

Healing efficacy in lung adenocarcinoma after targeted therapy, Covid 19 disease and radiosurgery of brain metastases

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Abstract

Lung adenocarcinoma is a common disease, in which high mortality is due to both men and women. In the article we present a 58-year-old man who has been diagnosed with metastatic pulmonary adenocarcinoma/T2B N2 M1a in 2018, on the occasion of dry irritating cough and shortness of breath. Also a positive EGFR mutations has been proven. Targeted therapy (TT) with gefitinib has been carried out for two years till 2020. The patient has been switched on osimertinib in 2020 due to local progression. Brain metastasis has been found in 2021. Radiosurgery (RS) with a singal fraction 15Gy was conducted for treatment of 4 brain metastases . The patient was infected after RS with Covid 19 in April 2021.

Patients with specific EGFR mutations can be effectively treated with TT. After treatment with TT, brain metastases of pulmonary adenocarcinoma with specific EGFR mutations are more radiosensibility and responded very well by high single radiation dose realized by radiosurgery (RS). Despite the worsened prognosis, including Covid 19 disease, by combining TT and RS, we achieved three-year survival in metastatic lung adenocarcinoma.

Keywords: Lung Adenocarcinoma, EGFR Mutations, Targeted Therapy, Covid 19, Brain Metastases, Radiosurgery.

Introduction

Lung cancer incidence has been decreasing for several years, particularly in males, however it is still the second most common cancer in both females and males, only behind breast and prostate cancer, respectively [1]. Lung cancer is commonly classified as small-cell carcinoma (SCC) and a heterogeneous group of nonsmall-cell carcinomas (NSCLC) [2]. NSCLC accounts for 85% of lung cancer cases, including three main subtypes, namely adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma (LCC) [3]. Adenocarcinoma rates continued to increase in men and women, and squamous cell rates increased in women only [4]. Over the past two decades, adenocarcinoma has replaced squamous cell carcinoma as the most common subtype of non-small cell lung cancer (NSCLC) in the United States and worldwide [5,6]. Lung adenocarcinoma (LADC) is a cancer treatable using targeted therapies (TT) against driver gene aberrations [7]. We present a clinical case with local advanced lung adenocarcinoma after TT and radiosurgery (RS) of four brain metastases. Despite the disease from COVID 19, three years of survival with local tumor control (LTC) of brain metastases in

good quality of life was achieved.

Clinical Case

We present a 58-year-old man who has been diagnosed with metastatic pulmonary adenocarcinoma/T2B N2 M1a in 2018, on the occasion of dry irritating cough and shortness of breath. Also a positive EGFR mutations has been proven. Histological result : Parietal pleura with an acinar adenocarcinoma infiltration. Cytology of pleural fluid: Papillary complexes of adenocarcinoma tumor cells. Immunohistochemistry: TTF1 (+); CK7 (+); CK 20 (-). Molecular/Cytogenetics description: EGFR mutation-positive. Targeted therapy (TT) with gefitinib has been carried out for two years. The patient has been switched on osimertinib in 2020 due to local progression. Radiosurgery with a singal fraction 15Gy was conducted for treatment of 4 brain metastases in 2021. (Figure 1). CT has been performed on 11.02.2021 and four brain metastases has been found (Figure 2 and Figure 3), Radiosurgery with a singal fraction 15Gy (Figure 4) was conducted for treatment of 4 brain metastases in March 2021.

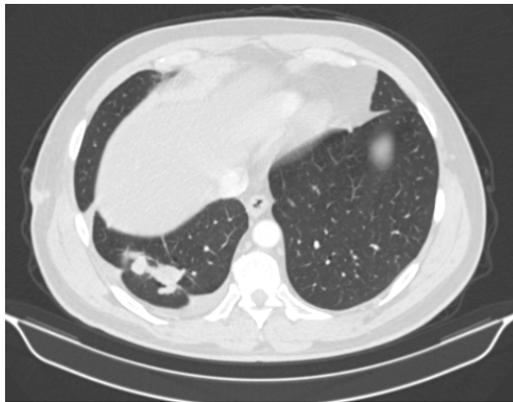


Figure 1: Lung CT with intravenous contrast enhancement 25.11.20 g-Spiculous lesions in the right basal lung with compacted and dragged pleura.

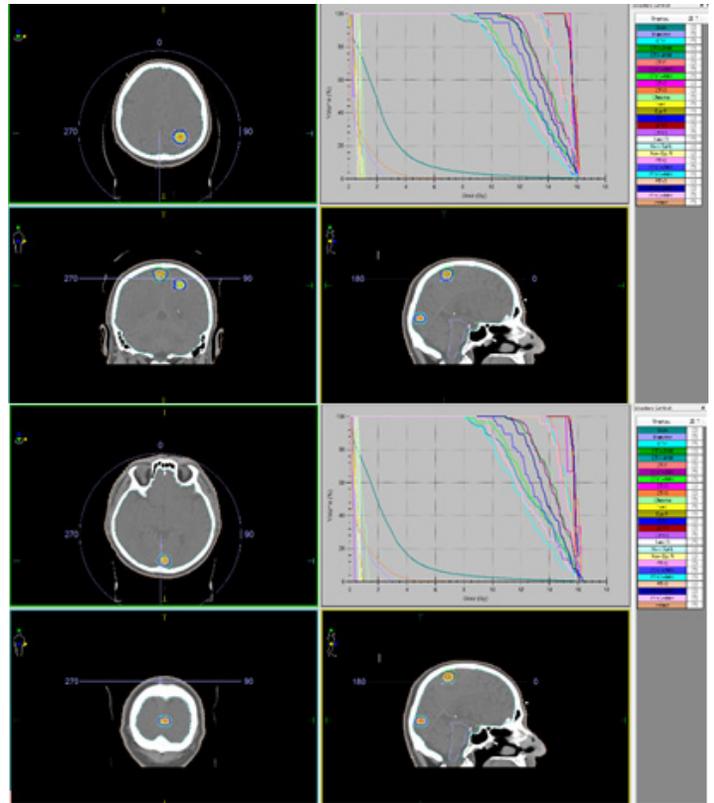


Figure 4: Radiosurgery/Intensity Modulated Radiotherapy (IMRT) by VMAT technique with a single fraction 15Gy of four brain metastases.

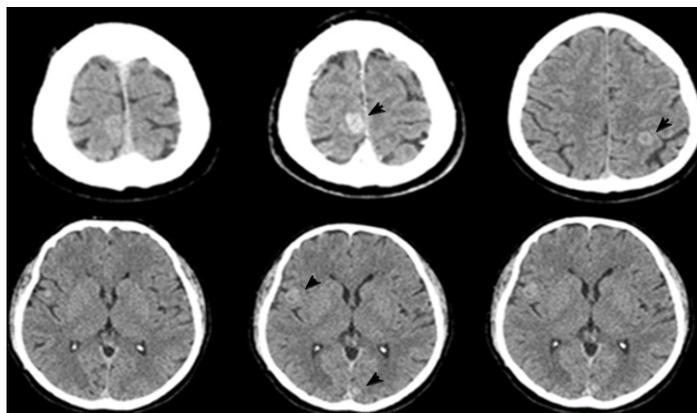


Figure 2: Brain CT with intravenous contrast/11.02.21-Four contrast-enhancing brain lesions on the right temporal cerebral lobe (11/11 mm), on high left parietal cerebral lobe (10/13 mm), around Falx cerebri on the right (11/11 mm) and occipital right side (6/6 mm). Metastases are indicated by black arrows.

The patient was infected with Covid 19 in April 2021. Chest and brain CT were performed after a negative PCR test which detects fibrous lung changes and lack of brain metastases (Figure 5 and Figure 6). The patient was directed to continued TT.

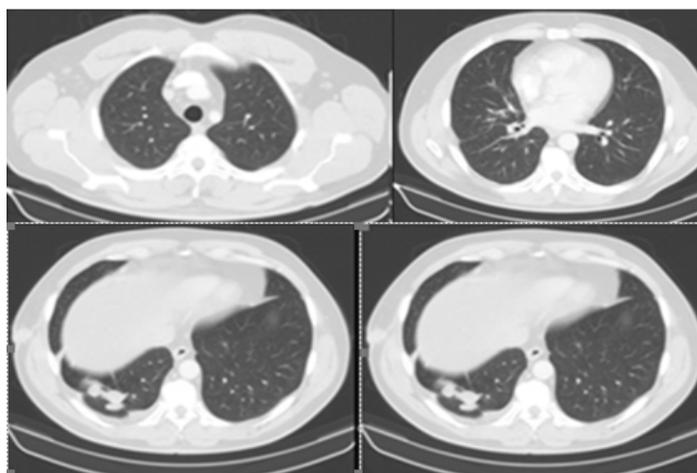


Figure 3: Lung CT with intravenous contrast/11.02.21-Spiculous lesions in the right basal lung with compacted and dragged pleura.

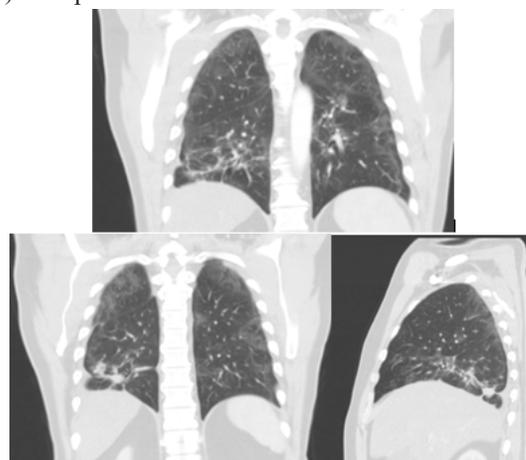


Figure 5: Lung CT/24.05.21 after a Covid 19 disease-persist the right basal lung lesions without density dynamics and dimensions compared to CT from 11.02.21. Diffuse post- Covid fibrous changes. The ground glass opacities are bilateral, asymmetrical, peripheral

and subpleural in location.

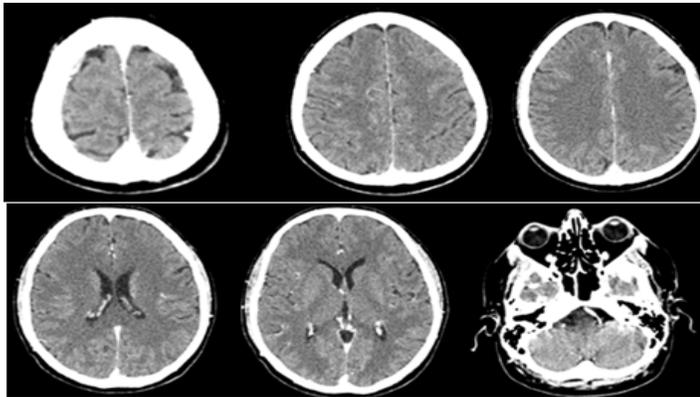


Figure 6: Brain CT with intravenous contrast/24.05.21 after radiosurgery-Brain without supra- and infratentorial lesions. There are no visualization of four metastases described by the previous CT. Symmetrical brain structures without dislocation or compression by means of a medium line. Symmetrical undilated ventricular system.

Discussion

Approximately 80% to 85% of lung cancers are non-small cell lung cancers (NSCLCs), and the most common subtype is adenocarcinoma [1,8,9]. For many years, treatment strategies have focused on traditional therapy, such as surgery, chemotherapy, radiotherapy, and, in the early stages, surgery [10]. Recent progress in oncology, radiology, and molecular biology has significantly advanced the understanding of lung adenocarcinoma and its subtypes, which has led to improvements in the paradigm for its clinical management [11]. The new classification has advantages not only for individual patient care but also for better selection and stratification for clinical trials and molecular studies [12]. For the assessment of the healing strategy, each patient is determining the histological subtype of pulmonary carcinoma, its molecular genetic characteristics as well as its clinical staging. Immunohistochemical analysis is of great importance for diagnosis of primary pulmonary adenocarcinoma. TTF-1 appears to be the best adenocarcinoma marker (excluding for invasive mucinous adenocarcinoma, where cytokeratin 7 may be more useful), providing added value as a confirmatory pneumocyte marker for primary lung origin [9,11].

Prognosis: NSCLC is the most common primary cancer associated with development of brain metastases (BMs) with approximately 30-40% of affected patients [13]. Overexpression of the epidermal growth factor receptor (EGFR) was frequently found in NSCLC and was reported to be a poor overall prognostic factor [14]. The patients with driver mutations (EGFR mutation and ALK rearrangement) have increased risks (44% to 60%) of BMs, both at the time of diagnosis and during the disease course [15-18]. Visceral pleural invasion (VPI) in NSCLC is known as a poor prognostic factor with worse survival and an important stage descriptor [19,20]. It has been reported that for nonmucinous adenocarcinoma, lepidic-predominant adenocarcinoma has a better 5-year survival rate (81.3%) compared with that of acinar-predominant adenocarcinoma-only 50.0% [21,22].

In the clinical case presented, brain metastases was developed after two years of diagnosis and treatment with TT of the locally advanced

LADC with overexpression of the EGFR and pleural infiltration (Figure 2, Figure 3). Despite these unfavorable prognostic factors, after combining TT for primary lung carcinoma and RS for brain metastases, as well as Covid 19, the patient is alive for three years and has a good quality of life.

Targeted therapy (TT): NSCLCs are associated with EGFR mutations [23]. The epidermal growth factor family of receptor tyrosine kinases (ErbBs) plays essential roles in regulating cell proliferation, survival, differentiation and migration [24]. The expression of EGFR by some lung cancers, the limited therapeutic options for advanced lung cancer, and the availability of new EGFR-targeted drugs led, in the early part of the decade, to clinical trials of small molecule EGFR TK inhibitors in unselected NSCLC patients [5]. This approach opens a new way in the management of advanced non-small cell lung cancer (NSCLC) [25-28]. To date, several molecular-targeted drugs against driver genes have been developed, and several clinical trials have been conducted to evaluate the efficacy [7]. In multiple recent prospective clinical trials of gefitinib or erlotinib, response rates of EGFR mutated cases range from 65 to 90% [29,30]. Besides the existing EGFR-TK inhibitor drugs gefitinib, erlotinib, canertinib, lapatinib, and poziotinib, many more novel drugs need development [27]. Next-generation tyrosine kinase inhibitors (TKIs) are capable of restoring the control of disease and cause a delay in cranial radiation therapy in patients with driver mutations (eg, epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK]), and asymptomatic BMs [31]. Whereas historically, chemotherapy had low CNS penetration and objective response rates (ORRs), novel agents have been introduced in the past decade with clinically meaningful intracranial response rates in advanced NSCLC [32]. The lung carcinoma with EGFR mutations, diagnosed in 2018 as a local advanced adenocarcinoma, was treated successfully over a period of two years with targeted therapy.

Radiotherapy (RT): Early local therapy for brain metastases remains the gold standard, and as such, multidisciplinary input and close monitoring are essential, particularly when using upfront systemic therapy alone [32]. Optimal radiotherapy treatment planning should consider both patient (age, performance status, expected life span) and tumor related factors (number and volume of brain metastases, extracranial disease control, molecular subtype) [33]. Press et al. explore the frequency and relationship of genetic aberrations in patients with brain metastases from lung adenocarcinoma and their response to treatment with RT [34]. Patients with EGFR-mutant adenocarcinoma and brain metastases (BMs) treated with icotinib exhibited prolonged survival, and a longer duration of cerebral control was observed with brain radiotherapy [35]. Initial whole-brain radiotherapy (WBRT) with radiosurgery (RS) is an effective therapy for selected patients with newly diagnosed or recurrent brain metastases from lung carcinoma and appears to improve brain control but not survival [36]. Based on Level I-III evidence, for selected patients with small (up to 4 cm) brain metastases (up to three in number and four in one randomized trial), the addition of radiosurgery boost to WBRT improves brain control as compared with WBRT alone [37]. Many later studies of patients with limited brain metastases showed no overall survival benefit with WBRT and stereotactic radiosurgery (SRS) versus SRS alone and additionally showed that SRS alone results in less neurocognitive deterioration

at 3 months [38,39]. In these patients with a limited number of BM from NSCLC, SRT is an effective treatment associated with high local control rate, low neurological deterioration, and with low morbidity [40]. There have been growing data on SRS without WBRT in patients with more than 3 brain metastases although the maximum number of metastases appropriate for SRS has not been established, yet [41]. Overall survival, local failure, distant in-brain recurrences, neurological death and toxicity were found to be similar both in patients presenting with 2-4 and 5-10 metastases [42]. Radiosurgery followed by EGFR-TKI resulted in the longest overall survival and allowed patients to avoid the potential neurocognitive sequelae of WBRT [43].

Due to the good general condition in the presented pulmonary adenocarcinoma, despite the presence of four brain metastases, we estimated to perform radiosurgery with a single radiation fraction 15 Gy (Figure 4). After one month of graduation of radiosurgery, the patient was infected with Covid 19, which requires control pulmonary and cerebral CT as long as the end of May 2021. It is visualized that despite the Covid infection and residual Covid pulmonary changes (Figure 5), the brain metastases are missing (Figure 6). The patient has a good quality of life without respiratory and neurological symptoms. It was aimed for continuing treatment with target therapy.

Conclusion

Lung adenocarcinoma is a common disease, in which high mortality is due to both men and women. Local advanced disease is associated with high risk of distant metastases, mostly BMs, which significantly worsen the prognosis. Major diagnostic studies are the imaging methods (CT, PET/CT), pathohistological, immunohistochemical and molecular genetic analyses. Patients with specific EGFR mutations can be effectively treated with targeted therapy. After treatment with TT, brain metastases of pulmonary adenocarcinoma with specific EGFR mutations are more radiosensitivity and responded very well by high single radiation dose 15 Gy realized by RS. Despite the worsened prognosis, including Covid 19 disease, by combining TT and RS, we achieved three-year survival in metastatic lung adenocarcinoma.

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