

不可切除肝细胞癌(CNLC-IIIb期肺转移)行转化治疗后成功切除一例并文献复习

窦 港^{1*}, 苏 强^{2*}, 杨凯帆², 白亮亮^{3#}

¹西安医学院研究生院, 陕西 西安

²空军军医大学唐都医院普通外科, 陕西 西安

³延安大学研究生学院, 陕西 延安

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摘 要

病史摘要: 患者, 59岁中年男性, 因“上腹部胀痛2月”于2021年4月6日入院, 既往史: 无。症状体征: 上腹部胀痛2月, 余未见异常。实验室检查: 乙肝病史, AFP升高, 上腹部CT结果显示肝右叶及肝左叶内侧段占位性病变, 考虑巨块型肝癌。治疗经过: 患者行介入栓塞治疗后, 行替雷利珠单抗于仑伐替尼4个周期, 复查发现肿瘤体积缩小, 双肺转移灶无明显进展后, 行肝脏部分切除。患者转归: 患者术后进行规律复查, 身体各项机能良好, 未见肿瘤复发迹象。原发性肝癌发病率居全球常见癌症第6位, 癌症相关死因居第4位, 是一种易复发、恶性程度高的疾病。其中肝细胞癌(Hepatocellular Carcinoma, HCC)占绝大多数, 且多数患者初次就诊时病情已处于中晚期, 预后相对较差, 尤其是无法一期手术切除的BCLC-C/CNLC-IIIb期肝癌为著。肝细胞癌(HCC)是主要的原发性肝癌类型。目前肝细胞癌的治疗方法主要包括肝切除术、肿瘤消融术、动脉内治疗、肝移植和免疫检查点抑制剂治疗。然而, 由于缺乏早期HCC的典型症状, 大多数患者已经处于初次就诊的中/晚期, 因此错过了最佳治疗时机。尽管HCC有多种治疗方法, 但肝细胞癌(HCC)的预后仍然不利, 5年生存率为18%。我们报道了一例双肺转移的CNLC-IIIb期肝癌患者诊疗过程, 旨在提示程序性死亡蛋白-1 (PD-1)抗体联合酪氨酸激酶抑制剂(Tyrosine Kinase Inhibitors, TKIs)加局部治疗转化后序贯外科手术方案对于同时具有远处转移的肝癌患者也可取得生存获益。

关键词

肝细胞癌, 肝动脉灌注化疗, 免疫检查点抑制剂, 仑伐替尼, 肝癌肺转移

*同一作者。

#通讯作者。

Unresectable Hepatocellular Carcinoma (CNLC-IIb Lung Metastasis) Was Successfully Resected after Conversion Therapy, and Literature Review

Gang Dou^{1*}, Qiang Su^{2*}, Kaifan Yang², Liangliang Bai^{3#}

¹Graduate School of Xi'an Medical University, Xi'an Shaanxi

²Department of General Surgery, Tangdu Hospital, Air Force Medical University, Xi'an Shaanxi

³Graduate School of Yan'an University, Yan'an Shaanxi

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Abstract

Summary of medical history: The patient, a 59-year-old middle-aged male, was admitted to the hospital on April 6, 2021 due to "epigastric distension pain for 2 months", past medical history: none. **Symptoms and signs:** Epigastric distension and pain for 2 months, and no abnormalities were seen in the remainder. **Laboratory tests:** History of hepatitis B, elevated AFP, and mass lesions in the right lobe and medial segment of the left lobe of the liver on CT scan of the upper abdomen were considered. **Treatment:** After interventional embolization, the patient was treated with tislelizumab and lenvatinib for 4 cycles, and the tumor volume was reduced and the metastases in both lungs did not progress, and the liver was partially resected. **Patient outcomes:** The patient underwent regular follow-up examinations after surgery, and all physical functions were good, and there was no sign of tumor recurrence. Primary liver cancer is the sixth most common cancer in the world and the fourth leading cause of cancer-related deaths. Hepatocellular carcinoma (HCC) accounts for the vast majority of patients, and most patients are in the middle and advanced stages of the disease at the time of initial presentation, and the prognosis is relatively poor, especially for BCLC-C/CNLC-III. Stage b liver cancer cannot be resected by primary surgery. Hepatocellular carcinoma (HCC) is the predominant type of primary liver cancer. Current treatments for hepatocellular carcinoma include liver resection, tumor ablation, intra-arterial therapy, liver transplantation, and immune checkpoint inhibitor therapy. However, due to the lack of typical symptoms of early HCC, most patients are already in the intermediate/advanced stages of their initial presentation and thus miss the optimal timing of treatment. Although there are multiple treatments for HCC, the prognosis for hepatocellular carcinoma (HCC) remains unfavorable, with a 5-year survival rate of 18 percent. We reported on the diagnosis and treatment of a patient with CNLC-III. b liver cancer with double lung metastases, aiming to suggest that sequential surgery after conversion of programmed death protein-1 (PD-1) antibodies plus tyrosine kinase inhibitors (TKIs) plus local therapy can also achieve survival benefits in patients with HCC with distant metastases.

Keywords

Hepatocellular Carcinoma, Hepatic Arterial Infusion Chemotherapy, Immune Checkpoint Inhibitors, Lenvatinib, Lung Metastasis of Liver Cancer



1. 临床资料

患者男性，59岁，因“上腹部胀痛2月”于2021年4月6日入院，既往史无特殊，实验室检查示：甲胎蛋白(AFP) 50.4 ng/ml，乙肝标志物 HBsAg (-)、Anti-HBe (-)、Anti-HBc (+)、HBeAg (-)、Anti-HBs (-)、Anti-HCV (-)；谷丙转氨酶(ALT) 20 U/L，谷草转氨酶(AST) 302 U/L；凝血酶原时间(PT) 10.5 S；上腹部 CT 结果显示肝右叶及肝左叶内侧段占位性病变，考虑巨块型肝癌(15.4 × 9.0 cm) (图 1)，胸部 CT 提示双肺多发转移瘤，三维重建提示肿瘤体积：1194 ml (图 2(a))。根据肿瘤典型的影像学特征，诊断为肝细胞癌。东部肿瘤协作组体能评分(ECOG-PS)评分为 1 分，Child-Pugh 评分为 5 分，中国肝癌诊疗指南分期(CNLC) IIIb 期，巴塞罗那分期(BCLC) C 期。

经肿瘤多学科治疗(MDT)专家组讨论后，患者接受 FOLFOX4 方案(全量 80%)经肝动脉持续灌注化疗(HAIC)，联合口服仑伐替尼 8 mg/次/1/日，静脉注射 200 mg 的替雷利珠单抗。替雷利珠单抗每 3 周重复 1 次。2 个疗程后，MRI 发现肿瘤坏死明显，体积明显缩小(图 1)。在接受第 3 个疗程的替雷利珠单抗治疗的 2 周后 MRI 再次评估，肿瘤边界清晰，体积继续缩小(图 1)，通过切除 S5、S8 和部分 S7 肝段实现肿瘤的根治性手术切除，残余肝体积(FLR)足够。手术后患者恢复顺利，无并发症，术后第 8 天出院。病理检查报告肿瘤组织完全坏死，随访至今，目前术后各项身体机能良好，无肿瘤复发的迹象(图 3 和图 4)。

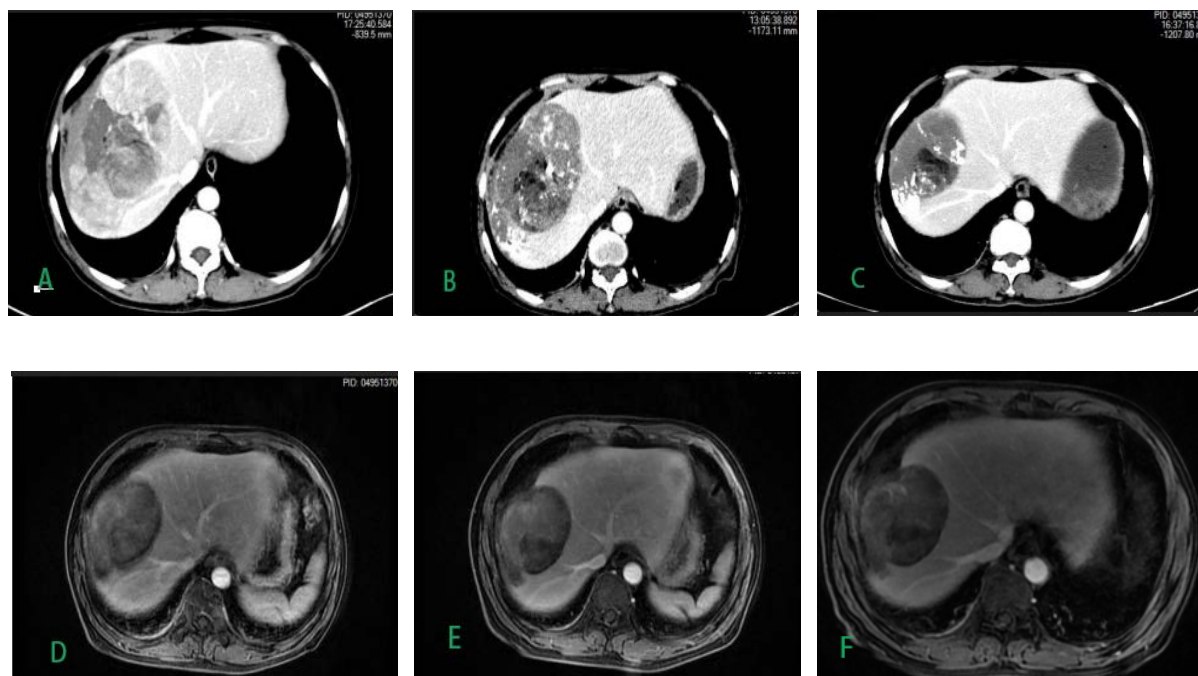


Figure 1. Abdominal imaging manifestations of patients with unresectable liver cancer at different stages of treatment. (A): Image at initial diagnosis; (B): image after the 1st course of treatment; (C): image after the 2nd course of treatment; (D): image after the 3rd course of treatment; (E): image after the 4th course of treatment; (F): preoperative image

图 1. 不同治疗阶段的不可切除肝癌患者腹部影像学表现。(A)：初始诊断时的图像；(B)：第 1 个疗程后的图像；(C)：第 2 个疗程后的图像；(D)：第 3 个疗程后的图像；(E)：第 4 个疗程后的图像；(F)：术前图像

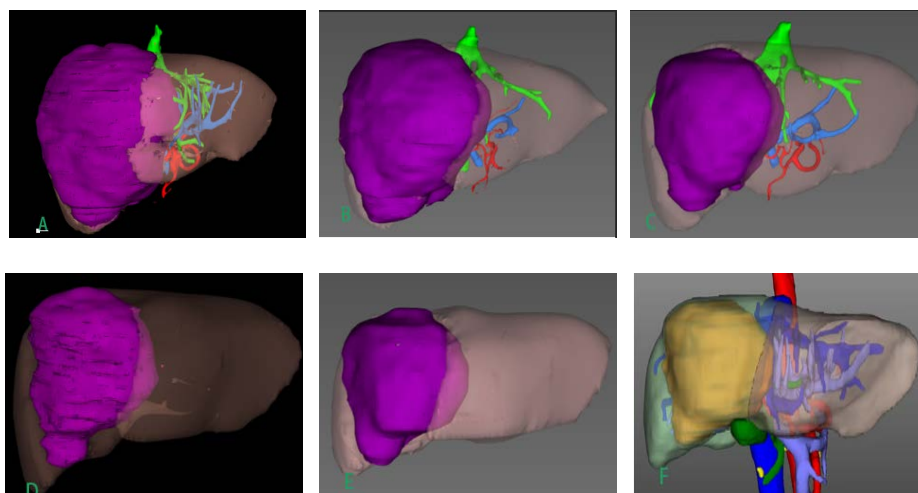


Figure 2. Three-dimensional reconstructed images of unresectable liver cancer patients at different stages of treatment. (A): Tumor volume at initial diagnosis; (B): tumor volume after the first course of treatment; (C): tumor volume after the second course of treatment; (D): tumor volume after the 3rd course of treatment; (E): tumor volume after the 4th course of treatment; (F): preoperative tumor volume

图 2. 不同治疗阶段的不可切除肝癌患者三维重建图像。(A): 初始诊断时的肿瘤体积; (B): 第 1 个疗程后的肿瘤体积; (C): 第 2 个疗程后的肿瘤体积; (D): 第 3 个疗程后的肿瘤体积; (E): 第 4 个疗程后的肿瘤体积; (F): 术前肿瘤体积

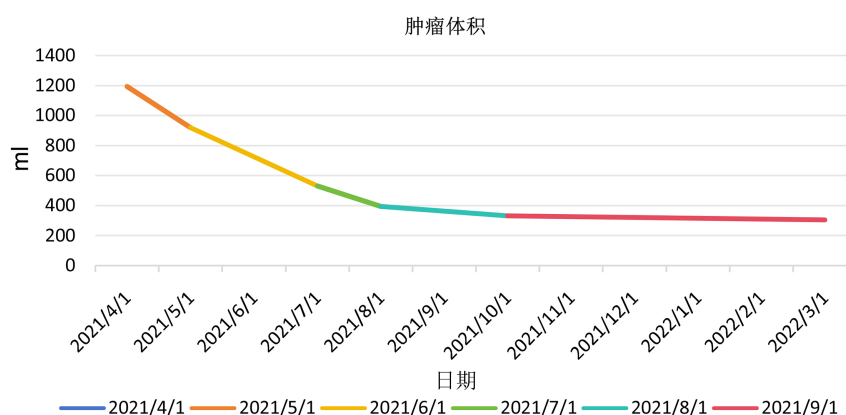


Figure 3. Tumor volume curves of unresectable liver cancer patients at different treatment stages

图 3. 不同治疗阶段的不可切除肝癌患者肿瘤体积变化曲线

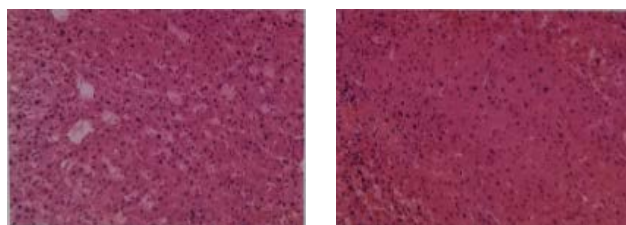


Figure 4. Postoperative pathological diagnosis. (liver) A large amount of coagulative necrosis, focal calcification and cholesterol crystal formation were found in the liver tissue, local liver tissue with chronic inflammatory cell and neutrophil infiltration, fibrous tissue hyperplasia and vitreous degeneration and histiocyte hyperplasia, and some hepatocytes were active, which could be consistent with post-treatment changes in combination with clinical history

图 4. 术后病理诊断。(肝脏)送检肝脏组织内见大量凝固性坏死, 灶状钙化及胆固醇结晶形成, 局部肝组织伴慢性炎细胞及中性粒细胞浸润、纤维组织增生并玻璃样变性及组织细胞增生, 部分肝细胞增生活跃, 结合临床病史可符合治疗后改变

2. 讨论

该案例展现了 1 例合并有肺转移的晚期不可切除的肝细胞癌患者在经肝动脉持续灌注化疗的基础上进行靶向治疗后进行手术切除, 并达到了控制肺部转移灶的进一步进展与切除肝内原发灶的目的, 使得病人生存获益。

肝细胞癌发病隐匿, 在疾病早前难以发现, 早期肝癌[主要是中国肝癌分期(CNLC-Ia、Ib 和部分 IIa 期)]适合手术切除、局部消融等方法, 大多数患者初诊时已处于中晚期[(CNLC-IIb、IIIa、IIIb 期)], 有研究显示, 在我国肝癌患者中有 64%在初诊时已处于中晚期[1]。针对具有肝外器官转移的 HCC, 即 CNLC-IIIb 期肝癌, 目前认为是进行一期手术的绝对禁忌症, 指南推荐使用局部治疗或者药物治疗[2] [3] [4]。张[5]等人使用程序性死亡受体 1 (Programmed Death 1, PD-1)抑制剂联合酪氨酸酶抑制剂(Tyrosine Kinase Inhibitor, TKI)治疗, 转化切除率可达到 42%。《肝癌转化治疗中国专家共识(2021 版)》中指出, 肝动脉持续灌注化疗(Hepatic Arterial Infusion Chemotherapy, HAIC)可显著降低肿瘤负荷, 并且拥有更高的肿瘤缓解率, 从而获得转化切除的机会[6]。TACE (Transarterial Chemoembolization)是中晚期肝癌最常用的治疗手段, 然而 TACE 具有一定的适用性, 如肿瘤的大小决定了 TACE 的有效率, 一项研究表明针对肿瘤大小小于 5 cm 的肿瘤患者, 使用 TACE 治疗 CRR 可以达到 65%, 然而肿瘤体积越大 TACE 的效果越不显著, 同时反复使用 TACE 会使得患者肝功能受损或对 TACE 产生抵抗, 单独使用 TACE 对于具有肝癌转移的患者效果也不是很理想[7] [8]。有研究结果显示 HAIC 联合 TKI 类药物较单一使用 TKI 类药物疗效更好[9]一项回顾性研究显示 HAIC 联合 TKI 与 PD-1 类药物较单一药物有更高的切除转化率(12.7%: 0)并且在联合组中患者获得了 60%的 ORR [10], 最新的 ASCO 年会中中山大学肿瘤防治中心郭荣平教授所牵头的一项多中心、前瞻性 III 期的研究表明术前新辅助 FOLFOX-肝动脉灌注化疗(HAIC)可使得 BCLC A/B 期 HCC 患者带来生存获益, 同时该方案的副作用也在患者可接受的范围之内。针对原发性肝癌患者对其实施手术切除是患者获得长期生存的必要方式[11] [12], 对于晚期肝癌患者, 通过转化治疗获得切除机会可使患者得到最大获益[13], 一项纳入 15 项研究的结果表明 HAIC 联合 TKI 与免疫检查点抑制剂(Immune Checkpoint Inhibitors, ICIs)三联方案的客观缓解率(Objective Response Rate, ORR)较单一方案有所提高, 同时转化切除率更高, 不良反应也在可接受范围之内, 使得患者获得更多的手术切除的机会, 显著改善患者的预后。

本中心在此之前使用 HAIC 联合仑伐替尼与替雷利珠单抗三联疗法进行了多次的转化治疗, 其中多数患者瘤体缩小明显, 术后恢复良好, 因此我们使用此方案对该患者进行治疗。在此次报道的案例中, 患者属晚期肝癌, 同时伴有远处转移, 有研究表明晚期肝细胞癌患者中有 40%会出现远处肺转移[14]目前对于伴有远处转移的肝细胞癌患者指南推荐使用全身治疗, 但肝细胞癌合并肝外转移的患者往往死于肝内肿瘤进展引起的肝衰竭, 而不是肝外转移[15]。因此积极控制并治疗原发灶显得尤为重要, 但有一部分患者可在我们使用 HAIC 联合仑伐替尼与替雷利珠单抗最终转化降期并成功手术切除, 目前转化治疗的方式多种多样, 本案例旨在探索更多更有益于患者预后的方案, 使得患者取得长期的生存获益, 本案例的成功转化, 也表明了 HAIC 联合仑伐替尼与替雷利珠单抗三联疗法针对于晚期伴有远处器官转移的肝癌患者也具有显著疗效, 是一种安全有效的治疗方案。

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