doi: 10.3978/j.issn.2095-6959.2020.06.045
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2020.06.045

·临床病例讨论·

# EGFR 突变肺腺癌靶向联合全脑放疗后假性进展 1 例并文献复习

张萍[1]，甄婵军[2]，白文文[2]，陈明月[1]，于汶卉[2]，周志国[2]

(河北医科大学第四医院 1. 放疗一科；2. 放疗五科，石家庄 050011)

[摘　要]　近年来，表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor-tyrosine kinase inhibitor，EGFR-TKI)已经成为驱动基因突变阳性肺癌患者的标准一线治疗。全脑放疗(whole brain radiation therapy，WBRT)在伴有多发脑转移的非小细胞肺癌的作用也被重新评估，EGFR-TKI治疗联合WBRT越来越多地被应用于临床。但至今尚无EGFR-TKI治疗联合放疗后出现颅内病灶假性进展的相关报道。本文介绍1例接受EGFR-TKI靶向治疗联合WBRT并出现假性进展的肺腺癌患者。本例患者初诊即为左肺腺癌IV期(脑转移)，因EGFR基因突变，一线给予易瑞沙靶向治疗同时联合WBRT，一线疗效为部分缓解(partial response，PR)，8个月后患者出现骨转移，考虑疾病进展，再次行基因检测结果提示T790M突变阳性，故二线方案换为奥希替尼口服，服药7个月后，因患者出现右枕后疼痛，行头颅磁共振检查结果提示右枕转移灶较前明显增大。后患者行右枕叶占位性病变切除术，术后病理提示脑组织内未见癌，可见坏死，考虑假性进展。

[关键词]　肺腺癌；全脑放疗；靶向治疗；假性进展

# Pseudoprogression in patient with EGFR mutation of lung adenocarcinoma receiving targeted treatment and whole brain radiotherapy: A case report and literature review

ZHANG Ping[1], ZHEN Chanjun[2], BAI Wenwen[2], CHEN Mingyue[1], YU Wenhui[2], ZHOU Zhiguo[2]

*(1. First Ward of Department of Radiation Oncology; 2. Fifth Ward of Department of Radiation Oncology, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China)*

**Abstract**　In recent years, Epidermal Growth Factor receptor-tyrosine Kinase Inhibitor (EGFR-TKI) has become the standard first-line treatment for patients with positive driver gene mutations. The role of whole brain radiation therapy (WBRT) in non-small cell lung cancer with multiple brain metastases has also been reassessed, and EGFR-TKI therapy combined with WBRT is increasingly used in clinical practice. However, there has been no relevant report on the pseudoprogression of intracranial lesions from the patients accepting EGFR-TKI treatment combined with radiotherapy till now. Nevertheless, the efficacy and prognosis of a patient with pulmonary adenocarcinoma who received WBRT combined with EGFR-TKI targeted therapy and then presented with pseudoprogression

收稿日期 (Date of reception)：2020–04–07
通信作者 (Corresponding author)：周志国，Email: chenk777@126.com

is to be introduced in this paper. This patient was initially diagnosed with left lung adenocarcinoma stage IV (brain metastasis). Because EGFR gene mutation was positive, first-line targeted therapy of gefitinib combined WBRT were given at the same time. First-line efficacy was partial response (PR). After 8 months, the patient developed with bone metastasis. Considering the disease progression, the results of the genetic test again suggested that the T790M mutation was positive. Therefore, the second-line treatment was replaced to Osimertinib. After 7 months, the patient presented with pain in the right posterior occipital region, and the result of cranial MRI examination indicated that the right occipital metastasis was significantly larger than before. Then, the patient received resection of right occipital space occupying lesions, and the postoperative pathology indicated that no cancer in the brain tissue, but necrosis was seen. So pseudoprogression was considered.

**Keywords** lung adenocarcinoma; whole brain radiation therapy; targeted therapy; pseudoprogression

肺癌是世界范围内癌症相关死亡的主要原因，非小细胞肺癌(non-small cell lung cancer，NSCLC)占肺癌总数的85%~90%，其中，肺腺癌发病率逐年增长，已经成为NSCLC中最常见的类型，几乎占全部肺癌的50%，且总体生存率较低[1]。近年来，肺腺癌在亚裔女性、非吸烟者或从不吸烟者，甚至年轻的成年人中越来越普遍，同时这部分人群也是表皮生长因子受体(epidermal growth factor receptor，EGFR)突变的典型人群，治疗首选EGFR酪氨酸激酶抑制剂(tyrosine kinase inhibitor，TKI)类药物[2-4]。在靶向治疗时代，很多患者会在EGFR-TKI治疗过程中出现局部脑进展，而全身其他病灶仍然稳定，这时候通常会选择脑局部治疗干预，同时继续靶向治疗。局部脑进展的主要原因在于现有药物的颅内穿透性较差，颅内不能达到有效的药物浓度，如果在EGFR-TKI治疗初始阶段就干预脑部放疗，是否能增强EGFR-TKI类药物的颅内穿透性？EGFR-TKI治疗联合放疗后是否也会出现类似化疗及PD-1抑制剂类药物应用后的假性进展？目前知之甚少。现将河北医科大学第四医院收治的1例接受全脑放疗(whole brain radiation therapy，WBRT)联合EGFR-TKI靶向治疗后颅内病灶出现假性进展的肺腺癌患者的病例报告如下，以期为临床积累更多的数据和用药经验。

## 1 临床资料

患者，男，53岁，患者于2015年11月体检时发现左肺占位，未予重视及进一步诊治，2016年9月无明显诱因出现声音轻度嘶哑，无饮水呛咳，未行诊治，自行口服药物(具体不详)，2016年11月患者出现头部轻度头晕不适，遂就诊行CT检查发现颅内占位。体格检查：声音轻度嘶哑，浅表淋巴结触诊未触及肿大淋巴结，双侧瞳孔正大等圆，对光反射存在，伸舌居中，心肺无阳性发现，全身骨骼无压痛，病理神经症未引出。吸烟史30余年，戒烟1年，少量饮酒史，戒酒1年。无化工等接触史。诊断为左肺腺癌IV期(cT2N2M1)EGFR1 9外显子突变。

### 1.1 实验室检查

肿瘤标志物CEA和NSE值轻度增高(CEA 5.54 ng/mL，NSE 28.68 ng/mL)，CT引导下左肺肿物穿刺病理报告：腺癌(图1)。未做免疫组织化学。组织EGFR基因检测：19外显子突变。血尿便常规检查未见异常。

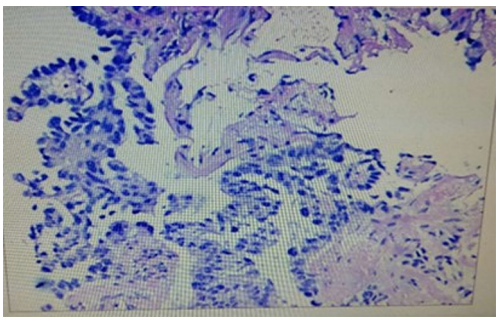

**图1 CT引导下左肺肿物穿刺病理报告：腺癌(HE，×100)**
**Figure 1 Pathological report of CT-guided puncture of left lung neoplasm: adenocarcinoma (HE, ×100)**

### 1.2 影像学检查

胸部CT/增强CT示：左肺上叶占位，纵膈淋巴结肿大(图2)。PET-CT示：左肺上叶前段高代谢团块影；纵隔2R，4R，6，7区多发高代谢肿大淋巴结；右枕叶环形高代谢影，考虑左肺癌伴纵隔淋巴结转移、脑转移(图3)。头部CT(胶片+报告)示：右枕叶占位伴周围水肿，考虑脑转移(图4)。

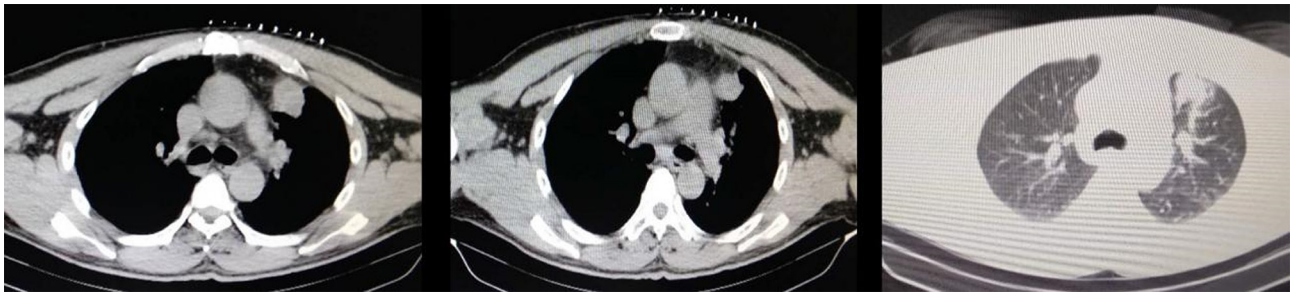

**图2 胸部增强CT(2016年12月1日)显示左肺上叶占位，纵隔淋巴结肿大**

**Figure 2 Chest enhancement CT (Dec. 1, 2016) shows occupying the upper lobe of the left lung and mediastinal lymph node enlargement**

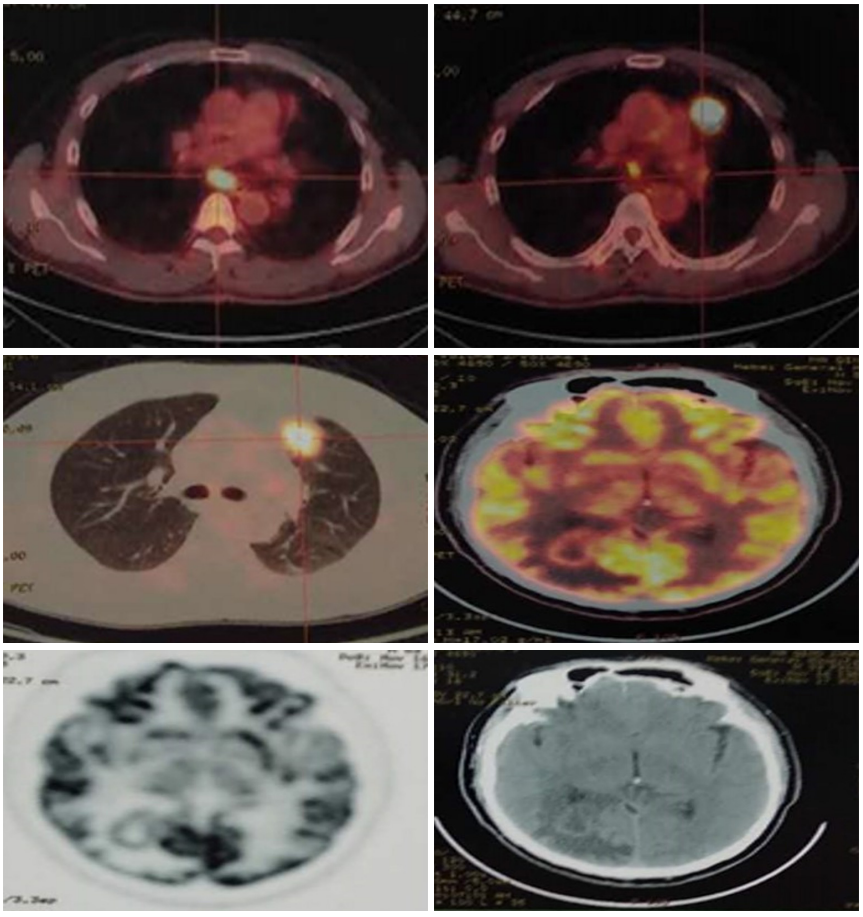

**图3 全身PET-CT(2016年11月17日)显示左肺上叶前段高代谢团块影；纵隔2R，4R，6，7区多发高代谢肿大淋巴结；右枕叶环形高代谢影，考虑左肺癌伴纵隔淋巴结转移、脑转移**

**Figure 3 Whole-body PET-CT (Nov. 17, 2016) shows hypermetabolic mass shadows in the anterior segment of the upper lobe of the left lung. multiple hypermetabolic enlarged lymph nodes in mediastinum regions 2R, 4R, 6 and 7, and the annular hypermetabolic shadow in the right occipital lobe, were considered for mediastinal lymph node metastasis and brain metastasis in left lung cancer**

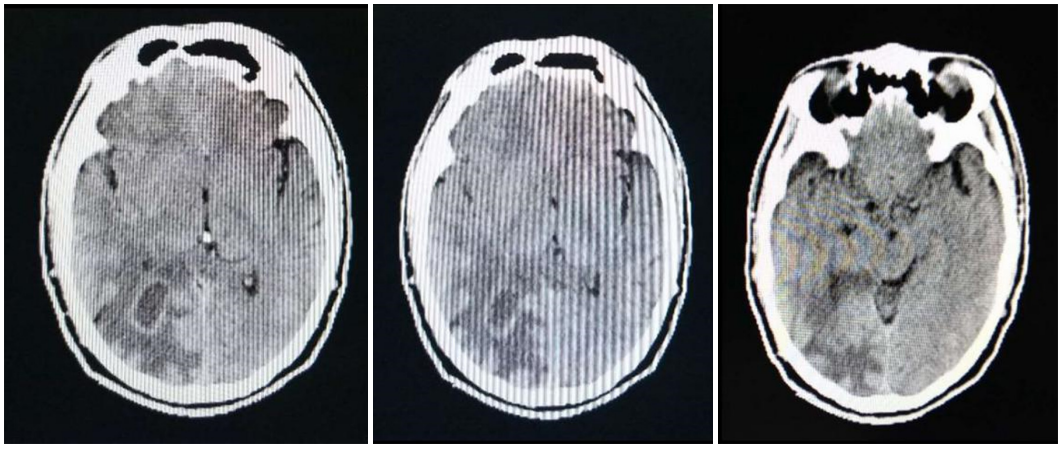

**图4 头颅CT(2016年12月28日)显示右枕叶占位伴周围水肿，考虑脑转移**

**Figure 4 Cranial CT (Dec. 28, 2016) shows right occipital lobe mass with peripheral edema, which was considered as brain metastasis**

### 1.3 治疗及随访

根据2016年NCCN指南、IPASS研究[2-4]等推荐EGFR突变阳性的NSCLC应用TKI药物，并且多篇文献[5-8]分析显示EGFR(+)的NSCLC脑转移患者EGFR-TKI联合WBRT优于单纯EGFR-TKI或WBRT。一线治疗方案为易瑞沙0.25 g、口服，1次/d，疗程为8个月；联合WBRT 30 Gy/10次，颅内肿物局部加量28 Gy/14次。主要不良反应为皮疹、乏力。一线治疗效果：PR。易瑞沙口服8个月后出现右肩背部疼痛症状，查骨显像(2017年7月7日)示：右侧肩胛骨可见异常放射性浓聚，右侧肩胛骨内侧可见溶骨性骨质破坏，考虑骨转移癌。一线治疗后出现进展(progression disease，PD)。再次行基因检测提示EGFR T790M突变，敏感药物为奥希替尼。二线治疗方案为奥希替尼80 mg口服1次/d，疗程为7个月。接受右肩胛骨肿瘤区30 Gy/10次，局部加量20 Gy/10次；唑来膦酸4 mg 1次/28 d。主要不良反应为皮疹、乏力。奥希替尼口服7个月后出现右枕后疼痛3 d，偶伴恶心。查脑MRI显示右枕叶环形强化，比7个月前明显增大(图5)。胸部CT提示病灶稳定(图6)。发射型计算机断层扫描仪(emission computed tomography，ECT)(2018年3月8日)显示右侧肩胛骨、左侧髂骨可见放射性浓聚，考虑骨转移癌(图7)，与上次(2017年7月7日)骨显像相比左髂骨出现新发病灶。因患者髂骨出现新发骨转移灶且右枕叶病灶复发，考虑患者PD。患者于2018年3月14日选择右侧枕叶占位性病变切除术，术后病理：脑组织内未见癌，可见坏死。免疫组织化学结果：AE1/AE3(−)。考虑假性进展。

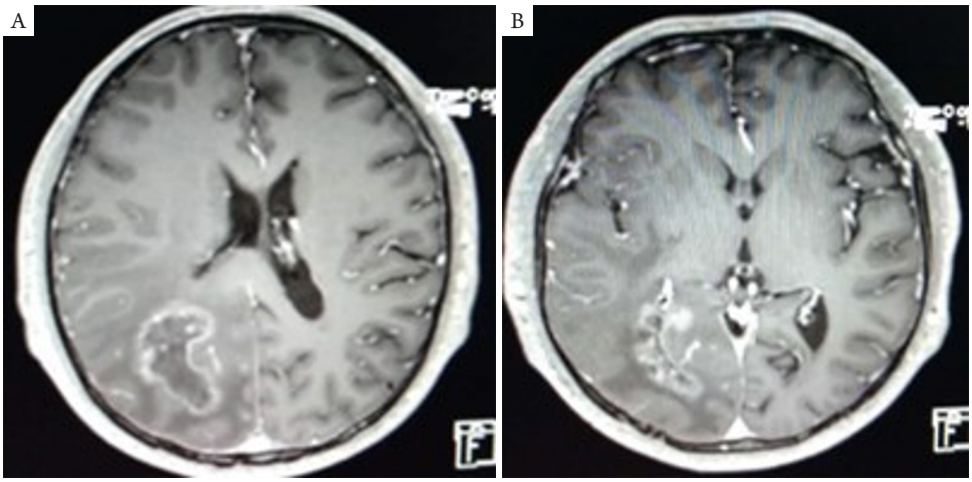


**图5 二线治疗7个月后脑MRI(2018年3月9日；A)：右枕叶环形强化，比7个月前(2017年7月12日；B)明显增大**

**Figure 5 Brain MRI after the second-line treatment for7 months (March 9, 2018; A) showed ring enhancement of the right occipital lobe, which was significantly larger than that in 7 months before (July 12, 2017; B)**

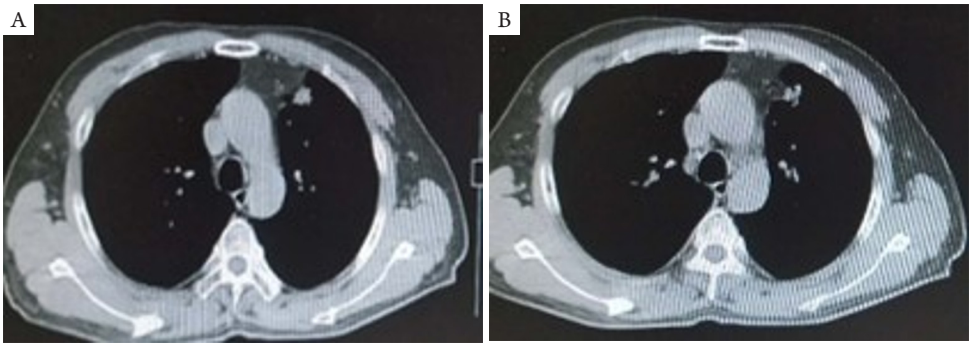


**图6 二线治疗7个月前(2018年3月9日；A)、后(2017年7月12日；B)胸部CT：疗效SD**

**Figure 6 Chest CT before (March 9, 2018; A) and after (July 12, 2017; B) second-line treatment for 7 months: efficacy is SD**

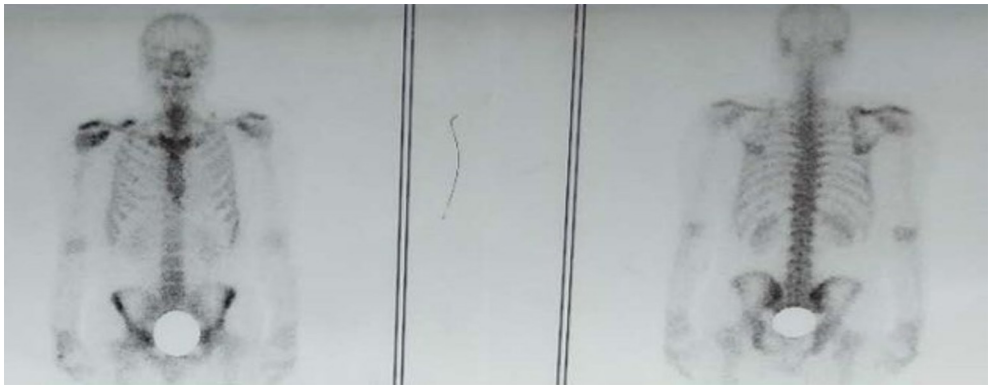

**图7 一线治疗8个月后ECT(2018年3月8日)：右侧肩胛骨、左侧髂骨可见放射性浓聚，考虑骨转移癌，与上次(2017年7月7日)骨显像相比左髂骨出现新发病灶**

**Figure 7 ECT after first-line treatment lasted 8 months (Mar. 8, 2018): radioactive concentration was observed at the right scapula and the left ilium, considering metastatic cancer of the bone, there was a new lesion at the left ilium compared with the previous ECT (July 7, 2017)**

## 2 讨论

脑转移在晚期NSCLC中较常见，而20%~40%的NSCLC患者可发展为脑转移，尤其在腺癌患者中较常见[9]。晚期NSCLC患者的主要治疗方案包括化疗、放疗以及分子靶向药物治疗等。分子靶向药物治疗为晚期NSCLC患者的治疗提供了新的选择，脑转移患者使用化疗药物的疗效受血脑屏障的影响。与常规化疗方案相比，靶向药物更容易穿透血脑屏障，且相关研究提示放疗可同时增加血脑屏障的通透性，故研究者推测在靶向药物基础上同期联合WBRT能够使血脑屏障通透性更强，脑脊液中药物浓度更高，有助于药物发挥作用[10-14]。本例患者首发症状即出现脑转移，一线治疗为易瑞沙靶向治疗联合WBRT，疗效评价为PR。8个月后出现进展。一般未经治疗的脑转移患者中位生存期仅1个月[15]，单独接受WBRT也仅能使大部分患者的中位生存期延长3~6个月[16]。本例患者一线治疗后PFS为8个月，生存期明显延长。此外，WBRT与靶向治疗联合时机也是非常关键的。许多研究多把WBRT作为巩固治疗或疾病进展后的治疗，而本例患者WBRT为一线治疗，因此提示放疗作为脑转移一线治疗可能比挽救性放疗获益更多。

根据MacDonald判定标准，在放疗(或同步放化疗)结束后3~4个月内、颅MRI复查提示基线病灶长径总和增加>20%或出现新病灶，则考虑早期进展。若基线病灶长径总和虽增加>20%，但临床症状无进展，且无严重占位效应，则可考虑为疑似假性进展，可继续行原方案二程化疗，若再次复查头颅MRI，病灶长径总和无变化或变小则可诊断为假性进展[17]。假性进展与治疗无效肿瘤本身发生进展在影像学上很难区别。一旦出现假性进展，与肿瘤复发不易鉴别，会使治疗进程受到很

大干扰，如果决策错误，甚至会缩短患者的生存期。本例患者EGFR-TKI联合脑部放疗后影像学表现为右枕叶病灶复发，但术后病理提示脑组织内未见癌，可见坏死。提示EGFR-TKI联合脑部放疗时，颅内病灶存在假性进展可能。有报道显示，虽然手术大部分切除占位能够改善严重的神经系统并发症，但和部分切除和活检相比，并不能延长患者的总生存期[18]，尤其在不能除外颅内病灶出现假性进展可能性的情况下，颅脑手术更须慎重考虑。

目前据文献[19]报道显示已有两种关于假性进展的发生机制的假说得到了广泛认可。1)血管损伤假说：放疗导致内皮细胞的死亡，血管内皮细胞损伤可能是导致急性和亚急性放射损伤的关键。放射诱导的内皮细胞死亡，导致血脑屏障损伤，同时伴随着血管源性水肿、缺血和缺氧。由于低氧反过来导致血管内皮生长因子上调，从而增加了血管系统的通透性，因此在MRI增强检查中会出现病灶不同程度的强化[20]。2)内皮细胞凋亡假说：除了细胞死亡之外，辐射也可以诱导内皮细胞凋亡[21]。辐射引起的内皮细胞凋亡主要通过两种途径，一个是神经酰胺介导的细胞凋亡，另一个是p53依赖的线粒体和死亡受体途径来诱导内皮细胞凋亡。因为替莫唑胺诱导的DNA损伤和放疗导致的DNA和细胞膜损伤具有相互协同，可以导致内皮细胞死亡增加，进一步导致细胞通透性增加，加剧低氧和坏死。这些分子通路也解释了同步放化疗中发生假性进展的比例较单纯放疗中高的原因。然而，EGFR-TKI靶向治疗联合放疗与单纯放疗相比是否增加假性进展的可能及其存在的机制，目前相关研究甚少，值得进一步探索和讨论。

综上，一线WBRT联合靶向治疗可以延长患者生存时间，且二者的联合时机是十分关键的。EGFR-TKI靶向治疗联合WBRT与单纯放疗相比是否增加假性进展可能及其存在的机制需要进一步扩大病例研究。

## 参考文献


1. Wu K, House L, Liu W, et al. Personalized targeted therapy for lung cancer[J]. Int J Mol Sci, 2012, 13(9): 11471-11496.
2. Aguilar KM, Winfree KB, Muehlenbein CE, et al. Treatment patterns by EGFR mutation status in non-small cell lung cancer patients in the USA: a retrospective database analysis[J]. Adv Ther, 2018, 35(11): 1905-1919.
3. Tang Y, Xia B, Xie R, et al. Timing in combination with radiotherapy and patterns of disease progression in non-small cell lung cancer treated with EGFR-TKI[J]. Lung Cancer, 2020, 140: 65-70.
4. Tiefenbacher A, Pirker R. EGFR tyrosine kinase inhibitors as first-line therapy in advanced EGFR mutation-positive non-small cell lung cancer: strategies to improve clinical outcome[J]. J Thorac Dis, 2017, 9(11): 4208-4211.
5. An N, Wang H, Li J, et al. Therapeutic effect of first-line EGFR-TKIs combined with concurrent cranial radiotherapy on NSCLC patients with EGFR activating mutation and brain metastasis: a retrospective study[J]. Onco Targets Ther, 2019, 12: 8311-8318.
6. Chen H, Wu A, Tao H, et al. Concurrent versus sequential whole brain radiotherapy and TKI in EGFR-mutated NSCLC patients with brain metastasis: A single institution retrospective analysis[J]. Medicine (Baltimore), 2018, 97(44): e13014.
7. Jiang T, Min W, Li Y, et al. Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis[J]. Cancer Med, 2016, 5(6): 1055-1065.
8. Zhu Q, Sun Y, Cui Y, et al. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC)[J]. Oncotarget, 2017, 8(8): 13304-13311.
9. Maher EA, Mietz J, Arteaga CL, et al. Brain metastasis: opportunities in basic and translational research[J]. Cancer Res, 2009, 69(15): 6015-6020.
10. 金福军, 曾川, 张献全. 全脑放疗联合靶向药物与单独全脑放疗治疗非小细胞肺癌脑转移疗效及安全性的Meta分析[J]. 中华肺部疾病杂志(电子版), 2016, 9(4): 366-371.
    JIN Fujun, ZENG Chuan, ZHANG Xianquan. A meta-analysis of the efficacy and safety of whole brain radiotherapy combined with targeted drugs contrast with whole brain radiotherapy alone in the treatment of non-small cell lung cancer with brain metastasis[J]. Chinese Journal of Pulmonary Disease (Electronic Edition), 2016, 9(4): 366-371.
11. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small cell lung cancer: a prospective trial[J]. Ann Oncol, 2004, 15(7): 1042-1047.
12. Hotta K, Kiura K, Ueoka H, et al. Effect of gefitinib ('Iressa ', ZD1839) on brain metastases in patients with advanced non-small cell lung cancer[J]. Lung Cancer, 2004, 46(2): 255-261.
13. Wu C, Li YL, Wang ZM, et al. Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain [J]. Lung Cancer, 2007, 57(3): 359-361.
14. Ma S, Xu Y, Deng Q, et al. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population[J]. Lung Cancer, 2009, 65(2): 198-203.

15. Park SJ, Kim HT, Lee DH, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation[J]. Lung Cancer, 2012, 77(3): 556-560.
16. 王飞, 邓东风, 潘庆刚, 等. 肺癌脑转移的显微手术治疗[J]. 脑与神经疾病杂志, 2007, 15(4): 250-252.
WANG Fei, DENG Dongfeng, PAN Qinggang, et al. Microsurgical treatment of lung cancer with brain metastases[J]. Journal of Brain & Nervous Diseases, 2007, 15(4): 250-252.
17. Galldiks N, Kocher M, Langen KJ. Pseudoprogression after glioma therapy: an update[J]. Expert Rev Neurother, 2017, 17(11): 1109-1115.
18. Grossman R, Shimony N, Hadelsberg U, et al. Impact of resecting radiation necrosis and pseudoprogression on survival of patients with glioblastoma[J]. World Neurosurg, 2016, 89: 37-41.
19. Brandsma D, van den Bent MJ. Pseudoprogression and pseudoresponse in the treatment of gliomas[J]. Curr Opin Neurol, 2009, 22(6): 633-638.
20. Wong CS, Van der Kogel AJ. Mechanisms of radiation injury to the central nervous system: implications for neuroprotection[J]. Mel Interv, 2004, 4(5): 273-284.
21. Rodemann HP, Blaese MA. Responses of normal cells to ionizing radiation[J]. Semin Radiat Oncol, 2007, 17(2): 81-88.

**本文引用：**张萍, 甄婵军, 白文文, 陈明月, 于汶卉, 周志国. EGFR突变肺腺癌靶向联合全脑放疗后假性进展1例并文献复习[J]. 临床与病理杂志, 2020, 40(6): 1605-1611. doi: 10.3978/j.issn.2095-6959.2020.06.045

***Cite this article as:*** ZHANG Ping, ZHEN Chanjun, BAI Wenwen, CHEN Mingyue, YU Wenhui, ZHOU Zhiguo. Pseudoprogression in patient with EGFR mutation of lung adenocarcinoma receiving targeted treatment and whole brain radiotherapy: A case report and literature review[J]. Journal of Clinical and Pathological Research, 2020, 40(6): 1605-1611. doi: 10.3978/j.issn.2095-6959.2020.06.045