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A 73-Year-Old Man With a Late Isolated Brain Metastasis of Clear Cell Renal Cell Carcinoma Following a Durable Complete Response to Lenvatinib-Pembrolizumab, Resulting in Deferred Cytoreductive Nephrectomy

Authors' Contribution:

Study Design A

Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

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Patient: Male, 73-year-old

Final Diagnosis: Metastatic renal cell carcinoma

Symptoms: Asymptomatic

Clinical Procedure: —

Specialty: Urology

Objective: Unusual clinical course

Background: A durable complete response, or sustained disappearance of measurable malignancy, can occur in selected patients with metastatic renal cell carcinoma after systemic therapy. Clear cell renal cell carcinoma is the most common renal cell carcinoma subtype. Lenvatinib is a multikinase inhibitor with antiangiogenic activity, and pembrolizumab is an anti-programmed death-1 immune checkpoint inhibitor. Although this combination can induce deep extracranial responses, central nervous system relapse after prolonged complete response remains incompletely characterized. This report describes a 73-year-old man with late isolated brain metastasis of clear cell renal cell carcinoma after durable complete response to lenvatinib-pembrolizumab and deferred cytoreductive nephrectomy.

Case Report: A 73-year-old man presented with right flank pain. Computed tomography showed a right renal tumor, level II inferior vena cava tumor thrombus, and multiple pulmonary metastases. Baseline brain computed tomography showed no intracranial metastasis. He received lenvatinib plus pembrolizumab, resulting in marked regression of the primary tumor, inferior vena cava thrombus, and lung metastases. Deferred cytoreductive nephrectomy with thrombectomy was then performed, and pathology confirmed clear cell renal cell carcinoma with extensive treatment effect. Lenvatinib was discontinued because of renal dysfunction, and pembrolizumab monotherapy was continued. The patient maintained complete extracranial radiographic remission for more than 2 years. He later developed headache, and brain magnetic resonance imaging revealed a solitary left occipital metastasis without systemic recurrence. Stereotactic body radiotherapy achieved local control.

Conclusions: This case shows that late isolated central nervous system relapse can occur despite durable extracranial complete response after lenvatinib-pembrolizumab and deferred cytoreductive nephrectomy. New neurological symptoms in long-term responders should prompt brain magnetic resonance imaging, because intracranial progression may occur even when systemic imaging remains negative.

Keywords: Case Reports • Central Nervous System Neoplasms • Immune Checkpoint Inhibitors • Oncology • Renal Cell Carcinoma • Tyrosine Kinase Inhibitors

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Introduction

Clear cell renal cell carcinoma (ccRCC) is the most common histological subtype of renal cell carcinoma (RCC), and RCC accounts for most malignant kidney tumors [1]. Patients can present with flank pain, hematuria, an abdominal mass, constitutional symptoms, or paraneoplastic findings, although many renal tumors are detected incidentally by cross-sectional imaging [1]. Diagnosis is based on radiological evaluation, pathological confirmation when clinically required, and staging to assess local extension, venous tumor thrombus, nodal disease, and distant metastases [1]. Management depends on disease stage and includes surgery, systemic therapy, and local treatment for selected metastatic sites [1].

Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor receptors and other proangiogenic

and oncogenic pathways [2,3]. Pembrolizumab is an anti-programmed death-1 immune checkpoint inhibitor that restores antitumor T-cell activity [4]. The combination of lenvatinib and pembrolizumab is an established first-line systemic option for advanced RCC and can produce deep tumor responses in selected patients [2].

A complete response (CR) refers to disappearance of measurable malignant disease, and durable CR indicates sustained disappearance of measurable malignant disease over time, including in some patients after treatment de-escalation or modification [5]. In metastatic RCC, durable systemic responses have renewed interest in deferred cytoreductive nephrectomy (dCN), in which systemic therapy is given first and surgery is considered only after favorable biological selection [6-11]. Previous reports have described successful deferred cytoreductive nephrectomy after immune checkpoint inhibitor-based therapy, including lenvatinib plus pembrolizumab [7,8,12,13]. However, late isolated central nervous system (CNS) relapse after prolonged extracranial complete response remains insufficiently characterized [14-16].

This report describes the case of a 73-year-old man with a late isolated brain metastasis of clear cell renal cell carcinoma following a durable complete response to lenvatinib-pembrolizumab, resulting in deferred cytoreductive nephrectomy.

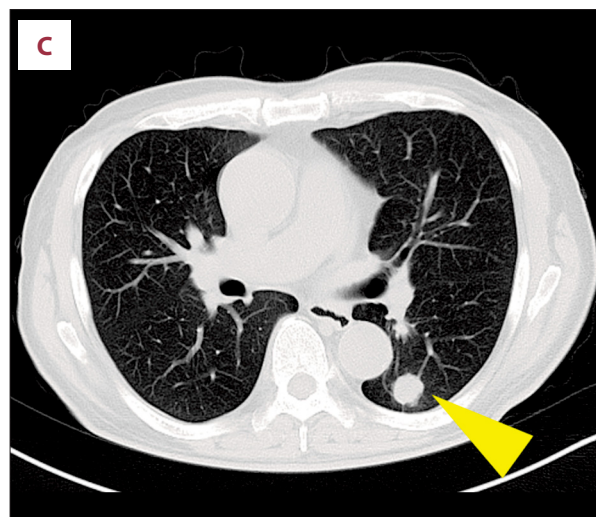
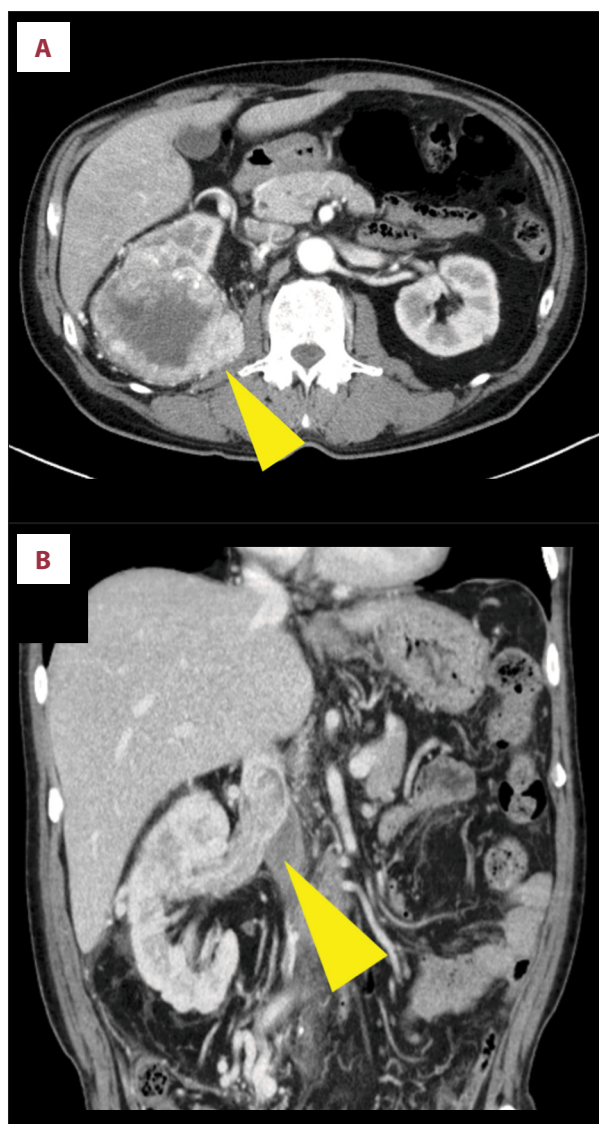


Figure 1. Baseline computed tomography showing clear cell renal cell carcinoma with an inferior vena cava tumor thrombus and pulmonary metastases. (A) Axial contrast-enhanced computed tomography (CT) image showing the right renal mass (arrow). (B) Coronal contrast-enhanced CT image showing a level II inferior vena cava (IVC) tumor thrombus (arrow). (C) Axial chest CT image showing multiple bilateral pulmonary metastases (arrows). These findings established metastatic renal cell carcinoma requiring initial systemic therapy.

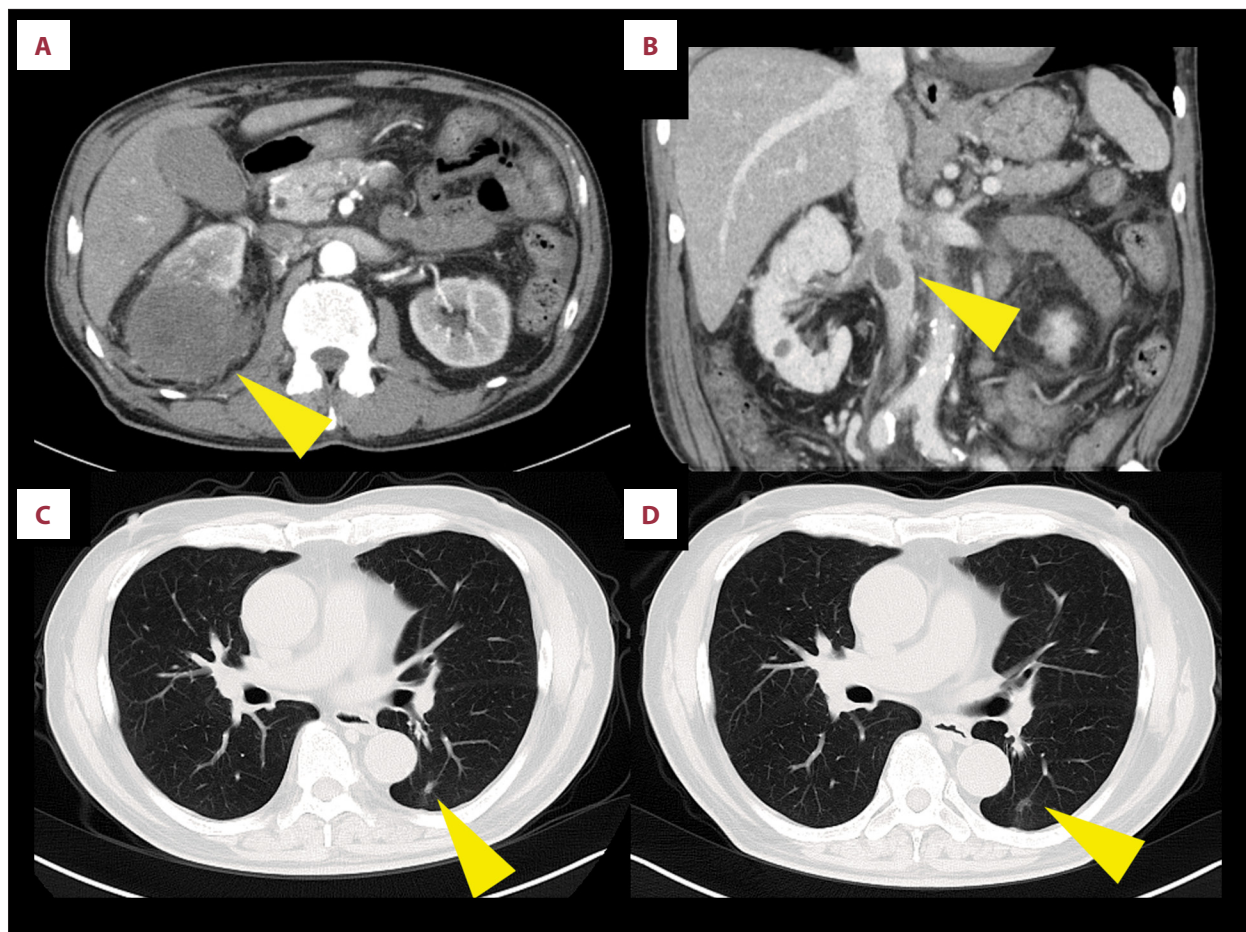


Figure 2. Radiological response after lenvatinib plus pembrolizumab and complete extracranial response after deferred cytoreductive nephrectomy. (A) Contrast-enhanced computed tomography (CT) after systemic therapy showing marked reduction of the right renal tumor (arrow). (B) Coronal CT image after systemic therapy showing shrinkage of the inferior vena cava (IVC) tumor thrombus (arrow). (C) Chest CT after systemic therapy showing near-complete resolution of pulmonary metastases (arrows). (D) Follow-up chest CT after deferred cytoreductive nephrectomy showing disappearance of pulmonary metastases, consistent with complete response (CR).

Case Report

A 73-year-old man presented with right flank pain. Contrast-enhanced computed tomography (CT) revealed a right renal mass with a level II inferior vena cava (IVC) tumor thrombus and multiple bilateral pulmonary metastases, consistent with cT3bN0M1 disease (Figure 1). Baseline brain CT showed no evidence of intracranial metastasis. Laboratory studies showed elevated C-reactive protein and mild anemia, and the patient was classified as intermediate risk according to the International Metastatic Renal Cell Carcinoma Database Consortium criteria.

Because of the metastatic burden and the presence of an IVC tumor thrombus, systemic therapy with lenvatinib plus pembrolizumab was initiated before surgery. Lenvatinib was started at 20 mg once daily and was later reduced stepwise to 10 mg

because of hypertension and fatigue. After 2 cycles, follow-up imaging showed marked regression of the primary renal tumor, substantial reduction of the IVC tumor thrombus, and near-complete resolution of the pulmonary metastases (Figure 2).

Following this favorable response, deferred cytoreductive nephrectomy with IVC thrombectomy was performed. The operative time was 268 min, and the estimated blood loss was 1000 mL. Histopathological examination showed clear cell renal cell carcinoma with extensive treatment-related necrosis and focal residual viable tumor (Figure 3). The postoperative course was uneventful except for transient renal dysfunction.

Lenvatinib was resumed at 8 mg after surgery but was discontinued soon afterward because of worsening renal function. Pembrolizumab monotherapy was continued without immune-related adverse events. Serial CT examinations during

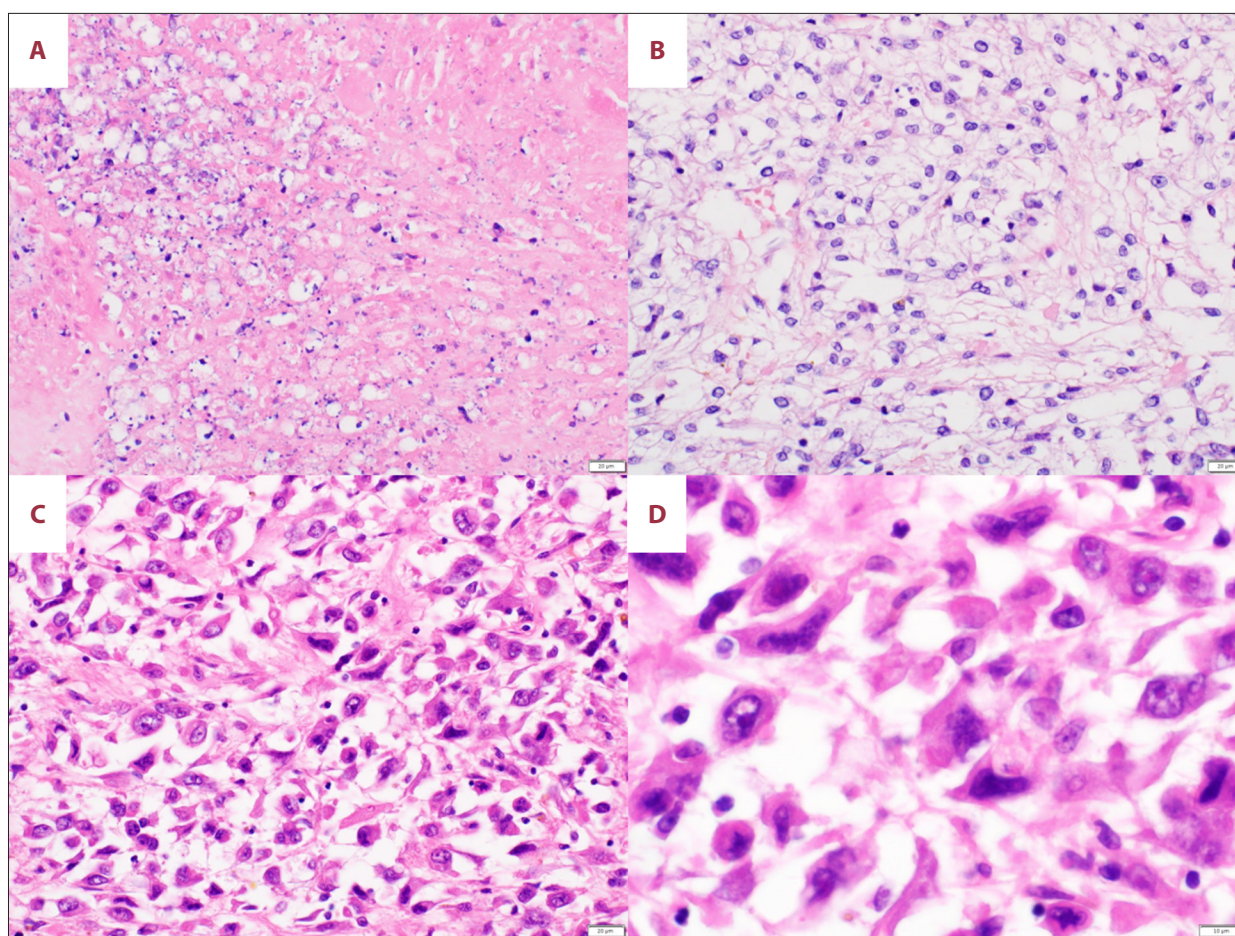


Figure 3. Histopathological findings of the resected primary renal tumor following neoadjuvant lenvatinib-pembrolizumab therapy and deferred cytoreductive nephrectomy. (A) Extensive treatment-related changes are present within the primary tumor bed, including fibrosis, hemorrhage, necrosis, and aggregates of foamy macrophages (hematoxylin and eosin [H&E], ×400). (B) Residual viable clear cell renal cell carcinoma composed of tumor cells with abundant clear cytoplasm arranged in nests and cords within a delicate vascular network (H&E, ×400). (C) Sarcomatoid differentiation characterized by spindle-cell proliferation with marked nuclear pleomorphism and loss of conventional clear cell morphology (H&E, ×400). (D) High-power view of the sarcomatoid component demonstrating severe nuclear atypia, hyperchromasia, and pleomorphic tumor cells (H&E, ×1000).

follow-up showed persistent complete extracranial radiographic remission and no extracranial recurrence.

More than 2 years after achieving systemic CR, the patient developed mild headache. Brain magnetic resonance imaging (MRI) revealed a solitary lesion in the left occipital lobe, whereas systemic imaging showed no evidence of extracranial disease (Figure 4). Stereotactic radiotherapy (SRT; 30 Gy in 3 fractions) was administered and achieved good local control. At the most recent follow-up, no further systemic recurrence was observed.

Discussion

This case provides 2 main clinical lessons. First, lenvatinib-pembrolizumab can induce marked downstaging of metastatic

ccRCC with an IVC tumor thrombus and enable dCN in a carefully selected responder. Second, durable extracranial CR does not eliminate the possibility of late isolated CNS relapse, suggesting that the brain may remain a clinically relevant sanctuary site.

The role of cytoreductive nephrectomy in metastatic RCC has changed substantially after trials that questioned routine upfront nephrectomy in patients requiring systemic therapy [9,10]. Current strategies increasingly use initial systemic therapy as a selection tool to identify patients with favorable tumor biology who may benefit from delayed surgery [8,11]. The present case is consistent with this approach: regression of both the primary tumor and IVC tumor thrombus after lenvatinib-pembrolizumab converted a technically complex presentation into an operable condition. Similar reports have described

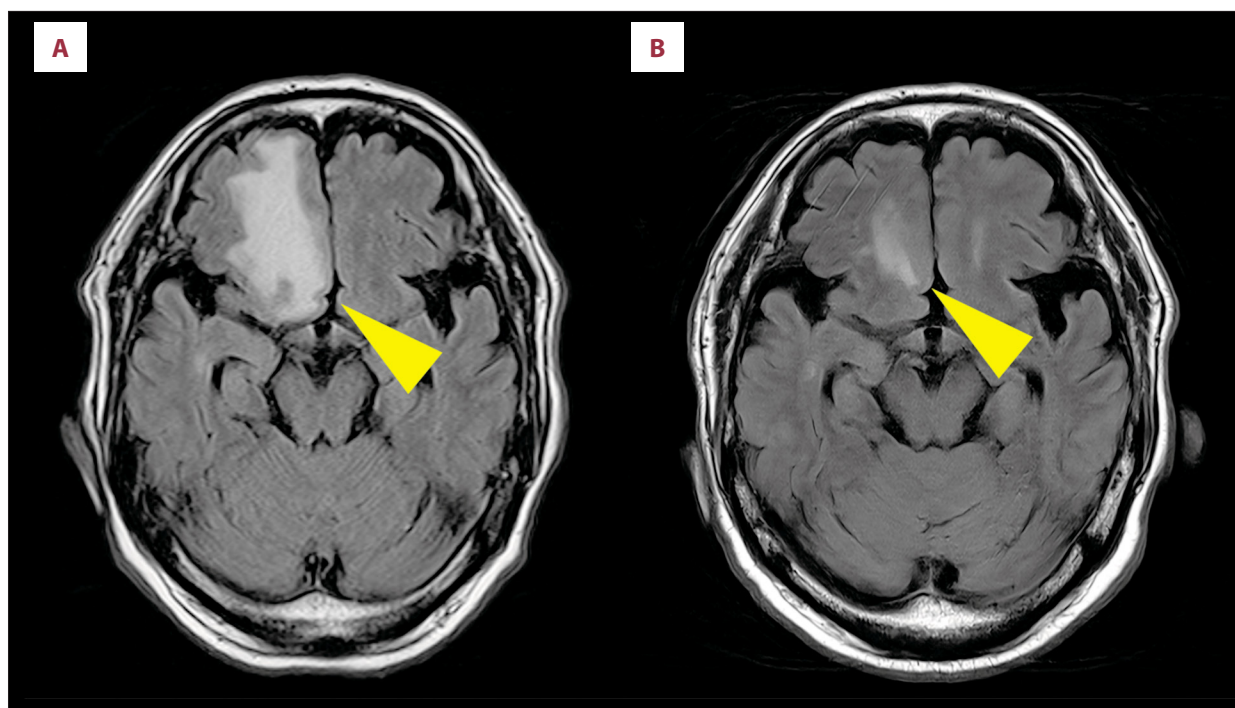


Figure 4. Brain magnetic resonance imaging before and after stereotactic body radiotherapy for isolated brain metastasis. (A) Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) showing a solitary hyperintense lesion in the left occipital lobe (arrow). Gadolinium contrast was not administered at diagnosis because of clinical considerations. (B) Follow-up axial FLAIR MRI after stereotactic radiotherapy (SRT) showing marked reduction in lesion size and good local control.

successful dCN after lenvatinib-pembrolizumab and favorable clinical or pathological outcomes after immune checkpoint inhibitor-based therapy [7,8].

Pathological examination in our patient showed extensive treatment effect with only focal residual viable tumor, supporting substantial cytoreduction at the primary site. Moreover, complete extracranial remission persisted after lenvatinib discontinuation because of renal dysfunction. This course is compatible with previous observations that some patients with deep responses to immunotherapy-based treatment can maintain prolonged disease control after treatment de-escalation [14].

The distinctive feature of this case is the late isolated brain metastasis after more than 2 years of extracranial CR. Brain metastases from RCC are clinically important because they can cause neurological morbidity, and intracranial efficacy of systemic regimens remains less well defined than extracranial efficacy [15,16]. The CNS can be a relative sanctuary site because of the blood-brain barrier and a distinct immune microenvironment [15-17]. Therefore, occult micrometastatic disease can persist intracranially despite durable extracranial control.

In patients treated with immune checkpoint inhibitors, new neurological symptoms also require careful differential diagnosis,

including brain metastasis, cerebrovascular events, and immune-related neurologic adverse events. A recent American Journal of Case Reports case of sintilimab-associated encephalitis and myocarditis illustrates that ICI-related neurological toxicity can mimic or coexist with oncologic complications, reinforcing the need for prompt neurological assessment and appropriate brain imaging in symptomatic patients [18].

Local therapy remains central for limited brain metastasis from RCC. Stereotactic radiosurgery or stereotactic radiotherapy can provide local control, and combined use with immune checkpoint inhibition has been associated with prolonged disease control in selected cases [15,19]. In our patient, SBRT achieved durable local control without subsequent extracranial relapse, supporting timely local treatment when CNS-only progression is detected.

This case does not establish a universal indication for routine brain surveillance in asymptomatic long-term responders. However, it supports careful neurological assessment during long-term follow-up and a low threshold for brain MRI when new neurological symptoms occur. In selected high-risk clinical contexts, individualized CNS imaging may be considered, but its optimal timing and impact on outcomes require further study.

Conclusions

Lenvatinib-pembrolizumab enabled marked tumor regression and deferred cytoreductive nephrectomy in a patient with metastatic clear cell renal cell carcinoma and an inferior vena cava tumor thrombus, resulting in durable extracranial complete response. However, late isolated brain metastasis occurred without systemic recurrence. Long-term responders should be monitored carefully for neurological symptoms, and brain magnetic resonance imaging should be performed promptly when clinically indicated.

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Department and Institution Where Work Was Done

Gifu Prefectural Tajimi Hospital, Tajimi, Gifu, Japan.

Patient Consent

Written informed consent for publication of clinical data and images was obtained from the patient.

Statement

During preparation of this manuscript, ChatGPT (OpenAI, GPT-5.5) was used only for English-language editing and formatting assistance. All scientific content, interpretation, and final manuscript revisions were performed and verified by the authors.

Declaration of Figures' Authenticity

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