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Clinical course of stage IV invasive mucinous adenocarcinoma of the lung

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ABSTRACT

Introduction: An invasive mucinous adenocarcinoma (IMA) is a distinct lung adenocarcinoma variant. The characteristics of stage IV IMAs are relatively unclear since most previous studies described resected cases from stage I to III. The present study aimed to investigate the clinical course of stage IV IMAs and compare the findings to those of stage IV invasive non-mucinous adenocarcinomas (INMAs).
Methods: The study included 36 IMA patients and 210 INMA patients. The clinicopathological parameters, treatment methods and responses, overall survival (OS), and progression-free survival (PFS) were evaluated.
Results: IMAs were predominantly located in the lower lobes and frequently presented with multifocal consolidation and lung-to-lung or pleural metastasis. *KRAS* mutations were noted in 60.0% of the examined IMAs. Non-TKI chemotherapy (CTx) was used in 72.2% of the IMA patients. OS was significantly better in untreated IMA patients than in untreated INMA patients. IMA patients treated with non-TKI CTx had no improvement of OS compared to the untreated IMA patients. However, among INMA patients, OS was best with TKIs in patients harbouring targetable mutations, followed by non-TKI CTx. IMA and INMA patients treated with non-TKI CTx had similar PFS.
Conclusions: Stage IV IMAs have distinct clinicopathological characteristics, and they might be less aggressive than INMAs. Since non-TKI CTx might not be beneficial in IMA patients, new therapeutic approach is necessary.

1. Introduction

A primary pulmonary invasive mucinous adenocarcinoma (IMA) is an adenocarcinoma variant, according to the current World Health Organization (WHO) classification of lung tumours [1]. The prevalence of IMAs is lower than that of invasive non-mucinous adenocarcinomas (INMAs), and they account for approximately 4–20% of non-small-cell lung cancers (NSCLCs) [2,3]. IMAs tend to present with multi-centric, multi-lobar, and bilateral involvement [1]. Histologically, IMAs show goblet and/or columnar cells with abundant intracytoplasmic mucin [1]. *KRAS* mutations are frequently observed in IMAs, whereas *EGFR* mutations are very rare and have been reported in only 0–5% of IMA cases [1,3–6]. INMA patients with *EGFR* mutations or *ALK/ROS1* rearrangements are eligible to receive targeted agents, such as tyrosine kinase receptor inhibitors (TKIs) [7–9]; however, IMA patients have a low chance of receiving targeted therapy owing to the rare occurrence or absence of targetable mutations. Most IMA patients in the advanced stage are ineligible for clinical trials of TKIs, and these patients generally receive non-TKI, platinum-based conventional chemotherapy (CTx). Most previous studies described resected IMA cases from stage I to III. However, the clinicopathological characteristics of stage IV IMAs and their prognosis and treatment responses are unclear, probably because of their rarity and low recognition on biopsy. The present study aimed to investigate clinicopathologic characteristics and prognosis of stage IV IMAs and compare the findings of stage IV IMAs to those of stage IV INMAs.

2. Materials and methods

2.1. Patient selection

This retrospective study was approved by the Institutional Review Board of Severance Hospital. A total of 96 patients were diagnosed with primary lung IMAs in our institution between

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Table 1
Comparison of clinicopathological characteristics between stage IV invasive mucinous adenocarcinomas (IMAs) and stage IV invasive non-mucinous adenocarcinomas (INMAs).

	IMA (n = 36)	INMA (n = 210)	P-value
Age, mean ± SD	63.7 ± 10.7	64.2 ± 11.7	0.834
Male, n (%)	17 (47.2)	107 (51.0)	0.679
Death, n (%)	27 (75.0)	150 (71.4)	0.659
Smoking history, n (%)			0.877
Never	20 (55.6)	123 (58.6)	
Former	10 (27.8)	50 (23.8)	
Current	6 (16.7)	37 (17.6)	
Pack-year, mean ± SD	17.4 ± 29.6	18.2 ± 33.1	0.975
Primary mass location, n (%)			**<0.001**
Upper/middle lobe	3 (8.4)	119 (56.7)	
Lower lobe	27 (75.0)	80 (38.1)	
Bilateral	4 (11.1)	10 (4.8)	
Ipsilateral multiple	2 (5.6)	1 (0.5)	
Progression to stage IV during follow-up, n (%)	15 (47.1)	17 (8.1)	**<0.001**
Metastasis sites, n (%)			**<0.001**
M1a	28 (77.8)	64 (30.5)	
M1b	4 (11.1)	100 (47.6)	
M1ab	4 (11.1)	46 (21.9)	
Initial radiologic diagnosis, n (%)			**0.038**
Cancer	31 (86.1)	201 (95.7)	
Pneumonia	5 (13.9)	9 (4.3)	
Chest CT finding, n (%)			**<0.001**
Solid mass	7 (19.4)	187 (89.0)	
Solid mass with consolidation	9 (25.0)	8 (3.8)	
Pneumonia/multiple consolidation	19 (52.8)	6 (2.9)	
Others (pseudomesotheliomatous or bilateral lymphangitic metastasis)	1 (2.8)	9 (4.3)	

SD, standard deviation; CT, computed tomography.

March 2000 and February 2015. Of these 96 patients, 36 had stage IV IMAs. Among the 36 patients, 21 had stage IV IMAs at the time of diagnosis and 15 had stage IV IMAs owing to tumour progression during follow-up. Of the 36 patients, 17 (47.2%) were diagnosed with biopsy of lung and 19 (52.8%) were diagnosed with resected specimens of lung. During the same period, 559 patients were diagnosed with INMAs. For comparison, 210 stage IV INMA patients were chosen with simple allocation in a 1:5 ratio. A 1:5 allocation was used to maximize statistical power, as this was a retrospective study [10,11]. Of the 210 INMA patients, 165 (78.6%) were diagnosed with biopsy or aspiration cytology of the affected lung, lymph nodes, and pleura; 8 (3.8%) were diagnosed with lung resection, and 37 (17.6%) were diagnosed with biopsy or resected specimens from distant metastasis sites. Among the 210 INMA patients, 193 had stage IV INMAs at the time of diagnosis and 17 had final stage IV INMAs owing to tumour progression during follow-up. All samples were reviewed by experienced pulmonary pathologists (Y.J.C. and H.S.S.). Diagnosis of IMA was based on the histopathologic description of WHO classification of lung tumours [1]; goblet and/or columnar cells with intracytoplasmic mucin and basally located nuclei (Supplementary Fig. 1). According to a previous study, biopsy specimens were considered to be representative for rendering the diagnosis of IMAs [12].

2.2. Clinicopathological analysis

The following clinicopathological parameters were recorded: age, sex, smoking status (never smokers, former smokers [quit smoking >1 year before diagnosis], and current smokers), pack-year smoking history (defined as the number of cigarette packs smoked per day multiplied by the number of years of smoking), location of the primary tumour, metastasis sites, and chest computed tomography (CT) findings. Treatment methods, treatment responses, overall survival (OS), and progression-free survival (PFS) were assessed. Additionally, the objective response rate (ORR) and disease control rate (DCR) were evaluated. Tumour response was determined according to Response Evaluation Criteria in Solid Tumours, version 1.1 [13].

Metastasis sites were categorised as follows: 1) M1a sites (pleural effusion, contralateral lung metastasis, and pleural seeding), 2) M1b sites (distant metastasis), and 3) M1ab sites (effusion and contralateral lung metastasis coexisting with distant metastasis). The patients were divided into the following two groups based on the first radiological impression: lung cancer group (lung cancer) and non-malignant group (non-malignant lesions, such as pneumonic consolidation and infection). The chest CT findings were categorised according to the features of the primary cancer lesion as follows: 1) solid mass without consolidation, 2) solid mass with any proportion of consolidation, 3) pneumonia pattern or multifocal consolidation involving the ipsilateral lung, and 4) others, including a pseudomesotheliomatous pattern or bilateral lymphangitic metastasis. Based on the treatment received, patients were categorised into the following groups: 1) TKI group (including *EGFR* TKIs and crizotinib for *ALK/ROS1* rearrangement) with or without targetable mutations, 2) non-TKI CTx group, 3) radiation therapy (RTx) only group, and 4) untreated group.

2.3. EGFR and KRAS mutation analysis

To determine the *EGFR* and *KRAS* mutation status, DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tissues using the DNeasy Isolation Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. For the *EGFR* gene, direct DNA sequencing of exons 18 through 21 was performed or the PNAClamp™ *EGFR* Mutation Detection Kit (PANAGENE, Daejeon, Korea) was used. For the *KRAS* gene, direct DNA sequencing of codons 12 and 13 was performed. Each tumour was classified as positive or negative for a mutation after comparison with the wild-type gene sequence.