



## FEATURE STORY

# Picking Up Momentum for Treating Renal Cell Carcinoma

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*Advanced treatments take form for a notoriously hard-to-beat cancer.*

“Get back up on the table.”

At the end of Gene Gillespie’s annual physical in March 2002, everything seemed fine. While he was dressing, his doctor impulsively told him to get back on the table, examined his abdomen, and found that he had an enlarged spleen. Further testing revealed a tumor in his kidney that was wrapped around his pancreas, spleen, and liver.

Renal cell carcinoma (RCC) is found in the lining of the very small tubes in the kidney that filter and clean blood, remove waste products, and produce urine. These cancers make up over 90 percent of all kidney cancers. RCC itself has several subtypes. The most common is clear-cell RCC, which accounts for around 80 percent of all RCC cases.

Men are more likely than women to develop RCC, but each year more people are getting this disease, and numbers are increasing faster among women than among men. Cigarette smokers have double the risk of kidney cancer compared with non-smokers. Obesity, high blood pressure, and occupational exposure to chemicals or other substances, such as asbestos or cadmium, can also increase the risk. However, most people who get kidney cancer have no known risk factors. As was the case for Gillespie, many patients don’t have symptoms that alert them to the presence of the disease.

Standard treatment for RCC remained the same for about 15 years. In the past, RCC that had not spread outside the kidney and nearby tissue would be surgically removed, and metastatic RCC (disease that has spread) would be treated with agents like Proleukin (interleukin-2, or IL-2) that use the body’s immune system to fight the cancer. Now, scientific advances have yielded new surgical and noninvasive techniques for treating localized disease, and new drugs have recently been approved for the treatment of metastatic disease.

## Drug-Free Techniques

Surgical removal of all or part of the kidney (called a nephrectomy) is the primary treatment for non-metastatic RCC. In a simple nephrectomy, the entire kidney is

removed. In a radical nephrectomy, the kidney is removed along with the adrenal gland, lymph nodes, and sometimes additional tissue. In a less invasive approach, nephrectomies can be performed laparoscopically. The technique involves use of a thin fiber optic scope to see inside the body, enabling surgeons to operate through smaller incisions. Disease-free survival and recurrence rates are about the same when compared with traditional, open surgery, and the hospital recovery time may be significantly shorter.

In some cases, only the tumor and part of the kidney is removed so that the patient can retain renal function. Partial nephrectomy, a form of nephron-sparing surgery, was initially reserved for patients with only one kidney or those who had tumors in both kidneys. It has since become a standard treatment for localized RCC (tumors smaller than 4 centimeters), with results similar to radical nephrectomy. With the partial procedure, doctors can completely remove the tumor in less time and with less trauma to the body than with complete removal of the kidney. The local recurrence rate is less than 5 percent, and the survival rate after 10 years approaches 100 percent for tumors smaller than 4 centimeters. In the overwhelming majority of cases, the kidney still functions after the surgery. The downside of partial nephrectomy is that the patient can experience prolonged pain and delayed recovery.

### View Illustration: A Modern Surgical Approach

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In recent years, the 4-centimeter tumor rule for partial nephrectomy eligibility has been challenged. A 2004 study at Mayo Clinic evaluated outcomes of 91 RCC patients with 4- to 7-centimeter tumors who were treated with partial nephrectomy. At five years, the recurrence-free survival rate for these patients was 94 percent. Some patients also have the option of a combination surgery called laparoscopic partial nephrectomy that is both less invasive and nephron-sparing. Although the procedure has been used for more than a decade, it is technically difficult and not widely available.

Several other nephron-sparing techniques can spare the kidney in patients who have tumors smaller than 4 centimeters, but their long-term effectiveness is not yet proven. Cryoablation, the most promising of these newer techniques according to some experts, involves inserting small needles into the kidney tumor and using chemicals to lower the temperature of the needle tips. The rapid freezing and thawing of the tumor kills the cancer cells.

Radiofrequency ablation, an outpatient procedure performed with conscious sedation and local anesthesia, uses localized heat to destroy tumor cells. Two or more 10- to 15-minute treatments are done per tumor. High-intensity—focused ultrasound (HIFU) is a noninvasive treatment applied from outside the body, where energy is focused on the specific tumor, and the tissue between transducer and tumor is theoretically unaffected. Problems with this procedure include imprecise targeting and thermal burns.

### Drugs for Metastatic RCC

Cancer has spread outside the kidney in about 25 percent of patients by the time of diagnosis, and about one third of all patients who are treated by surgery for localized disease will have a recurrence. Once cancer spreads outside the kidney, it has historically been difficult to treat. Prior to 2004, less than 10 percent of patients responded to conventional chemotherapy drugs.

Biologic therapies, which use the body's immune system to fight cancer, have been the mainstays of therapy for metastatic RCC. Cytokines are natural proteins produced by the body's immune system that allow immune system cells to communicate with each other. Some cytokines, such as interleukins and interferons, can be produced in the laboratory for treating cancer.

The current standard drug therapy for metastatic RCC is high-dose Proleukin because of its significant impact on long-term survival. Up to 20 percent of patients are alive 10 years after high-dose treatment with Proleukin. However, many patients cannot tolerate high-dose treatment because of its significant side effects, which can include low blood pressure, respiratory congestion and severe fatigue, requiring the drug to be given in a hospital setting. A low-dose regimen has been studied in order to lessen side effects, but only about 13 percent of patients respond to low-dose Proleukin.

Intron A, Roferon-A (interferon-alpha) was isolated from white blood cells in 1970 by investigators looking for antiviral substances. The cytokine stimulates the growth and action of immune system cells that fight disease, and it is frequently used to treat metastatic RCC. However, only about 14 percent of patients with clear-cell RCC respond to interferon-alpha alone. New discoveries about how RCC develops are leading to new drug treatments for metastatic disease.

## Pinpointing the Target

Recently, several familial syndromes have been linked to kidney cancer. Studying one of these syndromes, von Hippel-Lindau disease, led researchers to important discoveries about clear-cell RCC. In von Hippel-Lindau disease, patients inherit a defect in a specific gene called the von Hippel-Lindau, or VHL, gene. However, people without the inherited disease can also have problems with the VHL gene.

James Yang, MD, a senior principal investigator at the National Cancer Institute, says the proper functioning of the VHL gene can be damaged in a number of ways, but the end result is the same. The VHL gene is a tumor suppressor gene, so inactivation of the gene can cause up to 80 percent of all sporadic (non-hereditary) clear-cell RCC cases. These discoveries provided researchers with a specific target for developing therapies to treat RCC.

In order for a tumor to grow, it must have oxygen and nutrients. To get them, it has to grow new blood vessels, a process called angiogenesis. VHL genes that function normally produce VHL protein, which suppresses several other proteins involved in angiogenesis. When VHL protein is missing because of a mutated or malfunctioning VHL gene, conditions are favorable for tumor growth. Vascular endothelial growth factor (VEGF) is one of the primary proteins that drive

angiogenesis. The absence of VHL protein allows production of higher levels of VEGF and other proteins involved in angiogenesis, such as platelet-derived growth factor (PDGF). These pathways converge to promote blood vessel formation and proliferation of tumor cells.

### View Illustration: Targeting VHL

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The FDA recently approved two new RCC drugs, Nexavar (sorafenib) and Sutent (sunitinib), that target these pathways. Their ability to work at several levels is part of what makes them such exciting new weapons against RCC.

Nexavar, approved in December 2005, has the ability to block a variety of angiogenic pathways as well as a protein called raf. After 18 months of treatment on a clinical trial of Proleukin and interferon, Gene Gillespie's disease was stable, but increasingly intolerable side effects caused his doctor to suggest that he discontinue treatment. After eight weeks, scans showed slight disease progression. He then entered a clinical trial of Nexavar, and after six weeks, his tumors had shrunk 30 percent overall and some had completely disappeared. He has been taking Nexavar since April 2004 and the cancer has remained stable.



Gene Gillespie's kidney cancer is stable today thanks to Nexavar, a newly approved targeted drug. Photo by Robert Lyons.

In a randomized phase III study comparing Nexavar with placebo in previously treated patients, the tumor stayed stable for 24 weeks in patients treated with Nexavar compared with six weeks for those on placebo. A trend toward improved survival was also observed in patients taking Nexavar.

Nexavar, which costs about \$4,300 a month, is also being studied in advanced kidney cancer patients who have not had prior treatment. In July 2005, after removal of his left kidney and radiation treatment for metastases in his arm and foot, Lonnie Williamson of Chillicothe, Illinois, entered a clinical trial of Nexavar to treat additional metastases in his spleen, sternum, lung, and liver. "They told me they've had good luck with this drug, so I figured at least that's a start—it's better than sitting back doing nothing," he says. After about two months, during which his disease was stable, the trial's investigators told Williamson that he was taking the placebo. He was switched to Nexavar in September 2005, and as of December 2005, all of his tumors have shrunk or disappeared completely.

According to Ronald Bukowski, MD, director of Experimental Therapeutics at the Cleveland Clinic Taussig Cancer Center, the side effects associated with Nexavar are typically mild or moderate and can include high blood pressure, rash, and hand-foot syndrome (the skin on the hands and feet becomes red and tender). Williamson says his rash looks more like sores. He also has hand-foot syndrome. "On my feet I only have one bad spot that is really sore; it's hard to walk on." Recently, the foot problems have improved.

Gillespie had minimal side effects that have diminished or disappeared over time.

“I can do everything I want to do,” Gillespie reports. “I can work, I can travel. Just like a normal life.”

In June 2002, Julia Barchitta thought she had a bladder infection. Because of pain in her back and blood in her urine, her doctor sent her for ultrasound imaging to see if she had a kidney stone. The results showed a large mass on the kidney, and a CT (computed tomography) scan showed RCC. Her doctors thought the cancer was confined to her kidney and that a nephrectomy had successfully removed it. However, in December of that year, tests confirmed that a tumor at the base of one of her lungs was metastatic RCC.



Julia Barchitta participated in a clinical trial with Sutent after her RCC spread outside her kidney.

Barchitta began treatment with interferon and her RCC went into remission, but in May 2004, the cancer spread to her lymph nodes and bones. Barchitta’s husband had recently died from lung cancer, and she was determined to survive, explaining that their children had been emotionally devastated by the loss of their father. “I thought, ‘I have to help them by staying as well as I can. They can’t lose both parents in such a short time.’ ” In July 2004, she entered a phase II trial of Sutent, another drug that targets the pathways involved in angiogenesis that was approved in January 2006 for treating both metastatic RCC and gastrointestinal stromal tumors. She responded quickly to treatment and 20 months later she is still in remission.

Two consecutive phase II studies of Sutent involved patients whose tumors progressed during cytokine treatment. Results showed tumor shrinkage in about 40 percent of patients taking Sutent. A study comparing Sutent to interferon in untreated patients is currently under way. Additional studies in progress or planned for the near future will test Sutent combined with various drugs, including interferon, Avastin (bevacizumab), and chemotherapeutic agents, such as Gemzar (gemcitabine) and Xeloda (capecitabine). For patients receiving Sutent outside a clinical trial, the drug costs about \$4,300 for a six-week treatment cycle.

Robert Motzer, MD, of Memorial Sloan-Kettering Cancer Center, says Sutent’s side effects are similar to those of Nexavar and can include rash, hand-foot syndrome, high blood pressure, and gastrointestinal problems. Barchitta finds the foot problems most bothersome. “I get these terrible blisters on the bottoms of my feet that make it difficult to walk sometimes.” However, her treatment schedule gives her two weeks off treatment after every 28-day cycle. During that time, her side effects diminish.

## Under Investigation

Already approved for treating colorectal cancer, Avastin is an anti-angiogenesis drug being studied in RCC. Early randomized studies showed that high-dose Avastin can slow the time to tumor progression. In most patients, treatment delayed tumor progression by only a few months. Though unclear why, several patients in these studies have been taking Avastin for three to five years with no

tumor progression and minimal, manageable side effects.

Avastin is being tested in combination with other drugs. John Hainsworth, MD, director of clinical research at the Sarah Cannon Cancer Research Center in Nashville, is part of a team studying Avastin in combination with Tarceva (erlotinib) in metastatic RCC. Tarceva blocks the epidermal growth factor receptor (EGFR) and prevents the cancer cell from getting the signal to grow and divide. The theory of putting these two drugs together is that blocking both EGFR and VEGF will be more effective than blocking either one alone. In Hainsworth's phase II study, 25 percent of patients had objective responses to the drug combination, and an additional 61 percent had stable disease after eight weeks of treatment. After 18 months, 60 percent of patients were still alive.

Hainsworth cautions that the results should not be compared with results of previous trials using Avastin alone because the characteristics of the patients treated in different trials varied. Still, he says, the results are encouraging. Data about treatment with Avastin plus Tarceva are still being analyzed, and no additional trials of the combination for treatment of RCC are currently planned.

AG-013736 is another drug that targets VEGF receptors as well as the PDGF receptor. In a phase II trial of AG-013736 in patients whose cancers progressed after cytokine treatment, the best response found 24 of 52 patients having their tumors shrink by at least 30 percent.

Another approach under investigation is modifying the immune system of cancer patients to induce cancer regression. Inhibiting a molecule known as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) may help patients' immune systems fight cancer. CTLA-4 is a molecule that controls the activation of T cells, specialized immune cells that recognize and kill foreign cells that have invaded the body. CTLA-4 has recently been targeted with monoclonal antibodies, including one called MDX-010, with a response rate of about 25 percent. Clinical trials testing this concept in RCC are being conducted around the country.

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—John Hainsworth, MD

Another avenue of investigation involves drugs known as mTOR inhibitors. The mTOR pathway is critical in controlling a cancer cell's life cycle and replication. In a phase II trial, temsirolimus (CCI-779) showed promise in patients with poor prognosis, prompting a phase III trial in metastatic RCC. The drug is expected to be filed for approval in kidney cancer in late 2006. "The big message is that all of these drugs are better than anything that's been out there before for metastatic kidney cancer," says Hainsworth.

Researchers are conducting clinical trials and preclinical investigations of many additional drugs and combination therapies in patients who have the clear-cell variety of RCC. Investigators say that after efficacy is established in clear-cell

RCC, many of these new options may be tested on other types of RCC. However, their effectiveness for non-clear-cell RCC will depend on how similar the other tumors are to clear-cell RCC in terms of what makes them grow. For instance, if a specific non-clear-cell RCC has a VEGF imbalance, then it is likely that a VEGF inhibitor will have some anti-tumor effect. “Being a researcher, I see how many medicines are out there being tested in kidney cancer right now,” says Bukowski. “I anticipate that we are going to make great strides in the next five years.”

## Sorting Out the Options

Yang explains that it is difficult to compare the effectiveness of the new agents, because different studies use different measurements of outcome. According to Bukowski, this variance in how tumor size is measured can make it seem as though fewer patients are being helped with some of the new treatments than is actually the case. “The number of major decreases in tumor size is small, but in reality most patients had some effect on the size of their tumor,” Bukowski explains.

When treatments are changing, it is possible that patients seeing different oncologists could get different recommendations. Hainsworth says the new agents, and ongoing studies of various combinations of these agents, are already the best treatments available. “If I were a patient, I’d go straight to these newer drugs. I wouldn’t mess around with any of the older agents.”

Yang sees things differently. “It is important that we don’t lose track of the fact that, for some patients, there is curative treatment that should be used first. If you’re a good candidate for Proleukin and you can get it safely from someone who knows how to give it, I think you should try that first. If it works as well as it can for some people you don’t need anything else.” He adds that if Proleukin fails, as unfortunately it does for most people, then there are options that can put off tumor progression for quite impressive periods of time.

Doctors and patients are attracted to targeted therapies because they are simple and easy to take, says Yang. “But it’s important to realize that easy is not really what we want. We want curative.”

Yang explains that almost all patients will eventually progress on these new agents and will require something else. Barchitta understands that, and the number of new options being studied gives her hope. “Sutent is working right now, but I don’t know if it will stop someday like the interferon did. So it’s nice to know that they are working on other things and that I’m not at the point where they’re going to say there’s nothing else we can do for you.” Motzer sums it up: “These new targeted therapies open up a whole new era with multiple medications, multiple options, either sequenced or in combination. We can help patients again and again.”