Vascular invasion predicts the subgroup of lung adenocarcinomas ≤2.0 cm at risk of poor outcome treated by wedge resection compared to lobectomy

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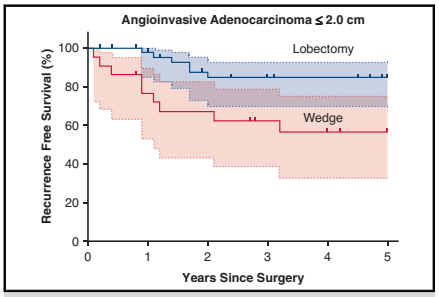
ABSTRACT

Background: Recent randomized control trials (JCOG0802 and CALGB140503) have shown sublobar resection to be noninferior to lobectomy for non–small cell lung cancer (NSCLC) ≤2.0 cm. We have previously proposed histologic criteria stratifying lung adenocarcinoma into indolent low malignant potential (LMP) and aggressive angioinvasive adenocarcinomas, resulting in better prognostication than provided by World Health Organization grade. Here we determine whether pathologic classification is reproducible and whether subsets of adenocarcinomas predict worse outcomes when treated by wedge resection compared to lobectomy.

Methods: A retrospective cohort of 108 recipients of wedge resection and 187 recipients of lobectomy for stage I/o lung adenocarcinomas ≤2.0 cm was assembled from 2 institutions. All tumors were classified by a single pathologist, and interobserver reproducibility was assessed in a subset (n = 92) by 5 pathologists.

Results: Angioinvasive adenocarcinoma (21%-27% of cases) was associated with worse outcomes when treated with wedge resection compared to lobectomy (5-year recurrence-free survival, 57% vs 85% [$P = .007$]; 5-year disease-free survival [DSS], 70% vs 90% [$P = .043$]; 7-year overall survival, 37% vs 58% [$P = .143$]). Adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and LMP exhibited 100% 5-year DSS regardless of the surgical approach. Multivariable analysis showed that angioinvasion, tumor size, margin status, and extent of nodal sampling were significantly associated with recurrence but not with surgical procedure. There was substantial interobserver reproducibility among the pathologists for the diagnosis of angioinvasive adenocarcinoma ($\kappa = 0.71$) and the combined indolent AIS/MIA/LMP group ($\kappa = 0.74$).

Conclusions: The majority (~75%) of lung adenocarcinomas ≤2 cm are adequately managed with wedge resection; however, angioinvasive adenocarcinomas (~25%) treated by wedge resection with suboptimal nodal sampling exhibit poor outcomes, with a 40% to 45% rate of recurrence within 5 years and 60% to 65% overall mortality at 7 years. (JTCVS Open 2023;16:938-47)



Angioinvasive adenocarcinoma ≤2.0 cm: wedge versus lobectomy (5-year recurrence-free survival: 57% vs 85%; $P = .007$).

CENTRAL MESSAGE

Angioinvasive adenocarcinomas (~25%) treated by wedge resection with suboptimal nodal sampling exhibit poor outcomes, with 40% to 45% recurrence within 5 years and 60% to 65% overall mortality at 7 years.

PERSPECTIVE

Recent randomized control trials have shown sublobar resection to be noninferior to lobectomy for non–small cell lung carcinoma ≤2.0 cm when both hilar and mediastinal lymph nodes are sampled. Here we report that angioinvasive adenocarcinomas (~25%) exhibit ~20% to 25% poorer outcomes when treated by wedge resection with deficient nodal sampling compared to lobectomy.

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Abbreviations and Acronyms

AIS = adenocarcinoma in situ
BMC = Boston Medical Center
CALGB = Cancer and Leukemia Group B
CIR = cumulative incidence of recurrence
DSS = disease-specific survival
H&E = hematoxylin and eosin
HR = hazard ratio
JCOG = Japan Clinical Oncology Group
LMP = low malignant potential
LR = limited resection
MIA = minimally invasive adenocarcinoma
MSK = Memorial Sloan Kettering
NSCLC = non–small cell lung carcinoma
OS = overall survival
RCT = randomized controlled trial
RFS = recurrence-free survival
STAS = spread through air spaces
WHO = World Health Organization

Lobectomy has historically been considered the standard of care for non–small cell lung cancer (NSCLC),[1] yet recent results from 2 prospective randomized controlled trials (RCTs), JCOG 0802[2] and CALGB 140503,[3] suggest that sublobar resection is not inferior to lobectomy for peripheral NSCLC ≤2.0 cm when both hilar and mediastinal lymph nodes are sampled. In the JCOG 0802 study, segmentectomy showed a 5-year recurrence-free survival (RFS) of 88.0%, compared to 87.9% for lobectomy, whereas the CALGB 140503 showed 5-year RFS rates of 70.2% for sublobar resection and 71.2% for lobectomy. CALGB 140503 further evaluated 5-year disease-free survival (defined as recurrence or death from any cause) and again showed no difference between sublobar and lobar resection (63.6% vs 64.1%).[3] Tumor size remains the main factor in determining the extent of resection; a marker of indolent or an aggressive tumor behavior potentially would help clinicians tailor the extent of resection.

We recently proposed histologic criteria for low malignant potential (LMP) adenocarcinoma, finding that these tumors exhibited 100% 10-year disease-specific survival, similar to adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA).[4] We subsequently showed that vascular invasion is the most predictive histologic feature of aggressive lung adenocarcinoma and proposed the nomenclature of angioinvasive adenocarcinomas to distinguish them from squamous cell carcinomas whose behavior is not predicted by the routine histologic identification of vascular invasion.[5,6] In the present study, we sought to further evaluate the biological potential and diagnostic reproducibility of adenocarcinomas stratified by our novel approach compared with World Health Organization (WHO) grade, comparing outcomes of patients with adenocarcinoma ≤2.0 cm in total tumor size treated by lobectomy and those treated by wedge resection. Our objective was to identify histologic features of aggressive adenocarcinomas ≤2.0 cm for which wedge resection might be considered inadequate.

METHODS

Patients and Study Design

Resected stage I/0 nonmucinous lung adenocarcinomas measuring ≤2.0 cm in total size removed by either wedge resection or lobectomy were identified from database queries from Boston Medical Center (BMC) between 2005 and 2018 (n = 126) and from Lahey Hospital & Medical Center between 2007 and 2020 (n = 169) after Institutional Review Board approval at each site (BU/BMC IRB H-37859, approved December 11, 2018; Lahey Clinic IRB-518308, approved November 12, 2022) with patient consent waived because this retrospective study posed no more than minimal risk of harm to subjects and involved no procedures for which written consent is normally required. Patients with prior history of lung cancer, synchronous primary cancers, or treatment with adjuvant chemotherapy or segmentectomy were excluded. BMC serves an urban safety net population, and Lahey Hospital & Medical Center serves a suburban population north of Boston. Age, sex, self-identified race, cigarette smoke exposure, total tumor size, tumor laterality, surgical procedure, absence of lymph node metastasis, lymph node stations sampled, surgical margin status, time to recurrence, sites of recurrence, death, and cause of death were determined by retrospective chart review and cross-referenced with institutional tumor registry data after approval by the Institutional Review Board at each site. Distant recurrence was distinguished from locoregional recurrence when it occurred in ipsilateral supraclavicular or contralateral mediastinal lymph nodes, contralateral lung (excluding metachronous primaries), or other nonregional sites, as previously established.[7]

Histopathologic Analysis

All histologic sections of completely submitted tumors were stained with hematoxylin and eosin (H&E) and reviewed by a single pathologist (E.J.B.). Tumors were assessed for proportions of lepidic, acinar, papillary, micropapillary, and solid patterns in 5% increments, with distinction of simple tubular acinar from complex and cribriform acinar patterns.[8,9] In addition, all cases were evaluated for the presence of necrosis, lymphatic, vascular, and visceral pleural invasion and spread through air spaces (STAS) by routine H&E staining. Vascular invasion was defined as luminal invasion of a muscular artery or vein either within or adjacent to the tumor. Lymphatic invasion was distinguished by the thin nonmuscular walls typically observed in a peribronchiolar distribution. Mitoses were counted in 2-mm^2 fields, starting in the field with the highest activity. Stage assignments were made retrospectively based on the 8th edition of the American Joint Committee on Cancer's cancer staging manual.

Tumors were graded based on WHO 2015 and WHO 2021 grading systems. WHO 2015 grade was defined as G1, lepidic; G2, acinar/papillary; or G3, micropapillary/solid.[10] WHO 2021 grade was defined as G1, lepidic predominant with <20% high-grade patterns; G2, acinar or papillary predominant with <20% high-grade patterns; and G3, ≥20% high-grade patterns (solid, micropapillary, and/or complex glands).[11,12] Mucinous adenocarcinomas (invasive mucinous and colloid) were excluded. Adenocarcinoma in situ (AIS) was rendered for purely lepidic tumors ≤3 cm, whereas minimally invasive adenocarcinoma (MIA) was diagnosed

when nonlepidic foci measured ≤0.5 cm as per WHO criteria.[12] Low malignant potential adenocarcinoma (LMP) was assigned as previously described for nonmucinous adenocarcinoma measuring ≤3 cm in total; exhibiting ≥15% lepidic growth; and lacking nonpredominant high-grade patterns (≥10% cribriform, ≥5% micropapillary, ≥5% solid); > 1 mitosis per 2 mm^2; vascular, lymphatic or visceral pleural invasion; STAS; or necrosis.[4] Angioinvasive adenocarcinoma was assigned when at least one focus of vascular invasion was identified.[5]

Survival and Statistical Analysis

Survival assessment was measured as RFS, defined as the time from initial surgery to recurrence of resected tumor or time of last follow-up (death from any cause censored at the time of the event); disease-specific survival (DSS), defined as the time from surgery to death from recurrence of resected tumor or time of last follow-up (unrelated deaths censored at the time of the event); and overall survival (OS), defined as the time from surgery to death from any cause or time of last follow-up. Survival estimates were computed using the Kaplan-Meier method comparing groups with the log-rank test. Statistical analyses were performed using SPSS version 28 (IBM). The χ^2 test for homogeneity or the Fisher exact test were used for categorical variables, as appropriate. Post hoc analysis involved pairwise comparisons using the z test of 2 proportions with a Bonferroni correction. Continuous variables were compared between groups using Welch's t test. All tests were 2-tailed. Univariate Cox proportional hazards analysis followed by multivariable analysis were performed to assess the impacts of clinical, pathologic, and surgical factors on the risk of recurrence for wedge resection versus lobectomy.

Reproducibility Assessment

The most representative H&E-stained slides (median, 2.5 slides per case) for each of 92 tumors were reviewed independently by 5 pathologists practicing general surgical pathology in an academic medical center. Reviewers were asked to classify each case as AIS/MIA, LMP, or angioinvasive; to identify the predominant pattern (lepidic, acinar, papillary, micropapillary, or solid); and to assign WHO grades for both 2015 and 2021 classifications. Reviewers were provided published images to familiarize them with both the filigree and classic micropapillary patterns,[13] as well as cribriform and fused gland acinar patterns,[9] as the latter is required for the WHO 2021 grade. The Fleiss κ statistic was used to measure the reliability of agreement between observers, in which perfect agreement was defined as $\kappa = 1.0$, near perfect agreement as $\kappa = 0.80$ to 0.99, substantial agreement as $\kappa = 0.60$ to 0.79, moderate agreement as $\kappa = 0.40$ to 0.59, fair agreement as $\kappa = 0.20$ to 0.39, poor agreement as $\kappa = 0.0$ to 0.19, and no agreement as $\kappa < 0$.[14]

RESULTS

Clinicopathologic Comparison of Surgical Cohorts

Table 1 presents the clinical and pathologic features of 295 surgically resected pathologic stage I/0 lung adenocarcinomas of ≤2.0 cm total size segregated by surgical procedure to include 108 wedge resections and 187 lobectomies. Most patients in our series were female (60%-65%), with median age of 67 to 68 years, who used to smoke (45%-47%). Wedge resected tumors were a median of 0.1 cm smaller than those treated by lobectomy. AIS/MIA were more frequent in the wedge resected cohort compared with the lobectomy cohort (12% vs 1%), whereas micropapillary pattern ≥5% and STAS were less frequent (17% vs 38% and 36% vs 50%, respectively). Microscopic surgical margin positivity (R1) was infrequent and observed in only 2 patients treated with wedge resection (2%). There was a striking difference between the groups in the extent of lymph node stations sampled, with only 34% of wedge resections and 93% of lobectomies in which both N1 (hilar) and N2 (mediastinal) stations were sampled ($N1_0N2_0$) compared to those who had no lymph nodes sampled from these stations ($N1_X$ and/or $N2_X$).

Outcome Analysis

Cancer-specific outcomes stratified by surgical cohort and pathologic grade are shown in Table 2 and Figure 1. Neither 5-year RFS nor DSS differed significantly between the wedge resection and lobectomy groups prior to pathologic stratification. On pathologic stratification, angioinvasive adenocarcinomas had significantly worse cancer-specific outcomes when treated with wedge resection compared to lobectomy (5-year RFS, 57% vs 85% [$P = .007$]; 5-year DSS, 70% vs 90% [$P = .043$]). Angioinvasive adenocarcinoma comprised 21% and 27% of the wedge and lobectomy resected tumors, respectively (Table 1). Neither WHO grading system was associated with statistically significant outcome differences between the surgical treatment groups (Table 2). The combined group of AIS/MIA and LMP, WHO 2015 G1, and WHO 2021 G1 were each associated with 100% 5-year DSS for both the wedge resection and lobectomy surgical groups (Table 2), with the former comprising 31% and 21% of adenocarcinomas, respectively (Table 1). The 5-year RFS for patients with STAS did not differ by procedure (85% each), whereas those without STAS did better with lobectomy (87% for wedge resection vs 98% for lobectomy; $P = .01$), (data not shown). The 5-year RFS for patients with micropapillary pattern ≥5% was 83% in the lobectomy group and 100% in the wedge resection group ($P = .072$). whereas those without micropapillary pattern ≥5% did better with lobectomy (96% vs 83% for wedge resection; $P = .005$) (data not shown).

Overall survival stratified by procedure and angioinvasion is shown in Table 3. When stratified by procedure, angioinvasive adenocarcinoma had worse 7-year OS compared with the other adenocarcinoma subtypes in both the lobectomy group (58% vs 79%; $P = .001$) and the wedge group (37% vs 66%; $P = .002$). A trend toward worse OS for wedge resection versus lobectomy was seen in all subgroups, likely reflecting the nonrandomized choice of surgical approach in this retrospective cohort, but the differences did not reach statistical significance (Table 3).

Recurrence Pattern

Table 4 shows the distribution of recurrences stratified by surgical procedure and angioinvasion. There was no significant difference in recurrence rate between the wedge

TABLE 1. Clinicopathologic comparison of the surgical cohorts

Characteristic	Wedge resection (N = 108)	Lobectomy (N = 187)	*P* value
Age, y, median (IQR)	68 (61-75)	67 (61-72)	.232
Sex, n (%)			
Female	70 (65)	113 (60)	.459
Male	38 (35)	74 (40)	
Race, n (%)			
White	86 (80)	153 (82)	.207
Black	16 (14)	22 (12)	
Asian	3 (3)	6 (3)	
Hispanic/Latino	0	5 (2)	
Not available	3 (3)	1 (1)	
Smoking status			.826
Current smoker, n (%)	44 (41)	77 (41)	
Former smoker, n (%)	51 (47)	84 (45)	
Never smoker, n (%)	11 (10)	24 (13)	
Unknown, n (%)	2 (2)	2 (1)	
Pack-years, median (IQR)*	40 (25-60)	40 (30-53)	.966
Quit years, median (IQR)*	14 (3-24)	13 (4-25)	.436
pStage, AJCC 8th edition, n (%)			.104
0 (pTis)	3 (2)	1 (1)	
IA1 (pT1mi/1a)	48 (44)	70 (37)	
IA2 (pT1b)	36 (33)	85 (45)	
IA3 (pT1c)	0	0	
IB (pT2a)	21 (19)	31 (17)	
Total size, cm, median (IQR)	1.4 (1.0-1.5)	1.5 (1.2-1.9)	**.001**
Invasive size, cm, median (IQR)	1.0 (0.7-1.3)	1.1 (0.8-1.5)	**<.001**
Nodal sampling, n (%)			
$N1_0N2_0$	**37 (34)**	**174 (93)**	**<.001**
$N1_xN2_0$	**42 (39)**	**3 (2)**	
$N1_0N2_x$	7 (7)	8 (4)	
$N1_xN2_x$	**22 (20)**	**2 (1)**	
Margin, n (%)			
R0	106 (98)	187 (100)	.133
R1	2 (2)	0	
WHO 2015 grade, n (%)			.204
G1	14 (15)	34 (18)	
G2	63 (66)	103 (55)	
G3	18 (19)	49 (26)	
WHO 2021 grade, n (%)			.505
G1	12 (13)	33 (18)	
G2	31 (33)	61 (33)	
G3	52 (55)	92 (49)	
AIS/MIA, n (%)	13 (12)	1 (1)	**<.001**
LMP, n (%)	20 (19)	37 (20)	.791
Angioinvasive adenocarcinoma, n (%)	23 (21)	51 (27)	.254
Other high-risk pathologic features, n (%)			
Lepidic (<15%)	49 (45)	96 (51)	.323
Cribriform (≥10%)	39 (36)	50 (27)	.091
Micropapillary (≥5%)	18 (17)	71 (38)	**<.001**
Solid (≥5%)	32 (30)	70 (37)	.175

(Continued)

TABLE 1. Continued

Characteristic	Wedge resection (N = 108)	Lobectomy (N = 187)	*P* value
Visceral pleural invasion	21 (19)	31 (17)	.534
Lymphatic invasion	26 (24)	53 (28)	.425
Tumor necrosis	24 (22)	35 (19)	.468
STAS	39 (36)	94 (50)	**.019**
Mitosis >1 per 2 mm^2	72 (67)	121 (65)	.733
Follow-up, y, median (IQR)	6.9 (4.2-9.7)	5.7 (3.9-8.2)	.154

The *P* values presented are for the omnibus test for overall difference across the groups. The values in bold type indicate which group(s) were noted as significantly different on post hoc comparison using a Bonferroni correction for multiple comparisons, where an adjusted *P* value < .05 was considered statistically significant. *IQR*, Interquartile range; *AJCC*, American Joint Committee on Cancer; *WHO*, World Health Organization; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma; *LMP*, low malignant potential adenocarcinoma; *STAS*, spread through air spaces. *Pack years and quit years reported for ever-smokers and former-smokers, respectively.

resection and lobectomy groups (16% vs 11%; $P = .207$) and no significant differences in type of recurrence observed (locoregional only vs distant). Subgroup analysis revealed significantly more recurrences in the angioinvasive subgroup treated with wedge resection compared to lobectomy (43% vs 18%; $P = .019$). When stratified by type of recurrence, only the rate of distant recurrence in angioinvasive adenocarcinomas was significantly greater in the wedge resection group compared to the lobectomy group (22% vs 6%). There was no significant difference in the rate of new primary lung cancers in the overall group or subgroup analysis (16%-18%, total).

Univariate and Multivariable Analyses

Table 5 shows the results of univariate and multivariable analyses for clinicopathologic features associated with recurrence. The univariate hazard ratio (HR) was 1.77 for wedge resection compared to lobectomy (*P* not significant). We performed a multivariable analysis using clinical and pathologic variables associated with recurrence on univariate analysis ($P \leq .2$) (Table 5). The multivariable HR was 0.69 for wedge resection compared to lobectomy (*P* not significant). On multivariable analysis, invasive tumor size, angioinvasion, positive surgical margin, and inadequate hilar lymph node sampling ($N1_x$) were each significantly associated with recurrence. Among pathologic variables significantly associated with recurrence on univariate analysis (angioinvasion, necrosis, lymphatic invasion, and STAS), only angioinvasion remained significant on multivariable analysis (HR, 2.85; $P = .016$).

Interobserver Reproducibility

Interobserver reproducibility results are summarized in Table 6. There was moderate interobserver agreement for the 3-tiered grading systems of WHO 2015 ($\kappa = 0.59$) and WHO 2021 ($\kappa = 0.51$) when AIS and MIA were included with G1. For comparison, a 3-tiered grading system incorporating AIS/MIA/LMP (G1), angioinvasive adenocarcinoma (G3), and the remaining adenocarcinoma of no special type (G2) showed substantial agreement among pathologists ($\kappa = 0.65$). Reproducibility among aggressive adenocarcinomas (G3) was substantial for all grading classifications ($\kappa = 0.69$-0.81). Reproducibility among indolent adenocarcinomas (G1) was substantial for

TABLE 2. Cancer-specific outcomes in the 2 surgical cohorts by grade

Grade	5-y RFS, % (95% CI)			5-y DSS, % (95% CI)		
	Wedge resection	Lobectomy	*P*	Wedge resection	Lobectomy	*P*
All	86 (78-92)	92 (86-95)	.125	92 (84-96)	94 (89-97)	.468
Novel classifier						
AIS/MIA/LMP	97 (80-100)	100	.282	100	100	1
NST	92 (79-97)	91 (83-95)	.936	96 (84-99)	93 (86-97)	.594
Angioinvasive	57 (33-75)	85 (70-93)	**.007**	70 (45-86)	90 (76-96)	**.043**
WHO 2015						
AIS/MIA/G1	96 (76-99)	100	.246	100	100	1
G2	87 (75-93)	90 (82-95)	.374	87 (75-94)	92 (85-96)	.288
G3	72 (46-87)	88 (73-95)	.149	94 (67-99)	93 (80-98)	.866
WHO 2021						
AIS/MIA/G1	96 (74-99)	100	.234	100	100	1
G2	83 (63-92)	89 (78-95)	.247	81 (60-92)	91 (80-96)	.162
G3	84 (70-92)	90 (80-95)	.352	94 (82-98)	94 (85-97)	.961

Bold type indicates significance. *RFS*, Recurrence-free survival; *CI*, confidence interval; *DSS*, disease-specific survival; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma; *LMP*, low malignant potential adenocarcinoma; *NST*, no special type; *WHO*, World Health Organization.

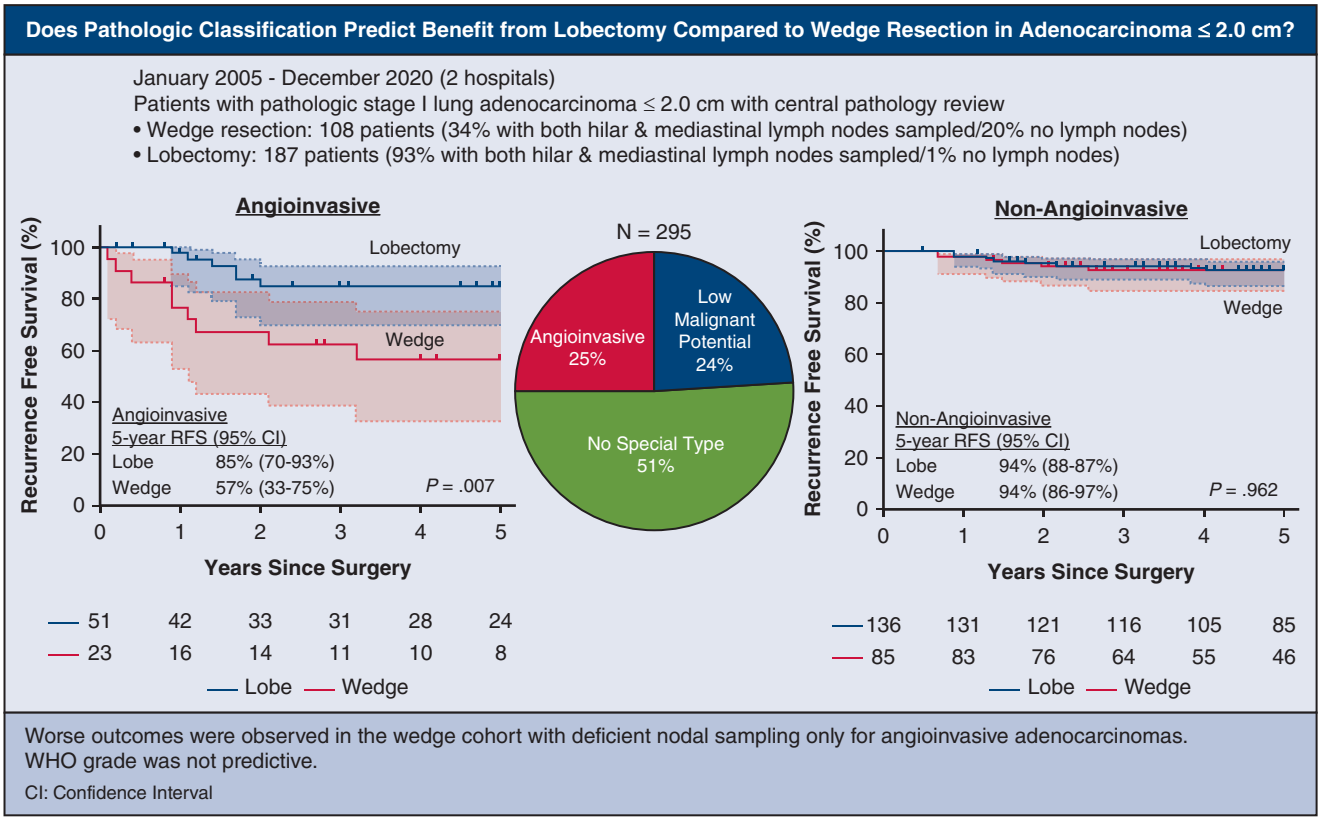

FIGURE 1. Graphical abstract comparing procedure specific recurrence free survival for adenocarcinoma stratified by angioinvasion. Pie chart demonstrates proportion of novel histologic grade among the entire cohort. *RFS*, Recurrence-free survival; *CI*, confidence interval; *WHO*, World Health Organization.

only AIS/MIA/LMP ($\kappa = 0.74$) and was moderate ($\kappa = 0.53$) for the AIS/MIA/G1 of WHO 2015 and WHO 2021.

DISCUSSION

Using a large retrospective comparative cohort of wedge versus lobectomy resections for small (≤2.0 cm total size) early-stage lung adenocarcinoma, we assessed the biological potential of our recently proposed lung adenocarcinoma subtypes.[4,5] Similar to other historical wedge resection cohorts,[15] our wedge resection group had high rates of inadequate nodal sampling compared to lobectomy (66% vs 7%) and absent nodal sampling (20% vs 1%), thus magnifying the effect of aggressive tumors at risk of understaging due to occult nodal metastasis, but which manifest with early distant recurrences rather than isolated locoregional recurrences. In this context, angioinvasive adenocarcinoma accurately predicts the biologically aggressive subset (~25%) of adenocarcinoma for which wedge resection with deficient nodal sampling is oncologically worse than lobectomy (~20%-25% worse 5-year RFS/DSS) and trend toward

TABLE 3. Seven-year OS of the surgical cohorts stratified by angioinvasion

Grade	Wedge resection, 7-y OS, % (95% CI)	Lobectomy, 7-y OS, % (95% CI)	*P* value
All	60 (49-69)	73 (66-79)	.061
No angioinvasion	66 (54-76)	79 (71-85)	.098
Angioinvasion	37 (18-56)	58 (42-70)	.143
P value	.002	.001	

OS, Overall survival; *CI*, confidence interval.

TABLE 4. Recurrence pattern stratified by surgical cohort and angioinvasion

Recurrence location	Wedge resection, n (%)	Lobectomy, n (%)	*P* value
All, n	108	187	
Total recurrence	17 (16)	20 (11)	.207
Locoregional*	10 (9)	10 (5)	.292
Distant	6 (6)	10 (5)	
Unclassified	1 (1)	0	
New primary lung cancer	19 (18)	30 (16)	.730
Nonangioinvasive, n	85	136	
Total recurrence	7 (8)	11 (8)	.969
Locoregional*	6 (7)	4 (3)	.120
Distant	1 (1)	7 (5)	
Unclassified	0	0	
New primary lung cancer	17 (20)	22 (16)	.468
Angioinvasive, n	23	51	
Total recurrence	**10 (43)**	**9 (18)**	**.019**
Locoregional*	4 (17)	6 (12)	**.040**
Distant	**5 (22)**	**3 (6)**	
Unclassified	1 (4)	0	
New primary lung cancer	2 (9)	8 (16)	.416

The *P* values presented are for the omnibus test for overall difference across the groups. Bold type indicates statistical significance. *Only locoregional recurrences without distant recurrence.

TABLE 5. Univariate analysis and Cox proportional hazards model for recurrence comparing wedge resection and lobectomy

	Univariate analysis		Multivariable analysis	
Variable	SHR (95% CI)	*P* value	SHR (95% CI)	*P* value
Wedge resection vs lobectomy	1.77 (0.84-3.71)	.131	0.69 (0.19-2.43)	.559
Clinical variables				
Age above median	1.18 (0.56-2.47)	.667	…	
Male vs female sex	1.10 (0.51-2.35)	.809	…	
Black vs other race	0.86 (0.26-2.85)	.803	…	
Safety net vs suburban hospital	0.71 (0.33-1.54)	.388	…	
Current vs former/never smoker	1.47 (0.70-3.08)	.311	…	
Total size above median	1.74 (0.83-3.65)	.146	0.77 (0.33-1.81)	.551
Invasive size above median	**8.07 (2.80-23.27)**	**<.001**	**6.40 (2.00-20.49)**	**.002**
Pathologic variables				
Angioinvasion	**4.46 (2.12-9.38)**	**<.001**	**2.85 (1.22-6.64)**	**.016**
Necrosis	**2.53 (1.17-5.48)**	**.019**	0.92 (0.40-2.15)	.850
Lymphatic invasion	**2.28 (1.08-4.82)**	**.031**	1.42 (0.63-3.16)	.396
STAS	**2.42 (1.12-5.24)**	**.025**	1.81 (0.80-4.07)	.155
Visceral pleural invasion	2.01 (0.88-4.56)	.096	0.81 (0.32-2.04)	.659
Solid ≥5%	1.32 (0.62-2.82)	.470	…	
Micropapillary ≥5%	1.31 (0.60-2.83)	.500	…	
Cribriform ≥10%	1.13 (0.51-2.49)	.767	…	
Surgical variables				
Positive margin (R1) vs R0	**9.13 (1.24-67.23)**	**.030**	**18.30 (1.55-216.38)**	**.021**
Deficient nodal stations vs $N1_0N2_0$				
$N1_0N2_x$	1.91 (0.44-8.42)	.391	1.78 (0.37-8.64)	.473
$N1_xN2_0$	**3.60 (1.60-8.10)**	**.002**	**6.42 (1.75-23.50)**	**.005**
$N1_xN2_x$	1.32 (0.30-5.82)	.712	3.65 (0.53-25.25)	.190

When 2 variables are listed, the second group served as the reference for analysis. Bold type indicates statistical significance. *SHR*, Subdistribution hazard ratio; *CI*, confidence interval; *STAS*, spread through air spaces.

TABLE 6. Interobserver reproducibility assessment of grading systems

Criteria	Fleiss κ	95% CI
Novel grade (overall)	0.65	0.60-0.69
AIS/MIA/LMP (G1)	0.74	0.68-0.81
NST (G2)	0.50	0.43-0.56
Angioinvasive (G3)	0.71	0.64-0.77
WHO 2015 (overall)	0.59	0.54-0.63
AIS/MIA/G1	0.53	0.46-0.59
G2	0.51	0.44-0.57
G3	0.81	0.74-0.87
WHO 2021 (overall)	0.51	0.47-0.56
AIS/MIA/G1	0.53	0.47-0.60
G2	0.26	0.20-0.33
G3	0.69	0.63-0.76

CI, Confidence interval; *AIS*, adenocarcinoma in situ; *MIA*, minimally invasive adenocarcinoma; *LMP*, low malignant potential adenocarcinoma; *NST*, no special type; *WHO*, World Health Organization.

worse OS (∼20% worse 7-year OS). AIS, MIA, and LMP (∼25% combined) predicted 100% 5-year DSS in both wedge and lobectomy treatment groups. The remaining adenocarcinomas (∼50%) exhibited similar cancer-specific outcomes with <10% recurring or causing disease-specific mortality at 5 years, regardless of the surgical procedure used. In contrast, WHO 2015 and WHO 2021 grades were less predictive of outcome differences between the surgical treatment groups.

Prior retrospective studies comparing limited resection (LR; wedge or segment) and lobectomy have yielded mixed results. An early study showed no advantage of lobectomy over LR regardless of architectural grade or lymphovascular invasion, but this study included only 26 LRs not limited to ≤2.0 cm.[16] Three studies have specifically assessed this question for adenocarcinomas ≤2.0 cm, all of which included entirely or in large proportion patients from Memorial Sloan Kettering (MSK).[17-19] Similar to our findings, the 5-year cumulative incidence of recurrence (CIR) among high-grade predominant architectural pattern tumors (WHO 2015 G3) treated by LR versus lobectomy was not significantly different (5-year CIR, 25% vs 21%, respectively).[19] In both the MSK cohorts and our study, vascular invasion (22% and 25% of cases, respectively) was associated with an increased risk of recurrence for LR (5-year CIR, 46% and 43%, respectively) but a 5-year CIR ≤20% in LR without vascular invasion or lobectomy regardless of vascular invasion status.[17] The MSK data sets further show that micropapillary pattern ≥5% (23%-39% of cases) and STAS (35%-38% of cases) were associated with higher rates of recurrence in LR (5-year CIR, 34%-40%) but low rates of recurrence (5-year CIR ≤20%) for LR without micropapillary pattern or STAS and lobectomy regardless of micropapillary pattern or STAS.[17,18] In contrast, we observed <20% recurrence for both wedge resection and lobectomy regardless of the presence of micropapillary pattern ≥5% or STAS. The reasons for these differences may reflect the small number (n = 18) of wedge resections with micropapillary pattern ≥5% and the variance of nodal sampling in our wedge resection cohort (20% $N1_XN2_X$) compared to the MSK LR cohort (40%-57% $N1_XN2_X$).[17-19] Multivariate analysis of the MSK cohort found that STAS remained significant over vascular invasion (HR, 3.08 vs 2.10) when analyzed among LR excluding nodal sampling as a variable.[17] In contrast, vascular invasion, but not STAS (HR, 2.85 vs 1.81), remained significant on multivariate analysis once nodal sampling and margin status were included as covariates for the entire cohort. Of note, the prognostic significance of STAS and/or micropapillary pattern ≥5% has been confirmed in other cohorts of stage I adenocarcinoma not limited to ≤2.0 cm, but again with high rates of absent nodal sampling in the LR group in one study (63% $N1_XN2_X$)[20] and not reported in another study.[21]

The historical preference of lobectomy over sublobar resection was established by the Lung Cancer Study Group RCT for chest X-ray–detected NSCLC ≤3.0 cm, which found a 3-fold increase in locoregional recurrence in those treated by LR compared to lobectomy.[1] Since that time, the use of computed tomography has improved early detection of smaller subsolid pulmonary nodules, particularly in the setting of computed tomography lung cancer screening, leading to a renewed interested in LR. Two large randomized surgical control trials (JCOG0802/WJOG4607L and CALGB 140503) enrolling 1106 and 697 patients, respectively, have shown noninferiority of sublobar resection compared to lobectomy for peripheral NSCLC radiographically measuring ≤2.0 cm and with pathologically confirmed negative hilar and mediastinal lymph nodes. The JCOG study was carried out in a multicenter Japanese population, of which 44% were never smokers, leading to a predominance (91%) of adenocarcinoma with exceptional 5-year RFS (88%) and 7-year OS (∼85%). The CALGB

study was carried out in a multicenter US, Canadian, and Australian cohort that included only 9% never smokers and a lower proportion (64%) of adenocarcinomas, with expectedly worse outcomes (5-year RFS, 70%; 7-year OS, ~70%). The JCOG study specifically examined segmentectomy (n = 552) for the LR arm, whereas the CALGB study included wedge resection (n = 201) and segmentectomy (n = 129) in its LR arm. Given our study design examining only adenocarcinoma, our oncologic outcomes are closer to those of the JCOG study that showed a similar 5-year RFS of 86% to 92%, whereas our population with more extensive cigarette smoke exposure (10%-13% never smokers) exhibited comparably worse 7-year OS (60%-73%), closer to the CALGB trial. Interestingly, the incidence of second primary lung cancers was similar in the 2 trials (15%-18%) and comparable to the incidence in the present study (16%-18%) over a generally similar median follow-up period (6-7 years). Likewise, the proportion of isolated locoregional to any distant recurrences was <2:1 in both surgical cohorts in the JCOG study, the CALGB study, and our present retrospective study.

Neither the JCOG study nor the CALGB study assessed pathologic features aside from major subtype (adenocarcinoma, squamous cell carcinoma, or NSCLC other). In contrast, we show that among adenocarcinomas, the angioinvasive subgroup is particularly aggressive and may be undertreated with wedge resection, specifically when adequate nodal sampling is not performed. Given that our retrospective wedge resected cohort included a majority of patients (66%) lacking both hilar and mediastinal lymph node sampling and 20% with no nodal sampling, we cannot conclude that angioinvasion renders wedge resection less effective than lobectomy due to systematic bias stemming from uncontrollable stage migration, a bias that also would apply to previously published retrospective studies advocating for lobectomy rather than LR for tumors with STAS and/or micropapillary pattern ≥5% described above.[17-20] As such, procedure-specific risks associated with angioinvasion, STAS, and micropapillary pattern ≥5% need to be confirmed by subset analysis in these prospective trials, in which the adequacy of pathologic assessment of lymph node stations was an inclusion criterion in the trial design. Furthermore, our study highlights the importance of guideline-concordant intraoperative lymph node sampling, which may be particularly relevant for tumors in the angioinvasive high-risk category. Given the clinical need to preoperatively risk-stratify adenocarcinoma, JCOG investigators devised a prospective radiologic/pathologic correlation study and determined that a consolidation/tumor ratio cutoff >0.5 in adenocarcinomas ≤3.0 cm total size (79% of cases) predicted pathologic invasion (vascular, lymphatic, or regional nodal) with a positive predictive value of 38%, a negative predictive value of 95%, and a 5-year recurrence rate of 18% versus 4%.[22,23]

This work suggests that radiomics has the potential to aid the preoperative prediction of vascular invasion but is insufficiently specific when used alone. To our knowledge, no previous studies have evaluated the accuracy of assessing vascular invasion with frozen sections, but given the focality of this finding in most cases and the limitations introduced by the frozen section process, it is unlikely to have high concordance with the final pathologic assessment. Furthermore, it is not possible to histologically detect vascular invasion on presurgical needle biopsies with significant sensitivity. Alternatively, we have shown that gene expression profiling can be leveraged to create a tumor biopsy biomarker predictive of angioinvasion,[24,25] which in conjunction with radiomic features may someday offer a more precise preoperative discrimination of the small number of patients (~25%) who might benefit from more aggressive surgical/medical management than LR alone.

Currently, risk stratification is limited to pathologic evaluation after complete surgical excision. Interobserver reproducibility studies conducted by the International Association for the Study of Lung Cancer among expert pulmonary pathologists has demonstrated moderate agreement for assessing the predominant pattern ($\kappa = 0.55$),[26] the basis of the WHO 2015 recommended grade,[10] and substantial agreement for the assessment of the WHO 2021 grade ($\kappa = 0.62$).[11] We confirm these findings, showing moderate interobserver agreement ($\kappa = 0.51$-0.59) among pathologists practicing in a nonspecialized setting. In this context, we show that our novel classification is at least as reproducible ($\kappa = 0.65$) as the current WHO- recommended grade, and uniquely shows substantial agreement for predicting both the aggressive (G3) angioinvasive ($\kappa = 0.71$) and the indolent (G1) AIS/MIA/LMP ($\kappa = 0.74$) ends of the disease spectrum.

Limitations of our study include its retrospective nature and nonrandomized approach to treatment with wedge resection versus lobectomy. There was a striking imbalance in the proportion of patients with inadequate nodal sampling in the wedge resection group compared to the lobectomy group. The low rate of nodal sampling in the wedge resection group is consistent with published rates from other major academic institutions with even higher rates (40%-77%) of inadequate nodal sampling, representing an area for surgical quality improvement.[15,17,18,27] Although other groups have shown margin distance to be associated with risk of locoregional recurrence,[27] we did not evaluate this parameter, as it was not recorded at the time of this review. Finally, although we observed no statistically significant differences in cancer-specific outcomes regardless of surgical approach for the remaining adenocarcinomas of no special type (non-LMP/angioinvasive), a power analysis was not conducted and the probability of a type II error was not calculated as would be appropriate for a prospective RCT.

CONCLUSIONS

Our pathologic subset analysis showed that the majority (∼75%) of lung adenocarcinomas ≤2 cm were adequately managed with wedge resection, even with inadequate nodal sampling. However, patients with angioinvasive adenocarcinomas (∼25%) treated by wedge resection with suboptimal nodal sampling exhibited poor outcomes, with a 40% to 45% rate of recurrence within 5 years and 60% to 65% overall mortality at 7 years.

Conflict of Interest Statement

Dr Servais reports from Intuitive Surgical and AstraZeneca. The other authors have no conflicts of interest to report.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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