Overview of the treatment of renal cell carcinoma

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Aug 2022. | **This topic last updated:** Sep 14, 2022.

INTRODUCTION

Renal cell carcinomas (RCCs), which originate within the renal cortex, constitute 80 to 85 percent of primary renal neoplasms. Urothelial (transitional cell) carcinomas of the renal pelvis account for approximately 8 percent of kidney tumors, and other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, are rare. Nephroblastoma (Wilms tumor) is common in children (5 to 6 percent of pediatric malignancies). (See "Epidemiology, pathology, and pathogenesis of renal cell carcinoma" and "Malignancies of the renal pelvis and ureter".)

An overview of the approach to treatment is presented here; more detailed discussions of specific aspects of treatment are discussed in other topics, as noted below.

GENERAL APPROACH

The initial approach to a patient with presumed RCC needs to consider the extent of disease, as well as the patient's age and comorbidity (algorithm 1).

RCC can be classified as:

- **Localized disease** – This includes stage I, II, and III (table 1). (See 'Localized renal cell carcinoma' below.)
- **Advanced disease** – This includes tumor invading beyond Gerota's fascia or extending into the ipsilateral adrenal gland (T4) and metastatic disease (M1). Either of these findings

constitutes stage IV RCC. (See 'Advanced renal cell carcinoma' below.)

An overview of the approach to treatment is presented here; more detailed discussions of specific aspects of treatment are discussed in other topics, as noted below.

LOCALIZED RENAL CELL CARCINOMA

When patients with RCC present with localized disease, definitive therapy can often be curative.

Definitive treatment — Surgery is curative in the majority of patients with RCC who do not have metastases. Surgery is therefore the preferred treatment for patients with stages I, II, and III disease.

Treatment may require a radical nephrectomy, although a partial nephrectomy to preserve renal parenchyma is preferred for appropriately selected patients. The choice of surgical procedure depends upon the extent of disease, as well as patient-specific factors such as age and comorbidity. Surgery may be carried out through a conventional approach or by a minimally invasive approach such as laparoscopy. (See "Definitive surgical management of renal cell carcinoma".)

In carefully selected patients who present with a resectable primary tumor and a concurrent single metastasis, surgical resection of the metastasis, in conjunction with radical nephrectomy, may be curative. (See "Role of surgery in patients with metastatic renal cell carcinoma".)

Other ablative procedures (eg, cryotherapy, radiofrequency ablation [RFA]) may be an important alternative for patients with relatively small renal masses who are not surgical candidates. (See "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Multiple primary renal cell carcinomas — Bilateral RCCs are more common among patients with inherited conditions (eg, von Hippel-Lindau disease, tuberous sclerosis, papillary RCC) and occasionally are seen in those with sporadic tumors. In these situations, we recommend surgery. Proper management should include sparing as much renal parenchyma as possible during the initial therapy and monitoring for the development of additional RCCs. (See "Hereditary kidney cancer syndromes" and "Definitive surgical management of renal cell carcinoma", section on 'Partial nephrectomy'.)

Active surveillance in nonsurgical candidates — Older adult patients and those with significant comorbidity may not be candidates for surgical resection [1]. Although nonsurgical procedures (eg, cryoablation, RFA) may be useful, most small tumors grow slowly and do not become symptomatic or metastasize [2-6]. In addition, up to 40 percent of tumors smaller than

1 cm in size may be benign [7]. In this setting, observation with periodic reevaluation is a reasonable option. (See "Definitive surgical management of renal cell carcinoma", section on 'Active surveillance' and "Diagnostic approach, differential diagnosis, and management of a small renal mass".)

Adjuvant therapy for locoregional disease

Approach to adjuvant therapy — Our approach to adjuvant therapy in patients with locoregionally advanced clear cell renal carcinoma treated with nephrectomy is as follows:

- For patients who meet pathologic criteria for intermediate-high or high risk of disease recurrence, particularly those with a higher estimated risk of recurrence at five years (≥30 percent), we suggest one year of adjuvant pembrolizumab rather than observation, as this approach improved disease-free survival (DFS) and was well tolerated in a phase III trial [8,9]. The risk of recurrence can be calculated using either the University of California, Los Angeles (UCLA) Integrated Staging System (UISS) [10,11] or the Mayo Clinic Leibovich prognostic model [12,13]. (See 'Pembrolizumab' below and "Prognostic factors in patients with renal cell carcinoma", section on 'Clinical factors' and "Definitive surgical management of renal cell carcinoma", section on 'Prognosis'.)

  However, observation remains a reasonable alternative in this patient population, as further follow-up data are necessary to confirm a long-term OS benefit with adjuvant pembrolizumab and distinguish whether this agent improves DFS because it truly prevents relapse (ie, cures disease) or simply delays relapse. (See 'Pembrolizumab' below.)

- We offer active surveillance after nephrectomy to patients who are at lower risk for disease recurrence (<30 percent) [10,12] or do not meet pathologic criteria for intermediate-high or high risk of disease recurrence. (See 'Pembrolizumab' below.)

- We do not suggest the use of adjuvant sunitinib. Although adjuvant sunitinib improved DFS in select patients with high-risk disease in one clinical trial, it confers no clear overall survival (OS) benefit and increases toxicity. (See 'Sunitinib' below.)

- For completely resected oligometastatic disease, the role of adjuvant therapy is discussed below. (See 'Adjuvant therapy after metastasectomy' below.)

Pembrolizumab — In a double-blind, placebo-controlled phase III trial (KEYNOTE-564), 994 patients with histologically confirmed clear cell renal carcinoma treated with nephrectomy were randomly assigned to either pembrolizumab 200 mg every three weeks for up to one year (17

cycles) or placebo [8,9]. Patients initiated adjuvant therapy within 12 weeks of undergoing nephrectomy.

Risk for disease recurrence was defined as follows:

- **Intermediate-high risk** – pT2 tumors with grade 4 or sarcomatoid features; or pT3, any grade, and node negative tumors.
- **High risk** – pT4, any grade, node negative tumors; or any pT, any grade, node positive tumors.
- **Metastatic, no evidence of disease** – resection of all oligometastatic sites (M1) with no evidence of disease (NED) within one year of nephrectomy.

At median follow-up of 30 months, pembrolizumab improved DFS compared with placebo in the entire study population (30-month DFS 75 versus 66 percent, HR 0.63, 95% CI 0.50-0.80) and those with intermediate-high tumors (median not reached for both treatments, HR 0.68, 95% CI 0.52-0.89). For the subgroup of 76 patients with high-risk tumors, median DFS for pembrolizumab versus placebo were 22 and 11 months, respectively (HR 0.60, 95% CI 0.33-1.10) [8,9].

Adjuvant pembrolizumab also demonstrated higher OS in the entire study population (30-month OS 96 versus 91 percent, HR 0.52, 95% CI 0.31-0.86); however, OS differences are not statistically significant, and these results are immature pending longer follow-up. Grade ≥3 toxicity rates were higher with pembrolizumab than placebo (32 versus 18 percent), with no new toxicity profiles noted.

Based on these data, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) granted regulatory approval for pembrolizumab for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or with following nephrectomy and resection of metastatic lesions [14].

Further data on the efficacy of adjuvant pembrolizumab in patients who underwent metastasectomy are discussed below. (See 'Adjuvant therapy after metastasectomy' below.)

Sunitinib — Although sunitinib is approved by the US Food and Drug Administration (FDA) for adjuvant therapy based on improved DFS in patients with high-risk disease, it has not shown an OS benefit in any subgroup and is associated with toxicities. Clinical trials evaluating other targeted agents, such as sunitinib and sorafenib (ASSURE and SORCE), pazopanib (PROTECT), and axitinib (ATLAS), have also failed to demonstrate a recurrence-free or OS benefit in the adjuvant setting [15-20]. As such, we do not suggest adjuvant use of any of these agents for

RCC. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Preferred VEGFR inhibitors'.)

Further details of these trials are discussed below.

- In the phase III ASSURE trial, 1943 patients with completely resected intermediate-, high-, or very high-risk RCC were randomly assigned to sunitinib, sorafenib, or placebo for up to one year [16]. After a median follow-up of 5.8 years, results demonstrated the following:
  - Similar DFS results for each of the treatment arms (for sunitinib versus placebo, median 5.8 versus 6.6 years, hazard ratio [HR] 1.02, 97.5% CI 0.85-1.23; for sorafenib versus placebo, median 6.1 versus 6.6 years, HR 0.97, 97.5% CI 0.8-1.17).
  - Similar OS for each of the treatment arms (for sunitinib versus placebo, HR 1.17, 97.5% CI 0.9-1.52; for sorafenib versus placebo, HR 0.98, 97.5% CI 0.75-1.28). Older women also experienced increased mortality in a post-hoc subgroup analysis [17].
  - Higher grade 3 or greater toxicities with both sunitinib and sorafenib compared with placebo (hypertension 17 and 16 versus 4 percent, hand-foot syndrome 15 and 33 versus 1 percent, rash 2 and 15 versus <1 percent, and fatigue 18 and 7 versus 3 percent).
- In the phase III S-TRAC trial, 615 patients with high-risk clear cell RCC were randomly assigned to sunitinib or placebo [15]. At a median follow-up of 5.4 years, DFS (the primary endpoint) was significantly increased in those receiving sunitinib (median 6.8 versus 5.6 years, 59.3 versus 51.3 percent five-year DFS, HR 0.76, 95% CI 0.59-0.95). OS data were immature, although the number of deaths was equal among the treatment arms. Toxicity was increased significantly with sunitinib compared with placebo, including palmar-plantar erythrodysesthesia and hypertension.

Other agents — The following agents either have failed to demonstrate a clear clinical benefit in the adjuvant setting or are under investigation in clinical trials:

- **Immunotherapy** – In phase III trials, nivolumab plus ipilimumab [21] and atezolizumab [22] failed to improve DFS in the adjuvant setting, and nivolumab failed to improve recurrence-free survival in the perioperative setting [23].

  Other clinical trials are comparing alternative immunotherapy agents with placebo (see "Systemic therapy of advanced clear cell renal carcinoma", section on 'Selection of initial therapy'):

- Durvalumab with or without tremelimumab (NCT03288532)

- **Pazopanib** – In a phase III trial (PROTECT) of 1538 patients with completely resected RCC, pazopanib (at a lower dose of 600 mg daily) did not improve DFS or OS compared with placebo [18,24]. However, DFS was improved for those assigned to a higher (800 mg daily) dosing (66 versus 56 percent, HR 0.66, 95% CI 0.49-0.9).

- **Axitinib** – In a phase III randomized, double-blind, placebo-controlled trial (ATLAS) conducted in 724 patients with localized RCC status post nephrectomy, axitinib failed to demonstrate a DFS advantage in the total study population [19]. OS data were not mature. Grade 3 or greater toxicities were more frequent in the axitinib arm (61 versus 30 percent).

- **Sorafenib** – In a phase III trial (SORCE) conducted in 1711 patients with completely resected RCC at intermediate or high risk of disease recurrence, sorafenib did not improve DFS or OS and increased toxicity, compared with placebo [20].

- **Girentuximab** – Another large phase III trial using girentuximab (an antibody targeting carbonic anhydrase IX) failed to demonstrate any benefit in either DFS or OS [25].

- **Everolimus** – In a phase III trial (EVEREST) of 1545 patients with resected non-metastatic RCC (including both clear cell and non-clear cell histologies), adjuvant therapy with everolimus failed to improve recurrence-free survival (RFS) or OS compared with placebo and resulted in high rates of treatment discontinuation due to toxicity [26]. However, RFS was improved among those at very high risk of disease recurrence (five-year RFS 57 versus 51 percent, HR 0.79, 95% CI 0.65-0.97), suggesting potential efficacy in this population.

Surveillance — Careful surveillance after definitive treatment is important to permit early diagnosis of relapse when the tumor burden is limited. The response to therapy of patients who relapse is best in patients with a good performance status and a limited tumor burden. Furthermore, some patients who have a solitary recurrence may be cured with surgical metastasectomy. (See "Surveillance for metastatic disease after definitive treatment for renal cell carcinoma".)

ADVANCED RENAL CELL CARCINOMA

Many RCCs are clinically silent for much of their natural history. Thus, the diagnosis is frequently not made until disease is locally advanced (and unresectable) or has metastasized. In addition, many patients who initially are resectable eventually recur. Systemic therapy (immunotherapy,

molecularly targeted agents), surgery, and radiation therapy (RT) all may have a role depending on the extent of disease, sites of involvement, and patient-specific factors.

The general treatment approach to clear cell RCC is discussed below. The treatment approach to non-clear cell RCC is discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma".)

General treatment approach

Clear cell renal cell carcinoma — Treatment-naïve patients with advanced or metastatic disease not controlled by definitive locoregional therapy receive systemic treatment with immunotherapy (checkpoint inhibitors) and/or molecularly targeted therapy (algorithm 2). Systemic therapy is initiated promptly in most patients with substantial disease burden. Active surveillance may be offered to asymptomatic patients with favorable-risk disease and limited disease burden to determine disease tempo. Patients should be encouraged to participate in formal clinical trials whenever possible. The approach to initial and subsequent systemic therapy in patients with advanced or metastatic RCC is discussed in detail separately. (See "Systemic therapy of advanced clear cell renal carcinoma".)

The choice of treatment for patients with advanced disease has been based on prognostic risk factors historically developed in the era of frontline vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs).

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model integrates six adverse factors and stratifies patients into favorable-, intermediate-, or poor-risk groups (table 2) [27].

The relevance of the IMDC prognostic criteria in the era of frontline combination immunotherapy remains to be established. In the absence of alternative immunotherapy-based prognostic criteria, these criteria continue to be used in clinical trials to risk-stratify patients and, to some extent, by providers and clinical guidelines to direct therapy. (See "Systemic therapy of advanced clear cell renal carcinoma", section on 'Risk stratification'.)

Non-clear cell renal cell carcinoma — The treatment approach to patients with metastatic non-clear cell RCC is varied and tailored to the histologic subtype and pathologic and molecular features of the tumor. The main histologic subtypes of non-clear cell RCC include papillary, chromophobe, collecting duct (including medullary carcinoma), translocation, and unclassified. Although many advances have been made in the treatment of metastatic non-clear cell RCC, there are limited high-quality data to help inform management, due to the infrequency of these

tumors. Details regarding the various treatment approaches for non-clear cell RCC are discussed separately. (See "The treatment of advanced non-clear cell renal carcinoma".)

Renal cell carcinoma with sarcomatoid features — Renal cell carcinoma with sarcomatoid features, or sarcomatoid RCC, is not considered a distinct subtype of RCC because sarcomatoid features can be seen in any histologic subtype of RCC, including both clear cell and non-clear cell histologies. Advanced or metastatic sarcomatoid RCC is clinically responsive to immunotherapy-based regimens. Further details on the management of sarcomatoid RCCs are discussed separately. (See "Renal cell carcinoma with sarcomatoid features".)

Treatment options

Immunotherapy — Immunotherapy is an important option for the management of patients with advanced clear cell RCC, both as initial therapy or as subsequent therapy after molecularly targeted therapy. (See "Systemic therapy of advanced clear cell renal carcinoma" and "Principles of cancer immunotherapy".)

Checkpoint inhibitor immunotherapy — Checkpoint inhibition targeting either the programmed cell death receptor 1 (PD-1) pathway and/or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) has represented an important advance in the treatment of multiple malignancies, including clear cell RCC.

The combination of nivolumab (an anti-PD-1 antibody) and ipilimumab (an anti-CTLA-4 antibody) has an established role in the treatment of intermediate- and poor-risk patients [28,29]. Single-agent nivolumab also demonstrated an overall survival (OS) benefit in patients who had progressed after initial antiangiogenic treatment [30,31]. (See "Systemic therapy of advanced clear cell renal carcinoma", section on 'Nivolumab plus ipilimumab' and "Systemic therapy of advanced clear cell renal carcinoma", section on 'Nivolumab'.)

Combined immunotherapy plus antiangiogenic therapy — Combinations of immunotherapy plus antiangiogenic therapy are active in patients with advanced or metastatic RCC. Examples of such combination with OS benefit include pembrolizumab plus axitinib, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab. Another available combination is avelumab plus axitinib. (See "Systemic therapy of advanced clear cell renal carcinoma", section on 'Initial treatment options'.)

Mature results from randomized trials will be required to define the role of these anti-VEGF/anti-PD-1 pathway combinations in comparison with combinations such as nivolumab plus ipilimumab. Furthermore, the results will need to analyze whether there are specific patient subsets that are more or less likely to benefit or to experience severe toxicity.

The important issues to be resolved regarding combination therapy include whether any observed improved efficacy with such trials is synergistic or simply additive, with similar results achievable through sequential use of these agents. Additional considerations of importance include the relative efficacy and toxicity associated with the different combination regimens, and the increase in drug costs from the simultaneous use of multiple agents.

Interleukin 2 — Immunotherapy with high-dose bolus IL-2 can activate an immune response against RCC that results in tumor regression in a minority of patients. Although treatment is associated with severe toxicity, responses often persist for many years, even in the absence of additional therapy, and the majority of complete responders remain free of relapse long term.

While high-dose IL-2 was considered an important option for carefully selected patients who are able to tolerate the toxicity associated with this approach and who have access to this treatment, its role in the setting of more active and better tolerated checkpoint inhibitor immunotherapy approaches is undefined. IL-2 still could be an option in patients whose disease has progressed on initial immunotherapy-based regimens. (See "Systemic therapy of advanced clear cell renal carcinoma", section on 'Interleukin 2 and other interleukins'.)

Molecularly targeted therapy — An understanding of the pathogenesis of RCC at the molecular level has identified the vascular endothelial growth factor (VEGF) pathway and mechanistic (mammalian) target of rapamycin (mTOR) as important targets for therapeutic intervention. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Molecular pathogenesis'.)

Antiangiogenic (VEGF pathway) — Two different approaches have clinical activity in blocking the vascular endothelial growth factor (VEGF) pathway (figure 1): the use of small-molecule TKIs (eg, sunitinib, pazopanib, cabozantinib, axitinib, sorafenib, lenvatinib, and tivozanib) to block the intracellular domain of the VEGFR, and the use of a monoclonal antibody (bevacizumab) to bind circulating VEGF and prevent it from activating the VEGFR [32]. VEGF inhibitors prolong progression-free survival compared with IFNa for the initial management of advanced RCC. Further data on the activity of these VEGF TKIs in patients with advanced or metastatic clear cell RCC are discussed separately. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Preferred VEGFR inhibitors'.)

mTOR inhibitors — The mechanistic (mammalian) target of rapamycin (mTOR) pathway is downstream of the phosphoinositide 3-kinase and Akt pathway that is regulated by the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene (figure 1). Inhibition of the

mTOR pathway has the potential to inhibit tumor progression at multiple levels. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Inhibitors of the mTOR pathway'.)

However, mTOR inhibitors have a limited role as single agents in advanced RCC. Their principal utility may be in patients whose disease is refractory to initial treatment with VEGFR TKIs and/or those patients whose tumors have mutations in the PI3K pathway. Except for this, their use is relegated to third- or greater-line therapy in patients whose disease has progressed on combination checkpoint inhibitor immunotherapy regimens and cabozantinib.

- **Temsirolimus** – In the four-armed phase II BEST trial of patients who had not received prior targeted therapy, temsirolimus plus either bevacizumab or sorafenib had a worse therapeutic index than either bevacizumab alone or the combination of bevacizumab plus sorafenib [33]. In the INTORSECT trial in patients who had previously been treated with sunitinib, OS was significantly worse than with sorafenib [34]. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Bevacizumab plus interferon alfa' and "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Temsirolimus'.)

- **Everolimus** – In the RECORD-3 trial, everolimus was inferior to sunitinib as first-line therapy with advanced RCC [35]. In phase III trials in previously treated patients, everolimus was inferior to both nivolumab [30] and cabozantinib [36]. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Everolimus'.)

Chemotherapy and hormonal therapy — Both chemotherapy and progestational agents had only very limited activity in early studies prior to the development of immunotherapy and molecularly targeted therapy [37-40]. The role of chemotherapy is limited to the use of platinum-based chemotherapy in patients with non-clear cell collecting duct and renal medullary carcinomas. (See "The treatment of advanced non-clear cell renal carcinoma", section on 'Collecting duct and renal medullary carcinoma'.)

Surgery — Most patients with stage IV RCC have unresectable disease and require systemic therapy. However, surgery has a role in the management of some patients.

Radical nephrectomy — For a subset of patients in whom the only evidence of advanced disease is the direct involvement of the ipsilateral adrenal gland, a radical nephrectomy that includes adrenalectomy is potentially curative. (See "Definitive surgical management of renal cell carcinoma", section on 'Adrenal gland involvement'.)

Cytoreductive nephrectomy — Removal of the primary tumor (cytoreductive or debulking nephrectomy) may be indicated prior to initiating systemic therapy in select patients (eg, good performance status, 75 percent debulking possible, no symptomatic metastatic disease). (See "Role of surgery in patients with metastatic renal cell carcinoma", section on 'Cytoreductive nephrectomy'.)

The role of cytoreductive nephrectomy among patients treated with molecularly targeted agents is less promising. This approach is discussed elsewhere. (See "Role of surgery in patients with metastatic renal cell carcinoma", section on 'Antiangiogenic therapy and immune checkpoint inhibitors'.)

Metastasectomy — Surgical resection of a single or limited number of metastases is a reasonable option for carefully selected patients. This occasionally is done in conjunction with a radical nephrectomy but may also be performed following a relapse after surgery. In addition, surgery is sometimes performed to resect residual disease in patients who have had a major but less than complete response to systemic immunotherapy. (See "Role of surgery in patients with metastatic renal cell carcinoma" and "Systemic therapy of advanced clear cell renal carcinoma" and "Surgical resection of pulmonary metastases: Outcomes by histology", section on 'Renal cell carcinoma'.)

Adjuvant therapy after metastasectomy — Among patients with completed resected oligometastatic clear cell renal carcinoma treated with nephrectomy and complete resection of all distant disease, we suggest one year of adjuvant pembrolizumab rather than observation, as this approach improved disease-free survival (DFS) in a phase III trial [8,9]. By contrast, adjuvant therapy using VEGF inhibitors does not confer a survival benefit in this setting.

The use of adjuvant therapy after surgical resection of locoregionally advanced RCC is discussed separately. (See 'Adjuvant therapy for locoregional disease' above.)

- **Pembrolizumab** – Adjuvant pembrolizumab was evaluated in a randomized, double-blind, placebo-controlled phase III trial (KEYNOTE-564) of 994 patients with clear cell renal carcinoma who had undergone nephrectomy [8,9]. This study included a subgroup of 58 patients with oligometastatic disease that was completely resected with no evidence of disease (NED) within one year of nephrectomy (M1, NED). In this subgroup of patients, adjuvant pembrolizumab improved DFS (median not reached versus 12 months, HR 0.28, 95% CI 0.12-0.66) versus placebo.

  Based on these data the US Food and Drug Administration (FDA) granted regulatory approval for pembrolizumab for the adjuvant treatment of patients with RCC at

intermediate-high or high risk of recurrence following nephrectomy, or with following nephrectomy and resection of metastatic lesions [14].

Further results of this trial in patients without oligometastatic disease are discussed above. (See 'Adjuvant therapy for locoregional disease' above.)

- **Other agents** – Other trials have not demonstrated survival benefit for adjuvant VEGF inhibition in the oligometastatic setting. For example, in a double-blind phase III trial (ECOG-ACRIN E2810), among 129 patients with RCC who were disease free after metastasectomy, pazopanib resulted in a similar disease-free survival (DFS) relative to placebo (median DFS 17.3 versus 14.2 months, hazard ratio [HR] 0.85, 95% CI 0.55-1.31) and worsened OS (HR 2.65, 95% CI 1.02-6.9) [41]. Reported toxicities for pazopanib included fatigue, diarrhea, hypertension, and transaminitis, and one patient died of intracranial hemorrhage. Similarly, sorafenib also failed to demonstrate improvement in recurrence-free survival in a randomized phase II trial conducted in a similar patient population [42].

  Immunotherapy agents under clinical trial evaluation after metastasectomy include pembrolizumab in KEYNOTE-564 (NCT03142334) and atezolizumab in IMmotion101 (NCT03024996).

Radiation therapy — Although RCC has been characterized as a radioresistant tumor, conventional and stereotactic RT are frequently useful to treat a single or limited number of metastases [43]. In these settings, the utility of RT is similar to that in metastases from other tumor types.

Examples of situations where RT is useful include:

- Painful bone metastases (see "Radiation therapy for the management of painful bone metastases")
- Brain metastases (see "Overview of the treatment of brain metastases")
- Painful recurrences in the renal bed

RT has been used as an adjuvant following nephrectomy in patients at high risk for local recurrence [44-46], but its role in this setting remains unproven and is generally discouraged.

Brain metastases, treatment naïve — Patients with brain metastases should be treated with surgery and/or RT (preferably stereotactic radiosurgery) prior to initiation of systemic therapy with either vascular endothelial growth factor (VEGF) inhibitors or immunotherapy, due to the potential hemorrhagic nature of untreated tumors. We offer nivolumab and ipilimumab, rather

than VEGF inhibitor therapy, for those with active or treated asymptomatic brain metastases not requiring steroids and with clinical indications for immunotherapy to treat extracranial systemic disease. Further details about the management of brain metastases in general are provided separately. (See "Overview of the treatment of brain metastases".)

The optimal sequencing of immunotherapy in patients with brain metastases is evolving [47-53]. The incidence of brain metastases among those with advanced RCC is approximately 10 percent [54]. Median OS for these patients is between 4 and 35 months [55]; graded prognostic assessments are available to estimate OS in individual patients and guide treatment options (table 3). However, most of the randomized trials evaluating immunotherapy in RCC have excluded patients with brain metastases. Most data come from small, phase II trials. Immunotherapy and antiangiogenic therapies have shown some intracranial efficacy in patients with asymptomatic treatment-naïve brain metastases, but durable response and safety in this setting have not been confirmed [56]. As an example, in one study, approximately one-third of patients receiving single-agent nivolumab for treatment-naïve brain metastases did not require subsequent locoregional brain RT for progressive disease [51]. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Role of VEGF inhibitors for brain metastases'.)

The following trials have evaluated immunotherapy in this setting:

- In one nonrandomized, open-label phase II trial (CheckMate 920), 28 patients with treatment-naïve RCC and asymptomatic untreated brain metastases received ipilimumab and nivolumab for four cycles, followed by maintenance nivolumab [52]. Responses were seen in 32 percent, with a median progression-free survival of nine months. Central nervous system immune-mediated adverse events included headache, myasthenia gravis, and tremor. Grade ≥3 immune-mediated toxicities included diarrhea, colitis, diabetic ketoacidosis, hepatitis, hypophysitis, and rash.

- In a separate, nonrandomized, open-label phase II trial (GETUG-AFU 26 NIVOREN), 73 patients with metastatic RCC and asymptomatic brain metastases received single-agent nivolumab after experiencing disease progression on antiangiogenic therapy [51]. Approximately one-half had untreated brain metastases, while the other one-half had previously received brain RT, most frequently with stereotactic radiosurgery. Median follow-up was approximately two years. Among the 39 patients with untreated brain metastases, the intracranial objective response rate was 12 percent, and the median intracranial progression-free survival was 2.7 months. Approximately 70 percent required subsequent intracranial locoregional therapy (RT or surgery). In contrast, there were no

objective responses seen in the 34 patients with prior RT. Grade ≥3 toxicities were reported in nine patients, with no treatment-related deaths.

SPECIAL POPULATIONS

von Hippel-Lindau disease — Patients with von Hippel-Lindau (VHL) disease are at risk for developing renal cell carcinoma (RCC) due to molecular alterations in the *VHL* gene. (See "Molecular biology and pathogenesis of von Hippel-Lindau disease".)

Due to their unique biology, the treatment of patients with VHL-associated RCC may differ from those with sporadic RCC. For patients with locoregional disease, options for therapy include surveillance; nephron-sparing approaches; and belzutifan, a hypoxia-inducible factor-2alpha inhibitor. Further details on the selection of therapy in patients with VHL-associated RCC are discussed separately. (See "Clinical features, diagnosis, and management of von Hippel-Lindau disease", section on 'Renal cell carcinomas'.)

Other hereditary kidney cancer syndromes — Other hereditary syndromes are also associated with the development of RCC, such as polycystic kidney disease and hereditary leiomyomatosis and renal cell cancer (HLRCC). These and other hereditary syndromes associated with RCC are discussed in detail separately. (See "Hereditary kidney cancer syndromes".)

SPECIAL CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has increased the complexity of cancer care. Important issues in areas where viral transmission rates are high include balancing the risk from treatment delay versus harm from COVID-19, minimizing the use of immunosuppressive cancer treatments whenever possible, mitigating the negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited health care resources. Additionally, immunocompromised patients are candidates for a modified vaccination schedule (figure 2), other preventive strategies (including pre-exposure prophylaxis), and the early initiation of COVID-directed therapy. These and other recommendations for cancer care during active phases of the COVID-19 pandemic are discussed separately. (See "COVID-19: Considerations in patients with cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cancer of the kidney and ureters".)

SUMMARY AND RECOMMENDATIONS

- **Localized disease** – For patients with localized, resectable renal cell carcinoma (RCC), we recommend surgery as the primary treatment approach (algorithm 1) (**Grade 1A**). (See "Definitive surgical management of renal cell carcinoma".)
  - Radical nephrectomy has been the most widely used approach and remains the preferred procedure when there is evidence of invasion into the adrenal, renal vein, or perinephric fat. (See "Definitive surgical management of renal cell carcinoma", section on 'Radical nephrectomy'.)
  - Partial nephrectomy (either open or laparoscopic) is an alternative for smaller tumors and is particularly valuable in patients with bilateral or multiple lesions, those with inherited syndromes in whom there is an increased risk of an additional subsequent primary tumor, and those with impaired renal function. (See "Definitive surgical management of renal cell carcinoma", section on 'Partial nephrectomy'.)
  - For older adult patients and those with significant comorbid disease, ablative techniques (cryoablation, radiofrequency ablation) are an alternative. (See "Radiofrequency ablation and cryoablation for renal cell carcinoma".)
  - Active surveillance may be an option for patients with small asymptomatic lesions. (See "Definitive surgical management of renal cell carcinoma", section on 'Active surveillance'.)
- **Adjuvant therapy for locoregional disease** – For patients with intermediate-high and high-risk locoregional clear cell RCC treated with nephrectomy, particularly those with an estimated risk of recurrence at five years of ≥30 percent, we suggest one year of adjuvant pembrolizumab rather than observation (**Grade 2B**), as this approach improved disease-free survival (DFS). However, observation remains a reasonable alternative in this patient population, pending further follow-up confirming long-term DFS and overall survival (OS) benefit. (See 'Adjuvant therapy for locoregional disease' above and 'Pembrolizumab' above.)

For those with lower-risk disease (estimated risk of recurrence at five years <30 percent) or those who do not meet the pathologic criteria for intermediate-high or high risk of disease recurrence, we offer active surveillance after nephrectomy.

- **Advanced or metastatic clear cell RCC** – Most treatment-naïve patients with advanced or metastatic clear cell RCC receive systemic therapy with immunotherapy and/or molecularly targeted therapy (algorithm 2). Systemic therapy is initiated promptly in most patients with substantial disease burden. Active surveillance may be offered to asymptomatic patients with favorable-risk disease (table 2) and limited disease burden to determine the pace of disease. Clinical trials are encouraged if available. (See 'General treatment approach' above and "Systemic therapy of advanced clear cell renal carcinoma", section on 'Active surveillance'.)

  - Preferred options for immunotherapy-based combination regimens include nivolumab plus ipilimumab, pembrolizumab plus axitinib, nivolumab plus cabozantinib, and lenvatinib plus pembrolizumab. Other available options include avelumab plus axitinib. (See "Systemic therapy of advanced clear cell renal carcinoma", section on 'Selection of initial therapy'.)

  - For patients who are ineligible for immunotherapy-based combinations, we offer antiangiogenic therapy with inhibitors of the vascular endothelial growth factor (VEGF) pathway. (See "Antiangiogenic and molecularly targeted therapy for advanced or metastatic clear cell renal carcinoma", section on 'Preferred VEGFR inhibitors'.)

  - For patients who relapse on immunotherapy and/or molecularly targeted agents, the choice of subsequent therapy is dependent on prior therapy received. (See "Systemic therapy of advanced clear cell renal carcinoma", section on 'Treatment approach for subsequent therapy'.)

- **Adjuvant therapy after metastasectomy** – For patients with metastatic clear cell RCC treated with nephrectomy and fully resected oligometastatic disease, we suggest one year of adjuvant pembrolizumab rather than observation (**Grade 2C**). (See 'Adjuvant therapy after metastasectomy' above.)

- **Brain metastases** – For patients with treatment-naïve brain metastases, we offer surgery and/or radiation therapy prior to initiation of antiangiogenic therapy and/or immunotherapy, due to the potential hemorrhagic nature of untreated tumors. Nivolumab plus ipilimumab remains an option for patients with active or treated asymptomatic brain metastases and with clinical indications for immunotherapy to treat extracranial disease,

but the efficacy and safety of this approach remain investigational. (See 'Brain metastases, treatment naïve' above.)

- **Cytoreductive nephrectomy** – Removal of the primary tumor (cytoreductive or debulking nephrectomy) may be indicated prior to initiating systemic therapy in select patients (eg, good performance status, 75 percent debulking possible, no symptomatic metastatic disease). (See "Role of surgery in patients with metastatic renal cell carcinoma", section on 'Cytoreductive nephrectomy'.)

- **Non-clear cell RCC** – The treatment approach to patients with metastatic non-clear cell RCCs is varied and tailored to the histologic subtype and pathologic and molecular features of the tumor. (See "The treatment of advanced non-clear cell renal carcinoma".)

- **Renal cell carcinoma with sarcomatoid features** – Renal cell carcinoma with sarcomatoid features, or sarcomatoid RCC, can be seen in both clear cell and non-clear cell histologies. Advanced or metastatic sarcomatoid RCC is responsive to immunotherapy-based regimens. (See "Renal cell carcinoma with sarcomatoid features".)

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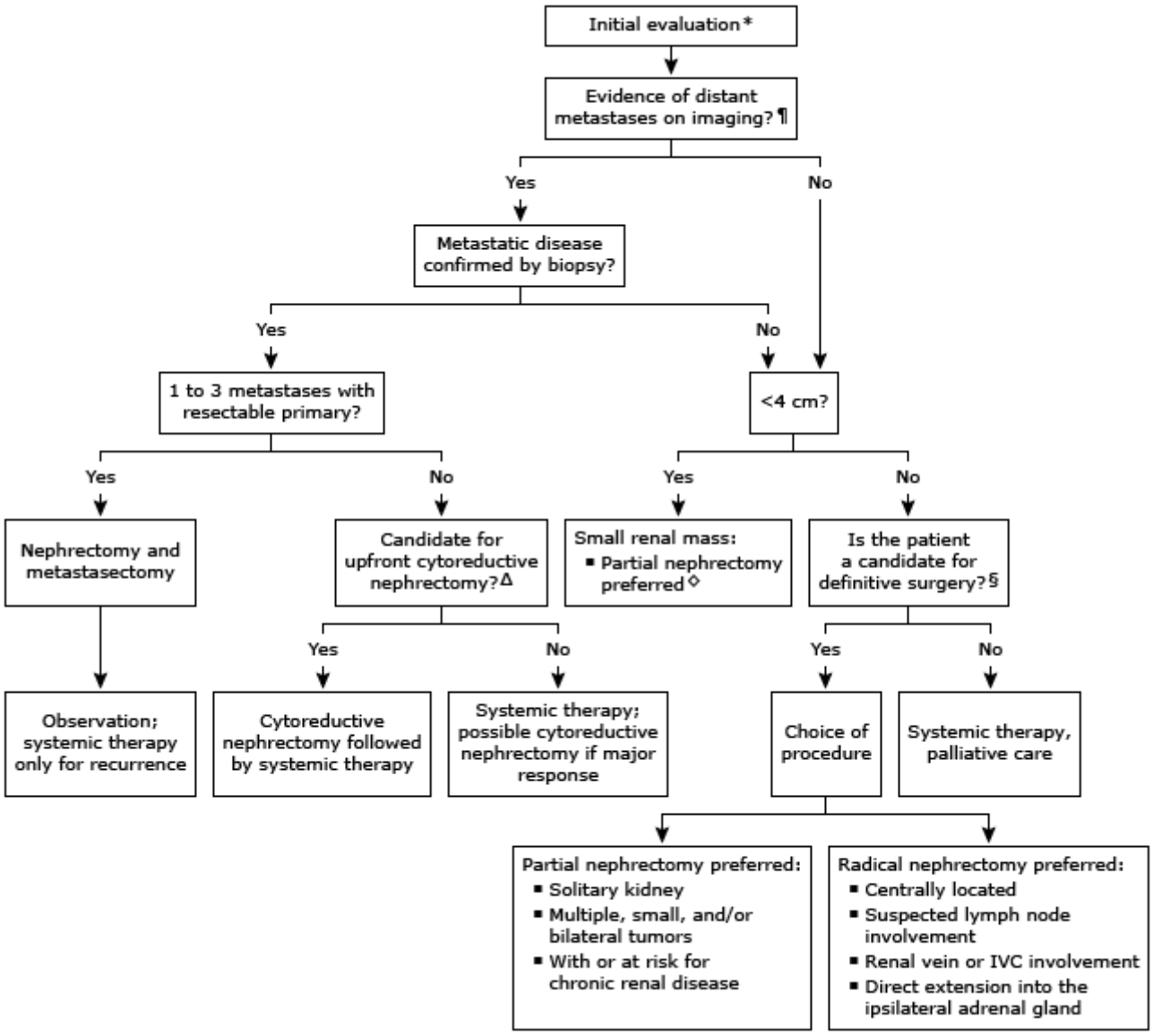
Topic 15719 Version 84.0

GRAPHICS

Initial evaluation and treatment of renal cell carcinoma



IVC: inferior vena cava; CT: computed tomography; MRI: magnetic resonance imaging.

* Preliminary diagnosis is based upon characteristic findings on imaging studies (CT/MRI); tissue diagnosis is generally obtained at time of definitive surgery.

¶ Chest imaging, additional studies as clinically indicated to look for evidence of metastases.

Δ Selection of patients should be done with considerable care so that appropriate patients can proceed with systemic therapy; important factors include good performance status, ability to perform adequate debulking, and favorable- or low-intermediate-risk diseases. Refer to UpToDate topic on the role of surgery in patients with metastatic renal cell carcinoma.

◇ Partial nephrectomy is the preferred approach to confirm the diagnosis and treat a renal mass <4 cm. However, thermal ablation (cryotherapy, radiofrequency ablation) or active surveillance may be appropriate alternatives for patients who are not surgical candidates. The choice between these

approaches is guided by local expertise and patient preference. Refer to UpToDate topic on the diagnostic approach, differential diagnosis, and treatment of a small renal mass.

§ Based upon factors including patient preference, age, and comorbidities.

Graphic 109427 Version 4.0

Kidney cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

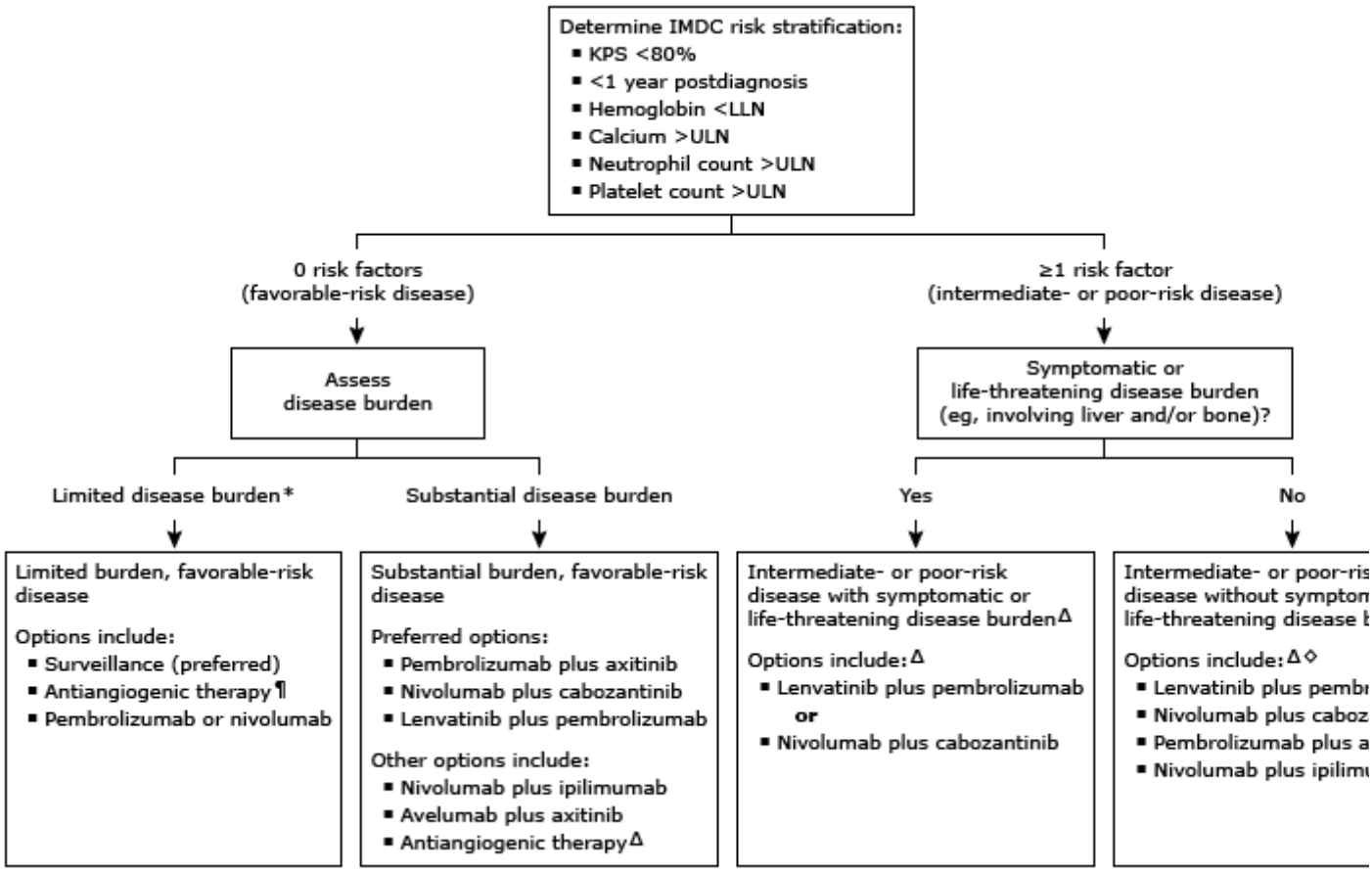
Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group**

			is...
T1	N0	M0	I
T1	N1	M0	III
T2	N0	M0	II
T2	N1	M0	III
T3	NX, N0	M0	III
T3	N1	M0	III
T4	Any N	M0	IV
Any T	Any N	M1	IV

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110735 Version 10.0

Approach to initial systemic therapy in patients with metastatic clear cell RCC



Patients with advanced or metastatic clear cell RCC are typically treated with systemic therapy as initial treat The decision to start systemic therapy and the selection of agent(s) depend on disease-related symptoms, p comorbidities, and tumor risk stratification. Listed treatments are preferred options, although alternative ag that are not listed may also be effective. Clinical trials are encouraged if available.

Select patients may be candidates for cytoreductive nephrectomy prior to initiation of immunotherapy. Refe UpToDate content on surgical management of RCC.

RCC: renal cell carcinoma; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; KPS: Karnofsky performance status; LLN: lower limit of normal; ULN: upper limit of normal; VEGFR: vascular endo growth factor receptor.

* Patients with limited disease on imaging are usually asymptomatic. However, the decision to treat must ta account multiple factors, including rate of growth, location of tumor (eg, proximity to vital organs with poter damage), and symptoms.

¶ For patients with limited burden, favorable-risk disease who desire a more aggressive management appro options include sunitinib or pazopanib. Refer to UpToDate content on targeted therapy for RCC.

Δ For patients who are ineligible for or decline initial treatment with immunotherapy combinations, we offer antiangiogenic therapy that incorporates a VEGFR inhibitor. For patients with substantial burden, favorable- disease, options include lenvatinib plus everolimus, sunitinib, pazopanib, and cabozantinib. For those with

intermediate- or poor-risk disease, options include lenvatinib plus everolimus or cabozantinib. Refer to UpTo
content on systemic therapy for advanced clear cell RCC and targeted therapy for RCC.

◇ All of these combinations improve overall survival, and the choice between these agents is based on toxic
profile, patient performance status, age, comorbidities and preferences, and the potential for a treatment-fr
interval (with nivolumab plus ipilimumab). Refer to UpToDate content on systemic therapy for advanced clea
RCC.

Graphic 116262 Version 5.0

International Metastatic Renal Cell Carcinoma Database Consortium criteria

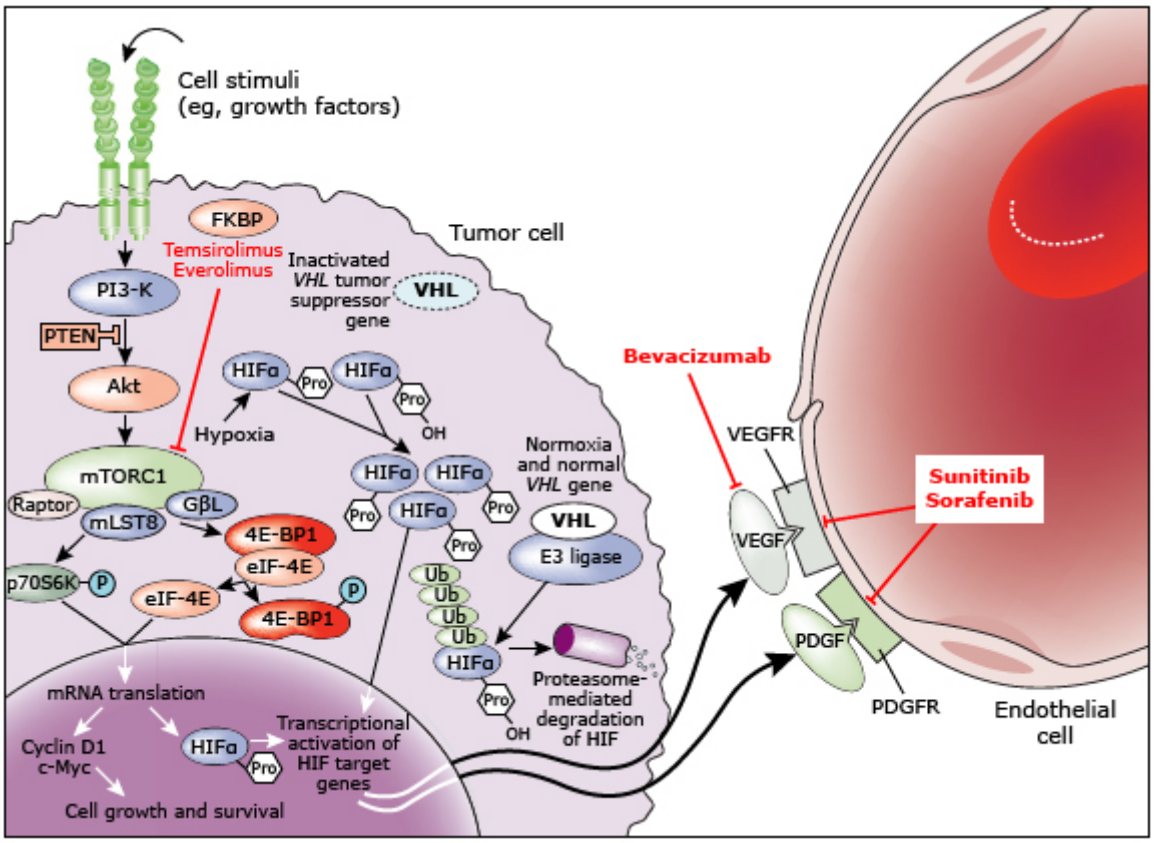
Karnofsky performance status score <80
Time from original diagnosis to initiation of targeted therapy <1 year
Hemoglobin less than the lower limit of normal
Serum calcium greater than the upper limit of normal
Neutrophil count greater than the upper limit of normal
Platelet count greater than the upper limit of normal

- Favorable risk: None of the above risk factors present.
- Intermediate risk: 1 or 2 of the above risk factors present.
- Poor risk: 3 or more risk factors present.

Adapted from: Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013; 14:141.

Graphic 116130 Version 3.0

Biological pathways and the resulting therapeutic targets in renal cell carcinoma



In conditions of normoxia and normal VHL gene function, von Hippel-Landau protein is the substrate recognition component of an E3 ubiquitin ligase complex that targets hypoxia-inducible factor (HIF) for proteolysis. In cellular hypoxia or with an inactivated VHL gene, the VHL proteinHIF interaction is disrupted, leading to stabilisation and accumulation of HIF transcription factors. HIF accumulation can also result from activation of the mammalian target of rapamycin (mTOR) through cellular stimuli and the phosphoinositide 3-kinase (PI3K)/Akt (protein kinase) pathway. mTOR phosphorylates and activates p70S6 kinase (p70S6K) leading to enhanced translation of certain proteins, including HIF. Activated mTOR also phosphorylates 4E binding protein-1 (4E-BP1), promoting dissociation of this complex and allowing eukaryotic initiation factor-4 subunit E (eIF-4E) to stimulate an increase in the translation of mRNAs that encode cell-cycle regulators such as c-myc and cyclin D1. Activated HIF translocates into the nucleus and leads to transcription of a large range of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These ligands bind to their cognate receptors present on the surface of endothelial cells, leading to cell migration, proliferation, and permeability. Temsirolimus binds to FK506-binding protein (FKBP), and the resultant proteindrug complex inhibits the kinase activity of the mTOR complex 1 (mTORC1). Bevacizumab is a VEGF ligand-binding antibody. Sunitinib and sorafenib are small molecule inhibitors of the VEGF receptor (VEGFR) and PDGF receptor (PDGRF) tyrosine kinases.

PTEN: phosphatase and tensin homologue; Pro: proline; Ub: ubiquitin.

Graphic 65979 Version 2.0

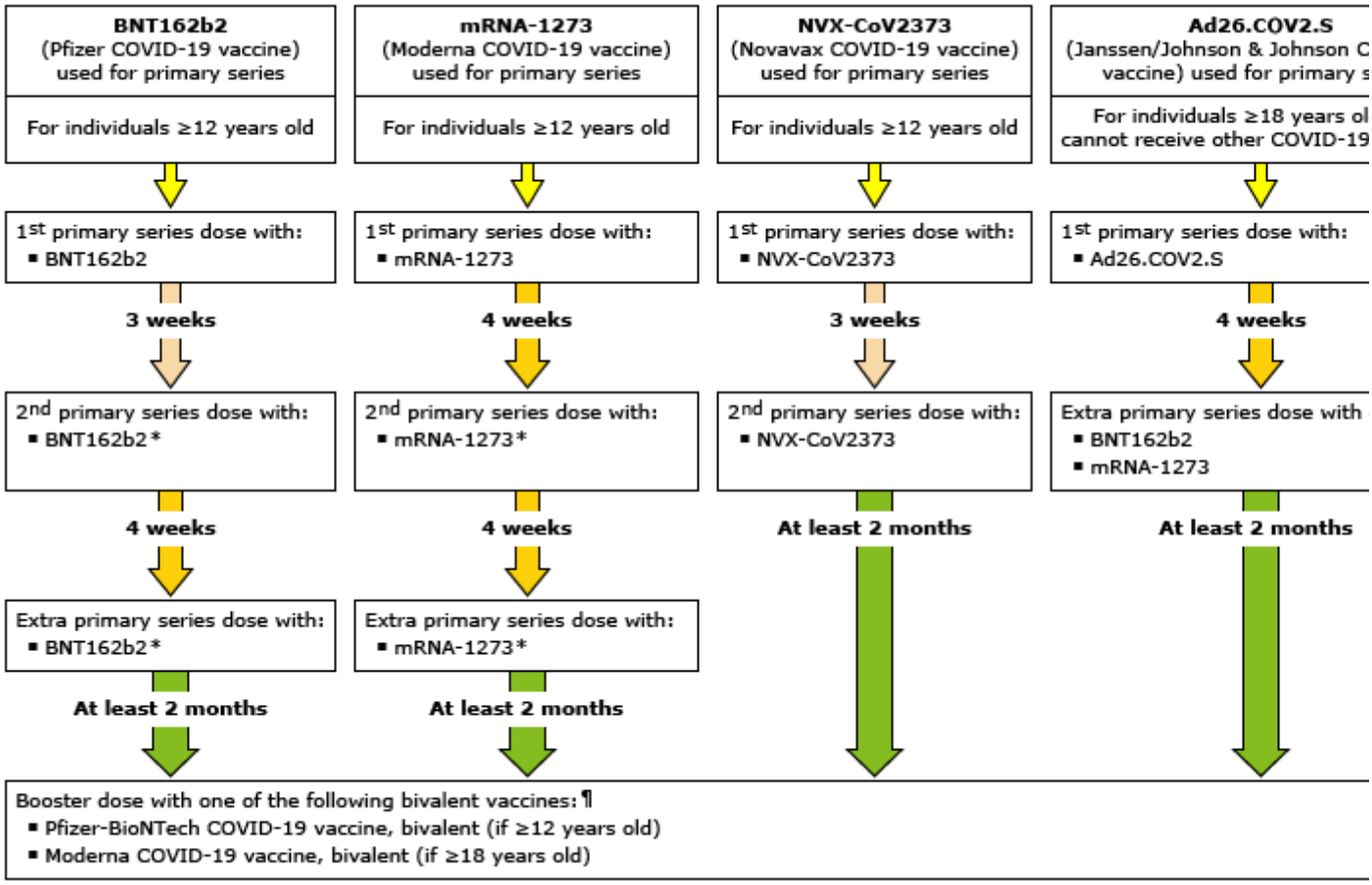
Worksheet for calculation of the renal cell carcinoma-specific GPA

Prognostic factor	GPA					Patient score
	0	0.5	1.0	1.5	2.0	
KPS	≤70		80		90-100	
Number of BM	≥5	1-4				
ECM	Present	Absent				
Hgb	<11.1	11.1-12.5 or unknown	>12.5			
						Sum = median survival by GPA: 0-1 = 4 months; 1.5-2.0 = 12 months; 2.5-3.0 = 17 months; 3.5-4.0 = 35 months

GPA: graded prognostic assessment; KPS: Karnofsky Performance Status; BM: brain metastases; ECM: extracranial metastases; Hgb: hemoglobin.

Graphic 129771 Version 1.0

COVID-19 vaccine schedule for adults and adolescents ≥12 years old with mode to severely immunocompromising conditions



Individuals with moderately to severely immunocompromising conditions have a higher risk of suboptimal response to COVID-19 vaccination. Thus, an additional primary series dose, is a strategy to improve vaccine effectiveness in this population. Such patients are also eligible for pre-exposure prophylaxis. Refer to other UpToDate content for examples of moderately to severely immunocompromising conditions that warrant th adjusted vaccination schedule.

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* If possible, the same vaccine formulation should used to complete the primary series. If the original vaccir not available or if the patient has developed a contraindication to that vaccine, a different, age-appropriate (19 vaccine can be used to complete the primary series; in such cases the new dose is given at least four wee after the last one.

¶ If the patient received monovalent booster doses in addition to the primary series, a single booster dose c bivalent vaccine is still recommended, at least 2 months following the most recent monovalent vaccine dose

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Graphic 138339 Version 6.0

Contributor Disclosures

Michael B Atkins, MD Equity Ownership/Stock Options: Pyxis [Immunotherapy];Werewolf Therapeutics [Immunotherapy]. Grant/Research/Clinical Trial Support: AstraZeneca [RCC];Bristol Myers Squibb [Melanoma and RCC];Merck [Melanoma and RCC]. Consultant/Advisory Boards: Adagene [Melanoma, RCC, immunotherapy];Agenus [Melanoma, RCC, immunotherapy];Apexigen [Melanoma, RCC, immunotherapy];Asher Bio [Melanoma, RCC, immunotherapy];AstraZeneca [Melanoma, RCC, immunotherapy];Aveo [Melanoma, RCC, immunotherapy];Bristol Myers Squibb [Melanoma, RCC, immunotherapy];Eisai [Melanoma, RCC, immunotherapy];Exelixis [Melanoma, RCC, immunotherapy];Fathom [Melanoma, RCC, immunotherapy];Idera [Melanoma, RCC, immunotherapy];Iovance [Melanoma, RCC, immunotherapy];Leads [Melanoma, RCC, immunotherapy];Merck [Melanoma, RCC, immunotherapy];Novartis [Melanoma, RCC, immunotherapy];PACT [Melanoma, RCC, immunotherapy];Pfizer [Melanoma, RCC, immunotherapy];Pneuma [Melanoma, RCC, immunotherapy];Roche [Melanoma, RCC, immunotherapy];SAB Bio [Melanoma, RCC, immunotherapy];SeaGen [Melanoma, RCC, immunotherapy];Simcha [Melanoma, RCC, immunotherapy];Surface [Melanoma, RCC, immunotherapy];Symphogen [Melanoma, RCC, immunotherapy];Takeda [Melanoma, RCC, immunotherapy]. All of the relevant financial relationships listed have been mitigated. **Jerome P Richie, MD, FACS** No relevant financial relationship(s) with ineligible companies to disclose. **Sonali Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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