REVIEW ARTICLE

Renal Cell Carcinoma from Screening to Surveillance: A Review

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KEYWORDS

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Staging

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ABSTRACT

Renal cell carcinoma (RCC) is the most common type of renal cancer, and it is usually found incidentally in asymptomatic individuals. Despite an increase in prevalence, RCC mortality has improved. Advancements have been made over the years in diagnostic and treatment modalities and screening guidelines to decrease mortality rates. These guidelines are important to all, especially the primary care physician. A significant part of family medicine is preventative medicine, which focuses on screening for various diseases, including numerous cancers. Understanding epidemiology, risk factors, and staging is imperative to appropriately address RCC from surveillance to treatment. RCC encompasses many subtypes, thus making anatomy and histology important as defining characteristics, especially in screening and diagnosis. When directing treatment modality, staging, localization, and risk factors are essential. Understanding the steps required to improve survival rates is imperative to all physicians.

INTRODUCTION

Kidney cancer is primarily confined to the kidneys, while a small percentage has either spread to regional lymph nodes or metastasized to distant areas.[1] Renal cell carcinoma (RCC) is the most common type of kidney cancer as defined by the National Cancer Institute and arises from the renal cortex.[2] Throughout the years, there have been improvements in imaging modalities and treatment of various cancers. Kidney cancer's 5-year survival rate has gone from 30% in the 1960s to 75% due to improvements in guidelines. Specifically, when RCC is detected earlier and at a smaller size, it allows for a better response to treatment.[3] RCC often requires a multifaceted approach in which staging and understanding of the disease dictate treatment and guidelines.

EPIDEMIOLOGY

The U.S. Centers for Disease Control and Prevention (CDC) reports that an estimated 628,255 people in the United States are living with kidney and renal pelvis cancer, with ~81,000 new cases and ~14,000 deaths from RCC yearly, with higher prevalence in those with nonmodifiable risk factors.[4-6]

RISK FACTORS

RCC has many modifiable and nonmodifiable risk factors, which are important for physicians to consider when deciding which patients to screen for RCC. Nonmodifiable risk factors include male gender, advanced age, race, and genetic predisposition (those with von Hippel-Lindau [VHL] disease). In terms of race, a higher prevalence of RCC is seen in those of African American and American Indian backgrounds.[4-6] Modifiable risk factors associated with RCC include smoking, hypertension, chronic kidney disease, end-stage renal disease on hemodialysis, and obesity, all of which are areas primary care physicians can target to mitigate risk.[7-9]

TYPES OF RENAL CELL CARCINOMAS: ANATOMY AND HISTOLOGY

Before understanding screening and treatment guidelines, it is important to be familiar with types of RCC and the anatomy and histology behind each. RCC arises from the renal tubules and renal pelvis. The renal tubules are where 80% to 85% of RCC originates, and types include clear cell RCC, papillary RCC, chromophobe RCC, collecting duct RCC, and medullary carcinoma.[10]

Clear cell RCC and papillary RCC arise from the proximal collecting duct (PCT), with clear cell RCC encompassing 70% to 80% of adult cases of renal cancer and papillary RCC encompassing 10% to 20%.11 Clear cell RCC is associated with a deletion of chromosome 3p and microscopically has very pale or clear cell.[12] Papillary RCC, however, is associated with activation of the proto-oncogene tyrosine kinase c-Met with the majority of sporadic cases showing trisomy of chromosome 7.[13,14] Cancer cells in papillary RCC form finger-like projections (papillae) and are called chromophilic because cells take in certain dyes and look pink.[11] This RCC type can be further subdivided into type 1 and type 2 where type 1 is at an earlier stage and has a more favorable prognosis and type 2 is more aggressive with poor prognosis, as the disease is at a more advanced stage.[13-15] Chromophobe RCC, unlike clear cell and papillary cell RCC, originates from intercalated cells of the collecting system and encompasses less than 5% of RCC cases.[11] Cells of this type demonstrate a lack of abundant lipid and glycogen and are darker than clear cell carcinoma and larger.[16,17] When chromophobe RCC manifests, it is usually at a

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lower stage and there is a lower risk of disease progression and death.[18,19] Rare forms of RCC, <1%, originating from the renal tubules are collecting duct RCC and medullary carcinoma.[11,20] Collecting duct RCC is usually found in younger Black patients and is aggressive at its presentation.[21] Medullary carcinoma is a highly aggressive variant of collecting duct carcinomas and arises in the renal medulla from the distal segment of the collecting duct and is associated with sickle cell disease (SCD), whereby chronic medullary hypoxia leads to sickled red cells.[22]

Although RCC primarily originates from the renal tubules, transitional cell RCC arises from the renal pelvis tubules, where transitional cells look like cells that line the ureters and bladder, and encompasses 8% of all renal neoplasms.[2] This carcinoma occurs at a younger age, is female-predominant, presents at a later stage, and is associated with a poor prognosis in comparison to other RCCs.[23,24] Additionally, this type of RCC is resistant to targeted therapies but may be sensitive to immune checkpoint inhibitors.[25]

The anatomy and histologic classification of RCC are important when discussing imaging modalities used to localize disease by radiologists, as well as when discussing prognostic and therapeutic implications. Those types that share similarities may respond similarly to the same treatments. Furthermore, distinction between clear cell RCC and nonclear cell is imperative in discussing surgical vs nonsurgical treatment options.

SCREENING AND DETECTION GUIDELINES

Screening for RCC depends on risk, and due to the low prevalence of RCC in the general population, screening in asymptomatic patients is not recommended. However, due to high mortality rates—which have improved over the years—establishment of a screening program, especially in those with risk factors, may be appropriate to discuss.

The goal of an RCC screening program is to reduce deaths by identifying tumors at an early and treatable stage, but there are unknowns that remain. These unknowns consist of variables like cost-effectiveness of screening, survival benefit of early treatment, optimal screening modality, and target populations.[26] Additionally, screening can be financially burdensome on patients and lead to overdiagnosis. Studies performed over the years to answer the above unknowns have all had drawbacks, and results of the current prospective trial being conducted are still pending.[27] One such study is the Yorkshire Kidney Screening trial, which is using lung cancer screening via computed tomography (CT) with CT for RCC. Combing RCC screening with established national health check programs may be viable as it will reduce cost, but its validity is yet to be determined.[27]

RCC primarily is found incidentally on imaging, as most patients with RCC are asymptomatic and do not have the classic triad of hematuria, flank pain, and palpable mass.[27] RCC can be considered on a patient's differential based on clinical presentation and laboratory results. Hepatic involvement is uncommon but delineates a poor prognosis.[28] Certain presentations may make one more suspicious of RCC, like a male with a left-sided varicocele and symptoms such as flank pain or hematuria, as there is a close relation between the spermatic vein and left renal vein.[29] Additionally, if a patient has a high risk based on modifiable and nonmodifiable risk factors such as genetics, family history of renal cancer, race, smoking history, as well as being on hemodialysis, periodic monitoring with imaging is recommended by the American Urological Association.[26] CT with intravenous (IV) contrast is the gold standard for diagnosis and staging as it delineates the extent of involvement that will aid in choosing treatment options. However, other imaging can be utilized, as there is no agreed upon RCC screening protocol. Magnetic resonance imaging (MRI) can be used if imaging is inconclusive or if there is a contraindication. Ultrasound (U/S) is cost-effective, but it is less sensitive than CT. Additionally, false negatives can occur with U/S when masses are <3 cm.[30,31]

STAGING

Once RCC is diagnosed and imaging is done to confirm advanced vs localized disease, staging needs to be undertaken to determine treatment modality. RCC is divided into 4 stages: Table 1 will aid in understanding surgical vs nonsurgical treatments as well as surveillance.[2]

TREATMENTS

Primary care physicians should consider the interrelationship of structure and histology to direct treatment modality. Every RCC does not need to be treated or resected; some can be surveilled. Due to advancements in treatment and imaging modalities, which allow for better surveillance, RCC has seen improved survival rates throughout the years.

Treatment of RCC differs based on staging and whether the tumor is localized or disseminated. Earlier stages use a more surgical approach, whereas later stages use more targeted or palliative therapy.[10]

Earlier/Localized Disease, Stages I-III: Surgical Options

For clear cell and nonclear cell RCC, in cases where disease is localized and patients are classified into Stages I-III (as defined in Table 1), surgery is the definitive and curative treatment." Usually, radical nephrectomy is preferred for stages I to III, but partial nephrectomy is preferred in stage T1a or VHL.[32] Additionally, preoperative biopsies are not done prior to surgery due to low specificity and risk of seeding into the peritoneum.[33]

Radical nephrectomy is the most common surgical option for stages I to III RCC, but it can be utilized in advanced disease if there is direct involvement of the ipsilateral adrenal gland.[32] This procedure is done laparoscopically, usually with robotic assistance, and it removes the kidney, adrenals, and surrounding tissue and nearby lymph nodes, which can be potentially curative. The use of robotic assistance allows for shorter hospital stays and faster recovery, and it mitigates pain. However, it cannot be used if the tumor has grown into the renal vein or metastasized.[34]

TABLE 1:

Staging Renal Cell Carcinoma

STAGING RCC			
STAGE	**TNM**	**LOCATION**	**SUBDIVISION**
Stage I	T1N0M0	• Confined to kidney <7 cm • No lymph node involvement (N0) • No distant metastases (M0)	• T1a: ≤4 cm • T1b: >4 cm to ≤7 cm
Stage II	T2N0M0	• Confined to kidney <7 cm • No lymph node involvement (N0) • No distant metastases (M0)	• T2a: ≥7 cm to <10 cm • T2b: ≥10 cm
Stage III	T3 or any TN1M0	• Extends into major veins or perinephric tissues but not ipsilateral adrenal gland and not beyond Gerota's fascia • Possible spread to one regional lymph node (N1) • No distant metastases (M0)	• T3a: tumor extends into renal vein, or invades into parenchymal system or invades perianal or renal sinus fat but not beyond Gerota's fascia • T3b: tumor extends into vena cava below diaphragm • T3c: tumor extends into vena cava above diaphragm or invades wall of vena cava
Stage IV	T4 or any M1	• Invades beyond Gerota's fascia including extension into ipsilateral adrenal gland • Spreads to distant lymph nodes (N2) • Spreads to liver, lung, bone (M1)	None

Data gathered from: Garfield K, LaGrange CA. Renal Cell Cancer. In: StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK470336.

Partial nephrectomy, also known as nephron sparing, is preferred in stage T1a and VHL, because it allows for retention of kidney function. Usually, tumors that are <4 cm, early in stage, or isolated fall under this surgical option.[32] This treatment is not useful if there are multiple tumors in the same kidney, the cancer is not located peripherally, or it has spread to multiple lymph nodes or distant organs.

Other surgical options, like cytoreductive nephrectomy and metastatectomy, can be utilized in certain circumstances. Cytoreductive therapy can be done prior to initial systemic therapy in certain patients in whom 75% of debulking is possible and there is no symptomatic metastatic disease.[35] Metastatectomy can be undertaken if the primary tumor can be resected and there is concurrent single metastasis, whereby resection of the primary tumor with radical nephrectomy can be curative.[36] This form of surgery can also be done in those with recurrent disease or for palliative purposes in symptomatic stage IV patients.

Earlier/Localized Disease, Stages I-III: Nonsurgical Options

The majority of stages I to III RCC are either surveilled or treated surgically; however, in some cases, surgery is not an option. For example, if the mass is small or the patient is older with multiple comorbidities, surgery is avoided. In these cases, thermal ablation (cryotherapy or radiofrequency ablation) can be used, since most small tumors grow slowly and do not metastasize.[37] Cryotherapy and radiofrequency ablation as primary treatments are only possible in stage T1a patients, as these patients have masses that are <3 cm, have a high rate of being benign, and have low metastatic potential. Ablation of a mass >3 cm is associated with higher rates of recurrence and increased risk of complications, and thus is not recommended.[38,39]

Advanced/Metastatic Disease, Stage IV: Nonsurgical Treatment

Stage IV treatment depends on how extensive the metastasis is, the type of RCC, and the overall health of the patient. Those with advanced disease undergo risk stratification as delineated by the International Metastatic RCC Database Consortium (IMDC) to direct therapy (Table 2). Some patients with advanced disease may be able to undergo surgery but the majority utilize immunotherapy or targeted therapy as well as palliative procedures like embolization or radiation.[40] Risk factors and disease burden dictate surveillance vs nonsurgical treatment as noted in Table 3. Unlike with other cancers, chemotherapy is not a viable option in RCC.[40]

TABLE 2

Risk Factors and Prognosis

IMDC risk factors
• Karnofsky performance status <80%
• Decreased hemoglobin level
• Elevated corrected serum calcium
• Time from initial diagnosis to initiation of systemic therapy <1 year
• Neutrophilia
• Thrombocytosis
Score prognostic assessment
0: favorable
1-2: intermediate
≥3: poor

Data gathered from: Guida A, Le Teuff G, Alves C, et al. Identification of international metastatic renal cell carcinoma database consortium (IMDC) intermediate-risk subgroups in patients with metastatic clear-cell renal cell carcinoma. *Oncotarget*. 2020;11(49):4582–4592. doi:10.18632/oncotarget.27762

TABLE 3:

Disease Burden and Treatment Options

DISEASE BURDEN	IMDC RISK FACTOR SCORE	TREATMENT
Limited	0	Surveillance > Immunotherapy
Substantial	0	• Immunotherapy, molecular • Targeted therapy
Asymptomatic disease burden	≥1	• Immunotherapy • Molecular targeted therapy
Symptomatic disease burden	≥1	• Immunotherapy • Molecular targeted • Therapy • Palliative therapy

In the setting of clear cell RCC, if metastasis is suspected, pathologic confirmation is required prior to treatment. In patients who are treatment-naive with advanced or metastatic disease not controlled by local therapy, systemic immunotherapy via checkpoint inhibitors, or molecular targeted therapy, is a viable option. If the patient is asymptomatic and has favorable risk factors and limited disease burden despite being stage IV, active surveillance can be offered.[41]

In nonclear cell advanced RCC, treatment varies and depends on the histologic, pathologic, and molecular features of the tumor. Due to the paucity of these tumors, data on management are limited, but those with advanced disease have historically been treated palliatively.[42]

IMMUNOMODULATORS VS PALLIATIVE THERAPY

Checkpoint inhibitors

There are multiple immunotherapy options available to treat advanced disease with the most common being checkpoint inhibitors, which target cell death pathways or cytotoxic T-lymphocyte–associated antigen pathways.[43] Choice of immunotherapy depends on risks to the patient and type of RCC. Nivolumab (a programmed cell death protein 1 [PD-1] inhibitor) and ipilimumab (a cytotoxic T-lymphocyte antigen 4 [CTLA-4] inhibitor) combination therapy is indicated in intermediate or poor-risk patients.[44] Nivolumab can be offered to those with disease progression on vascular endothelial growth factor receptor (VEGFR) inhibitors in transitional cell carcinoma.[43,44] VEGF-targeted therapy blocks angiogenesis or tyrosine kinases that help tumors grow and survive. There are other options that can activate immune response against RCC and can result in tumor regression in genetic conditions like VHL; however, because of cost and toxicity, these options are not first-line in advanced kidney cancer. There are also therapies such as pembrolizumab, a PD-1 inhibitor, which is used 1 year postsurgery in those with high rates of recurrence to shrink tumors and slow their growth.[45]

Molecular targeted therapy

Targeted therapies used to treat advanced nonclear cell RCC consist of VEGFR inhibitors and mechanistic target of rapamycin (mTOR) modulators, which are used in multiple subtypes of RCC. Both VEGFR inhibitors and mTOR modulators are used in papillary RCC as either initial or subsequent therapy and in chromophobe RCC as initial therapy, as delineated in Table 4. VEGFR inhibitors can also be used as initial therapy in transitional cell and unclassified RCC.[46] Sunitinib is one example of a VEGFR inhibitor, which is used as a risk-lowering adjuvant in those whose cancer has a high risk of recurring following surgery.[45] These options, as well as less frequently used weekly IV treatments, are the cornerstone of treating advanced disease.

Chemotherapy

Most kidney cancers are resistant to chemotherapy, so it is not usually a viable option unless immunotherapy and targeted therapy have been tried and failed.[47] Chemotherapy when utilized is limited to platinum-based therapies and is used only in nonclear cell collecting duct and renal medullary carcinomas, where there is limited information regarding immunotherapy with checkpoint inhibitors.[48]

Palliative therapy

Even when utilizing targeted therapy, advanced disease has limited options and, as such, palliative therapy may be necessary. Palliative procedures like arterial embolization or radiation therapy in advanced disease stages can be utilized for symptomatic relief, especially in those with painful bone metastasis, brain metastasis after effective stereotactic radiosurgery, and in those who are unable to undergo surgery in stages I to III.[49]

TABLE 1:

Immunomodulators and Chemotherapy

TREATMENT					
Cancer type	Checkpoint inhibitor	mTor	VEGFR inhibitor	PD-1 inhibitor	Platinum-based chemotherapy
Papillary	X		X		
Chromophobe		X	X		
Collecting duct					X
Renal medullary					X
Transitional cell			X	X	
Unclassified	X		X		

SURVEILLANCE

Surveillance as opposed to surgical management is an option for select individuals because around 40% of tumors are <1 cm and benign.[2] For example, stage II or III patients can only undergo surgery as a primary treatment but stage T1a and select T1b patients can undergo surveillance as a primary treatment.[50] In addition to being used as a form of treatment, surveillance is also done after treatment in surgical and nonsurgical circumstances. Surveillance consists of a mixture of subjective and objective findings on doctor's visits, as well as imaging and laboratory results.

Surveillance after surgery

Surveillance is important after surgery due to risk of recurrence. Recurrence usually occurs within the first few years following surgery, and half of these recurrences usually develop in the lungs.[51,52] The National Comprehensive Cancer Network guidelines recommend surveillance in terms of clinical benefit within the first 5 years following surgery, and these recommendations differ based on staging and type of surgical intervention.[53] Surveillance after 5 years is at the discretion of the provider, as there is no consensus about optimal strategy.

Stage I RCC patients must see their physician every 6 months for the first 2 years, then annually up to 5 years regardless of type of surgical intervention.[53] At this visit they should have a complete metabolic panel (CMP). Regardless of the type of nephrectomy a patient underwent, a baseline CT scan of the abdomen and pelvis (CTAP) or U/S is recommended within 3 to 12 months of surgery, then annually for 3 years if the baseline scan is negative. If a partial or radical nephrectomy was performed, then surveillance beyond initial imaging is optional.[53] Due to lung involvement in recurrent disease, a CT chest scan is recommended annually for the first few years.

Unlike in stage I, if a patient had undergone a radical nephrectomy, an office visit and CMP are recommended every 3 to 6 months for 3 years and then annually for the next 2 years.[53] Like in stage I, a baseline CTAP is recommended within 3 months; however, follow-up imaging is done more frequently in stages II and III. A repeat CTAP is done in 3- to 6-month intervals for the first 3 years, then annually for the next 2 years if baseline imaging is negative.[53] A chest CT scan is recommended within 3 to 6 months after surgery, every 3 to 6 months thereafter for a total of 3 years, and then annually for an additional 2 years if baseline is negative.[53]

Surveillance for Nonsurgical Candidates

As discussed, those who are not surgical candidates and who have a small renal mass may undergo active surveillance as a primary treatment. This entails baseline CT scan of the chest or chest x-ray (CXR), laboratory tests annually, and CTAP with contrast within 6 months of surveillance initiation if no contraindication.[54] Serial abdominal imaging should be done yearly to evaluate changes in the renal mass and, depending on those changes, further imaging evaluation for lung metastases may be warranted.

Like those with a small mass, those who underwent thermal ablation will need to undergo a thorough checkup with basic laboratory work annually. CTAP with and without IV contrast should be done 1 to 6 months after ablative therapy, then annually for 5 years.[53]

Follow-up for Relapsed or Stage IV With Surgically Unresectable Disease

As discussed, some stage IV patients will undergo systemic therapy, as their disease will not be surgically resectable. Prior to using any systemic therapy, baseline CTAP is needed, and baseline brain imaging, spinal imaging, and bone scan can be considered.[53] Patients receiving systemic therapy should be seen every 6

months and basic laboratory tests targeted towards therapeutic agents and their adverse effects should be done frequently. For example, pazopanib, a tyrosine kinase inhibitor, can cause severe liver damage, clotting disorder, and arrythmias. Thus, laboratory tests to check liver function, coagulation, and electrolytes must be done in addition to periodic electrocardiographs (EKGs).[55]

CONCLUSION

RCC is a condition that affects thousands throughout the United States. A solid foundation of anatomy and histology is required to dictate screening, surveillance, and treatment. A multifactorial approach is needed to appropriately treat the disease and continue improving survival outcomes. Primary care physicians are placed in a unique position: in their practicing of preventative medicine, they may play a role in screening for RCC in high-risk individuals. To adequately care for patients with RCC, primary care physicians must understand the risks pertaining to this disease process, as well as the options specialists will discuss with patients. Surgery is not always an option—or rather is not always the best option—especially in advanced disease where immunotherapy or palliative therapy plays a more significant role. Treatment for RCC is multifaceted. Understanding the role of surveillance and the nuances it entails is imperative because primary care physicians will be following the patient's disease course from screening to surveillance.

LITERATURE SEARCH AND DATA SOURCES

The author's search strategy was to first log onto the NYTCOM library website and find a textbook with an overview of RCC to create an outline. The author used the CDC website to get information on statistics of RCC. Various journals such as J*ournal of Urology, New England Journal of Medicine, JAMA*, and *Journal of Clinical Oncology* were then utilized to search subjects such as RCC epidemiology, risk factors for RCC, and RCC and nephrectomy. She also utilized ClinicalKey and PubMed as well as the Cochrane database to gather information on RCC treatment. In addition, she searched NCCN guidelines for RCC surveillance. The author gathered her information from October 20, 2023 to November 24, 2023. After the end of November, she began to compile the article and edit and identify additional resources.

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