Interactive CardioVascular and Thoracic Surgery 34 (2022) 229–235
doi:10.1093/icvts/ivab257 Advance Access publication 27 September 2021

ORIGINAL ARTICLE

Cite this article as: Kim DH, Bae SY, Na KJ, Park S, Park IK, Kang CH *et al.* Radiological and clinical features of screening-detected pulmonary invasive mucinous adenocarcinoma. Interact CardioVasc Thorac Surg 2022;34:229–35.

Radiological and clinical features of screening-detected pulmonary invasive mucinous adenocarcinoma

Dae Hyeon Kim [a], So Young Bae [a], Kwon Joong Na [a,b], Samina Park[a,b], In Kyu Park[a,b,*], Chang Hyun Kang [a,b] and Young Tae Kim [a,b,c]

[a] Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul, South Korea
[b] Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, Seoul, South Korea
[c] Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea

* Corresponding author. Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea. Tel: +82-2-20722342; fax: +82-2-7643664; e-mail: ikpark@snu.ac.kr (I.K. Park).

Received 23 March 2021; received in revised form 8 August 2021; accepted 14 August 2021

THORACIC

Key question

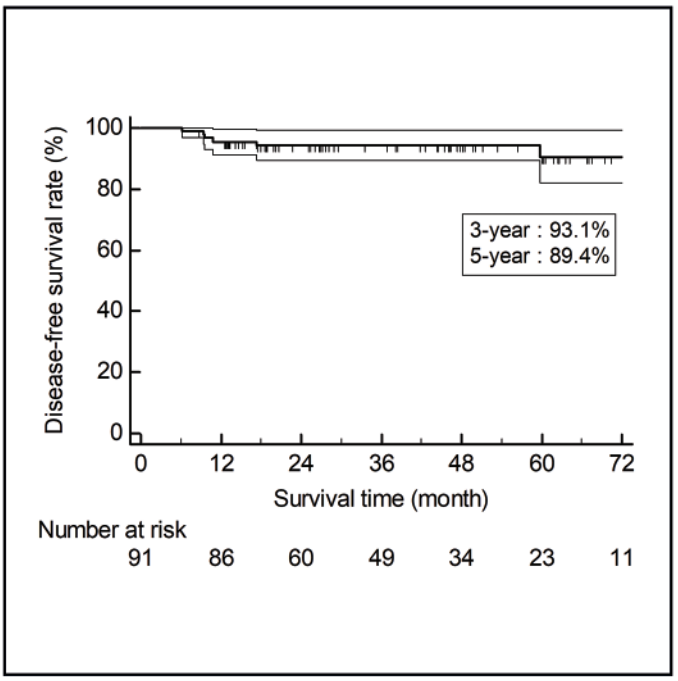
What is the prognosis of screening-detected pulmonary invasive mucinous adenocarcinoma (SD-IMA) after surgery?

Key finding(s)

The 5-year disease-free survival rate was 89.4% (lobectomy: 86.3%, sublobar resection: 100%).

Take-home message

Patients with SD-IMAs had good prognosis after surgical treatment.



Abstract

OBJECTIVES: The current understanding of pulmonary invasive mucinous adenocarcinoma is largely based on studies of advanced stage patients and data about early-stage invasive mucinous adenocarcinoma are sparse. We evaluated the radiological and clinical features of screening-detected early-stage invasive mucinous adenocarcinoma (SD-IMA).

METHODS: Data from 91 patients who underwent surgical treatment for SD-IMA (≤3 cm) from 2013 to 2019 were reviewed retrospectively. Data on radiological characteristics, clinicopathological findings, recurrence and survival were obtained. Disease-free survival rate was analysed.

RESULTS: Radiologically, SD-IMAs presented as a pure ground-glass nodule (6.6%), part-solid nodule (38.5%) or solid (54.9%). Dominant locations were both lower lobes (74.7%) and peripheral area (93.4%). The sensitivity of percutaneous needle biopsy was 78.1% (25/32). Lobectomy was performed in 70 (76.9%) patients, and sublobar resection in 21 (23.1%) patients. Seventy-three (80.2%), 15 (16.5%) and 3 (3.3%) patients had pathological stage IA, IB and IIB or above, respectively. Seven patients developed recurrence, and 3 died due to disease progression. Pleural seeding developed exclusively in 2 patients who underwent needle biopsy. The 5-year disease-free survival rate was 89.4%. The disease-free survival rates at 5 years were 86.3% in the lobectomy group and 100% in the sublobar resection group.

CONCLUSIONS: SD-IMAs were mostly radiologically invasive nodules. SD-IMAs showed favourable prognosis after surgical treatment.

Keywords: Adenocarcinoma of lung • Mucinous adenocarcinoma • Early detection of cancer • Disease-free survival

ABBREVIATIONS

C/T ratio	Consolidation-to-tumour ratio
CT	Computed tomography
DFS	Disease-free survival
IMA	Invasive mucinous adenocarcinoma
IQR	Interquartile range
MRI	Magnetic resonance imaging
NMA	Non-mucinous adenocarcinoma
NSCLC	Non-small-cell lung cancer
PCNB	Percutaneous needle biopsy
PET	Positron emission tomography
PSN	Part-solid nodule
SD-IMA	Screening-detected early-stage invasive mucinous adenocarcinoma

INTRODUCTION

Invasive mucinous adenocarcinoma (IMA), which accounts for 5% of pulmonary adenocarcinomas, has different characteristics than non-mucinous adenocarcinoma (NMA) in terms of histology, genetics and clinical features. IMA consists mainly of goblet or columnar tumour cells with intracytoplasmic mucin. Intrapulmonary metastasis presenting as skip lesions or multifocal lesions is a unique characteristic of IMA [1]. Thus, IMA is commonly detected in advanced stage and is more aggressive than NMA because of its higher recurrence rate and poorer prognosis [2, 3]. Genetic abnormalities in IMAs are also distinct from those of NMAs. Genetic alterations such as kirsten rat sarcoma viral oncogene mutation and thyroid transcription factor-1 expression are more frequent in IMA than in NMA. Epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement are rare [2, 4]. The recent increase in low-dose computed tomography (CT) screening highlights the need for better management of screening-detected early-stage IMA (SD-IMA), which had different features and prognosis compared with NMA. Precise understanding of the unique clinical features and outcomes after surgical management of early-stage IMA is necessary. However, most of what is currently known about IMAs is based on the studies of advanced stage IMAs [1, 2, 5], and the clinical data about early-stage IMAs, especially screening-detected IMAs, are sparse. Therefore, in this study, we investigated the radiological and clinical characteristics of SD-IMA, as well as the prognosis after surgical treatment.

MATERIALS AND METHODS

This study was conducted in compliance with the Declaration of Helsinki and approved by the institutional review board of Seoul National University Hospital (Approval Number: 1909-035-1062). The requirement for informed consent was waived.

A total of 197 patients underwent surgery for IMA from July 2013 to May 2019 in our institution. We included 91 patients with radiological tumours ≤3 cm whose IMAs had been detected by screening and who underwent surgical treatment (Fig. 1). Screening-detected IMAs in this study were the results of private medical check-up services.

Data on radiological characteristics, clinicopathological findings and postoperative surveillance were collected via review of medical records. Stage was classified according to the eighth edition of the International Association for the Study of Lung Cancer TNM classification system [6].

Radiological assessment

Radiological findings were obtained from the last CT scan before surgery. The radiological factors included nodule size, nodule type [pure ground-glass nodule/part-solid nodule (PSN)/solid

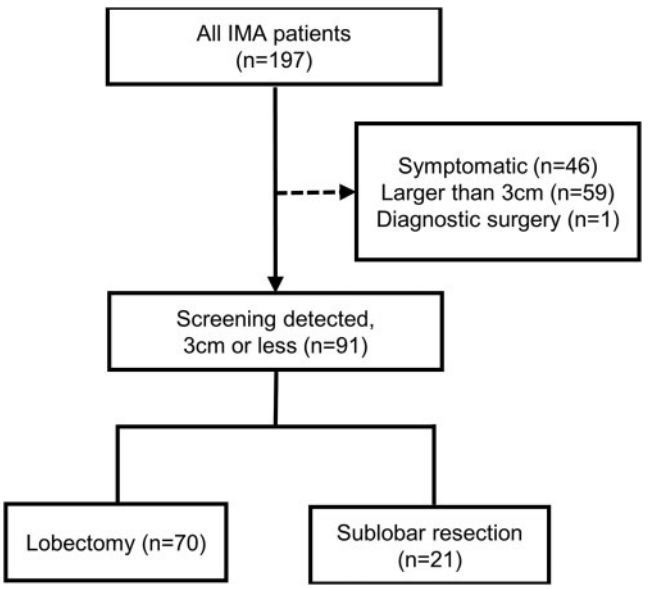


Figure 1: Flow diagram of the patient selection process. IMA: invasive mucinous adenocarcinoma.

nodule], consolidation-to-tumour ratio (C/T ratio), location of tumour (peripheral/central) and distance from visceral pleura to tumour margin. The lung CT screening reporting and data system category of each nodule was determined [3, 7]. The C/T ratio was defined as the proportion of the longest consolidation diameter divided by the longest tumour diameter in the lung window setting [8]. The location of the tumour was determined by a concentric line from the hilum and the division point was the peripheral third [9].

Preoperative work-up and surgical management

Pretreatment histological diagnosis was confirmed by percutaneous needle biopsy (PCNB) or intraoperative frozen section following diagnostic thoracoscopic resection. Diagnosis of primary pulmonary IMA in patients with history of previous gastrointestinal tract adenocarcinoma was made based on comprehensive pathological examination such as cytological comparison and molecular marker studies. Disease-free interval longer than 5 years was also considered in differential diagnosis. Positron emission tomography–CT (PET–CT) was performed in patients with invasive component in the nodule or suspicious metastatic lesions in CT scan. Brain magnetic resonance imaging (MRI) was performed in patients with clinical stage IB or higher. The standard procedure for curative surgery was lobectomy; however, sublobar resection was performed for radiologically indolent tumours considering tumour size, C/T ratio, tumour location and underlying pulmonary function. The pathological parenchymal resection margin was defined as the distance from the tumour edge to the nearest stapled resection margin confirmed by pathologist.

Statistical analysis

Disease-free survival (DFS) was defined the time from date of surgery to the date of recurrence or death whatever comes first. Patients without recurrent event or death were censored at the date of last follow-up. The last follow-up date was 30 August 2020. Local recurrence was defined as recurrence in the bronchial stump or parenchymal margin. Regional recurrence was defined as recurrence in the ipsilateral intrathoracic lymph node, other ipsilateral lobes or pleural dissemination. Other recurrences were considered distant metastases. Quantitative variables are expressed as the mean and, standard deviation or interquartile range (IQR), and categorical variables are expressed as the absolute numbers and relative frequencies. Time-to-event analyses were conducted using the Kaplan–Meier method and differences were compared using the log-rank test. The median follow-up duration was calculated using the reverse Kaplan–Meier method. The sensitivity of pathological diagnoses (needle biopsy or frozen examination) was calculated. Statistical analyses were conducted using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients

The characteristics of the patients are shown in Table 1. The majority of patients were women (62.6%, $n = 57$) and non-smoker (73.6%, $n = 67$). The mean age was 64.3 ± 10.0 years. The most common comorbidities were cardiovascular disease including hypertension (46.2%, $n = 42$). Twenty-four patients (26.4%) had a history of other malignancies with gastrointestinal tract cancers being the most frequent ($n = 9$). Almost all patients had normal pulmonary function and good performance status. The median time from screening detection to operation was 4 months (IQR 3–51).

Table 1: Patient demographics

Variables	Total ($n = 91$)
Age (years), mean ± SD	64.3 ± 10.0
Sex, *n* (%)	
Female	57 (62.6)
Male	34 (37.4)
Smoking history, *n* (%)	
Never smoker	67 (73.6)
Ex-smoker	20 (22.0)
Current smoker	4 (4.4)
ECOG performance status, *n* (%)	
0	82 (90.1)
1	9 (9.9)
Comorbidities, *n* (%)	66 (72.5)
Cardiovascular disease	42 (46.2)
Diabetes mellitus	14 (15.4)
Renal disease	1 (1.1)
Asthma	1 (1.1)
Cerebrovascular disease	3 (3.3)
Previous malignancy, *n* (%)	24 (26.4)
Gastrointestinal tract cancer	9 (9.9)
Breast cancer	5 (5.5)

ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

Table 2: Radiological characteristics

Variables	Total ($n = 91$)
Location, *n* (%)	
Right upper lobe	7 (7.7)
Right middle lobe	5 (5.5)
Right lower lobe	26 (28.6)
Left upper lobe	13 (14.3)
Left lower lobe	42 (46.2)
Nodule type, *n* (%)	
Pure ground-glass nodule	6 (6.6)
Part-solid nodule	35 (38.5)
Solid nodule	50 (54.9)
Tumour size, radiological (cm), mean ± SD	1.64 ± 0.58
Solid component size (cm), mean ± SD	1.30 ± 0.70
Consolidation-to-tumour ratio,[a] mean ± SD	0.49 ± 0.25
Distance from visceral pleural ≤1 cm, *n* (%)	85 (93.4)
SUV_{max}, mean ± SD	3.2 ± 3.0
Lung-RADS category, *n* (%)	
2	6 (6.6)
3	3 (3.3)
4A	15 (16.5)
4B	67 (73.6)

Lung-RADS: lung computed tomography screening reporting and data system; SD: standard deviation; SUV_{max}, maximal standardized uptake value in positron emission tomography.

[a]Part-solid nodule only.

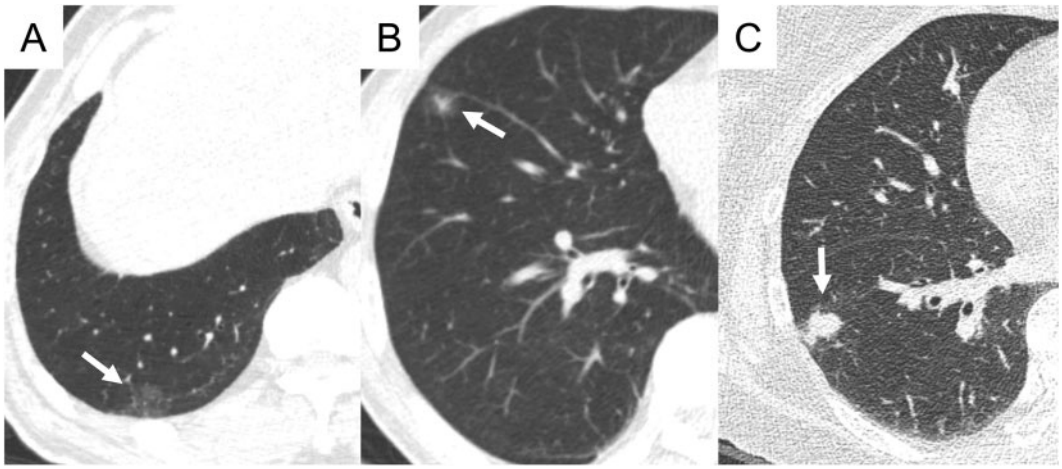


Figure 2: Heterogeneous radiological features of invasive mucinous adenocarcinomas of the lung; (**A**) 2.0 cm pure ground-glass nodule in the right lower lobe, (**B**) 1.5 cm part-solid nodule in the right middle lobe and (**C**) 1.5 cm sold nodule in the right lower lobe.

Radiological features

The dominant sites were the lower lobes ($n = 68$) and almost all nodules were located in the peripheral third of the lung (87.9%, $n = 80$). The distance from the visceral pleura to tumour margin was 1 cm or less in most tumours (93.4%, $n = 85$). Nineteen (20.9%) patients had synchronous non-dominant nodules.

The mean nodule size was 1.64 ± 0.58 cm (IQR 1.2–2.0). The type of nodules was pure ground-glass nodule in 6 (6.6%), PSN in 35 (38.5%) and solid nodules in 50 (54.9%) (Fig. 2). The mean C/T ratio of PSN was 0.49 ± 0.25 (IQR 0.40–0.66). The lung CT screening reporting and data system categories were 4A or 4B in most of cases (90.1%, $n = 82$). PET–CT was performed in 69 (75.8%) patients and the mean maximal standardized uptake value was 3.2 ± 3.0 (IQR 1.4–3.6) (Table 2). Brain MRI was performed in 42 (46.2%) and no patient had brain metastasis.

Pathology and surgery

Pretreatment histological diagnosis was attempted by PCNB in 33 patients and by intraoperative frozen section in 56 patients. Two patients underwent direct lobectomy due to combined NMAs. In the PCNB group, a diagnosis of non-small-cell lung cancer (NSCLC) was made in all patients (IMA−26, NMA−7). In the frozen section group, a diagnosis of NSCLC was made in 53 (94.6%) patients (IMA−29, NMA or carcinoma not otherwise specified−24). The frozen section results of 3 patients were false negative and 1 patient underwent lobectomy afterwards. The extent of pulmonary resection was lobectomy in 70 patients (76.9%), segmentectomy in 13 (14.3%) and wedge resection in 8 (8.8%) patients. Systematic lymph node dissection was performed in 85 patients (93.4%). The mean number of dissected lymph nodes was. 8.8 ± 5.2 in N1 stations and 12.5 ± 7.3 in N2 stations. In the sublobar resection group, the mean parenchymal resection margin distance was 2.72 ± 1.94 cm (IQR 1.25–4.35) and the mean margin-to-tumour ratio was 3.1 ± 2.7 (IQR 1.5–5.8). The margin-to-tumour ratio was <1 in 3 patients. Seven (7.7%) patients experienced postoperative complications. There was no postoperative mortality.

Seventy-three (80.2%), 15 (16.5%), 2 (2.2%) and 1 (1.1%) patients had stage pIA, pIB, pIIB and pIVA, respectively (Table 3). Two patients had mixed mucinous adenocarcinoma and NMA.

Table 3: Pathological results

Variables	Total ($n = 91$)
Tumour size, pathological (cm), mean ± SD	1.56 ± 0.84
pT T1mi, *n* (%)	1 (1.1)
T1a	22 (24.2)
T1b	41 (45.1)
T1c	10 (11.0)
T2a	16 (17.6)
T2b	0 (0.0)
T3	1 (1.1)
pN Nx, *n* (%)	5 (5.5)
N0	85 (93.4)
N1	1 (1.1)
pM M1a, *n* (%)	1 (1.1)
pStage pIA, *n* (%)	73 (80.2)
pIB	15 (16.5)
pIIB	2 (2.2)
pIVA	1 (1.1)
Synchronous double primary lung cancer	8 (8.8)
Visceral pleural invasion	11 (12.1)
Vascular invasion	2 (2.2)
Lymphatics invasion	3 (3.3)

SD: standard deviation.

Among 19 patients with non-dominant nodules, 2 had metastatic IMA, 8 had synchronous NMA, 5 had inflammatory nodules and the non-dominant nodules were not resected in 4. Adjuvant chemotherapy was not performed in 3 patients, who were indicated, considering comorbidities, low chemo-sensitivity nature of IMA and the patients' preference.

Thyroid transcription factor-1 was positive in 50% (8/16) and kirsten rat sarcoma viral oncogene mutations detected in 53.3% (8/15) of IMAs. The rates of epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement were 3.2% (2/62) and 4.2% (3/71), respectively.

Prognosis

The median follow-up duration was 42 months (IQR 20–61). Recurrence was detected in 7 patients. There was no local recurrence. Pleural seeding exclusively occurred in 2 (6.1%) patients

Table 4: Data of patients with recurrence

	PCNB	Surgery	Pathological stage	Recurrence site	DFI (months)	Recurrence treatment	Survival after recurrence (months)	Current status
1	-	Lobectomy	T2aN0M0	Brain	13.1	Radiation therapy	2.3	LD
2	+	Lobectomy	T2aN0M0	Contralateral lung	10.8	Operation Radiation therapy	40	L
3	+	Lobectomy	T2aN0M0	Contralateral lung/node/brain	6.2	Chemotherapy	9.0	D
4	-	Lobectomy	T1bN0M0	Contralateral lung	59.7	Operation	15.9	L
5	+	Lobectomy	T1bN0M0	Pleura/ chest wall	9.5	Chemotherapy	5.7	D
6	+	Lobectomy	T2aN1M0	Pleura	9.3	Chemotherapy	12.2	D
7	+	Lobectomy	T2aN0M0	Contralateral lung	17.4	No treatment	7.9	LD

D: dead; DFI: disease-free interval; L: live without disease; LD: live with disease; PCNB: percutaneous needle biopsy.

who had undergone PCNB and the disease-free intervals of these patients were 9.3 and 9.5 months, respectively. There was no pleural seeding in no-PCNB patients. Three patients experienced contralateral pulmonary metastasis and 1 patient experienced contralateral pulmonary metastasis and nodal recurrence. There were 2 extrathoracic metastases, both of which were brain metastases (Table 4).The 2 patients with pleural seeding died 5 and 12 months after recurrence, and 1 patient with brain metastasis died from treatment-related adverse events. The 5-year overall survival rate was 96.0% (Fig. 3A).

The 3- and 5-year DFS rates were 93.1% and 89.4%, respectively (Fig. 3B). The DFS rates at 5 years were 86.3% in the lobectomy group and 100% in the sublobar resection group, respectively (Fig. 4).

DISCUSSION

In this study, SD-IMA showed peripheral and lower lobe predominance, and 93.4% of SD-IMAs presented as radiologically invasive lesions. The prognosis after surgical treatment was favourable, and preoperative PCNB was associated with pleural seeding and dismal prognosis. Several distinctive clinicopathological features of IMA have previously been reported, including lower lobe predominance, bilateral involvement, distinguishing genetic mutation patterns and poorer prognosis [2, 3, 5, 10–12].

The distinct location pattern, lower lobe predominance, of IMA was observed in SD-IMA. Approximately three-quarter of SD-IMAs were in both lower lobes as has been reported in previous studies examining IMAs [10]. However, the anatomic and histological mechanism behind this lower lobe predominancy is still unknown. Another characteristic of IMAs is peripheral location. In this study, ∼93% of SD-IMAs were located adjacent to the visceral pleura. This feature may be related to the anatomical location of the cellular origin of IMA. IMAs are considered to arise from ciliated columnar cells via mucous columnar cell metaplasia in the non-terminal respiratory unit, which is a proximal part of respiratory unit of the lung [13, 14].

IMA has been divided into 2 radiological types, the pneumonic type and the solid type, and the prognoses of the 2 types are different [15]. Solid-type IMA tends to be diagnosed at relatively lower pathological stages and is associated with better outcomes, which is likely due to the larger extent of the tumour in pneumonic type IMA [16]. Few studies have reported the radiological characteristics of small IMAs. Lee *et al.* [5] reported that IMAs present as solid nodule or PSN. No pure ground-glass nodule was noted in their study. Shimizu *et al.* [16] reported that 19 small IMAs presented as a solid or part-solid (bubbling) nodule. No study has reported pneumonic type in small IMAs and there was no pneumonic type nodule in the present study. This finding suggests that pneumonic type does not have a different pathogenesis but rather appears as IMA progresses. Therefore, classification of IMA into the pneumonic or solid type is not a tumour characteristic but rather a status of progression.

Radiological nodule size and C/T ratio are important selection criteria for sublobar resection in small adenocarcinomas. Nodules ≤2 cm with a C/T ratio ≤0.25 are regarded as preinvasive or minimally invasive lesions and are candidates for sublobar resection if sufficient resection margin is guaranteed. To apply this strategy to SD-IMA, radiological–pathological correlations and oncological outcomes after sublobar resection in SD-IMA should be verified. The present study showed a high radiological–pathological correlation rate in SD-IMA. About 93% of SD-IMAs presented radiologically as invasive nodules such as solid nodule (53.8%) or PSN with C/T ratio >0.25 (39.8%). Only 6.6% of SD-IMAs presented radiologically as a preinvasive nodules. Considering the small portion of radiologically non-invasive SD-IMAs, the current strategy for determining the extent of resection based on radiological features would likely not affect the outcome of SD-IMA patients.

At another point, the prognostic effect of lepidic portion in SD-IMA should also be considered. In this study, approximately half of SD-IMAs had ground-glass components. It is unclear whether the prognosis of subsolid IMA depends on the size of the solid component as in NMA, or the entire tumour size, including the ground-glass component. The ground-glass component represents a lepidic growth pattern, which in IMA is considered an invasive component representing mucin spread to the alveolar spaces [4, 17]. Few studies have examined the correlation of the lepidic pattern in IMA with prognosis and survival. Hwang *et al.* [18] reported significantly better 5-year DFS among patients with pure lepidic IMA (100%) than those with minimally invasive IMA (95%) and the size of the invasive component was a significant prognostic factor in the multivariate analysis. Oki *et al.* [19] also reported that, in the pathological staging of IMA, exclusion of the lepidic component has higher discriminative power for overall survival than inclusion of the lepidic component. These findings suggest that ground-glass components in SD-IMA

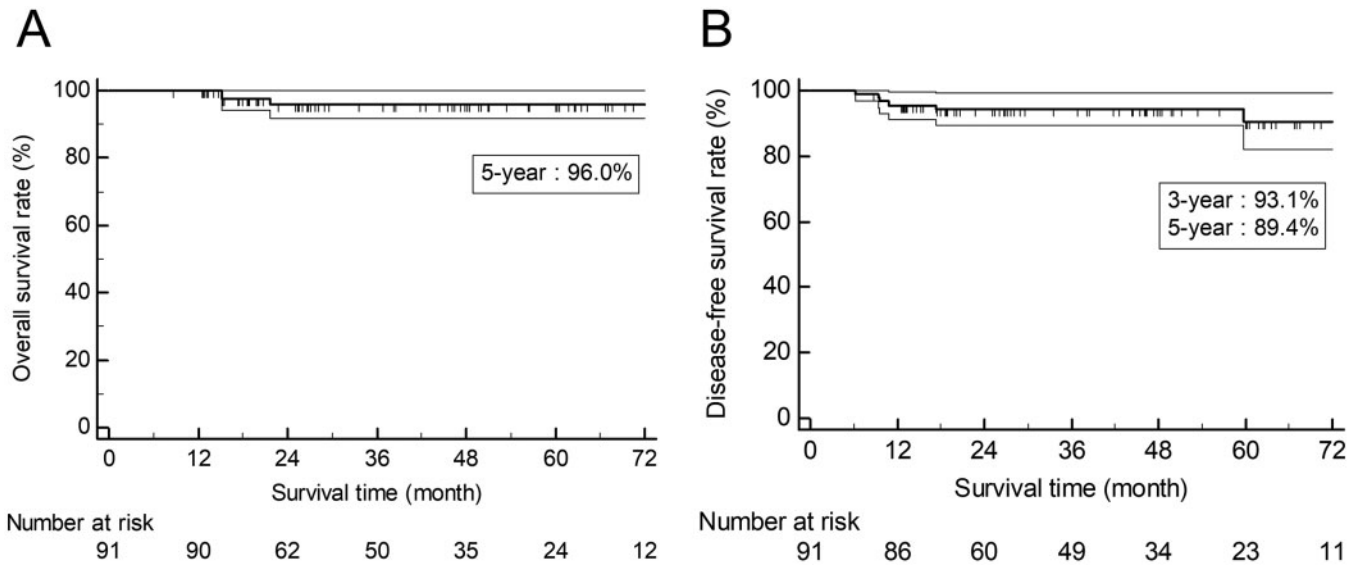


Figure 3: Kaplan–Meier curves for overall survival (**A**) and disease-free survival (**B**) (thin lines indicated the 95% confidence intervals).

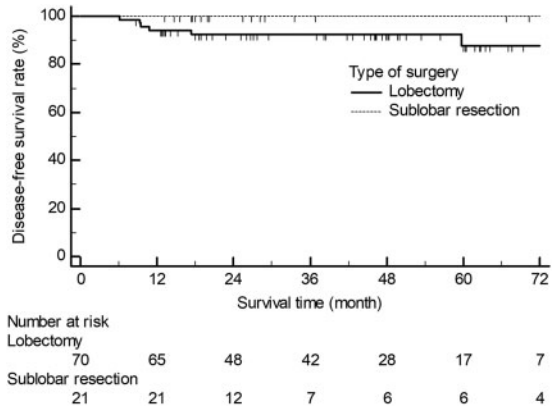


Figure 4: Kaplan–Meier curves for disease-free survival according to the extent of pulmonary resection.

would not affect oncological outcomes and the current strategy for determining extent of resection based on the size or ratio of the solid components can be applied in subsolid IMAs.

The long-term oncological outcomes of SD-IMAs in our study also support these recommendations. In this study, most SD-IMAs were pathological stage IA (80.2%) and the 3- and 5-year DFS rates were 93.1% and 89.4%, respectively. No local recurrence occurred even among patients who underwent sublobar resection. IMA is known to have a poorer prognosis than NMA [2, 5, 12]. However, some studies of early-stage IMA showed no significant difference in DFS and overall survival between NMA and NMA patients in the same stage [16, 20, 21]. In a study [5] of 81 solitary IMA cases in which 8% of patients underwent sublobar resection, the DFS rate of patients with IMA was between that of patients with low-grade (lepidic-predominant) NMA and that of patients with intermediate-grade (acinar/papillary-predominant) NMA, and the overall survival of patients with IMA was similar to that of patients with intermediate-grade NMA. In our study, the DFS of SD-IMA patients was similar to those of previous studies (79–89.2%), despite the higher proportion of sublobar resection (23% vs 8%) [5]. Unlike NMAs, extrapulmonary metastases are very rare in IMAs. A previous study showed that recurrences in IMA are limited to the lungs, and there is no extrapulmonary metastasis [21]. Primary failure pattern in our study was intrapulmonary metastasis in the contralateral lung and pleural seeding. Only 2 patients experienced extrathoracic metastases, both in the brain.

PCNB has been reported as a risk factor for pleural seeding in early-stage lung cancer [22–24]. Because SD-IMA is usually located in the subpleural area and consists of mucin, which can easily leak through the visceral pleural needle track, the risk of pleural seeding after PCNB is much higher than in NMA. In this study, pleural seeding exclusively developed in patients who underwent PCNB. Therefore, the effect of PCNB on pleural recurrence cannot be ruled out in this study too. PCNB should be reserved for highly selected cases in patients with subpleural nodule that requires surgical resection [25].

Limitations

This study had several limitations. First, it is a retrospective study that cannot be directly applied to screening and surgical planning protocols. A prospective study is necessary to evaluate the relationship between preoperative imaging results and surgical outcomes. Second, this was a single-institution study with limited number of cases. The statistical power of analyses would not be high and the results can be questionable since the number of cases and the number of events were small. To obtain a more definite conclusion, a multi-centred, large population, prospective study should be conducted.

CONCLUSION

The majority of SD-IMAs were radiologically invasive nodules in the periphery of the lower lobe. Patients with SD-IMAs showed favourable prognosis after surgical treatment.

Conflict of interest: none declared.

Author contributions

Dae Hyeon Kim: Data curation; Formal analysis; Investigation; Resources; Visualization; Writing—original draft; Writing—review & editing. **So Young Bae:** Data curation; Methodology; Resources. **Kwon Joong Na:** Data curation; Investigation; Methodology; Resources. **Samina Park:** Data curation; Formal analysis; Investigation; Resources. **In Kyu Park:** Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Validation; Writing—review & editing. **Chang Hyun Kang:** Conceptualization; Data curation; Investigation. **Young-Tae Kim:** Conceptualization; Data curation; Investigation; Methodology; Resources.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Emmanouil Ioannis Kapetanakis, Hitoshi Igai and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Dacic S. Pros: the present classification of mucinous adenocarcinomas of the lung. Transl Lung Cancer Res 2017;6:230–3.
[2] Cha YJ, Shim HS. Biology of invasive mucinous adenocarcinoma of the lung. Transl Lung Cancer Res 2017;6:508–12.
[3] Suzuki K, Kusumoto M, Watanabe S-I, Tsuchiya R, Asamura H. Radiologic classification of small adenocarcinoma of the lung: radiologic-pathologic correlation and its prognostic impact. Ann Thorac Surg 2006;81:413–19.
[4] Boland JM, Maleszewski JJ, Wampfler JA, Voss JS, Kipp BR, Yang P *et al.* Pulmonary invasive mucinous adenocarcinoma and mixed invasive mucinous/nonmucinous adenocarcinoma—a clinicopathological and molecular genetic study with survival analysis. Hum Pathol 2018;71:8–19.
[5] Lee HY, Cha MJ, Lee KS, Lee HY, Kwon OJ, Choi JY *et al.* Prognosis in resected invasive mucinous adenocarcinomas of the lung: related factors and comparison with resected nonmucinous adenocarcinomas. J Thorac Oncol 2016;11:1064–73.
[6] Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE *et al.*; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11:39–51.
[7] McKee BJ, Regis SM, McKee AB, Flacke S, Wald C. Performance of ACR Lung-RADS in a clinical CT lung screening program. J Am Coll Radiol 2016;13:R25–9.
[8] Nitadori J-I, Bograd AJ, Morales EA, Rizk NP, Dunphy MP, Sima CS *et al.* Preoperative consolidation-to-tumor ratio and SUVmax stratify the risk of recurrence in patients undergoing limited resection for lung adenocarcinoma ≤2 cm. Ann Surg Oncol 2013;20:4282–8.
[9] Casal RF, Vial MR, Miller R, Mudambi L, Grosu HB, Eapen GA *et al.* What exactly is a centrally located lung tumor? Results of an online survey. Ann Am Thorac Soc 2017;14:118–23.
[10] Moon SW, Choi SY, Moon MH. Effect of invasive mucinous adenocarcinoma on lung cancer-specific survival after surgical resection: a population-based study. J Thorac Dis 2018;10:3595–608.
[11] Motono N, Matsui T, Machida Y, Usuda K, Uramoto H. Prognostic significance of histologic subtype in pStage I lung adenocarcinoma. Med Oncol 2017;34:100.
[12] Kadota K, Nitadori J-I, Sima CS, Ujiie H, Rizk NP, Jones DR *et al.* Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 2015;10:806–14.
[13] Kim YK, Shin DH, Kim KB, Shin N, Park WY, Lee JH *et al.* MUC5AC and MUC5B enhance the characterization of mucinous adenocarcinomas of the lung and predict poor prognosis. Histopathology 2015;67:520–8.
[14] Park WY, Kim MH, Shin DH, Lee JH, Choi KU, Kim JY *et al.* Ciliated adenocarcinomas of the lung: a tumor of non-terminal respiratory unit origin. Mod Pathol 2012;25:1265–74.
[15] Nie K, Nie W, Zhang Y-X, Yu H. Comparing clinicopathological features and prognosis of primary pulmonary invasive mucinous adenocarcinoma based on computed tomography findings. Cancer Imaging 2019;19:47.
[16] Shimizu K, Okita R, Saisho S, Maeda A, Nojima Y, Nakata M. Clinicopathological and immunohistochemical features of lung invasive mucinous adenocarcinoma based on computed tomography findings. Onco Targets Ther 2017;10:153–63.
[17] Isaka T, Yokose T, Miyagi Y, Washimi K, Nishii T, Ito H *et al.* Detection of tumor spread through airspaces by airway secretion cytology from resected lung cancer specimens. Pathol Int 2017;67:487–94.
[18] Hwang S, Han J, Choi M, Ahn M-J, Choi YS. Size of non-lepidic invasive pattern predicts recurrence in pulmonary mucinous adenocarcinoma: morphologic analysis of 188 resected cases with reappraisal of invasion criteria. J Pathol Transl Med 2017;51:56–68.
[19] Oki T, Aokage K, Nomura S, Tane K, Miyoshi T, Shiiya N *et al.* Optimal method for measuring invasive size that predicts survival in invasive mucinous adenocarcinoma of the lung. J Cancer Res Clin Oncol 2020;146:1291–8.
[20] Qu Y, Zhao D, Mu J, Che N, Zhang C, Liu Z *et al.* Prognostic analysis of primary mucin-producing adenocarcinoma of the lung: a comprehensive retrospective study. Tumour Biol 2016;37:887–96.
[21] Shim HS, Zheng Z, Liebers M, Cha YJ, Ho QH, Onozato M *et al.* Unique genetic and survival characteristics of invasive mucinous adenocarcinoma of the lung. J Thorac Oncol 2015;10:1156–62.
[22] Matsuguma H, Nakahara R, Kitamura T, Kondo T, Kamiyama Y, Mori K *et al.* Pleural recurrence after needle biopsy of the lung: an analysis in patients with completely resected stage I non-small cell lung cancer. J Clin Oncol 2004;22:7177.
[23] Kashiwabara K, Semba H, Fujii S, Tsumura S. Preoperative percutaneous transthoracic needle biopsy increased the risk of pleural recurrence in pathological stage I lung cancer patients with sub-pleural pure solid nodules. Cancer Invest 2016;34:373–77.
[24] Wang T, Luo L, Zhou Q. Risk of pleural recurrence in early stage lung cancer patients after percutaneous transthoracic needle biopsy: a meta-analysis. Sci Rep 2017;7:42762.
[25] Vansteenkiste J, Crinò L, Dooms C, Douillard JY, Faivre-Finn C, Lim E *et al.*; Panel Members. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. Ann Oncol 2014;25:1462–1474.