Original Article

Effect of invasive mucinous adenocarcinoma on lung cancer-specific survival after surgical resection: a population-based study

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Background: In 2015, the World Health Organization (WHO) announced a new classification of lung tumors. Mucinous bronchioloalveolar adenocarcinomas were reclassified as invasive mucinous adenocarcinomas (IMAs). Due to the rarity or this tumor type, conflicting clinical outcomes have been reported based on small patient numbers.

Methods: Patients diagnosed as primary lung nonmucinous adenocarcinoma (NMA) or IMA from 2000 to 2014 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. General features of each IMA were explored and the effect of histological characteristics on lung cancer-specific survival was analyzed in matched samples using the TNM staging system.

Results: The incidence of IMA among all primary lung cancer patients was 0.2% (1,783/1,154,742), and the incidence of IMA among patients with a primary resected lung adenocarcinoma was 1.5% (531/35,406). IMAs tended to be located in the lower lobe (P<0.001), be well differentiated (P<0.001), and be N0 (91.7% *vs.* 72.3%, P<0.001), T1 or T2 (P<0.001), and stage I tumors (P<0.001) when compared with NMAs. After matching by stages, a stratified Cox PH analysis revealed that the tumor histologic type (P=0.2) did not increase the risk of lung cancer-specific death, while advanced age (HR 1.03, P<0.001), male sex, and the need for radiation, pneumonectomy or sublobar resections increased the risk of cancer-specific death.

Conclusions: The histologic type of the tumor, whether IMA or not, did not affect lung cancer-specific survival times among patients with a primary M0 stage lung adenocarcinoma. When stratified by the TNM staging system, patents that required pneumonectomy, sublobar resection or radiation had shorter lung cancer-specific survival times.

Keywords: Adenocarcinoma of lung; mucinous adenocarcinoma; survival analysis; SEER program

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Introduction

In 2015, the World Health Organization (WHO) reclassified a group of lung tumors (1). This new classification system divided adenocarcinomas into two categories of non-mucinous adenocarcinomas and adenocarcinoma variants, respectively. Nonmucinous and mucinous subtypes are the accepted types of preinvasive lesions (i.e., adenocarcinoma *in situ*) (1). Though debate remains, mucinous bronchoalveolar adenocarcinoma has been reclassified as invasive mucinous adenocarcinoma (IMA) (2,3). The classification of specific

variants is based on the tumor's pathological morphology, immunoprofile, and genetic and clinical characteristics. According to the new WHO classification system, mucinous adenocarcinoma and adenocarcinoma with mucin production are distinguished based on the presence of goblet or columnar cells in mucinous adenocarcinomas. Tumors previously designated as mucinous adenocarcinomas (ICD-O code 8480/3) are referred to as "colloid adenocarcinomas", and also been reclassified as an adenocarcinoma variant (1).

When performing surgery, a mucinous adenocarcinoma can be easily identified by the presence of abundant mucin; however, its histological diagnosis can be mucinous adenocarcinoma, adenocarcinoma with mucin production, or colloid adenocarcinoma. Because mucinous adenocarcinoma is not a common subtype of lung tumors, its reported clinical outcomes have varied, and the terminologies used in study reports tend to be very heterogeneous. Because both mucin-producing adenocarcinoma and mucinous adenocarcinoma are frequently used together in the same report, it has been difficult to obtain a clear understanding of the disease entity (4-8).

The mucinous type of adenocarcinoma comprises between 2% and 10% of all lung tumors, and a large amount of data is required for a proper analysis. The results of previous studies of IMA have been based on relatively patient populations; therefore, the prognosis for patients with IMA remains controversial (6,7,9-11). The Surveillance, Epidemiology, and End Results (SEER) program sponsored by the National Cancer Institute in the United States has created a database that includes epidemiological, pathological, and survival information for all cancer cases reported in 18 regions of the United States since 1972.

The objective of our study was to assess the clinical presentation of IMA and then compare it with that of nonmucinous adenocarcinoma (NMA). We also compared the cancer-specific survival times in a matched cohort of surgically resected adenocarcinoma patients.

Methods

Patient selection

SEER*Stat 8.3.4 software was used to extract data from the SEER database. Patients were selected using the 'SEER site Recode' variable and the phrase "Lung and Bronchus". Patients were also selected using the 'Site and Morphology Behavior recode for analysis' and the term "Malignant". The international classification of disease for oncology-3 was used to restrict the pathology types to (8253/3), and NMA (ICD-O-3 codes 8140/3, 8250/3, 8252/3, 8253/3, 8254/3, 8255/4, 8551/3) (1). The NMA group included adenocarcinoma (8140/3), lepidic adenocarcinoma (8250/3), nonmucinous bronchioloalveolar carcinoma (8252/3), adenocarcinoma with mixed subtype (8255/3), papillary adenocarcinoma (8260/3), and acinar cell adenocarcinoma (8551/3). Other mucin-producing adenocarcinoma variants (i.e., mucin-producing adenocarcinoma, colloid adenocarcinoma, and a rare form of adenocarcinoma) were excluded from this study to avoid confusion.

Next, the dataset was restricted to first malignancy, and the single primary malignancy in the patient's life. The type of reporting source was restricted to other than an autopsy report or death certificate only cases. The process used for data cleansing is summarized in *Figure 1*. Two datasets were created, the first one (dataset 1) was used for describing the general features of the IMAs at the time of its clinical presentation. The second dataset (dataset 2) was used to assess the effect of specific histological characteristics on clinical outcomes after surgery was performed as the first course of treatment. Also, inclusion of a surgical cohort made the diagnosis of IMA more accurate, because its definitive diagnosis by transbronchial biopsy prior to surgery is frequently challenging.

Additional patient characteristics extracted from the dataset included basic demographic data, follow-up data, first course of treatment variables (radiation, chemotherapy, and surgery), TNM stages, pathologic characteristics of the tumor [size, location, and additional solitary pulmonary nodules (SPNs)], and cause of patient death.

Statistical analysis

The primary endpoint of this study was lung cancer specific survival (LCSS), as measured in months. Patients who were alive at the last follow-up date in the SEER database were right-censored at this date in the survival analysis.

Characteristics were summarized using standardized statistical parameters, including the mean ± SD or median value for continuous variables, and frequencies and percentages for categorical variables. Distributions for continuous variables were analyzed using Student's *t*-test or the Mann-Whitney U-test depending on the result of the Shapiro-Wilk test of normality. Categorical variables were compared using the chi-square test or Fisher's exact test. The TNM and AJCC systems used for staging (3rd, 6th, and 7th system) were also used to match the IMA and NMA

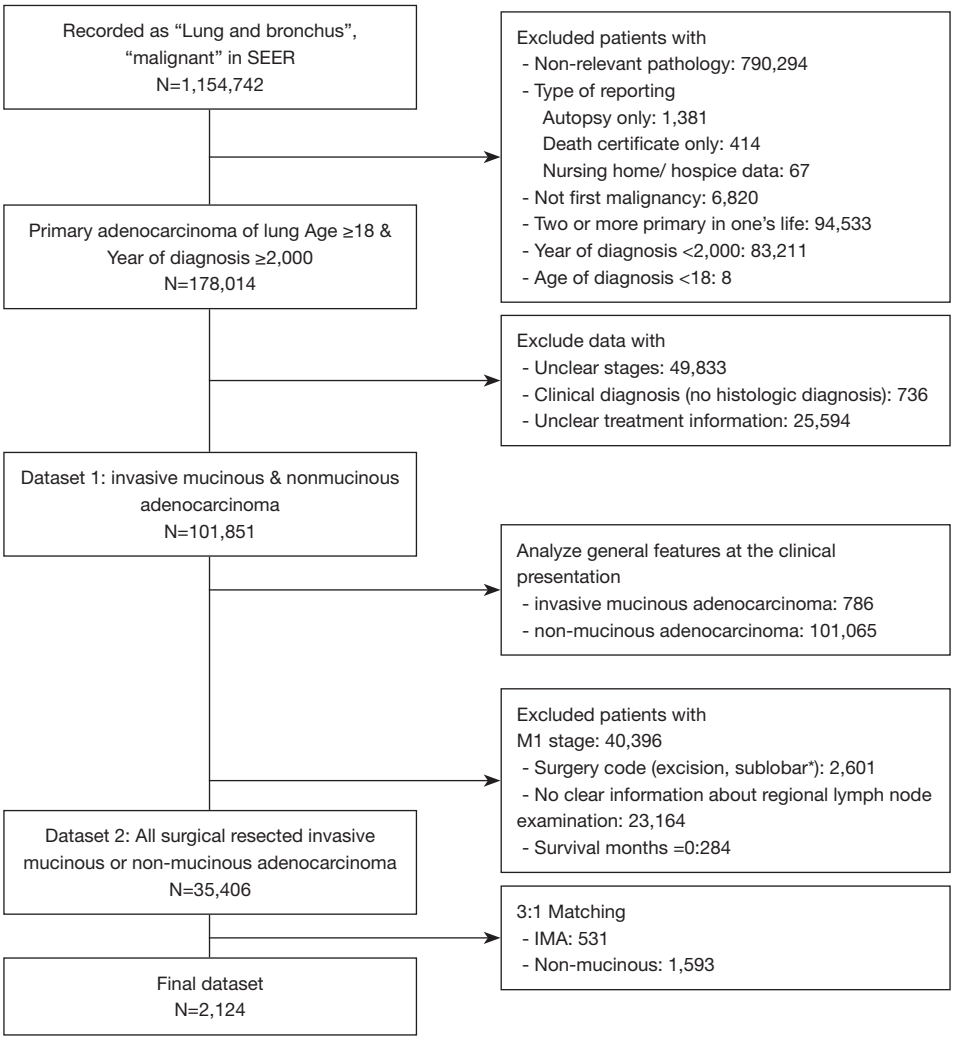

Figure 1 Study flow chart of the study, with patient counts and reasons for exclusion from the dataset. *, sublobar resections other than wedge resection or segmentectomy, i.e., such as excision, electrocautery, etc.

groups to enhance their comparability by the automated matching program from R (12). After matching, the balance between the two groups was checked via standardized mean differences, and the values for all the variables were <0.10 (*Figure S1*) (13,14).

The Kaplan-Meier method was used to obtain LCSS data and a log-rank test was used to compare survival curves for the IMA and NMA groups. Multivariate Cox proportional hazards (PH) models were used to estimate the association between tumor histological characteristics and cancer-specific survival in the unmatched group, and stratified Cox PH models were used for that purpose in the matched groups. The Shoenfeld residuals test was used to test the assumption of proportionality of hazards. The protocol for this study was approved by the Institutional Review Board for Seoul St. Mary's Hospital (approval no. KC18ZESI0277).

Results

General features of IMAs and NMAs at the time of diagnosis

The general comparative features of the IMAs are shown in 'dataset 1' (*Table 1*). The incidence of IMAs among all lung cancer patients was 0.2% (1,783/1,153,742). While there were no differences in the age at diagnosis or racial distribution, there was a slight female predominance. Except

Table 1 Basic characteristics of invasive mucinous and nonmucinous adenocarcinoma at the time of diagnosis

Variables	IMA (N=786)	NMA (N=101,065)	P value
Age (years)	65.97±12.02	66.09±10.99	0.458
Female sex	465 (59.2%)	52,792 (52.2%)	<0.001
Race			0.868
Black	92 (11.7%)	11,419 (11.3%)	
White	629 (80.0%)	80,384 (79.5%)	
Others	64 (8.1%)	9,063 (9.0%)	
Unknown	1 (0.1%)	199 (0.2%)	
Grade			<0.001
Grade I	427 (54.3%)	9,549 (9.4%)	
Grade II	101 (12.8%)	25,548 (25.3%)	
Grade III	17 (2.2%)	28,672 (28.4%)	
Grade IV	0 (0.0%)	691 (0.7%)	
Unknown	241 (30.7%)	36,605 (36.2%)	
Laterality			0.004
Left	309 (39.3%)	39,419 (39.0%)	
Single side, not specified	1 (0.1%)	149 (0.1%)	
Paired side	26 (3.3%)	1,586 (1.6%)	
Right	450 (57.3%)	59,911 (59.3%)	
Location			<0.001
Upper	228 (29.0%)	57,987 (57.4%)	
Middle	36 (4.6%)	4,910 (4.9%)	
Lower	442 (56.2%)	26,966 (26.7%)	
Main	1 (0.1%)	2,420 (2.4%)	
Overlapping lesion	20 (2.5%)	1,273 (1.3%)	
Unknown	59 (7.5%)	7,509 (7.4%)	
Operation			<0.001
No surgery	131 (16.7%)	59,691 (59.1%)	
Wedge	101 (12.8%)	5,545 (5.5%)	
Segmentectomy	16 (2.0%)	1,293 (1.3%)	
Other sublobar	8 (1.0%)	458 (0.5%)	
Lobectomy	514 (65.4%)	32,542 (32.2%)	
Pneumonectomy	16 (2.0%)	1,536 (1.5%)	
Chemotherapy	235 (29.9%)	56,089 (55.5%)	<0.001
Radiation	71 (9.0%)	46,355 (45.9%)	<0.001
Combinations			<0.001
Chemotherapy	87 (11.1%)	19,248 (19.0%)	
Chemoradiation	22 (2.8%)	25,756 (25.5%)	
Radiation	22 (2.8%)	14,687 (14.5%)	
Surgery only	518 (65.9%)	28,750 (28.4%)	
Surgery + chemotherapy	110 (14.0%)	6,712 (6.6%)	
Surgery + radiation	11 (1.4%)	1,539 (1.5%)	
Trimodality	16 (2.0%)	4,373 (4.3%)	
Tumor diameter (mm)	53.33±124.49	38.35±53.87	0.070
Number of lymph nodes positive	0.19±0.86	0.85±2.09	<0.001
Number of lymph nodes resected	6.05±7.85	3.49±6.44	<0.001
SPN*			<0.001
No data	440 (66.6%)	41,728 (47.7%)	
None	161 (24.4%)	33,921 (38.8%)	
SPN	60 (9.1%)	11,766 (13.5%)	
Pleural effusion†	12 (5.6%)	5,947 (13.0%)	0.001

*, data from the subset recorded from 2004; †, data from the subset recorded from 2010. IMA, invasive mucinous adenocarcinoma; NMA, nonmucinous adenocarcinoma.

when data for tumor differentiation was absent, most of the IMAs were well differentiated (Grade I), whereas the NMAs displayed various degrees of differentiation. Moreover, ~56.2% of the IMAs were located in the lower lobe of a lung. The IMAs tended to be larger than the NMAs at the time of diagnosis; however, this difference was not statistically significant. A subset of data recorded from 2010 onwards showed that pleural effusion was more common in the NMA group.

The AJCC staging system was used to create our dataset; therefore, we divided the entire cohort into three categories of 'First [2000–2003]', 'Second [2004–2009]', and 'Third [2010–2014]' periods according to the edition of the system used. Although there were several changes in the staging

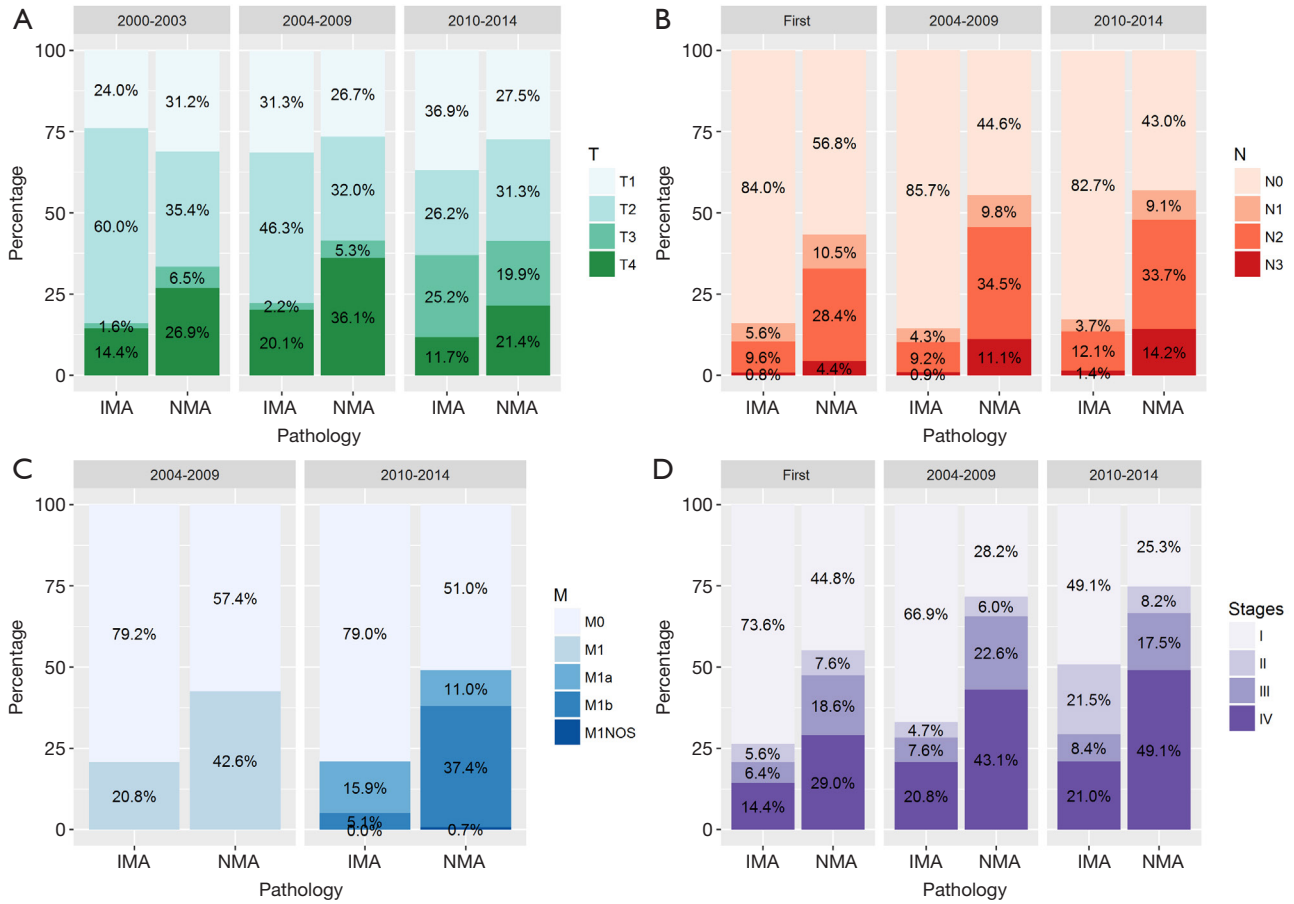

Figure 2 Distributions of T, N, M, and stages in the dataset of invasive mucinous adenocarcinoma and nonmucinous adenocarcinoma.

system, a comparison within the same period revealed that prior to and throughout 2009 the IMAs included more T2 stage tumors and fewer T1 stage tumors that did the NMAs. From 2010 onwards, the IMAs and NMAs had similar percentages of T1 and T2 tumors and greater percentages of T3 tumors (P<0.001, *Figure 2*). Regarding clinical and pathological N staging, most of the IMAs were N0 stage throughout the three periods. Approximately 20% of the IMA cases and 40% of the NMA cases had a distant metastasis at the time of diagnosis. Our dataset showed that no M1 cases of IMA or NMA were diagnosed prior to 2003. The most common first line therapy was surgery alone, and the most common type of surgery performed for cases of IMA was lobectomy.

Clinical features of IMAs and NMAs in the surgically resected group

To assess the effect of tumor histology on the prognosis of patients who received surgical treatment, we limited our dataset to the M0 stage and applied a surgery code of at least 'wedge' or more. Moreover, we excluded data for cases in which unclear tumor stages were reported and no definite information concerning the number of regional lymph node examinations was provided. Additionally, we limited our dataset to include patients with an observed survival time of ≥1 month, for the purpose of excluding the statistical effect of immediate postoperative mortality (*Figure 1*).

Our 'dataset 2' had 531 patients with an IMA and 34,875 patients with a NMA, for an overall incidence rate of 1.5%. There were no differences in the distributions of patient age, race, and insurance status at the time of diagnosis (*Table 2*). Patients in the IMA group had tumors that were more differentiated (either Grade I or II), showed a lower lobe location preference, and had larger diameters when compared with patients in the NMA group. The IMA patients also had more regional lymph nodes surgically examined than did the NMA patients. There were no

Table 2 Basic characteristics of surgically resected, primary M0 stages invasive mucinous and nonmucinous adenocarcinoma

Variables	Before matching			After matching		
	IMA (N=531)	NMA (N=34,875)	P value	IMA (N=531)	NMA (N=1,593)	P value
Age (years)	65.64±11.34	66.23±10.24	0.239	65.34±11.34	65.64±10.56	0.213
Female sex	326 (61.4%)	19,849 (56.9%)	0.043	205 (38.6%)	674 (42.3%)	0.147
Race			0.360			0.616
Black	54 (10.2%)	2,963 (8.5%)		54 (10.2%)	141 (8.9%)	
White	434 (81.7%)	28,879 (82.8%)		434 (81.7%)	1,327 (83.3%)	
Others	43 (8.1%)	3,033 (8.7%)		43 (8.1%)	125 (7.8%)	
Marriage			0.028			0.035
Married/partner	335 (63.1%)	20,493 (58.8%)		335 (63.1%)	919 (57.7%)	
Separated	119 (22.4%)	9,483 (27.2%)		119 (22.4%)	445 (27.9%)	
Single	51 (9.6%)	3,659 (10.5%)		51 (9.6%)	171 (10.7%)	
Unknown	26 (4.9%)	1,240 (3.6%)		26 (4.9%)	58 (3.6%)	
Insurance			0.082			0.135
Insured	259 (48.8%)	18,250 (52.3%)		259 (48.8%)	802 (50.3%)	
Medicaid	22 (4.1%)	1,971 (5.7%)		22 (4.1%)	84 (5.3%)	
Uninsured	6 (1.1%)	409 (1.2%)		6 (1.1%)	6 (0.4%)	
Unknown	244 (46.0%)	14,245 (40.8%)		244 (46.0%)	701 (44.0%)	
Grade			<0.001			<0.001
Grade I	304 (57.3%)	6,063 (17.4%)		304 (57.3%)	288 (18.1%)	
Grade II	84 (15.8%)	15,430 (44.2%)		84 (15.8%)	703 (44.1%)	
Grade III	14 (2.6%)	11,060 (31.7%)		14 (2.6%)	500 (31.4%)	
Grade IV	0 (0.0%)	257 (0.7%)		0 (0.0%)	18 (1.1%)	
Unknown	129 (24.3%)	2065 (5.9%)		129 (24.3%)	84 (5.3%)	
Laterality			0.420			0.722
Left	222 (41.8%)	13,859 (39.7%)		222 (41.8%)	650 (40.8%)	
Right	309 (58.2%)	21,008 (60.2%)		309 (58.2%)	943 (59.2%)	
One side	0 (0.0%)	8 (0.0%)		–	–	
Location			<0.001			<0.001
Upper	163 (30.7%)	21,472 (62.3%)		163 (30.7%)	974 (61.1%)	
Middle	29 (5.5%)	1,787 (5.1%)		29 (5.5%)	83 (5.2%)	
Lower	319 (60.1%)	10,327 (29.6%)		319 (60.1%)	486 (30.5%)	
Other	20 (3.8%)	1,019 (2.9%)		20 (3.8%)	50 (3.1%)	
SPN*	17 (4.0%)	1,174 (4.3%)	0.811	17 (4.0%)	48 (3.7%)	0.907

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Before matching			After matching		
	IMA (N=531)	NMA (N=34,875)	P value	IMA (N=531)	NMA (N=1,593)	P value
Pleura involvement[†]	N=138	N=13,490	<0.001	N=138	N=423	<0.001
Yes	13 (9.4%)	3,192 (23.7%)		13 (9.4%)	116 (27.4%)	
No	112 (81.2%)	8,810 (65.3%)		112 (81.2%)	262 (61.9%)	
Unknown	13 (9.4%)	1,488 (11.0%)		13 (9.4%)	45 (10.6%)	
Tumor diameter (mm)	40.14±34.44	29.63±18.84	<0.001	40.14±34.44	30.54±17.91	<0.001
Number of LNs positive	0.16±0.74	0.75±2.04	<0.001	0.16±0.74	0.22±1.03	0.779
Number of LNs resected	8.48±7.55	9.26±7.60	0.027	8.48±7.55	8.76±7.37	0.488
T stage [2000–2003]	N=102	N=7,686	<0.001	N=102	N=290	0.066
T1	26 (25.5%)	3,149 (41.0%)		26 (25.5%)	75 (25.9%)	
T2	66 (64.7%)	3,408 (44.3%)		66 (64.7%)	175 (60.3%)	
T3	1 (1.0%)	382 (5.0%)		1 (1.0%)	23 (7.9%)	
T4	9 (8.8%)	747 (9.7%)		9 (8.8%)	17 (5.9%)	
T stage [2004–2009]	N=291	N=13,699	<0.001	N=291	N=880	0.028
T1	104 (35.7%)	6,403 (46.7%)		104 (35.7%)	322 (36.6%)	
T2	168 (57.7%)	5,846 (42.7%)		168 (57.7%)	468 (53.2%)	
T3	4 (1.4%)	509 (3.7%)		4 (1.4%)	48 (5.5%)	
T4	15 (5.2%)	941 (6.9%)		15 (5.2%)	42 (4.8%)	
T stages [2010–2014]	N=138	N=13,490	0.001	N=138	N=423	0.014
T1a	38 (27.5%)	3,938 (29.2%)		38 (27.5%)	122 (28.8%)	
T1b	25 (18.1%)	2,420 (17.9%)		25 (18.1%)	60 (14.2%)	
T1NOS	0 (0.0%)	18 (0.1%)		0 (0.0%)	1 (0.2%)	
T2	0 (0.0%)	6 (0.0%)		–	–	
T2a	28 (20.3%)	4,313 (32.0%)		28 (20.3%)	141 (33.3%)	
T2b	12 (8.7%)	683 (5.1%)		12 (8.7%)	24 (5.7%)	
T2NOS	0 (0.0%)	22 (0.2%)		0 (0.0%)	1 (0.2%)	
T3	33 (23.9%)	1,571 (11.6%)		33 (23.9%)	58 (13.7%)	
T4	2 (1.4%)	519 (3.8%)		2 (1.4%)	16 (3.8%)	
N stages			<0.001			0.871
N0	487 (91.7%)	25,210 (72.3%)		487 (91.7%)	1,461 (91.7%)	
N1	21 (4.0%)	4,812 (13.8%)		21 (4.0%)	57 (3.6%)	
N2	23 (4.3%)	4,744 (13.6%)		23 (4.3%)	75 (4.7%)	
N3	0 (0.0%)	109 (0.3%)		–	–	

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Before matching			After matching		
	IMA (N=531)	NMA (N=34,875)	P value	IMA (N=531)	NMA (N=1,593)	P value
Stages [2000–2003]	N=102	N=7,686	0.001	N=102	N=290	0.070
I	81 (79.4%)	4,746 (61.7%)		81 (79.4%)	220 (75.9%)	
II	6 (5.9%)	934 (12.2%)		6 (5.9%)	10 (3.4%)	
IIIA	6 (5.9%)	1,239 (16.1%)		6 (5.9%)	43 (14.8%)	
IIIB	9 (8.8%)	767 (10.0%)		9 (8.8%)	17 (5.9%)	
Stages [2004–2009]	N=291	N=13,699	0.001	N=291	N=880	0.254
IA	103 (35.4%)	5,173 (37.8%)		103 (35.4%)	309 (35.1%)	
IB	152 (52.2%)	3,825 (27.9%)		152 (52.2%)	420 (47.7%)	
IIA	1 (0.3%)	633 (4.6%)		1 (0.3%)	5 (0.6%)	
IIB	15 (5.2%)	1,324 (9.7%)		15 (5.2%)	70 (8.0%)	
IIIA	5 (1.7%)	1,767 (12.9%)		5 (1.7%)	34 (3.9%)	
IIIB	15 (5.2%)	977 (7.1%)		15 (5.2%)	42 (4.8%)	
Stages [2010–2014]	N=138	N=13,490	0.001	N=138	N=423	0.010
IA	59 (42.8%)	5,422 (40.2%)		59 (2.8%)	177 (41.8%)	
IB	26 (18.8%)	3,031 (22.5%)		26 (18.8%)	135 (31.9%)	
II	0 (0.0%)	7 (0.1%)		–	–	
IIA	11 (8.0%)	1,530 (11.3%)		11 (8.0%)	27 (6.4%)	
IIB	32 (23.2%)	1,146 8.5%)		32 (23.2%)	54 (12.8%)	
IIIA	10 (7.2%)	2,191 (16.2%)		10 (7.2%)	27 (6.4%)	
IIIB	0 (0.0%)	163 (1.2%)		0 (0.0%)	3 (0.7%)	
Operation			0.063			0.011
Sublobar resection	40 (7.5%)	3,445 (9.9%)		40 (7.5%)	194 (12.2%)	
Lobectomy	477 (89.8%)	30,106 (86.3%)		477 (89.8%)	1,352 (84.9%)	
Pneumonectomy	14 (2.6%)	1,324 (3.8%)		14 (2.6%)	47 (3.0%)	
Chemotherapy	89 (16.8%)	8,850 (25.4%)	<0.001	89 (16.8%)	300 (18.8%)	0.315
Radiation	19 (3.6%)	4,425 (12.8%)	<0.001	19 (3.6%)	130 (8.2%)	0.001
Treatment			<0.001			0.002
Surgery	434 (81.7%)	24,935 (71.5%)		434 (81.7%)	1,260 (79.1%)	
Surgery + chemotherapy	78 (14.7%)	5,485 (15.7%)		78 (14.7%)	203 (12.7%)	
Surgery + radiation	8 (1.5%)	1,090 (3.1%)		8 (1.5%)	33 (2.1%)	
Trimodality	11 (2.1%)	3,365 (9.6%)		11 (2.1%)	97 (6.1%)	
Lung cancer death	363 (31.6%)	11,027 (31.6%)	>0.999	168 (31.6%)	477 (29.9%)	0.496
All-cause mortality	224 (42.2%)	15,463 (43.7%)	0.343	224 (42.2%)	699 (43.9%)	0.528

*, data from the subset recorded from 2004; †, data from the subset recorded from 2010. IMA, invasive mucinous adenocarcinoma; LN, lymph nodes; NMA, nonmucinous adenocarcinoma.

significant differences in the laterality of the tumor's location, and the stage distribution of the dataset 2 was similar to the dataset 1 (*Figure S1*). The data specific for SPNs and tumors that showed pleural invasion were available for patients entered into the SEER database after 2004 and 2010, respectively. This data subset showed that the occurrence of SPNs was not significantly different in the two groups (IMA and NMA), while pleural involvement occurred less frequently with IMAs than NMAs.

The dataset showed that the most common first-line treatment was surgery alone (81.7% of IMA cases and 71.5% of NMA cases). Approximately 15% of patients received chemotherapy as neoadjuvant or adjuvant therapy, and ~1.5% of IMA patients and 3.1% of all patients received both surgery and radiation. Approximately 2.1% of IMA patients and 9.6% of NMA patients received trimodality therapy as their first-line treatment. Among the patients who received surgery in both groups, >85% received a lobectomy or bilobectomy. Only ~10% of all surgical patients both groups received a pneumonectomy, segmentectomy or wedge resection as first-line therapy.

Effect of an IMA on survival after surgery: a matched dataset analysis

After matching via T stage, N stage, and the AJCC system (3rd, 6th, 7th systems), balance testing performed by using changes in absolute standardized mean values and mean differences gave results that were all <0.10, indicating well-balanced matching (*Figure S2*, *Table S1*). Based on results of a univariate analysis performed after matching, we then constructed a multivariate stratified Cox PH model. A univariate analysis performed with the matched dataset revealed that patient age at diagnosis, male sex, a higher tumor grade (Grade III or IV), and higher T and N stages were all associated with LCSS (*Table S2*). Tumor laterality (P=0.851), presence of a SPN (P=0.636), pleural involvement (P=0.541), and the total numbers of regional lymph nodes examined (P=0.826) were not associated with LCSS.

Because the tumors were matched by T, N, and AJCC system variables, we performed a Cox PH analysis that was stratified by those three variables. The results indicated that the pathological type of the tumor (either IMA or NMA) was not associated with LCSS when other confounding variables such as race, marital status, age, and sex were controlled (*Table 3*). Before matching, the IMA patients showed a longer mean survival time than the NMA patients (59.3±41.9 months for IMA patients *vs.* 49.8±42.0 months for NMA patients, P=0.04) (*Figure 3A*). However, after matching, the effect of histologic type on cancer-specific survival was no long observed (*Figure 3B*). The mean number of survival months in the matched dataset was 59.3±41.9 months for IMA patients and 56.2±41.8 months for NMA patients (P=0.93). Though statistically insignificant, the survival curve was located between the lepidic adenocarcinoma and general other types of adenocarcinoma (*Figure 3C*). An age and sex adjusted Cox PH model also showed no statistically significant differences in the matched dataset (*Figure 4*).

Discussion

A primary pulmonary IMA is distinguished from other tumors by its abundant intracytoplasmic mucin produced by goblet or other columnar cells. IMAs are rare, and account for <2–10% of all lung adenocarcinomas (15). ICD-O-3 histology code 8253/3 denotes an IMA; previously termed a 'mucinous bronchioloalveolar carcinoma' (16). We specifically wanted to focus on this entity because there remain some issues concerning tumor classifications. First, because NMAs are known to produce mucin, distinguishing an NMA from an IMA can be difficult. Second, the definition and quantification of mucin production have not been well-defined. Third, other types of mucin-producing adenocarcinomas have been identified, including colloid adenocarcinoma, cystadenocarcinoma, and signet ring cell carcinoma (3).

Due to the low incidence of IMAs, a large data source is necessary to overcome statistical power issues and accurately identify general features of the disease. The SEER database was well suited for this purpose, and revealed that the incidence of IMA among resected adenocarcinomas was 1.5%. A further analysis of the data allowed us to identify several features of IMAs. First, IMAs in the lung showed a strong tendency for a lower lobe location. At the time of diagnosis, 56.2% of IMAs were located in the lower lobe, while NMAs were predominantly located in an upper lobe. Second, the incidence of bilateral location was 3.3% in the IMA group, which was 2-fold higher than that in the NMA group. These findings are consistent with reports stating that IMAs have a tendency for bilateral lung involvement and lower lobe predominance (16-18). However, due to a lack of information, we could not confirm some other known features of IMAs, such as their multicentricity and multilobar location. Data for SPNs only become available starting in 2004, and was mostly absent for the period that we studied.

Table 3 Multivariate analysis for risk factors of lung cancer-specific mortality

Variables	Unmatched			Matched		
	HR	95% CI	P value	HR	95% CI	P value
IMA pathology	1.107	0.949–1.291	0.197	1.129	0.940–1.358	0.195
Age	1.020	1.018–1.022	<0.001	1.025	1.017–1.034	<0.001
Male sex	1.400	1.347–1.455	<0.001	1.550	1.312–1.831	<0.001
Race						
Black	1					
Other	0.767	0.697–0.843	<0.001	0.585	0.391–0.874	0.009
White	0.955	0.892–1.023	0.193	0.788	0.605–1.027	0.077
Marriage						
Married/partner	1			1		
Separated	1.151	1.101–1.204	<0.001	0.788	0.605–1.027	0.896
Single	1.153	1.080–1.230	<0.001	1.013	0.833–1.232	0.040
Unknown	0.996	1.891–1.114	0.948	1.319	1.013–1.718	0.282
Operation						
Lobectomy	1			1		
Pneumonectomy	1.310	1.209–1.419	<0.001	1.709	1.170–2.496	0.006
Sublobar	1.261	1.183–1.345	<0.001	1.620	1.270 –2.067	0.001
Radiation	1.361	1.291–1.435	<0.001	1.496	1.120–1.999	0.006
Insurance						
Medicaid	1.239	1.123–1.366	<0.001			
Uninsured	1.163	0.939–1.439	0.166			
Unknown	1.190	1.125–1.259	<0.001			
Location						
Middle	1.016	0.930–1.110	0.719			
Other	1.094	0.991–1.207	0.074			
Upper	1.866	0.831–0.903	<0.001			

CI, confidence interval; HR, hazards ratio; IMA, invasive mucinous adenocarcinoma.

Therefore, we cannot draw any conclusions concerning the multicentricity and preferred locations of SPNs. Finally, while IMAs are commonly thought to be diagnosed at an advanced inoperable stage, we found that at the time of diagnosis, ~70% of IMAs were either stage I or II.

Patients with an IMA are known to have poor overall survival and progression-free survival times when compared to patients with other lung adenocarcinoma subtypes. They are also thought to present at an advanced stage of their disease which cannot be treated by surgery (2,6,19). However, a very recent study by Shim *et al.* demonstrated that the overall survival time of IMA patients is comparable to that of patients with intermediate grade NMA (10). Furthermore, a Japanese study of 440 patients with an adenocarcinoma revealed that the disease-free survival times of IMA patients were intermediate between the low grade and high grade adenocarcinoma groups (20). Finally, a study by Warth *et al.* showed that IMA patients had a better prognosis than most adenocarcinoma patients (7). Though statistically insignificant, the IMA patients in our

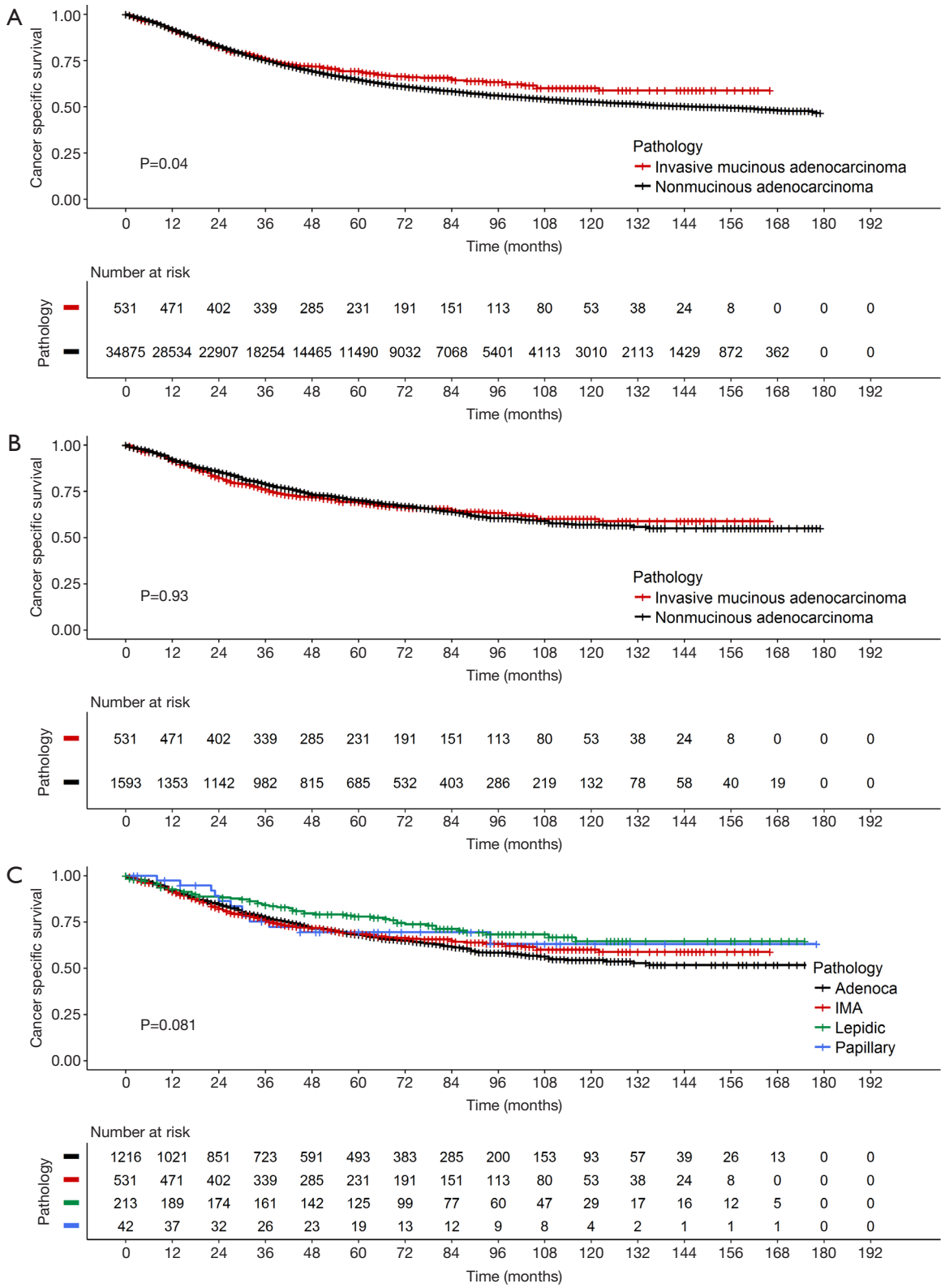

Figure 3 Kaplan-Meier survival curves comparing (A) IMA and NMA before-matching and (B) after matching, (C) survival curves according to the adenocarcinoma subtype and IMA. NMA, nonmucinous adenocarcinoma; IMA, invasive mucinous adenocarcinoma.

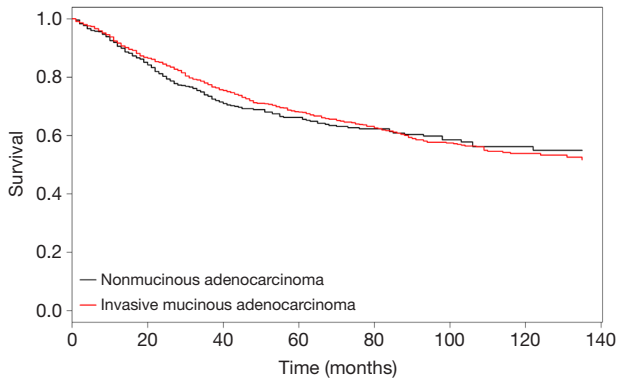

Figure 4 Adjusted Cox PH survival curves for IMA and NMA. Based on the stratified Cox PH model, age and sex adjusted Cox PH curves showed no significant differences between invasive mucinous adenocarcinoma and mucinous adenocarcinoma. NMA, nonmucinous adenocarcinoma; IMA, invasive mucinous adenocarcinoma; PH, proportional hazard.

study cohort also had survival curves that were intermediate between those for patients with lepidic adenocarcinoma and other adenocarcinomas (*Figure 3C*). A survival analysis of the matched dataset showed that the rate of 5-year LCSS was 69.3% with a median LCSS time of 51.0 months in the IMA group, and 70.1% with a median LCSS time of 49.0 months in the NMA group. Lee et al reported a 5-year disease-free survival rate of 79% and a median disease-free survival time of 46.2 months, which is comparable to the findings in this study (10). After matching was performed, univariate and multivariate stratified Cox PH analyses revealed that LCSS times were not affected by tumor histologic characteristics. Rather, after adjusting for confounding variables, the patients who required radiation (HR 1.5, P=0.01), pneumonectomy (HR 1.71, P=0.01) or sublobar resection (HR 1.620, P<0.001) had shorter LCSS times.

Data pertaining to nodal status in our study cohort revealed that at the time of diagnosis, >80% of IMA cases were at the N0 stage throughout the entire study period (84.0% for years 2000–2003, 85.7% for years 2004–2009, and 82.7% for years 2010–2014), which was double the percentage of N0 stage cases in the NMA group. This finding is in agreement with previous small studies that reported lower rates of nodal metastasis and fewer lymphatic invasions (9,10,21). Although the association between tumor genotype and histology is not absolute, the lower N stages might be related to the characteristic molecular profile of IMAs. For example, KRAS mutations have been observed in 60–76% of IMAs, while EGFR mutations are absent in IMAs (21,22). Kakegawa *et al.* suggested that KRAS mutant tumors might grow faster than tumors without KRAS mutations which might explain why in our study, the IMA group had larger tumor sizes than the NMA group (23). The effect of genotype on tumor behavior and clinical outcomes needs to be verified in future large-scale studies.

This study has several limitations. First, there was no data regarding disease-free survival or recurrence in the SEER database. However, as the SEER database is controlled by the National Cancer Institute, and the numbers of deaths caused by specific cancers are available, the rates and time periods of disease-free survival can be inferred from the rates and times periods of cancer-specific survival. Second, the SEER database lacks patient comorbidity profiles. This lack of comorbidity information is partially why we chose the surgically treated dataset for our main analysis, as the physical condition of patients eligible for surgery would be less heterogenous than that of the entire dataset. Third, because we could not review the pathology findings for individual tumor specimens, our grouping was based on the ICD-O-3 codes of the enrolled dataset. While issues concerning accuracy and inaccuracy might arise, the SEER registrar reviews the data on a continuous basis. Furthermore, we strictly limited the ratio of NMA cases to IMA cases to reduce any possible bias. Moreover, the sample sizes used in this study are the largest to have been reported. Although our study had neither a prospective nor randomized design, it was multi-institutional, and reflects real-world clinical presentations, practices, and disease outcomes. This fact compensates for its limitations and allows us to establish a tentative relationship between tumor pathological characteristics and LCSS.

In conclusion, the histologic subtype of IMA did not affect LCSS in surgically resected, M0 stage, primary lung adenocarcinoma patients. In this group of patients, those who needed radiation, chemotherapy or an extensive surgery such as pneumonectomy had shorter LCSS times.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The protocol for this study was approved by the Institutional Review Board for Seoul St. Mary's Hospital (approval no. KC18ZESI0277).

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Supplementary

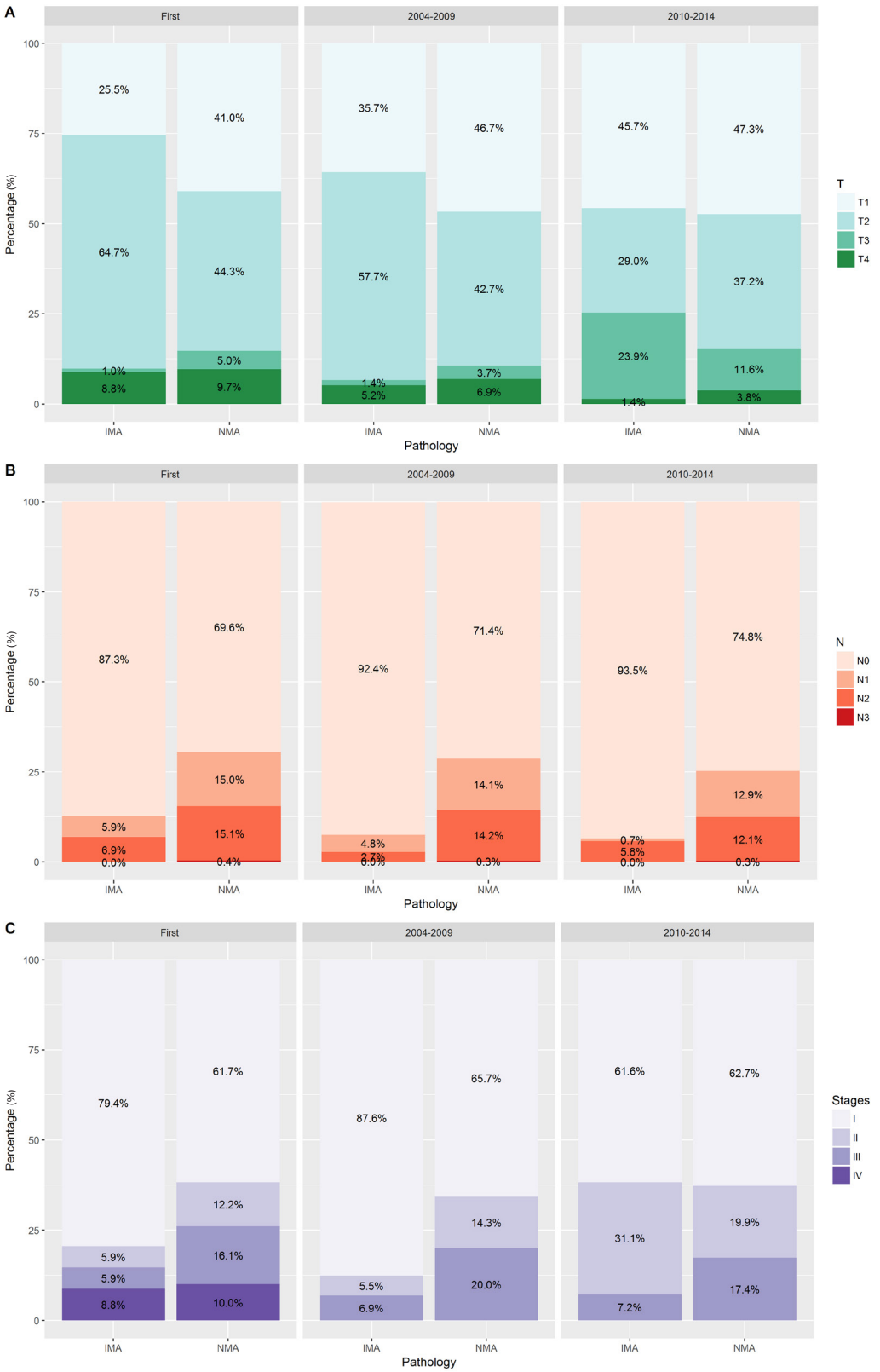

Figure S1 Distributions of T and N stages in the matched dataset of invasive mucinous adenocarcinoma and nonmucinous adenocarcinoma.

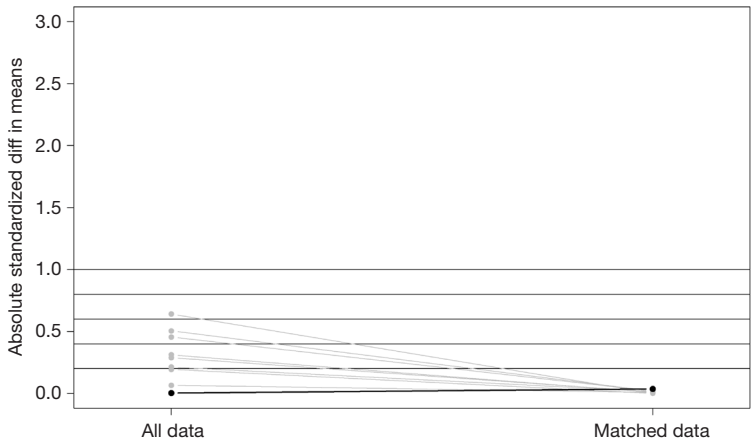

Figure S2 Absolute standardized differences in mean values before and after matching.

Table S1 Balance measured by standardized mean differences before and after matching

Variables	Total data set			Matched data set			Percent balance improvement
	Means IMA	Means NMA	Standardized mean Diff	Means IMA	Means NMA	Standardized mean Diff	
Distance	0.0214	0.0149	0.6413	0.0214	0.0214	–0.0017	99.7335
T1	0.3635	0.4567	–0.1937	0.3635	0.3641	–0.0013	99.3268
T2	0.5160	0.4094	0.2131	0.5160	0.5078	0.0163	92.3447
T3	0.0716	0.0706	0.0038	0.0716	0.0810	–0.0365	–872.6406
T4	0.0490	0.0633	–0.0663	0.0490	0.0471	0.0087	86.8479
N1	0.0395	0.1380	–0.5046	0.0395	0.0358	0.0193	96.1735
N2	0.0433	0.1360	–0.4550	0.0433	0.0471	–0.0185	95.9375
N3	0.0000	0.0031	–	0.0000	0.0000	–	100.0000
6^{th} AJCC system	0.5480	0.3928	0.3116	0.5480	0.5524	–0.0088	97.1690
7^{th} AJCC system	0.2599	0.3868	–0.2891	0.2599	0.2655	–0.0129	95.5487

AJCC, American Joint Committee on Cancer; Diff, differences; IMA, invasive mucinous adenocarcinoma; NMA, nonmucinous adenocarcinoma.

Table S2 Univariate Cox PH analysis for the risk factors of lung cancer-specific death

Variables	Before			After matching		
	HR	95% CI	P value	HR	95% CI	P value
Pathology: IMA	0.852	0.732–0.993	0.04	1.007	0.845–1.201	0.934
Age (years)	1.011	1.01–1.013	<0.001	1.019	1.011–1.026	<0.001
Male sex	1.415	1.363–1.468	<0.001	1.618	1.387–1.889	<0.001
Race						
Black	1			1		
Other	0.819	0.746–0.899	<0.001	0.647	0.440–0.952	0.027
White	0.972	0.909–1.039	0.397	0.859	0.669–1.104	0.235
Marriage						
Married/partner	1			1		
Separated	1.086	1.041–1.133	<0.001	1.001	0.842–1.211	0.919
Single	1.008	0.947–1.074	0.797	1.093	0.851–1.403	0.487
Unknown	0.899	0.805–1.005	0.060	1.800	0.499–1.284	0.355
Insurance status						
Insured	1			1		
Medicaid	1.246	1.132–1.371	<0.001	1.454	0.980–2.157	0.063
Uninsured	1.050	0.850–1.297	0.652	0.826	0.205–3.326	0.788
Unknown	1.482	1.423–1.543	<0.000	1.601	1.349–1.899	<0.001
Operation						
Lobectomy	1			1		
Pneumonectomy	2.347	2.178–2.529	<0.001	2.408	1.702–3.406	<0.001
Segmentectomy	1.016	0.900–1.147	0.801	1.011	0.623–1.638	0.966
Wedge	1.163	1.081–1.250	<0.001	1.534	1.183–1.989	0.001
Chemotherapy	1.932	1.858–2.008	<0.001	1.763	1.478–2.103	<0.001
Radiation	2.607	2.494–2.725	<0.001	2.663	2.119–3.348	<0.001
Treatment						
Surgery	1			1		
Surgery + CTx	1.669	1.588–1.753	<0.001	1.500	1.124–1.853	<0.001
Surgery – RTx	3.070	2.838–3.321	<0.001	2.701	1.791–4.074	<0.001
Trimodality	2.831	2.689–2.982	<0.001	2.905	2.222–3.798	<0.001
Grade						
Low (Grade I/II)	1			1		
High (Grade III/IV)	1.741	1.675–1.809	<0.001	1.551	1.309–1.837	<0.001
Unknown	1.063	1.981–1.153	0.137	0.879	0.667–1.159	0.362
Laterality						0.851
Left	1			1		
Right	0.947	0.912–0.983	0.005	0.985	0.842–1.152	
One side	1.353	0.507–3.605	0.546	–	–	
Location						
Lower	1			1		
Middle	0.955	0.875–1.043	0.306	1.075	0.754–1.533	0.688
Upper	0.789	0.844–0.916	<0.001	0.994	0.843–1.173	0.943
Other	1.634	1.486–1.795	<0.001	1.872	1.288–2.721	0.001
SPN*	1.520	1.349–1.713	<0.001	1.156	0.634–2.108	0.636
Pleura involvement†						
No	Ref.			1		
Yes	1.815	1.646–2.002	<0.001	1.198	0.637–2.14	0.541
No data	1.534	1.434–1.641	<0.001	1.631	1.172–2.27	0.004
Tumor size (mm)*	1.004	1.003–1.004	<0.001	1.003	1.003–1.004	<0.001
No. of LNs positive	1.088	1.085–1.091	<0.001	1.16	1.106–1.215	<0.001
No. of LNs resected	1.002	0.999–1.004	0.208	1.001	0.990–1.012	0.826
T stages [2000–2003]						
T1	1			1		
T2	1.809	1.685–1.943	<0.001	2.343	1.566–3.507	<0.001
T3	2.843	2.490–3.247	<0.001	4.367	2.423–7.873	<0.001
T4	2.981	2.693–3.300	<0.001	4.718	2.610–8.527	<0.001
T stages [2004–2009]						
T1	1			1		
T2	2.029	1.910–2.155	<0.001	2.727	2.122–3.504	<0.001
T3	3.436	3.040–3.884	<0.001	4.246	2.726–6.614	<0.001
T4	2.829	2.566–3.120	<0.001	2.845	1.802–4.490	<0.001
T stage [2010–2014]						
T1	1			1		
T2	2.111	1.892–2.355	<0.001	1.531	0.787–2.979	0.209
T3	3.525	3.100–4.009	<0.001	4.503	2.376–8.533	<0.001
T4	4.299	3.589–5.150	<0.001	2.944	0.674–12.859	0.151
N stages						
N0	1			1		
N1	2.850	2.718–2.987	<0.001	2.703	2.012–3.632	<0.001
N2	3.390	3.238–3.549	<0.001	2.643	1.997–3.497	<0.001
N3	4.592	3.634–5.803	<0.001	–	–	
Stages [2000–2004]						
I	1			1		
II	2.640	2.415–2.886	<0.001	1.879	1.014–3.481	0.045
IIIA	3.040	2.807–3.292	<0.001	2.533	1.755–3.656	<0.001
IIIB	2.995	2.723–3.294	<0.001	2.799	1.703–4.601	<0.001
Stages [2004–2009]						
IA	1			1		
IB	1.943	1.794–2.105	<0.001	2.555	1.965–3.322	<0.001
IIA	3.134	2.765–3.553	<0.001	3.3.66	1.061–10.679	0.039
IIB	4.370	3.988–4.790	<0.001	5.122	3.578–7.333	<0.001
IIIA	4.901	4.507–5.329	<0.001	4.723	2.909–7.667	<0.001
IIIB	3.943	3.557–4.371	<0.001	2.950	1.863–4.673	<0.001
Stages [2010–2014]						
IA	1			1		–
IB	2.042	1.745–2.389	<0.001	1.481	0.653–3.358	0.347
II	8.912	2.218 –35.806	0.002	–	–	–
IIA	4.127	3.517–4.843	<0.001	4.300	1.692–10.925	0.002
IIB	4.193	3.542–4.964	<0.001	6.130	3.047–12.330	<0.001
IIIA	6.617	5.773–7.584	<0.001	4.171	1.561–11.146	0.004
IIIB	10.410	7.944–13.641	<0.001	18.765	2.395–147.02	0.005

*, data from the subset recorded from 2004; †, data from the subset recorded from 2010. CI, confidence interval; CTx, chemotherapy; HR, hazards ratio; LN, lymph nodes; RTx, radiation; SPN, solitary pulmonary nodule.