

# Comparison of Surgical Outcomes Between Invasive Mucinous and Non-Mucinous Lung Adenocarcinoma



Takuya Matsui, MD, Noriaki Sakakura, MD, PhD, Shin Koyama, MD, Keita Nakanishi, MD, Eiichi Sasaki, MD, PhD, Seiichi Kato, MD, PhD, Waki Hosoda, MD, PhD, Yoshiko Murakami, MD, PhD, Hiroaki Kuroda, MD, PhD, and Yasushi Yatabe, MD, PhD

Department of Thoracic Surgery, Aichi Cancer Center, Nagoya, Japan; and Department of Pathology and Molecular Diagnostics, Aichi Cancer Center, Nagoya, Japan

**Background.** Invasive mucinous adenocarcinoma (IMA) is a rare subtype of invasive lung adenocarcinoma. However, the clinical course and prognostic outcomes following IMA resection, particularly postoperative recurrence, remain unclear.

**Methods.** We pathologically reevaluated 1362 lung adenocarcinoma resections performed at our institution, categorizing cases into the IMA group (72 cases) and non-IMA group (1290 cases). The IMA group was further classified into pneumonia and nodular types based on preoperative computed tomography.

**Results.** Overall, the IMA group had lower carcinoembryonic antigen levels (3 vs 8 ng/mL;  $P < .01$ ), fewer lymph node metastasis (4% vs 24%;  $P < .01$ ), and more *KRAS* mutations (56% vs 7%;  $P < .01$ ) than the non-IMA group. Although postoperative recurrence rates did not differ between both groups (32% vs 27%;  $P = 0.35$ ), lung

recurrence occurred more frequently in the IMA group (83% vs 17%;  $P < .01$ ). Propensity score-matched pair analysis showed that the IMA group had fewer lymph node metastasis (3% vs 35%;  $P < .01$ ), more *KRAS* mutations (56% vs 9%;  $P < .01$ ), and higher intrapulmonary recurrence rate (84% vs 31%;  $P < .01$ ) than the non-IMA group. The 5-year overall survival rates did not differ between both groups (74% vs 81%;  $P = 0.26$ ). However, among patients with intrapulmonary recurrence, those in the IMA group had significantly worse prognosis than those in the non-IMA group (35% vs 77%;  $P < .01$ ).

**Conclusions.** Intrapulmonary recurrence, which induced significantly worse prognosis, was more likely to occur in the IMA than non-IMA group.

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In 2011, the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) presented a new classification for lung adenocarcinoma<sup>1</sup> under which the term bronchioloalveolar carcinoma (BAC) was abolished. Furthermore, lung adenocarcinoma characterized by pneumonia-like shadows on imaging, which had been called mucinous BAC, was redefined as invasive mucinous adenocarcinoma (IMA). The World Health Organization (WHO) classification, which was subsequently revised in 2015, characterized IMA as a subtype of invasive adenocarcinoma.<sup>2</sup> IMA has been histologically characterized by goblet cells and high columnar epithelial cells with mucin production.<sup>1,3</sup> Moreover, typical immunohistochemical findings include the expression of cytokeratin 7, cytokeratin 20, and hepatocyte nuclear factor 4 alpha and the deletion of thyroid transcription factor 1 and napsin A.<sup>3,4</sup> Genetically, IMAs rarely exhibit

epidermal growth factor receptor (*EGFR*) mutations but frequently exhibit *KRAS* mutations ( $\geq 50\%$ ).<sup>4,5</sup>

Since the new IASLC/ATS/ERS classification was published in 2011, reports on the reclassification and analysis of resected adenocarcinoma cases throughout individual institutions have emerged.<sup>6-9</sup> Prior to the publication of this new classification, studies had shown that mucinous BAC had a poorer prognosis than non-mucinous BAC.<sup>10-12</sup> Nevertheless, studies on IMA have revealed inconsistent results, with some showing poor prognosis (similar to previous reports) and others showing relatively good prognosis.<sup>6-9</sup> Given the low frequency of IMA, constituting 2% to 5% of all adenocarcinoma cases, few reports have examined a large number of cases.<sup>6,7,13,14</sup> Furthermore, most previous reports on IMA have had short follow-up periods after surgery or have been limited to early cases, and few have focused on postoperative recurrence. Therefore, the clinical course and prognosis of IMA cases with postoperative recurrence remain unclear at present. This study aimed to pathologically reassess adenocarcinoma resections performed at our institution over the past 11 years based on the 2011 IASLC/ATS/ERS classification and 2015 WHO

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Address correspondence to Dr Sakakura, Department of Thoracic Surgery, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan; email: [nsakakura@aichi-cc.jp](mailto:nsakakura@aichi-cc.jp).

#### Abbreviations and Acronyms

ATS	= American Thoracic Society
BAC	= bronchioloalveolar carcinoma
CI	= confidence interval
CT	= computed tomography
DFS	= disease-free survival
EGFR	= epidermal growth factor receptor
ERS	= European Respiratory Society
IASLC	= International Association for the Study of Lung Cancer
IMA	= invasive mucinous adenocarcinoma
OS	= overall survival
WHO	= World Health Organization

classification, reclassify them as either IMA or non-IMA, and compare their clinicopathologic features and prognosis.

## Patients and Methods

### Study Design and Patients

This study was approved by the institutional review board of Aichi Cancer Center (approval no. 2018-1-254). Consent was obtained after informing each patient that their clinical data could be used for various studies.

We retrospectively analyzed the medical records of 2219 consecutive patients who underwent resection for non-small cell lung cancer at our institution between January 2005 and December 2015, subsequently identifying those with pathologic adenocarcinoma. Cases with insufficient pathologic slides for reevaluation ( $n = 5$ ), preoperative computed tomography (CT) examination suggesting no or insufficient evidence for evaluation ( $n = 11$ ), and pathologic stage IV disease ( $n = 28$ ) were excluded. Ultimately, 1362 cases were pathologically reassessed by pathologists, among which 72 (5%) and 1290 (95%) were classified into the IMA and non-IMA groups, respectively, based on the new IASLC/ATS/ERS classification (Figure 1). Both groups were compared retrospectively and examined clinically, pathologically, and genetically. All cohorts were analyzed based on the 7th edition of the Union for International Cancer Control Tumor–Node–Metastasis classification system. Further classification into pneumonia or nodular type based on imaging characteristics was qualitatively performed by 2 or more thoracic surgeons (mainly TM and NS). Prognostic data were collected mostly via the patients' electronic medical records and confirmed with the general practitioner if necessary. Postoperative recurrence was mainly detected through radiologic examination, including CT, and did not necessarily require histologic confirmation.

### Pathologic Specimens

Resected lung specimens were inflated and fixed using 10% formalin injections immediately after resection. Sliced tissues were embedded in paraffin and stained

with hematoxylin and eosin. Elastic staining and immunohistochemical staining were used when necessary. All tumor areas on the slides were evaluated, including all tumor foci if several were present. All slides were evaluated retrospectively based on the 2011 IASLC/ATS/ERS classification and 2015 WHO classification. Possible cases of IMA were discussed until consensus was reached by 2 or more experienced pathologists.

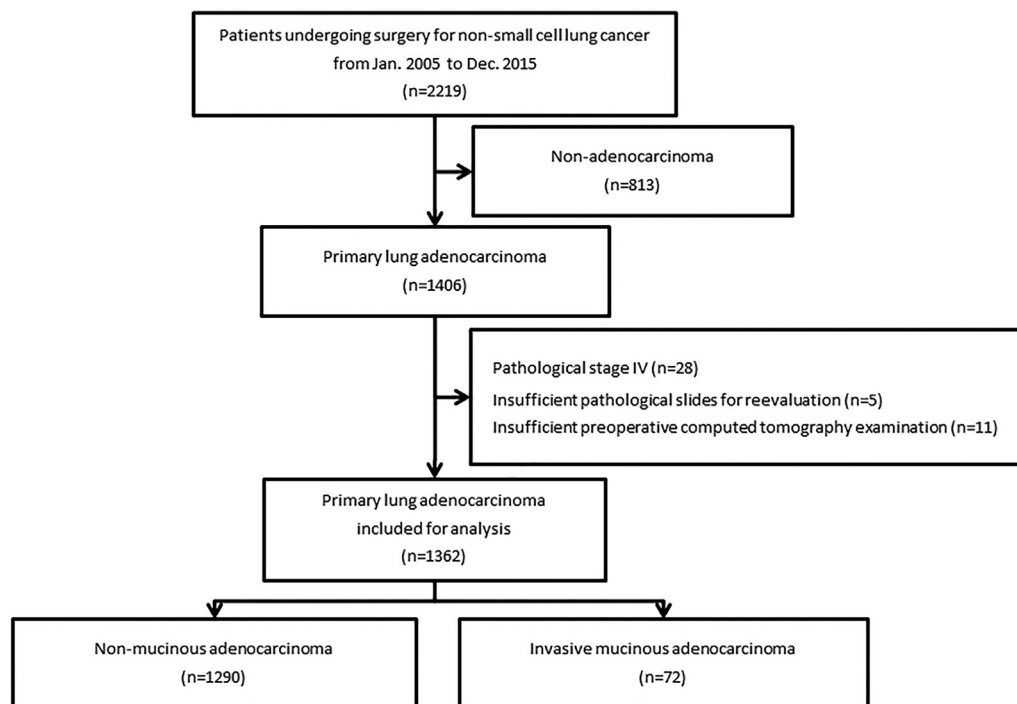
### Statistical Analysis

The Student  $t$  test, Mann-Whitney U test, and Fisher's exact test were used for comparisons between IMA and non-IMA groups. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method, while differences between groups were determined using the log-rank test. Multivariate survival analysis was performed using the Cox proportional hazards model. Variables with a  $P$  value of less than .01 on univariate analysis were used as input for multivariate analysis. Furthermore, propensity score matching was utilized to balance the number of eligible patients. Clinicopathologic variables, such as age, sex, side, year of surgery, smoking status, cardiopulmonary comorbidities, pulmonary function, carcinoembryonic antigen level, tumor location, clinical T factor, clinical N factor, induction therapy, surgical procedure, and adjuvant therapy, were multiplied by a coefficient calculated using logistic regression analysis. The sum of the values was taken as the propensity score for each patient. Those with IMA and non-IMA who had equivalent propensity scores were selected through 1-to-1 matching to better determine perioperative outcomes among the groups. Propensity scores were matched to two decimal places. All statistical analyses were performed using JMP for Windows (version 13.0, SAS Institute, Cary, NC). All  $P$  values were 2-sided, with  $P < .05$  being considered statistically significant.

## Results

Clinicopathologic features of overall patients in the IMA and non-IMA group are presented in Table 1. A total of 57 (79%) and 1051 (81%) cases in the IMA and non-IMA group completed follow-up, respectively. Preoperative CT patterns of the IMA group revealed 44 nodular-type cases (61%; Figure 2A) and 28 pneumonia-type cases (39%; Figure 2B). The average tumor size on preoperative CT was 42 mm (range, 10-107 mm), with nodular and pneumonia types having an average size of 26 (10-86) and 66 (32-107) mm, respectively. Lobectomy was performed most frequently (54 cases, 75%), although none of the cases required pneumonectomy. No patient received induction therapy, while 19 (26%) received adjuvant chemotherapy. Lymph node metastasis was positive in 3 (4%) cases (N1 in 1 [1%] case and N2 in 2 [3%] cases). Genetically, EGFR and KRAS mutations were observed in 1 (1%) and 40 (56%) cases, respectively. A total of 23 (32%) cases developed postoperative recurrence, and 17 (24%) cases died 5 years after surgery. Among the 23 cases that developed recurrence, 18 (78%) and 5 (22%) were

Figure 1. Flow chart showing patient selection.



pneumonia and nodular type, respectively. Among the 18 cases of recurrent pneumonia-type IMA, 17 were intrapulmonary and only 1 was pleural. The 5-year DFS and OS rates were 62% and 74%, respectively, with significant differences in 5-year DFS and OS according to pathologic stage (Figures 3A, 3B). Moreover, pneumonia-type cases had significantly worse 5-year DFS and OS rates than nodular-type cases (Figures 3C, 3D).

Overall, the IMA group had lower carcinoembryonic antigen levels (3 vs 8 ng/mL;  $P < .01$ ), fewer lymph node metastasis (4% vs 24%;  $P < .01$ ), fewer *EGFR* mutations (1% vs 47%;  $P < .01$ ), and more *KRAS* mutations (56% vs 7%;  $P < .01$ ) than the non-IMA group (Table 1). No significant difference in resection status was observed between both groups ( $P = .83$ ), although the non-IMA group included 42 (3%) cases with R1 resection and 9 (1%) cases with R2 resection. The non-IMA group had 346 (27%) postoperative recurrences and 197 (15%) deaths 5 years after surgery. No difference in postoperative recurrence rates was observed between the groups (32% vs 27%;  $P = .35$ ), although intrapulmonary recurrence was more frequent (83% vs 17%;  $P < .01$ ) and distant organ recurrence less frequent (4% vs 42%;  $P < .01$ ) in the IMA group.

Univariate analysis identified 4 prognostic factors affecting 5-year DFS and OS rates among patients with IMA (Table 2). In particular, pneumonia pattern on CT (hazard ratio [HR] 8.80, 95% confidence interval [CI] 3.72 to 24.2;  $P < .01$ ) was identified as a significant predictor of 5-year DFS, whereas pathologic tumor size ( $>70$  mm; HR 9.65, 95% CI, 3.65 to 28.1;  $P < .01$ ) was determined to be a significant predictor of 5-year OS. Multivariate analysis showed that pneumonia pattern on CT (HR 5.24, 95% CI, 1.55 to 17.6;  $P < .01$ ), pathologic tumor size ( $>70$  mm; HR

8.10, 95% CI, 2.40 to 37.3;  $P < .01$ ), and histologic differentiation ( $\geq G2$ ; HR 7.82, 95% CI, 2.76 to 28.3;  $P < .01$ ) were significant predictors of 5-year DFS, and pathologic tumor size ( $>70$  mm; HR 13.80, 95% CI, 2.37 to 270;  $P < .01$ ) and histologic differentiation ( $\geq G2$ ; HR 8.53, 95% CI, 2.29 to 55.7;  $P < .01$ ) were significant predictors of 5-year OS.

Table 3 shows the characteristics of propensity score-matched pairs in the IMA and non-IMA group. Propensity score-matched pair analysis also showed that the IMA group had fewer lymph node metastases (3% vs 35%;  $P < .01$ ), fewer *EGFR* mutations (2% vs 41%;  $P < .01$ ), more *KRAS* mutations (56% vs 9%;  $P < .01$ ), and more frequent lung recurrence (84% vs 31%;  $P < .01$ ) than the non-IMA group.

No significant differences in the 5-year DFS (62% vs 61%;  $P = .92$ ) and OS (74% vs 81%;  $P = .26$ ) were observed between the 2 groups (Figures 4A, 4B). However, the 5-year OS rate for intrapulmonary IMA recurrence was comparable to that of distant multiple-organ non-IMA recurrence (31% vs 29%) and worse than that of distant single-organ non-IMA recurrence (31% vs 47%;  $P < .01$ ) (Figure 4C). Furthermore, among patients who had lung recurrence, those in the IMA group had significantly worse 5-year OS than those in the non-IMA group (35% vs 77%;  $P < .01$ ) (Figure 4D). Among the entire cohort, 369 (27%) postoperative recurrences and 214 (16%) deaths 5 years after surgery were noted.

## Comment

Previous studies have frequently investigated mucinous BACs, given their characteristic clinical features and biological background.<sup>10-12</sup> Similarly, with the

Table 1. Clinicopathologic Factors of Overall Patients (N = 1362)

Characteristics	IMA (n = 72)	non-IMA (n = 1290)	
Age, y	66.4 (± 9.2)	64.8 (± 9.9)	.168
Sex, male	34 (47)	633 (49)	.809
Follow-up, y	5.3 (± 2.5)	5.4 (± 3.2)	.683
Smoking, never	29 (40)	650 (50)	.109
Brinkman index	388 (± 475)	423 (± 587)	.514
Carcinoembryonic antigen, ng/mL	3.0 (± 3.7)	8.3 (± 39.3)	.002
Tumor location lobe			<.001
Right upper, right middle	4 (6), 5 (7)	413 (32), 80 (6)	
Right lower, left upper	25 (35), 5 (7)	264 (21), 314 (24)	
Left lower, other	26 (36), 7 (9)	178 (14), 41 (3)	
Tumor size on CT, mm	42 (± 26)	27 (± 13)	<.001
Clinical stage			<.001
IA, IB, IIA	32 (44), 14 (20), 10 (14)	832 (64), 267 (21), 89 (7)	
IIB, IIIA, IV	11 (15), 4 (6), 1 (1)	27 (2), 71 (5), 4 (1)	
Induction therapy	0 (0)	20 (2)	>.999
Surgical procedure			<.001
Wedge resection, segmentectomy	7 (10), 5 (7)	120 (9), 146 (11)	
Lobectomy, bilobectomy	54 (75), 6 (8)	995 (77), 17 (2)	
Pneumonectomy	0 (0)	12 (1)	
Pathological tumor size, mm	41 (± 31)	25 (± 13)	<.001
Pathological stage			<.001
IA, IB, IIA	31 (43), 16 (23), 6 (8)	590 (45), 334 (26), 113 (9)	
IIB, IIIA, IIIB	15 (21), 3 (4), 1 (1)	49 (4), 198 (15), 6 (1)	
Pathological node status			<.001
Positive, negative, NA	3 (4), 62 (86), 7 (10)	306 (24), 856 (66), 128 (10)	
Resection status value			.831
R0, R1, R2	71 (99), 1 (1), 0 (0)	1239 (96), 42 (3), 9 (1)	
Histologic differentiation			<.001
G1 (well), G2 (moderate)	29 (40), 42 (59)	304 (24), 672 (52)	
G3 (poorly), NA	1 (1), 0 (0)	285 (22), 29 (2)	
EGFR mutation			<.001
Positive, negative, NA	1 (1), 71 (99), 0 (0)	608 (47), 528 (41), 154 (12)	
KRAS mutation			<.001
Positive, negative, NA	40 (56), 32 (44), 0 (0)	90 (7), 1033 (80), 167 (13)	
Adjuvant chemotherapy	19 (26)	374 (29)	.69
Postoperative recurrence	23 (32)	346 (27)	.353
Recurrence location			<.001
Lung, mediastinal lymph node	19 (83), 0 (0)	58 (17), 41 (12)	
Pleural cavity, distant single organ	3 (13), 1 (4)	56 (16), 77 (22)	
Distant multiple organs, NA	0 (0), 0 (0)	70 (20), 44 (13)	
First therapy after recurrence			<.001
Resection, chemotherapy	4 (17), 11 (48)	17 (5), 82 (24)	
Molecular-targeted therapy	0 (0)	127 (36)	
Immunotherapy, radiation	1 (4), 0 (0)	0 (0), 87 (26)	
Best supportive care, NA	7 (31), 0 (0)	17 (5), 16 (4)	
Prognosis, death	17 (24)	197 (15)	.067

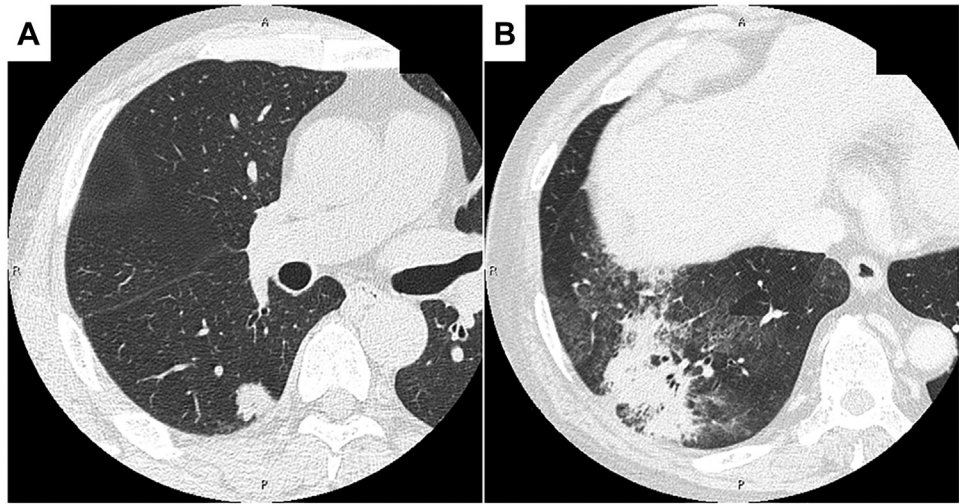
Values are presented as n (%) or mean (± SD).

CT, computed tomography; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; NA, not applicable.

establishment of the revised adenocarcinoma classification, several IMA studies have also been reported.<sup>6-9</sup> At our institution, the pneumonia type, considered to be

typical for IMA, was rather infrequent, with 28 cases (39%), whereas the nodular type comprised the majority, with 44 (61%) cases. Lee and associates<sup>9</sup> reported that

Figure 2. Preoperative computed tomography patterns of nodular type (A) and pneumonia type (B) invasive mucinous adenocarcinoma.



pneumonia types constituted only 19 (23%) of 82 IMA cases, further stating that the pneumonia-type IMAs were often clinically and pathologically advanced and tended to have poorer prognosis than nodular types.<sup>9</sup> Similarly, the present study showed that pneumonia types had poorer 5-year DFS and OS rates than nodular types. The proportion of pneumonia-type IMAs in our cohort was higher relative to those in previous reports, the reason for which remains unclear. Consequently, the significant differences in the 5-year DFS and OS rates observed between both types may have been influenced by the higher proportion of pneumonia-type IMAs. Considering that pneumonia-type IMAs are likely to be clinically misdiagnosed as intractable pneumonia and, in fact, may be treated in the long term with antibiotics, surgical intervention may be delayed, resulting in significantly worse outcomes compared with nodular types.

A comparison of the clinical and pathologic stages showed that IMA cases had fewer stage migrations than non-IMA cases. This may be explained by the low frequency of lymph node metastasis among IMA cases, wherein only 3 (4%) were positive. Indeed, several reports have found low rates of lymph node metastasis in IMA,<sup>6,9,14,15</sup> although most have been small studies. Lee and colleagues<sup>9</sup> reported that 4 (5%) of 81 IMA resection cases were positive for lymph node metastasis, a result consistent with that presented herein. Our results suggest that IMA is unlikely to cause lymph node metastasis and that the T factor has a greater effect on postoperative outcomes. Therefore, IMA may be an effective candidate for local treatment, with surgical resection possibly having considerable efficacy.

Although many reports have been published regarding mucinous BACs, only a few have investigated postoperative recurrence of IMA.<sup>10-12</sup> The most frequent recurrence site for mucinous BAC has been the lungs, throughout which the tumors spread as pneumonia worsens, making surgical resection difficult in many cases.<sup>10,11</sup> Here, postoperative recurrence was observed in

23 (32%) cases, with the majority of the recurrence sites being the lungs. Shim and coworkers<sup>8</sup> reported that 14 (18%) of 79 IMA cases that had undergone resection had relapsed, all of which developed in the lungs. Regarding post-recurrence treatment, IMA has been reported to have poor response to *EGFR* tyrosine kinase inhibitors, as well as radiation, which limits the treatment options.<sup>12</sup> In clinical practice, chemotherapy is often provided for advanced cases, although its efficacy remains unknown.<sup>16,17</sup> The results of the present study suggested that patients with intrapulmonary IMA recurrence had similar prognosis as those with distant multiple-organ non-IMA recurrence, which results in treatment difficulties after recurrence. In particular, among patients with intrapulmonary recurrence, those in the non-IMA group had relatively better prognosis than those in the IMA group. New effective and versatile treatments for postoperative IMA recurrence should therefore be established.

Multivariate analysis conducted for our study identified CT pattern (pneumonia type), pathologic tumor size (>70 mm), and histologic differentiation ( $\geq G2$ ) as prognostic factors. However, CT pattern (pneumonia type) was identified as a prognostic factor only for 5-year DFS and not for 5-year OS. Furthermore, we were unable to determine the standardized uptake value given that more than half of the patients did not undergo positron emission tomography.

Several study limitations of the present study should be considered. First, this was a single-center retrospective study that limited its analysis to records of patients who had undergone surgery. Second, given the smaller number of cases in the IMA group than in the non-IMA group, the significance of the differences between both groups may not be as reliable as that in a study with a larger sample size. Third, discrimination between pneumonia and nodular types on preoperative CT may have been influenced by observer bias, which may lead to variations in the reproducibility of the results.

In conclusion, our results showed that intrapulmonary recurrence was approximately five times

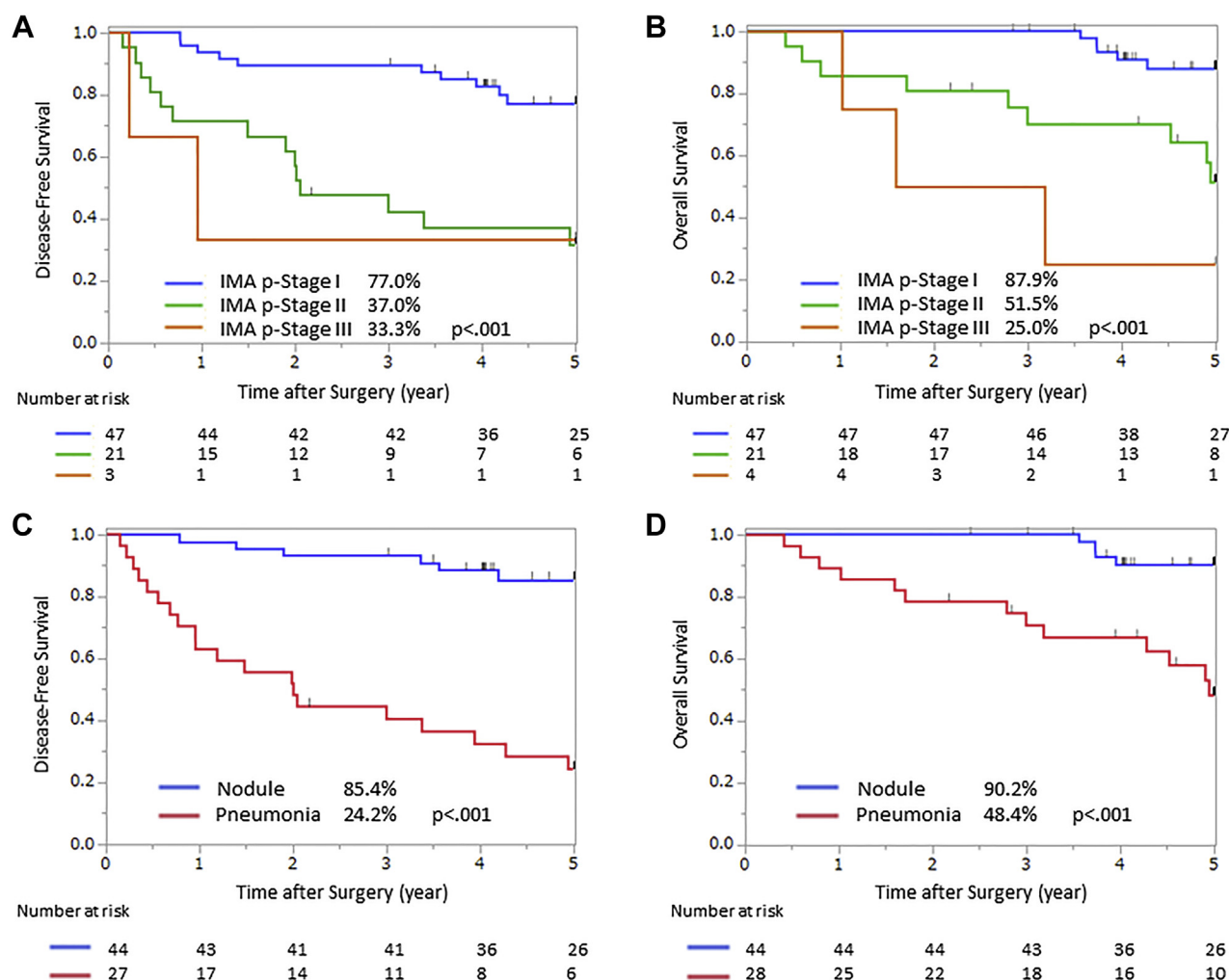


Figure 3. Five-year disease-free survival (DFS) (A) and overall survival (OS) (B) curves for patients with invasive mucinous adenocarcinoma (IMA) according to pathologic stages: stage I [IMA p-Stage I (blue)], stage II [IMA p-Stage II (green)], and stage III [IMA p-Stage III (orange)]. Five-year DFS (C) and OS (D) curves for patients with IMA according to preoperative computed tomography patterns: nodular type [Nodule (blue)] and pneumonia type [Pneumonia (red)].

Table 2. Cox Proportional Hazards Analysis for Disease-Free Survival and Overall Survival Among Patients With Invasive Mucinous Adenocarcinoma

Disease-Free Survival						
Prognostic Factors	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
CT pattern, pneumonia	8.80	3.72-24.2	<.001	5.24	1.55-17.6	.009
Pathologic tumor size, >70 mm	7.49	3.39-16.6	<.001	8.10	2.40-37.3	<.001
Pathologic stage, ≥II	4.72	2.16-10.8	<.001	2.16	0.10-1.76	.266
Histologic differentiation, ≥G2	5.03	1.92-17.2	<.001	7.82	2.76-28.3	<.001
Overall Survival						
Prognostic Factors	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P Value	HR	95% CI	P Value
CT pattern, pneumonia	6.65	2.35-23.7	<.001	1.49	0.19-8.44	.673
Pathologic tumor size, >70mm	9.65	3.65-28.1	<.001	13.80	2.37-270	<.001
Pathologic stage, ≥II	6.04	2.23-19.0	<.001	1.64	0.22-34.1	.659
Histologic differentiation, ≥G2	6.45	1.82-41.0	.002	8.53	2.29-55.7	<.001

CI, confidence interval; CT, computed tomography; HR, hazard ratio.

Table 3. Clinicopathologic Factors of Propensity Score–Matched Pairs

Characteristics	Propensity Score–Matched Pairs (N = 132)		P Value
	IMA (n = 66)	non-IMA (n = 66)	
Age, y	66.4 (± 9.1)	67.5 (± 8.6)	.554
Sex, male	31 (47)	36 (55)	.486
Follow-up, y	5.5 (± 2.5)	5.4 (± 3.0)	.602
Smoking, never	27 (41)	27 (41)	>.999
Brinkman index	398 (± 485)	596 (± 715)	.277
Carcinoembryonic antigen, ng/mL	3.1 (± 3.8)	3.8 (± 8.5)	.426
Tumor location lobe			.978
Right upper, right middle	4 (6), 5 (8)	4 (6), 5 (8)	
Right lower, left upper	22 (33), 5 (8)	19 (29), 5 (8)	
Left lower, other	24 (36), 6 (9)	24 (36), 9 (13)	
Tumor size on CT, mm	37 (± 23)	30 (± 14)	.167
Clinical stage			.833
IA, IB, IIA	32 (49), 14 (21), 10 (15)	29 (44), 16 (24), 10 (15)	
IIB, IIIA, IV	6 (9), 4 (6), 0 (0)	4 (6), 7 (11), 0 (0)	
Induction therapy	0 (0)	3 (5)	.244
Surgical procedure			.698
Wedge resection, segmentectomy	7 (11), 5 (8)	8 (12), 5 (8)	
Lobectomy, bilobectomy	49 (73), 5 (8)	44 (67), 9 (13)	
Pneumonectomy	0 (0)	0 (0)	
Pathologic tumor size, mm	37 (± 28)	29 (± 17)	.350
Pathologic stage			.024
IA, IB, IIA	31 (47), 15 (23), 5 (8)	24 (36), 12 (18), 10 (15)	
IIB, IIIA, IIIB	12 (18), 3 (4), 0 (0)	6 (9), 13 (20), 1 (2)	
Pathologic node status			<.001
Positive, negative, NA	2 (3), 57 (86), 7 (11)	23 (35), 35 (53), 8 (12)	
Resection status value			.119
R0, R1, R2	66 (100), 0 (0), 0 (0)	62 (94), 4 (6), 0 (0)	
Histologic differentiation			<.001
G1 (well), G2 (moderate)	27 (41), 38 (57)	11 (17), 36 (54)	
G3 (poorly), NA	1 (2), 0 (0)	17 (26), 2 (3)	
EGFR mutation			<.001
Positive, negative, NA	1 (2), 65 (98), 0 (0)	27 (41), 31 (47), 8 (12)	
KRAS mutation			<.001
Positive, negative, NA	36 (56), 30 (44), 0 (0)	6 (9), 51 (78), 9 (13)	
Adjuvant chemotherapy	17 (26)	20 (30)	.699
Postoperative recurrence	19 (29)	22 (33)	.707
Recurrence location			<.001
Lung, mediastinal lymph node	16 (84), 0 (0)	7 (31), 3 (14)	
Pleural cavity, distant single organ	2 (11), 1 (5)	3 (14), 3 (14)	
Distant multiple organs, NA	0 (0), 0 (0)	5 (22), 1 (5)	
First therapy after recurrence			<.001
Resection, chemotherapy	5 (26), 7 (37)	2 (9), 5 (23)	
Molecular-targeted therapy	0 (0)	6 (27)	
Immunotherapy, radiation	0 (0), 0 (0)	0 (0), 6 (27)	
Best supportive care, NA	7 (37), 0 (0)	1 (5), 2 (9)	
Prognosis, death	14 (21)	14 (21)	>.999

Values are presented as n (%) or mean (± SD).

CT, computed tomography; EGFR, epidermal growth factor receptor; IMA, invasive mucinous adenocarcinoma; NA, not applicable.

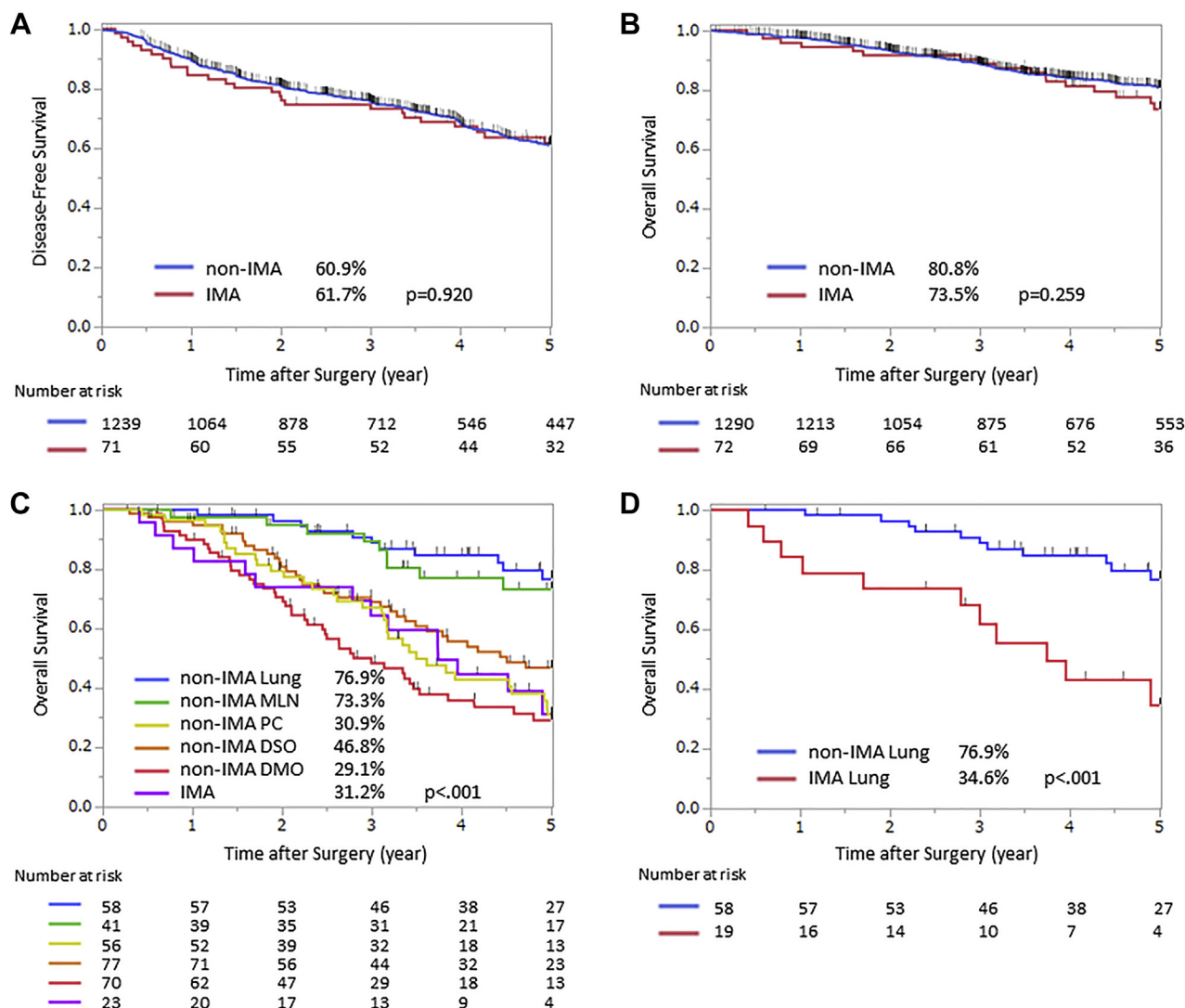


Figure 4. Comparison of the 5-year disease-free survival (A) and overall survival (OS) (B) curves between the invasive mucinous adenocarcinoma (IMA) group [IMA (red)] and non-IMA group [non-IMA (blue)]. (C) Comparison of the 5-year OS curves between the IMA and non-IMA groups according to recurrence locations: intrapulmonary recurrence in the non-IMA group [non-IMA Lung (blue)], mediastinal lymph node (MLN) recurrence in the non-IMA group [non-IMA MLN (green)], pleural cavity (PC) recurrence in the non-IMA group [non-IMA PC (yellow)], distant single-organ (DSO) recurrence in the non-IMA group [non-IMA DSO (orange)], and distant multiple-organ (DMO) recurrence in the non-IMA group [non-IMA DMO (red)] and IMA group [IMA (purple)]. (D) Comparison of the 5-year OS curves between the IMA group [IMA Lung (red)] and non-IMA group [non-IMA Lung (blue)] according to intrapulmonary recurrence.

more likely to occur in the IMA group than in the non-IMA group and that prognosis for intrapulmonary IMA recurrence was similar to that for distant multiple-organ non-IMA recurrence. We believe that the presented findings would be considerably helpful in daily clinical practice.

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## Notice From the American Board of Thoracic Surgery

The 2021 Part I (written) qualifying examination will be held **Monday, December 13, 2021**, at multiple sites throughout the United States using an electronic format. The closing date for applications is **August 15, 2021**. Those wishing to be considered for examination must apply by logging in to their ABTS portal online at [www.abts.org](http://www.abts.org).

A candidate applying for admission to the Part I (written) qualifying examination must fulfill all the requirements of the Board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery at (312) 202-5900 or [info@abts.org](mailto:info@abts.org).