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ONCOLOGY

Association of metastatic pattern and molecular status in stage IV non-small cell lung cancer adenocarcinoma

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Abstract

Objectives The aim of our study was to investigate the association between driver oncogene alterations and metastatic patterns on imaging assessment, in a large cohort of metastatic lung adenocarcinoma patients.

Methods From January 2010 to May 2017, 550 patients with stage IV lung adenocarcinoma with molecular analysis were studied retrospectively including 135 *EGFR*-mutated, 81 *ALK*-rearrangement, 47 *BRAF*-mutated, 141 *KRAS*-mutated, and 146 negative tumors for these 4 mutations (4N). After review of the complete imaging report by two radiologists (junior and senior) to identify metastatic sites, univariate correlation analyzes were performed.

Results We found differences in metastatic tropism depending on the molecular alteration type when compared with the non-mutated 4N group: in the *EGFR* group, pleural metastases were more frequent (32% versus 20%; $p = 0.021$), and adrenal and node metastases less common (6% versus 23%; $p < 0.001$ and 11% versus 23%; $p = 0.011$). In the *ALK* group, there were more brain and lung metastases (respectively 42% versus 29%; $p = 0.043$ and 37% versus 24%; $p = 0.037$). In the *BRAF* group, pleural and pericardial metastases were more common (respectively 47% versus 20%; $p < 0.001$ and 11% versus 3%; $p = 0.04$) and bone metastases were rarer (21% versus 42%; $p = 0.011$). Lymphangitis was more frequent in *EGFR*, *ALK*, and *BRAF* groups (respectively 6%, 7%, and 15% versus 1%); $p = 0.016$; $p = 0.009$; and $p < 0.001$.

Conclusion The application of these correlations between molecular status and metastatic tropism in clinical practice may lead to earlier and more accurate identification of patients for targeted therapy.

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Key Points

- *Bone and brain metastasis are the most common organs involved in lung adenocarcinoma but the relative incidence of each metastatic site depends on the molecular alteration.*
- *EGFR-mutated tumors preferentially spread to the pleura and less commonly to adrenals, ALK-rearrangement tumors usually spread to the brain and the lungs, whereas BRAF-mutated tumors are unlikely to spread to bones and have a serous (pericardial ad pleural) tropism.*
- *These correlations could help in the clinical management of patients with metastatic lung adenocarcinoma.*

Keywords Adenocarcinoma of lung · Neoplasm metastasis · Multimodal imaging · Mutation

Abbreviations

FISH	Fluorescent in situ hybridization
IHC	Immunohistochemistry
NSCLC	Non-small cell lung cancer
OS	Overall survival

Introduction

Lung cancer remains the first cause of cancer death worldwide, with an increased proportion in certain populations, such as female or non-smokers [1–3]. Most patients are still diagnosed in advanced stage, on which the systemic therapies are the main therapeutic strategy. However, the 5-year overall survival (OS) rate still remains inferior to 6% [4].

The discovery of oncogene driver alterations represents one of the most important progress in non-small cell lung cancer (NSCLC) patients, mainly somatic mutations (i.e., *EGFR*, *BRAF*, etc.) or chromosomal rearrangements (i.e., *ALK*, *ROS1*, etc.). These genomic alterations are responsible for more than 30% of NSCLC [5]. The development of targeted therapies against these specific molecular alterations has substantially improved the prognosis and quality of life for these populations [6, 7].

Certain clinical phenotypes are commonly associated with these molecular alterations, i.e., younger age, adenocarcinoma histology, or non-smoking habit [8–10], molecular testing is mandatory to prescribe targeted therapy, currently indicated at diagnosis of advanced disease in clinical routine, the detection of *EGFR*, *BRAF* mutations, and *ALK* and *ROS1* rearrangements [11].

Unfortunately, in up to 30% of the patients, the sample tissue is insufficient to perform molecular analyses after pathological assessment [12], and sometimes systemic therapy may be initiated even in the absence of known molecular status.

A better knowledge of the clinical phenotype of these patients can help to prioritize the tissue specimen for molecular testing, or can be a strong argument for performing a re-biopsy. Therefore, the radiological pattern could provide additional information. Small previous studies have been reported with no solid data (Table 1).

EGFR is the most frequently investigated mutation, but results are contradictory (lung, liver, and brain are more affected in a study of 456 *EGFR* patients [13], pleura and bone in another study of 218 *EGFR* patients [14]).

We aimed to investigate the association between metastatic patterns and driver oncogene alterations in a large cohort of metastatic lung adenocarcinoma patients.

Methods

Study population

Advanced metastatic NSCLC patients diagnosed between January 2010 and May 2017 in one tertiary oncological center were retrospectively assessed.

A complete imaging work-up (contrast-enhanced computed tomography included chest and upper abdomen, brain imaging, and body 18FluoroDG-PET) and the molecular analysis including at least *EGFR*, *KRAS*, *BRAF*, and *ALK* molecular alterations performed on the primary or metastatic tissue were mandatory for inclusion. Patients with previous medical of other metastatic cancer were excluded.

This study was approved by the institutional review board. No informed consent was required. Enrollment was conducted in two steps: during the first phase, between January 2010 and May 2015, enrolling all patients with metastatic lung adenocarcinoma, then, during the second phase, between May 2015 and May 2017 enrolling *EGFR*-mutated, *ALK*-rearranged, *or BRAF*-mutated patients.

Clinical data were retrospectively collected, including gender, age at inclusion, and smoking status, among others.

Molecular analysis

EGFR, *BRAF*, and *KRAS* mutations were analyzed by genome sequencing, according to the clinical routine in our institution. *ALK*-rearrangement was investigated either by fluorescent in situ hybridization (FISH) or by immunohistochemistry (IHC). We defined as control group a "fourth-negative" group (4N), in case of *EGFR*, *BRAF*, *KRAS*, and *ALK* negative detection by a clinical routine testing.

Table 1 Literature data on the association of metastatic organs and molecular status *X*/*Y*: *X* represents the number of patients carrying the mutation, and *Y* the control group not mutated or carrying another mutation when specified. Vs: versus

	pleura	lung	Liver	brain	bone	pericardium	adrenal gland	lymphangitis
More frequent	***EGFR*** -[16]: 139/88 -[17] : 71/720 -[18]: 138/144 -[14]: 218/1008 ***ALK*** -[31] : 41/80 -[35] : 31/254 -[32]Vs EGFR: 68/130	***EGFR*** -[22]: 98/148 -[27]: 103/160 -[28]: 116/166 -[29]: 22/33 -[30]Vs ALK-KRAS: 126/47-35 -[13]: 456/607 ***KRAS*** -[35]: 64/221 -[28]: 31/166 -[14]: 784/1008 ***HER2*** -[36]: 65/3735	***EGFR*** -[31]: 39/80 -[18] : 138/144 -[13] exon 21: 190/607 -[26]: 27/454 ***ALK*** -[31]: 41/80 -[14]: 42/1008	***EGFR*** -[19]exon 19: 18/31 -[20]: 37/63 -[21]: 12/19 -[22] : 98/148 -[23]: 138/176 -[24]: 16/79 -[25] : 108/126 -[13]: 456/607 -[26]: 27/454	***EGFR*** -[14]: 218/1008 ***KRAS*** -[26]: 91/390	***EGFR*** -[17]: 71/720 ***ALK*** -[31]: 41/80 -[32]Vs EGFR: 68/130		***ALK*** Versus EGFR -[30]: 47/126 -[32]: 68/130
Less frequent	***EGFR*** -[27]: 103/160 ***KRAS*** -[37]: 143/357 -[17]: 277/596 -[30]Vs ALK-EGFR: 35/47-126		***KRAS*** [37] : 143/357	***EGFR*** -[14] : 218/1008		***KRAS*** -[17] : 277/596	***EGFR*** -[14]: 218/1008	
No difference	***EGFR*** -[22]: 98/148 -[38]Vs ALK: 118/33	***EGFR*** -[31]: 39/80 -[18]: 138/144 ***ALK*** -[31]: 41/80	***EGFR*** -[22]: 98/148 -[38]Vs ALK: 118/44	***EGFR*** -[31] : 39/80 -[19] exon 21: 8/31 -[38]Vs ALK: 118/33 -[39] : 62/62; Vs KRAS: 62/65 ***ALK*** -[31]: 41/80 ***KRAS*** -[37]: 143/357 -[39] : 65/62; Vs EGFR: 65/62	***EGFR*** -[31]: 38/90 -[22]: 98/148 -[38]Vs ALK: 118/33 -[39]: 62/62; Vs KRAS: 62/65 ***ALK*** -[31]: 41/80 ***KRAS*** -[37]: 143/357 -[39]: 65/62; Vs KRAS: 65/62	***EGFR*** -[38]Vs ALK: 118/33	***EGFR*** -[31]: 38/80 -[22]: 98/148 ***ALK*** -[31]: 41/80 ***KRAS*** -[37]: 143/357	

Imaging assessment

The imaging review was performed by two independent radiologists A.D. (last year radiology fellow) and C.C. (senior lung cancer radiologist with 12 years of experience), blinded to the molecular status. Discrepancies were reviewed and consensus obtained. Metastasis sites were described and classified in different subgroups: bone, brain, lung, pleura, adrenal gland, lymph node, liver, peritoneum, carcinomatous lymphangitis, spleen, soft tissue, pericardium, skin, kidney, pancreas, and thyroid. Primary tumor of the lung and mediastinal lymph nodes was not considered as metastatic (according to the 8th edition of the TNM classification [15]).

Any histologically proven lesion or lesions whose appearance on imaging (conventional and metabolic) and evolution were consistent with the diagnosis were considered metastatic.

Statistical analysis

Univariate statistical analysis was performed with SPSS (version 20; SPSS Inc.). The rate of metastasis organ by organ was compared is each molecular subgroup (*EGFR*+, *BRAF*+, *KRAS*+, and *ALK*+), to the quadruple-negative subgroup (4N) using Fisher's exact test or chi-square test when applicable.

The age difference between molecular group and 4N group was compared by using Student's *t* test.

Clinical characteristics (including gender and smoking status) were described according to molecular status, and differences were assessed by the chi-square test.

A *p* value less than 0.05 was considered statistically significant.

Results

Study population

According to the inclusion and exclusion criteria, from the original database of 939 NSCLC patients, the final study cohort included 550 patients with stage IV lung adenocarcinoma (Fig. 1).

Among them, 444 patients were initially diagnosed with stage IV disease, and the remaining 106 were included at their first imaging showing progression to metastatic stage.

The study population consisted in 294 women (45%) and 362 men (55%), with a mean age of 59 years (23–88).

This cohort was composed of 135 *EGFR*-mutated, 81 *ALK*-rearranged, 47 *BRAF*-mutated, 141 *KRAS*-mutated, and 146 quadruple-negative patients (4N).

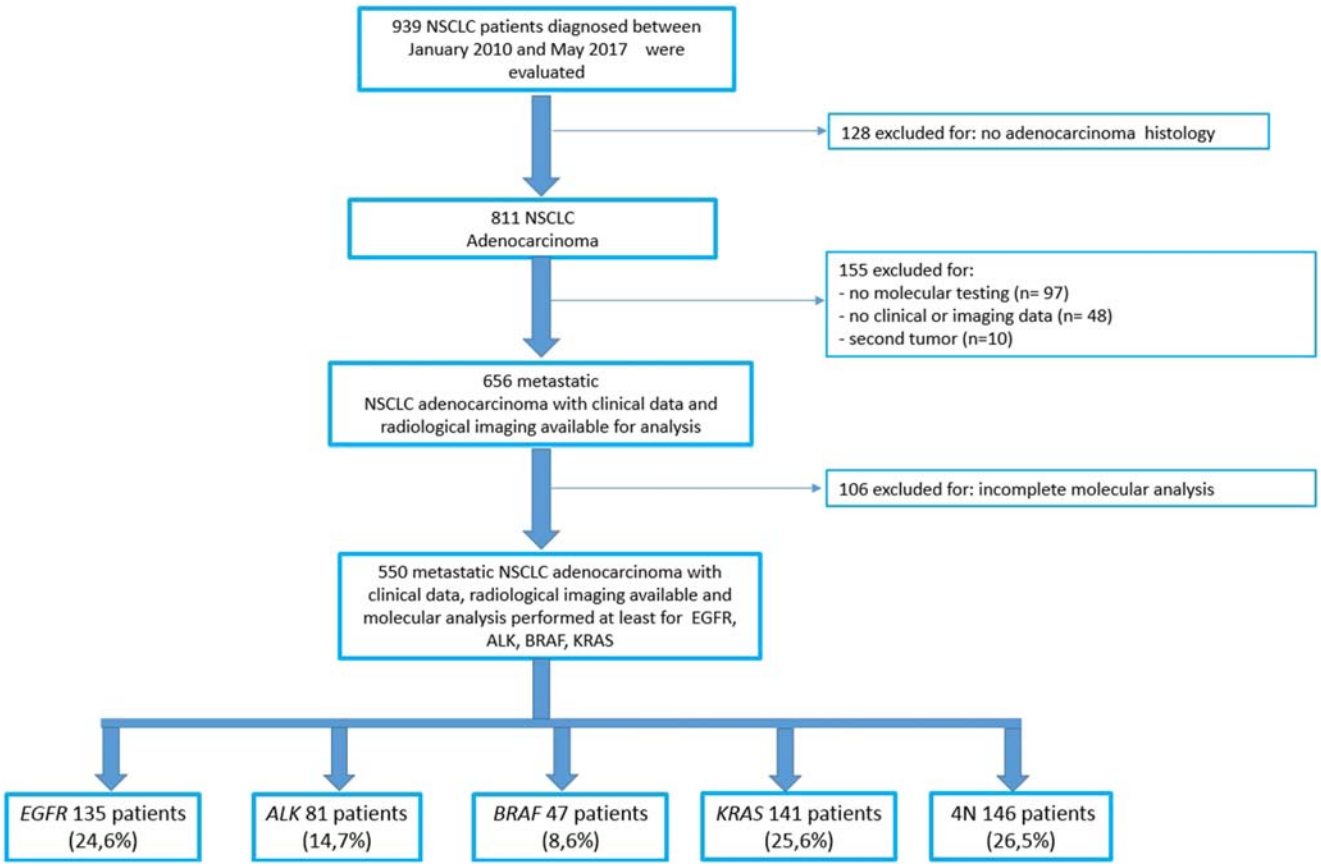

Fig. 1 Study flow chart

Table 2 Baseline characteristics of the study population

	EGFR $n = 135$ (%)	*ALK* $n = 81$ (%)	*BRAF* $n = 47$ (%)	*KRAS* $n = 141$ (%)	*4N* $n = 146$ (%)
Gender					
Female	96 (71)***	39 (48)	21 (45)	52 (37)	60 (41)
Male	39 (29)	42 (52)	26 (55)	89 (63)	86 (59)
Median, range	59, 25–88	52***, 23–82	63*, 35–88	59, 30–83	59, 29–89
Smoking status					
Non-smoker	78 (58)***	37 (46)***	17 (36)*	6 (4)***	28 (19)
Former smoker	40 (30)	26 (32)	16 (34)	55 (39)	48 (33)
Current smoker	17 (13)	18 (22)	14 (30)	80 (57)	70 (48)

*p value compared with control group 4N < 0.05

***< 0.001

Among the *EGFR*-mutated patients, 78 had *EGFR* exon 19 deletions, 40 *EGFR* L858R exon 21 mutations, 7 *EGFR* exon 18 mutations, and 10 *EGFR* exon 20 mutations.

Among the *KRAS*-mutated patients, mainly G12 ($n = 102$) (subtype C ($n = 59$) and V ($n = 25$)), G13 ($n = 11$), or uncommon ($n = 28$).

In case of *BRAF*-mutated patients, 40 had $BRAF^{V600E}$ mutation and 7 other uncommon mutations.

Compared with the 4N group, *EGFR*-mutated, *ALK*-rearranged, and *BRAF*-mutated patients were significantly associated with non-smoking status (respectively $p < 0.001$; $p < 0.001$; *and* $p < 0.05$); in contrast *KRAS*-mutated patients were more commonly smokers ($p < 0.001$).

ALK-rearranged and *BRAF*-mutated patients were the youngest and the oldest populations in the study, respectively ($p < 0.001$ *and* $p < 0.05$).

EGFR-mutated group had significantly more female than 4N group ($p < 0.001$) (Table 2).

Molecular alterations and metastatic pattern

Overall, the most common sites of metastatic disease were bone (44%), brain (34%), and lung (30%).

The distribution of metastatic organs according to the molecular alteration is described in Table 3 and Fig. 2.

Pleural metastases and lung lymphangitis were significantly more frequent in *EGFR*-mutated patients vs. 4N group (32% vs. 20%, respectively; $p = 0.021$ and 6% vs 1%; $p = 0.016$). Adrenal gland, lymph node, and soft tissue metastases were significantly less common in the EGFR group (respectively 6% versus 23%; $p < 0.001$; 11% versus 23%; $p = 0.011$; and 1% versus 8%; $p = 0.016$).

In *ALK*-rearranged patients, the involvement of central nervous system (42% vs. 29%; $p = 0.043$), lung (37% versus 24%; $p = 0.037$), and lymphangitis (7% versus 1%; $p = 0.009$) were more common, compared with 4N group.

Table 3 Distribution of metastatic sites according to the molecular alteration

	EGFR $n = 135$ (%)	*ALK* $n = 81$ (%)	*BRAF* $n = 47$ (%)	*KRAS* $n = 141$ (%)	*4N* $n = 146$ (%)
Bone	71 (53)	35 (43)	10 (21)*	66 (47)	61 (42)
Brain	48 (36)	34 (42)*	10 (21)	51 (36)	42 (29)
Lung	43 (32)	30 (37)*	14 (30)	41 (29)	35 (24)
Pleura	43 (32)*	19 (23%)	22 (47)***	23 (16)	29 (20)
Adrenal gland	8 (6)***	12 (15)	5 (11)	38 (27)	34 (23)
Lymph node	15 (11)*	17 (21)	7 (15)	20 (14)	33 (23)
Liver	26 (19)	15 (19)	6 (13)	24 (17)	20 (14)
Peritoneum	1 (1)	3 (4)	4 (9)	9 (6)	7 (5)
Lymphangitis	8 (6)*	6 (7)**	7 (15)***	3 (2)	1 (1)
Pericardium	2 (1)	3 (4)	5 (11)*	3 (2)	4 (3)
Soft tissue	2 (1)*	2 (2)	1 (2)	10 (7)	11 (8)

*p value compared with control group 4N < 0.05

**< 0.01

***< 0.001

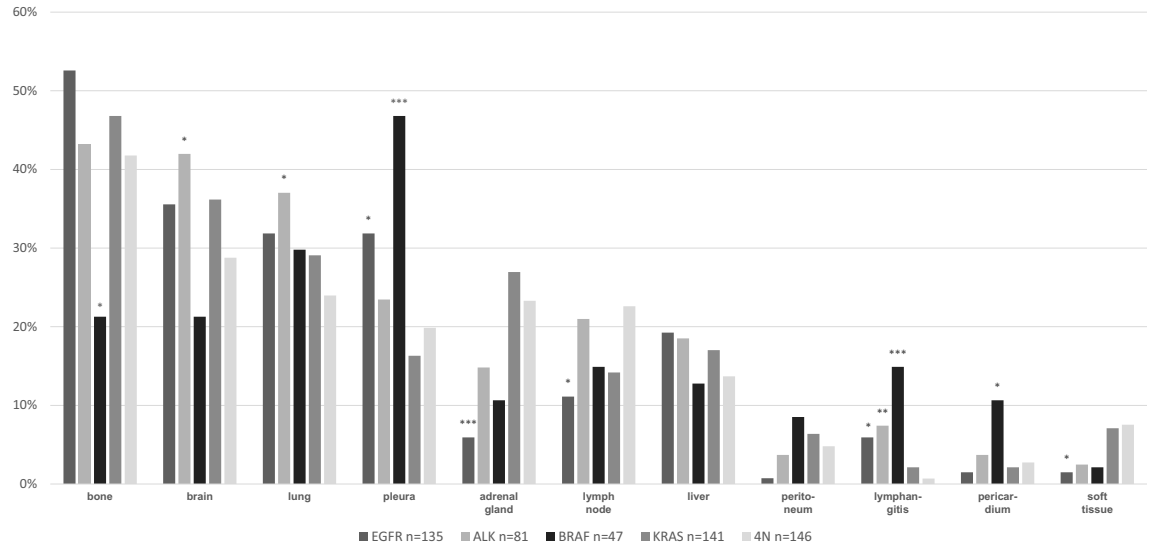

Fig. 2 Comparison of the distribution of metastasis sites by molecular subgroup. *p value compared with control group 4N < 0.05; **< 0.01; ***< 0.001

In *BRAF*-mutated patients, pleural (47% versus 20%; $p < 0.001$), pericardial metastases (11% versus 3%; $p = 0.040$), and lymphangitis (15% versus 1%; $p < 0.001$) were more frequent compared with 4N group; however, bone metastases were less common (21% vs. 42%; $p = 0.011$).

No differences were observed in the *KRAS*-mutated population compared with 4N group.

Discussion

We report in this article the correlation between molecular status and metastatic tropism in a large cohort of mutated and non-mutated lung adenocarcinoma patients. The strength of the present study relies on 2 main aspects: the retrospective reading of the complete multimodality imaging work-up by 2 dedicated radiologists and the number of molecular alterations investigated.

Similarly to the majority of previously published studies, *EGFR*-mutated patients have a higher rate of pleural metastases [14, 16–18] and a lower rate of adrenal metastases [14]. We found no difference on the incidence of brain metastases in the *EGFR* group compared with the 4N group according to previous studies (Table 1). Our results seem conflicting with those of Kuijpers et al who found a lower rate of brain involvement, but they considered neurologically asymptomatic patients without brain imaging as non-metastatic, which probably resulted in an under-diagnostic of this location [14]. On the contrary, some other authors described a higher rate of brain metastasis (interestingly, these are mainly Asian studies [13, 19–26]). A lower proportion of lymph node and soft tissue metastases were noted in the EGFR group, as well as a higher rate of lymphangitis: these observations have, to the best of our knowledge, never been described in the literature

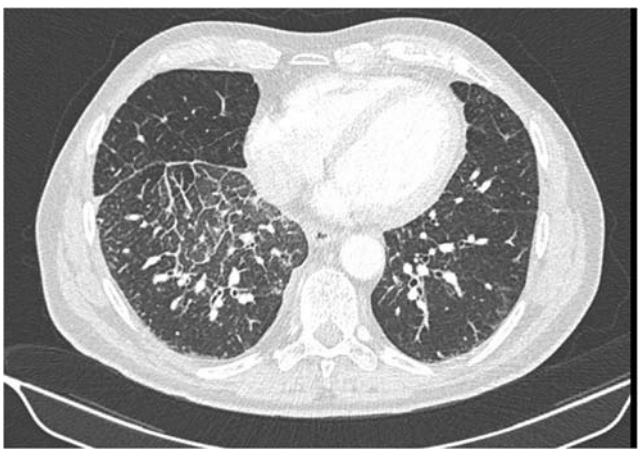

Fig. 3 Axial computed tomography (CT) image of a 72-year-old man with lung adenocarcinoma EGFR+, showing a carcinomatous lymphangitis of lower right lobe

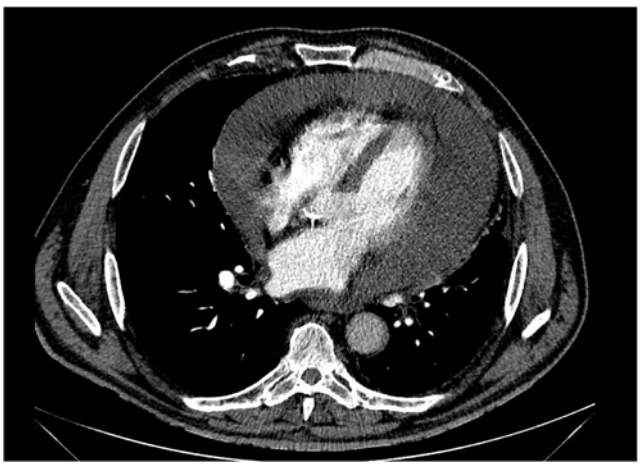

Fig. 4 Axial CT image of a 35-year-old woman patient with lung adenocarcinoma BRAF+, showing pericardial effusion

(Fig. 3). Several studies showed a higher incidence of lung metastases in *EGFR* group [13, 22, 27–30], but this trend does not appear significant in our study, similarly to the studies of Zhao et al and Doebele et al [18, 31].

In the *ALK* group, there were significantly more brain and lung metastases, which was not demonstrated in the Doebele et al's cohort of 41 patients [31].

Lymphagitis was more common in the *ALK* group, according to 2 other studies [30, 32].

Contrary to the literature, no significant difference was noted in regard to the rate of liver metastases [14, 31].

To our knowledge, our study is the first to describe *BRAF* lung tumors tropism as a unique pattern: pleural and pericardial metastases were significantly more frequent, confirming the findings of 3 previous case reports [33, 34] (Fig. 4). *BRAF*-mutated tumors also shown more lymphangitis and significantly inferior tropism for bone metastases compared with the 4N group.

In light of our results, we believe that the clinical management of patients with a diagnosis of metastatic lung adenocarcinoma could be transformed. In particular, It could improve and personalize the imaging interpretation by accurately identify metastases in the case of oligometastatic disease.

Our study has several limitations. First, there is a selection bias, related to the monocentric tertiary referral center effect. This could explain in particular the younger mean age of our patients than in other studies. The retrospective nature of our study is also a limitation; some patients had received systemic treatment prior to stage IV diagnosis, which may have changed the metastatic spread. There were a lot of excluded patients in the cohort, related to incomplete molecular profile, and we could not take into account other drivers such as *ROS1*, *RET*, *NTRK* fusions and *HER2* mutation, *MET* mutation, because of their rarity.

In conclusion, the application of these results in clinical practice will potentially lead to earlier and more accurate identification of patients for targeted therapy on basic imaging work-up.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Caroline Caramella.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was not required for this study because of the retrospective design.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Prospective
- Observational
- Performed at one institution

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