# Chemotherapy Resistance in Remutation of Epidermal Growth Factor Receptor Wild Type Becomes a Positive Type and Back Becomes a Wild Type in a Patient with Lung Adenocarcinoma

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**Abstract**

**Introduction**: Lung cancer is the most common type of cancer worldwide (11.6%) and the leading cause of death due to cancer throughout the world. One type of lung cancer that is often found is Adenocarcinoma, 35-40%. Mutations in EGFR often occur in patients with pulmonary Adenocarcinoma especially in Asia. Chemotherapy selection for pulmonary adenocarcinoma patients based on the status of their EGFR mutations. Positive EGFR mutations can get treatment with Tyrosine Kinase Inhibitors. Giving chemotherapy can affect changes in EGFR mutation status. Patients with chemotherapy treatment can experience resistance to chemotherapy either primary or acquired resistance through a variety of mechanisms.
**Case Description**: we reported one case of a 56-year-old man with pulmonary adenocarcinoma who had a positive change in EGFR-type from wild type mutations and then returned to a wild type. Patients were initially diagnosed with wild type pulmonary adenocarcinoma from EGFR examination of tissue biopsy and given conventional chemotherapy. During the evaluation, progression occurred so that the status of the EGFR mutation was examined using ct-DNA and the result was mutation deletion exon 19 so that the patient obtained Gefitinib. Due to progressive return, the patient again examined EGFR status from tissue biopsy obtained using pleuroscopy and obtained an EGFR wild type. Patients again get conventional chemotherapy.
**Discussion** Changes in the status of EGFR mutation in pulmonary adenocarcinoma patients and chemotherapy resistance can occur in patients with chemotherapy treatment.
**Keywords**: Adenocarcinoma bronchogenic, EGFR mutation, TKI, chemotherapy resistance

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## 1. Background

Primary lung cancer, also known as bronchogenic carcinoma, is a malignant tumor that develops from the bronchial epithelium (bronchogenic carcinoma). Lung cancer is classified into two forms for treatment: non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). Adenocarcinomas account for 35-40% of all lung cancers, squamous cell carcinomas for 20%-30%, large cell carcinomas for 10%, and SCLC for 15-20%[1,2]. Cigarette smoke, bacteria, inflammation, chemical factors, physical factors, dietary factors, obesity, and physical activity are only a few of the factors that can cause cancer. Currently, cigarette smoking is regarded as a significant cause of lung cancer[3].

Supportive examinations to determine the type of tumour anatomical pathology can be performed with sputum cytology, bronchoscopy (biopsy, washing, brushing), transthoracic needle aspiration (TTNA) or other invasive examinations such as thoracoscopy, mediastinoscopy or exploratory thoracotomy[1].

Other investigations in lung cancer include molecular biology not only to determine the prognosis of the disease but also to determine the effectiveness of treatment. Especially for the use of targeted therapy drugs by detecting the presence or absence of certain gene mutations in cancer tissue. The gene mutation detection tests that can be done are EGFR, K-ras, VEGF, and ALK[1]. There was a significant association between EGFR mutations (especially exon 19 deletions, exon 21 mutations) and the response to administration of Tyrosine Kinase Inhibitor (TKI). The existence of mutations that cause activation, the prevalence of EGFR mutations in adenocarcinoma is 10% in western countries and reaches 50% in the Asian population. The frequency of EGFR mutations is higher in female patients, non-smoking and non-mucinous cancer. The results of the IPASS study indicate that the occurrence of EGFR mutations in Asians is 2-3 times higher when compared to westerners for reasons that are not yet known. Most of the mutations that occur in the tyrosine kinase region occur in exon 19 or as point mutations at exon 21[4,5]. Tyrosine Kinase Inhibitor (TKI) binds to the tyrosine kinase inhibitor domain and inhibits its transduction pathway[6].

Lung cancer treatment is a multi-modality therapy. The choice of therapy is not only influenced by the histological type, stage, and appearance of the patient but also by looking at non-medical conditions such as the facilities owned by the hospital and the patient's economic ability. Management includes surgery, radiotherapy, chemotherapy and palliatives. The principle of selecting the type of anticancer and administering the chemotherapy regimen is platinum-based therapy (cisplatin or carboplatin)[1,7]. Several types of cancer drugs with selective work targets or targeted therapy are being used for NSCLC. TKI selectively inhibits EGFR signaling with the target ATP binding site and prevents activation of the intrinsic domain of tyrosine kinase[8].

The study of resistance to TKI EGFR in EGFR mutant NSCLC patients can be divided into primary and acquired resistance, which have different origins. Primary resistance refers to patients who have progressive or stable disease as the best response to EGFR TKI, whereas acquired resistance, or secondary, refers to patients who have progressive disease after an initial objective response or prolonged stable disease. Primary resistance can occur due to EGFR somatic mutations and EGFR Germ line polymorphisms[9]. The acquired resistance against the TKI EGFR resistance occurs through secondary EGFR mutations, gene copy alterations of alternative pathways, drug efflux, drug inactivation, drug target alteration, epigenetic and histological transformation from NSCLC to SCLC and epithelial to mesenchymal transition[9,10,11].

In addition to the above two resistance mechanisms, more recently, intratumoral heterogeneity EGFR mutations have attracted attention as a potential source of treatment failure and drug resistance to EGFR-TKI. Recent studies suggest that chemotherapy-induced shift in EGFR mutations may be related to heterogeneity of intratumoral EGFR mutations and to different levels of chemosensitivity of wild-type and mutant cells[12].

Based on RECIST Guideline, chemotherapy evaluations are carried out every 6-8 weeks (according to the end of the chemotherapy cycle). The prognosis of patients with NSCLC is poor with a 5-year survival rate of less than 10% regardless of the therapy given. In patients with NSCLC, the mean survival for limited disease is 14-16 months and extensive disease is 8-10 months[13].

## 2. Case Report

A male patient aged 56 years complained of right chest pain since 3 years ago. Pain especially when coughing and strenuous activity without spreading. The patient also complained of coughing for 3 years with watery white sputum, never having had a cough mixed with blood before. Shortness of breath since 3 years ago and heavy since the last 6 months. Fever and weight loss is denied. The patient was an ex-smoker with a history of smoking 24 cigarettes per day for 39 years.

On May 2015, the patient went to the hospital in Tenggarong due to chest pain and the chest X-ray result showed a suspicious tumor in the right lung. The patient was referred to RSSA Malang, where he underwent FOB in August 2015 and the findings of the anatomical pathology of Adenocarcinoma were obtained. He was diagnosed with Bronchogenic Adenocarcinoma Dextra. September 2015 - February 2016 the patient started chemotherapy treatment using carboplatin-gemcitabine and pemetrexed. September 2015 checked for EGFR mutases and the results were: "no mutation detected". March 2016 - July 2016 patients received chemotherapy treatment using docetaxel. August 2016 - November 2016 the patient received chemotherapy treatment using vinorelbine. December 2016 - May 2017 the patient received chemotherapy treatment using paclitaxel. August 2017 mutation was detected

EGFR Deletion exon 19. The patient began receiving Gefitinib treatment in August 2017.

Physical examination had shown VAS score 7/10. His lung examination showed decrease of stem fremitus, dull percussion on right hemithorax, and decreased breath sound on right hemithorax. His laboratory examination had shown anemia (Hb=9,9 g/dL) and CEA examination resulted in 4,76 ng/mL.

A serial chest x ray radiological examination was performed on the patient revealed increased of tumor mass and pleural effusion to evaluate therapy and disease progression **(Figure 1).**

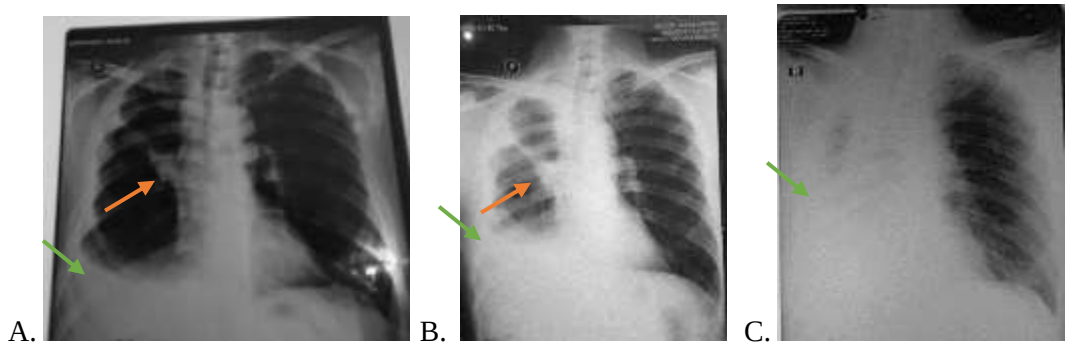
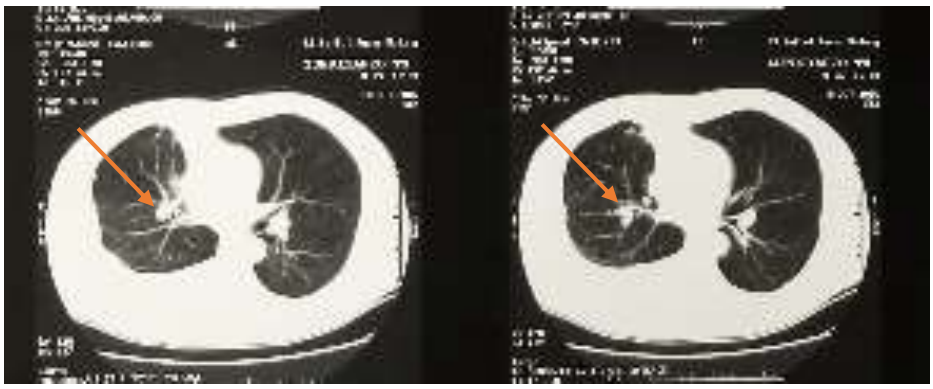



Figure1. A. CXR Mei 2015; B. CXR 26 September 2016; C. CXR 31 January 2018 (orange line shown tumor mass and atelectasis progression; green line shown pleural effusion)

Another radiological test performed is a CT scan of the chest without and with contrast to accurately identify the tumour's site, size, and spread so that the stage of lung cancer in this patient can be determined **(Figure 2).** A CT scan of the chest is also performed to evaluate the RECIST of chemotherapy administered



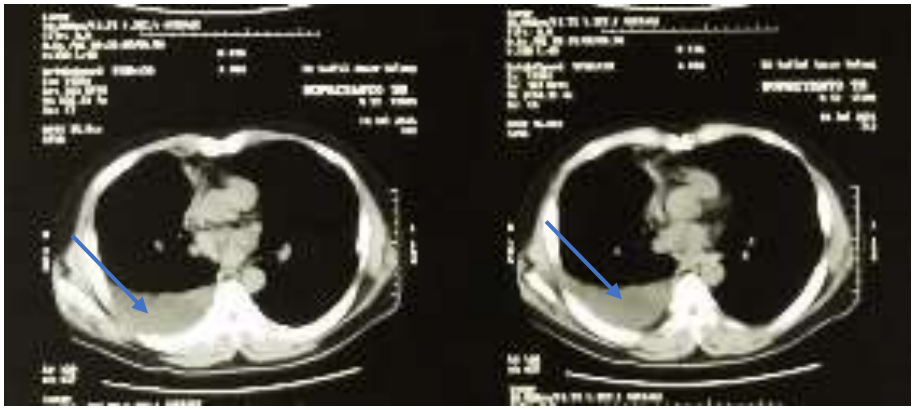


Figure 2. Thoracic CT scan in July 2016 (the orange line shown tumor mass; the blue line shown the pleural effusion

Thoracic CT Scan in July 2016 revealed a central stenoting right lung mass (size 3.4x3x3.6 cm) causing atelectasis of the superior segment with ipsilateral nodules; Right pleural effusion. In the next evaluation, CT scan of the thorax on September 1, 2018, obtained a right lung mass with the largest diameter of 4.4 cm with multiple nodules and thickening of the interlobular septum of the superior lobe of the right lung, with 6 segment atelectasis of the right lung.

A biopsy using the FOB modality was used to diagnose anatomic pathology in this patient, and the findings of the FOB biopsy on August 14, 2015 revealed Adenocarcinoma. Since the tumour size and pleural effusion deteriorated over time, the doctor returned to conduct a rebiopsy to establish the pathology anatomy of lung cancer, using pleuroscopy to take biopsy samples from nodules in the pleura while also inserting a chest tube to drain pleural fluid **(Figure 3)** and the pathology anatomy was adenocarcinoma **(Figure 4)**.

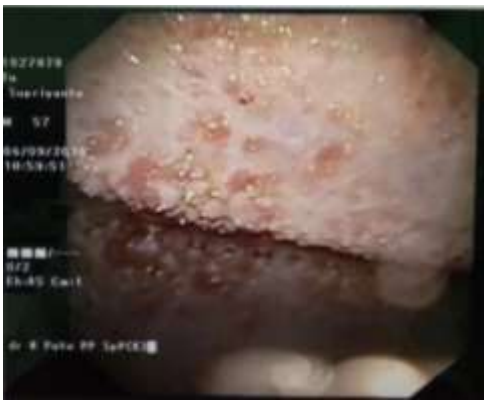


Figure 3. Pleuroscopy: Appears right parietal pleura hemithorax; pale, uneven and nodular surface

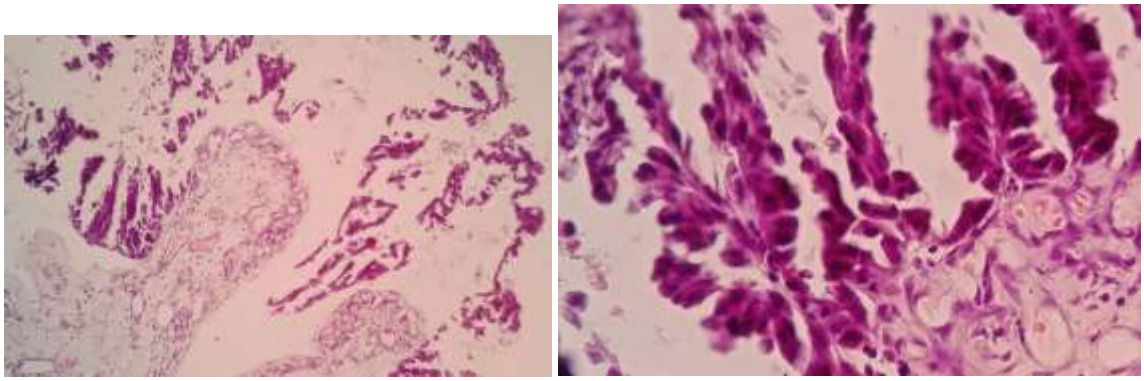


Figure 4. Histopathological examination of pleural tissue with magnification of 40x and 400x shown pleural tissue consist of proliferation of cells with a round-oval nucleus, pleomorphic, hyperchromatic, arranged to form acini glands which are mostly papillary, infiltration between the connective tissue stroma with proliferation of blood vessels and sebanous inflammatory cells of lymphocytes and plasma cells conclude is Adenocarcinoma

EGFR examination in patients was carried out because the anatomical pathology of adenocarcinoma was obtained, to see whether there was a mutase in the EGFR or not so that it could determine which chemotherapy was more appropriate for the patient. The results of the EGFR examination in September 2015 concluded: no mutation detected (wild type). In the next evaluation, ct-DNA examination was carried out in August 2017 and an EGFR mutation of exon 19 deletions was detected; ct-DNA in August 2018 obtained a positive conclusion for EGFR Exon 19 Deletion mutation. In January 2019, another EGFR examination was carried out to see the possibility of chemotherapy resistance caused by mutases on exon 20 T790M and obtained EGFR exon 20 (c.2369 C> T) / T790M: negative (-).

## 3. Discussion

In this case, it was reported that a 56-year-old man presented with complaints of chest pain, shortness of breath and cough with a history of smoking. This is in accordance with the literature which states that the incidence of lung cancer is more often found in male smokers, especially those aged over 40 years. Symptoms that can be found in lung cancer are coughing, chest pain and shortness of breath[14].

In this patient, physical examination showed decreased stem fremitus and a dullness sound on right chest field percussion, as well as decreased breath sounds. This can be caused by tumor development into the pleura, which can result in pleural effusion, resulting in reduced breath sounds in the affected chest fields[14,15].

In this patient, a chest x-ray was performed and the chest x-ray showed a

right lung mass followed by atelectasis and right pleural effusion. Chest CT scan using contras revealed a central stenoting right lung mass (size 3.4x3x3.6 cm) leading to superior segment atelectasis accompanied by ipsilateral nodules with pleural effusion and paratracheal, subaortic and subclavian lymphadenopathy. In the literature, it is stated that a chest CT scan was performed to determine the location of the tumor, the size of the tumor and the likelihood of metastasis. In addition to determining the location of the tumor and determining the initial level of TNM, CT scan can also be used to assess recist as an evaluation of chemotherapy[1].

Pleuroscopy was used to obtain one of the tissue biopsy samples in this patient, which was taken from a nodule in the pleura. According to the literature, in challenging circumstances, invasive procedures such as thoracoscopy, mediasnoscopy, exploratory thoracotomy, and open lung biopsy may be used to affirm the diagnosis of anatomical pathology[1]. Adenocarsioma can be present on the periphery, but it can also be found in the centre, as in this patient[16].

In the EGFR mutation examination, wild-type results were obtained which then also obtained mutation (+) results, namely deletion of exon 19 on subsequent evaluation using ctDNA. ctDNA is a liquid biopsy which is a method for obtaining tumour DNA that will be used in examining EGFR mutations[17,18]. The most common mutations are deletions at exon 19[19]. In this patient then received gefitinib TKI therapy in accordance with the existing literature that the 1st line therapy for EGFR mutations, one of which is Gefitinib[6,20].

From the available evaluation, it was found that the size of the tumour mass increased. Patients who receive gefitinib therapy are at risk of experiencing chemotherapy resistance so that the effectiveness of treatment does not respond[21]. The patient was then evaluated with another EGFR examination to see the possibility of mutases on exon 20 / T790M. in the literature it is said that one of the mechanisms of chemotherapy resistance is due to mutations in T790M[9]. In the literature, it is stated that the presence of intratumor heterogeneity factors allows the existence of two EGFR mutation states in a tumor[12]; and the occurrence of resistance after chemotherapy treatment[9,22]. In this patient, both of these things may occur because this patient has received all types of conventional chemotherapy drugs that are available

## 4. Conclusion

A 56-years-old man presented with chest pain, shortness of breath, and cough. Chest X-Ray and CT scan thorax indicating

right lung tumor with pleural effusion. Tumor biopsy was obtained via FOB and the result of the pathologic anatomy was adenocarcinoma with EGFR wild type. Thus, the patient was diagnosed with Adenocarcinoma bronchogenic dextra wild type and was given chemotherapy platinum based. Progressive disease and EGFR mutation changes became deletion exon 19 so the patient got TKI chemotherapy using gefitinib. Changes in status of EGFR mutation in lung adenocarcinoma patients can occur in patient with chemotherapy treatment. The progression of the disease can be due to chemotherapy resistance or heterogeneity of EGFR status intratumor that affect the therapy.

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