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Research progress on advanced renal cell carcinoma

Xin-da Song[1], Yi-nong Tian[2], Hao Li[3], Bin Liu[4], Ai-li Zhang[4] and Yang Hong[5]

Abstract

Renal cell carcinoma (RCC) is a malignant tumor and the third most common urinary disease. It was estimated that RCC affected over 350,000 individuals in 2013, and there are nearly 140,000 deaths annually due to this disease. The initial masses in RCC patients are mostly confined to a single organ. However, due to the metastatic spread of cancer cells through the circulatory system, more than 30% of RCC patients relapse after surgery. The appearance of distant metastases often means that patients enter the advanced stage of cancer with low quality of life and a short expected survival time. This review aims to describe the extant research on advanced RCC, including its pathophysiology, heterogeneity, diagnosis, treatment, and prospects. We try to highlight the most suitable means of treating advanced RCC patients, focusing on comprehensive personalized treatments.

Keywords

Renal cell carcinoma, metastatic, pathophysiology, heterogeneity, diagnosis, treatment

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[1]Department of Urinary Surgery, Graduate School of Peking Union Medical College, Beijing Hospital, National Center of Gerontology, Beijing, China
[2]Department of Urinary Surgery, Xinle City Hospital, Shijiazhuang, Hebei Province, China
[3]Department of Oncology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China
[4]Department of Urinary Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, P.R. China
[5]Department of Clinical Pharmacology Research, Hebei Medical University, Shijiazhuang, P.R. China

Xin-da Song and Yi-nong Tian contributed to the paper equally.

Bin Liu and Ai-li Zhang contributed to the paper equally.

Corresponding author:
Bin Liu, Department of Urinary Surgery, The Fourth Hospital of Hebei Medical University, No. 12 Jiankang Road, 050000, P.R. China.
Email: liubinsy123@163.com

Introduction

Renal cell carcinoma (RCC) is a common malignancy of the urinary system, behind bladder and prostate cancer in terms of occurrence, accounting for 4.18% of all adult malignancies and 21.82% of urinary malignancies.[1] The incidence of RCC is increasing annually.[2] Additionally, approximately 30% of RCC patients have distant metastases upon initial diagnosis, and approximately 40% of patients with localized RCC have distant metastases after surgery.[3] Advanced renal cell carcinoma (aRCC) has a particularly poor prognosis, with an average 5-year survival rate of 8%, compared with an overall 5-year survival rate of 74% for all RCCs.[4] Recently, the diagnosis and treatment options for aRCC have gradually increased. Higher diagnosis rates and increased progression-free survival times have improved clinical results and expanded aRCC treatment methods. This review aims to describe the research progress into aRCC since 2007, including in its pathophysiology, heterogeneity, diagnosis, and treatment; finally, we evaluate the future prospects for aRCC. An extensive search in the PubMed and Web of Science databases was performed using the keywords: *renal cell carcinoma*, *pathophysiology*, *heterogeneity*, *diagnosis*, and *treatment*.

Pathophysiology

Owing to genetic and biomolecular changes, RCC has a variety of histological subtypes. Clear cell carcinoma, papillary cell adenocarcinoma (types I and II), and chromophobe cell carcinoma are the three most common malignant tumors of the kidney,[5] accounting for approximately 85% to 90% of cases. Rarer are papillary adenoma, multilocular cystic clear cell carcinoma, mixed eosinophilic chromophobe cell carcinoma, renal myeloid carcinoma, and spindle cell carcinoma.[6] The occurrence of RCC has two modes, sporadic and hereditary, which are generally related to changes in the short arm of chromosome 3.[7] There is also a relationship between polygene mutation and RCC.[7] Mutations in the tumor suppressor gene von Hippel–Lindau (VHL) can be found in more than 80% of clear-cell renal carcinoma (ccRCC) subtypes. The occurrence of ccRCC may be related to inactivation or overexpression of VHL. The discovery of the signaling pathway that VHL is involved in has laid a deep foundation for molecular targeted therapy for metastatic renal cell carcinoma (mRCC). Gene sequencing studies have identified other driver genes that are involved in the pathogenesis of RCC, including BRM1, BAP1, SETD2, TCEB1, and KDM5C.[8–10]

Heterogeneity

Heterogeneity is a characteristic of malignant tumors, resulting in different tumor growth rates, invasion abilities, drug sensitivities, and prognoses. The nucleotide excision repair, mismatch repair, and telomere maintenance pathways are the main causes of the genetic heterogeneity observed in tumors.[11] Analyses of tumor genetics in RCC by parallel sequencing not only explained the pathogenesis of RCC but also revealed the widespread existence of tumor heterogeneity. Ball et al.[12] found that high-grade tumors often contain low-grade components, indicating that diagnoses based on pathological puncture biopsies may underestimate tumor grade and affect follow-up treatment. Therefore, tumor heterogeneity may be the primary factor hindering the successful treatment of aRCC.

Diagnosis

Clinical manifestations

RCC often occurs incidentally because of a clinically silent disease, so only 30% of

RCC patients are diagnosed in an early stage. Biological activators of multiple hormones or cytokine analogues that are produced in all stages of RCC are important factors that lead to paraneoplastic syndrome, which manifests as hypertension, anemia, weight loss, fever, polycythemia, and neuromuscular disease.[13] RCC may alter the results of laboratory blood tests. Abdominal masses, new varicoceles, and edema of the lower limbs often indicate retroperitoneal masses. Some patients may have bone pain, coughing, hemoptysis, and other metastatic symptoms.

Imaging examinations

The main purpose of imaging examinations is to more vividly describe tumor size, identify possible abdominal metastases, and clarify vascular conditions. Although abdominal ultrasound plays a significant role in the initial diagnosis of RCC, computed tomography (CT) and magnetic resonance imaging (MRI) scans have more accuracy and can be used to evaluate the efficacy of treatment for aRCC. Additionally, the emergence of new nuclear magnetic resonance techniques, such as MRI diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), will help clinicians better evaluate and describe tumor characteristics. Studies have shown that positron emission tomography (PET)-CT can be used to detect ccRCC. PET-CT can track carbonic anhydrase IX antigen-labeled antibodies, which are expressed in more than 90% of ccRCC cases, but not in normal kidneys.[14,15]

Puncture biopsy

The clinical role of renal tumor puncture biopsy technique is becoming increasingly important. Its utility was initially questioned because of safety and accuracy concerns, but given the progress in medical technologies spreading cancer cells through the puncture path is no longer a problem. For patients whose tumor characteristics cannot be determined by imaging or dynamic tumor monitoring, a puncture biopsy is feasible to clarify the nature of the tumor and provide important guidance for formulating a treatment plan.[16]

Treatment

For patients with early RCC, immunotherapy after surgical treatment (radical nephrectomy or partial nephrectomy) is the first choice. Radiofrequency ablation and cryoablation can be used to treat patients with a small RCCs.[17] The quality of life of RCC patients has been greatly improved by the increasing maturity of medical technologies and the development of targeted therapy. Treatments for mRCC have also entered a diversified and personalized era.

Surgical treatment

Surgery plays an important role in mRCC treatment. For patients with distant metastasis and significant symptoms, surgical resection of metastatic lesions can minimize pain, reduce the incidence of fracture, prevent further damage, and promote the recovery of related functions. Most notably, compared with other treatments, surgical resection can greatly reduce tumor load throughout the whole body, reduce the secretion of growth factors, enhance the body's anti-cancer ability, and improve patients' quality of life.[18]

Cytoreductive nephrectomy (CN). The National Comprehensive Cancer Network points out that CN can be performed before systemic treatment for mRCC patients who have good physical fitness, relatively normal physical indicators, and resectable primary tumors.[19] Studies have shown that CN

combined with interferon has a survival advantage over interferon treatment alone.[20,21] Therefore, in the field of immunotherapy, CN is the standard treatment for mRCC. Using the largest retrospective database of targeted therapy, Heng et al. found that CN effectively improved the overall survival rate of some patients. Patients undergoing CN must have no more than three adverse prognostic factors, including Karnofsky score greater than 80, thrombocytopenia, anemia, and hypercalcemia.[22] However, the role of CN in targeted therapy remains controversial. To date, there is no evidence that CN is beneficial in mRCC after targeted therapy.[18]

Renal artery chemoembolization. Renal artery chemoembolization was often used as a palliative conservative therapy to reduce tumor size and slow its growth by blocking the tumor's blood supply, but its long-term effects were poor. Renal artery chemoembolization is now primarily used to treat patients with severe hematuria and lower back pain. It is estimated that infusing chemotherapeutic drugs directly into the tumor tissue through a catheter has better outcomes than intravenous administration.[23]

Radiotherapy

The effect of radiotherapy on RCC remains controversial. The role of preoperative radiotherapy on mRCC and unresectable masses is still under evaluation. Retrospective studies have shown that preoperative radiotherapy has significant benefits for aRCC. However, a study from Rotterdam found that preoperative radiotherapy had no overall survival advantage over surgery.[24,25] Outcomes of radiotherapy after radical nephrectomy were evaluated in both prospective and retrospective studies. The latest stereotactic body radiotherapy (SBRT) technique uses multi-angle projection and focused beam technologies, which allow the targeting of specific tissues with a high dose of radiation without causing damage to normal tissues, meaning it can be applied to metastatic tumors that are relatively insensitive to radiotherapy. Radiation therapy therefore provides patients with a new option when they are inoperable and have no other treatment options.

Drug therapy

Immunotherapy. While the systemic treatment of mRCC had mostly relied on nonspecific cytokine immunotherapy, such as interferon-α (IFN-α) and interleukin-2 (IL-2), the effects were unsatisfactory. Large doses of IL-2 achieved lasting effects in no more than 10% of cases and caused serious side effects. Currently, only bevacizumab is allowed to be used as an immunomodulator in some mRCC patients.[26] Dendritic cells combined with cytokine-induced killer cells have also made some achievements as a treatment for aRCC. However, with the further development of anti-cancer immune modulators, the emergence of the nivolumab provides a new possibility for immunotherapy, as it can enhance the anti-tumor ability of the human body by effectively targeting the immunosuppression of tumor cells.[27] Additionally, other immune drugs such as T-cell receptor agonists and chimeric anti-meta receptor T-cells are new approaches to treating mRCC.[28]

Targeted therapy. Currently, seven targeted drugs have been approved by the U.S. Food and Drug Administration (FDA) and the EU Medical Administration to treat aRCC: sunitinib, sorafenib, axitinib, pazopanib, everolimus, bevacizumab, and temsirolimus. Among them, sunitinib and pazopanil are the first-line drugs for ccRCC, and temsirolimus has more advantages than interferon for non-clear cell carcinoma. The second-line drugs are mainly

tyrosine kinase inhibitors and mammalian target of rapamycin inhibitors. The main third-line drugs to choose from are sorafenib and everolimus.[29]

First-line treatment. Many first-line treatment options for mRCC can be used in patients with moderate or low risk factors. For patients with poor prognosis, everolimus has advantages over interferon and therefore can be used as a standard treatment for such patients, with pazopanil and sunitinib as alternatives.[30,31]

Sunitinib and pazopanil. Sunitinib is an orally administered pan-tyrosine kinase inhibitor, including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). In a clinical trial, patients in the sunitinib group had higher rates of objective response (31% vs. 6%) and longer progression-free survival (11 months vs. 5 months, hazard ratio [HR]: 0.42, 95% confidence interval [CI]: 0.32–0.54, $P < 0.001$), compared with those in the interleukin group, but its advantage in overall survival was uncertain (26.4 months vs. 21.8 months, HR: 0.821, 95% CI: 0.673–1.001, $P = 0.051$).[32,33] The adverse reactions associated with sunitinib were hypertension, fatigue, thrombocytopenia, diarrhea, and hand and foot syndrome. The standard dose of sunitinib was 50 mg orally once daily for 4 weeks, followed by 2 weeks without treatment.

Pazopanil is an orally administered second-generation inhibitor of tyrosine kinases, including VEGFR1, VEGFR2, VEGFR3, PDGFR-α, PDGFR-β, and c-KIT. Pazopanil can also be used as second-line therapy for patients who have received cytokine therapy.[34–38] In a phase III clinical trial, the pazopanil group significantly prolonged progression-free survival (9.2 months vs. 4.2 months, HR: 0.46, 95% CI: 0.34–0.62, $P < 0.0001$) and the overall response rate (30% vs. 3%, $P < 0.001$) compared with the placebo group. Similar to sunitinib, its advantage for overall survival was uncertain (22.9 months vs. 20.5 months, HR: 0.91, 95% CI: 0.71–1.16, $P = 0.224$).[39,40] The most common adverse reactions are diarrhea, fatigue, and hair fading, while severe liver injury occurred in more than 10% of patients, so patients with underlying diseases and/or poor health need to closely monitor their liver function during pazopanil treatment. In terms of side effects, pazopanil was more harmful to liver function, and sunitinib caused more severe fatigue, hand and foot syndrome, taste change, and thrombocytopenia.[40,41]

Bevacizumab combined with interleukin-α. Bevacizumab is a recombinant human IgG monoclonal antibody that inhibits vascular growth and tumor neovascularization through circulating VEGF-A. To compare the efficacy of bevacizumab combined with interferon-α versus interferon-α alone, 732 untreated mRCC patients were enrolled in the CALGB90206 study. There was no statistically significant difference in overall survival (18.3 months vs. 17.4 months, HR: 0.86, 95% CI: 0.73–1.01, $P = 0.069$).[42] Bevacizumab can cause side effects including fatigue, hypertension, albuminuria, and gastrointestinal perforation.[43]

Temsirolimus. Temsirolimus is a special mTOR inhibitor, which inhibits tumor angiogenesis by reducing the secretion of VEGF14. Temsirolimus is mainly used to treat aRCC patients with more than three adverse prognostic factors.[44] The most common side effects of temsirolimus are rash, edema, hyperglycemia, and hyperlipidemia. Compared with patients treated with interferon, only 7% of patients treated with temsirolimus stopped because of side effects. Temsirolimus can also be used to treat patients with non-clear cell carcinoma.

Second-line treatment. There are many second-line treatment options for mRCC at different levels of evidence and recommendations. Axitinib, everolimus, and sorafenib can be used in patients who have previously failed therapies targeted against vascular endothelial growth factor receptors. Patients who have received cytokine therapy for recurrence can choose axitinib, sorafenib, or pazopanil. Currently, researchers are not sure whether tyrosine kinase inhibitors or mTOR inhibitors are better as second-line therapy.

Everolimus. Everolimus is an oral mTOR inhibitor with the same targeting point as temsirolimus, which primarily inhibits tumor angiogenesis. In an international phase III clinical study (RECORD-1), patients who had received first-line treatment (sunitinib, sorafenib, or cytokines) were randomly assigned to the everolimus and placebo groups. The results showed that everolimus was superior to the placebo group in terms of median progression-free survival.[45] There was no difference in overall survival.[46] The main side effects of everolimus are stomatitis, rash, diarrhea, and non-infectious pneumonia. In 2009, everolimus was approved for mRCC patients who had previously failed a first-line tyrosine kinase inhibitor. In 2013, everolimus was recommended as a second-line drug for aRCC.

Sorafenib and axitinib. Sorafenib, the first targeted drug approved by the FDA for aRCC, is an oral small molecule polytyrosine kinase inhibitor that kills tumor or keeps tumors stable by inhibiting VEGFR.[47] A randomized phase III clinical study (TARGET) that included 903 aRCC patients who had failed standard treatment showed that sorafenib significantly prolonged progression-free survival compared with placebo and increased overall survival and partial response by 10% and 2%, respectively.[48] The most common adverse reactions to sorafenib are hand and foot syndrome, rash, high blood pressure, and gastrointestinal reactions. Approximately 9% of patients stop taking sorafenib because of side effects.

Axitinib is a highly selective and effective second generation multi-target tyrosine kinase inhibitor that destroys tumor angiogenesis by inhibiting VEGFR1-3, c-KIT, and PDGFR. It is mainly recommended for second-line treatment in aRCC patients who have failed to receive sunitinib or cytokine therapy. A phase III clinical study (AXIS) compared the efficacy of axitinib and sorafenib in aRCC. Patients with recurrence after first-line treatment were randomly divided into the axitinib and sorafenib groups. The results showed that the median progression-free survival was greater in the axitinib group (6.7 months vs. 4.7 months, HR: 0.665; 95% CI: 0.544–0.812, P 0.0001), with no significant difference in overall survival (15.2 months vs. 16.5 months, HR: 0.997; 95% CI: 0.782–1.27).[49] In fact, when sunitinib and sorafenib were used as first-line drugs, there was no significant difference in progression-free survival. The two groups were similar in terms of adverse reactions, but the axitinib group more commonly reported hypertension, fatigue, language disorders, and hypothyroidism than the sorafenib group.

Third-line treatment. Some aRCC patients still progress after receiving first- and second-line treatments, so maximizing their survival and improving their quality of life is a difficult problem. Owing to the lack of sufficient data from phase III clinical trials, we believe that patients in good health and with sufficient financial resources should receive third-line treatment. Although results from the GOLD trial did not prove that Dovitinib is more effective than sorafenib in treating patients with advanced refractory kidney cancer, it does

point to the efficacy and safety of sorafenib, indicating that sorafenib can be used as third-line treatment in patients who have received VEGFR and mTOR inhibitors.[50] In a subset analysis of the RECORD-1 study, patients who had received two types of TKI for recurrence were divided into everolimus and placebo groups and given the best supportive therapy at the same time. The results showed that the everolimus group had improved progression-free survival compared with the placebo group, suggesting that everolimus could play a role in third-line treatment.[51]

Conclusion and prospects

Thanks to in-depth studies of the biomolecular mechanisms of RCC and the emergence of a variety of treatment methods (surgery, radiotherapy, immunotherapy, and targeted therapy), we have made great progress in treating aRCC. Targeted therapy is currently the standard treatment for mRCC and can greatly reduce tumor load in the body and improve progression-free and overall survival. Additionally, the emergence of new drugs such as lenvatinib, capmatinib, erlotinib, and cediranib provides more options for aRCC patients. However, patients who are completely cured are a minority. We still face many challenges and doubts in this field, including how to determine the best order of drug use, how to reduce drug side effects, how to prolong drug activity, what are drug resistance mechanisms to targeted therapy, is it beneficial to combine multiple targeted drugs, and whether it is beneficial to use second-line drugs before disease progression. Solving these problems will help us further explore the biomolecular mechanisms of RCC and improve patient outcomes.

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ORCID iDs

Xin-da Song https://orcid.org/0000-0002-3223-9759
Bin Liu https://orcid.org/0000-0002-2951-9901

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