

Updates in the Systemic Therapy Options for Clear Cell and Non–Clear Cell Renal Cell Carcinoma

Presented by Philippe E. Spiess, MD, MS; Peter A.S. Johnstone, MD;
and Eric Jonasch, MD

ABSTRACT

At the NCCN 2023 Annual Conference, experts reviewed clinical data on established therapies for patients with metastatic renal cell carcinoma and discussed strategies to effectively manage both clear cell and non–clear cell tumor histologies in the setting of advanced stages. Depicted through 3 separate case studies, they strategized the selection of optimal first-line and subsequent-line therapies based on the individual case study and the tumor characteristics in each.

J Natl Compr Canc Netw 2023;21(5.5):1–4
doi: 10.6004/jnccn.2023.5020

Through the use of case studies, experts in renal cell carcinoma (RCC) explored the latest recommendations in the systemic treatment of patients with clear cell or non–clear cell disease at the NCCN 2023 Annual Conference. This discussion utilized the presentation of 3 case scenarios on locally advanced kidney cancer, oligometastatic papillary RCC, and disease progression after initial treatment.

Case 1: Locally Advanced Kidney Cancer

For the first case, on presentation, a 53-year-old female had no regional adenopathy or vascular invasion, and the incidentally detected bilateral renal masses caused no concern that it might be metastatic disease, began Philippe E. Spiess, MD, MS, Senior Member, Departments of GU Oncology and Tumor Biology; Assistant Chief of Surgical Services; and Medical Director, Moffitt Virtual Health, and Vice Chair of the NCCN Guidelines Panels for Bladder and Penile Cancers. Management of this case entailed several important questions regarding (1) metastatic workup, (2) consideration of pretreatment biopsy, and (3) role of genetic testing, he said.

This patient underwent a comprehensive blood panel, and results of the chest CT scan were normal; a renal scan showed differential renal function of approximately 50:50. Pretreatment biopsy was completed in interventional radiology and found to be consistent with clear cell RCC.

According to Dr. Spiess, there is an appreciation that genetic testing is critical in patients with kidney cancer, particularly for those aged <45 years. However, because of this patient's age, negative family history, and lack

of other clinical manifestations, genetic testing was not obtained.

Regarding the preoperative chest CT, an Italian study of >1,900 patients with renal masses showed evidence for when to justify this scan.¹ Patients in this study presented with a wide spectrum of localized disease (cT1–cT3), and all patients underwent chest CT as standard treatment over approximately 15 years. “Expected factors predicted having a positive chest CT: advanced clinical stage, nodal positivity, presence of symptoms, and platelet-to-hemoglobin ratio,” Dr. Spiess said.

Furthermore, the Larcher et al¹ study highlights that a chest CT should be obtained only in patients with higher-stage tumors, who are symptomatic, or who are displaying anemia or thrombocytopenia. For patients who do not fulfill any of these criteria, there is no role for chest CT.

Regarding image-guided renal biopsy, the literature has shown that it can play a role in patients with kidney cancer of the primary site, even in the localized setting when the underlying diagnosis is in question, including, but not exclusively, determining benign versus malignant histology, primary versus metastatic site, or whether the tumor histology or grade of the suspected renal tumor can have therapeutic implications.² A meta-analysis of 57 studies including >5,000 patients revealed that “not all biopsies are of similar diagnostic value,” noted Dr. Spiess. Core-needle biopsy versus fine-needle aspirations can be obtained, with core biopsies displaying higher sensitivity and specificity for detecting cancer. “So, if we’re going to get a tissue biopsy, we’ll often request a core biopsy, if at all possible,” he added.

In this patient presenting with bilateral large renal masses, clear cell histology, and no evidence of metastatic disease, optimal treatment should include surgery as the gold standard (preferably nephron-sparing surgery), with no neoadjuvant systemic therapy. Clinical trials with preoperative systemic therapy for RCC have limited value in decreasing tumor size, which only happens in a subset of patients and can be highly challenging to predict,³ said Dr. Spiess.

After a left complex open partial nephrectomy, postoperative pathology revealed pT2a clear cell RCC, with sarcomatoid features (10%) and negative surgical margins. The patient underwent a staged, right (subcostal) open partial nephrectomy 8 weeks later and has not experienced disease progression.

Most studies of adjuvant tyrosine kinase inhibitors (TKIs) for high-risk localized RCC with clear cell histology have been negative, but adjuvant immunotherapy has shown promise. Several negative studies of adjuvant immunotherapy reported at the 2022 ESMO Congress—IMmotion010, PROSPER RCC, and CheckMate 914 (ClinicalTrials.gov identifiers: NCT03024996, NCT03055013, NCT03138512, respectively)—used different selection criteria for high-risk disease, and some controversy still surrounds published findings. Researchers in this space are still searching for better biomarkers of risk to help determine which patients may benefit from immunotherapy, and are studying the potential roles of liquid biopsy and circulating-tumor DNA to identify early recurrence.

“I think it’s critical for these adjuvant trials to use consistent high-risk criteria to make sure we’re comparing apples to apples when we look at these trials,” Dr. Spiess said. However, he added, the patient in this case study fits the criteria for treatment with adjuvant immunotherapy, based on recent data from the phase III KEYNOTE-564 study.⁴ This trial demonstrated that adjuvant pembrolizumab improved disease-free survival in patients with high-risk localized RCC tumors after resection, including most notably in those with sarcomatoid features.

“Sarcomatoid is a risk factor for local, regional, and metastatic disease progression, so this patient will need to be kept on very stringent guidelines,” he said. “NCCN provides some really nice evidence-based recommendations related to this.”

Eric Jonasch, MD, Professor, Department of Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Center, and Vice Chair of the NCCN Guidelines Panel for Kidney Cancer, added that an objective and informed decision-making approach between the patient and treating team is crucial.

Case 2: Oligometastatic Papillary RCC

A 57-year-old, otherwise healthy female developed self-limited, gross hematuria. Her workup, including

abdominal imaging, revealed an exophytic, hypoattenuating right renal mass, measuring 8.3 cm in largest diameter. She underwent nephrectomy, and pathology revealed papillary histology.

A year later, 2 small left-sided pulmonary nodules were identified on surveillance imaging. Biopsy of the largest lesion revealed findings consistent with metastatic papillary RCC; there were no other signs of metastatic disease. Multidisciplinary team evaluation with medical oncology, thoracic surgery, and radiation oncology occurred, with several treatment options considered, including systemic therapy, surgery, and stereotactic body radiosurgery (SBRT) (Figure 1). Ultimately, the patient underwent SBRT.

“SBRT allows us to target areas with relatively few off-target side effects,” said Dr. Jonasch. “Being able to deliver this properly and in a reasonable manner has [necessitated] an evolution of the software, the tools, and the actual hardware.”

Peter A.S. Johnstone, MD, Vice Chair, Department of Radiation Oncology, and Professor, Oncologic Services, Moffitt Cancer Center, pointed out that radiation therapy did not have much of a role in RCC until approximately 15 years ago. “The location of the kidneys in the upper abdomen put them right next to some very important adjacent structures that are far more radiosensitive than kidney cancer,” he said. “With SBRT, we have a much better idea of where the tumor is, and we can even adapt on the fly if the tumor is moving.”

Following SBRT to the pulmonary lesions, active surveillance of the patient revealed several new pulmonary lesions 1 year later, as well as mediastinal lymphadenopathy; the patient remained oligometastatic.

For systemic therapy for non-clear cell RCC, preferred regimens in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer include cabozantinib and sunitinib. Other recommended regimens include doublets containing lenvatinib/everolimus or nivolumab/cabozantinib, as well as single-agent nivolumab or pembrolizumab.⁵

According to Dr. Jonasch, the rationale for using immunotherapy in this setting was borne of the KEYNOTE-427 study, which evaluated pembrolizumab monotherapy in clear cell and non-clear cell RCC. Results from this study demonstrated that pembrolizumab monotherapy showed some use in regard to objective response rates in the non-clear cell arm.⁶

In summary, a subset of patients with oligometastatic disease will show a small number of lesions with slow growth kinetics. “Observation or active surveillance—I’d call it active observation—up-front is reasonable for these individuals,” Dr. Jonasch said. “But oligometastatic disease also lends itself to things like surgical intervention or SBRT.”

From a systemic therapy perspective, the heterogeneous nature of this patient population (eg, papillary,

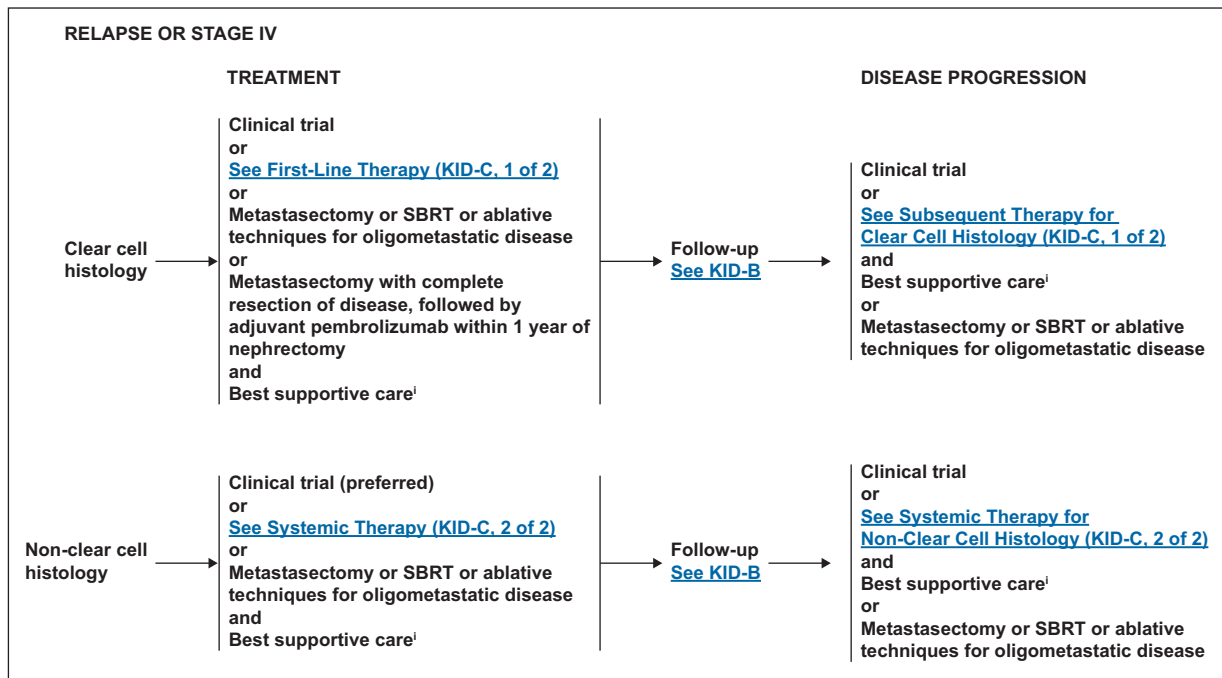


Figure 1. Approach to oligometastatic renal cell carcinoma. From the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer, Version 4.2023 [KID-3].

©2023 National Comprehensive Cancer Network, Inc. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN®. To view the most recent and complete version of these NCCN Guidelines, go to www.nccn.org.

chromophobe, medullary) results in a lower level of evidence for efficacy of these treatments, and further work is needed to refine the categorization of this patient population and to improve treatments. “In 2023, we still apply fairly similar agents [to this patient population] as we apply to clear cell RCC, while we’re working on getting better approaches for them,” said Dr. Jonasch.

Case 3: Disease Progression After Frontline Therapy

A 63-year-old male presented with weight loss and fatigue. Workup revealed an exophytic, enhancing right renal mass, mediastinal adenopathy, and multifocal bilateral pulmonary nodules. Biopsy of the primary tumor revealed clear cell histology. The patient was started on ipilimumab + nivolumab and experienced a slight regression in pulmonary and mediastinal lesions. “This is an intermediate-risk patient without a threatening disease burden,” noted Dr. Jonasch. “So, this is an ideal case for ipilimumab + nivolumab.” Approximately 1 year after beginning therapy, the patient demonstrated disease progression in lung lesions and developed a new liver lesion. Brain imaging was performed and revealed 4 new brain lesions.

For individuals with metastatic RCC, the NCCN Guidelines recommend an MRI brain scan at baseline.⁵ “You can pick up occult disease at that point and treat it more effectively,” he said. “Performing a baseline MRI,

and then periodic MRIs every year or so, makes sense from a standpoint of catching the disease early enough to intervene in a less morbid manner.” Dr. Jonasch added that the incidence of brain metastases in this patient population is not uncommon, occurring in 10% to 20% of individuals with advanced RCC.⁷ “Median survival used to be in the low single-digits,” Dr. Jonasch reported. “Now, especially in patients with oligometastatic brain metastases, these individuals can live for years if properly managed.”

Many brain metastases can be treated with stereotactic radiosurgery, determinants of which include size, location, and symptoms. There is some consensus that for those with <10 lesions (none being symptomatic or much larger than 1 cm), treatment with stereotactic radiosurgery is a reasonable first step, although treatment decisions beyond that are more controversial. Multidisciplinary input is always critical.

Dr. Johnstone reiterated that new technology with SBRT allows for easy targeting of brain lesions with minimal margins: 1 mm in most cases and 0 mm in the brain stem. It also allows for targeting of multiple lesions with a single isocenter. If lesions advance quickly (<3 months) or if the patient has upwards of 15 new lesions, treatment should move toward either whole-brain radiotherapy or hippocampal avoidance with whole-brain radiation. “You should monitor the patient every 3 months or so with MRI and decide at that point,” he said.

According to Dr. Jonasch, the NCCN Kidney Cancer Panel was in a quandary in 2023. “For the most part, the subsequent-line registrational studies published in the past 10 years have been on individuals who experienced disease progression on frontline TKIs; at this point, we have no studies with a background of patients who have experienced disease progression on a contemporary doublet, whether it be immunotherapy/immunotherapy, or immunotherapy/TKI,” he explained. “We want that to change.”

For subsequent therapy for patients with clear cell RCC, the NCCN Guidelines offer no current preferred regimens. For patients with immunotherapy-naïve disease, immunotherapy or a TKI doublet after a frontline TKI is reasonable, based on anecdotal evidence and smaller studies.⁵

For patients who have received prior immunotherapy, the treatment choice becomes more challenging. “It’s still evolving, but the main point is to look at the morbidities and previous treatments and choose a regimen based on those factors,” he said. “Most of the time, you are going to see some kind of benefit from one of these regimens in the subsequent-line setting.”

In this case study, the patient was treated with stereotactic radiosurgery. He tolerated treatment well and was started on cabozantinib at 60 mg and was dose-reduced to 40 mg after 1 month because of diarrhea, hand-foot syndrome, and fatigue. Restaging scans demonstrated stable brain lesions and partial response of his systemic disease.

“In terms of subsequent-line therapy for RCC, we are in a bit of a data-free zone because of the rapid evolution of frontline therapy,” Dr. Jonasch concluded. “Significant effort needs to be directed toward better defining treatment options for patients progressing on or refractory to frontline agents.”

Disclosures: Dr. Jonasch has disclosed receiving consulting fees from Aravive, Inc., AVEO Pharmaceuticals, Inc., Calithera Biosciences, Eisai Inc., Exelixis Inc., Ipsen, Merck & Co., Inc., NiKang Therapeutics, Inc., Novartis Pharmaceuticals Corporation, and Takeda Pharmaceuticals North America, Inc.; and receiving grant/research support from Arrowhead Pharmaceuticals, Merck & Co., Inc., and NiKang Therapeutics, Inc. The remaining presenters have disclosed no relevant financial relationships.

Correspondence: Eric Jonasch, MD, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1374, Houston, TX 77030. Email: ejonasch@mdanderson.org

References

1. Larcher A, Dell'Oglio P, Fossati N, et al. When to perform preoperative chest computed tomography for renal cancer staging. *BJU Int* 2017;120:490–496.
2. Marconi L, Dabestani S, Lam TB, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. *Eur Urol* 2016;69:660–673.
3. Borregales LD, Adibi M, Thomas AZ, et al. The role of neoadjuvant therapy in the management of locally advanced renal cell carcinoma. *Ther Adv Urol* 2016;8:130–141.
4. Powles T, Tomczak P, Park SH, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022;23:1133–1144.
5. Motzer RJ, Jonasch E, Agarwal N, et al. NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. Version 4.2023. Accessed May 4, 2023. Available at: <https://www.nccn.org>
6. McDermott DF, Lee JL, Bjarnason GA, et al. Open-label, single-arm phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced clear cell renal cell carcinoma. *J Clin Oncol* 2021;39:1020–1028.
7. Hasanov E, Yeboa DN, Tucker MD, et al. An interdisciplinary consensus on the management of brain metastases in patients with renal cell carcinoma. *CA Cancer J Clin* 2022;72:454–489.