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Radiogenomic Evaluation Of Lung Cancer – Are There Imaging Characteristics Associated With Lung Adenocarcinomas Harboring BRAF Mutations?

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Abstract

Introduction—We studied computed tomography (CT) features associated with BRAF mutated lung cancer.

Materials and Methods—CT features of BRAF mutated lung cancers were compared to stage matched lesions without BRAF mutation.

Results—47(25%) patients with BRAF mutation and 141(75%) without BRAF mutation were included. BRAF lesions were most frequently solid 37(84%), spiculated 22(50%), and peripheral 37(84%). No feature of the primary tumor was significantly different between BRAF and non-BRAF groups. BRAF patients were more likely than KRAS patients to have pleural metastases [5(11%) vs 0(0%), $p=0.045$].

Conclusion—No feature of the primary tumor differentiates BRAF lesions from non-BRAF lesions.

Keywords

Lung Carcinoma; BRAF Mutation; Computed Tomography; Radiogenomics

Introduction

Lung cancer is the leading cause of cancer related death worldwide and accounts for 13% of new cancer diagnoses [1]. Conventional chemotherapy for lung cancer has relied on the use

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of non-targeted cytotoxic agents, however the recent discovery of several somatic genomic alterations in driver oncogenes has led to the development of targeted medical therapy for some genetically distinct subtypes of lung cancer. The molecular abnormalities most frequently treated with targeted therapy are EGFR mutations and ALK rearrangements [2, 3].

BRAF is a protein kinase and a member of the Ras/mitogen-activated signaling pathway, which, when activated by mutation, leads to the phosphorylation of MEK and ultimately promotes cell proliferation and survival [4,5]. Somatic BRAF mutations are detected in several cancer subtypes, including melanoma, colorectal cancer and papillary thyroid cancer, and also occur in 2–5% of non-small cell lung carcinomas (NSCLC) [5, 6, 7]. Several subtypes of BRAF mutation exist. The most common is the BRAF V600E mutation which accounts for 50–81% of BRAF mutations [5, 6, 8] and in lung cancer is associated with responsiveness to treatment with the targeted agents vemurafenib, dabrafenib and trametinib [9, 10, 11, 12].

Recent clinical interest in the field of Radiogenomics has led to the radiological characterization of several genetic subtypes of lung cancer, including lesions with EGFR and KRAS mutations, and ALK rearrangements [13, 14, 15]. To our knowledge there has been no systematic description of the imaging features of lung cancers with BRAF mutations. The aim of this study was to compare the CT features of a cohort of lung carcinomas with BRAF mutation with a cohort of lung carcinomas without BRAF mutation, in an attempt to identify any imaging features associated with this genetically distinct subset of tumors.

Materials and Methods

Our institutional review board granted approval and waived the informed consent requirement for this retrospective study.

Patients

Patients were identified from a prospectively maintained institutional database of patients with a pathologic diagnosis of lung carcinoma with BRAF mutation. The date of pathologic diagnosis ranged from 9/13/2007 to 4/16/2013. Patients with a pathology report documenting lung carcinoma with a BRAF mutation and with CT images on the institutional Picture Archiving and Communication System (PACS, GE Centricity RA100) were included in the study. The CT images closest to the date of treatment for the lesion with BRAF mutation were studied (the CT analyzed was always performed prior to treatment). Clinical information was extracted retrospectively from the institutions electronic medical record, following lesion analysis. Clinical parameters documented were age, sex and smoking status (either former/current smoker or never smoker). As a control group we used a cohort of lung carcinoma patient without BRAF mutations selected from a separate institutional database. This group included both patients with documented mutations (EGFR mutations and KRAS mutations), and patients without documented mutations (EGFR/ KRAS/BRAF wild-type lesions). Each sub-group of control patients (EGFR, KRAS or wild-type) contained the same number of patient as the BRAF group and was frequency matched to the BRAF group with respect to the stage of the tumor at diagnosis. Dates of pathological diagnosis in the control

group ranged from 1/2/2009 to 9/6/2012. Patients with BRAF mutation were compared to all patients without BRAF mutation, and also to each of the EGFR, KRAS and EGFR/KRAS/BRAF wild-type groups individually. Additionally, all patients with a BRAF V600E mutation were compared to all patients without this mutation.

Image Analysis

All CTs were retrospectively reviewed in consensus by 2 thoracic radiologists (D.H. and A.P.). Both readers were blinded to the mutational status and other clinical details at the time of image interpretation. All images were reviewed on the institutional PACS system. 133 (71%) patients had the CT that was reviewed as part of this study performed at an outside institution. Imaging was consequently performed on a variety of multidetector CT scanners, with slice thicknesses ranging from 1.25 to 5 mm. 184 (98%) CT exams were performed with intravenous (IV) contrast.

CT features of the primary tumor assessed were: lesion contour, internal density and location. The contour of the primary tumor was characterized as either: round (spherically shaped lesions with smooth borders that could be clearly outlined radiologically without spiculations into the surrounding parenchyma), lobulated (lesions with smooth borders but without a spherical shape) or spiculated (lesions with linear radiating spicules extending from the border of the lesion in the adjacent lung parenchyma). The density of the primary tumor was classified as either: solid attenuation (increased density of the lung parenchyma with obscuration of the pulmonary vessels), ground glass attenuation (hazy increased attenuation of lung, with preservation of bronchial and vascular margins [16]), or mixed ground glass and solid attenuation. The location of the lesion was classified as either central (tumor involving segmental or larger bronchus) or peripheral (tumor involving subsegmental bronchus or smaller airway [17]). The presence of cavitation, air bronchograms, calcification, perilesional halo, post obstructive change, a pleural tail and necrosis were also documented. Additional features assessed were the presence/absence of a pleural effusion, pleural metastases, lymphangitic carcinomatosis. When a pre-treatment positron emission tomography (PET)/CT was available, the maximum standardized uptake value (SUVmax) was recorded.

Statistical Methods

Categorical CT features were compared between patients with BRAF mutation and patients with other mutation type(s) using the exact Cochran Mantel-Haenszel test, stratified by the frequency matching variable, stage. When examining associations between mutation types and continuous variables, including age, size of tumor, size of lymphadenopathy, SUVmax and pack year, a logistic regression was performed with each continuous variable and stage as covariates. A subgroup of BRAF, V600E, was further compared to other mutation type(s) to evaluate if any of associations with BRAF were significant, using the same sets of tests as when we compared BRAF mutation with others. No multiple testing adjustments were applied due to the hypothesis generating purpose of the study. A test with p-value < 0.05 was considered statistically significant. All statistical analyses were performed in software packages SAS 9.4 (SAS Institute Inc., Cary, NC) and R version 3.1 (The R Foundation for Statistical Computing).

Results

Patient characteristics

47 patients with lung cancer with a BRAF mutation and with CT images on the institutional PACS were identified. 25 (53%) had a BRAFV600E mutation, 13 (28%) had a BRAF G469A mutation, 6 (13%) had a BRAFG469V mutation and 3 (6%) had a BRAF D594G mutation. 141 patients without BRAF mutation were used as a control cohort (47 with EGFR mutation, 47 with KRAS mutation, 47 EGFR/KRAS/BRAF wild-type). Each group of 47 patients contained 14 (30%) stage I tumors, 3 (6%) stage II tumors, 12 (26%) stage III tumors, and 18 (38%) stage IV tumors.

The mean overall age was 64 years (range 42–85). There was no significant difference in age distribution between the groups. The mean age of patients in the BRAF group was 66 years [standard deviation (SD) 8.9], and the mean age in the non-BRAF group was 63 years (SD 11) [$p=0.099$]. Patients in the BRAF group were more likely to be male than patients in the EGFR group [24 (51%) v 11 (23%), $p=0.011$]. There were otherwise no significant differences in sex distribution between the groups. Smoking history was available in 45 (96%) patients in the BRAF group and 140 (99%) in the non-BRAF group. Patients in the BRAF group were more likely to be current or former smokers when compared to both the non-BRAF group [44 (98%) v 116 (83%) $p=0.011$], and the EGFR group [44 (98%) v 26 (57%), $p<0.001$]. In addition, patients in the BRAF V600E group were more likely to be current or former smokers compared to the non-BRAF V600E group [24 (100%) v 136 (85%) $p=0.049$]. There was otherwise no difference in smoking status between the groups. Patient characteristics are summarized in Table 1

Imaging findings

CT features of the primary tumor—44 (94%) tumors in the BRAF group and 138(98%) tumors in the non-BRAF group presented with a measurable primary pulmonary lesion ($p=0.164$). When a primary lesion was identified, tumors with BRAF mutations were most frequently peripherally located (37, 84%), solid in consistency (37, 84%) with a spiculated margin (22, 50%). There was no difference with respect to the presence of cavitation, necrosis, air bronchograms, calcification, a perilesional halo, post-obstructive changes or a pleural tail when the BRAF group was compared to the non-BRAF group, or to any of the genetically distinct groups of tumors. Mean axial long axis tumor size was 34mm (SD 22) in the BRAF group and 32mm (SD 16) in the non-BRAF group ($p=0.464$). When a subanalysis of patients with a BRAF V600E mutation was performed comparing them to all patients without a BRAF V600E mutation, there was no significant difference in any imaging feature. Results of primary tumor analysis are summarized in table 2.

Ancillary features—11 (23%) patients in the BRAF group had a pleural effusion and 5 (11%) had measurable pleural nodularity or a pleural mass. 4(9%) had CT evidence of lymphangitic carcinomatosis. There was no significant difference between the BRAF and non-BRAF groups with respect to the presence of any of these features. When the BRAF group was compared to the KRAS sub-group, patients with a BRAF mutation were more likely to have a pleural effusion [BRAF group 11 (23%) v KRAS sub-group 3(6%),

p=0.033] and a pleural mass [BRAF group 5 (10.6%) v KRAS sub-group 0(0%) p= 0.045]. 33 (70%) patients in the BRAF group and 100 (71%) patients in the non-BRAF group had pre treatment SUVmax measurement available. There was no significant difference in mean SUVmax measurement between the 2 groups, mean SUVmax 8.6 in the BRAF group and 9.8 in the non-BRAF group (p=0.726). The results of ancillary imaging feature analysis are summarized in table 2.

Discussion

In recent years molecular profiling of NSCLC has led to the discovery of several genetically distinct subtypes of lung cancer. The development of targeted medical therapies directed at some of these tumor subtypes has improved patient outcomes and led to a paradigm shift in how advanced NSCLC is treated [2, 18]. Interim results from an ongoing phase II study using the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in BRAF V600E mutation positive advanced NSCLC are promising, with an overall response rate of 63% [9]. In addition there are several reports of the in-vivo effectiveness of vemurafenib in advanced BRAF mutated lung cancer [10, 11, 12]. Although BRAF mutations, accounting for 3–5% of NSCLCs, are less frequent than other more common mutations such as EGFR and KRAS, [5, 6, 7], the above results suggest it will become vital to identify patients with BRAF mutated NSCLC, who may benefit from targeted treatment.

To date there have been a limited number of studies describing the clinical features of patients with BRAF mutated lung carcinoma. Paik et al and Villaruz et al both demonstrated that patients with BRAF mutations more frequently have a smoking history, when compared to patients with other genetically distinct lung cancers [5, 7]. A multi-center Italian study found that BRAFV600E mutations were associated with female sex, never smoking status and inferior overall survival, when compared to BRAF-wild-type lesions [6]. In the same study non-V600E mutations were associated with a smoking history and had no gender predilection [6].

As the use of clinic-pathologic genomic profiling has grown, the practice of correlating radiological images with genomic features of tumors has also expanded. Termed Radiogenomics, this practice has been used to define the radiological phenotypes associated with underlying tumor genotypes [19], and in some cases has also been used to predict the tumors responsiveness to targeted therapy [20]. In many scenarios genetic profiling of tumors has become routine clinical practice, however this is not universal, and by definition involves an invasive test in the form of a biopsy. The developing field of Radiogenomics holds promise as a non-invasive diagnostic tool which has the potential to link the fields of routine clinical imaging with molecular profiling [19]. 2 forms of Radiogenomics exist in the literature and can be broadly divided into either qualitative assessments of the macroscopic morphology of a tumor with particular genetic features [13, 15, 21], or quantitative analyses using large volumes of data extracted from a radiologic image in a semi automated fashion which are subsequently correlated with the genomic features of a lesion [22, 23, 24, 25, 26, 27] The latter practice is sometimes termed Radiomics.

With regards to lung cancer, there are a growing number of studies describing the imaging features associated with specific genetic aberrations. Tumors with ALK rearrangements have been associated with a solid appearance, and when compared to EGFR mutated lesions are more likely to have multi-focal bulky lymphadenopathy, lymphangitic metastasis [13, 15]. and pleural metastases [15]. In a separate study a “*Radiogenomic CT Biomarker*” consisting of central tumor location, absence of a pleural tail and a large pleural effusion in combination with a patient age <60 years was used to predict ALK positivity with a sensitivity of 83% and a specificity of 88% [28]. The same study demonstrated that ALK positive tumors with a disorganized vascular pattern had shorter progression free survival when treated with Crizotinib [28].

There have been mixed results in the few studies to date assessing the radiologic characteristic of KRAS mutated lung cancers. In a cohort of patients with bronchioloalveolar adenocarcinoma and either KRAS mutation, EGFR mutation or no mutation, Glynn et al did not find any imaging feature significantly associated with KRAS mutation [14]. More recently Rizzo et al demonstrated that KRAS mutated lesions were associated with a rounded lesion shape and additional pulmonary nodules in separate lung lobes. [29].

Several authors have demonstrated an association between small tumor size and the presence of EGFR mutation [29, 30, 31]. In addition, Rizzo et al described an association between the presence of air bronchograms and pleural retraction in lesions with EGFR mutation. Comparing EGFR lesions to wild-type tumors Hsu et al found that EGFR lesions were more likely to be oval in shape, that EGFR lesion with exon 19 deletions were more likely to contain air bronchograms and that wild type lesions were more likely to be calcified [30]. Lee et al compared the imaging characteristics of subtypes of *EGFR* mutations and found that ground glass opacity (GGO) volume was higher in lesions with exon 21 missense mutation than in wild type tumors. In addition, the prevalence of exon 21 mutation increased along with increasing volume of GGO in a given lesion [21].

To our knowledge this is the first study to assess the radiological characteristics of NSCLC with BRAF mutation. BRAF mutated NSCLCs are most frequently peripheral, solid, spiculated lesions and in this study did not demonstrate significantly different imaging features when compared to a group without BRAF mutation. When compared to other genetically distinct subtypes of NSCLC, BRAF lesions were more likely to have pleural metastases and pleural effusions than lesions with KRAS mutations. No other significant difference was found between BRAF lesions and lesions with EGFR mutations, KRAS mutations or BRAF/EGFR/KRAS wild type lesions.

The retrospective nature of this study and its relatively small sample size are inherent limitations, both of which could be overcome by larger prospective multi-institutional studies. Because of the retrospective nature of the study, the CT imaging protocols used were heterogeneous, resulting in some differences in the images that were available for analysis, particularly with respect to the image slice thickness. Varying slice thickness could affect the assessment of ground glass attenuation within a lesion, subtle lymphangitic carcinomatosis, and the presence of a perilesional halo.

In this study we present the first radiologic description of lung cancers with BRAF mutations which are most commonly solid, peripheral, spiculated lesions. While comprehensive molecular profiling is advocated for all patients with advanced lung cancers, both radiologists and clinicians should be aware of the radiological appearance of these lesions which can potentially benefit from targeted medical therapy. Given the low incidence of this genetic aberration in lung adenocarcinoma, larger multicenter studies are needed to further elucidate these radiologic features.

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Highlights

- CT findings in lung cancer patients with BRAF mutations were compared to patients without BRAF mutations
- BRAF patients were more likely than patients with EGFR mutations to be male ($p=0.011$) smokers ($p<0.001$)
- BRAF lesions were most frequently solid 37 (84%), spiculated 22 (50%), and peripheral 37 (84%)
- BRAF patients were more likely than KRAS patients to have pleural metastases [5(11%) vs 0(0%), $p=0.045$]
- No feature of the primary tumor was significantly different between BRAF and non-BRAF groups

Figure 1.

Chest CT on lung windows demonstrating a primary lung tumor (arrow) in the right upper lobe, in a patient with BRAF mutated lung cancer. The lesion is peripherally based, solid and spiculated, the most common imaging phenotype found in patients with a BRAF mutation. A loculated pleural effusion is also demonstrated (arrowheads), in this patient with pleural metastases (pleural metastases not visualized on this image).

Table 1

Summary of patient characteristics (the smoking history was not known in all patients)

	All BRAF	All non-BRAF lesions	BRAF – V600E	EGFR	KRAS	Wild Type	p-Value				
							BRAF v all others	V600E v all others	BRAF v EGFR	BRAF v KRAS	BRAF v Wild Type
Female	23 (49%)	92 (65%)	12 (48%)	36 (77%)	31 (66%)	25 (53%)					
Male	24 (51%)	49 (35%)	13 (52%)	11(24%)	16 (34%)	22 (47%)	0.058	0.124	<u>0.011</u>	0.146	0.837
Former/ current smoker Never smoker	44 (98%)	116 (83%)	24(100%)	26 (57%)	46 (98%)	44 (94%)	<u>0.011</u>	<u>0.049</u>	<u><0.001</u>	0.999	0.622
	1 (2%)	24 (17%)	0 (0%)	20 (44%)	1 (2%)	3 (6%)					
Age, Median (Range)	65 (48, 85)	63 (42, 86)	62 (48, 79)	60 (42, 86)	68 (43, 85)	65 (47, 86)	0.123	0.948	<u>0.014</u>	0.378	0.653

Table 2

Summary of the CT characteristics of the primary tumor and ancillary imaging features.

	All BRAF	All non- BRAF	BRAF – V600E	EGFR	KRAS	Wild Type	p-Value				
							BRAF v all others	V600E v all others	BRAF v EGFR	BRAF v KRAS	BRAF v Wild Type
Presence of measurable mass		44 (94%)	138 (98%)	23 (92%)	45 (96%)	47 (100%)	46 (98%)	0.164	0.251	0.999	0.243
Mean tumor size in mm (SD)		34 (22)	32 (16)	37 (25)	32 (17)	35 (18)	28 (11)	0.464	0.205	0.721	0.127
Consistency of primary tumor	Solid	37 (84%)	112 (82%)	18 (78%)	35 (78%)	38 (81%)	39 (85%)	0.805	0.759	0.560	0.775
	Part solid GGO	7 (16%)	26 (19%)	5 (22%)	10 (22%)	9 (19%)	7 (15%)	0.805	0.759	0.560	0.775
	Ground glass	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000	1.000
Location of primary tumor	Central	7 (15%)	34 (24%)	5 (20%)	11 (23%)	14 (30%)	6 (13%)	0.372	0.999	0.410	0.101
	Peripheral	37 (84%)	107 (76%)	18 (72%)	34 (72%)	33 (70%)	40 (85%)	0.830	0.788	0.610	0.433
Margin of primary tumor	Spiculated	22 (50%)	56 (41%)	10 (44%)	17 (38%)	20 (43%)	19 (41%)	0.309	0.588	0.269	0.518
	Lobulated	20 (46%)	66 (48%)	12 (52%)	22 (49%)	22 (47%)	22 (48%)				
	Circumscri- bed	2 (5%)	16 (12%)	1 (4%)	6 (13%)	5 (11%)	5 (11%)				
Cavitation	Yes	2 (5%)	9 (7%)	2 (9%)	3 (7%)	3 (6%)	3 (7%)	0.999	0.638	0.999	0.999
	No	42 (96%)	129 (94%)	21 (91%)	43 (94%)	44 (94%)	43 (94%)				
Air bronchogram	Yes	35 (80%)	103 (75%)	16 (70%)	10 (22%)	12 (26%)	13 (28%)	0.544	0.428	0.999	0.623
	No	9 (21%)	35 (25%)	7 (30%)	35 (78%)	35 (75%)	33 (72%)				
Calcification	Yes	2 (5%)	9 (7%)	2 (9%)	3 (7%)	3 (6%)	3 (7%)	0.999	0.638	0.999	0.999

	All BRAF	All non-BRAF	BRAF – V600E	EGFR	KRAS	Wild Type	p-Value				
							BRAF v all others	V600E v all others	BRAF v EGFR	BRAF v KRAS	BRAF v Wild Type
	No	42 (96%)	129 (94%)	21 (91%)	42 (93%)	44 (94%)	43 (94%)				
Perilesional halo	Yes	2 (5%)	17 (12%)	2 (8%)	3 (7%)	9 (19%)	5 (11%)	0.169	0.999	0.999	0.434
	No	42 (96%)	121 (88%)	21 (91%)	42 (93%)	38 (81%)	41 (89%)				
Post obstructive change	Yes	11 (25%)	32 (23%)	5 (22%)	11 (24%)	13 (28%)	8 (17%)	0.830	0.999	0.999	0.423
	No	33 (75%)	106 (77%)	18 (78%)	34 (76%)	34 (72%)	38 (83%)				
Pleural tail	Yes	15 (34%)	61 (44%)	6 (26%)	19 (42%)	22 (47%)	20 (44%)	0.294	0.113	0.515	0.399
	No	29 (66%)	77 (56%)	17 (74%)	26 (58%)	25 (53%)	26 (57%)				
Pleural effusion	Yes	11 (23%)	25 (18%)	8 (32%)	12 (26%)	3 (6%)	37 (79%)	0.354	0.156	0.999	1.000
	No	36 (77%)	116 (82%)	17 (68%)	35 (75%)	44 (94%)	10 (21%)				
Pleural mass	Yes	5 (11%)	14 (10%)	4 (16%)	6 (13%)	0 (0%)	8 (17%)	0.999	0.485	0.999	0.507
	No	42 (89%)	127 (90%)	21 (84%)	41 (87%)	47 (100%)	39 (83%)				
Lymphangitic spread	Yes	4 (9%)	8 (6%)	3 (12%)	4 (9%)	2 (4%)	2 (4%)	0.489	0.384	0.999	0.669
	No	43 (92%)	133 (94%)	22 (88%)	43 (92%)	45 (96%)	45 (96%)				

SD = standard deviation