

## Contribution of Next-generation Sequencing in a Case of Metastatic Breast Carcinoma with Pulmonary Lesions

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### Abstract

Next-Generation Sequencing (NGS) provide specific cancer-related gene-sequence information which can be helpful for diagnosis and clinical decision. Here we describe the case of a patient diagnosed with HER2 positive metastatic breast cancer and successive pulmonary lesions. Despite large immunohistochemical assays. It was not possible to distinguish on first thoracic specimen between primary lung adenocarcinoma and metastasis from breast carcinoma. NGS analysis on second thoracic sample detected somatic mutations in PIK3CA and TP53 genes. This mutation profile was identical to the previously resected adenocarcinoma. NGS contribute to diagnose metachronous primary lung carcinoma and to propose a thoracic treatment in addition to systemic management of metastatic breast carcinoma. Our case report emphasizes the usefulness of NGS to guide diagnosis and treatment in the objective of precision medicine.

**Keywords:** Next-generation sequencing; Lung adenocarcinoma; Breast carcinoma; Pulmonary metastasis; PI3KCA mutation; TP53 mutation; Precision medicine

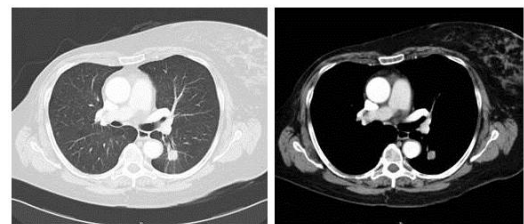
### Introduction

Cancer is a multi-genic disease. Currently, Next-Generation Sequencing (NGS) provide specific cancer-related gene-sequence information, which can be helpful for diagnosis and clinical decision [1]. Genomics-based analyses and the presence of molecular aberrations provides rationale for the use of targeted therapies as well as facilitate inclusion in early drug clinical trials and it's routine use is becoming more and more frequent. Moreover, genetic aberrations may be common across several cancer types or multiple molecular aberrations may coexist within a single tumor. In metastatic breast cancer, importance of molecular characterization is growing evidence [2]. Patient management may be affected by NGS analysis made on primary and also on metachronous lesions. Here we describe the case of a patient diagnosed with HER2 positive metastatic breast cancer included pulmonary lesions that turned out to be primary lung adenocarcinomas after NGS testing.

### Report

In April 2008, a non-smoking previously healthy 70-year-old woman, was referred for an invasive ductal Paget's disease of the breast. Radical mastectomy and axillary lumpectomy was performed. Immunohistochemistry revealed an estrogen and progesterone receptors negative and HER2 positive tumor. Before starting adjuvant chemotherapy, a complete work-up revealed bilateral lung, bone and liver metastasis. First line chemotherapy with docetaxel and

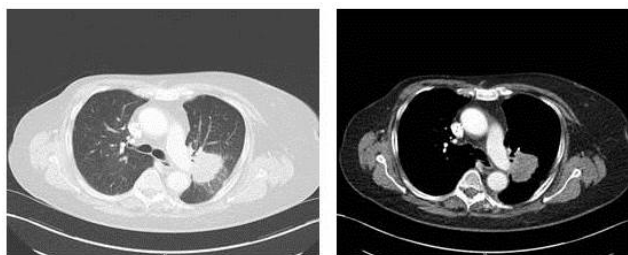
trastuzumab was started followed by trastuzumab monotherapy with complete response on all metastatic sites. In 2010, thoracic CT scan showed a pulmonary nodule in the lower left lobe firstly considered as a probable recurrent metastatic lesion (Figure 1).



**Figure 1:** Thoracic CT scan (2010): solitary nodule in the left lower lobe. Pathological and IHC analysis cannot distinguish between metastatic lesion from breast carcinoma and primary lung cancer.

Successive treatments as Neratinib and Capecitabine associated with lapatinib were proposed without efficacy and thoracic surgery was performed. Pathological findings concluded to an adenocarcinoma. Despite large immunohistochemistry assays its primary or secondary nature could not be specified and no further systemic treatment was done. In 2014, docetaxel and trastuzumab were administered for a micronodular bilateral lung, bone and liver disease progression. Due to partial response trastuzumab monotherapy was pursued. In 2015, bone and thoracic CT scan revealed respectively T7-T8 meets with epiduritis and a lingular nodule whose CT guided biopsy was in favor of a primary lung adenocarcinoma TTF1 negative (Figure 2). Lung tumor was analyzed by NGS with a 22-gene targeted mutation panel and

somatic mutations in *PIK3CA* and *TP53* genes were detected (Table 1). Retrospective analysis of the 2011 lung tumor sample showed a mutational profile identical to that of the present adenocarcinoma. For us, NGS analysis seems to confirm the occurrence in this patient of two metachronous lung cancer with the same cancer gene signature. To avoid missing a bone metastatic lung adenocarcinoma a vertebral CT-guided biopsy was performed. Histological findings confirmed a HER2 amplified breast carcinoma T8 metastasis. Systemic treatment for HER2 positive bone metastatic breast carcinoma and thoracic radiotherapy for localized lung adenocarcinoma were proposed.



**Figure 2:** Thoracic CT scan (2015): Lung adenocarcinoma in left upper lobe (CT guided biopsy).

Gene	Sequence	Variant	Protein
<i>PIK3CA</i>	NM 006218	c.3140A>G	p.His1047Arg
<i>TP53</i>	NM 000546	c.637C>T	p.Arg213Ter

**Table 1:** NGS analysis detected identical somatic mutations *PIK3CA* and *TP53* on 2011 and 2015 samples.

## Discussion

Breast cancer pulmonary metastases are mainly multiple and bilateral, but sometimes it might be difficult to determine whether the lesion represents a primary lung cancer or a metastasis and require appropriate management [3]. European Society for Medical Oncology clinical practice guidelines for metastatic breast cancer suggest that in case of an isolated metastatic lesion histopathological confirmation should be obtained whenever possible as well as the seek for biomarkers with therapeutic impact such as hormone receptor and HER2 status [4]. In a large cohort of 1416 breast cancer patients, Casey and coll. reported 42/1416 (3%) cases with solitary pulmonary nodule among which final diagnosis was primary lung tumor, benign lesions and metastatic breast cancer in respectively 52%, 5% and 43% of these

patients [5]. But even if primary lung adenocarcinoma can be frequently distinguished from lung metastases using an immune histological panel, distinction may be challenging, especially in the estrogen receptor negative/progesterone receptor negative breast cancer as in our case [6,7]. NGS has revolutionized the molecular knowledge of cancer by increasing the feasibility and possibility to sequence DNA to establish molecular portraits of cancer [8]. Shih and coll. reported a case in which the NGS detection of 3 somatic mutations (*HER2*, *TP53* and *SMARCB1*) permitted to diagnose a thoracic recurrence of an HER2 positive metastatic breast carcinoma instead of lung adenocarcinoma initially mentioned [9]. These authors emphasized the therapeutic consequences of such NGS analysis. Our case illustrates also the contribution of NGS to distinguish between metastatic and synchronous or metachronous primary lesions in cancer patient and its therapeutic impact.

We do think, based on this observation, that there is a need for NGS implementation in the clinic for cases in which these data may be of importance for decision-making.

NGS testing is not yet standard in patients with cancer but become essential for diagnostic information and therapeutic decision for precision medicine [8,9].

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