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CASE REPORT

Sarcomatoid Renal Clear Cell Carcinoma with Brain Metastasis: A Case Report and Literature Review

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Abstract

Sarcomatoid renal cell carcinoma typically signifies an exceptionally poor prognosis, with patients rarely surviving beyond one year. An 83-year-old male presented to our hospital with complaints of headache and left-sided limb weakness. Computed tomography (CT) scans of the head and lungs disclosed a mass within the right temporal lobe, accompanied by peritumoral edema in the right cerebral hemisphere. Brain magnetic resonance imaging (MRI) with contrast enhancement and diffusion-weighted imaging (DWI) delineated a mass in the right temporal lobe, measuring 3 × 3 × 3 cm. He underwent cytoreductive surgery successively in the neurosurgery and urology departments. Despite experiencing postoperative tumour recurrence, the patient has lived close to four years to date. This case report illustrates that cytoreductive surgery combined with systemic pharmacotherapy can still confer significant survival benefits for elderly patients.

Key words: sarcomatoid renal clear cell carcinoma; brain metastasis; cytoreductive surgery

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Introduction

Kidney cancer is the seventh most common malignancy in the United States, with an estimated 81,800 new cases diagnosed in 2023, of which 16% and 15% will present with regional lymph node spread or distant metastatic disease, respectively (Nicaise et al, 2024). The poor prognosis of clear cell renal cell carcinoma (ccRCC) is attributed to the heterogeneous and aggressive nature of the disease and the lack of biomarkers to guide therapy (Warren and Harrison, 2018; Zhao et al, 2014). Sarcomatoid renal cell carcinoma (sRCC) accounts for only 5% of renal cancer cases and represents a highly drug-resistant and lethal manifestation of renal cancer (Shuch et al, 2012). Patients diagnosed with sRCC typically present with advanced or metastatic disease, leading to an exceptionally poor prognosis (Blum et al, 2020). Survival beyond one year is uncommon for this type of RCC (Blum et al, 2020). The most common metastatic sites are the lung, liver, lymph nodes, contralateral kidney, or adrenal gland; however, brain metastasis (BrM) has only

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been seen in 1.3% of cases. Previous genomic studies have not conclusively identified the mutational drivers behind this condition. However, sRCC exhibits higher expression levels of Programmed Death 1 (PD1) and Programmed Death Ligand1 (PDL1) compared to other RCC subtypes, suggesting that novel immunotherapies targeting these immune checkpoints may offer enhanced treatment responses and improved patient outcomes. In 2014, Heng et al (2014) conducted a study on 189 patients with sRCC. Median survival was 10.2 months in patients who underwent cytoreductive nephrectomy (CN) and 5.5 months in those who did not (Heng et al, 2014). In addition, Alevizakos et al (2019) analyzed clinical data from 879 sRCC patients and found that surgery significantly improved outcomes among patients who were eligible. Although the proportion of patients undergoing CN has declined steadily since the introduction of targeted therapies for metastatic renal cancer (Pal et al, 2013), multiple studies have shown that patients with sRCC have limited systemic therapy options and few treatments produced durable responses (Golshayan et al, 2009; Shuch et al, 2012; Voss et al, 2014). On the other hand, the role of debulking or CN in patients with metastatic RCC has been widely debated (Nicaise et al, 2024). Moreover, the role of CN in the treatment of sRCC remains poorly understood. Therefore, exploring the role of CN in the context of systemic treatment of sRCC may yield beneficial findings for treatment strategies.

Case Report

The patient, an 83-year-old male, presented to our hospital with a one-month history of headaches. He reported persistent, dull pain localized to the right side of his head in August 2020. He also experienced weakness in his left limbs. The headache persisted without improvement, prompting his visit to our hospital's neurosurgery department. Since the onset of the headache, the patient has not exhibited fever, limb twitching, chest tightness, palpitations, nausea, vomiting, or significant weight loss. The patient had a 10-year history of chronic bronchitis and denied a history of hypertension, diabetes, heart disease, and other significant illnesses, as well as chronic conditions like hepatitis and kidney disease. He also had no history of blood transfusions, surgical trauma, or allergies to drugs or food. The patient, a farmer with a junior high school education, has a smoking history spanning over 40 years. There was no family history of similar diseases. Upon admission, the patient's vital signs were as follows: temperature, 36.6 °C; pulse, 64 beats per minute; respiratory rate, 15 breaths per minute; and blood pressure, 122/72 mmHg. He stood at 160 cm in height and weighed 60 kg, with a body mass index (BMI) of 23.4. Physical examination revealed alertness, a Glasgow Coma Scale (GCS) score of 15, and bilaterally equal and round pupils measuring approximately 0.3 cm. He exhibited a brisk light reflex, with no depression of the frontalis lines and negative cervical resistance. Normal muscle strength was noted in the right limbs, whereas the left limbs demonstrated muscle strength graded at 4/5, with no increased muscle tone. Sensory perception in the limbs was intact, knee tendon reflexes were 2+, and bilateral Babinski signs were absent.

Laboratory Examinations

No significant abnormalities were identified in the routine blood tests, coagulation profile, liver and renal function tests, thyroid function tests, cardiac enzymes, or electrocardiogram (ECG). Notably, lactate dehydrogenase, haemoglobin, serum calcium, and platelet counts were within normal limits.

Imaging and Histological Examinations

Computed tomography (CT) scans of the head and lungs revealed a mass in the right temporal lobe, associated with edema in the right cerebral hemisphere, as well as localized bronchiectasis and evidence of infection in both lungs. Brain magnetic resonance imaging (MRI) with contrast enhancement and diffusion-weighted imaging (DWI) at 3.0T identified a mass in the right temporal lobe measuring 3 × 3 × 3 cm (Fig. 1A–F). The postoperative pathology confirmed a diagnosis of metastatic adenocarcinoma with extensive necrosis in the right temporal lobe. Tissue specimens were fixed in 10% neutral buffered formalin for 24 h at room temperature (18–25 °C). The specimens were dehydrated in a conventional series of gradient alcohols, cleared in xylene, dipped in wax, embedded in paraffin, sectioned to 3 μm, and stained with conventional hematoxylin-eosin (HE) staining using a Sakura autostainer (Sakura Finetek, Prisma 81D, Torrance, CA, USA), cleared and sealed. Finally, the sections were examined microscopically at ×400 magnification using an Olympus light microscope (Olympus Corporation, BX61, Tokyo, Japan) (Fig. 2). The radiologist thought that the mass might be a metastatic tumour. Subsequently, clinicians performed an enhanced abdominal CT scan on the patient, which indicated the presence of a renal tumour in the right kidney (Fig. 3A).

Treatment and Follow-Up

With informed consent from the patient and his family, the patient underwent resection of a deep supratentorial lesion in the neurosurgery department on September 13, 2020. The postoperative histopathological and immunohistochemical analysis confirmed the diagnosis of metastatic renal cell carcinoma (mRCC) in the brain. Immunohistochemical detection was performed using an EnVision technology system (Agilent Technologies, Inc., Agilent-062716, Santa Clara, CA, USA). The sections were examined microscopically using an Olympus light microscope. Immunophenotyping of the tumor revealed the following results: CK7 (–), CK20 (–), TTF-1 (–), Napsin A (–), GFAP (–), CK-P (+), CD10 (+), CA IX, PAX-8 (+), TFE3 (±), CD117 (–), Oligo-2 (–). On November 5, 2020, the patient underwent cytoreductive nephrectomy in the department of urology. Tissue specimens were fixed in 10% neutral buffered formalin for 24 h at room temperature (18–25 °C). The specimens were dehydrated in a conventional series of gradient alcohols, cleared in xylene, dipped in wax, embedded in paraffin, sectioned to 3 μm, stained with conventional HE staining using a Sakura autostainer (Sakura Finetek USA, Inc.), cleared and sealed. Finally, the sections were examined microscopically at ×400 magnification using an Olympus light microscope (Olympus Corporation).

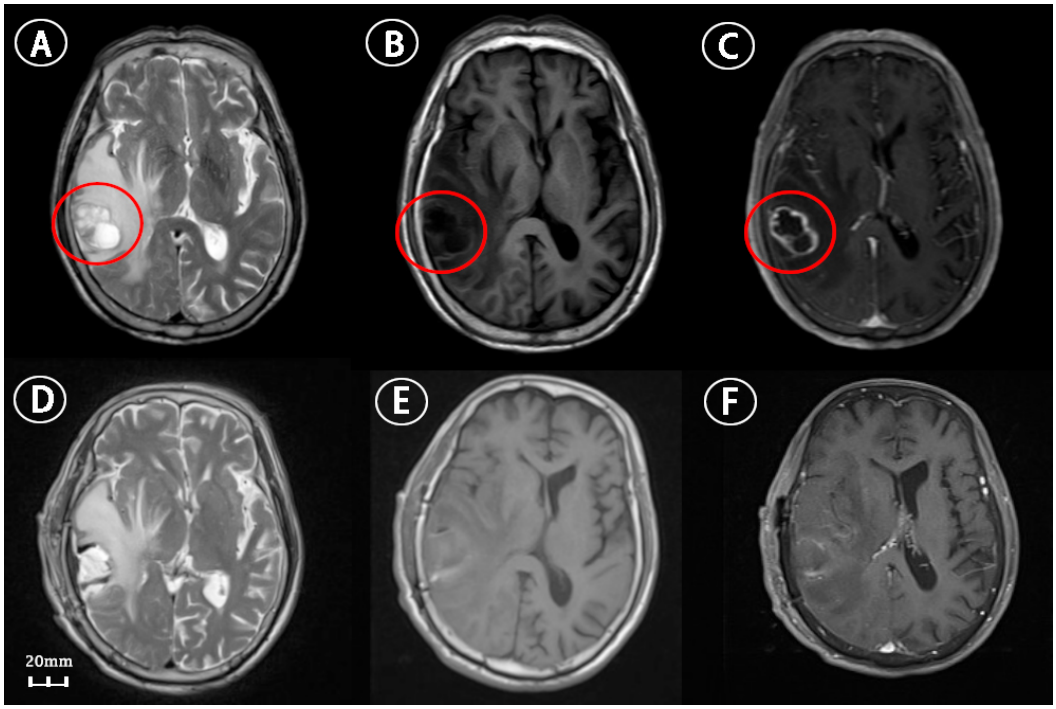

Fig. 1. Preoperative cranial contrast-enhanced magnetic resonance imaging (MRI) axial images. (A–C) reveal a mass (30 × 30 × 30 mm) (the location of the tumor is circled in red): T2 (A) hyperintense signal and T1 (B) hypointense signal in the right temporal lobe, adjacent brain tissue edema, midline shift, and compression of the right lateral ventricle. The contrast-enhanced sequence shows uniform ring enhancement (C). Postoperative cranial contrast-enhanced MRI axial images (D–F) show a large, patchy, mixed high signal intensity on T2 (D), surrounded by a few areas of low signal intensity. T1 (E) shows low signal intensity and a few scattered areas of high signal intensity. No obvious abnormal enhancement focus is observed on the post-contrast images (F).

The postoperative pathology report indicated clear cell carcinoma with sarcomatous changes, characterized by grey-white to grey-red nodules measuring 6 × 5 × 4 cm, with extensive necrosis, and was classified as grade 4 according to the WHO/ISUP system (Fig. 3B).

Intravascular tumour emboli (positive), perineural invasion (positive), and the ureteral margin (negative). The patient was discharged following an uneventful recovery. However, the administration of timely postoperative adjuvant therapy was delayed due to the patient's economic limitations and negative attitude. On April 7, 2021, the patient returned to our hospital for a follow-up examination. Brain MRI (enhanced +DWI, 1.5T) revealed a mass in the left frontal lobe and basal ganglia (Fig. 4A–C). Based on the patient's medical history, a recurrence of brain metastasis was suspected. Consequently, the patient received stereotactic body radiotherapy in the Department of Radiotherapy on April 9, 2021, with a 95% prescription target volume (PTV) dose of 3200 cGy in four fractions. In addition, the patient received a certain amount of financial assistance from his friends during this period. Then the patient agreed to proceed with systemic therapy. A regimen of pazopanib 400 mg to be taken orally twice daily was prescribed.

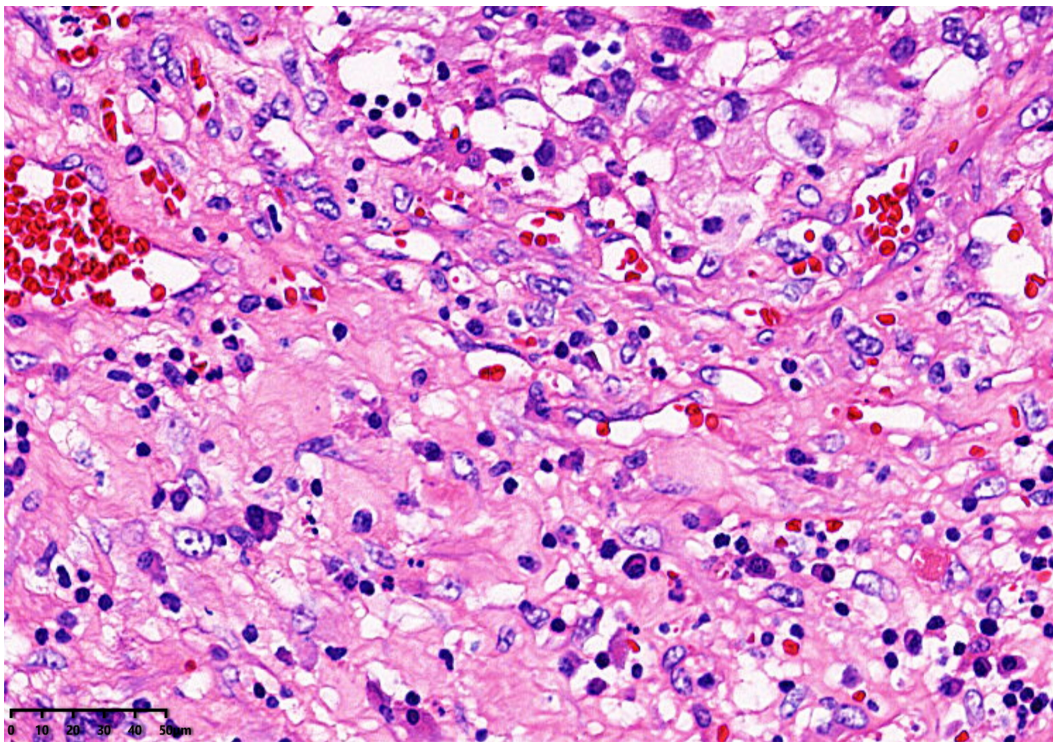

Fig. 2. The hematoxylin-eosin (HE: 400×) staining of brain tissue shows that there is a large amount of glycogen and lipid substances in the cytoplasm, making it appear transparent. Acidophilic granules can be seen in the cytoplasm. The cells are arranged in solid nests, some in tubular, glandular, or papillary arrangements. The interstitium contains abundant capillaries.

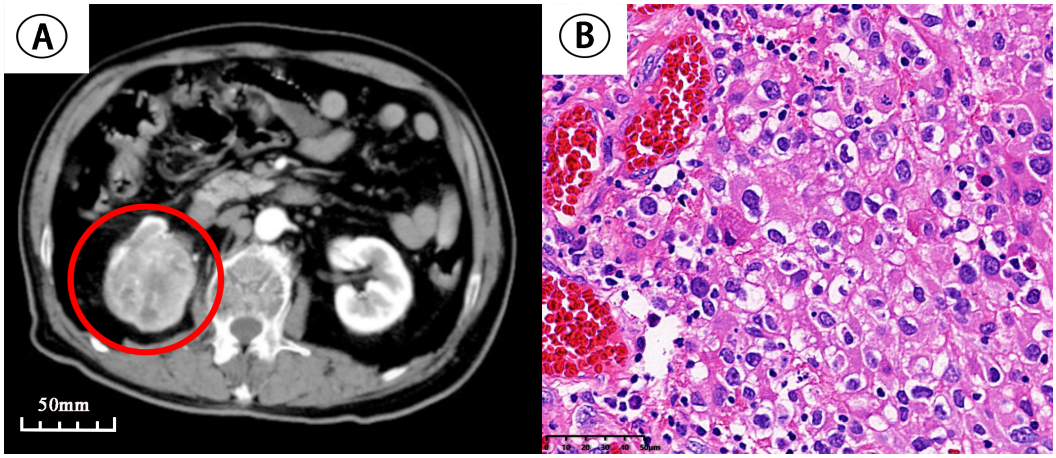

Fig. 3. Preoperative abdominal enhanced Computed tomography (CT) revealed a right renal tumour (60 × 50 × 40 mm) (A). The location of the tumour is circled in red. The kidney tissue (B, HE×400) shows that there is a large amount of glycogen and lipid substances in the cytoplasm, making it appear transparent. Acidophilic granules can be seen in the cytoplasm. The cells are arranged in solid nests, some in tubular, glandular, or papillary arrangements. The interstitium contains abundant capillaries.

On August 2, 2023, the patient visited our facility for a subsequent follow-up. Cranial CT imaging indicated a hypodense area in the left frontal lobe with a decrease in edema since the initiation of treatment. The ventricular system was

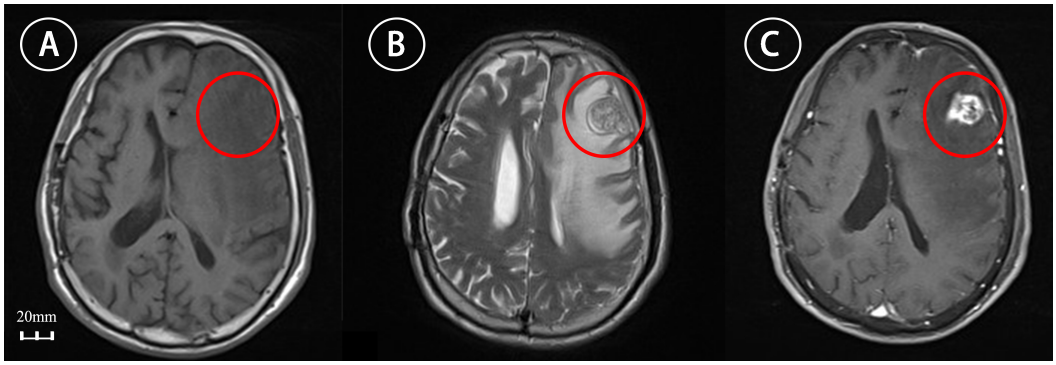

Fig. 4. The cranial MRI with contrast enhancement at 7 months postoperatively revealed the presence of a tumour (28 × 21 mm) in the left frontal lobe, which appeared to have slightly longer T1 (A) and T2 (B) signals. The tumour showed heterogeneous enhancement after the administration of contrast (the location of the tumor is circled in red) (C).

unremarkable, exhibiting no evidence of compression (Fig. 5A–C). The abdominal contrast-enhanced CT scan showed no apparent signs of tumour relapse (Fig. 5D).

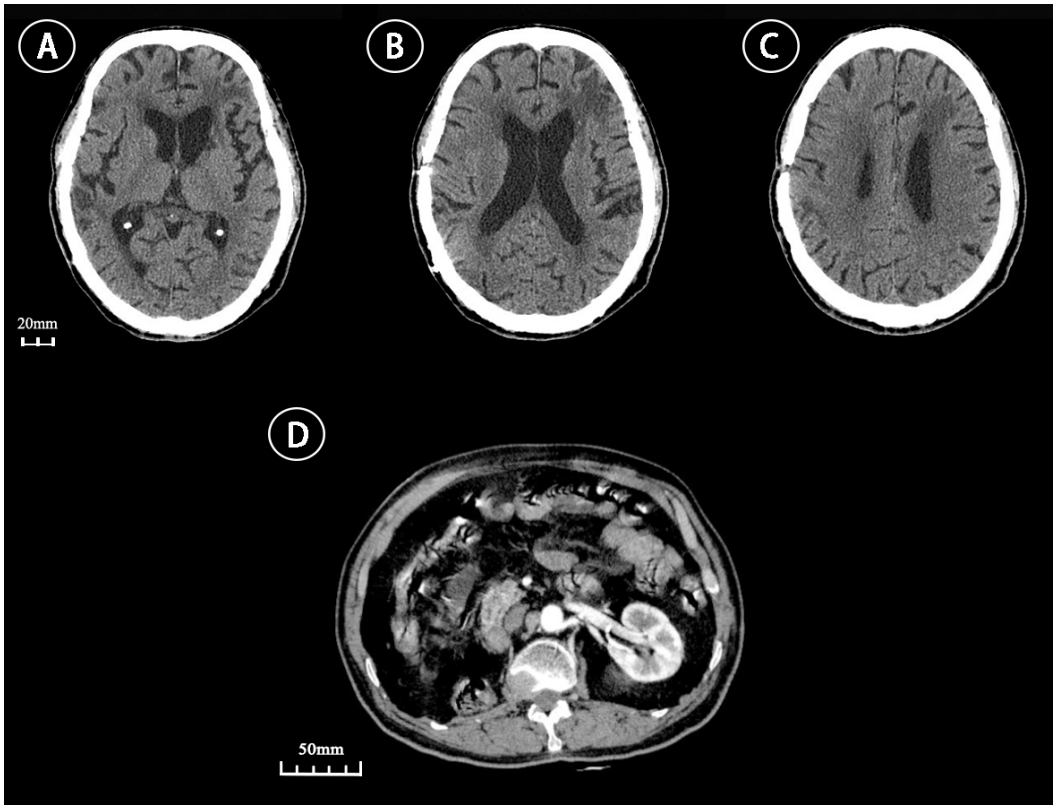

Fig. 5. The most recent cranial CT images (A–C) showed a low-density shadow in the left frontal lobe, with improved edema compared to before treatment. The structure appeared centred, and there was no apparent compression of the ventricular system. There was no significant evidence of tumour recurrence. Abdominal enhanced CT showed no obvious signs of tumour recurrence (D).

Discussion

Currently, there is a lack of conclusive evidence that can help determine the most effective treatment for patients with mRCC with sarcomatoid degeneration who also have involvement of the central nervous system (Motzer et al, 2019, 2018; Parmar and Chan, 2020). This poses a considerable challenge for both healthcare professionals and researchers, given that mRCC is inherently a complex disease to manage, with CNS involvement and sarcomatoid degeneration introducing additional layers of complexity. Currently, many first-line phase 3 studies related to systemic supportive therapies exclude patients with CNS involvement. For instance, the CheckMate 214 trial explored the combination therapy of nivolumab plus ipilimumab versus sunitinib, which excluded all patients with CNS metastases. Consequently, there is a significant deficiency in the efficacy assessment of systemic supportive therapies for this subgroup. However, for the behaviour of later treatment lines, especially in cases with compromised CNS, there is only the GETUG-AFU 26 NIVOREN study. The GETUG-AFU 26 NIVOREN study emphasizes the importance of local therapy before systemic therapy (Flippot et al, 2019). This underscores the potential benefits of a combined approach in enhancing patient outcomes. Additional studies have also indicated that patients with resected metastases experience significantly prolonged median overall survival (OS) compared to those with untreated metastases (median OS: 40.75 months vs. 14.8 months) (Alt et al, 2011; Kwak et al, 2007).

Nephrectomy refers to the surgical procedure of removing the entirety or a segment of the kidney. The objective of CN is to alleviate the tumour load for patients with confirmed metastatic illness. CN is commonly integrated with systemic anticancer therapy. The systemic therapy can be initiated before the operation or deferred until radiological signs of disease progression (Dahm et al, 2024). However, the role of CN remains a subject of debate. The CARMENA trial has concluded that CN is not indicated for patients with intermediate- or high-risk mRCC. The SURTIME trial showed no difference in the progression-free rate between deferred and upfront CN (43% vs. 42%, respectively; $p = 0.61$) (Bex et al, 2019). The OS hazard ratio (HR) of deferred versus immediate CN was 0.57 (95% confidence interval, 0.35–0.94), with a median OS of 32.4 versus 15.0 months for upfront and deferred CN, respectively (Bex et al, 2019).

Indeed, the current challenge encompasses rare histological subtypes such as sRCC, for which robust study data are lacking, particularly regarding the optimal treatment for sRCC patients with CNS involvement. Given this rare pathological subtype, clinicians must contemplate the following questions: Does CN still serve to prolong patient survival? Do patients still benefit from targeted therapy or immunotherapy in terms of survival? If a patient undergoes CN, which treatment sequence should surgeons select: upfront or deferred CN? A report from the Memorial Sloan Kettering Cancer Center indicates that patients with sRCC accompanied by distant metastasis should undergo CN prior to systemic therapy (Blum et al, 2020). Compared to systemic therapy alone, upfront CN has significantly improved survival rates. These findings underscored the importance of carefully con-

sidering the potential benefits and risks of CN in the context of individual patient characteristics and disease profiles, and it contributes to the ongoing discussion regarding the optimal management strategy for sRCC patients (Méjean et al, 2018). Additionally, the expression of PD-1 and PD-L1 has been investigated in sRCC, further highlighting the complexity and the need for tailored therapeutic strategies in this rare subtype (Joseph et al, 2015).

Significant survival benefits were notably observed in patients who received CN plus systemic therapy, with CN emerging as an independent predictor of survival after controlling for diverse patient and tumour characteristics, which highlights the necessity for further investigation into the role of CN in conjunction with systemic therapies to determine the best treatment sequence and regimen for patients with BrM from sRCC. This encompasses symptom management, such as alleviating pain or fatigue related to sRCC or its therapeutic side effects, alongside offering emotional support during an undeniably demanding period (Donskov et al, 2020). By adopting a patient-centred approach (Sugiyama et al, 2024), healthcare providers can optimize therapeutic outcomes and improve the quality of life for individuals grappling with the complexities of sRCC and CNS involvement.

Conclusion

Approximately 60–80% of patients of sRCC present with metastatic disease. In these patients, CN prior to systemic treatment may improve survival, and large collaborative efforts are needed to improve our understanding of sRCC.

Learning Points

- Patients with resected metastases experience significantly prolonged median OS compared to those with untreated metastases.
- In contrast to the common mRCC subtypes, sRCC with BrM may derive benefits from immediate cytoreductive surgery.
- Given the high malignancy grade of sRCC, adjuvant systemic therapy is imperative to prevent rapid recurrence.
- Immunotherapies targeting the PD-1/PD-L1 pathway could be a viable option.
- When financial circumstances permit, genomic testing might offer valuable information to clinicians for informed decision-making.

Availability of Data and Materials

The data and materials can be achieved by contacting the corresponding author.

Author Contributions

MX, HYS, JWJ and ZWC had provided conception and design. YLC, YH and JWZ had collected and evaluated data. QT, ZKX and LNZ had provided data analysis and interpretation. QT and ZKX drafted and wrote the manuscript. All

authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Affiliated Jinhua Hospital, Zhejiang University School of Medicine (No. 2023-119). This study was conducted in full accordance with the Declaration of Helsinki, having obtained ethical approval and informed consent from the patient.

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Conflict of Interest

The authors declare no conflict of interest.

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