Utility of Genomic Analysis in Differentiating Synchronous and Metachronous Lung Adenocarcinomas from Primary Adenocarcinomas with Intrapulmonary Metastasis

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Abstract

Distinguishing synchronous and metachronous primary lung adenocarcinomas from adenocarcinomas with intrapulmonary metastasis is essential for optimal patient management. In this study, multiple lung adenocarcinomas occurring in the same patient were evaluated using comprehensive histopathologic evaluation supplemented with molecular analysis. The cohort included 18 patients with a total of 52 lung adenocarcinomas. Eleven patients had a new diagnosis of multiple adenocarcinomas in the same lobe \((n = 5)\) or different lobe \((n = 6)\). Seven patients had a history of lung cancer and developed multiple new tumors. The final diagnosis was made in resection specimens \((n = 49)\), fine needle aspiration \((n = 2)\), and biopsy \((n = 1)\). Adenocarcinomas were non-mucinous, and histopathologic comparison of tumors was performed. All tumors save for one were subjected to ALK gene rearrangement testing and targeted Next Generation Sequencing (NGS). Using clinical, radiologic, and morphologic features, a confident conclusion favoring synchronous/metachronous or metastatic disease was made in 65% of patients. Cases that proved challenging included ones with more than three tumors showing overlapping growth patterns and lacking a predominant lepidic component. Genomic signatures unique to each tumor were helpful in determining the relationship of multiple carcinomas in 72% of patients. Collectively, morphologic and genomic data proved to be of greater value and achieved a conclusive diagnosis in 94% of patients. Assessment of the genomic profiles of multiple lung adenocarcinomas complements the histological findings, enabling a more comprehensive assessment of synchronous, metachronous, and metastatic lesions in most patients, thereby improving staging accuracy. Targeted NGS can identify genetic alterations with therapeutic implications.

Introduction

Lung cancer remains the leading cause of cancer-related death in both men and women in the United States with an estimated 221,000 new diagnoses and 158,000 deaths in 2015 [1]. Of all the subtypes of lung carcinoma, adenocarcinoma has shown a dramatic rise in incidence worldwide and currently accounts for approximately half of all newly diagnosed primary lung malignancies [2–4]. Although most patients are diagnosed with a single primary lung adenocarcinoma, the frequency of identifying two or more adenocarcinomas at presentation is not uncommon and has an estimated incidence ranging from 1% to 8% [5–13]. Depending on the stage at
presentation, 20% to 52% of lung cancer patients eventually develop recurrent locoregional or metastatic disease [14,15]. Moreover, the incidence of developing a second primary lung cancer ranges from 1% to 4% per patient-year [8,16–19].

The diagnostic workup and treatment approach for a solitary primary lung adenocarcinoma are well established; however, identification of multiple carcinomas at presentation introduces new challenges both from a clinicopathologic standpoint and in relation to treatment strategy [20]. In the absence of a history of lung cancer, multiple adenocarcinomas could arise independently or may represent an advanced stage at presentation. In the setting of a previously diagnosed lung adenocarcinoma, newly identified lung cancers may represent new independent primary cancers, a new independent primary carcinoma with intrapulmonary metastasis, or recurrence of the previously diagnosed tumor.

In 1975, Martini and Melamed developed criteria defining two categories of multiple primary lung carcinomas: “synchronous” and “metachronous” [7]. Briefly, synchronous and metachronous refer to independent, unrelated, primary lung carcinomas arising simultaneously or at different points in time, respectively. The definition holds even when the histology is comparable if the tumors occur in different segments in the absence of common lymphatic involvement, and mediastinal or systemic metastases [7,20,21]. In patients with a history of lung cancer, a newly diagnosed lung carcinoma is considered metachronous if it is histologically different from the prior tumor. Identical histology does not preclude this categorization as long as the new carcinoma involves a different lobe, lacks common lymphatic involvement and extrapulmonary metastases, is detected 2 or more years later, or is associated with an in situ component [7,20,21]. The concept of comparable histology, however, can be challenging due to interobserver variability. The classification strategy set forth by the International Association for the Study of Lung Cancer (IASLC) recommended recording the percentages of different histologic patterns in lung adenocarcinoma. This allowed for more precise histologic comparison between multiple tumors and a greater level of consistency among pathologists [22,23]. The effort to distinguish multiple lung carcinomas was further reinforced by studies utilizing immunohistochemistry [24], DNA microsatellite analysis [25,26], clonality analysis [27], comparative genomic hybridization [28], and targeted gene sequencing [29–33].

The aim of this study is to determine the utility of targeted gene profiling using Next Generation Sequencing (NGS) in aiding the histomorphologic assessment for the classification of multiple lung adenocarcinomas as synchronous, metachronous, or metastatic.

Materials and Methods

Study Group

Pulmonary adenocarcinomas histologically diagnosed and subject to NGS between January and December 2015 were identified by computerized search of existing records. During this period, all specimens including cytology, biopsy, or resection were subject to NGS analysis. Of the 380 patients with lung tumors diagnosed as nonmucinous lung adenocarcinomas and in which targeted genomic profiling was successful, 18 with two or more concurrent lung tumors were identified for analysis. Clinical, demographic, and radiographic information including the number and location of tumors, history of lung carcinoma, and history of systemic therapy was obtained. Tumor size determination and measurement of distance of the tumors from one another were performed at the time of gross assessment and microscopic examination and were correlated with the radiologic findings. In patients with a history of lung adenocarcinoma, the original slides were reviewed when available, and NGS was performed on the paraffin-embedded tumor tissue sections. Approval for the study was obtained from the Institutional Review Board of from the New York Presbyterian Hospital-Weill Cornell Medicine in New York, NY.

Histologic Features and Relatedness

Tumor-containing hematoxylin and eosin–stained slides from formalin-fixed, paraffin-embedded tissue were blindly reviewed by two pathologists. The number of slides reviewed per case ranged from 2 to 10. Histologic subtyping was performed in all resection specimens showing a heterogeneous mixture of morphologic patterns as recommended by the IASLC [22]. Histologic patterns were quantified in 5% increments and included acinar, papillary, micropapillary, solid, cribriform, and lepidic. Resected adenocarcinomas with a purely lepidic growth pattern, an acinar or papillary component, and a micropapillary or solid component were graded as well, intermediate, and poorly differentiated, respectively [22,34,35]. The clinical, radiologic, and morphologic features of each patient’s tumors were used to categorize them as synchronous, metachronous, and metastatic. Immunohistochemical stains including TTF-1 (thyroid transcription factor-1, monoclonal: 8G7G3 Thermo Fisher Scientific), Napsin-A (polyclonal Cell Marque), and p40 (polyclonal Biocare Medical) were used to differentiate glandular from squamous differentiation in a subset of cases.

The relatedness of multiple lung carcinomas was determined using the following algorithm. Invasive adenocarcinomas exhibiting similar morphologies, primary growth patterns, and cytologic features; lacking a conspicuous lepidic component; and demonstrating identical NGS results were considered metastatic in nature irrespective of their location. Tumors with different predominant growth patterns and cytology arising in different lung lobes and exhibiting different NGS findings were considered independent and synchronous if identified at the same time and metachronous if one tumor was diagnosed at a different point in time. Tumors with similar growth patterns but distinct genomic findings were favored to be independent of one another [28,36]. Lastly, in the setting of identical molecular findings, tumors were favored to be independent if they exhibited different growth patterns, predominant lepidic growth, and/or dissimilar cytology.

Genomic and Cytogenetic Analysis

Ten unstained slides with 5-μm sections were obtained from formalin-fixed, paraffin-embedded tumor tissue. The tumor-enriched area was encircled on the hematoxylin and eosin–stained slides, and the neoplastic cellularity of the selected area was estimated by a pathologist. The scored slide was used to guide the macrodissection of tumor cells from the unstained slides. DNA was extracted using the Maxwell 16 FFPE DNA kit (Promega Corp., WI). NGS using 1 to 10 ng of input DNA was performed on the Ion Torrent Personal Genome Machine using the AmpliSeq Cancer Hotspot Panel v2 (Thermo Fisher Scientific, MA). Sequencing data were analyzed using the Variant Caller v4.4 (Thermo Fisher Scientific, MA). The NGS assay used for the study was validated and approved for accuracy, reproducibility, precision, and sensitivity in accordance with the guidelines of the New York State department of health. For cytogenetic
analysis, the LSI ALK dual-color break-apart rearrangement probe (Vysis/Abbott Molecular Inc., Des Plaines, IL) was used to test for rearrangements of the ALK gene. NGS and ALK FISH testing were performed in all tumors except one due to the unavailability of the tissue block.

Results
Eighteen patients comprising 13 women and 5 men with a total of 52 lung adenocarcinomas were included in the study. Presenting symptoms included cough ($n = 7$) and shortness of breath ($n = 2$); identification of the tumors in the remaining patients either was incidental ($n = 5$) or was detected on annual chest radiography ($n = 4$). The mean age at initial diagnosis was 66 years (median: 67, range: 51-78). A history of former or current smoking was present in 15/18 (83%) patients. Seventeen of the 18 patients harbored clinically relevant variants in one or more of the tumors. Patients were divided into three categories depending on tumor location and history of prior lung carcinoma (Figure 1). Eleven of the 18 patients were diagnosed with multiple lung adenocarcinomas at initial presentation. A clinical decision was made to treat the tumors as separate primaries in all patients. Five of the 11 patients presented with two tumors in the same lung lobe (Table 1). Different growth patterns were noted in the tumors of three patients. In the remaining two patients, the growth patterns were similar; however, cytoplasmic and/or nuclear features were dissimilar in the paired tumor samples (Figure 2). Molecular alterations were dissimilar in the tumors of the four patients that harbored variants (Table 1). Based on the combined histologic and molecular findings, all tumors were considered as synchronous lung adenocarcinomas.

Of the 11 patients presenting with multiple lung adenocarcinomas at initial presentation, 6 presented with tumors in different lobes (Table 2). Histologic comparison was possible in four patients and revealed distinct growth patterns and dissimilar cytoplasmic and/or nuclear features in the paired tumor samples. Five of the 11 patients presented with two tumors in the same lung lobe (Table 1). Different growth patterns were noted in the tumors of three patients. In the remaining two patients, the growth patterns were similar; however, cytoplasmic and/or nuclear features were dissimilar in the paired tumor samples (Figure 2). Molecular alterations were dissimilar in the tumors of the four patients that harbored variants (Table 1). Based on the combined histologic and molecular findings, all tumors were considered as synchronous lung adenocarcinomas.

Table 1. Clinical, Pathologic, and Molecular Characteristic of Patients Newly Diagnosed with Multiple Lung Adenocarcinomas in the Same Lobe

| Age/| Sex | Site | Procedure | Size (cm) | DX | Growth Patterns | Cytology/Stroma | NGS Results | Interpretation |
|-----|-----|------|-----------|-----------|----|----------------|----------------|-------------|---------------|
| 70/F | RU  | Segment | 1.2 | AC | Acinar, lepidic, solid | Different | EGFR G719C, EGFR S768I, TP53 A159P | Synchronous |
| 69/M | RU  | Lobe | 1.5 | AC | Lepidic, acinar | Different | KRAS Q61H | Synchronous |
| 51/M | RU  | Lobe | 4 | AC | Solid, lepidic, micropapillary | Different | TP53 G266* | Synchronous |
| 68/M | LU  | Wedge | 1.8 | AC | Acinar, lepidic | Different | NONE | Synchronous |
| 59/F | RL  | Lobe | 2.4 | AC | Acinar, micropapillary | Different | KRAS G12D, BRAF V600E | Synchronous |

Legend: AC, adenocarcinoma; AIS, adenocarcinoma in situ; DX, diagnosis; F, female; FNA, fine needle aspiration; LU, left upper lobe; M, male; MIA, minimally invasive adenocarcinoma; RL, right lower lobe; RU, right upper lobe.

* The proportion of different growth patterns was categorized from most common (predominant pattern) to least common.
nuclear features (Figure 3). Despite the presence of lymphatic involvement and regional nodal disease in three of these patients, distinct molecular alterations were identified. Based on these findings, these four patients were considered to have synchronous tumors. One patient was a poor surgical candidate and was diagnosed with two adenocarcinomas on FNA and biopsy; histologic comparison was not possible, but molecular findings were different, supporting categorization as synchronous. The last patient in this group presented with three tumors involving different lobes; two tumors were resected, and the third tumor was diagnosed by FNA and treated with radiation and chemotherapy. The resected tumors exhibited similar growth patterns but distinct cytologic features and molecular alterations (KRAS G12C and an EGFR exon 19 deletion). The tumor with the KRAS gene variant showed lymphatic involvement and nodal disease. The nonresected tumor also harbored a KRAS G12C variant, possibly representing an intrapulmonary metastasis.

The clinicopathologic characteristics and molecular signatures of the seven remaining patients with a prior history of lung adenocarcinoma and new multiple lung adenocarcinomas are

| Age/Sex | Site | Procedure | Size (cm) | DX | Growth Patterns * | Cytology/Stroma | NGS Results | Interpretation |
|---------|------|-----------|----------|----|------------------|-----------------|-------------|----------------|
| 71/F    | LU   | Lobe      | 3        | AC | Solid, acinar,   | Different       | EGFR L747_T751del15 | Synchronous |
|         |      |           |          |    | micropapillary   | EGFR L858R |             |                |
| 64/M    | LL   | Segment   | 1.5      | AC | Acinar, lepidic  | Different       | KRAS G12 V | Synchronous |
|         | RL   | Lobe      | 4.5      | AC | Solid, micropapillary | EGFR |             |                |
| 66/F    | LL   | Lobe      | 2.5      | AC | Acinar, lepidic, | Different       | PIK3CA H1047L | Synchronous |
|         | RL   | Wedge     | 1.5      | AC | Acinar, micropapillary, lepidic | EGFR L746_A750del15 |             |                |
| 54/M    | RU   | Lobe      | 3.2      | AC | Solid, acinar    | Different       | KRAS G12C | Synchronous |
| 64/F    | RM   | Biopsy    | <1       | AC | N/A              | Different       | EGFR L746_A750del15 | Synchronous |
|         | LL   | FNA       | 2.5      | AC | N/A              | N/A KRAS G12C | TPS3 R273C | Synchronous |
|         | LU   | Wedge     | 2.9      | AC | Acinar, lepidic, | Different       | KRAS G12C | Synchronous |
| 66/F    | LL   | Segment   | 1.6      | AC | Acinar, lepidic, | Different       | EGFR L747_T751del15, PIK3CA T1025A | KRAS G12C | Synchronous |
|         | RU   | FNA       | 1        | AC | N/A              | N/A KRAS G12C |             | Undetermined |

Legend: LL, left lower lobe; N/A, not applicable; RM, right middle lobe.

* The proportion of different growth patterns was categorized from most common (predominant pattern) to least common.
† N1 disease identified.
‡ N2 disease identified.
highlighted in Table 3. All patients had node-negative disease on initial presentation. Patients subsequently presented with two to five new tumors including adenocarcinoma (n = 16), adenocarcinoma in situ (n = 3), and minimally invasive adenocarcinoma (n = 1). The tumors involved the contralateral lung in six patients and another lobe of the same lung in one patient. The time spanning the initial and the new diagnosis ranged from 1 to 10 years. Molecular testing was performed on all but one specimen, and histologic data were available

### Table 3. Characteristics of Patients with a History of Lung Adenocarcinoma and New Multiple Lung Adenocarcinomas

| Age/Sex | Site   | Procedure | Size (cm) | DX              | Growth Patterns | Cytology/Stroma | NGS Results | Interpretation                  |
|---------|--------|-----------|-----------|-----------------|----------------|----------------|-------------|---------------------------------|
| 79/F    | LL     | Wedge 1   | 1         | AC              | Acinar, lepidic, solid, micropapillary | Similar          | EGFRL747_T751del15 | Intrapulmonary metastasis       |
| 71/F    | LU     | Wedge 1.5 | 1.5       | AC              | Micro papillary, cribriform, acinar, solid | Different        | EGFRL747_T751del15 | Tumor at first presentation      |
| 76/F    | RU     | Wedge 1.9 | 1.9       | AC              | Lepidic, acinar | Similar          | EGFRL858R | Metachronous                    |
| 72/F    | LU     | Wedge 1.5 | 1.5       | AC              | Acinar, solid, lepidic | Different        | TP53 N131 | Tumor at first presentation      |
| 71/F    | RU     | Wedge 2.7 | 2.7       | AIS             | Lepidic       | Different        | KRAS G12C | Metachronous                    |
| 71/F    | RU     | Wedge 2.8 | 2.8       | AC              | Solid          | Different        | Tissue not available | Tumor at first presentation      |
| 69/F    | LL     | Wedge 1.2 | 1.2       | AC              | Sol i d        | TP53 R273L       | Metachronous |                                |
| 67/F    | LU     | Wedge 2   | 2.6       | AC              | Acinar, lepidic | Different        | KRAS G12C |                                |
| 67/F    | RL     | Wedge 2.2 | 2.2       | AC              | Papillary, lepidic | Different        | KRAS G12C | Tumors at first presentation     |
| 68/F    | RU     | Segment 1.1| 1.1       | AC              | Lepidic, acinar | KRAS G12C | Metachronous                    |
| 67/F    | RU     | Segment 0.8| 0.8       | AC              | Cribriform, solid | Different        | TP53 S2151 |                                |
| 67/F    | LU     | Wedge 0.9 | 0.9       | AC              | Acinar, micropapillary | Similar          | KIT M541 |                                |
| 78/F    | RU     | Segment 1  | 1         | AC              | Acinar        | Different        | KRAS G12C | Tumors at first presentation     |
| 78/F    | RU     | Segment 0.7| 0.7       | AC              | Cribriform, lepidic | Different        | KRAS G12C | Favor metachronous               |
| 72/F    | LU     | Wedge 1.5 | 1.5       | AC              | Lepidic, acinar, papillary | Similar          | KRAS G12C | Metachronous                    |
| 62/F    | RU     | Wedge 2   | 2         | AC              | Lepidic, papillary | EGFRL863Q       | Tumor at first presentation      |

* The proportion of different growth patterns was categorized from most common (predominant pattern) to least common.
in all patients. Of the seven patients, six were determined to have metachronous tumors; findings favoring classification as metachronous included in situ adenocarcinoma, dissimilar predominant growth patterns, distinct cytologic features, and distinct molecular findings (Figure 4). The newly diagnosed tumor pair in one patient showed an identical EGFR exon 19 deletion and similar growth patterns and was favored to represent an intrapulmonary metastasis. The same deletion was identified in the patient’s original tumor diagnosed 8 years earlier; however, the tumor showed dissimilar cytologic features, and a definitive interpretation regarding the relatedness of all three tumors could not be made (Table 3, patient #1). None of the tumors tested harbored ALK gene rearrangements. In summary, all tumors arising in the same lung lobe and identified at the same time in patients without a history of lung cancer were interpreted as independent primary malignancies (Table 1). Similarly, in patients without a history of lung cancer, all simultaneously detected tumors arising in different lung lobes were also determined to be independent primary adenocarcinomas when morphologic assessment was possible (Table 2). Newly diagnosed carcinomas in patients with a history of lung adenocarcinoma were unrelated to the original tumor in all but one patient (Table 3).

Discussion

Identification of two or more primary lung carcinomas at presentation is not uncommon, with an incidence ranging from 5.7% to 11.5%. Specifically, a diagnosis of multiple primary lung adenocarcinomas can be seen in up to 8% of patients [12,17,37,38]. Determining whether these tumors are truly independent can be challenging given that lung adenocarcinomas frequently displays a spectrum of histologic subtypes, even within the same tumor, and tumors may show histologic overlap. Documented criteria were originally proposed to address this matter but may lack the power to differentiate between a metastatic lesion and a second primary lung cancer, a distinction that directly impacts prognosis and treatment options [6,20,22,27–29,36]. In 2011, the IASLC aimed to unify the terminology and diagnostic criteria for lung adenocarcinoma and recommended recording the percentages of the different histologic patterns and noting certain cytologic and stromal features [22,23,34,35,39–46]. This diagnostic approach allowed for a more accurate histologic comparison between multiple adenocarcinomas and was potentially useful in distinguishing multiple primary tumors from intrapulmonary metastases in two thirds of the cases in our study. Nevertheless, histologic overlap in predominant and secondary growth patterns was encountered in the tumors of three patients (Table 1, patient #3; Table 2, patient #6; Table 3, patient #6).

Cytologic and stromal features frequently differed in tumors with overlapping growth patterns. Conclusions regarding the relatedness of multiple lung adenocarcinomas that were made by assessing growth patterns agreed with those reached by examining cytologic/stromal features in 9 of 17 cases (53%). Using clinical, radiologic, and morphologic features, a confident conclusion favoring synchronous/metachronous or metastatic disease was made in 11 of 17 evaluable cases (65%). Cases that proved challenging included patients with more than three tumors showing overlapping growth patterns and lacking a predominant lepidic component. Genomic data were able to ascertain the relationship of carcinomas in 13 of 18 patients (72%). When used together, clinicopathologic and molecular data proved to be of greater value in this endeavor, and a conclusion was reached in 17 of 18 patients (94%). Determining the relationship of multiple tumors was challenging in patient #6 in Table 2, where one tumor was diagnosed by FNA alone and featured the same genomic variant as another tumor.

In addition to its potential therapeutic implications, genomic testing using capture-based and amplicon-based technologies has been used by several studies attempting to unravel the relatedness of multiple lung carcinomas. Assessment of TP53 and EGFR mutations by clonality analysis revealed that approximately half of all cases display different clonality [27]. Mutational profiling evaluating EGFR, KRAS, and TP53 was shown to improve discrimination between independent multiple primary lung carcinomas and intrapulmonary metastasis [29–33]. These findings along with studies utilizing DNA microsatellite analysis [25,26], loss of heterozygosity [47], comparative genomic hybridization [28], and immunohistochemistry [24] highlight the importance of using genomic profiling in conjunction with clinicopathological criteria in order to better differentiate independent primary tumors from intrapulmonary metastasis [25–29,36,48,49]. Recent investigations stress the significance of a multidisciplinary approach for studying the clonal relationship of multifocal lung tumors [50].

NGS assays for detection of genomic alterations with therapeutic, diagnostic, and prognostic significance in lung cancer are now routinely utilized in major medical centers. Targeted NGS panels are robust and sensitive for identification of somatic variants in cancer hotspots or the entire coding region of a gene. Utilizing a 50-gene

Figure 4. A 72-year-old woman with a history of lung adenocarcinoma presenting with two left upper lobe tumors having similar growth patterns and cytologic features (Table 3, patient #7). One tumor showed KRAS G13D and GNAS Q227L mutations (A, 400×), whereas the second tumor had a KRAS G12C mutation (B, 400×). The tumors were classified as independent of one another and unrelated to the prior tumor.
targeted NGS panel, our pilot study showed that interrogation of clinically relevant variants in conjunction with histomorphologic features can be informative for assessment of synchronous, metachronous, and metastatic lesions in patients with pulmonary adenocarcinomas. We detected a total of 63 clinically relevant variants predictive of response to approved therapies and/or clinical trials, including seven deletions in the exon 19 of the EGFR gene. The patterns of variants from KRAS (n = 23), EGFR (n = 14), TP53 (n = 13), BRAF (n = 3), KIT (n = 3), and PIK3CA (n = 2) genes and single variants of NRAS, STK11, MET, CTNNB1, and GNAS genes were comparable to genomic signatures of the 700 lung adenocarcinomas that have been sequenced in our clinical molecular pathology laboratory to date. Interestingly, of the 23 KRAS variants detected, 19 were the more deleterious transversion mutations, and all occurred in current or former smokers as previously described [51]. Studies on larger patient cohorts with long-term follow-up are needed to determine whether KRAS transversion mutations are more common in the setting of synchronous lung adenocarcinomas and if they portend more aggressive disease.

Several observations can be made about the utility of NGS in classifying multiple lung adenocarcinomas. Collectively, our observations suggest that most multiple lung adenocarcinomas arising in patients without a history of lung cancer are truly independent primaries whether they arise in the same or different lung lobe, even in the setting of regional nodal disease. These tumors are therefore best regarded as separate primaries and should be staged and treated as such. Similarly, the majority of tumors detected in patients with a history of lung adenocarcinoma are distinct from the original primary and from each other. When histologic comparison is not possible, such as in patients unable to tolerate resection, NGS may provide prognostic and predictive value. A limitation of the current study is the relatively small number of targets in the gene panel and its inability to interrogate fusion and copy number alterations, both of which have the capability to further discriminate primary lung adenocarcinomas from metastases [52]. Studies with a larger cohort of patients and more informative panels, long-term follow-up, and survival data would be helpful in substantiating our observations and those of other investigators.

Conclusions
Our findings highlight the importance of using clinicopathological criteria in conjunction with genomic profiling for better elucidation of the differences between independent primary tumors from intrapulmonary metastasis and for identifying molecular alterations with therapeutic implications. NGS panels provide surrogatic genomic information that is important for classification of patients with multiple lung adenocarcinomas with similar morphology and are less prone to the potential interobserver variability associated with assessment of tumor growth patterns and cytology.

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