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Short communication

Investigation of patterns of nodal metastases in BRAF mutant lung cancer

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ABSTRACT

Axillary lymph nodes (axLN) are a rare site of nodal metastases in patients with lung cancer. BRAF mutated lung cancer is a genetically distinct subtype that occurs in 2–5% of non-small cell lung carcinomas (NSCLC). A recent study identified a highly unusual pattern of metastatic spread to axLN in patients with BRAF mutated colorectal cancer (CRC). The purpose of the study is to assess the incidence of axLN metastases in BRAF mutated NSCLC.

Baseline computed tomography (CT) imaging at diagnosis and all follow up CTs of patients with BRAF mutated NSCLC treated at our institution were retrospectively reviewed by two radiologists for evidence of axLN metastases. Positron emission tomography (PET)/CT was reviewed when available. A control group of patients with non-BRAF mutated NSCLC was assessed. Three criteria were used for the diagnosis of a metastatic node; pathologic confirmation, radiologic size greater ≥1.5 cm in short axis diameter or fluorodeoxyglucose avidity on PET/CT and radiologic size ≥1.0 cm in short axis diameter.

Forty-six patients with BRAF mutated NSCLC and CT images on the institutional PACS were identified. 7 (15%) patients with BRAF mutated NSCLC had axLN metastases using the proposed diagnostic criteria. One patient had a pathologic proven axLN metastasis, 3 had axLNs measuring ≥1.5 cm in short axis, and 3 had nodes which were FDG avid on PET/CT and measured ≥1.0 cm in short axis. By comparison, 1 of 46 (2%) control patients with non-BRAF mutated NSCLC had axLN metastases. Previous series have reported the prevalence of axLN metastases in patients with NSCLC as 0.61–0.75%.

We have found a higher incidence of axLN metastases in BRAF mutated NSCLC patients than described in non-BRAF mutated NSCLC patients. Examination of the axilla should be a routine part of physical examination in this genetically distinct subgroup of lung cancer patients.

1. Introduction

Lung cancer is the leading cause of cancer related death worldwide and accounts for 13% of new cancer diagnoses [1]. Axillary lymph nodes (axLN) are a rare site of nodal metastases in patients with lung cancer. Previous series have reported the prevalence of axLN metastases as 0.61–0.75% [2,3]. BRAF mutated lung cancer is a genetically distinct subtype that occurs in 2–5% of non-small cell lung carcinomas (NSCLC) [4–6]. Several subtypes of BRAF mutation exist. The most common is the BRAF V600E mutation which accounts for 50–81% of BRAF mutations and is associated with responsiveness to treatment with the targeted agents vemurafenib, dabrafenib and trametinib [7–9].

A recent study identified a highly unusual pattern of metastatic spread to axLN in patients with BRAF mutated colorectal cancer (CRC) [10]. The aim of our study is to assess the incidence of axLN metastases in BRAF mutated NSCLC.

2. Materials and methods

Our institutional review board approved this retrospective study and waived the requirement for informed consent. This study was HIPAA compliant.

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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 of BRAF mutation ranged from 4/21/2004 to 6/3/2013. Patients with a pathology report documenting lung cancer with a BRAF mutation and with CT images on the institutional picture archiving and communication system (PACS) were included in the study. Baseline CT images were obtained between 5/9/2003 and 5/31/2013. Due to local referral patterns, some of the imaging studies included in the analysis were performed at outside institutions. CT studies obtained in our institution were performed on a variety of 16- and 64-slice multidetector CT scanners, with slice thicknesses ranging from 1.25 to 5 mm. Baseline CTs (at diagnosis, prior to treatment), and all follow-up CTs obtained were included for analysis. When a PET/CT was available, it was also reviewed. Images were retrospectively reviewed by 2 radiologists in consensus on commercially available PACS software (Centricity, GE Healthcare). Both readers were blinded to the clinical details at the time of image interpretation. Clinical information was extracted retrospectively from the institution's electronic medical record, following analysis. Clinical parameters documented were age, sex and smoking status (either current/former smoker or never smoker). BRAF mutation subtype and TNM stage were also recorded. A control group of patients with a pathological diagnosis of lung carcinoma with non-BRAF mutations was selected for comparative assessment from an institutional database of lung cancer patient who had genetic profiling of their tumors. They were matched with the BRAF group for stage at diagnosis. They consisted of 4 ALK, 9 EGFR, 9 KRAS and 24 tumors without documented mutation.

2.2. Image analysis

Imaging studies were assessed for evidence of axLN metastases. Three criteria were used for the diagnosis of a metastatic node: (1) pathologic confirmation, (2) radiologic size greater ≥1.5 cm in short axis diameter (based on response evaluation criteria in solid tumors (RECIST 1.1)) or (3) focal fluorodeoxyglucose (FDG) avidity on positron emission tomography (PET)/CT and radiologic size ≥1.0 cm in short axis diameter (i.e. a non-target RECIST lesion with PET positivity) [11]. The presence or absence of additional thoracic metastases was also documented in patients with BRAF mutated lung cancer including mediastinal and supraclavicular nodal metastases, lung and pleural metastases, lymphangitis carcinomatosis (defined as irregular interlobular septal thickening) and chest wall invasion (defined as extension of the primary tumor through the chest wall).

2.3. Statistical analysis

Grey's method was used to compare the risk of developing axLN metastases between BRAF and non-BRAF mutated lung cancer groups, treating death as a competing event.

3. Results

3.1. Patient characteristics

Forty-six patients with BRAF mutated lung cancer and CT images on the institutional PACS were identified. Twenty-four patients were male, 22 were female. The mean age of patients was 64 years (range 42–85). Forty-five of the 46 patients (98%) were current or former smokers. Twenty-six (57%) had a BRAFV600E mutation. The group contained 13 (28%) stage I tumors, 2 (4%) stage II tumors, 13 (28%) stage III tumors, and 18 (40%) stage IV tumors. Forty-six patients with non-BRAF mutated lung cancer and CT images available on the institutional PACS were identified for comparison. Median follow up for the 2 groups was 27.8 months (range: 0.7–133.6).

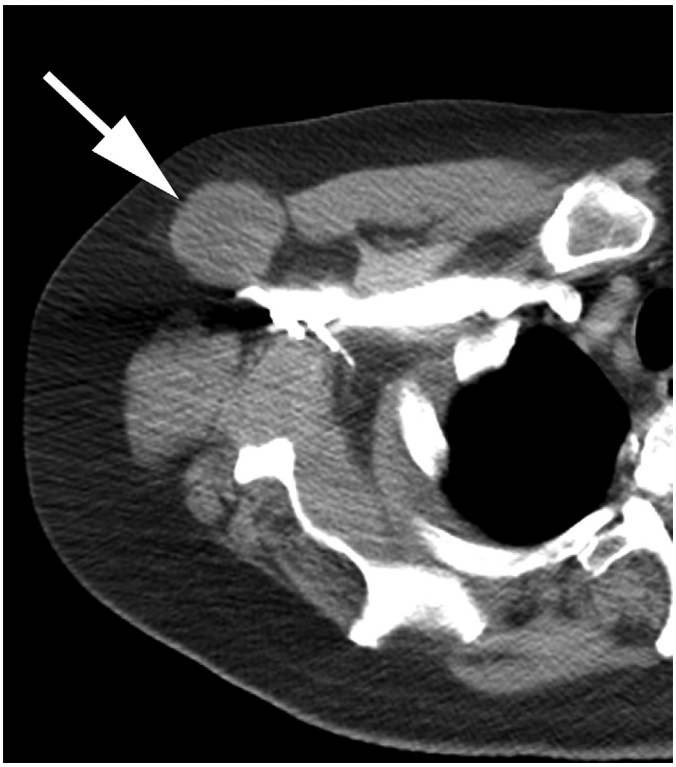

Fig. 1. Axial contrast enhanced CT image of a patient with BRAF mutated NSCLC, with an enlarged right axillary node, measuring 3.5 cm in short axis diameter (arrow).

Table 1
Incidence of thoracic metastases in patients with BRAF mutated lung cancer with and without axillary nodal metastases. *Abbreviations*: LN, lymph node; axLN, axillary lymph node; +ve, positive; −ve, negative.

BRAF patients (N = 46)	axLN metastasis +ve	axLN metastasis −ve
Total number	7	39
Supraclavicular LN metastases	2 (29%)	7 (18%)
Mediastinal LN metastases	7 (100%)	24 (62%)
Pleural metastases	3 (43%)	13 (33%)
Chest wall invasion	0 (0%)	1 (3%)
Lung metastases	3 (43%)	22 (56%)
Lymphangitis carcinomatosis	1 (14%)	4 (10%)

3.2. Imaging findings

Seven (15%) patients with BRAF mutated lung cancer had axLN metastases at diagnosis and/or during follow up using the proposed diagnostic criteria. One patient had a pathologic proven axLN metastasis, 3 patients had axLNs measuring ≥1.5 cm in short axis (Fig. 1), and 3 had nodes which were FDG avid on PET/CT and measured ≥1.0 cm in short axis. Five of the seven patients with positive axLNs had a BRAF V600E mutation on sub-analysis.

Table 1 shows the incidence of thoracic metastases in patients with BRAF mutated lung cancer with and without axillary nodal metastases (Table 1). A higher percentage of patients with axLN metastases had supraclavicular and mediastinal nodal metastases. A single patient with chest wall invasion did not have axLN metastases.