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Malignant pleural disease is highly associated with subsequent peritoneal metastasis in patients with stage IV non-small cell lung cancer independent of oncogene status

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ABSTRACT

Introduction: Peritoneal metastasis from lung cancer is an uncommon clinical event and there are limited data on what factors predict peritoneal progression. This study retrospectively investigated whether patterns of metastatic spread and oncogene status in patients with advanced non-small cell lung cancer (NSCLC) are associated with peritoneal metastasis.
Methods: Patients with metastatic non-squamous NSCLC (n = 410) were identified at the University of Colorado Cancer Center. Sites of metastatic disease and baseline oncogene status (EGFR, ALK, KRAS, or triple negative) were documented via a retrospective chart review. In patients with EGFR mutations who developed peritoneal disease, we documented the presence of known resistance mechanisms. Median time to peritoneal metastasis, time from peritoneal disease to death, and overall survival were collected.
Results: Eight percent (33/410) patients in this study developed peritoneal metastasis. Malignant pleural disease at baseline was significantly associated with subsequent peritoneal spread. There was no association between oncogene status and peritoneal metastasis. Three patients with EGFR mutations who developed peritoneal metastasis had documented resistance to tyrosine kinase inhibitors (TKIs) in the ascitic fluid. Median time from stage IV disease to peritoneal metastasis was 16.5 months (range 0.6–108 months). There were no differences in overall survival between patients who developed peritoneal metastasis and those who did not.
Conclusions: Malignant pleural disease is highly associated with peritoneal metastasis in patients with advanced NSCLC. The underlying mechanism is not clear. The presence of resistance mutations in ascitic fluid implies that poor drug penetration is unlikely to be the dominant mechanism. Despite being a late clinical finding, there were no differences in overall survival between patients who developed peritoneal metastasis and those who did not. Additional studies exploring treatment related factors in patients with malignant pleural disease that can reduce risk of peritoneal metastasis are warranted.

1. Introduction

Lung cancer is the most frequent cause of cancer death and metastatic disease at the time of initial diagnosis is common [1]. The most common sites of metastasis are the brain, bone, liver, and adrenal glands. Although numerous case reports documenting peritoneal carcinomatosis have been reported [2–4], peritoneal metastasis from lung cancer is considered a rare clinical event [5].

Peritoneal carcinomatosis has been well described in the ovarian and colorectal literature. The pathophysiological mechanism remains controversial. Several leukocyte-associated adhesion molecules, integrins, and selectins have been implicated in tumor-mesothelial interaction. The peritoneal stromal environment provides abundant supply of growth factors and chemokines for aggressive tumor spread [6]. Cancer cells stimulate a pro-inflammatory response within the peritoneal cavity. These inflammatory markers can disrupt the protective mesothelial cell

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lining, which promotes cancer cell attachment by exposing the pro-adhesive extracellular membrane [4,6,7]. Finally, cancer cells that infiltrate the peritoneum develop contractile behavior (via integrin attachments) and spheroid formation that likely hinders chemotherapeutic delivery.

There are limited data on what factors predict peritoneal progression in lung cancer. A large retrospective study of peritoneal carcinomatosis in lung cancer described a clinical frequency of 1.2% [5]. In this series, adenocarcinoma and large cell carcinoma histological subtypes were noted to have highest association with peritoneal spread. Of note, all patients had metastatic sites outside of the peritoneum at stage IV diagnosis. 9/12 patients who developed peritoneal carcinomatosis presented with a malignant pleural effusion. Similar findings were reported by Su et al. [7]. In both of these retrospective studies, pleural disease at diagnosis was the most common baseline clinical feature in patients who developed peritoneal disease, though this association was not statistically characterized.

Over the last decade, molecular analysis of non-small cell lung carcinoma (NSCLC) has provided more detailed classification of patterns of metastatic spread. It has also been shown that oncogene-addicted subsets of NSCLC have different patterns of metastatic spread [8]. For example, it has been well described that patients with *ALK* gene rearrangement have a higher propensity towards pleural and pericardial metastases [8]. There have been case reports of peritoneal carcinomatosis in patients with *EGFR*+ mutations who have been on targeted therapy with tyrosine kinase inhibitors (TKIs) [7,9,10], raising the possibility that dominant oncogene drivers may play a role in the underlying metastatic pattern. We initially made a clinical observation that several patients with *EGFR* mutations had metastatic disease to the peritoneum. We hypothesized that the underlying oncogene status might account, at least in part, for this pattern of metastatic spread. We therefore formally analyzed if baseline patterns of metastatic spread or underlying oncogene status were associated with peritoneal metastasis in patients with stage IV NSCLC.

2. Materials and methods

2.1. Patient selection

A protocol approved by the institutional review board permits clinical correlates to be made on all patients in whom molecular analyses have been conducted within the Colorado Molecular Correlates Laboratory (CMOCO). All patients with NSCLC who had stage IV cancer (classified by TNM 7th edition) tested within CMOCO from June 2008 to October 2015 were eligible for assessment if there were pathology reports with mutation analysis documenting testing for *ALK*, *EGFR*, and *KRAS* mutations. Patients that had driver mutations other than *ALK, EGFR,* or *KRAS* (such as patients with *BRAF, MET, HER2, RET)* or patients with no identifiable driver mutations were classified as triple negative.

Data and imaging were collected by retrospective chart review. We captured age, sex, smoking status, histology, oncogene status, and clinical stage at diagnosis, and presence of metastatic disease in predefined sites at stage IV diagnosis. These predefined sites included brain, liver, lung, adrenal, bone, soft tissue, and pleural disease. Soft tissue metastases were defined as any metastatic site involving skin, subcutaneous tissues, or muscle that was distinct from underlying bone involvement. Pleural disease was defined as cytological proven adenocarcinoma from thoracentesis, biopsy-proven pleural disease from video-assisted thorascopic surgery (VATS), cytology-proven adenocarcinoma from pericardiocentesis provided there was also radiographic imaging also demonstrating a pleural effusion at time of stage IV diagnosis, or CT imaging demonstrating clear pleural metastases.

Patients with squamous histology were excluded given that prevalence of predominant oncogene driver abnormalities would be significantly lower in this population. Two patients tested positive for more than one mutation (*ALK*, *EGFR*, or *KRAS)* and were excluded. We also excluded any patient who did not develop stage IV disease during June 2008 to October 2015, any patient that did not have at least 4 months of clinical follow-up from initial diagnosis of NSCLC, any patient who died within 30 days of diagnosis, and any patient with incomplete clinical data.

We defined peritoneal metastases as the presence of cytology-proven adenocarcinoma from peritoneal fluid, biopsy-proven adenocarcinoma from omental biopsy, or radiographic patterns consistent with peritoneal carcinomatosis. For patients who developed peritoneal metastases, we calculated median time from stage IV diagnosis to peritoneal disease, median time from peritoneal disease to death, and overall survival.

2.2. Oncogene testing

Mutation analyses were conducted at CMOCO, a CLIA certified laboratory. Mutational analysis was performed using laboratory assays that were independently validated [11,12]. Over the course of time of this study, the standard approach in the laboratory varied, and always allowed for accommodation of methodology to the limitations of the sample, and therefore testing for individual patients may have been performed using a variety of assay approaches. These approaches included: Sanger Sequencing of relevant targeted regions, Singe nucleotide base extension assay (SNaPshot), Real-time PCR and targeted Next Generation Sequencing using a 26 gene panel. All *ALK* assessments were performed by FISH testing using the Abbott Vysis *ALK* Break-Apart Probe. Patients were deemed *ALK* FISH–positive if >15% of tumor cells showed split red and green signals and/or single red (residual 3′) signals. Otherwise, the specimen was classified as *ALK* FISH negative.

2.3. Statistical testing

We created 2×2 contingency tables for each site of metastatic disease. Within each site of metastasis, a Fisher exact test was used to compare the proportion of patients that developed peritoneal metastases to the proportion of patients that did not develop peritoneal metastases. We also performed a similar analysis to explore the association between mutation status and subsequent peritoneal spread. An unpaired *t*-test was used to compare overall survival between patients who developed peritoneal metastases and those that did not. Given the rarity of peritoneal metastases, a two-sided P value <0.01 was considered statistically significant. Fisher exact analyses were performed using GraphPad Prism (Version 6.00 for Windows, GraphPad Software, La Jolla, CA)

3. Results

A total of 545 patients with stage IV non-squamous NSCLC between June 2008 and October 2015 were identified as candidates for this study. Of these, 135 were excluded due to pre-specified exclusion criteria and 410 patients were included in the analysis, as shown in Fig. 1. There were no major differences in age, sex, and smoking status. 77% (315/410) patients had stage IV disease at diagnosis and 23% (94/410) had recurrent disease. The percentage of patients grouped by oncogene driver status was as follows: *ALK* 23% (96/410), *EGFR* 40% (163/410), *KRAS* 18% (73/410), and triple negative 19% (78/410) Baseline characteristics of the 410 patients included in this study are shown in Table 1.