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Prognosis of resected invasive mucinous adenocarcinoma compared with the IASLC histologic grading system for invasive nonmucinous adenocarcinoma: Surgical database study in the TKIs era in Korea

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Abstract

Background: The prognosis of invasive mucinous adenocarcinoma (IMA) remains controversial and should be clarified by comparison with the International Association for the Study of Lung Cancer (IASLC) histologic grading system for invasive nonmucinous adenocarcinoma (INMA).

Methods: This study included patients with IMA who underwent curative resection. Their clinicopathological outcomes were compared with those of patients with INMA. Propensity score matching was performed to compare the prognosis of IMA with IASLC grade 2 or 3. Kaplan–Meier survival curves and log-rank tests were used to analyze recurrence-free survival (RFS) and overall survival (OS).

Results: The prognoses of IMA and IASLC grade 2 were similar in terms of RFS and OS. Although patients with IMA had better RFS than patients with IASLC grade 3, the OS was not significantly different. After propensity score matching, IMA demonstrated similar RFS to IASLC grade 2 but superior to IASLC grade 3; there was no difference in the OS compared with grades 2/3. Multivariate analysis revealed that tumor size (hazard ratio [HR] = 1.20, $p = 0.028$), lymphovascular invasion (HR = 127.5, $p = 0.003$), and maximum standardized uptake value (HR = 1.24, $p = 0.005$) were poor prognostic predictors for RFS. Patients with IMA demonstrated RFS similar to and significantly better than that of patients with IASLC grades 2 and 3, respectively. For OS, IMA prognosis was between that of IASLC grades 2 and 3.

Conclusions: Since the prognosis of IMA among lung adenocarcinomas appears to be relatively worse, further clinical studies investigating IMA-specific treatment and follow-up plans are necessary to draw more inferences.

KEYWORDS
classification, lung adenocarcinoma, mucinous adenocarcinoma, pathologic subtype, prognosis

INTRODUCTION

Invasive mucinous adenocarcinoma (IMA) is histopathologically characterized by tumors with goblet or columnar cells

Wongi Woo and Young Ho Yang are considered as Co-first authors.

containing abundant intracytoplasmic mucin.[1] IMA is a rare variant of adenocarcinoma, accounting for approximately 5% of all pulmonary adenocarcinomas (ADCs).[2] In the 2011 lung adenocarcinoma classification system by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS), IMAs were classified as invasive ADC variants.[3] Moreover, according to the 2015 World Health Organization (WHO) classification, IMA is an invasive ADC variant.[4]

In June 2020, the IASLC pathology committee proposed a new histologic grading system for invasive pulmonary ADC[5] taking into account predominant histologic and high-grade patterns based on the 2015 WHO classification.[4] This grading system classifies any tumor with ≥20% high-grade patterns, including solid, micropapillary, and complex glandular patterns, as IASLC grade 3. Moreover, three further validation studies confirmed that this grading system provides significant prognostication.[5–8] However, IMA differs from invasive nonmucinous adenocarcinoma (INMA) because of major clinical, radiologic, pathologic, and genetic differences. Therefore, IMA was excluded from this grading system.

The prognosis of IMA remains controversial. Russell et al.[9] and Amin et al.[10] suggested that IMAs are usually associated with poor survival outcomes. In contrast, Warth et al.[11] reported that IMAs had better prognosis than conventional INMA. It is necessary to confirm the prognosis of IMA by comparing it with INMA based on the new grading system. This study aimed to compare the prognosis between patients with IMA and those with INMA classified according to the IASLC histologic grading system and review the clinicopathologic and radiologic features of surgically resected IMA tumors.

METHODS

Study population

The institutional review boards of two institutions (Hospital A: approval No. 4-2021-1633; Hospital B: approval No. 3–2021-0509) approved this study. The requirement for informed consent was waived owing to the study's retrospective design.

Of the 3132 patients who underwent curative resection for lung cancer between 2012 and 2017 in both hospitals, 2323 lung ADCs were identified. Of these, 853 were excluded for the following reasons[1]: previous cancer history ($n = 434$),[2] concomitant presence of other malignancies in the lung ($n = 112$),[3] neoadjuvant treatment ($n = 45$),[4] incomplete resection ($n = 4$), and[5] 30-day mortality ($n = 5$). Patients with the following types of ADC were also excluded: mixed invasive mucinous and nonmucinous ADC ($n = 16$), ADC in situ or minimally invasive ADC ($n = 202$), and semiquantitative assessment not reported ($n = 34$). Ultimately, 112 patients with completely resected solitary IMAs and 1358 patients with INMA were included in this study (Supplementary Figure S1).

Data on clinical presentation, tumor stage, surgical treatment methods, and survival outcomes were obtained from electronic medical records. The tumor, node, and metastatic stages for each lung cancer were determined according to the eighth edition of the Cancer Staging Manual of the American Joint Committee on Cancer.[10] The survival and disease progression were also assessed according to medical records and data from the Korea National Statistical Office.

Pathologic evaluation

Two experienced lung pathologists (Y.C. and H.S.S.) interpreted all the tissue sections. The histopathologic criteria for IMA included tumor cells with a goblet or columnar cell morphological pattern with abundant intracytoplasmic mucin. In case of INMAs, histologic subtyping was carried out according to the 2011 IASLC/ATS/ERS and 2015 WHO classifications. The percentage of each histologic component was recorded in 5% increments (lepidic, acinar, papillary, micropapillary, and solid). In addition, we analyzed and scored the complex glandular patterns. Discrepancies in classification were resolved through consensus discussion.

Tumor spread through air spaces (STAS) was defined as the presence of tumor cells within the lung parenchyma's air spaces beyond the primary tumor's edge. Nonmucinous tumors were categorized into three subgroups based on the new histologic grading system of the IASLC: grade 1, lepidic predominant tumor with no or <20% of high-grade patterns; grade 2, acinar or papillary predominant tumor, both with no or <20% of high-grade patterns; and grade 3, any tumor with ≥20% high-grade patterns (solid, micropapillary, and complex glandular patterns).

Statistical analysis

For continuous variables (age, pathologic size, and pulmonary function test), we present data as median and interquartile range after their normality was checked. They were later compared using the Mann–Whitney *U* test. Fisher's exact test was used to compare categorical variables of IMA and INMA. Overall survival (OS) was defined as the time from surgery to death from any cause or censored at the last follow-up. Recurrence-free survival (RFS) was defined as the time from surgery to recurrence or death from any cause or censored at the last follow-up. RFS and OS were estimated using the Kaplan–Meier method. The log-rank test and pairwise comparison using the Holm method were used to evaluate the differences among subgroups.

To adjust unbalanced compounding variables, a propensity score matching method was used to compare IMA and IASLC grades 2 and 3. The propensity score for each participant was measured using a logistic model that included the following variables: age, sex, comorbidities (diabetes mellitus

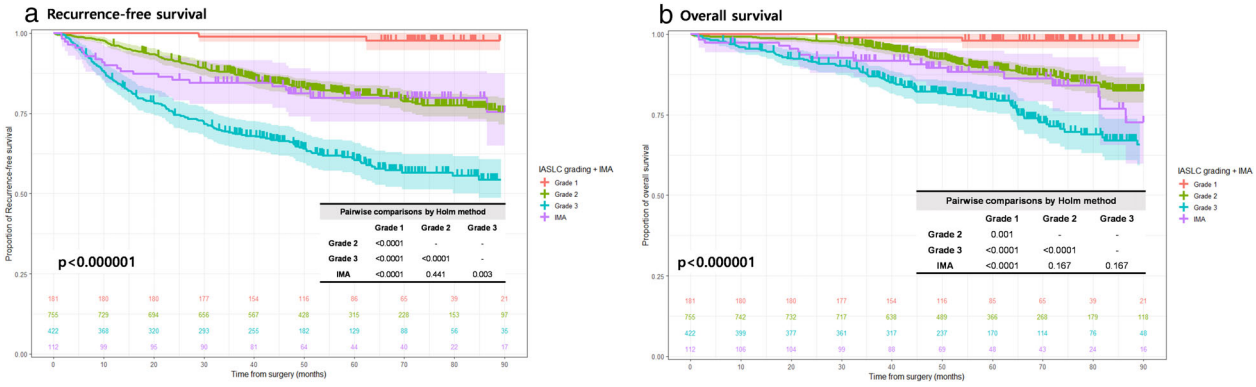

FIGURE 1 Recurrence-free (a) and overall (b) survival curves of patients with IMA and INMA (IASLC grades 1–3). IALSC, International Association for the Study of Lung Cancer; INMA, invasive non-mucinous adenocarcinoma; IMA, invasive mucinous adenocarcinoma

and hypertension), smoking history, pathologic tumor size, and pathologic nodal stages. Then, nearest-neighbor matching within 0.2 caliper width without replacement was used to perform 1:1 matching of patients in the two groups.

Multivariate Cox proportional hazards regression was performed to identify RFS and OS risk factors among patients with IMA. Variables with a p value <0.10 on univariate analysis were used as the input variables for the multivariable Cox regression analysis. Statistical analyses were performed using R version 4.0.4 (R Core Team, Vienna, Austria). Statistical significance was set at ≤0.05.

RESULTS

Patient baseline characteristics

Compared to patients with INMA ($n = 1358$, IASLC grades 1–3), patients with IMA ($n = 112$) had similar characteristics in all clinical variables other than the primary lesion location ($p < 0.001$). IMA was more frequently observed in the lower lobes (Table 1). According to histopathologic results, IMA demonstrated lower nodal stages ($p < 0.001$), lower frequency of lymphovascular invasion ($p < 0.001$), and visceral pleural invasion ($p < 0.001$) than INMA; however, positivity in STAS was more frequently observed in IMA than in INMA (Table 2). Generally, the stage I portion was lower in patients that underwent curative resection ($p = 0.049$). There was no difference between the two groups in the number of recurrences, deaths, or patients who underwent adjuvant treatments. The specific recurrence sites and causes of death are described in Supplementary Table S1 and S2.

Survival analyses between IMAs and INMA

Figure 1 shows the survival curves for patients with IMA or INMA (IASLC grade 1–3). Patients with IMA demonstrated similar RFS to patients with IASLC grade 3 in the early postoperative period (within 10 months), but the difference became evident in the long term (Figure 1a). Finally, patients with IMA had a superior prognosis to patients with IASLC grade 3 ($p = 0.003$), but similar to patients with IASLC grade 2 ($p = 0.441$). With respect to OS, patients with IMA had a worse outcome than patients with IASLC grade 1 ($p < 0.0001$), but it was not significantly different from patients with IASLC grade 2 ($p = 0.167$) or 3 ($p = 0.167$) INMA (Figure 1b). Patients with IMA had a prognosis similar to that of patients with IASLC grades 2 and 3 in terms of OS.

Clinical outcomes between IMA and IASLC grade 2–3 after propensity score matching

Table 3 describes the clinicopathological characteristics of patients with IMA and IASLC grade 2 after propensity score matching. Compared to patients with IASLC grade 2, those with IMA had more lesions in the lower lobes ($p < 0.001$) and STAS positivity ($p < 0.001$). The Kaplan–Meier curves for RFS ($p = 0.628$) and OS ($p = 0.585$) did not differ between the two groups (Figure 2a,b).

Compared to patients with IASLC grade 3 after adjusting for covariates (Table 4), the FEV1/FVC ratio was slightly higher with fewer lobar lesions in the patients with IMA. However, lymphovascular ($p < 0.001$) and visceral pleural invasion ($p < 0.001$) were less frequently detected in patients with IMA. STAS did not differ between the two groups. With respect to RFS, patients with IMA had a superior outcome compared to patients with IASLC grade 3 (Figure 2c, $p = 0.026$), but the difference was not observed in OS (Figure 2d, $p = 0.342$).

Identification of prognostic factors for RFS among patients with IMA

In univariate analysis, sublobar resection, maximum standardized uptake value (SUVmax), lymphovascular invasion, tumor size, and nodal stage (N2 vs. N0) were considered as

TABLE 1 The clinical characteristics of mucinous and nonmucinous (IASLC grade 1–3) invasive pulmonary adenocarcinoma

Factor	IMA *N* = 112	INMA *N* = 1358	*p* value[a]	IASLC grading subgroups in INMA Grade 1 *n* = 181	 Grade 2 *n* = 755	 Grade 3 *n* = 422
Age	64.5 [56.8, 71.3]	63.0 [55.0, 71.0]	0.319	64.0 [58.0, 71.0]	63.0 [55.0, 70.0]	64.0 [55.0, 71.0]
Gender			0.844			
Female	57 (50.9)	707 (52.1)		97 (53.6)	444 (58.8)	166 (39.3)
Male	55 (49.1)	651 (47.9)		84 (46.4)	311 (41.2)	256 (60.7)
Diabetes mellitus	21 (18.8)	224 (16.5)	0.512	34 (18.8)	121 (16.0)	69 (16.4)
Hypertension	43 (38.4)	566 (41.7)	0.550	73 (40.3)	315 (41.7)	178 (42.2)
Smoking history			0.224			
Ex and current	36 (32.1)	520 (38.3)		66 (36.5)	239 (31.7)	215 (50.9)
Never	76 (67.9)	838 (61.7)		115 (63.5)	516 (68.3)	207 (49.1)
ECOG			0.913			
ECOG 0	98 (96.1)	1288 (95.9)		174 (96.1)	720 (96.4)	394 (94.9)
ECOG 1	3 (2.9)	36 (2.7)		2 (1.1)	20 (2.7)	14 (3.4)
ECOG 2	1 (1.0)	19 (1.4)		5 (2.8)	7 (0.9)	7 (1.7)
FEV1 (%)	106.0 [93.0, 118.5]	104.0 [93.0, 114.8]	0.442	103.0 [94.0, 118.8]	105.0 [95.0, 115.0]	101.0 [90.8, 113.0]
FEV1/FVC ratio (%)	77.0 [73.2, 80.9]	76.0 [70.9, 80.0]	0.053	75.7 [71.0, 79.0]	76.0 [71.0, 81.0]	75.0 [69.0, 79.2]
Extent of surgery			0.330			
Wedge resection	6 (5.4)	62 (4.6)		15 (8.3)	36 (4.8)	11 (2.6)
Segmentectomy	3 (2.7)	74 (5.4)		25 (13.8)	39 (5.2)	10 (2.4)
Lobectomy	99 (88.4)	1195 (88.0)		140 (77.3)	671 (88.9)	384 (91.0)
Bilobectomy	4 (3.6)	21 (1.5)		0 (0.0)	9 (1.2)	12 (2.8)
Pneumonectomy	0 (0.0)	6 (0.4)		1 (0.6)	0 (0.0)	5 (1.2)
Primary site of lesion			<0.001			
LUL	12 (10.7)	316 (23.3)		47 (26.0)	168 (22.3)	101 (23.9)
LLL	45 (40.2)	214 (15.8)		24 (13.3)	113 (15.0)	77 (18.2)
RUL	6 (5.4)	437 (32.2)		69 (38.1)	247 (32.7)	121 (28.7)
RML	6 (5.4)	122 (9.0)		18 (9.9)	69 (9.1)	35 (8.3)
RLL	43 (38.4)	269 (19.8)		23 (12.7)	158 (20.9)	88 (20.9)

Note: All data are presented as *n* (%), *n*/*N* (%), or median [interquartile range (IQR)].

Abbreviations: ECOG, European Cooperative Oncology Group; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IASLC, International Association for the Study of Lung Cancer; IMA, invasive mucinous adenocarcinoma; INMA, invasive non-mucinous adenocarcinoma; LLL, Left lower lobe; LUL, Left upper lobe; RLL, Right lower lobe; RML, Right middle lobe; RUL, right upper lobe.

[a]*p* value was measured between IMA and total INMA.

TABLE 2 Clinical outcome and histopathologic findings of mucinous and nonmucinous (IASLC grades 1–3) invasive pulmonary adenocarcinoma

Factor	IMA $N = 112$	INMA $N = 1358$	p value[a]	IASLC grading subgroups in INMA		
				Grade 1 $n = 181$	Grade 2 $n = 755$	Grade 3 $n = 422$
Adjuvant treatment			0.913			
No	81 (72.3)	968 (71.3)		176 (97.2)	599 (79.3)	193 (45.7)
Yes	31 (27.7)	390 (28.7)		5 (2.8)	156 (20.7)	229 (54.3)
Death	16 (14.3)	189 (13.9)	0.672	4 (2.2)	87 (11.5)	98 (23.2)
Recurrence	15 (13.4)	260 (19.1)	0.165	0 (0.0)	121 (16.0)	139 (32.9)
Type of recurrence			0.213			
Loco-regional	5 (33.3)	65 (25.0)		0 (0.0)	30 (24.8)	33 (23.7)
Distant	4 (26.7)	112 (43.1)		0 (0.0)	58 (47.9)	68 (48.9)
Combined	6 (40.0)	83 (31.9)		0 (0.0)	33 (27.3)	38 (27.4)
Tumor size, cm	2.40 [1.50, 4.45]	2.20 [1.50, 3.00]	0.057	1.70 [1.30, 2.20]	2.10 [1.50, 2.80]	2.50 [1.80, 3.50]
TNM stage			0.125			
IA1	11 (9.8)	89 (6.6)		20 (11.0)	61 (8.1)	8 (1.9)
IA2	38 (33.9)	433 (31.9)		99 (54.7)	258 (34.2)	76 (18.0)
IA3	22 (19.6)	290 (21.4)		45 (24.9)	194 (25.7)	51 (12.1)
IB	8 (7.1)	242 (17.8)		13 (7.2)	141 (18.7)	88 (20.9)
IIA	8 (7.1)	35 (2.6)		0 (0.0)	19 (2.5)	16 (3.8)
IIB	13 (11.6)	111 (8.2)		3 (1.7)	44 (5.8)	64 (15.2)
IIIA	10 (8.9)	135 (9.9)		0 (0.0)	36 (4.8)	99 (23.5)
IIIB	2 (1.8)	23 (1.7)		1 (0.6)	2 (0.3)	20 (4.7)
Nodal stages			<0.001			
N0	108 (96.4)	1127 (83.0)		178 (98.3)	691 (91.5)	258 (61.1)
N1	0 (0.0)	103 (7.6)		2 (1.1)	38 (5.0)	63 (14.9)
N2	4 (3.6)	128 (9.4)		1 (0.6)	26 (3.4)	101 (23.9)
Lymphovascular invasion			<0.001			
No	107 (95.5)	1121 (82.5)		181 (100.0)	692 (91.7)	248 (58.8)
Yes	5 (4.5)	237 (17.5)		0 (0.0)	63 (8.3)	174 (41.2)
Perineural invasion			0.616			
No	112 (100.0)	1345 (99.0)		181 (100.0)	748 (99.1)	416 (98.6)
Yes	0 (0.0)	13 (1.0)		0 (0.0)	7 (0.9)	6 (1.4)
Visceral pleural invasion			<0.001			
No	106 (94.6)	1073 (79.0)		178 (98.3)	629 (83.3)	266 (63.0)
Yes	6 (5.4)	285 (21.0)		3 (1.7)	126 (16.7)	156 (37.0)
Spread through air spaces[b]			<0.001			
Negative	17 (33.3)	524 (69.5)		117 (100.0)	342 (81.6)	65 (29.8)
Positive	34 (66.7)	230 (30.5)		0 (0.0)	77 (18.4)	153 (70.2)
Follow-up periods, months	58.7 [43.6, 75.7]	59.1 [43.3, 74.1]	0.803	59.3 [43.5, 75.4]	59.7 [45.3, 78.1]	54.0 [40.1, 71.2]

Note: All data are presented as *n* (%), *n*/*N* (%), or median [interquartile range (IQR)].

Abbreviations: IASLC, International Association for the Study of Lung Cancer; IMA, invasive mucinous adenocarcinoma; INMA, invasive nonmucinous adenocarcinoma; TNM, tumor nodes and metastases .

[a]*p* value was measured between IMA and total INMA.

[b]Data were available: 45.5% (51/112) in IMA and 55.5% (754/1358) in INMA.

input variables for RFS. The multivariate Cox proportional hazards analysis revealed that tumor size (hazard ratio [HR] = 1.20, 95% confidence interval [CI] 1.02–1.40, $p = 0.028$), lymphovascular invasion (HR = 127.5, 95% CI 5.22–3116, $p = 0.003$), and SUVmax (HR = 1.24, 95% CI 1.07–1.43, $p = 0.005$) were significant independent poor prognostic predictors for RFS (Table 5).

DISCUSSION

Clinical investigations for IMAs are scarce, despite there being several studies on INMAs assessing the prognostic value of histologic patterns,[9–16] including a recently proposed IASLC grading system.[5] With the introduction of the new IASLC classification, the heterogeneity in INMAs was

TABLE 3 Clinicopathologic characteristics of IMA and IASLC grade 2 after propensity score matching

Factor	IMA $N = 100$	IASLC grade 2 $N = 100$	p value
Age	64.00 [55.75, 71.00]	64.00 [56.00, 70.00]	0.909
Gender			0.572
Female	52 (52.0)	47 (47.0)	
Male	48 (48.0)	53 (53.0)	
Diabetes mellitus	19 (19.0)	17 (17.0)	0.854
Hypertension	38 (38.0)	34 (34.0)	0.659
Smoking history			0.644
Ex and current	32 (32.0)	28 (28.0)	
Never	68 (68.0)	72 (72.0)	
ECOG			0.835
ECOG 0	87 (95.6)	97 (97.0)	
ECOG 1	3 (3.3)	3 (3.0)	
ECOG 2	1 (1.1)	0 (0.0)	
FEV1, %	106.0 [94.0, 119.5]	106.0 [96.0, 115.0]	0.944
FEV1/FVC ratio, %	78.0 [73.7, 80.9]	75.0 [70.8, 81.0]	0.102
Extent of surgery			0.444
Wedge resection	6 (6.0)	3 (3.0)	
Segmentectomy	3 (3.0)	7 (7.0)	
Lobectomy	88 (88.0)	86 (86.0)	
Bilobectomy	3 (3.0)	4 (4.0)	
Location of primary lesion			<0.001
LLL	40 (40.0)	19 (19.0)	
LUL	10 (10.0)	21 (21.0)	
RLL	39 (39.0)	24 (24.0)	
RML	6 (6.0)	7 (7.0)	
RUL	5 (5.0)	29 (29.0)	
Hospital (%)			0.459
Hospital A	68 (68.0)	62 (62.0)	
Hospital B	32 (32.0)	38 (38.0)	
Tumor size	2.20 [1.40, 3.23]	2.00 [1.50, 3.50]	0.836
Lymphovascular invasion			1
No	96 (96.0)	97 (97.0)	
Yes	4 (4.0)	3 (3.0)	
Visceral pleural invasion			0.051
No	95 (95.0)	86 (86.0)	
Yes	5 (5.0)	14 (14.0)	
Spread through air spaces			<0.001
No	17 (38.6)	55 (84.6)	
Yes	27 (61.4)	10 (15.4)	
TNM stages			0.133
IA1	11 (11.0)	9 (9.0)	
IA2	37 (37.0)	38 (38.0)	
IA3	22 (22.0)	15 (15.0)	
IB	8 (8.0)	21 (21.0)	
IIA	8 (8.0)	7 (7.0)	
IIB	9 (9.0)	5 (5.0)	

(Continues)

TABLE 3 (Continued)

Factor	IMA $N = 100$	IASLC grade 2 $N = 100$	*p* value
IIIA	3 (3.0)	5 (5.0)	
IIIB	2 (2.0)	0 (0.0)	
Adjuvant treatment			0.476
No	78 (78.0)	83 (83.0)	
Yes	22 (22.0)	17 (17.0)	
Death	13 (13.0)	10 (10.0)	0.658
Recurrence	10 (10.0)	17 (17.0)	0.214
Type of recurrence			0.576
Loco-regional	5 (50.0)	5 (29.4)	
Distant	2 (20.0)	6 (35.3)	
Combined	3 (30.0)	6 (35.3)	
Follow-up duration, months	59.3 [45.3, 78.9]	56.2 [41.5, 71.8]	0.438

Note: All data are presented as *n* (%), *n*/*N* (%), or median [interquartile range (IQR)].
Abbreviations: ECOG, European Cooperative Oncology Group; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IASLC, International Association for the Study of Lung Cancer; IMA, invasive mucinous adenocarcinoma; LLL, Left lower lobe; LUL, Left upper lobe; RLL, Right lower lobe; RML, Right middle lobe; RUL, right upper lobe, TNM, tumor nodes and metastases.

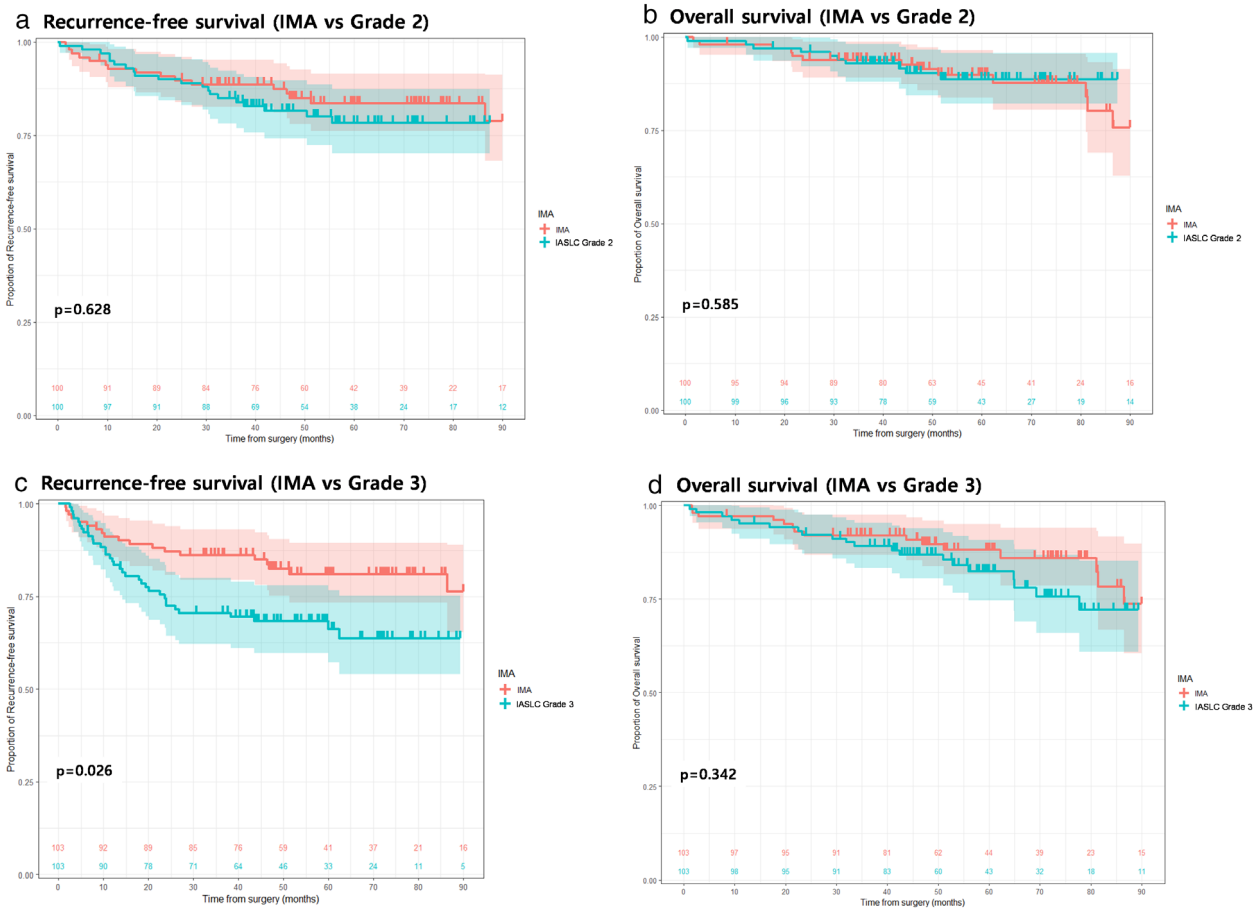

FIGURE 2 Recurrence-free and overall survival curves between patients with IMA and IASLC grades 2 (a–b) and 3 (c–d) after propensity score matching. IALSC, International Association for the Study of Lung Cancer; IMA, invasive mucinous adenocarcinoma

further clarified by dividing them into three categories. To the best of our knowledge, this study is the first to attempt to compare the prognosis of IMA to that of the new IASLC classification of INMA based on data from two institutions. Moreover, our study compared IMA with IASLC grades 2 and 3 after adjusting for compounding variables to better

TABLE 4 Clinicopathologic characteristics of IMA and IASLC grade 3 after propensity score matching

Factor	IMA $N = 103$	IASLC grade 3 $N = 103$	*p* value
Age	64.00 [57.00, 71.00]	64.00 [56.00, 72.00]	0.968
Gender			0.485
Female	51 (49.5)	45 (43.7)	
Male	52 (50.5)	58 (56.3)	
Diabetes mellitus	19 (18.4)	17 (16.5)	0.855
Hypertension	41 (39.8)	37 (35.9)	0.667
Smoking history			0.884
Ex and current	35 (34.0)	37 (35.9)	
Never	68 (66.0)	66 (64.1)	
ECOG			0.872
ECOG 0	89 (95.7)	97 (96.0)	
ECOG 1	3 (3.2)	2 (2.0)	
ECOG 2	1 (1.1)	2 (2.0)	
FEV1, %	106.00 [93.00, 119.50]	101.00 [89.50, 113.00]	0.076
FEV1/FVC ratio, %	77.00 [73.21, 80.75]	74.00 [68.46, 77.00]	<0.001
Extent of surgery			0.881
Wedge resection	6 (5.8)	7 (6.8)	
Segmentectomy	3 (2.9)	2 (1.9)	
Lobectomy	90 (87.4)	92 (89.3)	
Bilobectomy	4 (3.9)	2 (1.9)	
Location of primary lesion			<0.001
LLL	42 (40.8)	25 (24.3)	
LUL	11 (10.7)	25 (24.3)	
RLL	39 (37.9)	20 (19.4)	
RML	6 (5.8)	5 (4.9)	
RUL	5 (4.9)	28 (27.2)	
Hospital (%)			0.649
Hospital A	70 (68.0)	74 (71.8)	
Hospital B	33 (32.0)	29 (28.2)	
Tumor size	2.20 [1.45, 3.50]	2.50 [1.80, 3.50]	0.105
Lymphovascular invasion			<0.001
No	98 (95.1)	77 (74.8)	
Yes	5 (4.9)	26 (25.2)	
Visceral pleural invasion			<0.001
No	97 (94.2)	76 (73.8)	
Yes	6 (5.8)	27 (26.2)	
Spread through air spaces			0.834
No	16 (34.0)	17 (31.5)	
Yes	31 (66.0)	37 (68.5)	
TNM stages			0.136
IA1	11 (10.7)	3 (2.9)	
IA2	37 (35.9)	29 (28.2)	
IA3	21 (20.4)	16 (15.5)	
IB	8 (7.8)	32 (31.1)	
IIA	8 (7.8)	10 (9.7)	
IIB	10 (9.7)	4 (3.9)	

(Continues)

TABLE 4 (Continued)

Factor	IMA $N = 103$	IASLC grade 3 $N = 103$	*p* value
IIIA	6 (5.8)	8 (7.8)	
IIIB	2 (1.9)	1 (1.0)	
Adjuvant treatment			0.035
No	78 (75.7)	63 (61.2)	
Yes	25 (24.3)	40 (38.8)	
Death	15 (14.6)	20 (19.4)	0.458
Recurrence	12 (11.7)	28 (27.2)	0.008
Type of recurrence			0.489
Loco-regional	4 (33.3)	7 (24.1)	
Distant	3 (25.0)	13 (44.8)	
Combined	5 (41.7)	9 (31.0)	
Follow-up duration, months	59.20 [43.50, 77.85]	56.00 [42.15, 71.90]	0.571

Note: All data are presented as *n* (%), *n*/*N* (%), or median [interquartile range (IQR)].
Abbreviations: ECOG, European Cooperative Oncology Group; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IASLC, International Association for the Study of Lung Cancer; IMA, invasive mucinous adenocarcinoma; LLL, Left lower lobe; LUL, Left upper lobe; RLL, Right lower lobe; RML, Right middle lobe; RUL, right upper lobe,. TNM, tumor nodes and metastases.

TABLE 5 Cox proportional hazard regression for recurrence-free survival among invasive mucinous adenocarcinoma

	Univariate		Multivariable	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.03 (0.99–1.08)	0.132		
Diabetes mellitus	0.80 (0.27–2.33)	0.681		
Gender (male)	1.37 (0.62–3.02)	0.432		
Never smoker	0.73 (0.33–1.63)	0.441		
Sublobar resection	2.68 (0.91–7.95)	0.075		
SUVmax	1.28 (1.11–1.47)	<0.001	1.24 (1.07–1.43)	0.005
LVI	17.2 (5.86–50.2)	<0.001	128 (5.22–3116)	0.003
STAS (+)	1.65 (0.45–6.1)	0.452		
Tumor size	1.27 (1.13–1.42)	<0.001	1.20 (1.02–1.40)	0.028
VPI	2.13 (0.63–7.23)	0.230		
N stage (N2 vs N0)	12.9 (4.12–40.6)	<0.001	0.06 (0.00–1.19)	0.064

Abbreviations: CI, confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; STAS, spread through air spaces; SUVmax, the maximum standardized uptake value; VPI, visceral pleural invasion.

reflect the unique characteristics of IMA. This will deliver more precise information for determining the prognosis of IMA.

IMA has different clinical characteristics from INMA in imaging studies. Previous studies have suggested distinctive computed tomography findings of IMA, such as mixed airspace consolidation, ground-glass opacity, and air bronchogram.[17–19] Several imaging characteristics, such as spontaneous regression of airspace opacities[20] and pneumonic-type IMA,[21] were considered poor prognostic radiological factors. Moreover, the prognostic value of the SUVmax on[10] (18)F-fluorodeoxyglucose positron emission tomography has been investigated in previous IMA studies.[22] SUVmax highly correlated with tumor or pathological invasive size, although (18)F-fluorodeoxyglucose uptake was not notably high in the IMA.[17,22] We also found that SUVmax significantly predicted RFS, in line with a previous study.[23] However, this study could not comprehensively review all radiologic findings because of the diversity and ever-changing protocols in diagnosis. Further systematic reviews of this radiological perspective are warranted.

Compared to INMA, IMA is mostly found in the lower lobes of the lungs. This study also confirmed this unique characteristic. Ichinokawa et al. suggested a correlation between this type of occurrence and KRAS mutation.[24] While IMAs were regarded to present at an advanced stage during diagnosis and might not be treated by surgery,[10,25,26] a study that analyzed the Surveillance, Epidemiology, and End Results database reported a high proportion of up to 70% IMA in the early stages.[27] Most studies concerning the

surgical outcome of IMA also included stage I or II rather than advanced stages.[18,23,28,29] In this study, the patient population comprised patients with stages I–II disease, and approximately 10% of patients had stage III disease. Due to this difference, the RFS and OS results were different from those of previous studies.

The clinical outcome of IMA has been controversial[10,23,30,31] due to its low incidence, which is approximately 1.5% of total lung cancers.[27] Lee et al. reported a relatively favorable prognosis of IMA and that it was better than acinar or papillary predominant type INMA in disease-free survival.[23] This contradicts the results of our study, and it could be attributed to differences in age, sex, and the number of advanced staged cases in the study population. However, when the prognosis of patients with IMA was compared to that of patients with lepidic-predominant INMA, it had inferior clinical outcomes. Notably, Chang et al. classified IMA into various predominant patterns, as observed in INMA, and the presence of >10% micropapillary and cribriform patterns was associated with more aggressive behavior.[32] Interobserver agreement was not assessed in this study. However, if this predominant pattern could be applied to predict the prognosis of IMA, it would specifically differentiate between IMAs similar to IALSC grading for INMAs.[5]

In the pathologic findings of this study, IMA was associated with lower rates of nodal metastasis and lymphovascular and visceral pleural invasion than INMA. Similar patterns were observed in previous studies.[9,13,23,33] This implies that IMA and INMA have different disease characteristics. Although lymphovascular invasion was low, its prognostic impact was evident in our study. More attention should be paid to IMAs with lymphovascular invasion. An aerogenous spread pattern, equivalent to STAS in INMA, was also significant in IMA despite these pathological differences. Previous studies reported a higher incidence of STAS in IMA (50–72.3%)[34–36] than in INMA (14.8–47.6%).[37–39] Similar results were observed in this study despite the limited data. This could be attributable to different mucin protein expression, which could affect cell polarity and cancer cell migration.[40,41] STAS was also a significant poor prognostic factor and was suggested to be related to older age and lobulated and spiculated computed tomography margins.[36] Matsui et al. reported a higher intrapulmonary recurrence in IMA, which could be supported by its higher STAS positivity,[42] therefore further studies incorporating these pathological findings are necessary.

In the case of advanced cancer, adjuvant therapy is performed according to genetic alterations, such as EGFR, ALK, ROS, and KRAS mutations. In the case of IMA, there is almost no EGFR mutation,[31,43–45] therefore tyrosine kinase inhibitors (TKIs) are not used, affecting survival. Due to these differences in adjuvant treatments, we believe that RFS is a better assessment tool for comparing clinical prognosis in various histologic findings. Specifically, aggressive INMA (such as IASLC grade 3) could benefit from TKI treatment, as OS in this study did not represent the difference with IMA. To minimize the effect of post-surgery treatment, we suggest RFS as a reliable parameter to overcome the impact of confounding factors.

Our study had several limitations. Although we had the largest number of patients with IMA from the two institutions, categorization into a large-scale population was lacking. However, we aimed to overcome this problem using propensity score matching to increase the statistical power. Second, this study did not present molecular mutation data, although we obtained those results from approximately half of the patients. As specific mutational studies of IMA have not yet been clearly defined, we leave this as a future study topic. We expect to obtain these results in the near future. Third, the presence of STAS was not fully confirmed in the total population. As STAS was recently proposed, we could not find satisfactory results in the population that underwent surgery in the early period.

In conclusion, patients with IMA demonstrated better RFS than those with IASLC grade 3, but similar to the patients with IASLC grade 2. Additionally, the OS of patients with IMA was between that of patients with IASLC grades 2 and 3. Since the prognosis of IMA among lung adenocarcinomas appears to be relatively advanced, further clinical studies investigating IMA-specific treatment and follow-up plans are necessary to draw more implications from these findings.

AUTHOR CONTRIBUTIONS

Wongi Woo: Conceptualization, methodology, data curation, formal analysis, resources, investigation, software, writing—original draft, writing—review and editing. Young Ho Yang: Conceptualization, methodology, data curation, formal analysis, investigation, writing—original draft, writing—review and editing. Yoon-Jin Cha: Investigation, writing—review and editing. Duk Hwan Moon: Data curation, investigation, writing—review and editing. Hyo Sup Shim: Investigation, writing—original draft, writing—review and editing. Arthur Cho: Investigation, writing—original draft, writing—Review and editing. Ha Eun Kim: Writing—review and editing. Byung Jo Park: Writing—review and editing. Jin Gu Lee: Writing—review and editing. Dae Joon Kim: Writing—review and editing. Sungsoo Lee: Conceptualization, methodology, validation, supervision, project administration writing—review and editing. Chang Young Lee: Conceptualization, methodology, validation, supervision, project administration writing—review and editing.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The corresponding authors will share this article's data upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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