National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

（NCCN腫瘍学臨床診療ガイドライン）

腎　癌

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NCCN.org

NCCN Guidelines for Patients®はwww.nccn.org/patientsにてご利用になれます。

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NCCN Guidelines Version 1.2021
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臨床試験：NCCNは、すべてのがん患者にとって最良の管理法は臨床試験にあると考えている。
臨床試験への参加が特に推奨される。

NCCN加盟施設における臨床試験のオンライン検索はこちらから：
nccn.org/clinical_trials/member_institutions.html

NCCNのエビデンスとコンセンサスによるカテゴリー：特に指定のない限り、すべての推奨はカテゴリー2Aである。

NCCNのエビデンスとコンセンサスによるカテゴリーを参照。

NCCNの望ましさによるカテゴリー：
いずれの推奨も適切と考えられる。

NCCNの望ましさによるカテゴリーを参照

NCCN腎癌ガイドライン2020年第2版から2021年第1版への更新内容は以下の通りである:

新たなアルゴリズム

HRCC-1

• 遺伝性腎細胞癌に対する指針を示す新たな節が追加された。

腎癌

KID-1

• 初回精査
  ▸ 2つ目の項目が変更された:「白血球分画を含む全血算、生化学検査(comprehensive metabolic panel)、LDH」
  ▸ 6つ目の項目の4つ目の下位項目が変更された:「コア針生検を考慮*(FNAでは不十分)*」
  ▸ 8つ目の項目が変更された:「複数の腎腫瘤、~~また~~は年齢46歳以下*または家族歴陽性の場合*、遺伝学的評価を考慮。*遺伝性腎細胞癌(HRCC-1)を参照*」

KID-B, 1 OF 5

アブレーション治療後のフォローアップ

• 3つ目の項目の最初の下位項目が変更された:「 他に禁忌がない限り、アブレーション治療の~~3～6~~*1*～6ヵ月後時点で腹部CTまたはMRI*(静注造影剤を使用または不使用)*、それ以降はCTまたはMRI(望ましい)もしくは超音波を1年毎に臨床的な適応に従って5年以上。*患者が静注造影剤の投与を受けられない場合は、MRIが望ましい画像検査法である*」

KID-B, 3 OF 5

IIまたはIII期のフォローアップ:2つ目の項目が変更された:「適応があれば、生化学検査(comprehensive metabolic panel)とその他の検査を~~2~~3年間は3～6ヵ月毎、その後は最長5年まで1年毎、以降は臨床的な適応に従って」

KID-B,4 OF 5

再発例または外科的に切除不能のIV期症例に対するフォローアップ

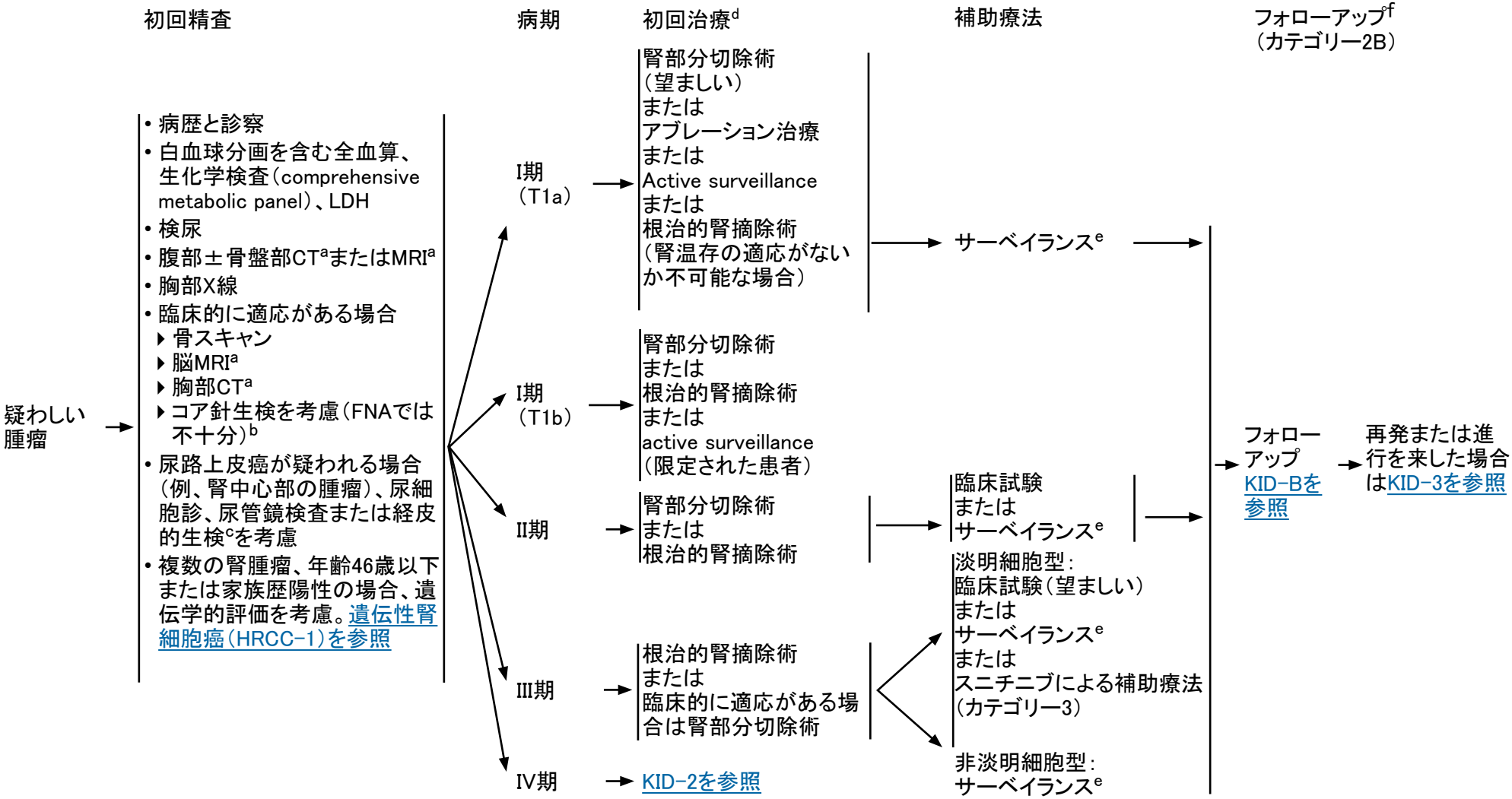
• 4つ目の項目が変更された:「ベースライン時および臨床的に適応となった時点で頭部MRI(望ましい)またはCT~~またはMRI~~を考慮する。医師の判断で1年毎にサーベイランス目的の画像検査を施行する。」

KID-C, 1 of 2

• 全身療法の原則
  ▸ すべての免疫療法の選択肢に脚注bが追加された:「NCCN免疫療法関連毒性管理ガイドラインを参照のこと。」(KID-C, 2 of 2も同様)
  ▸ 脚注fが「バイオシミラーの選択肢:ベバシズマブ-awwb、ベバシズマブ-bvzr」から「FDAの承認を受けたバイオシミラーはベバシズマブの代替として適切である。」に変更された。(KID-C, 2 of 2も同様)

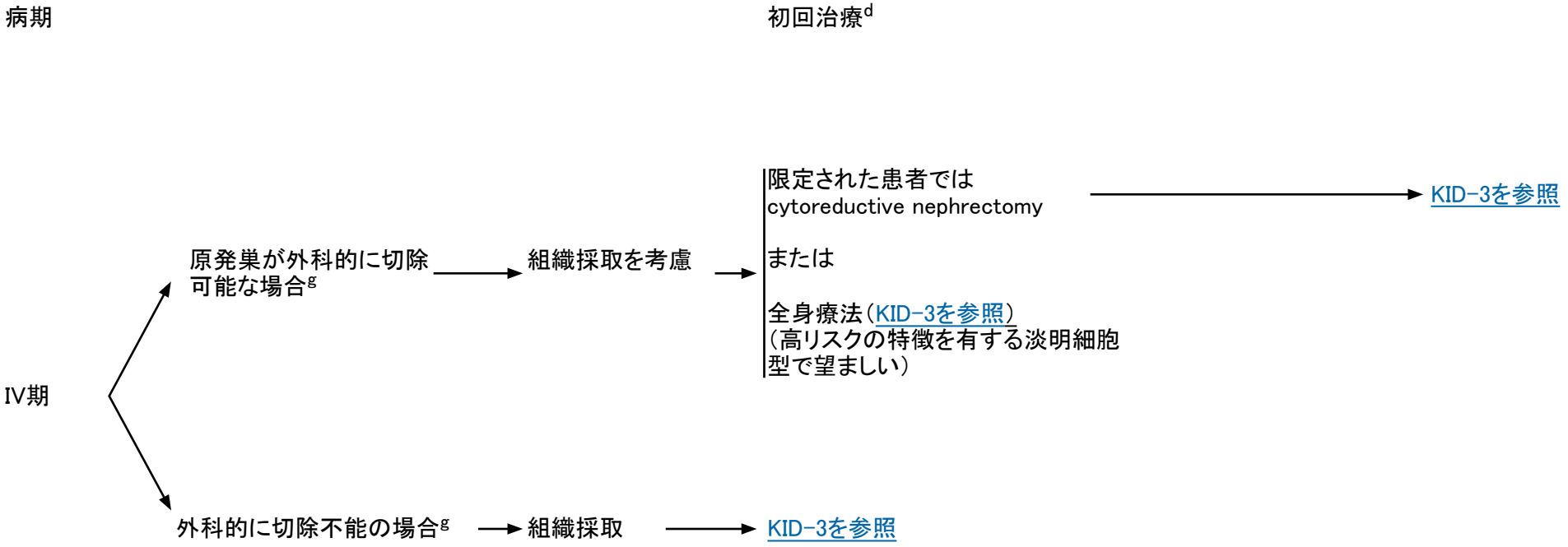
KID-C, 2 of 2

• 全身療法の原則
  ▸ レンバチニブ+エベロリムスが「特定の状況で有用」から「その他の推奨レジメン」に移された。
  ▸ 脚注gが変更され、「腎髄質癌ではゲムシタビン+ドキソルビシンでも奏効が得られる(Roubaud G, et al. Oncology 2011;80:214-218; Shah AY, et al. BJU Int 2017;120:782-792)。」が追加された。



[a] 腎撮影用プロトコルなどの造影が非常に望ましい。
[b] 小径病変に対しては、悪性腫瘍の診断または確定診断を下してサーベイランスまたはアブレーション治療、凍結療法およびラジオ波焼灼術による管理戦略の指針とするべく、生検を考慮してもよい。
[c] 転移巣がある場合または患者が尿管鏡検査に耐えられない場合。
[d] 手術療法の原則（KID-A）を参照のこと。
[e] フォローアップ（KID-B）を参照のこと。
[f] 単独ですべての患者に適切となるようなフォローアップ計画は存在しない。フォローアップは患者毎の要件に応じて個別化すべきである。

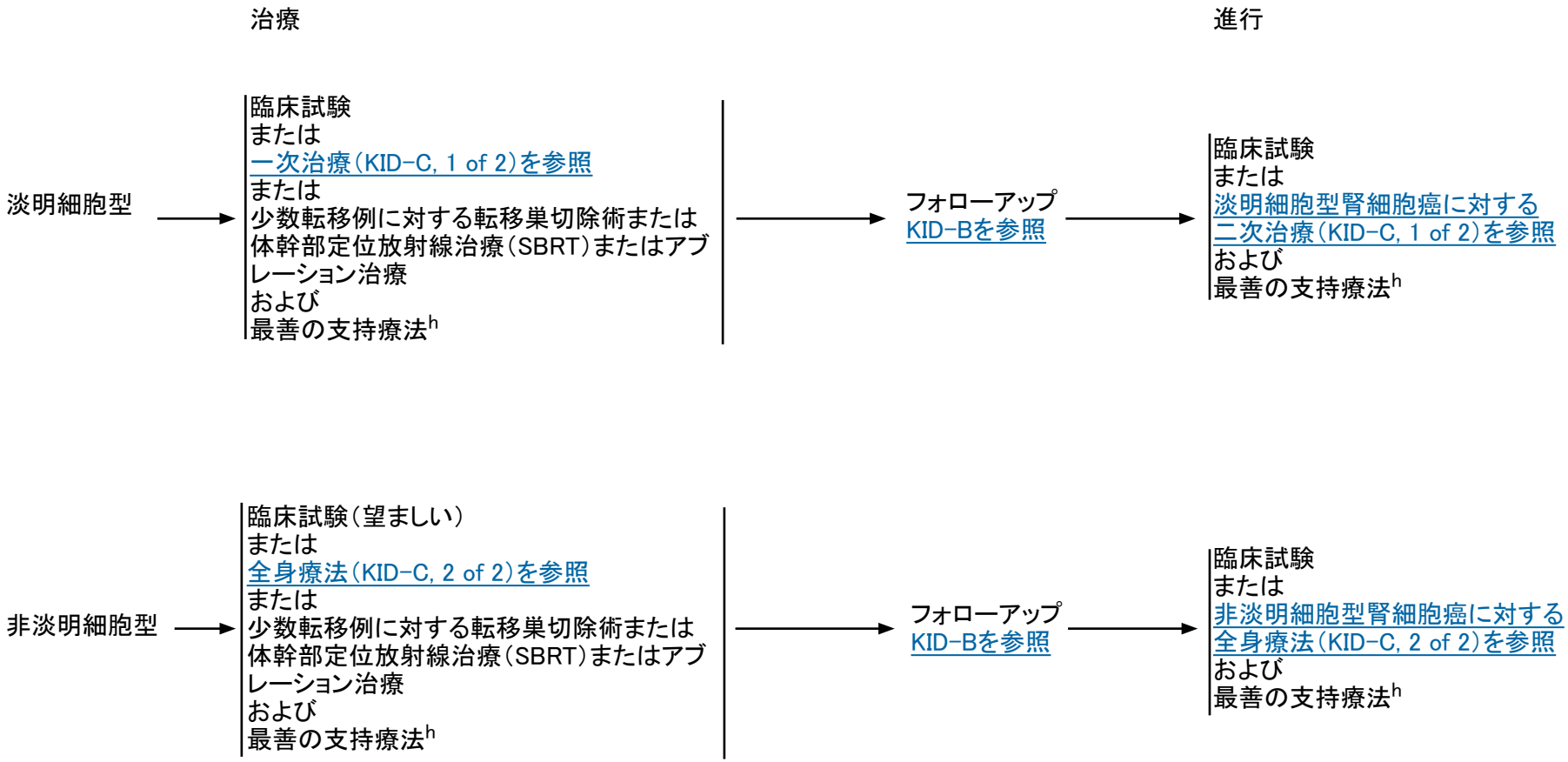
注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



d 手術療法の原則（KID-A）を参照のこと。
g 症状と転移巣の進展度に応じて個別化した治療を行う。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発例またはIV期症例



h 最善の支持療法には、緩和的放射線療法、骨転移巣に対するビスホスホネート系薬剤またはRANKL阻害薬を含めることができる。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

手術療法の原則

- 例えば次のような場合など、限定された患者では腎温存手術（腎部分切除術）が適応となる：
  - 技術的に可能な片側性のI～III期腫瘍
  - 単腎状態、腎不全、両側腎腫瘤および家族性腎細胞癌
  - 若年または医学的危険因子（高血圧、糖尿病、腎結石症）のために進行性の慢性腎臓病を発症する相対リスクが高い患者

- 根治的腎摘除術および腎部分切除術では、開腹下、腹腔鏡下またはロボット支援下の術式を用いることができる。

- 所属リンパ節郭清術は任意であるが、術前の画像検査でリンパ節腫脹が認められた患者や手術時に触知/目視可能なリンパ節腫脹が認められた患者では推奨される。

- 副腎への浸潤がない場合、副腎摘除は省略してもよい。

- 広範な下大静脈腫瘍血栓に対する手術には心血管外科チームの援助または手術件数の多い施設への紹介が必要になる場合もある。

- 臨床病期T1の患者の管理ではアブレーション治療（例、凍結療法、ラジオ波焼灼術）が選択肢となる。
  - アブレーション治療は3cm未満の腫瘤に対する選択肢であるが、限定された患者ではより大きな腫瘤に対しても選択肢となりうる。3cm以上の腫瘤におけるアブレーションは、局所再発率/腫瘍残存率および合併症発生率がより高い。
  - 小径病変に対しては、サーベイランス、凍結療法およびラジオ波焼灼術による管理戦略のために生検で悪性腫瘍の確定診断を下す。
  - アブレーション治療は従来の手術と比べて局所再発率が高く、局所的に同じ腫瘍学的成績を得るために複数回の治療を要する可能性がある[a,b]。

- 例えば、以下に示すような臨床病期T1の患者に対しては、active surveillanceが初回管理の選択肢の1つとなる：
  - 良性腫瘍の割合が高く、転移の可能性が低いことから、腎腫瘤が小さい（2cm未満）患者。
  - 嚢胞性成分が優位なT1a（≦4 cm）の患者にはactive surveillanceが推奨される。
  - 臨床病期T1の腫瘤があり、介入による死亡または合併症の競合リスクが有意である患者。
  - 転移の可能性の高まりを示唆する変化（例、腫瘍サイズ、増殖速度、浸潤パターンの増加）が腫瘤にみられる場合は、active surveillanceの一環として一連の腹部画像検査と適時の介入を行う。
  - Active surveillanceには血液検査や胸部画像検査などの転移に対する定期的なサーベイランスを含めるべきであり、腫瘤の増大がみられる場合は特に重要である。

- 一般に、次のような患者では全身療法の施行前にcytoreductive nephrectomyが適応となる：
  - 一般全身状態が非常に良好（ECOG PS < 2）
  - 脳転移なし

[a] Campbell S, Uzzo R, Allaf M, et al. Renal mass and localized renal cancer: AUA Guideline. J Urol 2017;198:520-529.
[b] Pierorazio P, Johnson M, Patel H, et al. Management of renal masses and localized renal cancer: Systematic review and meta-analysis. J Urol 2016;196:989-999.

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

フォローアップ[a,b]
（カテゴリー2B）

I期（T1a）

Active surveillance中のフォローアップ[c]

- 病歴聴取と身体診察を1年毎
- 臨床的な適応に従って、臨床検査を1年毎
- 腹部画像検査：
  - 禁忌がなければサーベイランスの開始から6ヵ月以内に腹部造影CTまたはMRIを施行し、それ以降はCT、MRIまたは超音波検査を少なくとも年1回
- 胸部画像検査：
  - 肺転移について評価するため、胸部X線またはCTをベースライン時および臨床的な適応に従って1年毎
- 臨床的な適応に従って、active surveillanceの開始時点またはフォローアップ時点で腎腫瘤の生検を考慮する。
- フォローアップは、手術の状況、治療スケジュール、副作用、併存症および症状に基づいて個別化してよい。

アブレーション治療後のフォローアップ[c]

- 病歴聴取と身体診察を1年毎
- 臨床的な適応に従って、臨床検査を1年毎
- 腹部画像検査：
  - 他に禁忌がない限り、アブレーション治療の1～6ヵ月後時点で腹部CTまたはMRI（静注造影剤を使用または不使用）、それ以降はCTまたはMRI（望ましい）もしくは超音波を1年毎に臨床的な適応に従って5年以上。患者が静注造影剤の投与を受けられない場合は、MRIが望ましい画像検査法である
  - 画像または臨床所見から再発が懸念される場合は、画像検査の頻度増加、腎腫瘤の生検または更なる治療が適応となる場合がある
- 胸部画像検査：
  - 生検で証明された低リスク腎細胞癌（RCC）の患者、生検で診断に至らなかった患者、および過去に生検を受けていない患者には、胸部X線またはCTを5年間にわたり1年毎

a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
b 単独ですべての患者に適切となるようなフォローアップ計画は存在しない。フォローアップの頻度および期間は患者毎の要件に応じて個別化すべきであり、5年を超えて継続してもよい（KID-B, 5 of 5を参照）。最適なフォローアップ期間の決定には、更なる研究が必要である。
c 臨床的に適応がある場合は造影剤を用いた画像検査。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

フォローアップ[a,b]
（カテゴリー2B）

I期（pT1aおよびpT1b）[c]

腎部分切除術または根治的腎摘除術後のフォローアップ

- 病歴聴取と身体診察を1年毎
- 臨床的な適応に従って、臨床検査を1年毎
- 腹部画像検査：
  - ベースラインの腹部CTまたはMRI（望ましい）もしくは超音波を手術後3～12ヵ月以内に施行、その後は1年毎に臨床的な適応に従って3年以上
  - 断端陽性の場合または望ましくない病理学的特徴（例えば、肉腫様型、高異型度[grade 3/4]）を認める場合は、より厳格な画像検査スケジュールまたは画像検査法を考慮してもよい。
- 胸部画像検査：
  - 胸部X線またはCTを少なくとも5年間は1年毎、その後は臨床的な適応に従って
  - 断端陽性の場合または望ましくない病理学的特徴を認める場合は、より厳格な画像検査スケジュールまたは手法を考慮してもよい。

a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
b 単独ですべての患者に適切となるようなフォローアップ計画は存在しない。フォローアップの頻度および期間は患者毎の要件に応じて個別化すべきであり、5年を超えて継続してもよい（KID-B, 5 of 5を参照）。最適なフォローアップ期間の決定には、更なる研究が必要である。
c 臨床的に適応がある場合は造影剤を用いた画像検査。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

フォローアップ[a,b]
（カテゴリー2B）

IIまたはIII期のフォローアップ

- 病歴聴取と身体診察を3年間は3～6ヵ月毎、最長5年まで1年毎、その後は臨床的な適応に従って
- 適応があれば、生化学検査（comprehensive metabolic panel）とその他の検査を3年間は3～6ヵ月毎、その後は最長5年まで1年毎、以降は臨床的な適応に従って
- 腹部画像検査：
  - ベースラインの腹部CTまたはMRIを3～6ヵ月以内に施行し、その後はCTまたはMRI（望ましい）もしくは超音波（III期ではUSはカテゴリー2B）を少なくとも3年間は3～6ヵ月毎、以降は最長5年まで1年毎に施行する
  - 5年以降の画像検査：臨床的な適応に従って施行する
- 胸部画像検査：
  - ベースラインの胸部CTを3～6ヵ月以内に施行し、その後は画像検査（CTが望ましい）を少なくとも3年間は3～6ヵ月毎、以降は最長5年まで1年毎の頻度で継続する
  - 5年以降の画像検査：各患者の特徴と腫瘍の危険因子に基づき臨床的に適応ありと判断した時点で施行する
- 追加の画像検査（すなわち、骨スキャン、脳画像検査）：
  - 症状から妥当と判断した時点で施行

a Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
b 単独ですべての患者に適切となるようなフォローアップ計画は存在しない。フォローアップの頻度および期間は患者毎の要件に応じて個別化すべきであり、5年を超えて継続してもよい（KID-B, 5 of 5を参照）。最適なフォローアップ期間の決定には、更なる研究が必要である。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

フォローアップ
（カテゴリー2B）

補助療法後のフォローアップ

- II期またはIII期症例で補助療法を受けた患者には臨床的なフォローアップを行うべきである。

再発例または外科的に切除不能のIV期症例に対するフォローアップ[c,d]

- 全身療法を受けている患者には病歴聴取と身体診察を6～16週毎に行い、臨床的に適応があればより頻回に行い、受けている全身療法の種類に応じて調整する。
- 使用中の治療薬に対する要件に応じた臨床検査
- 胸部、腹部および骨盤の画像検査：
  - 治療前または経過観察前のベースライン評価を行うためのCTまたはMRI
  - 医師の判断、患者の臨床状態および治療スケジュールに応じて6～16週間毎にフォローアップの画像検査。病状の変化の速さと活動性疾患がみられる部位に応じて画像検査の実施間隔を調整する。
- ベースライン時および臨床的に適応となった時点で頭部MRI（望ましい）またはCTを考慮する。医師の判断で1年毎にサーベイランス目的の画像検査を施行する。
- 臨床的な適応に従って脊椎MRI
- 臨床的な適応に従って骨スキャン

c 臨床的に適応がある場合は造影剤を用いた画像検査。
d 単独ですべての患者に適切となるようなフォローアップ計画は存在しない。フォローアップは、治療スケジュール、副作用、併存症および症状に基づいて個別化すべきである。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

フォローアップ
（カテゴリー2B）

長期のフォローアップ（＞5年）

- フォローアップは、競合する死因、RCCの個人的な危険因子、患者の一般全身状態、および患者の希望を評価した結果に基づいて考慮すべきである。
- 適切な場合はプライマリケア医がフォローアップを行ってもよい。
- 病歴聴取と身体診察を1年毎に施行して、遠隔転移または治療の後遺症の発生について評価すべきである。
- 手術施行例では臨床検査を1年毎に施行して、腎機能を評価し、糸球体濾過量を決定すべきである。
- 画像検査：
  - 異時性腫瘍および/または遅発性の再発が起きるリスクが低いものの有意にあるため、腹部画像検査は施行間隔を広げながら推奨されるフォローアップの枠を超えて継続してもよい。
  - 遅発性の再発が起きるリスクが低いものの有意にあるため、病期がより進行している患者に対する胸部画像検査と施行間隔を広げることを考慮する。

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注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発例またはIV期症例に対する全身療法の原則

淡明細胞型腎細胞癌に対する一次治療			
リスク	望ましいレジメン	その他の推奨レジメン	特定の状況で有用
低リスク[a]	• アキシチニブ＋ペムブロリズマブ[b] • パゾパニブ • スニチニブ	• イピリムマブ＋ニボルマブ[b] • アキシチニブ＋アベルマブ[b] • カボザンチニブ（カテゴリー2B）	• Active surveillance[c] • アキシチニブ（カテゴリー2B） • 高用量IL-2[d]
高/中リスク[a]	• イピリムマブ＋ニボルマブ[b]（カテゴリー1） • アキシチニブ＋ペムブロリズマブ[b]（カテゴリー1） • カボザンチニブ	• パゾパニブ • スニチニブ • アキシチニブ＋アベルマブ[b]	• アキシチニブ（カテゴリー2B） • 高用量IL-2[d] • テムシロリムス[e]

淡明細胞型腎細胞癌に対する二次治療		
望ましいレジメン	その他の推奨レジメン	特定の状況で有用
• カボザンチニブ（カテゴリー1） • ニボルマブ[b]（カテゴリー1） • イピリムマブ＋ニボルマブ[b]	• アキシチニブ（カテゴリー1） • レンバチニブ＋エベロリムス（カテゴリー1） • アキシチニブ＋ペムブロリズマブ[b] • エベロリムス • パゾパニブ • スニチニブ • アキシチニブ＋アベルマブ[b]（カテゴリー3）	• ベバシズマブ[f]（カテゴリー2B） • ソラフェニブ（カテゴリー2B） • 限定された患者[d]には高用量IL-2（カテゴリー2B） • テムシロリムス[e]（カテゴリー2B）

[a] 治療指針を得るためのリスクモデル（IMDC基準またはMSKCC予後予測モデル）（KID-D）を参照のこと。
[b] NCCN免疫療法関連毒性管理ガイドラインを参照のこと。
[c] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[d] 一般全身状態が非常に良好で臓器機能が正常な患者。
[e] Global ARCC Trialでテムシロリムスによる治療の指針を得るために採用されたモデルでの高リスクの定義は、6つの予後不良因子、すなわち診断から全身療法開始までの期間が1年未満、Karnofskyの一般全身状態スコアが60～70、ヘモグロビン値が正常下限値未満、補正カルシウム値が10mg/dL以上、LDH値が正常上限値の1.5倍以上、複数臓器への転移ありのうち3つ以上を認めるというものであった。Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[f] FDAの承認を受けたバイオシミラーはベバシズマブの代替として適切である。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

再発例またはIV期症例に対する全身療法の原則

非淡明細胞型腎細胞癌に対する全身療法[g]		
望ましいレジメン	その他の推奨レジメン	特定の状況で有用
• 臨床試験 • スニチニブ	• カボザンチニブ • エベロリムス • レンバチニブ＋エベロリムス	• アキシチニブ • ベバシズマブ[f] • エルロチニブ • ニボルマブ[b] • パゾパニブ • 遺伝性平滑筋腫症・腎細胞癌症候群（HLRCC）を含む乳頭状RCCの限定された進行例にはベバシズマブ[f]＋エルロチニブ • ベバシズマブ[f]＋エベロリムス • テムシロリムス[e]（高リスク群ではカテゴリー1、その他のリスク群ではカテゴリー2A）

b NCCN免疫療法関連毒性管理ガイドラインを参照のこと。

e Global ARCC Trialでテムシロリムスによる治療の指針を得るために採用されたモデルでの高リスクの定義は、6つの予後不良因子、すなわち診断から全身療法開始までの期間が1年未満、Karnofskyの一般全身状態スコアが60～70、ヘモグロビン値が正常下限値未満、補正カルシウム値が10mg/dL以上、LDH値が正常上限値の1.5倍以上、複数臓器への転移ありのうち3つ以上を認めるというものであった。Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.

f FDAの承認を受けたバイオシミラーはベバシズマブの代替として適切である。

g 集合管癌と髄質癌に対しては、細胞傷害性薬剤（カルボプラチン＋ゲムシタビン、カルボプラチン＋パクリタキセル、またはシスプラチン＋ゲムシタビン）および尿路上皮癌に対して現在用いられている他のプラチナベースの化学療法で部分奏効が認められている。腎髄質癌ではゲムシタビン＋ドキソルビシンでも奏効が得られる（Roubaud G, et al. Oncology 2011;80:214-218; Shah AY, et al. BJU Int 2017;120:782-792）。腎髄質癌の患者では、一般に経口薬による分子標的療法で奏効が得られない。臨床試験以外では、プラチナベースの化学療法レジメンが腎髄質癌に対して望ましい治療となるはずである。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

治療指針を得るためのリスクモデル

Memorial Sloan Kettering Cancer Center（MSKCC）の予後予測モデル[a]

予後因子
- 診断から治療までの期間が1年未満
- Karnofskyの一般全身状態スコアが80%未満
- 血清乳酸脱水素酵素（LDH）値が正常上限値（ULN）の1.5倍を超える
- 補正血清カルシウム濃度がULNを超える
- 血清ヘモグロビン値が正常下限値（LLN）未満

予後リスク群
- 低リスク群（low-risk）：予後因子なし
- 中リスク群（intermediate-risk）：予後因子が1つまたは2つ
- 高リスク群（poor-risk）：予後因子が3つ以上

International Metastatic Renal Cell Carcinoma Database Consortium（IMDC）の基準[b]

予後因子
1. 診断から全身療法までの期間が1年未満
2. 一般全身状態スコアが80%未満（Karnofsky）
3. ヘモグロビン値＜正常下限値（正常下限：120g/Lまたは12g/dL）
4. カルシウム値＞正常上限値（正常範囲：8.5～10.2mg/dL）
5. 好中球数＞正常上限値（正常範囲：2.0～7.0×10^9/L）
6. 血小板数＞正常上限値（正常範囲：150,000～400,000）

予後リスク群
- 低リスク群（favorable-risk）：予後因子なし
- 中リスク群（intermediate-risk）：予後因子が1つまたは2つ
- 高リスク群（poor-risk）：予後因子が3つから6つ

[a] Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289-296.
[b] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. J Clin Oncol 2009;27:5794-5799.

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

遺伝性腎細胞癌症候群の更なる遺伝学的リスク評価の基準[a]

- 癌感受性遺伝子の病的バリアント（pathogenic/likely pathogenic）が判明している近親者[b]がいる個人 → GENE-1を参照

- 以下の基準のいずれかを満たすRCCを有する個人：
  - 診断時年齢が46歳以下
  - 腫瘍が両側性または多発性
  - 第一度または第二度近親者[b]にRCC患者がいる

→ 癌遺伝学の専門家への紹介を考慮
および
特異的症候群を参照 — 遺伝性腎細胞癌症候群の概要（HRCC-2）を参照 → GENE-1を参照

- 腫瘍に以下の組織学的特徴が認められる個人
  - 多巣性の乳頭状組織像
  - 遺伝性平滑筋腫症・腎細胞癌症候群（HLRCC）関連RCC、フマル酸ヒドラターゼ（FH）欠損またはHLRCCに関連するその他の組織学的特徴
  - Birt-Hogg-Dubé症候群（BHDS）に関連する組織像（多発性の嫌色素癌、オンコサイトーマ、またはこれらの混在）
  - 1人の個人に腎血管筋脂肪腫に加えて結節性硬化症の基準を1つ認める（表1を参照）
  - コハク酸脱水素酵素（SDH）欠損RCCの組織像[c]

[a] 表はACMG Practice Guidelinesより改変。Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med 2015;17:70-87. Schuch B, Vourganti S, Ricketts CJ, et al. Defining early-onset kidney cancer: Implications for germline and somatic mutation testing and clinical management. J Clin Oncol 2014;32:431-437.

[b] 対象とする近親者には患者の第一度（親、同胞、子）および第二度（片親の異なる同胞、おば、おじ、姪、甥、祖父母、孫）近親者を含める。

[c] SDHBの染色喪失を示す腫瘍は、SDH欠損腫瘍と呼ばれている。それらの腫瘍の形態学的特徴としては、充実性または局所的に嚢胞性の増殖、綿毛状構造を有する好酸性細胞質を示すを示す均一な細胞像、細胞質内の空胞形成および封入体、円形から卵円形の低異型度の核などがある。（Ricketts CJ, Shuch B, Vocke CD, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol 2012;188:2063-71; Gill AJ, Hes O, Papathomas T, et al. Succinate dehydrogenase [SDH]-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol 2014;38:1588-1602; Gill AJ. Succinate dehydrogenase [SDH] and mitochondrial driven neoplasia. Pathology 2012;44:285-292.）

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

遺伝性腎細胞癌症候群の概要

症候群/遺伝子	組織像	遺伝形式 主な臨床像	スクリーニングに関与する他の専門医
フォンヒッペル-リンドウ(VHL)/*VHL*遺伝子	淡明細胞型	• 常染色体優性 • 表2を参照	• 脳神経外科 • 眼科 • 耳科 • 内分泌科 • 内分泌外科
遺伝性乳頭状腎細胞癌(HPRC)/*MET*遺伝子	1型乳頭状	• 常染色体優性 • 多巣性、両側性の腎細胞腫瘍	• 腎臓科
Birt-Hogg-Dubé症候群(BHDS)/*FLCN*遺伝子[d,e]	嫌色素癌、オンコサイトーマとのハイブリッド	• 常染色体優性 • 皮膚の線維毛包腫(fibrofolliculoma)または毛盤腫(trichodiscoma)、肺嚢胞および自然気胸	• 呼吸器科 • 皮膚科
結節性硬化症(tuberous sclerosis complex:TSC)/*TSC1, TSC2*遺伝子	血管筋脂肪腫、淡明細胞型	• 常染色体優性 • 表1を参照	• 神経内科 • 皮膚科
遺伝性平滑筋腫症・腎細胞癌症候群(HLRCC)/*FH*遺伝子	HLRCCまたはFH関連RCC/2型乳頭状	• 常染色体優性 • 皮膚および子宮の平滑筋腫、片側性、孤立性および進行の速い腎細胞腫瘍 PET陽性の副腎腺腫	• 婦人科 • 皮膚科
BAP1 tumor predisposition syndrome(TPDS)/*BAP1*遺伝子[f,g]	淡明細胞型、嫌色素性	• 常染色体優性 • 黒色腫(ぶどう膜および皮膚)、腎癌、中皮腫	• 皮膚科 • 眼科 • 胸部腫瘍科
遺伝性傍神経節腫/褐色細胞腫(PGL/PCC)症候群/*SDHA/B/C/D*遺伝子	淡明細胞型(通常は*SDHB*ではない)、嫌色素性、2型乳頭状、腎オンコサイトーマ、オンコサイトーマ成分を含む腫瘍(oncocytic neoplasm)	• 常染色体優性 • 頭頸部傍神経節腫および副腎または副腎外褐色細胞腫、良性肺病変、GIST	• 内分泌科 • 内分泌外科

GENE-1を参照

d Schmidt LS, Nickerson ML, Warren MB, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dubé syndrome. Am J Hum Genet 2005;76:1023-1033.
e Sattler EC, Steinlein OK. Birt-Hogg-Dubé Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle;1993-2020.
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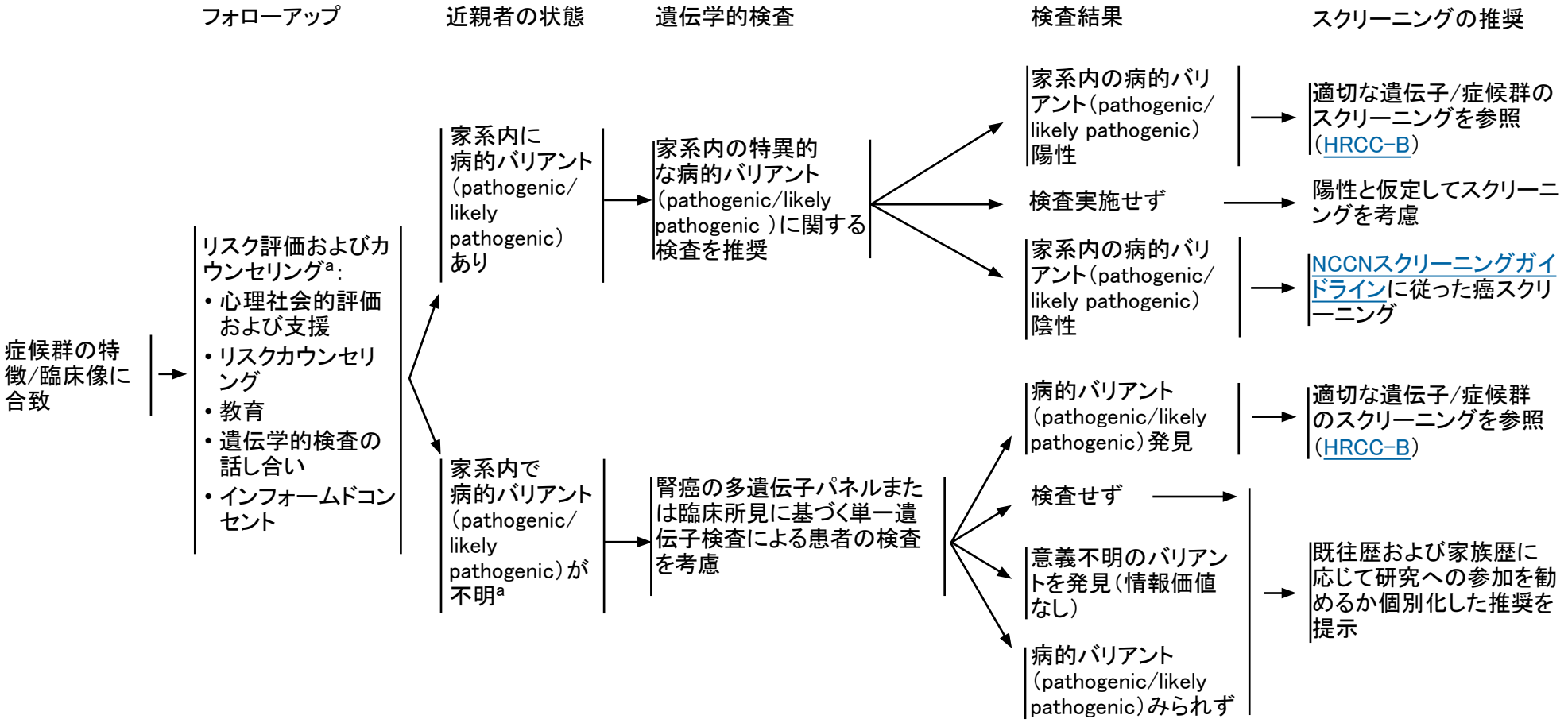
注意:特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験:NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。



[a] 診断基準に合致するが生殖細胞系列変異が同定されていない個人では、モザイクを検出するための精査を考慮すること。

注意:特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験:NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

表1：結節性硬化症（TSC）の特徴

大症状	小症状
• 腎血管筋脂肪腫（AML）[1,2] • 心横紋筋腫 • 結節や大脳白質神経細胞移動線などの皮質異形成 • 血管線維腫（3つ以上）または頭部の線維性局面 • 低色素斑（直径5mm以上が3個以上） • リンパ脈管筋腫症（LAM）[1] • 結節状の多発性網膜過誤腫 • 粒起革様皮（shagreen patch） • 上衣下巨細胞性星細胞腫（SEGA） • 上衣下結節（SEN） • 爪線維腫（2つ以上）	• 多発性腎嚢胞 • 紙吹雪様皮膚病変または金平糖様白斑（上肢や下肢などの領域に1～3mmの低色素斑が多数散在） • 歯エナメル小窩（3つを超える） • 口腔内線維腫（2つ以上） • 腎以外の過誤腫 • 網膜無色素斑

表2：フォンヒッペル-リンドウ（VHL）病の特徴

意義の大きい特徴	意義の小さい特徴
• 網膜、脊髄または脳の血管芽腫 • 40歳未満で診断された淡明細胞型RCC（ccRCC）または診断年齢を問わない多発性/両側性のccRCC • 副腎腫瘍または傍神経節腫 • 腹部、胸部または頸部の傍神経節腫 • 網膜血管腫	• 内リンパ嚢腫瘍 • 精巣上体または子宮広間膜の乳頭状嚢胞腺腫 • 膵漿液性嚢胞腺腫（2つ以上） • 膵神経内分泌腫瘍または多発性膵嚢胞（2つ以上）

[1] AMLとLAMの併発は確定診断の基準を満たさない。
[2] 多発性のAMLは大症状である。

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

RCCの画像および病理学的診断を受けていない
遺伝性RCCの確定例に対する腎特異的なスクリーニングに関する推奨

全般

- フォローアップは、治療スケジュール、副作用、併存症および症状に基づいて個別化すべきである。
- 可能であれば常に、患者のケアに関与する他の専門医とスクリーニングについて調整を図るべきである。
- 妊娠を計画している妊娠可能年齢の女性は、妊娠前に腎画像検査を考慮すべきである。
- 若年で診断された家系員がいる場合は、家系内で最も低い診断年齢の10歳前からスクリーニングを開始すべきである。
- 腹部CTを手術計画に用いることができるが、遺伝性症候群患者の生涯にわたる放射線被曝量を考慮すると、サーベイランス目的での施行は可能であれば制限すべきである。
- 病変が検出されたら、病変の増殖速度および大きさに基づき画像検査の頻度を増やす。
- 各症候群の手術に関する推奨についてはHRCC-Cを、全身療法についてはHRCC-Dを参照のこと。

BAP1-TPDS

- 腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）を30歳から2年毎に施行[1]

BHDS

- 腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）を20歳から3年毎に施行[2]

HLRCC

- 腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）を8～10歳から1年毎に施行[3]

HPRC

- 腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）を30歳から1～2年毎に施行[4,5]

PGL/PCC

- 腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）を12歳から4～6年毎に施行[5,6,8]

TSC

- 腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）を12歳から3～5年毎に施行[7]

VHL

- 腎臓、膵臓および副腎を評価するための腹部MRI（望ましい）またはCT（静注造影剤を使用または不使用）によるを15歳から2年毎に施行[5]

参考文献はHRCC-B 2 of 2

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

RCCの画像および病理学的診断を受けていない遺伝性RCCの確定例に対する腎特異的なスクリーニングに関する推奨

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注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

遺伝性RCCの確定例に対する腎特異的な手術に関する推奨

- 術前の注意：PGL/PCCまたはVHLが疑われるかその診断を受けた患者は、褐色細胞腫のリスクが高いため、種類を問わず外科的処置を受ける前に血液および/または尿検査による褐色細胞腫のスクリーニングを受けるべきである。

BAP1-TPDS
- 本症候群の外科的管理に関する特異的なガイドラインはない（KID-Aを参照）。

BHDS
- 可能な場合は常に腎温存手術が腎腫瘍に対する第一選択の治療法であり、生涯で複数の腫瘍が発生する可能性があることも考慮する[1]。
- 手術を受けるには有意な医学的または外科的リスクがある患者には、アブレーション治療の選択肢を考慮してもよい。

HLRCC
- この種の腫瘍は進行が速い可能性があるため、腎腫瘍のサーベイランスは推奨されず、根治的腎摘除術を考慮すべきである[2]。

HPRC
- 可能な場合は常に腎温存手術が腎腫瘍に対する第一選択の治療法であり、生涯で複数の腫瘍が発生する可能性があることも考慮する。
- 手術を受けるには有意な医学的または外科的リスクがある患者には、アブレーション治療の選択肢を考慮してもよい。

PGL/PCC
- 進行が速いことを示す組織所見がみられない早期の悪性腫瘍には、外科的切除を施行すべきであり、腎部分切除術を考慮してもよい。
- 大きな腫瘍と進行が速いことを示す組織所見（例えば、高異型度、肉腫様型）を認める腫瘍には、根治的腎摘除術を考慮すべきである[3]。

TSC
- AMLはTSCに合併する良性病変であり、別途管理される[4,5,6]。
- 可能な場合は常に腎温存手術が悪性腎腫瘍に対する第一選択の治療法であり、生涯で複数の腫瘍が発生する可能性があることも考慮する[7]。
- 手術を受けるには有意な医学的または外科的リスクがある患者には、アブレーション治療の選択肢を考慮してもよい。

VHL
- VHL患者における限局性腎腫瘤の管理では、典型的には「3cmルール」が指針とされる[7]。
- 考え方としては、患者にとって最も有益となる時点で介入を行うことで遠隔転移が発生する可能性を低減するのと同時に、本疾患の患者の多くが生涯を通じて繰り返し受けることになる複数回の切除と、その後に発生する慢性および進行性の腎不全のことも考慮する[7,8]。
- もし可能であれば腎部分切除術を施行し、複雑な腎部分切除術の外科的な専門知識・技能を保有し、VHL患者の管理に対応できる施設への紹介を考慮すべきである[8]。
- 手術を受けるには有意な医学的または外科的リスクがある患者には、アブレーション治療の選択肢を考慮してもよい。

参考文献はHRCC-C 2 of 2

注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

遺伝性RCCの確定例に対する腎特異的な手術に関する推奨
参考文献

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注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

遺伝性RCCの確定例に対する腎特異的な全身療法

HLRCC

- HLRCCに対してFDAの承認を受けた特異的な治療法はない。エルロチニブ＋ベバシズマブ[1]による治療は、HLRCCからの転移性RCC患者においてベネフィットを示した（KID-Cを参照）[2]。

TSC

- エベロリムスは、直径3cmを超えて増殖を続けている無症状の血管筋脂肪腫を適応としてFDAが承認した治療薬である[3]。

VHL病

- 現時点では、VHL病で発生する非転移性RCCに対してFDAの承認を受けた特異的な治療法はない。しかしながら、31例を対象とした第II相試験では、腎病変におけるパゾパニブの客観的奏効率が50%を超えていた[4]。

1 An FDA-approved biosimilar is an appropriate substitution for bevacizumab.
2 Srinivasan R, Su D, Stamatakis L, et al. Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib [abstract]. Eur J Cancer 2014;Abstract 50.
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注意：特に指定のない限り、すべての推奨はカテゴリー2Aである。
臨床試験：NCCNはすべてのがん患者にとって、最良の管理法は臨床試験にあると考えている。臨床試験への参加が特に推奨される。

表1. American Joint Committee on Cancer（AJCC）
腎癌のTNM病期分類（2017年第8版）

T	原発腫瘍
TX	原発腫瘍の評価が不可能である
T0	原発腫瘍を認めない
T1	腫瘍の最大径が7cm以下であり、かつ腎臓に限局している
T1a	腫瘍の最大径が4cm以下であり、かつ腎臓に限局している
T1b	腫瘍の最大径が4cmを超えているが7cmは超えず、かつ腎臓に限局している
T2	腫瘍の最大径が7cmを超えており、かつ腎臓に限局している
T2a	腫瘍の最大径が7cmを超えているが10cmは超えず、かつ腎臓に限局している
T2b	腫瘍の最大径が10cmを超えており、かつ腎臓に限局している
T3	主要な静脈内への進展または腎周囲組織への浸潤を認めるが、同側副腎への浸潤はなく、Gerota筋膜は越えていない
T3a	腎静脈またはその領域内の分枝への進展を認めるか、腎盂腎杯への浸潤を認めるか、周囲および/または腎洞脂肪組織への浸潤を認めるが、Gerota筋膜は越えていない
T3b	横隔膜までの下大静脈内への進展を認める
T3c	横隔膜を越える下大静脈内への進展または下大静脈壁への浸潤を認める
T4	腫瘍がGerota筋膜を越えて浸潤している（同側副腎への連続的な進展を含む）
N	所属リンパ節
NX	所属リンパ節の評価が不可能である
N0	所属リンパ節転移を認めない
N1	所属リンパ節に転移を認める
M	遠隔転移
M0	遠隔転移を認めない
M1	遠隔転移を認める

表2. AJCC予後分類

	T	N	M
I期	T1	N0	M0
II期	T2	N0	M0
III期	T1-T2	N1	M0
	T3	NX,N0-N1	M0
IV期	T4	すべてのN	M0
	すべてのT	すべてのN	M1

表3. 組織学的グレード（G）

GX	グレードの評価が不可能である
G1	核小体が400倍の拡大像で認められないか目立たず好塩基性である
G2	核小体が400倍の拡大像で目立たず好酸性であり、100倍の拡大像で視認できるが目立ってはいない
G3	核小体が100倍の拡大像で目立たず好酸性である
G4	著明な核の多形性および/または多核巨細胞および/またはラブドイドおよび/または肉腫様型分化を認める

イリノイ州シカゴのAmerican College of Surgeonsの許可を得て使用。この情報の原本は、Springer International Publishing発行のAJCC Cancer Staging Manual 第8版（2017年）である。

NCCNのエビデンスとコンセンサスによるカテゴリー	
カテゴリー1	高レベルのエビデンスに基づいており、その介入が適切であるというNCCNの統一したコンセンサスが存在する。
カテゴリー2A	比較的低レベルのエビデンスに基づいており、その介入が適切であるというNCCNの統一したコンセンサスが存在する。
カテゴリー2B	比較的低レベルのエビデンスに基づいており、その介入が適切であるというNCCNのコンセンサスが存在する。
カテゴリー3	いずれかのレベルのエビデンスに基づいてはいるが、その介入が適切であるかという点でNCCN内に大きな意見の不一致がある。

特に指定のない限り、すべての推奨はカテゴリー2Aである。

NCCNの望ましさによるカテゴリー	
望ましい介入	優れた有効性、安全性およびエビデンスと（状況に応じて）費用の手頃さに基づいた介入
その他の推奨される介入	その他の介入のうち、いくらか有効性が低いもの、毒性が強いもの、比較的未成熟のデータに基づくもの、あるいは同様の結果を得るのに費用の手頃さで有意に劣るもの
特定の状況で有用	その他の介入のうち、特定の患者集団（推奨とともに定義を示す）に使用できるもの

いずれの推奨も適切と考えられる。

Discussion

This discussion corresponds to the NCCN Guidelines for Kidney Cancer. Last updated on 02/16/2019.

Table of Contents

Overview

An estimated 73,820 Americans will be diagnosed with cancers of the kidney and renal pelvis and 14,770 will die of the disease in the United States in 2019.[1] Renal cell carcinoma (RCC) comprises approximately 3.8% of all new cancers, with a median age at diagnosis of 64 years.[2] Approximately 85% of kidney tumors are RCC, and approximately 70% of these have a clear cell histology.[3-5] Other less common cell types include papillary, chromophobe, translocation, and Bellini duct (collecting duct) tumors. Medullary renal carcinoma is a rare and aggressive RCC variant that almost exclusively arises in patients who are sickle-cell trait positive.[6]

Smoking, obesity, and hypertension are established risk factors for RCC development. Several hereditary types of RCC also exist, with von Hippel-Lindau (VHL) disease being the most common. VHL disease is caused by an autosomal-dominant constitutional mutation in the *VHL* gene that predisposes to clear cell RCC and other proliferative vascular lesions.[7-10] Analysis of the SEER database indicates that RCC incidence has been rising on average 0.6% each year and death rates have been falling on average 0.7% each year from 2006 through 2015.[2] The 5-year survival for localized RCC has increased from 88.4% (during 1992–1995) to 92.6% (during 2007–2013) and for advanced disease from 7.3% (during 1992–1995) to 11.7% (during 2007–2013).[11] The most important prognostic determinants of 5-year survival are the tumor stage, grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation.[12-21] RCC primarily metastasizes to the lung, bone, liver, lymph nodes, adrenal gland, and brain.[8,22,23]

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for the clinical management of patients with clear cell and non-clear cell RCC. These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Kidney Cancer, an electronic search of the PubMed database was performed to obtain key literature in Kidney Cancer, published since the previous Guidelines update, using the following search terms: Renal Cell Carcinoma or Kidney Cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[24]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search results was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and/or discussed by the panel have been included in this version of the Discussion section (ell , e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Initial Evaluation and Staging

Patients with RCC typically present with a suspicious mass involving the kidney that has been visualized using a radiographic study, often a CT scan. As the use of imaging methods (eg, abdominal CT with or without pelvic CT, ultrasound [US]) has become more widespread, the frequency of incidental detection of RCC has increased[25,26] and fewer patients present with the typical triad symptoms (hematuria, flank mass, and flank pain).

Less frequently, patients present with signs or symptoms resulting from metastatic disease, including bone pain, adenopathy, and pulmonary symptoms attributable to lung parenchyma or mediastinal metastases. Other presentations include fever, weight loss, anemia, or a varicocele. RCC in younger patients (≤46 years) may indicate an inheritable disorder,[27] and these patients should be referred to a hereditary cancer clinic for further evaluation.

A thorough physical examination should be performed along with obtaining a complete medical history of the patient. Laboratory evaluation includes a complete blood count (CBC) and comprehensive metabolic panel. The metabolic panel may include serum corrected calcium, serum creatinine, liver function studies, and urinalysis.

CT of the abdomen with or without pelvic CT and chest x-ray are essential studies in the initial workup.[28] For metastatic evaluation, at the very least, chest radiography must be performed, although chest CT is more accurate than chest radiograph for chest staging.[29,30] Abdominal MRI is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT for detecting renal masses and for staging when contrast material cannot be administered because of allergy or moderate renal insufficiency.[31,32] All imaging studies should be performed with contrast, such as renal protocol.

A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology, uteroscopy, and percutaneous mass biopsy (if metastatic disease is present or the patient cannot tolerate ureteroscopy) should be considered.

Most bone and brain metastases are symptomatic at diagnosis. Therefore, a bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase (ALP) or complains of bone pain.[33] CT or MRI of the brain can be performed if clinical signs, presentation, and symptoms suggest brain metastases.

The recommended abdominal imaging studies provide high diagnostic accuracy. Therefore, a needle biopsy is not always necessary before surgery, especially in patients and clear findings in the imaging studies. In selected individuals, needle biopsy may be considered for small lesions to establish diagnosis of RCC and guide active surveillance strategies, cryosurgery, radiofrequency, and ablation strategies.[34] As noted above, biopsy should also be considered if a central lesion or a homogeneous infiltration of renal parenchyma is observed on scans to rule out urothelial carcinoma or lymphoma, respectively.

The value of PET in RCC remains to be determined. Currently, PET alone is not a tool that is standardly used to diagnose kidney cancer or follow for evidence of relapse after nephrectomy.[35]

The use of current TNM classification[36] and classification of histologic subtypes[37] are important in making treatment decisions.

Treatment of Localized Disease

Surgical resection remains an effective therapy for clinically localized RCC, with options including radical nephrectomy and nephron-sparing surgery—each detailed below. Each of these modalities is associated with

its own benefits and risks, the balance of which should optimize long-term renal function and expected cancer-free survival.

Nephron-Sparing Surgery and Radical Nephrectomy

A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava. Open, laparoscopic, or robotic surgical techniques may be used to perform radical nephrectomy. Long-term outcomes data indicate that laparoscopic and open radical nephrectomies have equivalent cancer-free survival rates.[38-45]

Originally, partial nephrectomy (nephron-sparing surgery) was indicated only in clinical settings in which a radical nephrectomy would render the patient functionally anephric, necessitating dialysis. These settings include RCC in a solitary kidney, RCC in one kidney with inadequate contralateral renal function, and bilateral synchronous RCC.

Partial nephrectomy has well-established oncologic outcomes data comparable to radical nephrectomy.[46-51] Radical nephrectomy can lead to an increased risk for chronic kidney disease[52,53] and is associated with increased risks of cardiovascular morbidity and mortality according to population-based studies.[54] When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality, and reduced frequency of cardiovascular events.[54-58] Patients with a hereditary form of RCC, such as VHL disease, should also be considered for nephron-sparing therapy. Nephron-sparing surgery has been used increasingly in patients with T1a and T1b renal tumors (ie, up to 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.[49,59-61] Radical nephrectomy should not be employed when nephron sparing can be achieved. A more recent study showed that among Medicare beneficiaries with early-stage kidney cancer, treatment with partial rather than radical nephrectomy was associated with improved survival.[62]

Studies with limited follow-up data show that the oncologic outcome for laparoscopic versus open nephron-sparing surgery appears to be similar.[63,64] A study of oncologic outcomes at 7 years after surgery found metastasis-free survival to be 97.5% and 97.3% (P = 0.47) after laparoscopic and open nephron-sparing surgery, respectively.[65]

The goals of nephron-sparing surgery should be optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.[66] However, in some patients with localized RCC, nephron-sparing surgery may not be suitable because of locally advanced tumor growth or because tumor is in an unfavorable location. Laparoscopic, robotic, and open partial nephrectomy all offer comparable outcomes in the hands of skilled surgeons. Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors.

Lymph Node Dissection

Lymph node dissection has not been consistently shown to provide therapeutic benefit. The EORTC phase III trial compared radical nephrectomy with a complete lymph node dissection to radical nephrectomy alone. The results showed no significant differences in overall survival (OS), time to progression of disease, or progression-free survival (PFS) between the two study groups.[67] However, primary tumor pathologic features such as nuclear grade, sarcomatoid component, tumor size, stage, and presence of tumor necrosis were all factors that influenced the likelihood of regional lymph node involvement at the time of radical nephrectomy.[68] Assessment of lymph node status is based on enlargement of imaging (CT/MRI) and on assessment by direct palpation at time of surgery. CT/MRI may not detect small metastases in normal lymph nodes.[69]

The NCCN Kidney Cancer Panel recommends regional lymph node dissection for patients with palpable or enlarged lymph nodes detected on preoperative imaging tests.

Adrenalectomy

Ipsilateral adrenal gland resection should be considered for patients with large upper pole tumors or abnormal-appearing adrenal glands on CT.[70-72] Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high risk, based on size and location.[73]

Active Surveillance and Ablative Techniques

Active surveillance[74,75] is defined as the initial monitoring of tumors using abdominal imaging techniques with delayed intervention when indicated. Elderly patients and those with small renal masses (<2 cm) and other comorbidities often have a low RCC-specific mortality.[76] Active surveillance and ablative techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks.

Randomized phase III comparison of ablative techniques with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been performed.

The NCCN Kidney Cancer Panel has addressed the utility of each of the above-mentioned treatment modalities for localized disease in the context of tumor stages: stage I (T1a and T1b), stage II, and stage III.

Management of Stage I (T1a) Disease

The NCCN Panel prefers surgical excision by partial nephrectomy for the management of clinical stage I (T1a) renal masses. Adequate expertise and careful patient selection are important. Partial nephrectomy is most appropriate in patients with small unilateral tumors or whenever preservation of renal function is a primary issue, such as in patients having one kidney or those with renal insufficiency, bilateral renal masses, or familial RCC. Both open and laparoscopic approaches to partial nephrectomy can be considered, depending on tumor size, location, and the surgeon's expertise.

Some localized renal tumors may not be amenable to partial nephrectomy, in which case radical nephrectomy is recommended. The NCCN Guidelines also list radical nephrectomy as an alternative for patients with stage I (T1a) RCC if a partial nephrectomy is not technically feasible as determined by the urologic surgeon.

Other options in selected patients with stage I (T1a) RCC include active surveillance and ablative techniques. Active surveillance is an option for the management of localized renal masses and should be a primary consideration for patients with decreased life expectancy or extensive comorbidities that would place them at excessive risk for more invasive intervention. Short- and intermediate-term oncologic outcomes indicate that an appropriate strategy is to initially monitor small renal masses, and, if required, to treat for progression.[74]

Although distant recurrence-free survival rates of ablative techniques and conventional surgery are comparable, ablative techniques have been associated with an increased risk of local recurrence.[77-80] Judicious patient selection and counseling remain of paramount importance for these less invasive technologies.

The NCCN Guidelines recommend active surveillance and ablative techniques only in selected patients with stage I (T1a) RCC.

Management of Stage I (T1b) Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.[81,82] Surgery by partial nephrectomy, whenever feasible, or by radical nephrectomy is the

standard of care for clinical T1b tumors according to the NCCN Kidney Cancer Panel.

Management of Stage II and III Disease

The curative therapy for patients with stages II and III disease remains radical nephrectomy.[44] Radical nephrectomy is the preferred treatment for the tumors that extend into the inferior vena cava. Resection of a caval or atrial thrombus often requires the assistance of cardiovascular surgeons because treatment-related mortality may reach 10%, depending on the local extent of the primary tumor and the level of vena caval extension. Partial nephrectomy is generally not suitable for patients with locally advanced tumors; however, they may be performed in patients with locally advanced tumors if technically feasible and clinically indicated. For example, partial nephrectomy may be considered for those with small, polar, unilateral tumors.

The NCCN Panel lists radical nephrectomy or partial nephrectomy, if feasible or indicated, as options for stage II and III tumors.

Adjuvant Treatment for Clear Cell, High-Risk Localized RCC

For most patients with localized RCC, adjuvant treatment after nephrectomy has no established role in patients who have undergone a complete resection of their tumor. An exception is for patients with stage III disease, clear cell histology, and a high risk for relapse. For these patients, patients may be treated with adjuvant sunitinib (category 2B) for 1 year. There are several ongoing clinical trials testing additional targeted therapies in the adjuvant setting. Eligible patients should be offered enrollment in randomized clinical trials. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or incomplete tumor resection.

Historically, several trials involving adjuvant therapy failed to show a reduced likelihood of relapse. Randomized trials comparing adjuvant interferon alpha (IFN-α), high-dose interleukin-2 (IL-2), or cytokine combinations with observation alone in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy.[83] A multicenter, phase III study (ASSURE; ECOG-ACRIN E2805) in patients with high-grade tumors T1b or greater found no disease-free survival (DFS) or OS benefit with use of sunitinib or sorafenib versus placebo as adjuvant therapy after nephrectomy.[84] In addition, a subgroup analysis of the ASSURE trial found that neither the prognostic category of the tumor (ie, high-risk, clear cell subset of patients) nor the dose intensity of therapy altered the lack of difference in DFS or OS reported in the original study.[85] Similarly, a primary analysis of the phase III PROTECT study for patients with high-risk, locally advanced RCC reported no significant benefit in DFS for patients treated with adjuvant pazopanib compared to placebo.[86]

In contrast, the phase III S-TRAC trial was the first to show a benefit in DFS with adjuvant treatment following nephrectomy in RCC. S-TRAC was a multicenter, randomized study including 615 patients with locoregional, high-risk, clear cell cancer treated with adjuvant sunitinib (50 mg once daily; 4 weeks on, 2 weeks off) or placebo. Patients treated with sunitinib had a longer median DFS duration compared to those treated with placebo (6.8 years vs. 5.6 years; $P = .03$). Grade 3 or higher adverse events occurred in 63.4% of patients treated with sunitinib compared to 21.7% of those on placebo.[87] A subsequent subgroup analysis of patients on the S-TRAC trial found that the benefit of adjuvant sunitinib was observed across subgroups.[88] Median OS had not been reached in the sunitinib or placebo groups in either of these publications.[87,88]

The NCCN Panel recommended including sunitinib as an option for adjuvant therapy in patients at high risk for recurrence based on the DFS benefit demonstrated in the S-TRAC trial. Due to concerns from some panel members about toxicity, lack of a demonstrated OS benefit, and

conflicting results between the ASSURE and S-TRAC trials, there was not uniform consensus that this intervention is appropriate, leading to a category 2B recommendation.

Follow-up After Treatment of Localized Disease

After surgical excision, 20% to 30% of patients with localized tumors experience relapse. Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients. The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years.[89]

The NCCN Panel has provided a framework for follow-up of patients undergoing surveillance of a small renal mass and for patients who underwent surgery or ablative therapy of a primary RCC. The NCCN Panel has reiterated in a footnote that no single follow-up plan is appropriate for everyone, and follow-up should be modified for the individual patient using clinical judgment. Since uniform consensus among the panel members regarding the most appropriate follow-up plan is lacking, these recommendations are listed as category 2B. Also, the guidance for follow-up has been provided for the first 5 years after nephrectomy, with follow-up evaluation to be extended beyond 5 years at the discretion of the physician. Results from a retrospective analysis indicate that in a subset of patients, relapses occur more than 5 years after surgery for their primary RCC.[90] The analysis suggests that continued follow-up/surveillance after 5 years may be of potential value in some patients. Another retrospective analysis suggests that patients with lower risk are more likely to relapse later.[91] Identification of subsets of patients with higher risk who require longer follow-up has not been defined, and further research is required to refine follow-up strategies for patients with RCC.

The NCCN Guidelines incorporate a risk-stratified use of imaging that may target those patients most in need of intensive surveillance and/or imaging tests during follow-up.

Follow-up During Active Surveillance for Stage T1a

For follow-up during active surveillance, the NCCN Panel recommends a history and physical examination, a comprehensive metabolic panel, and other tests every 6 months for 2 years and then annually for up to 5 years after diagnosis. In order to study the growth rate of the tumor, the NCCN Panel recommends abdominal imaging (with CT or MRI) within 6 months for 2 years from initiation of active surveillance; subsequent imaging (with CT, MRI, or US) may be performed annually thereafter. All three modalities (US, CT, and MRI) have been found to accurately predict pathologic tumor size in a retrospective analysis.[92] Therefore, best clinical judgment should be used in choosing the imaging modality. For patients with biopsy positive for RCC, the recommendation is to annually assess for pulmonary metastases using chest imaging techniques (chest x-ray or chest CT). The panel recommends imaging of the pelvis; CT or MRI of the head or spine, if there are neurologic symptoms; or bone scan in cases of elevated ALP, bone pain, or abnormal radiologic findings.

Follow-up After Ablative Therapy for Stage T1a

Most follow-up tests after ablative therapy included by the NCCN Panel are similar to the follow-up tests included during active surveillance. For imaging tests after ablative therapy, the NCCN Panel recommends abdominal CT or MRI with and without IV contrast unless otherwise contraindicated at 3 and 6 months to assess treatment response followed by annual abdominal CT or MRI scans for five years. The NCCN Panel recommends annual chest x-ray or CT to assess for pulmonary metastases for five years for those who have biopsy-proven low-risk RCC, non-diagnostic biopsies, or no prior biopsy to assess for liver metastases. The panel suggests repeat biopsy if there is radiographic evidence of

progressive increase in size of an ablated neoplasm with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, or evidence of satellite or port site lesions.

Follow-up After Nephrectomy for Stages I–III

For patients with stages pT1a and pT1b after partial or radical nephrectomy, the NCCN Panel recommends a history and physical examination, comprehensive metabolic panel, and other tests every 6 months for 2 years and then annually for up to 5 years after nephrectomy. The panel recommends a baseline abdominal scan (CT, MRI, or US) for patients undergoing either partial nephrectomy or radical nephrectomy within 3 to 12 months following renal surgery. If the initial postoperative imaging is negative, abdominal imaging beyond 12 months for patients who have undergone radical nephrectomy may be performed at the discretion of the physician. For those who have undergone partial nephrectomy, abdominal scans (CT, MRI, or US) may be considered annually for 3 years based on individual risk factors. The rates of local recurrence for smaller tumors after partial nephrectomy are 1.4% to 2% versus 10% for larger tumors.[63,93,94]

The panel recommends yearly chest imaging (chest x-ray or CT) for three years as clinically indicated thereafter and recommends imaging of the pelvis, CT or MRI of the head and spine, or bone scan performed as clinically indicated.

For patients with stage II–III after radical nephrectomy, larger tumors have a substantially higher risk of both local and metastatic recurrence; therefore, an increased frequency of examinations is recommended compared with patients with stages pT1a or pT1b. The NCCN Panel recommends a history and physical examination every 3 to 6 months for 3 years, then annually for 5 years after radical nephrectomy. The follow-up evaluation may be extended beyond 5 years at the discretion of the physician as clinically indicated. A comprehensive metabolic panel and other tests are recommended as clinically indicated every 6 months for 2 years, then annually for 5 years after radical nephrectomy, and thereafter as clinically indicated.

The panel recommends baseline chest imaging (with CT) and abdominal scans (CT or MRI) within 3 to 6 months following surgery with continued imaging (chest CT; CT, MRI, or US of the abdomen) every 6 months for at least 3 years, and annually thereafter for up to 5 years after radical nephrectomy.[95] While the use of US imaging for follow-up is an option for low-risk patients, CT is the preferred modality for those with a high risk of recurrence. There is disagreement among the panel members regarding the usefulness of US in patients with stage III disease; therefore, it is listed as a category 2B option specifically for patients with stage II disease. The panel has noted that imaging beyond 5 years may be performed as clinically indicated, and site-specific imaging may be performed as symptoms warrant. Other tests such as imaging of the pelvis, CT or MRI of the head or spine, or bone scan are recommended as clinically indicated.

Alternate surveillance programs have been proposed, such as the surveillance protocol based on the University of California Los Angeles (UCLA) Integrated Staging System (UISS).[96] The UISS is an evidence-based system in which patients are stratified based on the 1997 TNM stage, grade, and ECOG performance status into low-, intermediate-, or high-risk groups for developing recurrence or metastases post-surgical treatment of localized or locally advanced RCC.[96]

Management of Relapsed or Stage IV Disease

Patients with stage IV disease also may benefit from surgery. For example, lymph nodes suspicious for metastatic disease on CT may be hyperplastic and not involved with tumor; thus, the presence of minimal regional adenopathy does not preclude surgery.

Cytoreductive nephrectomy before systemic therapy is generally recommended in patients with a potentially surgically resectable primary tumor mass. A retrospective analysis conducted in the cytokine era indicated that patients most likely to benefit from cytoreductive nephrectomy before systemic therapy were those with lung-only metastases, good prognostic features, and good performance status.[97] Retrospective data from the International Metastatic RCC Database Consortium (IMDC) suggested that cytoreductive nephrectomy continues to play a role in patients treated with vascular endothelial growth factor (VEGF)-targeted agents.[98] The efficacy of newer systemic therapies is challenging the standard in some patients with metastatic disease. Recent results from the CARMENA phase III trial of patients with metastatic RCC who were eligible for cytoreductive nephrectomy found that sunitinib alone was non-inferior to sunitinib after nephrectomy.[99] The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the sunitinib after nephrectomy group (hazard ratio [HR], 0.89; 95% CI, 0.71–1.10), which did not exceed the fixed non-inferiority limit (1.20). However, many of the patients in this trial had poor-risk features, underscoring the importance of patient selection to obtain the greatest benefit from nephrectomy or targeted therapy.[99,100] At this point in time there are no prospective data defining the role of cytoreductive nephrectomy in patients who subsequently receive checkpoint antibody therapy. Further study will better define the role of cytoreductive nephrectomy in the rapidly evolving treatment landscape for RCC.

Patients with metastatic disease who present with hematuria or other symptoms related to the primary tumor should be offered palliative nephrectomy if they are surgical candidates. In addition, the small subset of patients with potentially surgically resectable primary RCC and oligometastatic sites are candidates for nephrectomy and management of metastases by surgical metastasectomy or with ablative techniques for selected patients who are not candidates for metastasectomy. Candidates include patients who: 1) initially present with primary RCC and oligometastatic sites; or 2) develop oligometastases after a prolonged disease-free interval from nephrectomy. Oligometastatic sites that are amenable to this approach include the lung, bone, and brain. The primary tumor and the metastases may be resected during the same operation or at different times. Most patients who undergo targeted treatment of oligometastases experience recurrence, but long-term relapse-free survival has been reported in these patients.

In patients whose tumors are surgically unresectable, the NCCN Panel recommends performing tissue sampling to confirm diagnosis of RCC to determine histology and guide subsequent management. Systemic therapy is generally recommended after recurrence, cytoreductive nephrectomy in patients with multiple metastatic sites, or for patients with surgically unresectable tumors.

Patients who have undergone a nephrectomy and years later develop an oligometastatic recurrence also have the option of metastasectomy, stereotactic body radiation therapy (SBRT),[101-103] or ablative techniques, in addition to the first-line therapy options below.

Systemic Therapy Options for Patients with Relapsed or Stage IV Disease

The cytokine era introduced IFN-α and high-dose IL-2 as therapies for RCC, which are now only used in selected patients. Targeted therapy utilizing tyrosine kinase inhibitors (TKIs), and/or anti-VEGF antibodies, is now widely used in first- and second-line treatments. Agents targeting the mammalian target of rapamycin (mTOR) are also used in this setting. A number of targeted agents have been approved by the FDA for the treatment of advanced RCC in the first and/or subsequent lines of therapy: sunitinib, sorafenib, pazopanib, axitinib, temsirolimus, everolimus, bevacizumab in combination with interferon, cabozantinib, and lenvatinib (plus everolimus). Immune checkpoint inhibitors are the new revolution in

treatment options. Checkpoint antibodies alter the interaction between immune cells and antigen-presenting cells, including tumor cells. These agents can augment an anti-tumor immune response and have shown promise in a number of tumor indications. Recent studies have shown efficacy of nivolumab checkpoint monotherapy in the second-line setting for patients with advanced RCC and the combination of nivolumab and ipilimumab in the first-line setting.

Tumor histology and risk stratification of patients is important in therapy selection. The histologic diagnosis of RCC is established after surgical removal of renal tumors or after biopsy. According to WHO, the three most common histologic RCC types are clear cell RCC, papillary RCC, and chromophobe RCC.[104] Prognostic systems are used for risk stratification in the metastatic setting.[105,106]

To further guide management of advanced RCC, the NCCN Kidney Cancer Panel has categorized all systemic kidney cancer therapy regimens as “preferred,” “other recommended,” or “useful under certain circumstances.” This categorization provides guidance on treatment selection by considering the efficacy, safety, evidence, and other factors that play into treatment selection. These factors include pre-existing comorbidities, nature of the disease, and in some cases consideration of access to agents. For first-line therapies, the NCCN Kidney Cancer Panel further stratified treatment preferences according to prognostic risk categories.

Prognostic Models

Prognostic scoring systems have been developed to define risk groups of patients by combining independent prognostic factors for survival in patients with metastatic RCC.

The most widely used prognostic factor model is from the Memorial Sloan Kettering Cancer Center (MSKCC). The model was derived from examining prognostic factors in patients (n = 463) with metastatic RCC enrolled in clinical trials and treated with IFN.[105] Prognostic factors for multivariable analysis included five variables: interval from diagnosis to treatment of less than 1 year; Karnofsky performance status less than 80%; serum lactate dehydrogenase (LDH) greater than 1.5 times the upper limit of normal (ULN); corrected serum calcium greater than the ULN; and serum hemoglobin less than the lower limit of normal (LLN). Patients with none of these factors are considered low risk or with good prognosis, those with 1 or 2 factors present are considered intermediate risk, and patients with 3 or more of the factors are considered poor risk. The MSKCC criteria have been additionally validated by an independent group at the Cleveland Clinic.[107]

A prognostic model derived from a population of patients with metastatic RCC treated with VEGF-targeted therapy has been developed, and is known as the IMDC or Heng’s model.[106] This model was derived from a retrospective study of 645 patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus interferon. Patients who received prior immunotherapy (ie, received their targeted therapy as second-line treatment) also were included in the analysis. The analysis identified six clinical parameters to stratify patients into favorable, intermediate, and poor prognosis groups. Four of the five adverse prognostic factors are those previously identified by MSKCC as independent predictors of short survival: hemoglobin less than the LLN, serum-corrected calcium greater than the ULN, Karnofsky performance status less than 80%, and time from initial diagnosis to initiation of therapy of less than 1 year. Additional, independent, adverse prognostic factors validated in this model are absolute neutrophil count (ANC) greater than ULN and platelets greater than ULN.[106]

Patients with none of the identified six adverse factors were in the favorable-risk category (n = 133; 22.7%) in which a median OS was not

reached and a 2-year OS was 75% (95% CI, 65%–82%). Patients with one or two adverse factors were in the intermediate-risk category (n = 301; 51.4%) in which a median OS was 27 months and a 2-year OS was 53% (95% CI, 46%–59%). Finally, those patients with three to six adverse factors were in the poor-risk category (n = 152; 25.9%) in which a median OS was 8.8 months and a 2-year OS was 7% (95% CI, 2%–16%).[106] This model was validated in an independent dataset.[108]

First-line Therapy for Patients with Clear Cell RCC

Pazopanib as First-line Therapy for Clear Cell RCC

Pazopanib is an oral angiogenesis inhibitor targeting VEGF receptors (VEGFR-1, -2, and -3), platelet-derived growth factor receptors (PDGFR-α and –β), and stem cell factor receptor (c-KIT). The safety and effectiveness of pazopanib were evaluated in a phase III, open-label, international, multicenter study. Four hundred thirty-five patients with clear cell advanced RCC and measurable disease with no prior treatment or 1 prior cytokine-based treatment were randomized 2:1 to pazopanib or placebo. PFS was prolonged significantly with pazopanib in the overall study population, averaging 9.2 months versus 4.2 months for patients assigned to placebo.[109] The treatment-naive subpopulation of 233 patients, randomized 2:1 to pazopanib versus placebo, had a median PFS of 11.1 months on pazopanib versus 2.8 months on placebo.[109] The overall response rate (ORR) was 30% with pazopanib and 3% with placebo (all results were statistically significant). Common adverse reactions to pazopanib (any grade) included diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting, fatigue, weakness, abdominal pain, and headache. Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase. Therefore, it is critical to monitor liver function before and during treatment with the drug.

The final analysis of OS and updated safety results of pazopanib did not show a statistically significant effect on OS.[110] The lack of correlation between OS and PFS is attributed to the extensive crossover of placebo-treated patients to pazopanib via the parallel open-label extension, as well as other subsequent anticancer treatments that patients from both arms received after progression.[110] In the updated analyses,[110] no differences in the frequency or severity of adverse events or grade 3/4 adverse events were seen compared with the previous report.[109]

Results of a large non-inferiority study (COMPARZ) of sunitinib versus pazopanib showed that these two drugs have a similar efficacy profile and a differentiated safety profile.[111] Among 1110 patients with clear cell metastatic RCC who were randomized to receive pazopanib or sunitinib, patients receiving pazopanib achieved a median PFS of 8.4 months compared with 9.5 months for patients receiving sunitinib (HR, 1.047). ORRs were 31% for pazopanib and 25% for sunitinib. Pazopanib was associated with less fatigue than sunitinib, less hand-foot syndrome, less alteration in taste, and less thrombocytopenia. However, pazopanib was associated with more transaminase elevation than sunitinib.[111] The results of the final OS analysis were similar in the two groups (HR for death with pazopanib vs. sunitinib, 0.92; 95% CI, 0.79–1.06) and for all risk subgroups.[112]

The results of the COMPARZ trial[111,112] are supported by the results of another smaller phase III study (PISCES).[113] The primary endpoint was patient preference, assessed at 22 weeks. When asked about reasons for selecting one drug over another, about 70% selected pazopanib due to better quality of life (QOL), compared with 22% of the sunitinib-treated patients and the remaining 8% of patients having no preference.[113]

The NCCN Kidney Cancer Panel has listed pazopanib as a category 1 preferred option for first-line treatment of patients with favorable risk features with relapsed or medically unresectable clear cell stage IV RCC.

Additionally, the Panel has listed pazopanib as a category 1 other recommended option for first-line treatment of patients with poor-/intermediate-risk features.

Sunitinib as First-line Therapy for Clear Cell RCC

Sunitinib is a multikinase inhibitor targeting several receptor tyrosine kinases, including PDGFR-α and -β; VEGFR-1, -2, and -3; c-KIT; FMS-like tyrosine kinase (FLT-3); colony-stimulating factor (CSF-1R); and neurotrophic factor receptor (RET).[114,115]

Preclinical data suggested that sunitinib has anti-tumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.[116,117] After promising phase I and II data, the efficacy of sunitinib in previously untreated patients with metastatic RCC was studied in a large multinational phase III trial in which 750 patients with metastatic (all risk) clear cell histology RCC were randomized to receive either sunitinib or IFN-α.[114] The patients selected for the trial had no prior treatment with systemic therapy, good performance status, and measurable disease. The median PFS was 11 months for the sunitinib arm and 5 months for the IFN-α arm. Outcomes were better for patients in the favorable risk group, but for all risk groups the patients in the sunitinib arm had longer median PFS than in the IFN-α arm. Severe adverse events (grade 3–4 toxicities) were acceptable, with neutropenia, thrombocytopenia, hyperamylasemia, diarrhea, hand-foot syndrome, and hypertension being noteworthy in the sunitinib arm and fatigue being more common with IFN-α.

Updated results demonstrate a strong trend towards OS advantage of sunitinib over IFN-α in the first-line setting (26.4 months vs. 21.8 months, $P = .051$).[118] The OS based on pretreatment IMDC prognostic risk was not reached for patients in the favorable risk groups, but also had a trend towards OS advantage in the sunitinib over IFN-α arm for intermediate-risk (20.7 months vs. 15.4 months) and poor-risk groups (5.3 months vs. 4 months).[118] Results from an expanded access trial revealed that sunitinib possesses an acceptable safety profile and has activity in subgroups of patients with brain metastases, non-clear cell histology, and poor performance status.[119] Phase II studies using modified[120] or intermittent[121] sunitinib dosing schedules in patients with metastatic RCC showed high efficacy and lower toxicity.

A retrospective study using the IMDC studied the efficacy of first-line treatment with sunitinib compared with pazopanib at the population-based level. No difference in OS was seen between the two treatment options (22.3 vs. 22.6 months, respectively, $P = .65$).[122] In addition, no difference was observed in PFS and response rates between the two treatment options.[122]

Based on these studies and its tolerability, the NCCN Kidney Cancer Panel has also listed sunitinib as a category 1 preferred option for first-line treatment of patients with relapsed or medically unresectable clear cell stage IV RCC with good-risk features. The Panel has listed sunitinib as a category 1 other recommended option for first-line treatment of patients with relapsed or medically unresectable clear cell stage IV RCC with poor-/intermediate-risk features.

Nivolumab and Ipilimumab in Combination as First-line Therapy for Patients with Clear Cell RCC

Nivolumab is an antibody that selectively blocks the interaction between programmed death-1 (PD-1; expressed on activated T cells) and its ligands (expressed on antigen-presenting cells, including immune cells and tumor cells). Ipilimumab is an antibody that selectively blocks the interaction between the negative regulator cytotoxic T-lymphocyte antigen 4 (CTLA-4; expressed early on activated T cells) and its ligands CD80/CD86 (expressed on antigen-presenting cells).

An open-label, multicenter, phase III trial (CheckMate 214) compared nivolumab (3 mg/kg body weight) plus ipilimumab (1 mg/kg) intravenously every 3 weeks for 4 doses followed by nivolumab monotherapy (3 mg/kg) every 2 weeks versus sunitinib monotherapy 50 mg (4 weeks on and 2 weeks off schedule) in patients with advanced RCC.[123] One thousand ninety-six patients were randomized (1:1) to nivolumab plus ipilimumab or sunitinib monotherapy; 425 and 422 treated patients, respectively, had intermediate or poor-risk. The co-primary endpoints for the trial included ORR, PFS, and OS in the intermediate- and poor-risk patients. The combination of nivolumab plus ipilimumab produced a higher ORR compared to sunitinib monotherapy (42% vs. 27%, $P < .001$), and a higher complete response rate (9% vs. 1%, $P < .001$) in the intermediate- and poor-risk patients. The 18-month OS rate was 75% (95% CI, 70–78) with nivolumab plus ipilimumab and 60% with sunitinib (95% CI, 55–65). The median PFS (11.6 months vs. 8.4 months; HR, .82; $P = .03$) was not statistically significant, since it didn't meet the prespecified .009 threshold.[123] Treatment-related adverse events were seen in 93% of patients who received nivolumab plus ipilimumab and 97% of patients who received sunitinib; grade 3 or 4 events occurred in 46% and 63% of patients, respectively. Treatment-related adverse events led to discontinuation in 22% and 12% of patients, respectively.[123]

The data for first-line nivolumab in combination with ipilimumab for favorable-risk patients has been mixed.[123,124] The intent-to-treat population in CheckMate 214 also included favorable-risk patients treated with nivolumab plus ipilimumab (n = 125) or sunitinib (n = 124), for a total of 550 and 546 patients, respectively.[123] The 18-month OS in the overall intent-to-treat population favored nivolumab plus ipilimumab versus sunitinib (78% vs. 68%), but exploratory analyses of just the favorable-risk patients favored sunitinib (88% vs. 93%). The ORR (29% and 52%; $P < .001$) and median PFS (14.3 months and 25.1 months; HR, 2.18; 99.1% CI, 1.29–3.68; $P < .001$) were also lower in favorable-risk patients taking nivolumab plus ipilimumab versus sunitinib in this study. However, the CR rates were 11% and 6% for the nivolumab plus ipilimumab combination and sunitinib arms, respectively. A separate phase I trial (CheckMate 016) supports the use of nivolumab plus ipilimumab in patients at any risk with confirmed advanced or metastatic RCC with a clear cell component, including those who received prior therapy.[124] The study included patients with poor (n = 6), intermediate (n = 47), or favorable risk (n = 47) according to MSKCC risk categorization. Patients with favorable risk comprised 44.7% of those taking nivolumab (3 mg/kg body weight) and ipilimumab (1 mg/kg) and 44.7% of those taking nivolumab (1 mg/kg) and ipilimumab (3 mg/kg), every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks until progression or toxicity. The data for the favorable-risk patients alone was not published, but the 2-year OS for the entire cohort was 67.3% and 69.6%, respectively. The confirmed ORR for the cohort at a median follow-up time of 22.3 months was the same in both arms (40.4%).[124]

Based on these data, the NCCN Kidney Cancer Panel has listed nivolumab and ipilimumab in combination as a category 1, preferred treatment option for first-line treatment for intermediate- and poor-risk patients with previously untreated, relapsed or medically unresectable, clear cell, stage IV RCC. Due to conflicting data for favorable-risk patients in the phase III compared to the phase I trials, the NCCN Kidney Cancer Panel recommends nivolumab and ipilimumab in combination as a category 2A other recommended treatment option for first-line treatment in these patients. The FDA approval for nivolumab plus ipilimumab is narrower, only including patients with intermediate- or poor-risk RCC.

Cabozantinib as First-line Therapy for Clear Cell RCC

Cabozantinib is a small-molecule inhibitor of tyrosine kinases such as VEGFRs, MET, and AXL. An open-label, phase II trial (CABOSUN) randomized 157 patients with advanced RCC to first-line therapy with

either cabozantinib (60 mg once daily) or sunitinib (50 mg once daily; 4 weeks on, 2 weeks off).[125] Patients in the CABOSUN trial were either intermediate or poor risk based on IMDC criteria. Patients treated with cabozantinib showed a significantly increased median PFS compared to those treated with sunitinib (8.2 vs. 5.6 months). Cabozantinib also showed a significantly higher ORR compared to sunitinib (46% vs. 18%). All-causality grade 3 or 4 adverse events were 67% for cabozantinib and 68% for sunitinib with diarrhea, fatigue, hypertension, palmar-plantar erythrodysesthesia, and hematologic abnormalities most commonly reported.[125]

Based on these results, the NCCN Panel has included cabozantinib as a category 2A preferred first-line treatment option for poor- and intermediate-risk groups. Extrapolating on the data for poor/intermediate risk, the NCCN Kidney Cancer Panel has listed cabozantinib as a category 2B other recommended first-line treatment option for favorable-risk groups.

Active Surveillance for Select, Asymptomatic Patients with Clear Cell RCC

A subset of patients with advanced RCC show indolent progression of disease and could benefit from initial active surveillance because of the toxicity and non-curative nature of systemic therapies. A prospective phase II trial of patients with treatment-naïve, asymptomatic, metastatic RCC followed patients on active surveillance through radiographic assessment at defined intervals until a decision was made to initiate systemic therapy.[126] Of the 48 patients included in the analysis, the median time of surveillance from registration to initiation of systemic therapy was 14.9 months. This study demonstrated that a subset of patients with advanced RCC can safely undergo active surveillance before starting systemic therapy. Therefore, the NCCN Panel included active surveillance as an option for select, asymptomatic patients with favorable-risk clear cell RCC.

Axitinib as First-line Therapy for Clear Cell RCC

Axitinib is a selective, second-generation inhibitor of VEGFR-1, -2, and -3.[127] As second-line therapy for patients with clear cell RCC, treatment with axitinib has clearly demonstrated greater ORR and longer median PFS compared with those treated with sorafenib. To determine whether this holds true in the first-line setting, a randomized, open-label, phase III trial was carried out in newly diagnosed patients randomized (2:1) to receive axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).[128] The median PFS seen in patients treated with axitinib was 10.1 months (95% CI, 7.2–12.1) and for those treated with sorafenib was 6.5 months (95% CI, 4.7–8.3).[128] The adverse events more commonly seen with axitinib (≥10% difference) than with sorafenib treatment were diarrhea, hypertension, weight loss, decreased appetite, dysphonia, hypothyroidism, and upper abdominal pain; adverse events more commonly seen with sorafenib treatment included palmar-plantar erythrodysesthesia, rash, alopecia, and erythema.[128] The difference in PFS between patients treated with axitinib versus sorafenib is not statistically significant; however, the results demonstrated clinical activity of axitinib with acceptable toxicity profile in the first-line setting.

Another randomized, multicenter, phase II trial evaluated the efficacy and safety of axitinib dose titration in newly diagnosed patients with metastatic RCC.[129] In this study, all patients received axitinib 5 mg twice daily for 4 weeks. After this they were assigned (1:1) to placebo titration or axitinib twice-daily dose titrated stepwise to 7 mg and, if tolerated, this was titrated up to a maximum dose of 10 mg daily. More patients in the axitinib titration group achieved an objective response compared with the placebo group (54% vs. 34%).

Based on these results, the NCCN Panel has included axitinib as a first-line treatment option (category 2B) for use under certain circumstances for patients of all risk groups.

Bevacizumab Along with Interferon as First-line Therapy for Clear Cell RCC

Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes circulating VEGF-A. A multicenter phase III trial (AVOREN) compared bevacizumab plus IFN-α versus placebo plus IFN-α. The trial was a randomized, double-blind trial. Six hundred forty-nine patients were randomized (641 treated).[130] The addition of bevacizumab to IFN-α significantly increased PFS (10.2 vs. 5.4 months) and objective tumor response rate (30.6% vs. 12.4%). No significant increase or novel adverse effects were observed with the combination over IFN-α alone. A trend toward improved OS also was observed (23.3 months with bevacizumab plus IFN-α vs. 21.3 months for IFN-α), although the difference did not reach statistical significance.[130]

In the United States, a similar trial was performed by the Cancer and Leukemia Group B (CALGB), with 732 previously untreated patients randomized 1:1 to receive either IFN-α or the combination of bevacizumab plus IFN-α. Bevacizumab plus IFN-α produced a superior PFS (8.5 months vs. 5.2 months) and higher ORR (25.5% vs. 13.1%) versus IFN-α alone. However, toxicity was greater in the combination therapy arm.[131] There were no significant differences in median survival between the two groups (18.3 vs. 17.4 months for bevacizumab plus IFN-α vs. IFN-α alone).[132]

The NCCN Kidney Cancer Panel recommends bevacizumab in combination with IFN-α as a category 1 option, useful under certain circumstances, for first-line treatment of patients of all risk groups with relapsed or medically unresectable clear cell stage IV RCC.

High-Dose IL-2 as First-line Therapy for Clear Cell RCC

IL-2–based immunotherapy is reported to achieve long-lasting complete or partial remissions in a small subset of patients. High-dose IL-2 is associated with substantial toxicity and to date attempts to characterize tumor or patient factors for best response to this therapy have been unsuccessful.[133-135] Thus, the best criteria to select patients for IL-2 therapy are based in large part on safety and include the patient's performance status, medical comorbidities, tumor histology (clear cell), MSKCC or Survival After Nephrectomy and Immunotherapy (SANI) risk scores,[105,136,137] and the patient's attitude toward risk.

According to the NCCN Kidney Cancer Panel, for highly selected patients with relapsed or medically unresectable stage IV clear cell RCC, high-dose IL-2 is listed as a first-line treatment option with a category 2A designation.

Temsirolimus as First-line Therapy for Clear Cell RCC

Temsirolimus is an inhibitor of the mTOR protein. mTOR regulates micronutrients, cell growth, apoptosis, and angiogenesis by its downstream effects on a variety of proteins. Efficacy and safety of temsirolimus were demonstrated at a second interim analysis of the ARCC trial, a phase III, multicenter, randomized, open-label study in previously untreated patients with advanced RCC who had 3 or more of 6 unfavorable prognostic factors.[138] The prognostic factors included: less than one year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin less than the LLN, corrected calcium greater than 10 mg/dL, LDH greater than 1.5 times the ULN, and metastasis to one or more than one organ site. Six hundred twenty-six patients were randomized equally to receive IFN-α alone, temsirolimus alone, or the combination of temsirolimus and IFN-α. Patients in both temsirolimus-containing groups were recommended pre-medication with an antihistamine to prevent infusion reactions.

Patients were stratified for prior nephrectomy and geographic region. Seventy percent were younger than 65 years of age and 69% were male. The group of patients who received temsirolimus alone showed a significant improvement in OS over those receiving IFN-α alone or both drugs. The median OS was 10.9 months for patients on temsirolimus alone versus 7.3 months for those treated with IFN-α alone. The median PFS (the study's secondary endpoint) was increased from 3.1 months with IFN-α alone to 5.5 months with temsirolimus alone. The combination of temsirolimus and IFN-α not only failed to improve OS or PFS but also led to an increase in multiple adverse reactions, including grade 3 or 4 rash, stomatitis, pain, infection, peripheral edema, thrombocytopenia and neutropenia, hyperlipidemia, hypercholesteremia, or hyperglycemia.

Based on these data, the NCCN Kidney Cancer Panel has included temsirolimus as a category 1 recommendation, useful under certain circumstances, for first-line treatment of poor-risk patients with relapsed or medically unresectable clear cell stage IV RCC.

Subsequent Therapy for Patients with Clear Cell RCC

Cabozantinib as Subsequent Therapy for Clear Cell RCC

A phase III trial (METEOR) randomized 658 patients with disease progression after previous TKI therapy to receive 60 mg/d of oral cabozantinib (n = 331) or 10 mg/d of oral everolimus (n = 321).[139] The estimated median PFS for patients randomized to cabozantinib was 7.4 months, versus 3.8 months for everolimus (HR, 0.58; 95% CI, 0.45–0.75; *P* < .001). The ORR was 21% for cabozantinib and 5% for everolimus (*P* < .001).[139]

The final analysis of the METEOR trial shows a statistically significant increase in OS in the cabozantinib arm.[140] A median OS of 21.4 months was shown for those treated with cabozantinib, and a median OS of 16.5 months was shown for patients treated with everolimus (HR, 0.66; 95% CI, 0.53–0.83; *P* = .00026).[140] A long-term follow-up analysis of the phase III METEOR trial similarly found significant improvement in median OS with cabozantinib compared to everolimus.[141] QOL reported outcomes in the METEOR trial showed improved time to deterioration in the cabozantinib arm, but no difference compared to the everolimus arm for FSKI-19, FSKI-DRS, or EQ-5D questionnaires.[142]

In a subgroup analysis of the METEOR trial involving patients with bone metastases at baseline, PFS, OS, and ORR were improved for patients treated with cabozantinib compared to everolimus. Median PFS was 7.4 months versus 2.7 months (HR, 0.33; 95% CI, 0.21–0.51), median OS was 20.1 months versus 12.1 months (HR, 0.54; 95% CI, 0.34–0.84), and ORR was 17% versus 0% for cabozantinib and everolimus, respectively.[143]

The most commonly reported grade 3 or 4 treatment-related adverse effects with cabozantinib in the trial were hypertension, diarrhea, and fatigue and with everolimus were anemia, fatigue, and hyperglycemia.[140] The rate of treatment discontinuation due to adverse effects of the treatment was similar in both arms (9% with cabozantinib arm vs. 10% with everolimus). The longer PFS and increased OS with cabozantinib when compared to everolimus makes cabozantinib a preferred choice in the second-line setting for advanced RCC. Based on the METEOR trial results,[139,140] the NCCN Panel has included cabozantinib as a category 1 preferred subsequent therapy option.

A network meta-analysis comparing the relative effectiveness of treatment options for RCC after failure of first-line therapy found the probability of longer PFS during the analyzed 3 years to be higher with cabozantinib compared to everolimus, nivolumab, axitinib, sorafenib, and best supportive care.[144]

Nivolumab as Subsequent Therapy for Clear Cell RCC

In a phase III trial (CheckMate 025), patients (N = 821) with advanced clear cell RCC, previously treated with one or more lines of therapy (excluding mTOR), were randomly assigned (in a 1:1 ratio) to receive nivolumab (3 mg/kg body weight) intravenously every 2 weeks or everolimus 10 mg/d orally.[145] The primary endpoint of the trial was OS. The median OS was 5.4 months longer with nivolumab compared with everolimus (25.0 vs.19.6 months). The HR for death (from any cause) with nivolumab versus everolimus was 0.73 (*P* = .002). The ORR was also reported to be 5 times greater with nivolumab (25% vs. 5%; odds ratio, 5.98; 95% CI, 3.68–9.72; *P* < .001).[145] The FDA-approved dose of nivolumab is 240 mg IV every 2 weeks or 480 mg IV every 4 weeks administered over 30 minutes until disease progression or unacceptable toxicity.

Treatment-related adverse events of any grade were seen in 79% of those who received nivolumab and 88% of those who received everolimus; grade 3-4 events occurred in 19% and 37%, respectively. The most common grade 3-4 events were fatigue (2%) with nivolumab and anemia (8%) with everolimus. Toxicities led to treatment discontinuations in 8% and 13% of patients, respectively. Two deaths were reported in the everolimus arm; there were no treatment-related deaths in the nivolumab arm.[145]

An independent analysis was carried out to determine the efficacy of nivolumab-based baseline factors such as number and location of metastases, risk group, number of prior therapies, and specific prior therapies (ie, sunitinib, pazopanib, IL-2). A consistent OS benefit and ORR were observed across all baseline factors.[146]

The FKSI-DRS[147] questionnaire was used to obtain a score for QOL of patients enrolled in the trial. The median change from baseline in the FKSI-DRS score in the nivolumab group increased over time, suggesting a significant and consistent improvement in QOL of patients in this group.[145] Due to the OS advantage shown by nivolumab over everolimus in the second-line setting, nivolumab is preferred over everolimus in the second-line setting for advanced RCC after an antiangiogenic agent.

Since immunotherapy response patterns differ from traditional systemic therapies, the effect of continuing treatment with nivolumab was retrospectively reviewed in patients enrolled in the CheckMate 025 trial who had disease progression on nivolumab treatment.[148] Results showed that nivolumab treatment beyond first progression was associated with reduced tumor burden in approximately 50% of patients with advanced RCC and 13% achieved greater than or equal to 30% reduction in tumor burden. It should be noted that patients treated with nivolumab after progression generally had more favorable disease characteristics versus those who discontinued treatment after first progression. In patients receiving nivolumab after progression, adverse events (any grade) occurred less frequently after progression versus before progression. These data suggest that a subset of patients benefit from treatment beyond progression, but this approach needs to be prospectively validated.[148]

Based on the results of the CheckMate 025 trial[145] demonstrating superior OS with nivolumab compared with everolimus, the NCCN Panel has included nivolumab as a category 1 preferred subsequent therapy option.

Nivolumab and Ipilimumab in Combination as Subsequent Therapy for Clear Cell RCC

The phase I trial (CheckMate 016), mentioned above, included patients who had received one prior treatment. This trial demonstrated safety and durable response after treatment with nivolumab plus ipilimumab in patients with confirmed advanced or metastatic RCC with a clear cell component, regardless of risk.[124] Efficacy results for patients regardless of risk were stratified by treatment status; 22 patients in the nivolumab (3

mg/kg body weight) and ipilimumab (1 mg/kg) group and 26 patients in the nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) groups were previously treated. Confirmed ORR in previously treated patients was 45.5% and 38.5%, respectively.[124]

Based on the above data, the NCCN Kidney Cancer Panel considers nivolumab and ipilimumab a category 2A preferred subsequent therapy option for patients with clear cell RCC.

Axitinib as Subsequent Therapy for Clear Cell RCC

A multicenter, randomized phase III study (AXIS) compared axitinib versus sorafenib as second-line therapy after 1 prior systemic therapy (with mostly cytokines or sunitinib).[149] The patients (n = 723) were stratified for performance status and type of prior therapy, and randomized 1:1 to axitinib (5 mg twice daily) or sorafenib (400 mg twice daily).[149] The overall median PFS was 6.7 months for axitinib versus 4.7 months for sorafenib (HR, 0.665; *P* < .0001), and the response rate was 19% for axitinib- versus 9% for sorafenib-treated patients (*P* = .0001). The PFS favored axitinib in both groups treated with a prior cytokine (12.1 vs. 6.5 months; *P* < .0001) and prior sunitinib (4.8 vs. 3.4 months; *P* = .01).[149] Adverse events of all grades more frequent with axitinib were hypertension, fatigue, dysphonia, and hypothyroidism. Adverse events more frequent with sorafenib were hand-foot syndrome, rash, alopecia, and anemia.

The updated results of AXIS reported median OS of 20.1 months (95% CI, 16.7–23.4) with axitinib and 19.2 months (17.5–22.3) with sorafenib (HR, 0.969; 95% CI, 0.800–1.174).[150] Although OS did not significantly differ between the two groups, median investigator-assessed PFS was longer with axitinib; PFS was 8.3 months (95% CI, 6.7–9.2) versus 5.7 months (4.7–6.5) with sorafenib (HR, 0.656; 95% CI, 0.552–0.779).[150] The patient-reported outcomes were comparable for second-line axitinib and sorafenib.[147]

In a phase II study of patients with cytokine-refractory metastatic RCC the 5-year survival rate after treatment with axitinib was 20.6% (95% CI, 10.9%–32.4%), with a median follow-up of 5.9 years.[151] Axitinib is listed as a category 1, other recommended, subsequent therapy option by the NCCN Kidney Cancer Panel.

A *post-hoc* analysis of the AXIS trial evaluated the efficacy of axitinib and sorafenib by response to prior therapy, duration of prior therapy, and tumor burden in patients previously treated with sunitinib or cytokines.[152] The analysis suggests that patients who have longer duration of response on first-line therapy have better outcomes; however, lack of response to first-line therapy does not preclude positive clinical outcomes with a second-line TKI.[152]

Lenvatinib with Everolimus as Subsequent Therapy for Clear Cell RCC

Lenvatinib is a multi-targeted TKI initially developed for use in differentiated thyroid carcinoma that is refractory to standard therapy.

In a phase II trial, 153 patients with metastatic or unresectable, locally advanced, clear cell RCC who had received prior antiangiogenic therapy were randomly assigned to lenvatinib plus everolimus or single-agent lenvatinib or single-agent everolimus.[153] The PFS was significantly prolonged with lenvatinib plus everolimus versus everolimus (median 14.6 vs. 5.5 months; HR 0.40; 95% CI, 0.24–0.68).[153] The median OS was also increased for lenvatinib plus everolimus compared with everolimus monotherapy (25.5 months vs. 15.4 months; HR, 0.67; 95% CI: 0.42–1.08).[154] Median OS for lenvatinib alone was 18.4 months.[154]

Lenvatinib plus everolimus is listed as a category 1, other recommended, subsequent therapy by the NCCN Kidney Cancer Panel.

Everolimus as Subsequent Therapy for Clear Cell RCC

Everolimus (RAD001) is an orally administered inhibitor of mTOR. In the RECORD 1 trial, an international, multicenter, double-blind, randomized phase III trial, everolimus was compared with placebo for the treatment of metastatic RCC in patients whose disease had progressed on treatment with sunitinib or sorafenib.[155] Four hundred ten patients were randomly assigned 2:1 to receive either everolimus or placebo, and the primary endpoint was PFS. The median PFS assessed by an independent review committee was in favor of everolimus, 4.0 versus 1.9 months.[155] The most common adverse events reported in patients on everolimus (mostly of mild or moderate severity) versus patients in the placebo group were: stomatitis in 40% versus 8%, rash in 25% versus 4%, and fatigue in 20% versus 16%.[155] According to the updated results of this trial, median PFS determined by independent central review was 4.9 months for everolimus versus 1.9 months (95% CI, 1.8–1.9) for placebo.[156]

The primary objective of the phase II (RECORD-3) study was to assess non-inferiority of first-line everolimus compared with first-line sunitinib with respect to PFS and to determine the role of first-line mTOR inhibitor in metastatic RCC.[157] The median PFS after first-line sunitinib was 10.71 months compared with 7.85 months for everolimus. When patients progressed on first-line therapy, they were then crossed over to the alternative therapy and the combined PFS for the two sequences of treatment were also compared. The results indicated that the median PFS for patients treated with everolimus followed by sunitinib was 21.13 months compared with 25.79 months for those treated with sunitinib followed by everolimus (HR, 1.4; 95% CI, 1.2–1.8).[157] The median OS for first-line everolimus followed by sunitinib was 22.41 months compared with 32.03 months for first-line sunitinib followed by everolimus (HR, 1.2; 95% CI, 0.9–1.6).[157] The final OS analysis of RECORD-3 continues to support first-line sunitinib followed by everolimus (median OS was 29.5 months compared to 22.4 months for everolimus followed by sunitinib).[158]

Everolimus is listed as a category 2A, other recommended, subsequent therapy option in the NCCN Guidelines. It is important to note that two recent randomized phase III trials (discussed in sections above) compared the efficacy of everolimus with nivolumab and cabozantinib. The results of the CheckMate 025[145] trial demonstrated superior OS with nivolumab compared with everolimus. The METEOR trial[139] demonstrated longer PFS and OS with cabozantinib when compared to everolimus. Based on the results of these two phase III trials, eligible patients should preferentially receive either nivolumab or cabozantinib over everolimus.

Pazopanib as Subsequent Therapy for Clear Cell RCC

The phase III trial comparing pazopanib with placebo, detailed earlier under the section titled *Pazopanib as First-line Therapy for Clear Cell RCC*, included 202 patients who received prior cytokine therapy. The average PFS in cytokine pre-treated patients was 7.4 versus 4.2 months.[109]

A prospective phase II trial examined the activity and toxicity of second-line treatment with pazopanib (800 mg orally daily) in 56 patients with advanced metastatic RCC previously treated with a targeted agent.[159] The patients enrolled in this trial had previously received first-line treatment with sunitinib (n = 39) or bevacizumab (n = 16). Responses were evaluated after 8 weeks of treatment using RECIST. The trial showed that 27% of patients (n = 15) had objective response to pazopanib; 49% (n = 27) had stable disease.[159] After a median follow-up of 16.7 months, the median PFS was 7.5 months (95% CI, 5.4–9.4 months).[159] The PFS was similar whether previous treatment was with sunitinib or bevacizumab. The estimated OS rate at 24 months was 43%.[159]

Another retrospective analysis reported data on 93 patients with metastatic RCC treated with multiple lines of prior targeted therapies.[160] Among evaluable patients (n = 85) in this study, 15% (n =13) had a partial

response and the median PFS observed was 6.5 months (95% CI, 4.5–9.7).

Based on the above data, the NCCN Kidney Cancer Panel considers pazopanib a category 2A, other recommended, subsequent therapy option.

Sunitinib as Subsequent Therapy for Clear Cell RCC

Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.[115,161] Studies investigating the sequential use of sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, that suggest a lack of total cross resistance between TKIs, either sorafenib followed by sunitinib failures or vice versa—an observation that is consistent with their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another.[162-166] Sunitinib is considered a category 2A, other recommended, subsequent therapy option.

Sorafenib as Subsequent Therapy for Clear Cell RCC

Sorafenib tosylate is a small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase, RAF, and also other receptor tyrosine kinases, including VEGFR-1, -2, and -3; PDGFR-β; FLT-3; c-KIT; and RET.[167-171]

Efficacy of sorafenib was studied in patients who progressed on a prior therapy (mostly cytokines) in a phase III, placebo-controlled, randomized trial, TARGET.[172,173] Nine hundred three patients were enrolled in this trial. The patients selected had measurable disease, clear cell histology, one prior systemic therapy in the last 8 months, an ECOG performance status of 0 to 1, and a good or intermediate prognosis. Almost all patients had undergone nephrectomy. The primary endpoint of the trial was to assess OS, and the secondary endpoint was to assess PFS.

An interim analysis conducted via independent assessment reported that sorafenib-treated patients had PFS that was significantly higher than for patients assigned to placebo (5.5 vs. 2.8 months, respectively; HR, 0.44; 95% CI, 0.35–0.55; *P* = .000001).[173] With the large difference in PFS, crossover to the sorafenib treatment arm was recommended, which likely resulted in the failure of this trial to demonstrate an OS benefit for sorafenib in the final analysis. With censoring of crossover data, treatment with sorafenib was found to be associated with an improved survival compared with placebo, 17.8 vs. 14.3 months (HR, 0.78; 95% CI, 0.62–0.97; *P* = .0287).[173] Common grade 3 to 4 adverse effects reported more in the sorafenib group than in the placebo group were hand-foot syndrome, fatigue, and hypertension.[173] This study showed the effectiveness of sorafenib was primarily in patients who progressed on prior cytokine therapy. Sorafenib has also been studied as second-line therapy in patients treated with sunitinib or bevacizumab and has been found to be safe, feasible, and effective.[166,174]

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN-α in previously untreated patients with clear cell RCC.[175] One hundred eighty-nine patients were randomized to receive continuous oral sorafenib (400 mg twice daily) or IFN-α, with an option of dose escalation of sorafenib to 600 mg twice daily or crossover from IFN-α to sorafenib (400 mg twice daily) upon disease progression. The results showed that more sorafenib-treated (68.2% vs. 39.0%) patients had tumor regression.[175]

Sorafenib is listed as a category 2B subsequent therapy option, useful under certain circumstances.

Based on multiple alternative options and lack of current clinical use as first-line therapy among NCCN Panel Members, the NCCN Kidney Cancer Panel no longer recommends sorafenib as first-line treatment for patients with relapsed or medically unresectable stage IV clear cell RCC. Sorafenib

is still widely used internationally due to its relative affordability and favorable clinical efficacy and safety for certain patient demographics (eg, Asian populations).[176,177] Therefore, sorafenib remains an appropriate option for first-line treatment in these countries.

Other Agents as Subsequent Therapy for Clear Cell RCC

Phase II trials have shown benefit of bevacizumab monotherapy after prior treatment with a cytokine.[178] Bevacizumab is a category 2B subsequent therapy option for use under certain circumstances.

High-dose IL-2 as subsequent therapy is listed as a subsequent therapy option useful for selected patients with excellent performance status and normal organ function (category 2B).

A phase II trial suggested benefit to temsirolimus therapy after prior treatment with a cytokine.[179] A phase III trial (INTORSECT) compared the efficacy of temsirolimus to sorafenib following first-line sunitinib as a treatment for patients with RCC.[180] The trial enrolled 512 patients with a performance status of 0 or 1 and either clear cell or non-clear cell histology. Patients were randomized to receive sorafenib at 400 mg twice daily or intravenous temsirolimus at 25 mg weekly. The difference in PFS, the primary endpoint of the trial, was not statistically significant (P = .1933) between the two arms. PFS was 4.28 months with temsirolimus compared to 3.91 months with sorafenib. A statistically significant OS advantage was observed for sorafenib. The median OS with temsirolimus was 12.27 months compared to 16.64 months with sorafenib (P = .0144).[180] However, the subgroup of individuals who had been treated with sunitinib for less than or equal to 180 days and were then treated with sorafenib did not show a survival benefit. Based on this study, in patients with a shortened response to first-line TKI, mTOR inhibition may be considered as second-line therapy.[181] The NCCN Panel considers temsirolimus a category 2B subsequent therapy option, useful under certain circumstances.

Systemic Therapy for Patients with Non-Clear Cell RCC

Clinical trials of targeted agents have predominantly focused on patients with clear cell versus non-clear cell histology due to the high prevalence of the clear cell RCC.[182] The role of targeted agents in non-clear cell RCC warrants investigation. Therefore, according to the NCCN Panel enrollment in clinical trials is the preferred strategy for non-clear cell RCC.

There are data indicating that targeted therapies approved for clear cell RCC may have benefit for non-clear cell RCC as well. In addition, there are randomized phase II studies showing activity of systemic therapy in patients with non-clear cell RCC. Systematic reviews, meta-analysis of phase II studies, and retrospective studies with targeted agents also show some activity in patients with non-clear cell RCC. Compared with responses in clear cell histologies, however, the response rates with these agents are significantly lower for non-clear cell RCC.

Sunitinib for Non-Clear Cell RCC

Data from expanded-access trials, phase II trials, and retrospective analyses support clinical activity of sunitinib for non-clear cell RCC.[183-189] A phase II trial of 31 patients with non-clear cell RCC treated with sunitinib reported an ORR of 36% (95% CI, 19%–52%) and median PFS of 6.4 months (95% CI, 4.2–8.6 months).[186] In another study of 53 patients with non-clear RCC (papillary or chromophobe), the ORR to sunitinib or sorafenib was 23%; median PFS was 10.6 months.[184]

Two other recent phase II studies compared treatment of sunitinib with everolimus. In the ASPEN trial, 108 previously untreated patients were randomly assigned to either everolimus or sunitinib.[190] Overall, median PFS, the primary endpoint of the trial, was longer in patients treated with sunitinib (8.3 vs. 5.6 months). When the results were analyzed based on risk, median PFS was longer in those treated with sunitinib (14.0 vs. 5.7 months and 6.5 vs. 4.9 months) in patients with good and intermediate

risk. Patients with poor-risk features, however, did better with everolimus treatment compared with sunitinib (median, 6.1 vs. 4.0 months).[190] In the ESPN trial, patients with metastatic non-clear cell RCC were randomized to treatment with everolimus or sunitinib.[191] In an interim analysis of 68 patients, first-line therapy with sunitinib resulted in median PFS of 6.1 months versus 4.1 months with first-line everolimus (*P* = .6). There was no statistically significant difference observed in final OS between the two treatment arms (16.2 for first-line sunitinib vs. 14.9 months with everolimus, *P* = .18).[191] In patients with tumors with *no* sarcomatoid features (n = 49), the median OS was 31.6 months with sunitinib and 10.5 months with everolimus (*P* = .075).

A meta-analysis of randomized clinical trials for patients with non-clear cell RCC found that treatment with TKIs reduced the risk of progression compared with mTOR inhibitors.[192] The study found sunitinib reduced the risk of progression compared to everolimus in the first-line setting (HR 0.67; 95% CI, 0.56–0.80; *P* < .00001). However, no significant differences between TKIs and mTOR inhibitors were found for OS and ORR.

Sunitinib is listed as a category 2A preferred option for treatment-naïve patients with stage IV non-clear cell RCC.

Cabozantinib for Non-Clear Cell RCC

While no prospective trials have been done for cabozantinib in patients with non-clear cell RCC, a few retrospective studies[193,194] and real-world data reports[195] support its use as systemic therapy in this population. A retrospective study of 30 patients with non-clear cell RCC found clinical benefit for patients treated with cabozantinib.[193] The median PFS was 8.6 months and median OS was 25.4 months. The ORR was 14.3% among the 28 patients with measurable disease. The NCCN Panel included cabozantinib as a category 2A, other recommended option for patients with relapsed or stage IV, non-clear cell RCC.

Everolimus for Non-Clear Cell RCC

The data on the benefit of everolimus in patients with non-clear cell RCC are limited. Data from subgroup analyses of an expanded-access trial and case reports support clinical use of everolimus in patients with non-clear cell RCC.[196-198]

The efficacy and safety of everolimus in patients with metastatic RCC of non-clear cell histology were evaluated in a subgroup of patients (n = 75) enrolled in the RAD001 Expanded Access Clinical Trial in RCC (REACT).[196] Median duration of treatment with everolimus was similar in the non-clear cell subgroup and in the overall REACT trial population (12.14 weeks vs. 14.0 weeks, respectively). The ORR (1.3% vs. 1.7%) and rate of stable disease (49.3% vs. 51.6%) were similar as well, suggesting similar efficacy in clear and non-clear cell RCC.[196] The most commonly reported Grade 3 and 4 adverse events, respectively, in the non-clear cell RCC subgroup included: anemia (9.3% and 8.0%), pleural effusion (9.3% and 0%), dyspnea (8.0% and 2.7%), fatigue (8.0% and 0%), asthenia (4.0% and 1.3%), stomatitis (4.0% and 0%), and pneumonitis (4.0% and 0%).[196]

In a phase II study, 49 patients with non-clear cell RCC previously treated with sunitinib or sorafenib were given everolimus 10 mg orally daily until disease progression or unacceptable toxicity.[198] The histology of the enrolled patients included papillary (n = 29), chromophobe (n = 8), collecting duct (n = 2), sarcomatoid (n = 4), and unclassified (n = 6). The median PFS was 5.2 months. The ORR was 10.2% with all of the responses being partial. Twenty-five patients (51%) had stable disease; 16 patients (32.7%) progressed despite everolimus. Adverse events reported in the trial, greater than Grade 3, included anemia (10.2%), hyperglycemia (8.2%), infection (6.1%), and pneumonitis (4.1%).[198]

Final results from a phase II trial (RAPTOR) suggest that everolimus (10 mg once daily) provides an anti-tumor effect in previously untreated

patients with advanced papillary RCC.[199] The median PFS for type 1 and type 2 histology was 7.9 months (95% CI, 2.1–11.0) and 5.1 months (95% CI, 3.3–5.5), respectively. Median OS was 28.0 months (95% CI, 7.6–not estimable) for type 1 and 24.2 months (95% CI, 15.8–32.8) for type 2 histology. Common adverse events grade 2 or greater included asthenia, anemia, and fatigue.[199]

Based on these trials, the NCCN Panel has included everolimus as a category 2A, other recommended option for patients with non-clear cell RCC.

The NCCN Panel also lists lenvatinib plus everolimus as a category 2A, useful under certain circumstances, treatment option for patients with non-clear cell RCC.

Pazopanib and Axitinib for Non-Clear Cell RCC

The clinical benefit of pazopanib or axitinib has not yet been established in patients with non-clear RCC. There is an ongoing clinical trial evaluating the efficacy of pazopanib in patients with non-clear cell RCC in the second-line setting.[200] Two phase II trials with pazopanib or axitinib had promising efficacy and tolerable toxicity.[201,202] A phase II trial of pazopanib in 28 evaluable patients in Korea with locally advanced or metastatic non-clear cell RCC, excluding collecting duct or sarcomatoid type, had promising efficacy: 8 patients achieved a confirmed partial response with ORR of 28%.[201] A phase II trial of axitinib in 40 patients with recurrent or metastatic non-clear cell RCC who had failed treatment with temsirolimus found a median PFS of 7.4 months and ORR of 37.5%.[202] A retrospective analysis of an Italian multicenter cohort of non-clear cell RCC patients found treatment with pazopanib to be effective and safe.[203]

Based on extrapolation, the NCCN Kidney Cancer Panel has included these therapies as a therapy option for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology (category 2A) for use under certain circumstances.

Bevacizumab Monotherapy for Non-Clear Cell RCC

A small phase II trial studied bevacizumab monotherapy in patients with papillary RCC. This study closed early due to a very small and slow accrual of 5 patients; 3 patients had undergone a prior nephrectomy, 1 patient had resection of a liver metastasis, and 1 patient had received prior temsirolimus. The PFS reported for each of these patients was 25, 15, 11, 10, and 6 months. Main toxicities reported were grade 1–2 toxicities, such as hypertension, creatinine elevations, and proteinuria.[204] The NCCN Panel has included bevacizumab as a therapeutic option for patients with non-clear cell RCC (category 2A).

Erlotinib for Non-Clear Cell RCC

The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) TKI, was studied in patients with advanced papillary RCC.[205] Fifty-two patients were treated with erlotinib given orally once daily. The ORR was 11% (5 of 45 patients; 95% CI, 3%–24%), and the disease control rate (defined as stable disease for 6 weeks, or confirmed partial response or complete response using RECIST) was 64%. The median OS was 27 months.[205] This study demonstrated disease control and survival outcomes of interest with an expected toxicity profile with single-agent erlotinib.

The NCCN Kidney Cancer Panel has included erlotinib as a category 2A option, useful under certain circumstances, for first-line therapy for patients with relapsed or medically unresectable stage IV non-clear cell RCC.

Nivolumab for Non-Clear Cell RCC

A retrospective analysis evaluated the response to at least one dose of nivolumab in patients with metastatic, non-clear cell RCC.[206] This study

evaluated 35 patients for response and found 20% had partial response and 29% had stable disease, with a median follow-up of 8.5 months and median PFS of 3.5 months. Treatment-related adverse events of any grade were noted in 37% of patients, most commonly: fatigue, fever, and rash.

A separate retrospective analysis found modest responses with PD-1/PD-L1 inhibitors in 43 patients also with metastatic, non-clear cell RCC.[207] An objective response was achieved in 8 patients (19%), including 4 patients (13%) that received PD-1/PD-L1 monotherapy.

The NCCN Panel recommends nivolumab as a category 2A option for select patients with advanced RCC with non-clear cell histology.

Bevacizumab + Erlotinib for Advanced Papillary RCC Including Hereditary Leiomyomatosis and RCC

Hereditary leiomyomatosis and RCC (HLRCC) is a hereditary condition in which affected patients are at risk for development of skin and uterine leiomyomas, as well as an aggressive form of papillary kidney cancer.[208] Bevacizumab in combination with either erlotinib or everolimus is currently being investigated for treatment of advanced papillary RCC, including HLRCC.

An abstract detailed the results of a phase II trial of 41 patients with advanced papillary RCC (HLRCC-associated RCC; n = 20 or sporadic papillary RCC; n = 21) treated with bevacizumab plus erlotinib.[209] Nineteen patients in this study had received at least one prior line of therapy. The ORR was 60% for those with HLRCC compared to 29% with sporadic papillary RCC. Median PFS was 24.2 months in the HLRCC group compared to 7.4 months in the sporadic papillary RCC group. Most adverse events were grades 1 or 2, with the most frequent grade 3 and 4 adverse events being hypertension (24.3%) and proteinuria (12%). One patient died of gastrointestinal hemorrhage, possibly related to treatment with bevacizumab.[209]

Based on these results, the NCCN Panel recommends bevacizumab plus erlotinib for select patients with advanced RCC and papillary histology, including HLRCC (category 2A).

Bevacizumab + Everolimus for Advanced Non-Clear Cell RCC

A phase II trial of treatment-naïve patients with metastatic non-clear cell RCC studied the efficacy and safety of treatment with bevacizumab plus everolimus.[210] For the 34 evaluable patients, median PFS, OS, and ORR were 11.0 months, 18.5 months, and 29%. Patients with tumors that contained significant papillary or chromophobe elements showed higher PFS and ORR than other histologies ($P < .001$). The most common grade 3 or higher adverse events were hyperglycemia (11%), hypertriglyceridemia (14%), lymphopenia (20%), hypertension (29%), and proteinuria (18%).[203]

Based on these results, the NCCN Panel recommends bevacizumab plus everolimus (category 2A) for select patients with advanced RCC with non-clear cell histology.

Temsirolimus for Non-Clear Cell RCC

A retrospective subset analysis of the global ARCC trial demonstrated benefit of temsirolimus not only in clear cell RCC but also in non-clear cell histology.[138,211] In patients with non-clear cell RCC (predominantly papillary RCC), the median OS was 11.6 months with temsirolimus and 4.3 months with IFN-α. This is the only reported phase III trial that included patients with RCC with non-clear cell histologies.

Randomized clinical trials in rarer subgroups of patients are often challenging. Consistent with the results of this phase III trial, a case report of a patient with a diagnosis of metastatic chromophobe RCC that was

refractory to treatment with sunitinib achieved durable clinical response lasting 20 months upon treatment with temsirolimus.[212]

Temsirolimus is a category 1 recommendation for non-clear cell RCC patients with poor prognosis features (according to MSKCC risk criteria) and is a category 2A recommendation for patients belonging to other prognostic non-clear cell risk groups. The panel has categorized temsirolimus as a regimen useful under certain circumstances for patients with non-clear cell histology regardless of risk group.

Chemotherapy for Metastatic RCC

Treatment of RCC with sarcomatoid features and non-clear cell histologies remains a challenge. Sarcomatoid variant is an aggressive form of RCC that can occur in any histologic subtype.[213] Sarcomatoid RCC is associated with a poor prognosis.[214-218] Chemotherapy plays a role in the management of a variety of sarcomas; therefore, its use in sarcomatoid RCC patients has been explored. Gemcitabine in combination with doxorubicin or in combination with capecitabine has shown some activity in patients with non-clear cell or clear cell tumors with sarcomatoid features.[219-224] The potential role of sunitinib in combination with gemcitabine has been investigated in a phase II trial of RCC with sarcomatoid features.[225] The role of bevacizumab in combination with capecitabine and gemcitabine has been studied in a phase II trial of sarcomatoid RCC with low response rates.[226] The results show that the combination was well tolerated and is active, especially in patients with rapidly progressing disease.[225] There are ongoing trials studying sunitinib in combination with gemcitabine compared to sunitinib alone in patients with sarcomatoid features.[227]

Among the non-clear cell histologies, renal medullary carcinoma is extremely rare, comprising approximately 2% of all primary renal tumors in young people.[228,229] Metastatic disease is seen at presentation in 67% to 95% of patients.[228-230] Chemotherapy remains the focus of treatment for this subtype, although the prognosis remains dismal.

Collecting-duct carcinoma is also a very rare type of non-clear cell RCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation, and most patients die within 1 to 3 years from the time of primary diagnosis.[231-234] Collecting duct carcinoma shares biologic features with urothelial carcinoma. In a multicenter prospective study, 23 patients with no prior therapy were treated with a combination of gemcitabine and either cisplatin or carboplatin.[235] The results showed a response rate of 26% and an OS of 10.5 months.[235]

The NCCN Kidney Cancer Panel has noted in a footnote that chemotherapy is an option for treatment of clear cell and non-clear cell RCC with predominant sarcomatoid features. The chemotherapy regimens that have shown some benefit for patients with predominant sarcomatoid features include: gemcitabine in combination with doxorubicin or sunitinib (both category 2B). In addition, the panel has noted that in patients with other non-clear cell subtypes such as collecting duct or medullary subtypes, partial responses to cytotoxic chemotherapy have been observed (gemcitabine in combination with carboplatin or cisplatin; or paclitaxel with carboplatin) and other platinum-based chemotherapies currently used for urothelial carcinomas.

Sorafenib is No Longer Recommended for Non-Clear Cell RCC

Phase II trials and retrospective analyses support clinical activity of sorafenib[236,237] in patients with non-clear cell histologies. Similar to sunitinib, the data indicate that compared with clear cell type RCC, clinical activity of these drugs expressed seems to be reduced in patients with non-clear cell histologies. In another study of 53 patients with non-clear RCC (papillary or chromophobe), the ORR to sunitinib or sorafenib was 23%; median PFS was 10.6 months.[184]

The NCCN Panel does not recommend sorafenib use for patients with stage IV non-clear cell RCC.

Follow-up Recommendations for Relapsed or Stage IV Disease and Surgically Unresectable Disease

The NCCN Panel recommends a history and physical examination of patients every 6 to 16 weeks for patients receiving systemic therapy, or more frequently as clinically indicated. Other laboratory evaluations may be carried out as per the requirements for the therapeutic agent being used.

Imaging tests such as CT or MRI should be performed prior to initiating systemic treatment/observation; subsequent imaging may be performed every 6 to 16 weeks as per the physician's discretion and per the patient's clinical status. Imaging interval frequency should be altered according to rate of disease change and sites of active disease. The panel recommends additional imaging such as CT or MRI of the head or spine, and bone scan at baseline and then as clinically indicated.

Supportive Care

Supportive care remains a mainstay of therapy for *all* patients with metastatic RCC (See NCCN Guidelines for Palliative Care). This includes surgery for patients with oligometastatic disease in the brain whose disease is well controlled extracranially. Stereotactic radiotherapy, if available, is an alternative to surgery for limited-volume brain metastasis, and whole brain irradiation is recommended for those patients with multiple brain metastases.[238]

Surgery also may be appropriate for selected patients with malignant spinal cord compression, or impending or actual fractures in weight-bearing bones, if the rest of the disease burden is limited or patients remain symptomatic. Also, radiation therapy along with bisphosphonates is considered for palliation, particularly for painful bone metastases. The frequency of clinic visits or radiographic and laboratory assessments depends on the individual needs of the patient.

Bone metastasis occurs in 30% to 40% of patients with advanced RCC.[239-241] Bone lesions in patients with RCC are typically osteolytic and cause considerable morbidity, leading to skeletal-related events (SREs), including bone pain with need for surgery or radiotherapy, hypercalcemia, pathologic fractures, and spinal cord compression. Two studies of patients with bone metastases showed an improvement in bone pain using different radiotherapy modalities.[242,243]

The role of bone-modifying agents such as bisphosphonates (eg, zoledronic acid) has been well established in this setting.[244,245] The newer bone-modifying agent approved for use in patients with RCC that has metastasized to the bone is the RANK-L inhibitor, denosumab. A phase III randomized trial directly compared the development of SREs on either denosumab or zoledronic acid in patients with multiple myeloma or bone metastases with a solid tumor (excluding breast or prostate cancer). The study enrolled 1776 patients with bone metastases from a wide range of cancer types, including patients with RCC (6%) not previously treated with a bisphosphonate.[246] Denosumab was reported to be non-inferior to zoledronic acid in delaying time to first on-study SRE (HR, 0.84; 95% CI, 0.71–0.98; P = .0007).[246]

The NCCN Kidney Cancer Panel recommends a bisphosphonate or a RANK ligand inhibitor for selected patients with bony metastases and creatinine clearance greater than or equal to 30 mL/min. Daily supplemental calcium and vitamin D are strongly recommended. Treatment for the palliation of symptoms, especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management (See NCCN Guidelines for Adult Cancer Pain).

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