

Brief Report: Contralateral Lobectomy for Second Primary NSCLC: Perioperative and Long-Term Outcomes



Jennie K. Choe, MD,^a Amy Zhu, BS,^a Alexander J. Byun, MD,^a Junting Zheng, MS,^b Kay See Tan, PhD,^b Joe Dycoco, BS,^a Manjit S. Bains, MD,^a Matthew J. Bott, MD,^a Robert J. Downey, MD,^a James Huang, MD,^a James M. Isbell, MD,^a Daniela Molena, MD,^a Valerie W. Rusch, MD,^a Bernard J. Park, MD,^a Gaetano Rocco, MD,^a Smita Sihag, MD,^a David R. Jones, MD,^a Prasad S. Adusumilli, MD, FACS^{a,c,*}

^aThoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York

^bDepartment of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

^cCenter for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, New York

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ABSTRACT

Introduction: Anatomical resection—often by lobectomy—is the standard of care for patients with early stage NSCLC. With increased diagnosis, survival, and prevalence of persons with early stage NSCLC, the incidence of second primary NSCLC, and consequently, the need for contralateral lobectomy for a metachronous cancer, is increasing. Perioperative outcomes after contralateral lobectomy are unknown.

Methods: Among patients who underwent contralateral lobectomy for second primary NSCLC during 1995 to 2020, we evaluated 90-day mortality and major morbidity (Clavien-Dindo grades 3–5) rates and their association with clinicopathologic variables, including the year of contralateral lobectomy and duration between lobectomies.

Results: A total of 98 patients underwent contralateral lobectomy for second primary NSCLC; 51 during an early time period (1995–2009) and 47 from a late time period (2010–2020). There were five mortalities and 23 patients with major morbidities after contralateral lobectomy; both rates decreased in 2010 to 2020 compared with 1995 to 2009 (mortality 10%–0%, major morbidity 35%–11%). Major morbidity was associated with an interval of less than 1 year between lobectomies, a diffusing capacity of the lung for carbon monoxide <80%, and right lower lobe resections. Mortality was associated with squamous cell carcinoma. Patients who underwent contralateral lobectomy for stage I NSCLC had 74% (95% confidence interval: 64%–85%) 3-year overall survival and 15% (95% confidence interval: 6.5%–24%) 3-year lung cancer cumulative incidence of death.

Conclusions: Contralateral lobectomy for second primary early stage NSCLC was associated with poor outcomes before 2010. Since 2010, perioperative and long-term outcomes of contralateral lobectomy have been comparable with reported outcomes after unilateral lobectomy.

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Keywords: Bilateral lobectomy; Sequential lobectomy; Outcomes; Complications

*Corresponding author.

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Address for correspondence: Prasad S. Adusumilli, MD, FACS, Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. E-mail: adusump@mskcc.org

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Introduction

Lung cancer mortality decreased from 55.8 to 33.4 per 100,000 during 2000 to 2019, predominantly due to a decrease in NSCLC mortality. Decreased NSCLC mortality is associated with stage shift in diagnosis; from 2006 to 2016, the proportion of stage I and II NSCLC diagnosis increased from 26.5% to 31.2%, and that of stage III and IV diagnosis decreased from 70.8% to 66.1%.¹ In addition to early stage diagnosis, 5-year relative survival among patients with localized disease increased from 52% to 59% from 2004 to 2013.² Consequently, the prevalence of NSCLC increased from 175.3 to 198.3 per 100,000 from 2010 to 2016.³

With increased detection, survival, and prevalence of early stage NSCLC, there has been an expected increase in second primary NSCLC from surveillance and survivorship programs. We and others have reported an 11.6% to 13.5% incidence of second primary lung cancer among NSCLC survivors.^{4–6} Anatomical resection—often by lobectomy—is the standard of care for early stage NSCLC. With an expected increase in second primary NSCLC amenable to resection, there is paucity of data on outcomes after second lobectomy.

Materials and Methods

After approval by the Institutional Review Board at Memorial Sloan Kettering Cancer Center, we conducted a retrospective investigation by review of a prospectively maintained database of all patients who underwent contralateral lobectomy for second primary NSCLC at the Memorial Sloan Kettering Cancer Center from January 1, 1995, to December 31, 2020. Diagnosis of second primary NSCLC rather than pulmonary metastases was confirmed by following an algorithmic approach (Supplementary Fig. 1).

Outcomes

The objective of this investigation was to determine the incidence of perioperative (90-d) mortality and morbidity according to the Clavien-Dindo classification,⁷ after contralateral lobectomy for second primary NSCLC. Grades 3, 4, and 5 were considered major morbidities.

Statistical Analysis

The Wilcoxon ranked sum test, Pearson's chi-square test, and Fisher's exact test were used to compare clinical variables between early and late time periods and determine their associations with mortality and major morbidity. The Kaplan-Meier method was used to estimate overall survival (OS). The cumulative incidence rate was estimated for lung cancer-specific death, treating other causes of death as a competing event. Landmark survival analyses on morbidity grade were

performed with the landmark time at day 90 after contralateral lobectomy using the log-rank test and Gray's test.

Results

Initial Versus Contralateral Lobectomies

A total of 98 patients underwent contralateral lobectomy to treat metachronous NSCLC from 1995 to 2020 (Supplementary Table 1). Median preoperative diffusing capacity of the lung for carbon monoxide (DLCO) and median forced expiratory volume in 1 second (FEV1) decreased (DLCO: 82 [interquartile range or IQR: 70–93] to 72 [IQR: 63–82]; FEV1: 92 [IQR: 79–102] to 79 [IQR 69–92]). Distributions of pathologic stage and histology were similar. The median time between initial and contralateral lobectomies was 2.1 years (IQR: 0.4–4.8).

Early Versus Late Time Period

Overall, there were 23 patients with major morbidities (23%), including five mortalities (5%), after contralateral lobectomy (Fig. 1A and B and Supplementary Table 2). When stratified into early (1995–2009) and late (2010–2020) time periods, 51 patients underwent contralateral lobectomy from 1995 to 2009 and 47 patients from 2010 to 2020. Mortality and major morbidity both decreased (mortality 10%–0%, major morbidity 35%–11%) from the early to the late time period (Table 1 and Supplementary Table 3). Median DLCO and FEV1 before contralateral lobectomy both increased (DLCO: 70–73, $p = 0.034$; FEV1: 76–81, $p = 0.047$). Pathologic stage of the contralateral lobectomy exhibited a shift toward stage I tumors ($p = 0.005$), and the histologic subtype was more frequently adenocarcinoma (ADC) ($p = 0.003$).

Variables Associated With Major Morbidity

When stratified by time between lobectomies, patients who underwent initial and contralateral lobectomies within one year had the highest incidence of mortality (9%); the incidence was 3% among patients with a time interval of 1 to 5 years and 4% among patients who underwent contralateral lobectomy more than five years after the initial lobectomy (Fig. 1C).

When stratified by anatomical location of the resected lobe, patients who underwent right lower lobe (RLL) resection during either lobectomy had the highest incidence of mortality (24%) after contralateral lobectomy (Fig. 1D).

When stratified by histology, patients who had squamous cell carcinoma (SCC) on initial lobectomy had the highest incidence of mortality (20%) after contralateral lobectomy; the incidence was 3% among patients

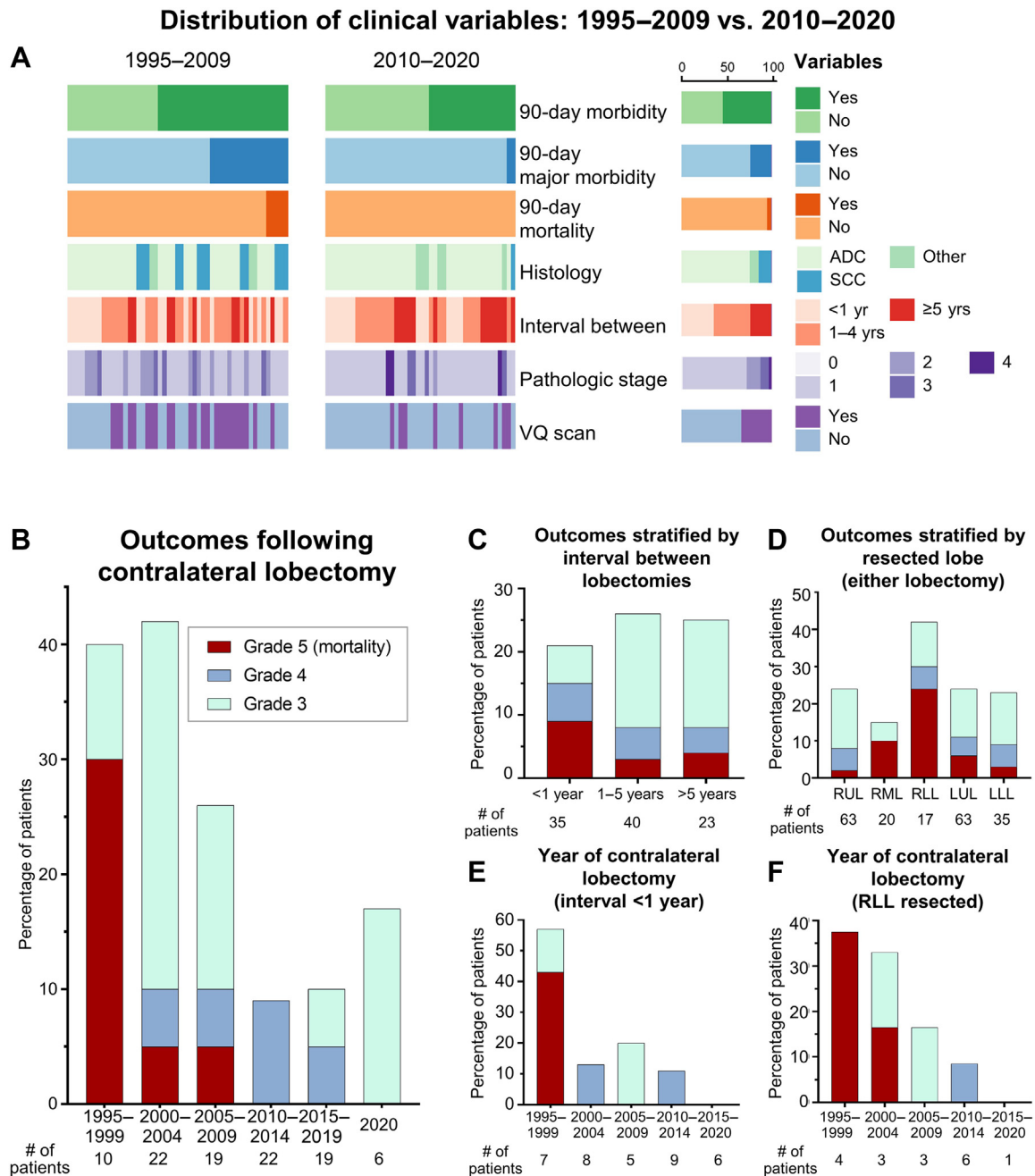


Figure 1. Incidence of perioperative mortality and major morbidity and distributions of clinical variables during 1995 to 2009 versus 2010 to 2020. (A) The incidence of mortality (Clavien-Dindo grade 5), major morbidity (Clavien-Dindo grades 3-5), and all morbidity events (Clavien-Dindo grades 1-5) was lower in 2010 to 2020 compared with that in 1995 to 2009. The distributions of histologic subtype, interval between lobectomies, pathologic stage, and the use of ventilation and perfusion scans from 1995 to 2009 versus 2010 to 2020 are presented (left: distribution by year, right: cumulative). (B) Incidence of mortality and major morbidity after contralateral lobectomy was stratified by year of second lobectomy. Among patients who underwent contralateral lobectomy after 2010, there were no mortalities and few major morbidities. (C) Incidence of mortality and major morbidity was stratified by the interval between lobectomies. Patients who underwent both lobectomies within one year had the highest incidence of mortality. (D) Incidence of mortality and major morbidity was stratified by anatomic location of the resected lobe. Patients who underwent right lower lobe resection had the highest incidence of mortality. (E) When outcomes of patients who underwent both lobectomies within one year were stratified by the year of contralateral lobectomy, all mortalities had occurred before 2000. (F) When outcomes of patients who underwent right lower lobectomy were stratified by the year of contralateral lobectomy, all mortalities had occurred before 2005. #, number; ADC, adenocarcinoma; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; SCC, squamous cell carcinoma; VQ, ventilation-perfusion; yr, year.

Table 1. Patient and Tumor Characteristics of Contralateral Lobectomy and Their Associations With Major Morbidity and Mortality

Characteristics	Major Morbidity (Grades 3-5)		Mortality (Grade 5)		
	No (n = 75)	Yes (n = 23)	No (n = 93)	Yes (n = 5)	p Value ^b
	n (%), Median (IQR)	p Value ^a	n (%), Median (IQR)	p Value ^a	
Time period					0.057
1995-2009	33 (44)	18 (78)	46 (49)	5 (100)	
2010-2020	42 (56)	5 (22)	47 (51)	0 (0)	
Age	68 (61-73)	71 (65-76)	69 (62-74)	70 (64-71)	0.8
Sex					0.3
Male	25 (33)	9 (39)	31 (33)	3 (60)	
Female	50 (67)	14 (61)	62 (67)	2 (40)	
Smoking					0.2
Never	6 (8)	4 (17)	9 (10)	1 (20)	
Former	65 (87)	15 (65)	77 (83)	3 (60)	
Current	4 (5)	4 (17)	7 (8)	1 (20)	
Pack years	32 (19-50)	50 (25-68)	34 (20-55)	50 (35-60)	0.5
FEV1	80 (71-96)	71 (64-87)	79 (69-93)	73 (71-82)	0.8
Unknown	13 (17)	4 (17)	15 (16)	2 (40)	
DLCO	72 (63-88)	69 (54-74)	72 (63-83)	57 (54-66)	0.2
Unknown	13 (17)	4 (17)	15 (16)	2 (40)	
VQ scan performed	21 (28)	12 (52)	32 (34)	1 (20)	0.7
Chemotherapy	12 (16)	4 (17)	16 (17)	0 (0)	0.6
Neoadjuvant	0 (0)	2 (9)	2 (2)	0 (0)	>0.9
Adjuvant	12 (16)	2 (9)	14 (15)	0 (0)	>0.9
XRT	4 (5)	1 (4)	5 (5)	0 (0)	>0.9
Laterality					0.4
Right	24 (32)	14 (61)	35 (38)	3 (60)	
Left	51 (68)	9 (39)	58 (62)	2 (40)	
Approach					0.3
VATS	26 (35)	1 (4)	27 (29)	0 (0)	
Open	49 (65)	22 (96)	66 (71)	5 (100)	
T stage					0.8
T0	0 (0)	1 (4)	1 (1)	0 (0)	
T1	49 (65)	14 (61)	60 (65)	3 (60)	
T2	17 (23)	6 (26)	21 (23)	2 (40)	
T3	7 (9)	2 (9)	9 (10)	0 (0)	
T4	2 (3)	0 (0)	2 (2)	0 (0)	
N stage					0.6
N0	61 (81)	19 (83)	76 (82)	4 (80)	
N1	6 (8)	4 (17)	9 (10)	1 (20)	
N2	8 (11)	0 (0)	8 (9)	0 (0)	
M stage					>0.9
M0	72 (96)	23 (100)	90 (97)	5 (100)	
M1 (isolated brain metastasis)	3 (4)	0 (0)	3 (3)	0 (0)	
Pathologic stage					>0.9
1	54 (72)	17 (74)	67 (72)	4 (80)	
2	10 (13)	5 (22)	14 (15)	1 (20)	
3	8 (11)	1 (4)	9 (10)	0 (0)	
4	3 (4)	0 (0)	3 (3)	0 (0)	
Histology					0.031
Adenocarcinoma	59 (79)	15 (65)	72 (77)	2 (40)	
Squamous cell carcinoma	8 (11)	6 (26)	11 (12)	3 (60)	
Other	8 (11)	2 (9)	10 (11)	0 (0)	

Note: When there are multiple morbidities, the highest grade was selected for analysis.

^aWilcoxon ranked sum test; Pearson's chi-square test; Fisher's exact test.

^bWilcoxon ranked sum test; Fisher's exact test.

IQR, interquartile range; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of lung for carbon monoxide; VQ, ventilation-perfusion; XRT, radiotherapy; VATS, video-assisted thoracoscopic surgery.

with ADC and 9% among patients with other histology. Patients who had SCC on contralateral lobectomy had 21% mortality, compared with 3% among patients with ADC and 0% among patients with other histology (Supplementary Fig. 2A and B).

Higher incidences of mortality (5% versus 0%) and major morbidity (32% versus 4%) were associated with lower (<80%) DLCO before contralateral lobectomy (Supplementary Fig. 2C and D).

No association was observed between outcomes and FEV1 or percentage changes in DLCO or FEV1 from initial to contralateral lobectomy (Supplementary Fig. 2E-H) or receiving chemotherapy during initial lobectomy and experiencing major morbidity after contralateral lobectomy (Supplementary Fig. 2I).

Changes in Variables Between Time Periods

Among patients who had contralateral lobectomy within one year of initial lobectomy, all mortalities occurred in the early time period (Fig. 1E). Among patients who underwent RLL resection, all mortalities also occurred in the early time period (Fig. 1F). The proportion of patients with SCC on contralateral lobectomy decreased from early to late time period (25%–2%, $p < 0.001$; Supplementary Fig. 3A). Median DLCO increased from early to late time period. DLCO before contralateral lobectomy had a positive correlation with year across the study period ($p = 0.0048$), whereas DLCO before initial lobectomy had no correlation with year ($p = 0.27$; Supplementary Fig. 3B–E).

Characteristics of Patients Who Had Major Morbidities

Among the 18 patients who had grade 3 or 4 morbidities after contralateral lobectomy, DLCO value before contralateral lobectomy was available for 16 patients. Of 16 patients, 15 (94%) had DLCO less than 80% (Supplementary Fig. 4A).

Among the five mortalities, DLCO value before contralateral lobectomy was available for three patients. Three of three patients (100%) had DLCO less than 80%. Three of five patients (60%) underwent both lobectomies within 1 year. Four of the 10 resected lobes (40%) from initial and contralateral lobectomies were RLLs (Supplementary Fig. 4B), and five of the 10 resected tumors (50%) had SCC histology (Supplementary Fig. 4C and D).

Landmark Analysis of Survival Outcomes

In a landmark analysis using 90-day post-contralateral lobectomy, the median OS was 4.2 years (95% confidence interval [CI]: 1.4–not reached) in patients who experienced grade 3 or 4 morbidities after

contralateral lobectomy compared with 8.2 years (95% CI: 4.5–12 y) in patients who had grade 0 to 2 morbidities (Supplementary Fig. 4E and F). Patients who underwent contralateral lobectomies for stage I cancers had a median OS of 8.3 years (95% CI: 4.7–18 y) and 3-year OS of 74% (95% CI: 64%–85%) (Fig. 2A and B and Supplementary Table 4A).

Three-year lung cancer-specific cumulative incidence of death (LC-CID) of patients who experienced grade 3 or 4 morbidities was 25% (95% CI: 3%–47%), compared with 14% (95% CI: 5%–22%) among patients who had grade 0 to 2 morbidities. Three-year LC-CID of patients who underwent contralateral lobectomies for stage I cancers was 15% (95% CI: 7%–24%) (Fig. 2C and D and Supplementary Table 4B).

Discussion

At a time when there is an increase in the incidence of second primary lung cancer requiring contralateral lobectomy, there is an often held view among thoracic surgeons (unsupported by data) that a second lobectomy is equivalent to pneumonectomy with respect to perioperative outcomes. An investigation by Hattori et al.⁸ reported high rates of in-hospital mortality (24%) and major morbidity (19%) in a cohort of 21 patients who underwent staged bilateral lobectomies for lung cancers from 1996 to 2012. Other studies that reported sequential resections included either lobar and sublobar or sublobar and sublobar resections or ipsilateral second lobectomies (Supplementary Table 5)^{9,10}; comparison across these studies is not feasible due to lack of uniform classification used to report outcomes. In our study, we excluded ipsilateral second lobectomies because they are feasible only for the right lung and would almost certainly involve a right middle lobectomy, which is anatomically very small; nevertheless, we report the 90-day mortality of ipsilateral lobectomies separately (Supplementary Table 6).

As the largest series to date investigating outcomes exclusively in patients who underwent bilateral lobectomies, our study reveals a decrease in 90-day mortality and major morbidity after contralateral lobectomy. The time periods of analysis in our study (Supplementary Fig. 5) split the data into two comparable cohorts by number, and the second time period is relevant to current clinical practice. Although patients who underwent contralateral lobectomy for second lung cancer from 1995 to 2009 had outcomes that were similar to published outcomes after pneumonectomy,¹¹ those who underwent contralateral lobectomy from 2010 to 2020 had 90-day mortality and major morbidity similar to published outcomes after unilateral lobectomy.^{12,13} Factors associated with higher major morbidity include

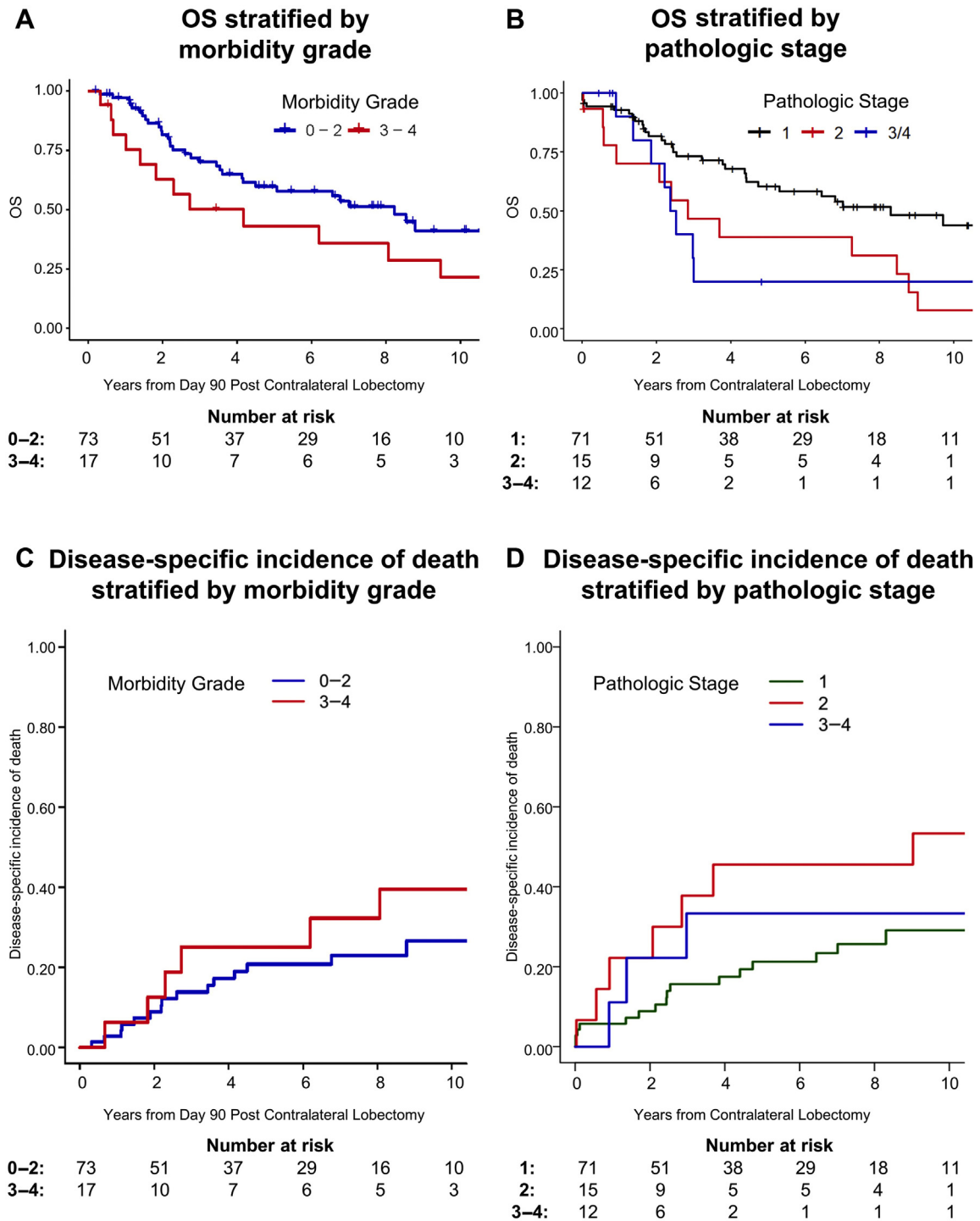


Figure 2. OS and disease-specific incidence of death. (A) Patients who had no major morbidities (Clavien-Dindo grades 0-2) after contralateral lobectomy had median OS of 8.2 years (95% CI: 4.5-12 y) and 60% 5-year OS (95% CI: 49%-73%). Patients who had major morbidities (Clavien-Dindo grades 3-4) had median survival of 4.2 years (95% CI: 1.4-not reached) and 43% 5-year OS (95% CI: 24%-76%). (B) Patients who underwent contralateral lobectomy for a pathologic stage 1 cancer had median survival of 8.3 years (95% CI: 4.7-18 y) and 61% 5-year OS (95% CI: 50%-75%). Patients who underwent contralateral lobectomy for a pathologic stage 2 or stage 3 to 4 cancer had median survival of 2.9 (95% CI: 0.9-not reached) and 2.5 years (95% CI: 1.9-not reached) and 5-year OS of 39% (95% CI: 20%-77%) and 22% (95% CI: 7%-75%), respectively. (C) Patients who had no major morbidities after contralateral lobectomy had 21% 5-year LC-CID (95% CI: 11%-31%). Patients who had major morbidities had 25% 5-year LC-CID (95% CI: 3%-47%). (D) Patients who underwent contralateral lobectomy for a pathologic stage 1 cancer had 21% 5-year LC-CID (95% CI: 11%-31%), compared with 46% (95% CI: 17%-75%) and 33% (95% CI: 0%-67%) for stage 2 and stages 3 to 4, respectively. CI, confidence interval; LC-CID, lung cancer-specific cumulative incidence of death; OS, overall survival.

short intervals between lobectomies, RLL resections, and low values of DLCO before contralateral lobectomy; higher incidence of mortality is associated with high incidence of SCC.

Our report should be interpreted within the limitations of a retrospective study with selected patients from a single institution. Nevertheless, patient selection and resections in this large series performed by multiple surgeons (>15) in 25 years reflect clinical practice.

In conclusion, although contralateral lobectomy for second primary NSCLC was associated with high rates of perioperative mortality and morbidity before 2010, perioperative outcomes are currently comparable with those of unilateral lobectomy. After contralateral lobectomy for pathologic stage I NSCLC, 3-year OS and LC-CID in patients are comparable with those in patients who underwent single lobectomy for early stage NSCLC.

CRedit Authorship Contribution Statement

Jennie K. Choe: Data curation, Formal analysis, Visualization, Roles/Writing—original draft, Writing—review and editing.

Amy Zhu: Data curation, Visualization, Writing—review and editing.

Alexander J. Byun: Data curation, Writing—review and editing.

Junting Zheng: Formal analysis, Software, Roles/Writing—original draft, Writing—review and editing.

Kay See Tan: Formal analysis, Software, Validation, Roles/Writing—original draft, Writing—review and editing.

Joe Dycoco: Data curation, Writing—review and editing.

Manjit S. Bains, Matthew J. Bott, Robert J. Downey, James Huang, James M. Isbell, Daniela Molena, Valerie W. Rusch, Bernard J. Park, Gaetano Rocco, David R. Jones: Resources, Writing—review and editing.

Smita Sihag: Writing—review and editing.

Prasad S. Adusumilli: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Roles/Writing—original draft, Writing—review and editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at <https://doi.org/10.1016/j.jtocrr.2022.100362>.

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