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Concordant and Discordant EGFR Mutations in Patients with Multifocal Adenocarcinomas: Implications for EGFR Targeted Therapy

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Abstract

Purpose—Adenocarcinoma remains the most common subtype of lung cancer in the United States. Most patients present with tumors that are invasive and often metastatic, but some patients develop multiple precursor in-situ or minimally invasive adenocarcinoma tumors which can be synchronous and metachronous. These precursor lesions harbor the same spectrum of genetic mutations found in pure-invasive adenocarcinomas, such as EGFR, KRAS and p53 mutations. It is less clear, however, if separate lesions in patients who present with multifocal disease share common underlying genetic driver mutations.

Methods—Here we review the relevant literature on molecular driver alterations in adenocarcinoma precursor lesions. We then report four cases with multifocal EGFR mutant adenocarcinomas in whom we performed molecular testing on 2 separate lesions.

Findings—In two of these patients, the mutations are concordant, and in two cases the mutations are discordant. A review of the literature demonstrates increasing evidence that lesions with discordant mutations may confer a more favorable prognosis, since they are unlikely to represent metastases.

Implications—Our findings suggest that the emergence of the dominant EGFR driver alteration is often independent between lesions in patients with multifocal adenocarcinomas, and thus the same targeted therapy may not be effective for all lesions. However, genetic testing of multiple lesions can help distinguish separate primary tumors from metastatic disease.

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INTRODUCTION

Precursors to invasive lung adenocarcinoma have been well recognized and described. Previously known as bronchioloalveolar carcinoma (BAC) [1], this term has now been replaced with newer designations. The 2011 revised classification for pulmonary adenocarcinoma, introduced by joint multidisciplinary specialists from the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), now includes a spectrum of precursor lesions from lowest to highest risk: atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA). [2] The tighter delineation of lesions has proven clinical significance, as several studies have shown the newer classification to have better prognostic value. [3–11]

The relationship between precursor lesions and invasive adenocarcinoma can be further strengthened by the finding that individual precursor lesions often harbor the same genetic mutations found in adenocarcinomas, such as *EGFR* [12, 13], *KRAS* [12, 14] and *p53* mutations [15]. Some patients develop multiple foci of AAH, AIS, or MIA, which can appear synchronously or metachronously. [16–18] They typically present as multiple ground glass opacities (GGOs), with or without small solid foci, on CT scans. These lesions can progress slowly to standard, invasive carcinoma and may eventually metastasize. Therefore, current management typically includes careful CT surveillance and surgical resection and/or radiotherapy to areas that grow beyond a certain size (some propose 2 cm if the lesion remains pure ground glass) or develop a solid component of more than a few millimeters. Prognosis can be excellent, in contrast to the typical short prognosis for patients with metastatic lung cancer. [19]

In patients with multifocal adenocarcinomas, the separate adenocarcinomas may share a common genetic ancestry or arise divergently over time. Here we first report four cases with multifocal adenocarcinoma in whom we tested *EGFR* mutation status for more than one lesion. We then review our current understanding of the underlying molecular pathologies of multifocal adenocarcinoma lesions and the potential for targeted therapies in this setting.

CASE SERIES

Based on the above reports of interlesional heterogeneity, we were interested in examining available tumor molecular data from our patients with mMIA. From 2009 to 2015, we identified 4 patients who had resection or biopsy of more than one adenocarcinoma lesions in the setting of additional GGOs, with results of molecular testing available on multiple separate lesions. We report their clinical characteristics and molecular testing results below. This retrospective chart review project was performed under an Institutional Review Board approved protocol. The clinical characteristics of these patients and representative images are reported below and in Figure 1 and Table 1.

Patients with discordant EGFR mutations

Patient #1 is a 56-year-old Asian female, never-smoker, who was first diagnosed with lung adenocarcinoma after presenting with atypical chest pain. CT scan performed initially

showed a 5cm right upper lobe (RUL) nodule, then a subsequent PET-CT scan showed 3 focal lesions—RUL, right middle lobe (RML), and left upper lobe (LUL). Biopsy of the RUL nodule showed adenocarcinoma with *EGFR* exon 19 deletion mutation (L747_T751) by outside EGFR testing, and the LUL nodule showed atypical cells. Subsequent workup including MRI brain and mediastinoscopy were negative for metastases. Patient then had a RML wedge resection two months later that revealed adenocarcinoma, 1.8cm in largest diameter, with an *EGFR* exon 21 (L858R) mutation. She was treated with erlotinib for 4 months with stable disease as her best response, with a plan to proceed with surgical resection of RUL and RML and stereotactic ablative radiotherapy (SABR) to LUL lung nodule; however, repeat PET/CT then showed new mediastinal lymph node involvement. The patient was then started on systemic "neoadjuvant" chemotherapy with carboplatin and pemetrexed, followed by definitive surgery with right thoracotomy and right upper and middle bilobectomy with mediastinal lymph node dissection

Patient #2 is a 79-year-old Asian male with a distant 30-pack-year smoking history. He was incidentally diagnosed with multiple lung nodules, all roughly 1–2cm in diameter, which appeared mostly to have mixed solid and ground glass (GG) components. Biopsy of the left lower lung (LLL) nodule showed adenocarcinoma with an *EGFR* exon 21 (L861Q) mutation by multiplex polymerase chain reaction (PCR) followed by single nucleotide mutation detection, and subsequent workup showed no metastases. He underwent left lower lobectomy that revealed T1N0M0 moderately differentiated adenocarcinoma, lepidic predominant subtype. At delayed follow up 3 years later, a repeat CT scan showed one RUL nodule had been slowly growing, as well a multiple other sites that were likely low-grade adenocarcinoma. Biopsy of the RUL nodule showed well-differentiated adenocarcinoma, with *EGFR* exon 19 (L747_T751) deletion mutation and *TP53* (H178D) mutation by next generation sequencing (NGS). Patient declined surgery in favor of SABR to the RUL nodule with favorable response.

Patients with concordant EGFR mutations

Patient #3 is a 60-year-old Asian female, never smoker, who was diagnosed with right pheochromocytoma when she presented with headaches, palpitations, flushing, and sweating. Subsequent to surgical resection, she continued to have occasional tachycardia. A PET-CT scan was ordered and showed a 3.9X2.6cm hypermetabolic, spiculated RUL apical mass, as well as a 1 cm nodular opacity in the LUL. Patient eventually underwent right VATS thoracoscopic right upper lobectomy revealing a T3 N0 adenocarcinoma. Final pathology showed acinar adenocarcinoma with papillary and lepidic patterns, and molecular testing by NGS showed the following mutations: *EGFR* L858R, *PIK3CA* E545K, and *FBXL7* H98Y. Six months after surgery, the patient's repeat CT scan showed enlargement of the previously present, small anterior LUL nodule, and confluence/growth of a 10 mm spiculated multilobulated nodule in the posterior LUL. She then underwent LUL wedge excision 9 months after the initial lobectomy, and pathology showed invasive adenocarcinoma, 0.7cm in diameter, with the same three mutations noted from the previous surgical resection by NGS. Patient was to undergo SABR for her other LUL lesion; however, she then developed biopsy proven chest wall metastases, and was started on systemic erlotinib.

Patient #4 is a 70-year-old Asian female, never smoker, who was diagnosed with multiple lung lesions when she developed cough. CT scan showed an ill-defined 1.3 × 1.8 cm nodule in the RUL, and two lesions in the LUL: 2.1 × 1.1 cm and 1.3 cm infiltrates. PET-CT and MRI brain showed no metastatic disease, though PET-CT noted additional opacities in RLL. CT-guided biopsy of the right nodule revealed adenocarcinoma. She underwent surgical resection with RML lobectomy as the tumor was palpated to be in the middle lobe during surgery, and pathology showed well differentiated invasive adenocarcinoma, mixed lepidic and acinar patterns, 1.3cm, with *EGFR* L858R mutation by NGS. Patient was under regular surveillance until 2 years later when CT scan shows the lesions in LUL were slowly progressing. She then underwent left VATS and lingula sparing LUL lobectomy. Pathology showed a 1.6 cm and a 1.2 cm well-differentiated adenocarcinoma, lepidic predominant, the larger of which was positive for *EGFR* L858R mutation by NGS. Another year later surveillance CT scan shows mild gradual increase in nodularity along R fissure, and patient underwent SABR treatment for that. She continues to do well and remains under active surveillance.

REVIEW OF CURRENT LITERATURE

Molecular Tumor Biology

The understanding of how recurrent oncogenic mutations “drive” invasive lung adenocarcinoma has advanced over the years, with research effort focused on development and testing of potential targeted therapies. However, a deeper understanding of molecular alterations for minimally invasive precursor lesions and their treatments is still lacking. Another challenge is that many of the studies were done using the previous designation of BAC rather than the newer term AIS or MIA. For clarity within this review, the term BAC will still be used for studies performed using this previous designation.

Whether multifocal adenocarcinomas share a common genetic origin, or arise independently, remains controversial. Barsky *et al.* [20] showed BAC clonal nonidentity or multiclonality in three separate cases, by using PCR amplification of a 511-base pair region located within the first intron of the human hypoxanthine phosphoribosyltransferase gene. On the other hand, Holst *et al.* [21] studied multifocal BAC in 28 patients using a topographic genotyping approach for the presence of KRAS exon 1 mutations and p53 loss of heterozygosity (LOH), and suggested a monoclonal origin with spread by intraalveolar route, intrapulmonary lymphatics, or aerosolization leading to implantation at different sites. In a study by Zhong *et al.* looking at multifocal disease using *EGFR* analysis, the results suggest that both of the above models can exist. [22] In a more recent study by Murphy *et al* [23], the authors addressed this question using next-generation sequencing performed using an Illumina mate-pair library protocol. A total of 41 tumor samples were sequenced, with a range of three to 276 breakpoints per tumor identified. Lung tumors predicted to be independent primary tumors based on different histologic subtype did not share any genomic rearrangements. In patients with lung primary tumors and paired distant metastases, shared rearrangements were identified in all tumor pairs, emphasizing the patient specificity of identified breakpoints. Concordance between histology and genomic data occurred in the majority of samples. Discrepant tumor samples were resolved by genome sequencing. This study

suggests the importance of detailed molecular testing in distinguishing independent primary tumors from intrapulmonary metastases. However, a remaining question is how frequently separate primary lesions share common underlying genetic driver mutations, especially in patients with little smoking history. In another similar study by Wu et al [24], the authors analyzed tumors from 35 patients with multiple lesions resected, including confirmed non-small cell lung cancer (NSCLC) and at least one ground glass nodule (GGN), were analyzed for mutations in EGFR, KRAS, HER2, BRAF, and PIK3CA together with fusions in ALK, ROS1, and RET. A total of 72 lesions (60 were GGNs) were analyzed. Among these, 33 tumor lesions (45.8 %) were found to harbor EGFR mutations: 13 tumors with exon 19 deletion, 18 with L858R on exon 21, and two with both exon 19 del and L858R mutation. There were 5 tumors (6.9 %) harboring EML4-ALK fusion, four HER2 mutations (5.6%), three KRAS mutations (4.2%), one ROS1 fusion and one BRAF mutation. Only six out of 30 patients harbored identical mutations. The discordance rate of driver mutations was 80% (24 of 30) in those patients harboring at least one of the detected driver mutations. The authors concluded there is a high discrepancy of driver mutations among NSCLC patients with GGNs and a favorable prognosis after multiple lesions resection.

Loss of heterozygosity—LOH is an indirect index of genetic alterations in tumors. A number of markers have also been implicated in the stepwise progression from precursor lesions to fully invasive adenocarcinomas. LOH of 3p and 9p might be an early event of carcinogenesis, as studied by Yamasaki *et al.* in which the authors compared two types of BAC with AAH. [25] Takamochi *et al.* analyzed AAH and concomitant adenocarcinoma in 11 patients, and results suggest a causal relationship of LOH on 9q and 16p in a fraction of AAH lesions and adenocarcinomas of the lung. [26] In another study by Sasatomi *et al.* the authors found the most frequently affected chromosome regions in BAC were 8q and 17p. LOH of 1p, 3p, 7q, and 18q, as well as fractional allele loss (FAL) were more frequent in stage 1 adenocarcinomas than BAC. [27] While these genomic alterations are present in many precursor lesions, it is challenging to use LOH analysis to identified shared ancestry between independent lesions.

KRAS, EGFR, and p53 Mutations—*KRAS* mutations are the primary driver genetic alteration in up to 25% of NSCLC adenocarcinomas. It has hypothesized that these lung adenocarcinomas develop through a series of genetic mutations that are sequentially accumulated, leading eventually to the phenotype of invasive adenocarcinoma. This model was based on several lines of evidence. One mouse model study using a conditionally activated allele of oncogenic *KRAS* showed progression from AAH to conditions similar to BAC to adenocarcinoma. [28] In a separate study, regional pulmonary stem cells were identified, termed bronchioalveolar stem cells (BASCs), that are capable of giving rise to bronchiolar Clara cells and alveolar cells of the distal lung. BASCs expanded in response to oncogenic *KRAS* in culture and in precursors of lung tumors *in vivo*, thus may be the putative cells of origin for this subtype of lung cancer. [29]

EGFR mutations are also frequently found in both precursor lesions and invasive adenocarcinomas, with the reported frequency ranging from 11% to 58% depending on the patient population [12, 30, 31]. *EGFR* and *KRAS* mutations are mutually exclusive in BAC

lesions [31]. Another distinction between these two mutations is that *KRAS* mutations are more frequently found in mucinous disease, whereas *EGFR* mutations are more frequently found in non-mucinous disease, with the latter more responsive to EGFR targeted therapies even without *EGFR* mutation testing. [31–33] *EGFR* mutations and HER2 overexpression (defined by positive immunohistochemistry staining) often co-exist in BAC lesions, but the role for HER2 as a co-driver or passenger genomic alteration remains unclear.[34]

Mutations in p53 are commonly found in invasive adenocarcinomas, with incidence of 50% or higher depending on testing methodology. [35] However, the incidence of p53 mutation is much lower in BAC lesions, reported to be 0–11% [36, 37], leading to speculation that p53 mutation may be a later event in the development of invasive adenocarcinoma from precursor lesions [15].

Mutational progression within precursor lesions—A recent study by Izumchenko *et al.* [38] examining genetic drivers in each of the precursor categories of adenocarcinoma (using the 2011 classification) ties some of the knowledge about individual gene alterations together. The authors studied the full spectrum of early histologic progression using next generation sequencing of coding regions from 125 well-characterized cancer-driving genes. They found that in AAH lesions, the most frequently mutated genes were not the classical drivers, but rather genes involved in DNA repair and chromatin remodeling, suggesting these lesions are predisposed to clonal expansion and acquisition of secondary genetic mutations. In AIS tumors, the mutational landscape varied considerably, but began to include more driver mutations such as *EGFR* and *KRAS*. In MIA tumors, even more driver oncogenes were identified, but mostly so in the denser or invasive zones of tumors. Genes such as *KRAS*, *EGFR* and *TP53* are highly connected nodes in the mutational landscape, consistent with their potential as drivers of glandular tumorigenesis, and likely have a role in aggressive transformation of small premalignant lesions. In addition, there appears to be a high degree of intertumoral and even intratumoral genetic heterogeneity even in a single patient.

Targeted therapy in multifocal precursor disease

As multifocal minimally invasive adenocarcinoma became recognized as a distinct clinical entity, it was recognized that this histology predicted a better response to gefitinib, an EGFR tyrosine kinase inhibitor. This is likely due to the high prevalence of EGFR mutations in these lesions. [39–42] Several studies examining the effects of EGFR targeted therapy have since been conducted.

In a study by Kris *et al.* in 2004, 127 patients with stage IIIB/IV, inoperable NSCLC underwent central review of biopsies, BAC was found in 65%, and 69 have received erlotinib. Partial responses to erlotinib occurred in 15 of 59 evaluated, 25% (95% CI 15 to 38%). Responses occurred in 1/14 (7%) of patients with “pure” BAC and 13/44 (30%) with adenocarcinoma with BAC features. Never smoking and a lower number of cigarettes smoked predict sensitivity to erlotinib in patients with BAC. [43]

In the phase II S0126 study by West *et al*, a total of 136 chemotherapy-naïve and chemotherapy-pretreated patients with advanced BAC were treated with gefitinib 500 mg daily until progression or prohibitive toxicity. The Response Evaluation Criteria in Solid

Tumors response rate was 17%, with 6% complete responses (CRs) among 69 previously untreated patients with measurable disease, and 9% with no CRs among 22 pretreated patients. Exploratory subset analyses revealed improved survival among women (P = .031), patients developing a rash (P = .003), never-smokers (P = .061), and patients with a PS of 0 or 1 (P = .015). [44] Further analysis by Hirsch *et al.* showed that increased EGFR gene copy number detected by FISH is associated with improved survival after gefitinib therapy in patients with advanced BAC: 12 of 19 EGFR/FISH-positive patients (63%) demonstrated disease control versus 14 (39%) of 36 patients in the FISH-negative group (P = .087). [45] In another separate analysis, Franklin *et al.* showed low pMAPK and combined low ErbB2 and pMAPK predict increased survival with gefitinib therapy in patients with advanced BAC and that dual inhibition of ErbB1 and ErbB2 may lead to improved therapeutic efficacy. [46]

Another phase II study by Miller *et al.* treated patients (n = 101) with BAC (n = 12) or adenocarcinoma, BAC subtype (n = 89) with erlotinib 150 mg daily. Overall response rate (RR) was 22% (95% CI, 14% to 31%). In patients with pure BAC, the RR and median survival were 20% and 4 months, as compared with 23% and 19 months in those with adenocarcinoma, BAC subtype. Patients with EGFR mutations had an 83% RR (15 of 18; 95% CI, 65% to 94%) and 23-month median OS. [47]

The phase II IFCT-0401 trial enrolled 88 chemotherapy-naïve patients with BAC and they were treated with 250 mg/d of gefitinib. Disease control was achieved in 25 patients (29.4%); 11 patients (12.9%) had partial response and 14 (16.4%) had stable disease. Median progression-free survival was 2.9 months (95% confidence interval [CI], 2.3–3.2) and median overall survival was 13.2 months (95% CI, 10.2–17.3). Never smokers, patients with low respiratory symptoms score, occurrence of cutaneous rash, and nonmucinous subtype were associated with increased probability of disease control. [48]

Ramalingam *et al.* conducted a phase II study using cetuximab in which patients with advanced-stage pure BAC or adenocarcinoma with BAC features, fewer than two prior chemotherapy regimens and no prior EGFR therapy, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were eligible. Approximately 50% of patients received more than two cycles of therapy (> 8 weeks). The confirmed response rate was 7%, and stable disease was observed in 35%. The median survival and progression-free survival were 13 and 3.3 months, respectively.

Overall, response rates from these studies to EGFR inhibitor therapy (7–25%) are substantially lower than in patients with widely metastatic EGFR in whom response rates of 60% or better are anticipated. This suggests that intralesional and interlesional heterogeneity may limit the effectiveness of a single targeted therapeutic in this patient population.

Prognostic value of EGFR and KRAS in early stage NSCLC

The prognostic value from molecular testing of a single site of disease remains controversial, and may depend on the mutation itself. In a systemic review and meta-analysis that included 16 studies (n=3337) to determine the prognostic value of EGFR mutations in resected NSCLC by Zhang *et al.* [49], the combined hazard ratio (HR) evaluating EGFR mutations on disease free survival (DFS) was 0.96 (95% CI [0.79–1.16] P =0.65). The combined HR

evaluating EGFR mutations on overall survival (OS) was 0.86 (95% CI [0.72–1.04] P = 0.12). The subgroup analysis based on univariate and multivariate analyses in DFS and OS showed no statistically significant difference. There was also no difference in DFS and OS of stage I NSCLC patients. In a separate study examining the prognostic value of KRAS mutational status in resected stage I lung adenocarcinoma, Izar et al. [50] examined mutational status in a total of 312 patients who had complete resection of stage I lung adenocarcinoma without any adjuvant therapy, using a multiplex PCR-based assay; 127 harbored KRAS mutations (KRAS-MUT) and 185 had KRAS-wild type (KRAS-WT) tumors. When compared with KRAS-WT, KRAS-MUT was associated with significantly shorter OS and DFS. When stratifying KRAS-WT patients based on EGFR status, KRAS-MUT patients had worse OS and DFS than patients with EGFR-MUT and EGFR-WT/KRAS-WT (WT/WT). Multivariate analysis identified KRAS mutation as independent predictor of worse OS ($p = 0.001$) and DFS ($p < 0.0001$). The authors concluded that KRAS appears to be an independent prognostic marker in resected stage I lung adenocarcinoma.

CONCLUSION

While the treatment of advanced invasive lung adenocarcinoma has made tremendous advancement in the recent years, our understanding of the pathogenesis of minimally invasive lung adenocarcinoma, especially in the precursor stage, remains less clear. As a result of the new United States Preventive Services Task Force recommendation for low-dose CT screening for lung cancer for select populations [51], we hope that more lung cancers will be identified in the early stages, and therefore more research effort will be invested in understanding of precursor lesions. The implementation of the 2011 revised classification for pulmonary adenocarcinoma has provided tighter delineations of subtypes, to form a common framework for future studies to investigate the pathogenesis and treatment options for adenocarcinoma precursor lesions.

Multifocal adenocarcinoma remains a unique disease entity with a distinct presentation from typical non-small cell lung cancer. It is important, but not always easy, to differentiate between multiple primaries versus metastatic intrapulmonary disease. Controversies still exist also as to how these lesions develop, whether through clonal expansion and metastasis or multi-clonal origin. From our limited case series, and review of the literature, we believe molecular testing of more than one lesion helps distinguish these two possibilities for staging and treatment purposes, with some tumors sharing a common genetic driver and some tumors appearing to have arisen independently. In our experience, molecular testing may not only give treatment options, but also potentially give prognostic value, because multifocal lesions that share the same mutations are more likely to behave like metastatic disease over time, as with patient #3.

However, we also note there can be limitations to this approach. For example, patient #4 was found to have two tumors with L858R mutations in two separate lobes, seemingly arguing for her disease to have come from one origin, but this is a common EGFR mutation. To further distinguish these possibilities, more deeper NGS-based molecular analysis of these tumors should frequently identify additional somatic tumor gene alterations that may also be concordant or discordant, as with patient #3. We also note the prognostic value of molecular

testing of one lesion is unclear, but KRAS mutations may generally confer a worse prognosis.

Targeted therapy based on molecular status of a dominant lesion is an appropriate first step in therapy, as is often the practice for metastatic disease; however, the same targeted therapy may not be effective for all lesions. This is consistent with our review of previous reports that patients with EGFR mutant multifocal GGO's often have only modest responses to EGFR TKIs. Further evaluation of underlying mutations in these synchronous and metachronous lesions can help shed light on these pathogenetic processes, and hopefully will serve to not only develop better targeted therapeutics to not only control advanced disease, but also potentially to halt the process of tumorigenesis within these lesions before they progress.

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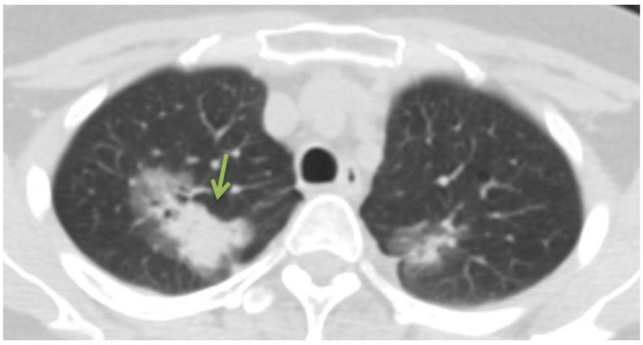
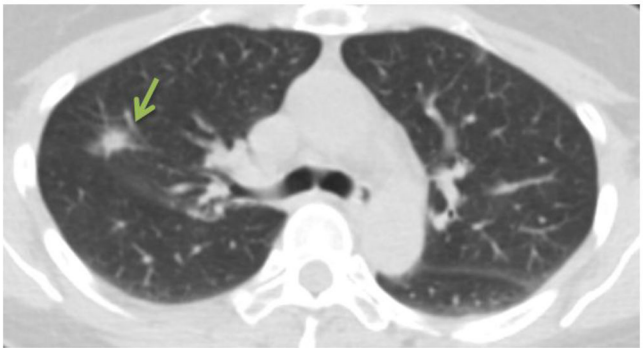
Patient #1

A. RUL lesion

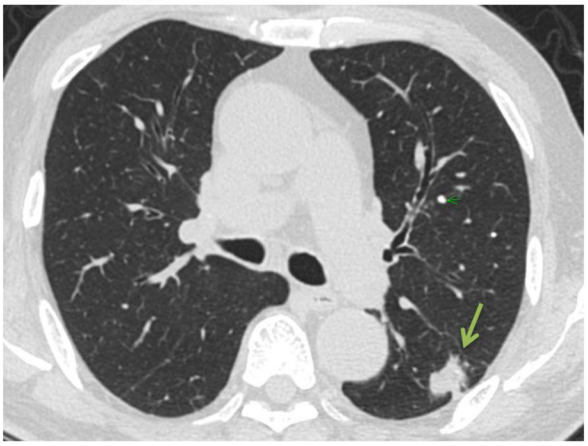


B. RML lesion

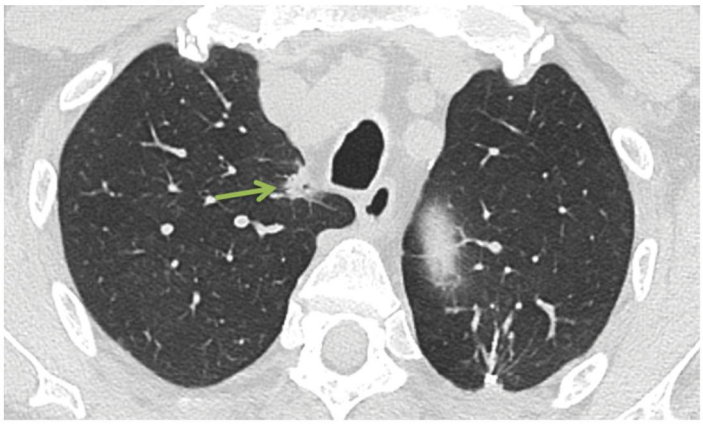


Patient #2

A. LLL lesion

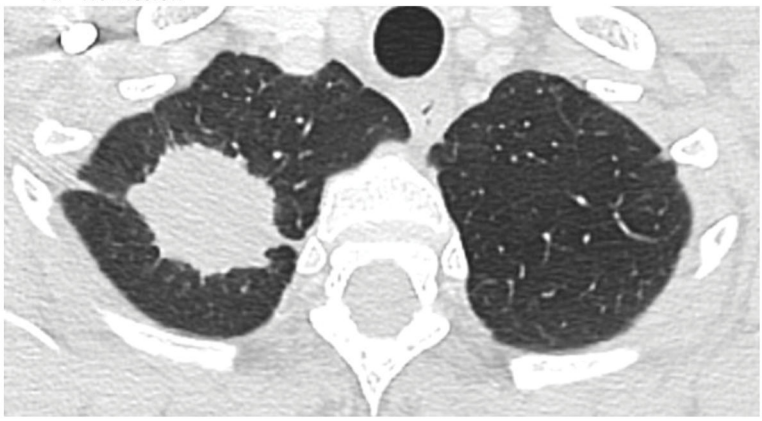


B. RUL lesion

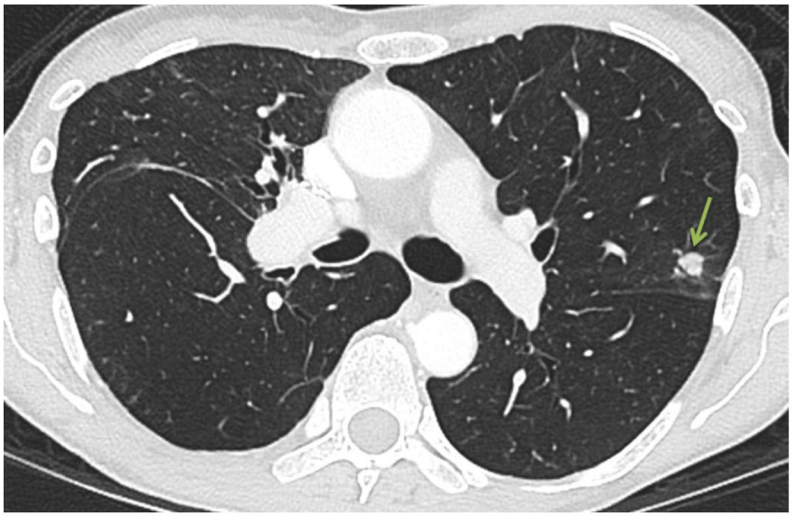


Patient #3

A. RUL lesion

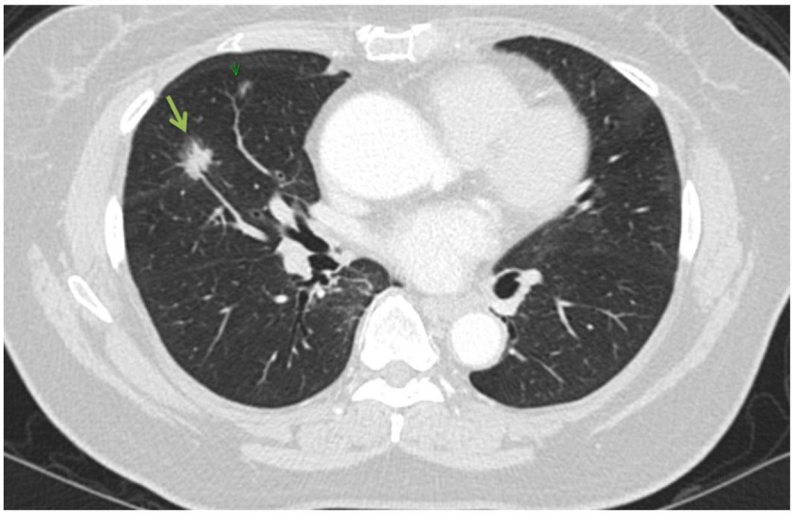


B. LUL lesion



Patient #4

A. RML lesion



B. LUL lesion

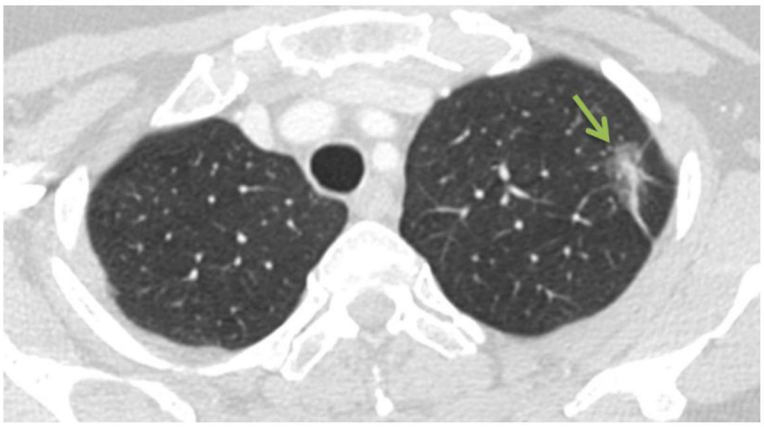


Figure 1.

Imaging of Lesions Studied in Case Series

Representative CT imaging of analyzed lesions in patients. (labeled with large light green arrow when there is more than one lesion present)

RUL: right upper lobe

RML: right middle lobe

LUL: left upper lobe

LLL: left lower lobe

Table 1

Summary of target lesions in patients

Patient	Gender	Age	Smoking status	Lesion(s) location	Lesion(s) size	Lesion(s) radiological appearance	Lesion histology	Mutation(s)
#1	F	56	Never	RUL	5cm in greatest dimension	Irregular mixed nodular and groundglass mass	Adenocarcinoma	EGFR exon 19 L747_T751 deletion
				RML	1.8cm in greatest dimension	Opacity	Invasive adenocarcinoma, acinar predominant	EGFR exon 21 L858R
#2	M	79	Distant 30 pack year	LLL	2.0 cm	predominantly solid lobulated lesion containing cystic air lucencies	Moderately differentiated adenocarcinoma, lepidic predominant	EGFR L861Q
				RUL	1cm	Spiculated nodule	Well differentiated adenocarcinoma	EGFR exon 19 L747_T751 deletion, p53 H178D
#3	F	60	Never	RUL	3.9×2.6cm	Spiculated RUL apical mass	acinar adenocarcinoma with papillary and lepidic patterns	EGFR L858R, PIK3CA E545K, FBXL7 H98Y
				LUL	1cm	Spiculated nodule	Invasive adenocarcinoma, acinar predominant	EGFR L858R, PIK3CA E545K, FBXL7 H98Y
#4	F	70	Never	RML	1.3×1.8cm	Nodule	well differentiated invasive adenocarcinoma, mixed lepidic and acinar patterns	EGFR exon 21 L858R
				LUL	2.1 × 1.1 cm and 1.3 cm	Infiltrates	well-differentiated adenocarcinoma, lepidic predominant	EGFR exon 21 L858R

RUL: right upper lobe

RML: right middle lobe

LLL: left lower lobe

LUL: left upper lobe