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IV 期 EGFR 阳性肺腺癌综合治疗 1 例并文献复习

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[摘　要] 报告1例IV期表皮生长因子受体(epidermal growth factor receptor，EGFR)阳性肺腺癌患者，在治疗过程中局部治疗及多次活体组织检查(以下简称活检)在综合治疗中起重要作用。患者，女，76岁，2017年2月以“持续背部疼痛1个月余，发现左肺占位1周”为主诉来郑州大学第一附属医院就诊。外院PET-CT检查示左肺上叶占位代谢活跃，考虑肺癌，胸11椎体、胸12椎体及腰2椎体代谢活跃，考虑转移。行肺占位穿刺活检，穿刺病理示：肺腺癌，EGFR第19外显子缺失突变。诊断为“左肺腺癌cT2aN0M1c IVB期”。一线治疗方案：“靶向治疗+局部治疗”(吉非替尼+椎体转移癌微波消融并椎体成形术+唑来膦酸)，无进展生存(progression-free survival，PFS)8个月。2017年10月疾病出现局部进展，再次行穿刺活检，病理示：肺腺癌，EGFR第19外显子缺失突变。治疗方案：“靶向治疗+局部治疗”(吉非替尼+左肺癌射频消融术)，PFS为4个月。2018年2月疾病出现快速进展，第3次穿刺活检肺新发转移结节，病理示：肺腺癌，EGFR第19外显子缺失突变。EGFR第20外显子T790M错义突变。二线治疗方案：靶向药物(甲磺酸奥希替尼)，PFS为18个月。2019年8月疾病出现快速进展，肺多发结节，脑多发结节。第4次穿刺活检病理示：EGFR第19外显子缺失突变。EGFR 第20外显子T790M 错义突变。三线治疗方案：化学药物治疗(培美曲塞二钠+洛铂+重组人血管内皮抑制素)2个周期。患者目前仍在随访中。

[关键词] 非小细胞肺癌；IV期；活体组织检查；局部治疗

Comprehensive treatment of stage IV EGFR positive lung adenocarcinoma: A case report and literature review

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Abstract A patient with stage IV epidermal growth factor receptor (EGFR)-positive lung adenocarcinoma admitted to the First Affiliated Hospital of Zhengzhou University demonstrated that multiple biopsy and local treatment played an important role in the treatment. The patient, female, 76 years old, came to our hospital for complaints in February 2017 because of “continuous back pain for more than 1 month and found left lung mass for 1 week”. PET-CT examination in the external hospital suggested that the left upper lobe occupied the metabolism of the upper lobe. Considering lung cancer, the T11, T12 and L2 vertebral bodies were active and metastatic. Lung biopsy, puncture pathology showed: lung adenocarcinoma, EGFR 19 exon deletion mutation. The diagnosis was “left lung

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adenocarcinoma cT2aN0M1c IVB phase". First-line treatment: "targeted therapy + topical treatment" (gefitinib + vertebral metastases microwave ablation and vertebroplasty + zoledronic acid), Progression-free survival (PFS) for 8 months. In October 2017, local disease progressed, and a biopsy was performed again. The pathology showed: lung adenocarcinoma, EGFR exon 19 deletion mutation. Treatment plan: "targeted therapy + topical treatment" (gefitinib + left lung cancer radiofrequency ablation), PFS for 4 months. In February 2018, the disease progressed rapidly, and the third puncture biopsy targeted new metastasis of the lung. The pathology showed: lung adenocarcinoma, EGFR exon 19 deletion mutation. EGFR 20exon T790M missense mutation. Second-line treatment: targeted drug (oheptinib mesylate), PFS for 18 months. In August 2019, the disease progressed rapidly, with multiple nodules in the lungs and multiple nodules in the brain. The fourth biopsy path showed: EGFR exon 19 deletion mutation. EGFR exon 20 T790M missense mutation. Three-line treatment regimen: chemotherapy (pemetrexed + lobaplatin + recombinant human endostatin) 2 cycles. The patient is still in follow-up.

Keywords　non-small cell lung cancer; stage IV; biopsy; topical treatment

我国肺癌发病率目前居恶性肿瘤首位(57.25/10万)，新发肺癌病例约为78.7万例[1]，其中非小细胞肺癌(non-small cell lung cancer，NSCLC)占85%[2]，我国约50%患者为EGFR突变型，可应用靶向药物治疗。而靶向药物在治疗过程中不可避免地会出现耐药，所以需要及时调整治疗方案，而包含有靶向、免疫、化学药物治疗(以下简称化疗)、放射治疗(以下简称放疗)、微创介入治疗的个体化综合治疗手段将给患者带来更多的受益。郑州大学第一附属医院收治1例IV期表皮生长因子受体(epidermal growth factor receptor，EGFR) 阳性肺腺癌患者，在治疗过程中局部治疗及多次活体组织检查(以下简称活检)在综合治疗中起重要作用，现报告如下。

1 临床资料

患者，女，76岁，2017年2月来郑州大学第一附属医院就诊。以"持续背部疼痛1月余，发现左肺占位1周"为主诉入院。1个月余前无明显诱因出现背部疼痛，持续性，夜间重，进行性加重，于当地医院按"腰肌劳损"治疗，给予"依托考昔"口服，疼痛无缓解。1周前行CT检查(图1)提示：左肺上叶占位性病变，考虑肺癌。T_{11}，T_{12}，L_2椎体骨质破坏，考虑转移。外院PET-CT检查示：左肺肿块代谢增高，SUVmax值10.2，考虑肺癌；T_{11}，T_{12}，L_2骨质破坏，SUVmax值17.2，考虑转移。目前已服用"盐酸羟考酮缓释片40 mg，每天2次"1周，止痛效果欠佳。既往史无特殊。查体：T_{11}~L_2椎体平面压痛、叩击痛阳性。实验室检查：CEA 331.3 ng/mL，CA125 102.2 U/mL，CYFRA21-1 8.72 ng/mL，NSE 16.42 ng/mL。血尿粪常规、肝肾功、电解质、血凝试验、传染病、心电图检查等未见异常。入院诊断：1)左肺上叶占位，肿瘤？2)多发椎体骨质破坏，考虑转移。

入院后行左肺占位穿刺活检(图2)，病理显示：肺腺癌，免疫组织化学TTF-1(+)，CK7(+)，NapsinA(+)，Ki-67(20%+)。行数字PCR基因检测显示：EGFR第19外显子缺失突变。患者初步诊断"左肺腺癌cT2aN0M1c IVB期EGFR第19外显子缺失突变多发骨转移"。

患者因椎体疼痛严重，影响正常生活，PS评分2。一线治疗方案制订为靶向治疗+局部治疗。口服吉非替尼250 mg每天1次。T_{11}，T_{12}，L_2椎体均采用椎体转移癌微波消融并椎体成形术(图3)，局部治疗肿瘤的同时加固椎体，预防骨不良事件的发生。同时应用"唑来膦酸4 mg，每4周1次"方案。术后3 d，患者腰部疼痛症状立刻缓解，无需服用任何止痛药物。

患者于第3，6个月定期复查，疗效评价部分缓解(partial response，PR)。第8个月复查时，CT左肺上叶病变较前增大，疗效评价疾病进展(progressive disease，PD)。PFS为8个月(图4)。

2017年10月行第2次穿刺活检，穿刺部位仍为左肺上叶病变，穿刺病理显示腺癌，免疫组织化学CK(+)，TTF-1(上皮+)，PD-1(−)，PD-L1(−)。高通量测序技术基因检测：EGFR 第19外显子缺失突变，未检测到20外显子T790M突变。病变为局部进展，治疗方案"靶向治疗+局部治疗"，继续口服吉非替尼，左肺上叶病变行射频消融术(图5)。术后2个月复查，左肺上叶病变完全消融。术后4个月复查，右肺多发结节，肝尾叶新发结

节，疗效评价PD。PFS为4个月(图6)。

2018年2月行第3次穿刺活检，穿刺部位为右肺新发结节(图7)。

穿刺病理显示为腺癌。高通量测序技术基因检测结果显示：EGFR 第19外显子缺失突变，丰度20.4%；EGFR 第20外显子T790M错义突变，丰度16.3%。给予靶向药物“甲磺酸奥希替尼 80 mg，每天1次，口服”方案治疗。第2，6，12个月复查时疗效评价完全缓解(图8)。

第18个月复查时(2019年8月)疾病进展，肺CT：双肺多发结节。头颅MRI：左侧额叶中线旁、双侧顶叶、右侧枕叶、右侧小脑半球多发转移(图9)。

第4次穿刺活检部位仍为右下肺新发结节(图10)，穿刺病理示腺癌。免疫组织化学：CK(+)，TTF-1(+)，Napsin A(+)，P40(−)，PD-1(−)，PD-L1(−)，Ki-67(约25%+)。全组基因测序检测结果：肿瘤突变负荷(TMB)：9.2个突变/Mb。EGFR 19外显子缺失突变，丰度31.9%。20外显子T790M错义突变，丰度9.8%。ATRX，CTNNB1，KMT2A错义突变。SMAD4移码突变。TP53剪切区域突变。VEGFR拷贝数变异。三线治疗方案选择为化疗“培美曲塞二钠+洛铂+重组人血管内皮抑制素”。目前患者已进行2个周期化疗，正在随访中。

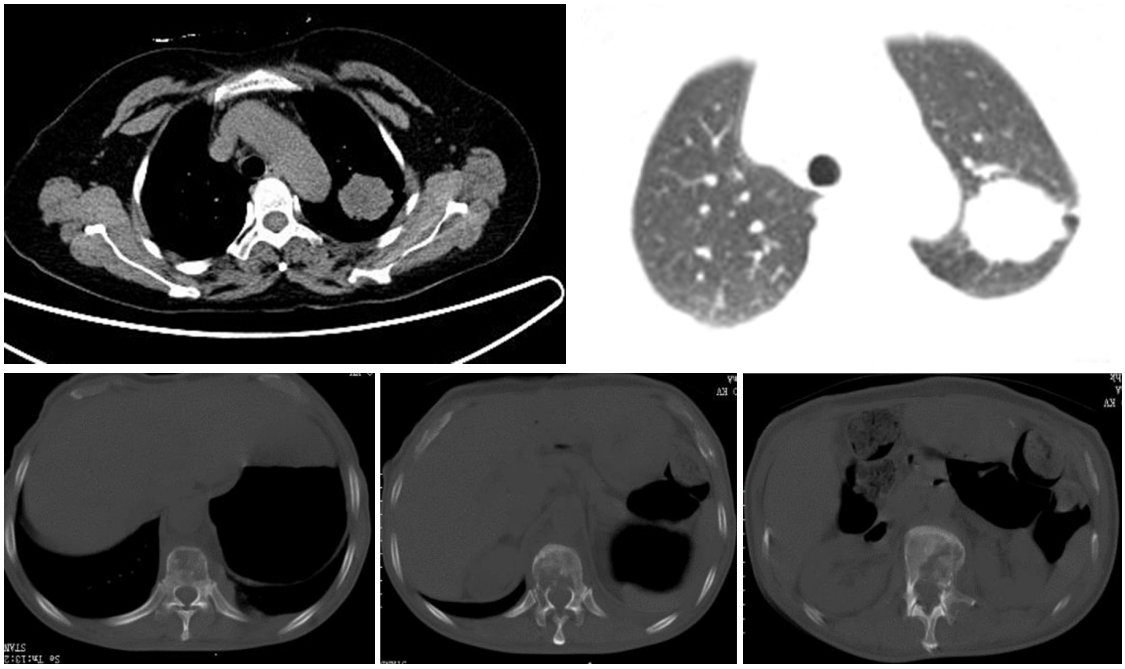

图1 患者第1次入院时CT显示左肺上叶占位，T_{11}，T_{12}及L_2椎体骨质破坏

Figure 1 On the first admission, CT showed the left upper lobe occupying, and the bones of T_{11}, T_{12} and L_2 vertebrae were damaged

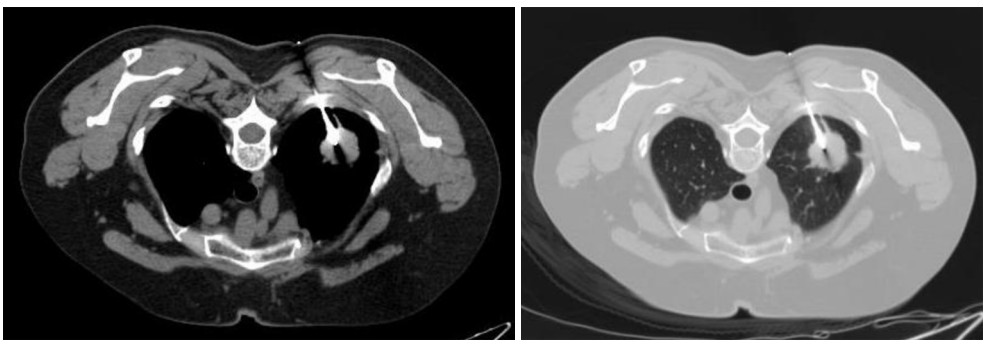

图2 第1次穿刺术中，CT引导下穿刺左肺肿块

Figure 2 CT guided puncture of the left lung mass during the first puncture

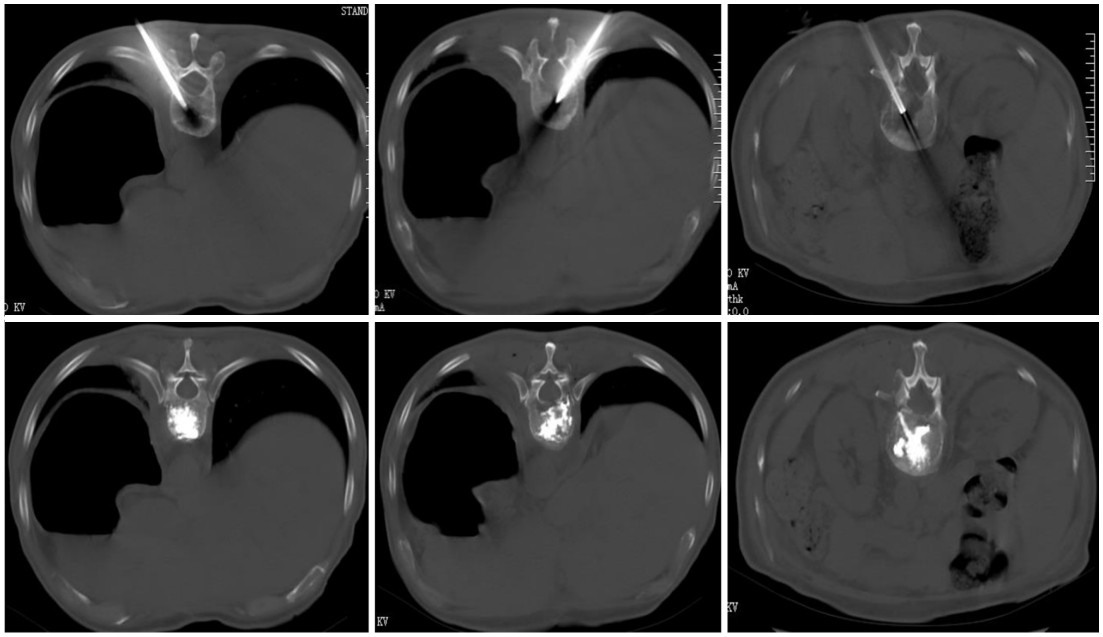

图3 T_{11}，T_{12}及L_2椎体转移癌微波消融并椎体成型术中及术后

Figure 3 Microwave ablation and vertebroplasty of T_{11}, T_{12} and L_2 vertebral metastases during and after surgery

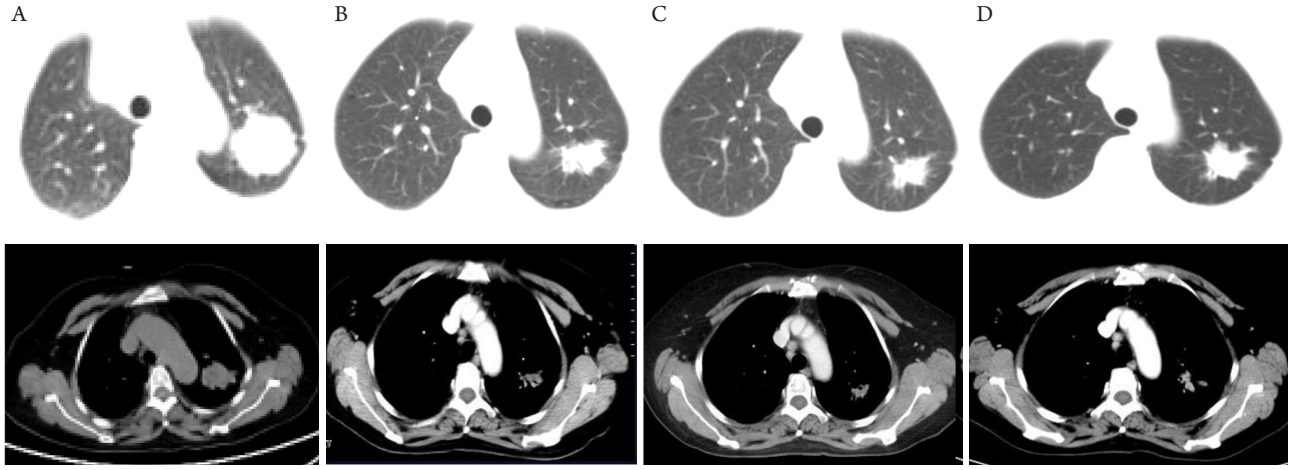

图4 吉非替尼治疗前后疗效评价

Figure 4 Efficacy evaluation before and after gefitinib treatment

(A)治疗前；(B)治疗3个月后，疗效评价部分缓解；(C)治疗6个月后，疗效评价部分缓解；(D)治疗8个月后，疗效评价进展。

(A) Before treatment; (B) After 3 months of treatment, the efficacy evaluation was partial response; (C) After 6 months of treatment, the efficacy evaluation was partial response; (D) After 8 months of treatment, the efficacy evaluation was progressive disease.

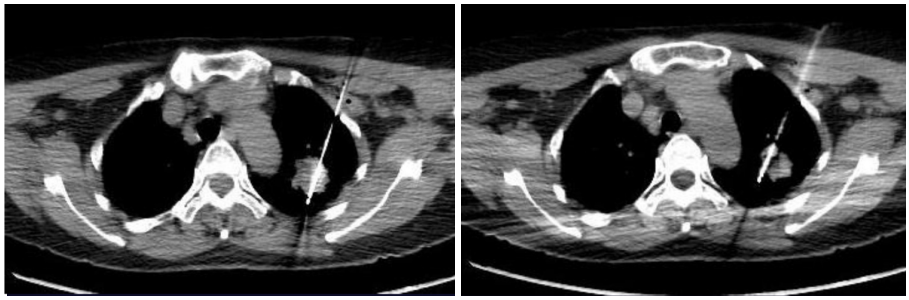

图5 左肺腺癌射频消融术中

Figure 5 Radiofrequency ablation of left lung adenocarcinoma

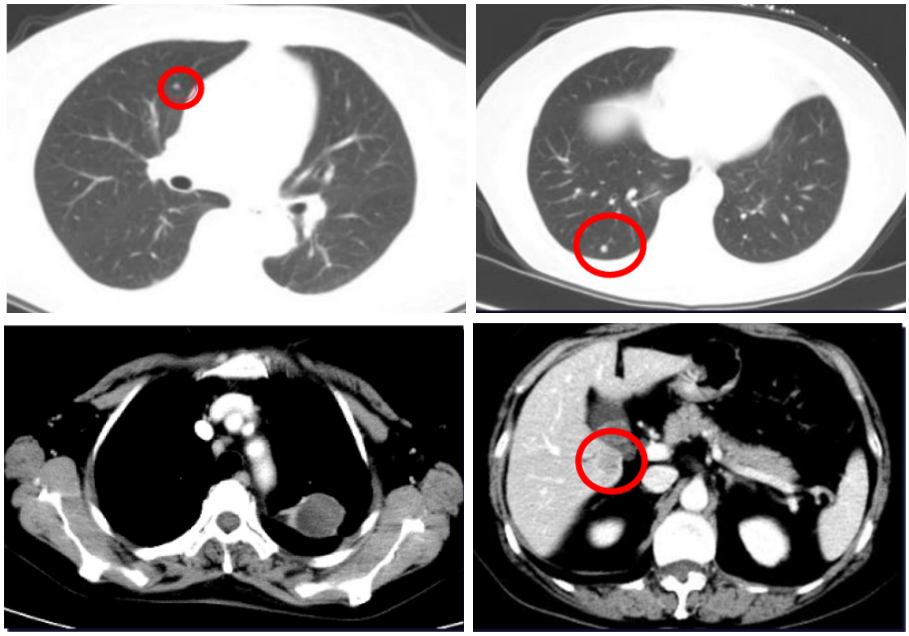

图6 消融术后4个月，两肺多发转移、肝转移，消融病灶稳定，疗效评价进展

Figure 6 Four months after ablation, multiple metastases in both lungs and liver metastases, stable ablation lesions, and progress in efficacy evaluation

图中圆圈标识的为肺部转移病灶及肝转移灶。

The circles in the picture indicate the metastatic lesions in the lungs and liver.

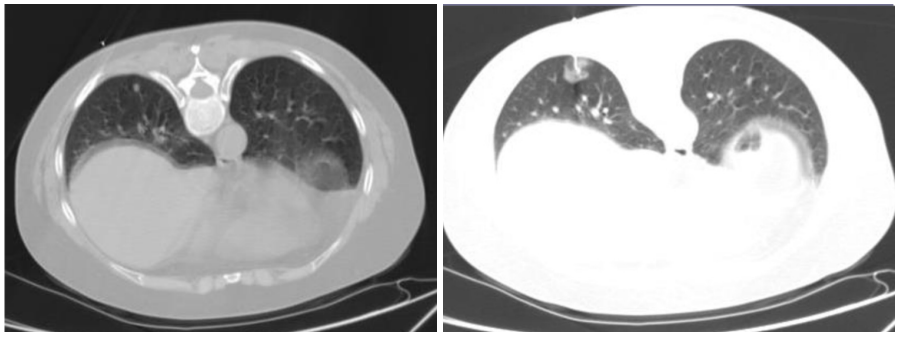

图7 第3次穿刺活检术中，穿刺右肺新发结节

Figure 7 In the third puncture biopsy, a new nodule of the right lung was punctured

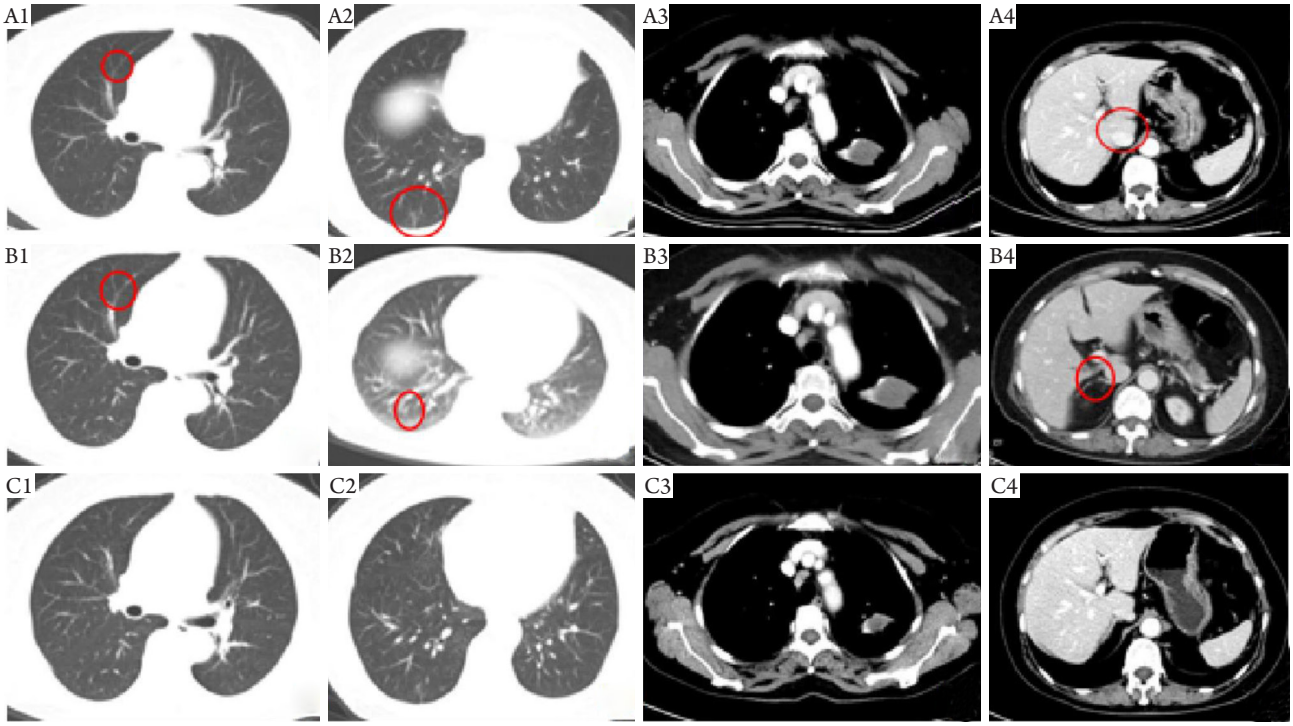

图8 奥希替尼治疗前后疗效评价

Figure 8 Efficacy evaluation before and after oxitinib treatment

(A1~A4)治疗2个月后，疗效评价完全缓解；(B1~B4)治疗6个月后，疗效评价完全缓解；(C1~C4)治疗12个月后，疗效评价完全缓解。图中圆圈标识的为肺部转移病灶及肝转移灶。

(A1–A4) After 2 months of treatment, the effect evaluation was complete response; (B1–B4) After 6 months of treatment, the effect evaluation was complete response; (C1–C4) After 12 months of treatment, the effect evaluation was complete response. The circles in the picture indicate the metastatic lesions in the lungs and liver.

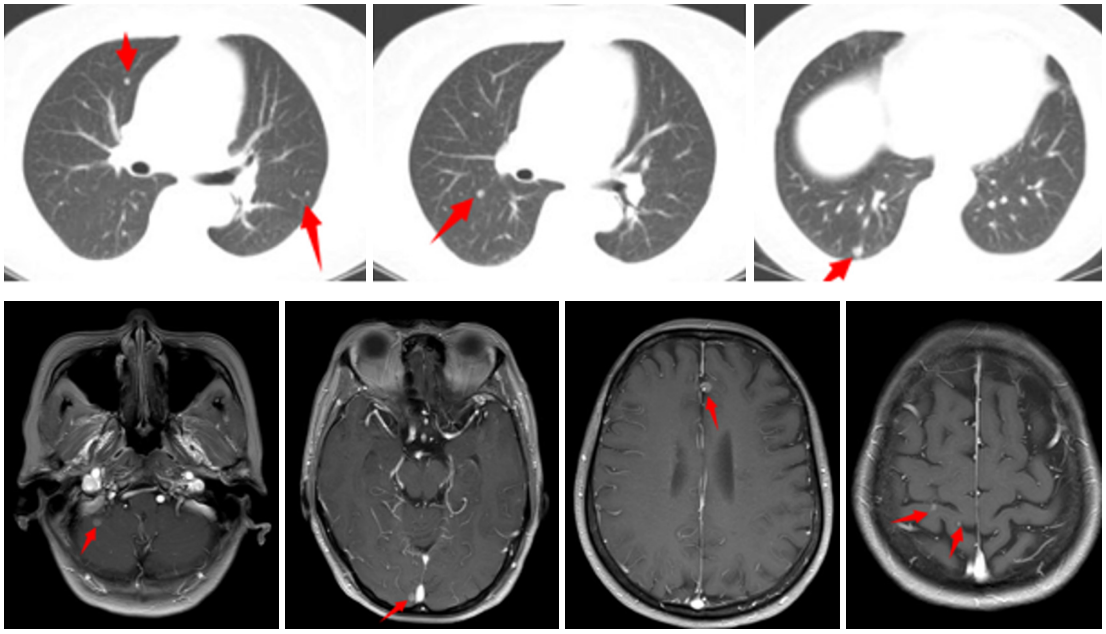

图9 奥希替尼治疗18个月后出现双肺多发结节，颅脑多发结节，考虑转移，疗效评价进展

Figure 9 Multiple lung nodules and craniocerebral multiple nodules appeared after 18-month treatment of oxitinib, progression of efficacy evaluation was considered after metastasis

图中箭头标识的为肺部转移病灶及脑部转移灶。

The arrows in the picture indicate the metastatic lesions in the lungs and brain.

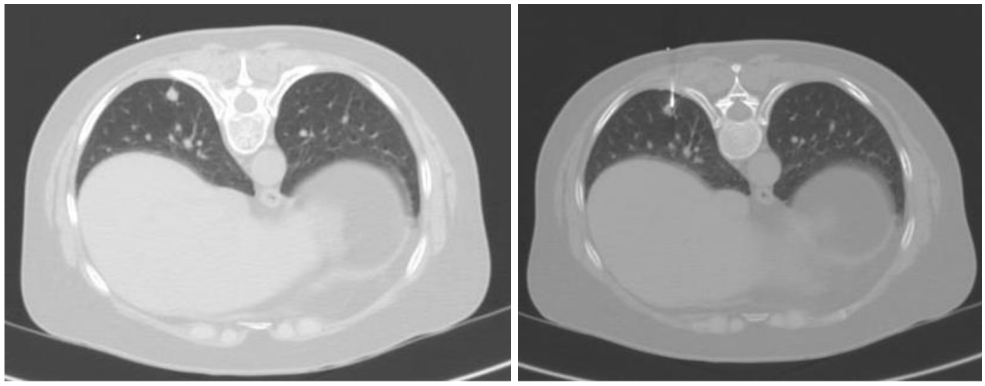

图10 第4次穿刺术中，穿刺右肺新发结节

Figure 10 In the fourth puncture, a new nodule of the right lung was punctured

2 讨论

本病例为1例IV期EGFR阳性NSCLC患者，EGFR小分子靶向药物治疗显著地改善了晚期患者的总生存时间(overall survival，OS)和生存质量，但几乎所有患者在接受治疗后均出现继发耐药。本病例特点在于该肿瘤治疗过程中经历了多次局部治疗。

第1次局部治疗是在入院时，因患者腰疼剧烈，行椎体转移癌微波消融术并椎体成形术，术后第3天患者不用服用任何止痛药物。椎体转移性肿瘤是一种常见的肺癌并发症，分为溶骨性、成骨性骨转移、复合性骨转移。骨转移癌不仅造成患者的疼痛，溶骨性骨转移更可能会造成病理性骨折等骨不良事件的发生。消融对于骨转移的治疗具有较高的局部控制率。不管是氩氦刀冷冻消融、射频消融还是微波消融，不仅有效缓解疼痛，速度快，时间长，具有较高的肿瘤局部控制率，局部控制率可高达96.7%[3-4]。椎体成形术对于治疗脊椎转移性肿瘤时主要适用于溶骨性或复合性转移性肿瘤，其能够缓解肿瘤转移后对椎体骨质、骨髓等的损坏，避免骨质产生塌陷，减轻神经受压迫的程度，同时还能够对椎体的进一步塌陷进行有效预防，对于缓解或消除由椎体转移性肿瘤引起的疼痛有明显的治疗效果[5]。如果射频消融联合椎体成形术不仅可以治疗肿瘤，缓解疼痛，还可有效增加椎体稳定性，降低骨水泥渗漏的风险，同时可以使溶骨性病变骨水泥分布更好[6]。第2次局部治疗在应用吉非替尼治疗出现局部进展后，对左肺上叶肺癌原发病灶进行射频消融手术，术后继续应用吉非替尼治疗，延长PFS 4个月。目前多项研究表明对于具有寡转移(≤3个病灶)的晚期患者，可加用局部治疗延长PFS和OS。Weickhardt等[7]的研究表明TKI耐药局部进展后如果加上局部治疗可延长PFS 6.2个月。一项前瞻性研究[8]探讨了积极的局部巩固治疗用于系统治疗后无进展的晚期NSCLC患者中的获益。与单纯维持治疗相比，联合局部治疗延长PFS 8个月(11.9个月vs 3.9个月)。局部治疗立体定向放疗不仅可以延长维持治疗和耐药治疗的PFS，对于具有寡转移病灶的晚期肺癌，如果一线治疗的同时加用局部治疗，可以延长PFS 6个月，延长OS 13个月[9]。由此可见，局部治疗在肺癌的综合治疗中起重要作用。

肺癌的治疗需多学科综合治疗，局部治疗不仅可以起到局部缓解症状的效果，在配合全身治疗的基础上尤其是对于寡转移病灶还可以延长患者的PFS和OS。

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