the serratus anterior muscle. Video-assisted thoracic surgery (VATS)-based procedures were performed fully endoscopically with an anterior approach to the hilum placing all three ports in the seventh intercostal space.

Study Outcomes

The main outcome measures were early postoperative mortality after contralateral anatomic lung resection (evaluated 90 days after surgery) and overall survival. The secondary outcome measures analyzed were postoperative morbidity and risk factors affecting long-term survival after contralateral anatomic lung resection.

Statistical Analysis

Continuous patient variables are expressed as the mean ± standard deviation, and dichotomous or categorical variables are expressed as frequencies and percentages. Statistical analysis was performed with SAS software (version 9.4, SAS Institute Inc., Cary, North Carolina, United States). Lung cancer stage was determined according to the eighth edition of the American Joint Committee on Cancer manual for TNM status. Early postoperative mortality is expressed as a frequency and percentage, and long-term survival was estimated with Kaplan–Meier's curves. Risk factors for long-term survival were investigated by univariate Cox-model regression analysis. The threshold for statistical significance was set at $p \leq 0.05$.

Results

Patient Characteristics

Fifty-five patients met the inclusion criteria for this study. The characteristics of these patients are summarized in ►**Table 1**. The rates of VATS approach (74.5 vs. 41.8%, $p \leq 0.001$), and segmental resection (16.4 vs. 36.4%, $p = 0.02$), were higher for the second surgical resection than for the first. The pathological findings for the two surgical resections

Table 1 Patient characteristics

Characteristics	Value *n* (%) or mean ± SD
First surgery	
Side of the first intervention	30 right (53.7%)–25 left (46.3%)
VATS approach	23 (41.8%)
Segmentectomy	9 (16.4%)
Lobectomy	45 (81.8%)
Bilobectomy	1 (1.8%)
Mean number of segments resected	3.7 ± 1.2
Comorbidities before second surgery	
Age at second surgery	65.9 ± 8.6
Male	41 (74.5%)
Prior ENT cancer	7 (12.7%)
Type 2 diabetes	5 (9.1%)
Cardiac arrhythmia	4 (7.3%)
Ischemic heart disease	7 (12.7%)
BMI	25.4 ± 5.1
Albumin (g/L)	38.9 ± 5.3
Prealbumin (g/L)	0.27 ± 0.07
Interval between operations	
Interval between resections (mo)	38.4 ± 40
Preoperative FEV1 (%)	74.4 ± 17.6
Predicted postoperative FEV1 (%)	56.1 ± 15.5
Second surgery	
VATS approach	41 (74.5%)
Segmentectomy	20 (36.4%)
Lobectomy	35 (63.6%)
Number of segments resected	3.4 ± 1.3
Total number of resected segments	7.1 ± 1.7

Abbreviations: BMI, body mass index; ENT, ear, nose, and throat; FEV1, forced expiratory volume in 1 second; SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

are displayed in ►**Table 2**. The proportion of patients undergoing surgery for metachronous multiple lung cancer was higher than the proportion of patients with synchronous multiple lung cancer. Adenocarcinoma predominated, and a concordance of histological subtype was observed in 42 patients (76.4%) (►**Table 3**). Complete resection (R0) was achieved in all patients, and 11 patients received multimodal treatment (20%). The mode and time frame for chemotherapy and/or radiotherapy are summarized in ►**Table 3**.

Early and Late Postoperative Outcomes

Early postoperative mortality was assessed in 6 of 55 patients (10.9%) within 90 days of surgery. The causes of death were postoperative pneumonia and its consequences in five patients (9.1%), and early postoperative acute respiratory distress syndrome in one patient (1.8%). The results, including those for postoperative morbidity are summarized in ►**Table 4**.

Table 2 Pathological findings

Characteristics	Number of patients, *n* (%)
First surgery	
Histology	
Adenocarcinoma	41 (74.5%)
Squamous cell carcinoma	11 (20%)
Other	3 (5.5%)
T stage	
T1	37 (67.3%)
T2	13 (23.6%)
T3	3 (5.5%)
T4	2 (3.6%)
N and M stages	
N0	48 (87.3%)
N1	2 (3.6%)
N2	5 (9.1%)
M1	2 (3.6%)
Second surgery	
Histology	
Adenocarcinoma	41 (74.5%)
Squamous cell carcinoma	7 (12.7%)
Other	7 (12.7%)
T stage	
T1	43 (78.2%)
T2	10 (18.2%)
T3	2 (3.6%)
T4	0 (0%)
N and M stages	
N0	52 (94.5%)
N1	1 (1.8%)
N2	2 (3.6%)
M1	2 (3.6%)

Table 3 Chronology of multiple primary lung cancer and the multimodal treatment administered

Characteristics	Number of patients, *n* (%)
Chronology of multiple lung cancer	
Metachronous	28 (50.9%)
Synchronous	25 (45.5%)
Metastatic (M1a-tumor in contralateral lung)	2 (3.6%)
Histology subtype concordance rate	42 (76.4%)
AdenoCa–AdenoCa	36 (65.5%)
SCC–SCC	6 (10.9%)
AdenoCa–other	5 (9.1%)
SCC–other	6 (10.9%)
Other	2 (3.6%)
Multimodal treatment	
First surgery, neoadjuvant ChemoTx (synchronous)	1 (1.8%)
First surgery, neoadjuvant ChemoTx (metachronous)	1 (1.8%)
First surgery adjuvant ChemoTx for ≥T2b or N+ (metachronous)	8 (14.5%)
Interval ChemoTx (synchronous)	1 (1.8%)
Second surgery, adjuvant ChemoTx for ≥T2b or N+	5 (9.1%)

Abbreviations: AdenoCa, adenocarcinoma; ChemoTx, chemotherapy; SCC, squamous cell carcinoma.

Table 4 Postoperative morbidity and mortality after contralateral surgery

Characteristics	Number of patients, *n* (%)/value (%)
Pneumonia	13 (23.6%)
Need for bronchoscopy	13 (23.6%)
Reintubation	4 (7.3%)
Cardiac arrhythmia	5 (9.1%)
Bronchopleural fistula	2 (3.6%)
Laryngeal paralysis	4 (7.3%)
Chest tube duration	6.7 ± 6.2 d
Length of stay	9.2 ± 6.3 d
30-d mortality	5 (9.1%)
90-d mortality	6 (10.9%)

Overall survival was estimated at 83.4% at 1 year, 77% at 3 years, and 72.7% at 5 years; median overall survival was not reached, for a median duration of follow-up of 28 months (range: 0–95 months) (►**Fig. 1**). The cause of death was lung

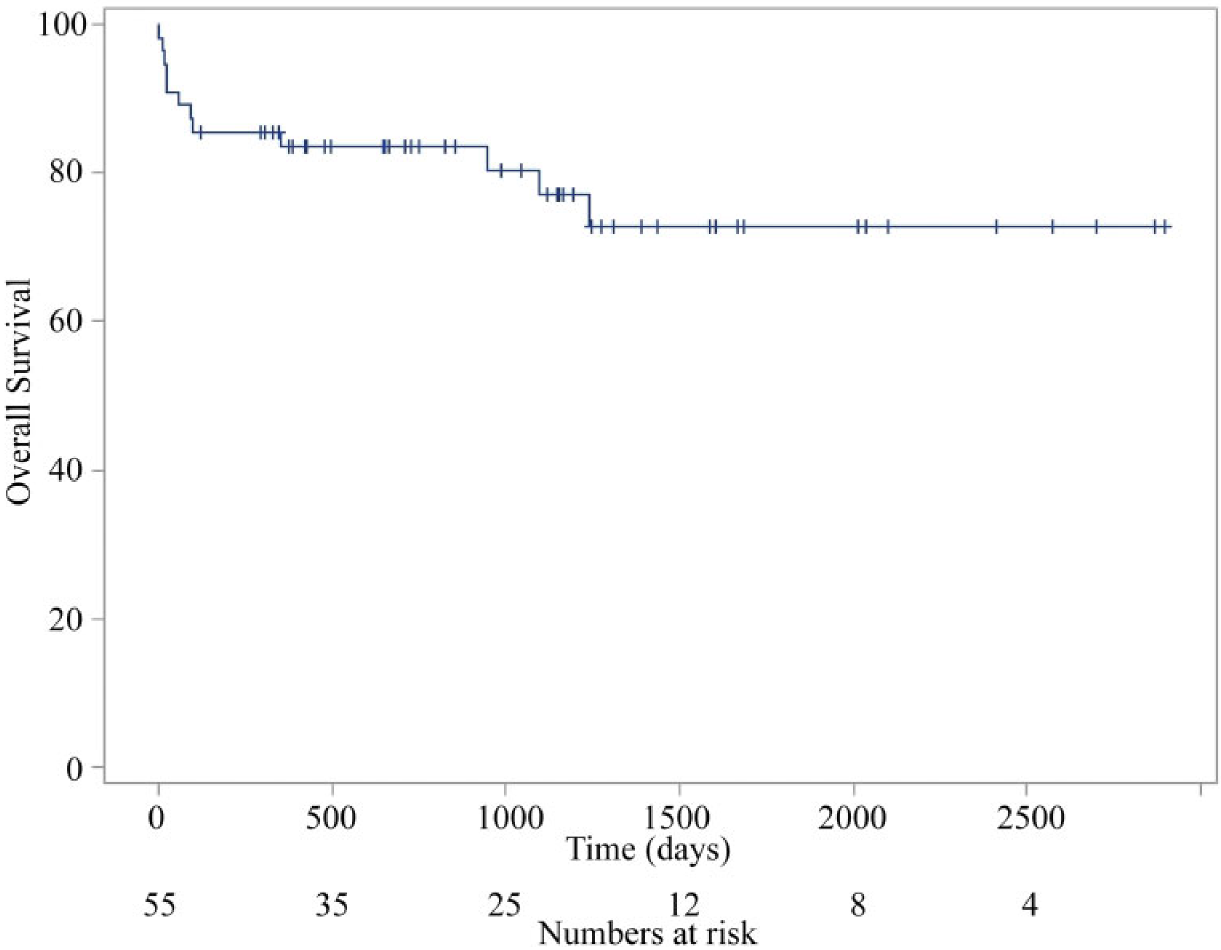

Fig. 1 Overall survival following second contralateral anatomic surgical resections for lung cancer.

cancer recurrence in two of the six patients who died more than 90 days after surgery. Disease-free survival was estimated at 79.9% at 1 year, 63.8% at 3 years, and 63.8% at 5 years: median disease-free survival was not reached, for a median duration of follow-up of 23 months (range: 0–95 months) (►**Fig. 2**).

Analysis of Risk Factors for Long-Term Overall Survival

All patients were followed up. Univariate Cox-model regression analysis showed that overall survival outcomes were worse for patients undergoing surgery for advanced-stage lung cancers at the second resection than for those undergoing a second resection for a stage T1 tumor (for T2 stage: odds ratio [OR] = 5.08 [95% confidence interval, CI: 1.51–17.11]; for T3 stage: OR = 3.49 [95% CI: 0.42–29.01], $p = 0.03$). Patients without pathologic node involvement tended to have a better prognosis (OR = 0.30 [95% CI: 0.07–1.36], $p = 0.12$) (►**Table 5**). A limited extent of parenchymal resection, including a smaller total number of segments resected, tended to have a favorable impact on overall survival (OR = 1.30 [95% CI: 0.95–1.79], $p = 0.10$). Overall survival was also tended to be better in patients treated by segmentectomy at the second resection than in those treated by lobectomy (OR = 6.46 [95% CI: 0.83–50.22], $p = 0.07$) (►**Table 5**). The use of a VATS approach also tended to be associated with better overall survival (OR = 2.99 [95% CI: 0.96–9.29], $p = 0.06$) (►**Table 5**).

Discussion

Several authors have reported early and late outcomes in patients with multiple synchronous[5,9–13] or metachronous[14–16] lung cancers. These studies evaluated ipsilateral and contralateral multiple primary lung cancers, often considering data for both these situations, but few studies have specifically described outcomes following contralateral surgical resection.[12,17–20] De Leyn et al reported results for a cohort of 36 patients treated by bilateral lung resection for lung cancer, including 10 patients undergoing bilateral anatomic resection (lobectomy). They reported an early postoperative mortality of 2.8% and a 5-year survival rate of 38%[17] (►**Table 6**). Shah et al reported results for a cohort of 47 patients, including 11 bilateral anatomic resections (6 lobectomy/segmentectomy and 5 lobectomy/lobectomy), with an early postoperative mortality of 2% and a 3-year survival rate of 35%[18] (►**Table 6**). Hattori et al reported an early postoperative mortality of 23.9% and a 5-year survival rate of 61.7% for a cohort of 21 patients, all treated by bilateral lobectomy[19] (►**Table 6**). A larger cohort (88 patients) studied by Yang et al, including 39 bilateral anatomic resections, had an early postoperative mortality of 0% and 3- and 5-year

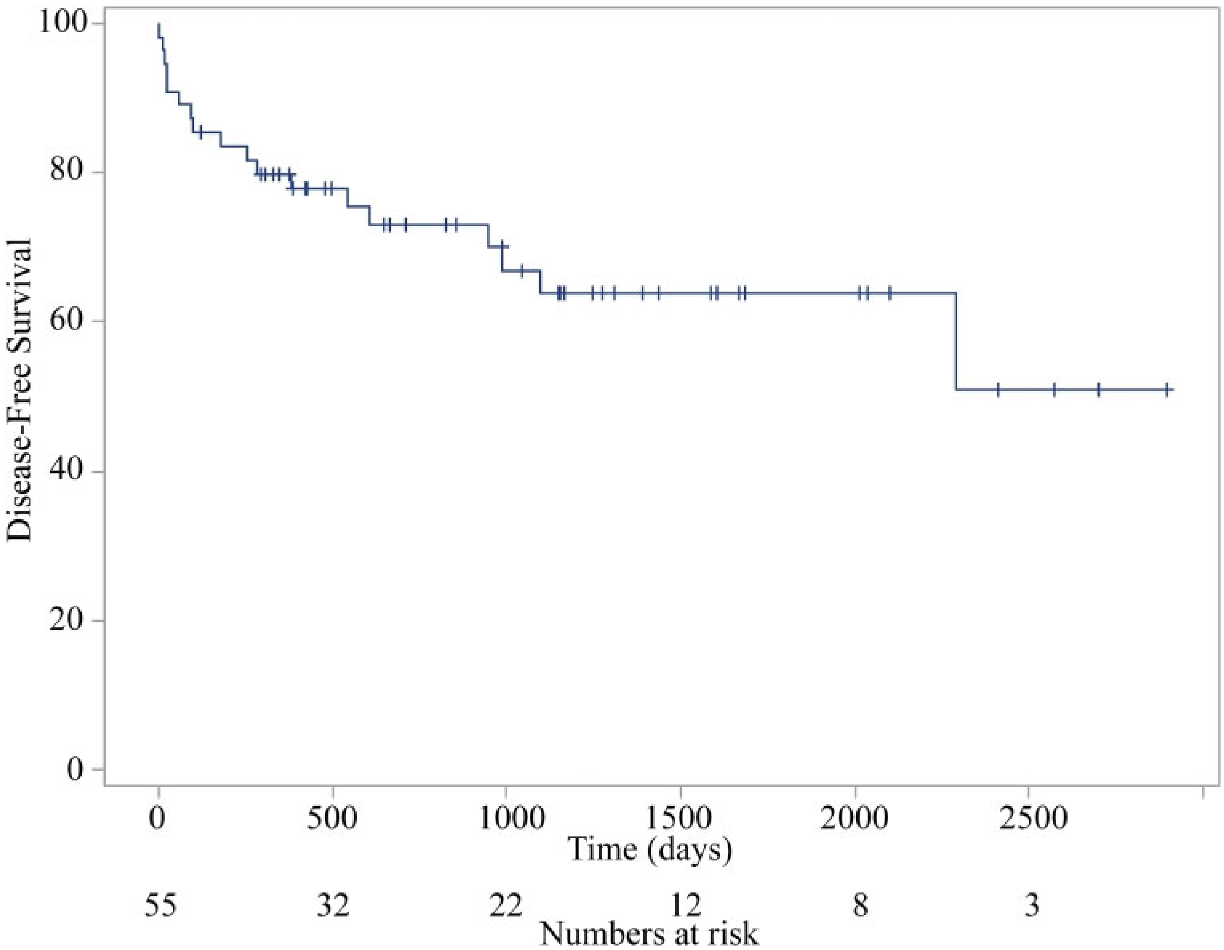

Fig. 2 Disease-free survival following second contralateral anatomic surgical resections for lung cancer.

Table 5 Analysis of risk factors for overall survival

Prognostic factor for OS	*p*-Value, hazard ratio (95% CI)
Small total number of resected segments	$p = 0.10$, 1.30 (0.95–1.79)
Segmental resection (vs. lobar)	$p = 0.07$, 6.46 (0.83–50.22)
VATS for second surgery	$p = 0.06$, 2.99 (0.96–9.29)
Tumor stage after second surgery	$p = 0.03$
T1	1
T2	5.08 (1.51–17.11)
T3	3.49 (0.42–29.01)
No nodal involvement (vs. nodal involvement)	$p = 0.12$, 0.30 (0.07–1.36)

Abbreviations: CI, confidence interval; VATS, video-assisted thoracoscopic surgery.

survival rates of 84.5 and 75%, respectively[20] (►**Table 6**). Our results were consistent with these previous findings for higher proportions of anatomic resection, with an early postoperative mortality of double or almost triple that for the first resection,[1] and an overall survival of 77% at 3 years and 72.7% at 5 years after bilateral anatomical resection (►**Table 6**). The previous retrospective studies did not assess differences in long-term survival between anatomic and nonanatomic resections for bilateral primary lung cancer, despite the reported trend toward better survival in patients undergoing anatomic resections.[17,18,20] A recent study involving a propensity score analysis of 454 pairs of matched patients revealed better long-term survival outcomes for patients treated by bilateral lobectomy than for those treated by sublobectomy, particularly for stage I multiple primary lung cancer, following a first resection performed by lobectomy in 85% of patients, and including mostly bilateral lesions (80 vs. 20% ipsilateral).[21] However, the proportions of anatomic segmentectomy and nonanatomic sublobar resection among the interventions were unknown for the sublobectomy group.[21]

Only Hattori et al have analyzed the risk factors of in-hospital death (early postoperative mortality). They identified age older than 70 years, higher tumor stage, right lower lobectomy, and bilateral lower lobectomy as factors independently associated with a poor prognosis.[19] The findings of our univariate analysis suggest that impaired lung function and a larger total number of resected segments are also risk factors for in-hospital death.

Yang et al found that age, sex, tumor size, nodal stage, extent of surgery (lobectomy vs. sublobectomy), year of diagnosis, histologic type, and pathologic stage of the initial cancer were prognostic predictors of long-term survival in multiple primary

Table 6 Findings of previous studies for early postoperative mortality and long-term survival after bilateral lung resection for multiple primary lung cancer

	Number of patients	Anatomic resection *n* (%)	Early postoperative mortality	3-y survival	5-y survival
De Leyn et al (2008)[17]	36	10/36 (27.8%)	2.8%	NR	38%
Kocaturk et al (2011)[12]	12	7/12 (58.3%)	8.3%	NR	62.8%
Shah et al (2012)[18]	47	11/47 (23.4%)	2%	35%	29%
Hattori et al (2015)[19]	21	21/21 (100%)	23.9%	NR	61.7%
Yang et al (2016)[20]	88	39/88 (44.3%)	0%	84.5%	75%
Current study (2020)	55	55/55 (100%)	10.9%	77%	72.7%

Abbreviation: NR, not reported.

lung cancer.[21] This study by Yang et al is the largest performed to date, but the proportions of anatomic/nonanatomic resections were not detailed in the sublobectomy group, preoperative lung function tests and intraoperative lymphadenectomy were not reported, and 20% of the patients in the cohort were treated for ipsilateral lesions.[20] Some previous studies focused specifically on bilateral surgery for multiple primary lung cancer, with much smaller population samples, and found no differences in survival between resection types or histologic features.[17,19] However, Yang et al found that a higher tumor or nodal stage, the presence of more than two pulmonary lesions, and similar histologic features between the multiple primary lung cancers were negative prognostic factors for long-term survival in a cohort of 88 patients including 39 bilateral anatomic resections.[20] Our results are consistent with these findings, as they indicate a poorer prognosis in patients with higher tumor stages and nodal involvement, in a cohort of 55 patients treated by bilateral anatomic resection with systematic lymph node dissection. We also present new data concerning the impact of surgical approach, highlighting the positive prognostic value of VATS resection, and of a smaller number of resected segments at second surgery or cumulative, limited anatomic resection (favoring anatomic segmental over lobar resection).

The sequence of surgery in case of synchronous multiple primary lung cancer has not been studied. If a segmentectomy and a contralateral lobectomy are both required, our institutional strategy is to perform the segmentectomy as the first lung resection, to preserve lung function prior to the lobar resection, and to decrease the incidence of postoperative complications.

Based on our results and those of previous studies, patient selection appears to be crucial when considering bilateral multiple primary lung cancer surgery. A meticulous multimodal preoperative nodal assessment is required, and the importance of minimally invasive surgery and sublobar anatomic resection approaches in multiple primary lung cancer surgery should be stressed.

This study has several strengths and limitations. Its main limitation is the small sample size, with only 55 patients evaluated, which made it possible to perform a univariate logistic regression analysis of risk factors, but not a multivariate analysis. Nevertheless, unlike many other published studies, it included a homogeneous cohort, with all patients treated bilaterally for multiple primary lung cancer (synchronous or metachronous), by anatomic resection with systematic radical lymph node dissection. A second limitation is the retrospective design of the study, leading to potential biases, which were minimized by the use of a prospective indexed database with a follow-up rate of 100% and evaluation at two centers. Another limitation was the merging into a single cohort of synchronous and metachronous lung cancers, defined according to the Martini and Melamed criteria,[4] as these two types of cancers may have different outcomes. Moreover, we had too few data for molecular biology evaluations in these patients, and such studies may become essential in the future, to move beyond the current dichotomous criteria, which have been in place for 40 years.[22] Finally, we report the early and late outcomes of a strategy of repeat surgery for bilateral lesions. A comparison of our data with those for a multimodal approach (stereotactic ablative body radiotherapy or percutaneous ablative techniques) would have given a certain perspective to our results, but recent reports have suggested that outcomes are better for repeat surgery strategies.[8]

In conclusion, a second, contralateral anatomic surgical resection for synchronous or metachronous lung cancer is possible, with a higher early mortality rate than for the first resection, but acceptable long-term survival. The identification of risk factors should make it possible to select patients carefully, through meticulous preoperative evaluation, and to propose minimally invasive surgery and sublobar anatomic resection approaches for multiple primary lung cancer resection.

Note
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Conflict of Interest
None declared.

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