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Radiogenomic evaluation of lung cancer — Are there imaging characteristics associated with lung adenocarcinomas harboring BRAF mutations?

Darragh F Halpenny [a,*], Andrew Plodkowski [a], Gregory Riely [b], Junting Zheng [c], Anya Litvak [b], Chaya Moscowitz [c], Michelle S Ginsberg [a]

[a] Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
[b] Department of Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
[c] Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

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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.

1. 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 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) [5–7]. 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 [9–12].

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 [13–15]. 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.

2. Materials and methods

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

2.1. 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

* Corresponding author.
E-mail address: halpennd@mskcc.org (D.F. Halpenny).

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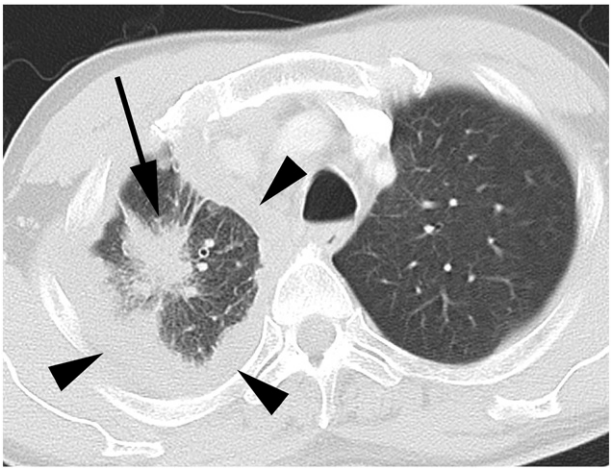

Fig. 1. Chest CT on lung windows demonstrating a primary lung tumor (arrow) in the right upper lobe, in a patient with BRAF mutated lung cancer. The lesion is peripherally based, solid and spiculated, the most common imaging phenotype found in patients with a BRAF mutation. A loculated pleural effusion is also demonstrated (arrowheads), in this patient with pleural metastases (pleural metastases not visualized on this image).

(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.

2.2. 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.

2.3. 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).

3. Results

3.1. 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%) vs 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%) vs 116 (83%) $p = 0.011$], and the EGFR group [44 (98%) vs 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%) vs 136 (85%) $p = 0.049$]. There was otherwise no difference in smoking status between the groups. Patient characteristics are summarized in Table 1.

3.2. Imaging findings

3.2.1. 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%),