Eleventh International Kidney Cancer Symposium

Presentation Notes: An Overview of the Proceedings

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During the Symposium

James Larkin, Ph.D., MRCP - Royal Marsden Hospital, London, England displayed a slide showing alternative routes around a blocked passage in the London Subway System

In his presentation: *Biologic Mechanisms of Resistance*

Kidney Cancer Association
www.KidneyCancer.org

The Eleventh International Kidney Cancer Symposium 2012

Reporting by Joyce W. Graff, VHL Family Alliance

Executive Summary

I was honored to be invited again this year to report on this important conference. This report is prepared with patients and families in mind. The meeting was designed as a Continuing Medical Education event for doctors, providing them with enrichment in this important area. Kidney cancer is the sixth most common cancer in the United States. Most local hospitals see few cases each year, so their knowledge of how to treat may be limited. Most patients are referred to larger teaching hospitals, where more cases are seen. Nonetheless, people are diagnosed locally, and it is important that their cases be handled well from the beginning, to give them the optimal chance for life and quality of life.

The standard of care for **small renal masses** has shifted from radical nephrectomy to a strategy to preserve the volume of working kidney as well as the quality of life of the patient. Depending on the size of the tumor and the tissue type (as determined by biopsy), small masses might be watched, or a partial nephrectomy performed to remove the tumor and save as much kidney as possible. Masses larger than 3 cm should be removed, and the need for follow-up drug treatment evaluated. There were good discussions of the role of ablation, open versus laparoscopic or robot-assisted partial nephrectomy, or even radical nephrectomy. Loss of kidney volume tends to lead to chronic kidney disease, which can depreciate the patient's quality of life.

When the tumor is quite large, or when there is evidence of **locally advanced disease**, then the patient should be evaluated for surgery. The preference is for open partial nephrectomy, removing the tumor and doing a "cancer operation." There was a discussion of the value of removing nearby lymph nodes to reduce the risk of movement of the disease to other parts of the body. Many patients are older and may have additional health issues which might make them poor risks for surgery.

There were a number of fascinating presentations on **understanding kidney cancer biology**. As we understand the cascade of events leading up to the formation of a kidney cancer tumor, and evolving through the life cycle of that tumor to the point where it gains metastatic potential, we are gaining insights into ways we might intervene in this process and stop or reverse tumor growth. We now have seven drugs on the market for advanced kidney cancer. However, there are still no complete responses, no cure. There is still a great deal of work to be done.

Four speakers shared their thoughts on **patient management issues**; figuring out the optimal dose in RCC therapy, providing support to kidney cancer survivors and their families, and helping more people gain access to kidney cancer care.

On Saturday morning a series of speakers talked about the **role of surgery** in management of a patient with metastatic disease: should the primary tumor be removed to reduce primary source of metastatic cells being put forth into the body? Should metastatic sites also be surgically removed? Should drugs be used before the surgery in an effort to shrink the tumor? In general the current drug offerings do not

significantly shrink the tumor, so surgery is probably the first course of action, but there should be a plan in place for what to do after the surgery. Some of the treatment options require analysis of the tumor tissue itself, or even tissue for formulation of personalized treatments. Without this prior planning, some options might be lost.

There was a section on treatment options for a patient with metastatic disease who has had **no prior drug therapy**. We are now in our third generation of drugs, each one of which is getting to be more specific and more efficient in attacking the tumor. Each year there is a new line-up of preferred drugs. At the same time, nearly all of them work along the VEGF pathway, and the tumor eventually figures out how to grow in spite of the action of the drug – a phenomenon known as "resistance." The tumor becomes resistant to the action of the drug.

The following section dealt with what to do when **resistance** develops. Should one take a break from the drug and then go back on the same drug? In some cases this does work. Should the patient go on a different drug? Again, there is some success with this strategy. Might we add two drugs together and get a better response, or prevent resistance from occurring? Success with combination therapies has been very disappointing.

Dr. William Kaelin, in his Eugene Schonfeld Lecture, the keynote lecture, shared his own thoughts on **science-driven clinical trials**. What he learned in medical school, he said, was that we should use two or more drugs together, at pretty much their full strength, in order to attack the tumor from multiple directions at the same time. When we add more than one VEGF inhibitor together, however, we are working along the same molecular pathway, hitting the same pathway twice. Too much VEGF inhibition tends to end in cardiac events, as the VEGF process is important in cardiac care. What we really need is to add an agent that takes a different angle of attack – like, for example, PD-1 immune therapy; or inhibition of HIF2alpha (if it can be done). And instead of massive very expensive trials we should do small proof-of-concept trials to test out novel ideas.

The final segment of the program was an exploration of **emerging therapeutic approaches**, including vaccine strategies to enhance the immune system, and the impact of drug therapies on the tumor microenvironment. Once you have taken one of these drugs, how does that change the nature of the tumor itself? Dr. Michael Atkins outlined his vision of the future of medical therapy for RCC.

The first time I attended one of these symposia, there were no drugs. Then there was IL-2. Now there is a smorgasbord of possible drugs to try. Unfortunately, there are still no magic bullets, few complete responses, and with the exception of Interluekin-2 and its brutal treatment regimen with a small total response rate, no durable and lasting "cures." But many people are living longer lives with good quality of life. Even without a cure, there is more hope today for someone with kidney cancer than ever before. Working together and trying new strategies, we will find even better options in the next few years.

Be Well; and be a Powerful Patient! Joyce

Commentary/Layout

Michael B. Lawing, KCA Patient Advocacy Volunteer

Dear Fellow Travelers:

As I complete my fifteenth year of survivorship of clear-cell RCC, and a dozen years of dealing with active metastatic disease the information presented at the 11th International Kidney Cancer Symposium in Chicago can only begin to speak of how far we have come in dealing with this cancer. Presently we have more options for treatment than most other cancers. Despite the advances and breakthroughs that dedicated researchers and clinicians have made there are still numerous issues and frustrations that present themselves to the medical community and consequently to the patients and family members that are diagnosed with kidney cancer.

Once again this annual symposium drew together a very skilled and experienced faculty who are recognized authorities in the investigation and treatment of renal cell carcinoma. The information presented to those in attendance represents not only the best practices but raises the pressing questions being addressed in facilities throughout the United States and other nations as the quest for making kidney cancer a treatable chronic disease is pursued with the ultimate goal of finding durable and complete responses for future generations.

It is my great pleasure to have worked with Joyce Graff in compiling and making this summary of proceedings available in a version which is hopefully understandable, informative, and enjoyable for patients, caregivers, and friends of those who are affected by kidney cancer. Because of her vast experience in reporting on numerous similar meetings throughout the world, her notes taken during the presentations serve as the prime narrative for this document.

During the symposium, Dr. Michael Jewett of the Princess Margaret Hospital, Toronto Canada gave a presentation on *Collaborating to Improve Survivorship Care*. Because of the vital link and the importance of the doctor/patient relationship not only in kidney cancer but other cancers and maladies, I have utilized some of his material in an appended editorial which appears at the end of the overview of these proceedings.

The information, knowledge, and treatments available to today's survivor of kidney cancer in comparison to 15 years ago are incredible. While there is still much to do, much to learn, and much to strive for; I am so thankful for the efforts of those who so tirelessly and faithfully look for the answers.

I would like to thank the directors and staff of the Kidney Cancer Association for allowing me the privilege of experiencing and sharing the proceedings of the 11th Annual International Kidney Cancer Symposium and for paring me with Joyce Graff in submitting this overview for your consideration.

Warmest Wishes; Best of Success: Michael B Lawing

A World Without Kidney Cancer – The Vision of the Kidney Cancer Association

The Kidney Cancer Association (KCA) is a charitable organization made up of patients, family members, physicians, researchers, and other health professionals globally. It is the world's first international charity dedicated specifically to the eradication of death and suffering from renal cancers. It is also by far the largest organization of its kind, with members in more than 100 countries. We fund, promote, and collaborate with the National Cancer Institute (NCI), American Society for Clinical Oncology (ASCO), American Urological Association (AUA), and other institutions on research projects. We educate families and physicians, and serve as an advocate on behalf of patients at the state and federal levels in the United States and globally.

The Association was founded in 1990 by a small group of patients, including Eugene P. Schonfeld, Ph.D., and medical doctors in Chicago, Illinois. It is a nonprofit charity incorporated in the State of Illinois. It has also been designated as a tax exempt organization under Section 501(c)(3) of the U.S. Internal Revenue Service code. Donations to the Association are tax deductible. Our federal taxpayer identification number is 36-3719712.

We encourage both private and public sector institutions to do more research on kidney cancer. We help researchers in academic medical centers, government, and industry with money and information. We are a catalyst for new ideas. For example, we provide financial grants for basic research into the biology of kidney cancer. Members of the Association work to raise funds. These competitive awards are made from a pool of funds named in honor of the Association's late founder, Eugene P. Schonfeld, Ph.D.

Our Vision: A World Without Kidney Cancer
Our Mission: The Elimination of Death and Suffering From Renal Cancers

Since it was established in 1990, consistent with the vision of the organization's founder, Eugene P. Schonfeld, Ph.D., the KCA's plan of work continues to be executed in these primary areas:

1) Education
2) Research
3) Advocacy

During the Fiscal Year ending October 31, 2011, we provided more than 65 education and support opportunities for patients, survivors, and caregivers in various U.S. cities, including a national meeting held at M. D. Anderson Cancer Center, Houston, from which enduring educational materials were produced. We hosted online weekly informal Facebook Group chats for survivors and caregivers, and our Facebook presence has grown to include more than 40,000 people from around the world. We launched KidneyCancer.me, a peer-to-peer collaboration website for patients, survivors, and caregivers. The KCA developed and released patient-friendly

smartphone educational applications for the iPad, iPhone, and Android platforms. We sponsored the Sixth European Kidney Cancer Symposium in Warsaw, Poland. More than 700 medical professionals registered. Later in the year, more than 300 medical professionals attended the annual International Kidney Cancer Symposium in Chicago. Patient advocates who attended this meeting prepared summaries of the medical presentations that can be easily understood by patients and their families. From our suburban Chicago offices, we mailed several hundred information packets to families and provided physician referrals to hundreds of patients. Our membership database includes people in North America and more than 100 countries.

Research

Our Nurse Advisory Board completed a comprehensive revision of We Have Kidney Cancer, our patient publication that has grown to more than 100 pages, now distributed around the world. Our partnership with EmergingMed, and other companies, resulted in the referral of dozens of patients to sites conducting clinical trials. Our Nuse Telephone Information Service answered hundreds of calls from patients. We made grants to the AUA Foundation and to the ASCO Conquer Cancer Foundation to support the work of young investigators. We also made a financial commitment to support a project associated with the Kidney Cancer SPORE.

Council, Foundation for NIH, National Cancer Comprehensive Network, Patient Advocate Foundation, the National Coalition for Cancer Research, Friends of Cancer Research, and various groups concerned with improving the nation's health care. We continued highly effective collaborations with institutions interested in conducting cancer research, including our CEO's membership on NIH committes that are advisory to the Biomarkers Consortium, The Cancer Genome Atlas, and an NIH group dedicated specifically to renal cancers.

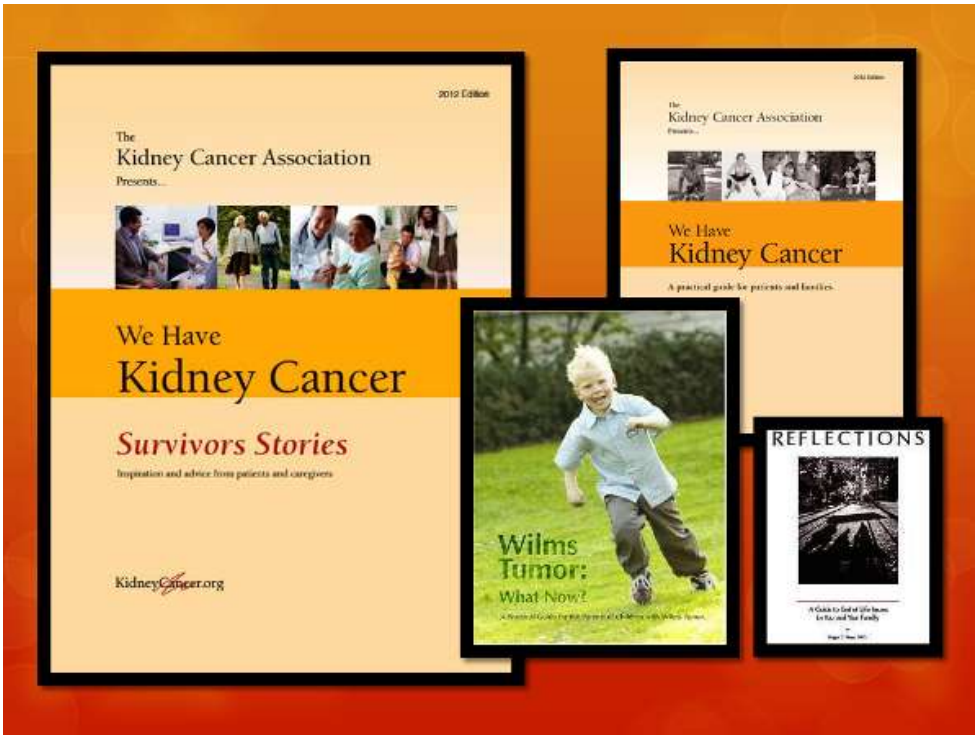
In our role as an advocate on behalf of patients, we continued collaborations with organizations such as, Cancer Leadership Council, Foundation for NIH, National Cancer Comprehensive Network, Patient Advocate Foundation, the National Coalition for Cancer Research, Friends of Cancer Research, and various groups concerned with improving the nation's health care. We continued highly effective collaborations with institutions interested in conducting cancer research, including our CEO's membership on NIH committes that are advisory to the Biomarkers Consortium, The Cancer Genome Atlas, and an NIH group dedicated specifically to renal cancers.

The number of relationships we have established continues to grow. As an example, in 2010 and 2011 we participated in various meetings in North America, Europe, Latin America, and Africa aimed at increasing public awareness of the need for improvement of public healthcare and the promotion of research.

Our capacity to attain these objectives, as well as being able to identify new ones, relies primarily on the level of public support for our mission. Monetary contributions are essential to this accomplishment. Even in the most difficult times, we strive to identify new sources of revenue, as well as identify new volunteers willing to assist us, so that our goals continue to be met. Our fulltime staff is very small, so volunteers are an essential sustaining asset.

This efficiency would not be possible without the dedication of our governing board, medical advisers, volunteers, and other collaborators who contribute selflessly to advance our objective: the elimination of death and suffering from renal cancers.

From the KCA website: www.kidneycancer.org by. Michael Lawing



Throughout this overview quotes from *We Have Kidney Cancer* and *We Have Kidney Cancer: Survivors Stories* can be found.

Both of these excellent books are available from the Kidney Cancer Association in Print, Kindle Edition, or as a PDF download.

Every effort has been made to present information in the general context of which it was delivered and as accurately as possible. While the material in this overview is intended to be informative, it has not been reviewed by a scientific or medical advisor for accuracy or completeness. No endorsement of any Facility, treatment, procedure or clinician is implied in this overview, nor is it a substitute for the medical advice provided by the reader's physician. ML

Contents

Management of Small Renal Masses

This section, moderated by **Dr. Jason Abel of the University of Wisconsin**, was framed as a case study of a 30-year-old man with a 3 cm tumor found when he had appendicitis. He underwent an appendectomy, followed by a closer evaluation of this kidney tumor. The six following presentations constituted a debate of the optimal surgical approaches for this patient.

Dr. Jeffrey Cadeddu (UTSW, Dallas) recommended percutaneous ablation, even more so if a patient were older. This is a procedure done under the skin, using Radio Frequency Ablation or cryotherapy with laparoscopic instruments to destroy the tumor in place rather than actually removing it, avoiding the large incision necessary for open surgery. The published data about these procedures is very encouraging, with no difference in survival between partial nephrectomy versus ablation. It is also less expensive, the patient spends less time in the hospital, and the recovery time is minimal compared to open surgery.

"There is nothing less invasive than Percutaneous Ablation except for active surveillance. ...93 months of follow-up data indicate there is low risk of metastases and almost 100% survival."

DR. JEFFERY A. CADEDDU, University of Texas, Southwestern Medical Center Dallas

Dr. Cadeddu stressed that tumor selection is important. It is not enough to evaluate the tissue for stage, it is also important to look at the size of the tumor. In a recently published paper (J Urol 2012) the survival rates for treatment of different size tumors was noticeably different. Larger tumors were not always completely disabled during the first procedure, and a second procedure might be required.

5-year survival data

Tumor size	<2.5	2.5-2.9	>3
single ablation	99%	88%	73%
repeat ablation	99%	86%	78%

Another study found that tumor size of 2.5 cm should be the cutoff for choosing percutaneous ablation.

"Pro" and "Con" Discussion on Robotic Assisted vs. Open Partial Nephrectomies

Dr. Brian Lane, Michigan State University, College of Human Medicine ("Pro") said that the "gold standard" according to the American Urologic Association (AUA) is partial nephrectomy, though there is no clear preference stated for how that procedure should be done. It has to be evaluated on a case-by-case basis. Robotic-assisted partial nephrectomy provides a new option for removing the tumor through small "ports" in the skin, without a large open incision. Similar to laparoscopic surgery in many respects, the difference is that the robot arms have "wrists" so that the action of the machine is more similar to

the natural movements of the surgeon's hands, so the training time is lower. Nonetheless the technology is still relatively new; not all centers own these expensive machines, and not all surgeons have had significant experience in operating in this manner. Open surgery may be preferred for anyone who is a good surgical candidate with at least a 10-year life expectancy.

The goal is to remove the tumor completely, minimize injury to kidney function, minimize the risk of metastasis and death from kidney cancer, and also minimize ischemia, or the time that the kidney is deprived of oxygen, in other words, the "clamp time". The surgeon has to not only evaluate the size and stage of the tumor, but also the position of the tumor and the complexity of the approach. When the tumor complexity is greater, the choices are reduced. Open partial nephrectomy may be the only way to control all the complexities.

What are the factors that lead to recurrence? The data shows that it is not the choice of procedure that contributes to recurrence, but the characteristics of the tumor itself.

Dr. Lane stated that open partial nephrectomy is still the reference standard because of

- shorter ischemia time
- more precise incision
- learning curve – more surgeons are trained and prepared to skillfully do an open procedure than to do robotic-assisted partial nephrectomy

There is an increase in the number of robot-assisted procedures being performed, and this method will gain acceptance as more surgeons are trained to use it to full advantage. Nonetheless he reminded us that

- Partial Nephrectomy *is still* a cancer operation
- it needs to be accomplished with similar complication rates and functional outcomes
- for more complex tumors, open partial nephrectomy is still the best choice

"When I see a patient that is a good surgical candidate with at least a ten-year life expectancy, I'm asking myself if this is a patient who is amenable for minimally invasive partial: if not, an open partial; and if not a laparoscopic radical; and if not an open radical? It's not a question of which is best – it's what is best in this situation."

Brian Lane, M.D., Ph.D.,
Michigan State University College of Human Medicine

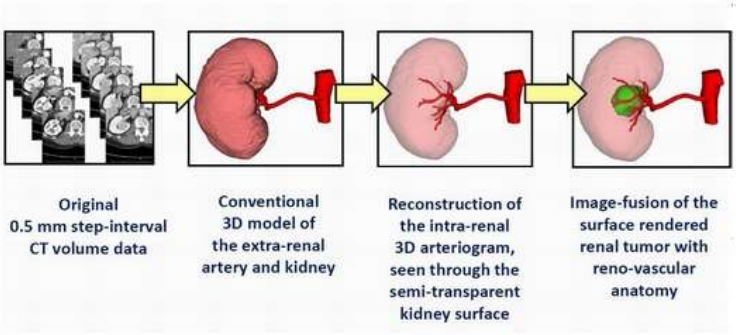
Dr. Inderbir "Andy" Gill, University of Southern California, was tasked with taking the **"Con"** position.

He began by telling us that in his practice, robotic partial nephrectomy is a well established technique. His team has now done more than 2000 robotic or laparoscopic partial nephrectomies. The most important goal is to save nephrons. 33% of partial nephrectomies are now being done robotically or laparoscopically.

The greatest risks to kidney function, and factors that may lead to follow-up radical nephrectomy are:

- significant reduction in the number of healthy nephrons, or the amount of kidney removed
- ischemic time greater than 20-25 minutes.

Dr. Gill's team has worked out a method of "anatomical partial nephrectomy," where they map the blood vessels to and from the tumor to determine the best place to clamp off the blood flow to the tumor itself, while minimizing clamping of blood flow to the rest of the kidney. It has been shown that kidney function is most often reduced when the blood flow to the kidney is stopped for more than 20 minutes. Traditionally, most blood to the kidney is clamped to provide the surgeon with a dry field to work with. By allowing blood to flow to the rest of the kidney while the tumor is clamped off, damage to the kidney function is minimized. They use computer-assisted 3D modeling to do this mapping prior to surgery. He feels that mapping the vascular anatomy is as important as planning the approach to the tumor itself.



In the concept of Renovascular based planning,
Vascular Anatomy is equally as important as Tumor Anatomy.

The Ischemic time and percentage of Kidney Function
preserved are Inextricably Linked

Indebir S. Gill, M. D., Mch
University of Southern California
Los Angeles

He noted that practice is a significant factor. As his team has done this procedure many times, they have reduced their average ischemia time to 14 min, and have also reduced the number of renal bleeds, urine leaks, and kidney loss from this procedure. Minimizing ischemia improves preservation of kidney function. He reiterated the goals of the procedure: to excise the tumor completely, preserve kidney volume (or the number of working nephrons), eliminate "global ischemia" or stopping blood flow to the entire kidney, secure the partial nephrectomy bed to make sure it is cancer-free, minimize complications, and provide a speedy recovery for the patient.

Dr. Houston Thompson (Mayo Clinic, Minnesota) presented methods for saving nephrons during partial nephrectomy for small renal masses, in order to preserve kidney function and quality of life.

In previous years it was thought that it was safe to clamp off the kidney for 30-90 minutes. A series of studies have helped us to understand better what happens when the kidney is deprived of blood flow, and just how long it is safe to do so.

In brief, "every minute counts." Each additional minute of ischemia increases the risk of one or more of these consequences:

- acute renal failure
- acute GFR<15 (glomerular filtration rate)
- GFR<30 in follow-up

25 minutes seems to be the maximum for each of these end points

He also evaluated no ischemia (no clamping) versus warm ischemia (clamping a warm kidney). Warm ischemia increased the risk of these events by 2.5 to 6 times. He feels that no ischemia can be achieved laparoscopically.

He also compared warm ischemia with cold ischemia (clamping and using ice to cool the kidney so its requirements for oxygen are lowered). When the kidney is chilled, the ischemia time can be extended to 45 minutes. He found that 45 minutes cold was equivalent to 22 minutes warm ischemia.

Preoperative GFR was greatest predictor of post-op GFR. The percentage of kidney preserved is also a very important predictor of kidney function after surgery.

Dr. Antonio Finelli (Princess Margaret Hospital, Toronto) was asked to make the case for radical nephrectomy for small renal masses. He began with the disclaimer that his own personal preference is for partial nephrectomy, so "this is an academic exercise."

The data in the literature does support a survival advantage for radical nephrectomy vs. partial nephrectomy. It is a much easier procedure for the surgeon, and has a more straightforward recovery process for the patient. Nonetheless, he believes that treatment choices should be customized based on tumor factors, patient factors, and surgeon factors.

He would begin by doing a biopsy to confirm the tissue type. One issue that was not covered in this series of presentations but that came out in the Q&A was that in a 30-year-old man with a 3 cm kidney cancer tumor, the odds are that there is some genetic factor at work. If this man in fact has a genetic predisposition factor (VHL, MEN2, etc.), then there is likely another kidney cancer tumor in his future. If we do a radical nephrectomy now, that could put him in serious danger of losing all kidney function in the future. This patient should also be referred for genetic screening, as other parts of the body may be at risk for other issues involved in whatever genetic syndrome might be present.

Dr. David Miller (U Michigan) spoke about partial nephrectomy. As a clinical oncologist, he works with outcome analysis: how can we reduce death and suffering for patients with small renal masses?

- Who needs treatment at all?
- What is the role of surveillance?
- How can we reduce morbidity and mortality from local therapy?
- We need better treatments for patients who progress despite local therapy.
- We need to improve palliative care.

Radical nephrectomy is a great treatment: safe, widely available, cost-effective, "curative" in most cases (though not in the case of people with genetic predisposition as discussed above).

As a field, we are moving away from radical nephrectomy for tumors 4 cm or smaller (which is 50% of all partial nephrectomies). We are doing this because we believe that there is a benefit in preserving the volume of normal kidney tissue as long as we are not compromising cancer control.

With partial nephrectomy there is admittedly a higher risk in the short term. However over the longer term, radical nephrectomy can lead to a higher risk of chronic kidney disease and overall survival, and of cardiovascular events. It is important to keep in mind not only tumor size and position, but also the preservation of kidney volume.

Dr. Steven Campbell (Cleveland Clinic) summarized these options. He listed as guidelines:

- Save the kidney whenever possible
- Partial nephrectomy is the reference standard for nephron-sparing

How important is it to avoid radical nephrectomy? Most of the studies that show a survival advantage with radical nephrectomy were retrospective studies, subject to selection bias. In these very studies, it was clear that if a patient showed an annual decline in renal function of more than 4%, that was an indicator of trouble.

It is pretty clear at this point that partial nephrectomy should be preferred for all T1A tumors. The real controversy is what to about those of higher grades (T1B and greater). With thermal ablation (cryo or RFA) recurrence rates are higher, and there is still little long-term data (one study with 5-year data). Warm ischemia coordinates with the amount of kidney removed.

Panel discussion

Biopsy is more accurate now than we had expected it to be. Active surveillance is also more frequently done now. There is less RFA because active surveillance is often chosen instead for smaller tumors (under 3 cm). Nearly everyone now gets biopsy, cell type, percutaneous core biopsies. Biopsy should be factored into the daily care of this type of patient.

What protections are being used to protect patients from negative effects of contrast media? This topic was raised in passing but was not explored in depth.

Management of Localized and Locally Advanced RCC


Drs. Christopher Weight, Alan Pantuck, Jose Karam

Dr. Christopher Weight (U Minnesota)
Case presentation
56 year old man with RCC and tumor thrombus into the artery. What to do?

Dr. Alan J. Pantick (UCLA), Update on CAIX Imaging

CAIX (say CA-nine) is also called G25, MN75. It is a membrane-associated enzyme induced by tissue hypoxia. It is a member of the carbonic anhydrasse family, and is expressed in many cancer tissues, most frequently in RCC, where VHL loss creates a kind of "pseudo-hypoxia".

It is a marker for clear cell tumors as it indicates VHL loss. A Czech group identified MN75 as a marker for cervical cancer.

It is also prevalent in papillary type 2, negative in type 1, chromophobe and oncocytoma. CAIX can be used to identify tissue type on PET/CT (95%), overall 87%.

FDA looks for specificity, sensitivity, diagnostic usefulness of the agent. The FDA found 16/0 in favor of the clinical usefulness of identifying the tumor type, essentially a non-invasive tumor biopsy. If scan is positive, you know that it's a clear cell tumor. It can be used to find clear cell kidney cancer (ccRCC) in the kidney, and may possibly also find mets outside the kidney (Motzer).

Dr. Jose Karam, M.D. Anderson Cancer Center:
Managing patients with competing medical comorbidities

Patients ask "Is this cancer? How bad is it?" The doctor can usually answer whether it is cancer, but assessing how bad it is (tumor grade and stage) and predicting how well or badly the patient may do on treatment are more complex questions. In addition to testing to assess the tumor, the doctor will look at age, gender, tumor size, symptoms, and smoking history. Fox-Chase has a prediction scale based on age/gender/size, and tumor characteristics; MSK uses flow studies; some use G250 contrast-enhanced Ultrasound (more in Europe than in the U.S.).

"Comorbidities" is the term doctors use to describe people who in addition to their kidney cancer have other significant medical issues that have to be taken into consideration when planning treatment. When considering anyone for surgery, one must look not only at the tumor, but also at the patients' age, anesthesia risk, and other health issues.

> Your doctor has just told you that you have cancer. Your mind whirls with emotion. Suddenly, you are facing a health crisis. Now, more than ever, you need to think clearly, despite strong emotions.
>
> ... There is hope: An estimated 100,000 to 200,000 kidney cancer survivors are living in the United States right now. Recent advances in diagnosis, surgical procedures, and treatment options will allow even more patients to live with the disease, continuing to maintain their normal schedules and lifestyles.
>
> Your ability to think, to use information, and to make choices about treatment can help bend the odds in your favor.
>
> *WE HAVE KIDNEY CANCER (2012) p.5*

A Biopsy can tell you about the tissue type, but not about the grade and stage.

The ECOG performance status scale rates the vigor of an individual from normal and healthy (1) to dead (5).

ECOG Performance Status

(Eastern Cooperative Oncology Group)

Grade	ECOG
0	Fully active
1	Restricted in physically strenuous activity but ambulatory
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken MM. Am J Clin Oncol, 1982

There is no standard measure for comorbidities. The more points accumulated, the greater the risk. This index is not a predictor of overall survival but it does indicate the complexity of management. It is important to manage comorbidities before surgery, especially diabetes, smoking, pulmonary rehabilitation, and cardiac issues.

Charlson Comorbidity Index

Points	Factors	
1 Point	Myocardial infarction Congestive heart failure Peripheral vascular disease Connective tissue disease Cerebrovascular disease	Dementia Chronic obstructive pulmonary disease Peptic ulcer disease Mild liver disease Diabetes
2 Points	Hemiplegia Moderate or severe chronic renal failure Diabetes with end organ damage Any tumor, leukemia and lymphoma	
3 Points	Moderate-severe liver disease	
6 Points	Metastatic solid tumor AIDS	

Charlson ME. J Chronic Dis, 1987
Charlson M. J Clin Epidemiol, 1994

Charlson Comorbidity Index (Combined Age-Comorbidity)

Points	Factors
0 Points	Younger than 50 years
1 Point	50–59 Years
2 Points	60–69 Years
3 Points	70–79 Years
4 Points	80–89 Years
5 Points	Older than 90 years
1-6 Points	*Comorbidities*

Charlson ME. J Chronic Dis, 1987
Charlson M. J Clin Epidemiol, 1994

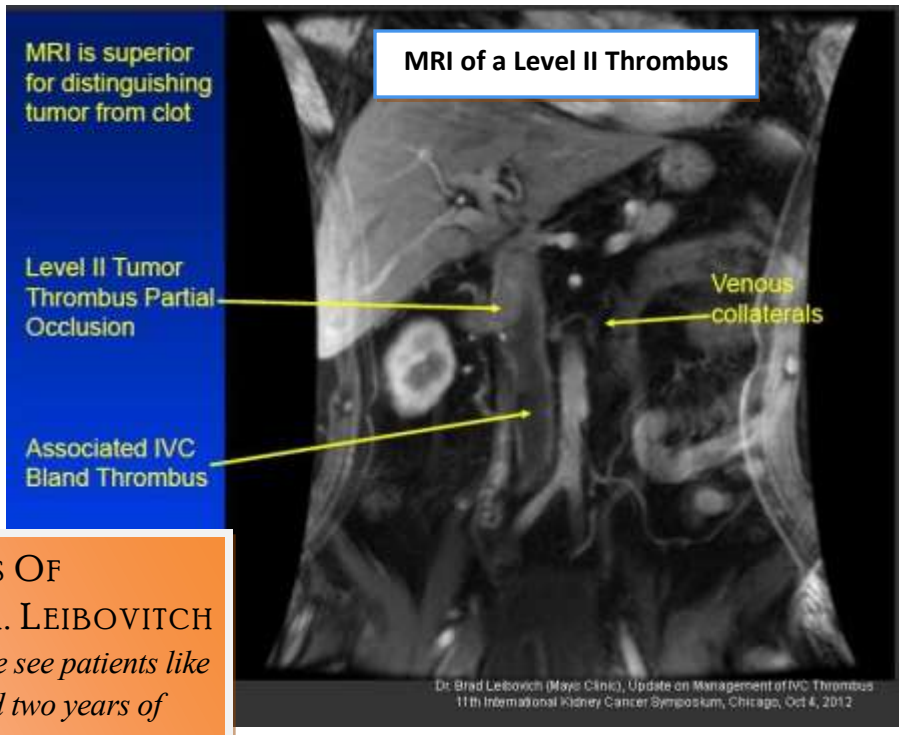
Dr. Brad Leibovich (Mayo Clinic), Update on Management of IVC Thrombus

An IVC thrombus is a blood clot in the interior vena cava. It most commonly occurs in ccRCC (clear-cell renal cell carcinoma), but may also occur in other related issues. Some level of IVC thrombus is seen in somewhere between 4% and 40% of kidney cancer cases. An MRI or multi-detector CT will find a thrombus, which may be inhibiting the blood flow to the kidney.

The surgeon will be best served by an enhanced MRI, which will show the thrombus more clearly. The image must be less than one week old, as the situation can change quickly.

Consider pre-treatment with anticoagulation medication to keep from encountering more problems during surgery. Dr. Leibovich recommends not installing a filter before surgery, as they get clogged and are difficult to remove.

The larger the thrombus, the greater the risk that it has invaded the wall of the vein. He does frozen sections of the wall during surgery, to ensure that all the cancer has been removed. If necessary, he removes the affected wall of the vein and patches it.



From the Case Files Of Dr. Leibovitch

"What upsets us is when we see patients like this… This 81 year old had two years of intermittent gross hematuria [visible blood in the urine] and finally after two years somebody [ordered] a CT scan. He had a 15 cm. Right renal mass with a tumor thrombosis level II; he had some expected comorbidities, but he is not one of those patients… where you just can't think about operating on him. His local physicians recommended that he go straight to hospice, and two months after being referred to hospice he came to visit us and said, "is there anything that can be done"? His imaging was basically unchanged, so he underwent a radical nephrectomy, a tumor thrombectomy, and he had an IPC patch which was necessitated by vein wall invasion. He was in the hospital for five days and is still doing well."

What is the prognostic significance of invasion of the wall? Since 1990 outcomes are much better, with death rates below 1%. In the published data, patients who did not have surgery did badly. This is difficult to analyze, though, since they may have had comorbidities that ruled out surgery.

What about doing some targeted therapy before the surgery? This usually results in little change and is not recommended.

In order to remove the thrombus an experienced team is needed. The blood vessels need to be operated on first. Surgery can provide durable survival in node negative patients without metastases and remains the preferred approach. Experienced multi-disciplinary teams can reduce morbidity and complications.

Dr. E. Jason Abel (U Wisconsin), Role of Lymph Node Dissection

"Many studies have suggested that metastatic spread is not predictable through the lymph nodes like it is in testes or bladder cancer."

"Two studies show that over 50% of patients who had metastatic disease did not have disease in their lymph nodes."

"[This is]with the caveat that they might not have sampled these lymph nodes accurately so it might be under represented."

E. JASON ABEL, M.D.
University of Wisconsin
Carbone Cancer Center
Madison, WI

Dr. Abel began by stating that all studies of this question are retrospective and involve a small number of patients, selection bias, and the lack of a standardized template for the procedure.

Do RCC patients benefit from lymph node dissection?

- NO in patients with small organ-confined tumors
- YES if the patient has enlarged lymph nodes or is at high risk for lymph node mets

In the published data, more than 50% of patients with mets do not have lymph node involvement (this may be problematic number).

Many will get a durable cure from surgery

In one study of 772 patients randomized to radical nephrectomy (RN) vs RN + lymph node dissection (LND) there was no difference in overall survival (3.3% had RN+LND)

Can we identify patients before surgery with lymph node metastases? Determinants of High risk are:

- stage T3 or T4
- Fuhrman grade 3-4
- necrosis
- sarcomatoid features
- tumor size > 10 cm

It should be noted that 38% had mets not detected on imaging.

Which lymph nodes need to be removed? Most follow the arterial drainage pattern, but not always. There is no clear consensus on this question. It is clear, however, that hilar dissection alone is inadequate. We need a better way to diagnose LN involvement before surgery, and a standardized definition of high-risk patients.

Asking questions is a very important way to reduce fear and anxiety and is the only way to truly empower yourself to make the best decisions regarding treatment for your kidney cancer.

History has shown that assertive patients who actively work to overcome cancer often increase the odds of survival, live longer, and enjoy life more.

WE HAVE KIDNEY CANCER (2012) p.10

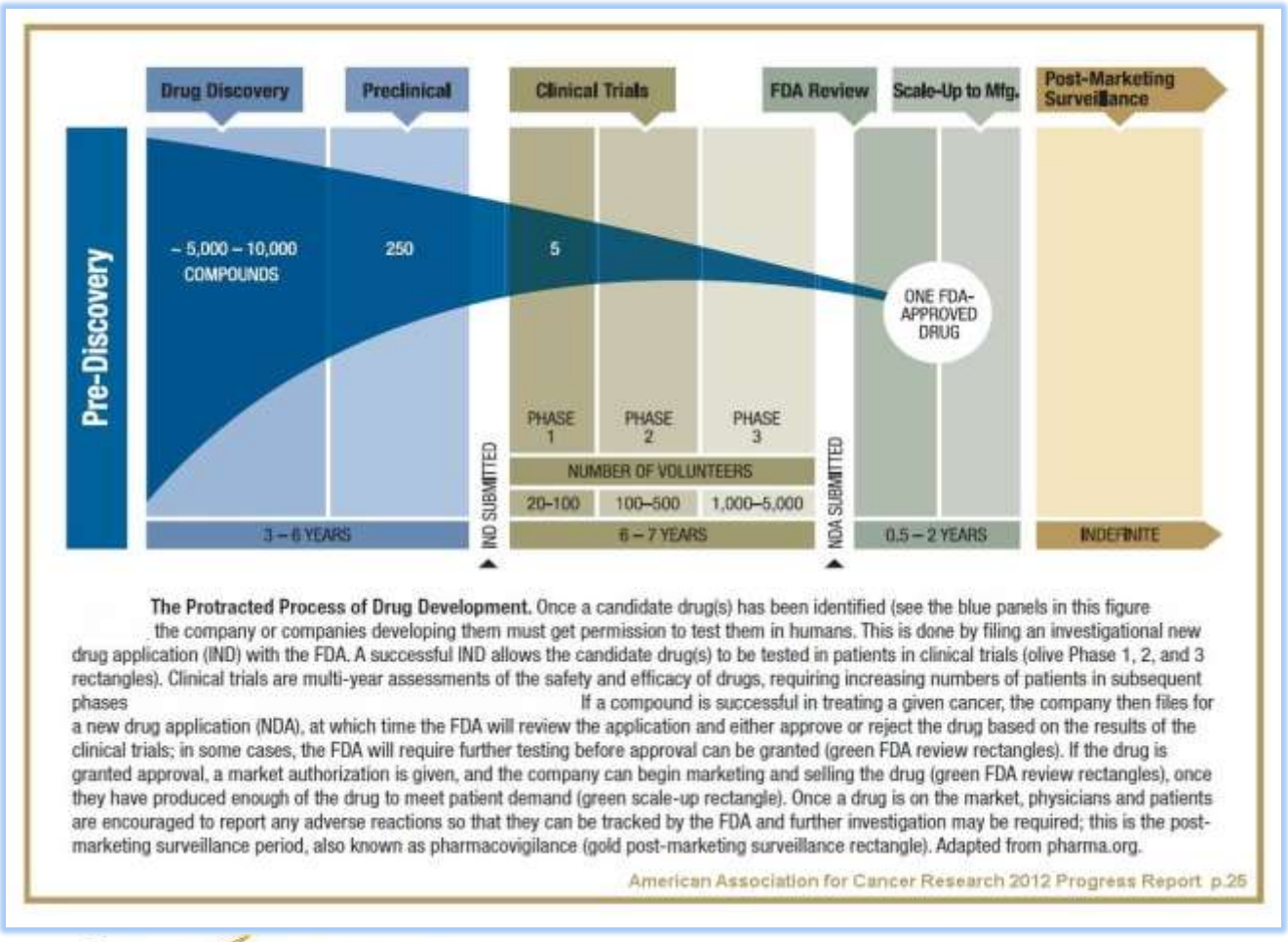
Dr. Chris Wood (MD Anderson Cancer Center), Summary of Options for Locally Advanced Disease

Dr. Wood summarized by presenting a patient case for the panel to consider:

A 58yo WM presents with gross hematuria and shortness of breath (pulmonary embolism); workup revealed ECOG performance status of 1, multiple medical comorbidities including a drug eluting stent (to help prevent arterial fibrosis and blood clots) and was placed six months ago, a previous appendectomy, and medications for heart, blood pressure, and stent. Testing revealed an IVC thrombus and a locally advanced tumor involving the right kidney with no evidence of node metastasis or metastatic disease. Nephrectomy was performed, the thrombus was removed, but clear margins in the IVC wall were not attainable.

What is the role of adjuvant therapy in managing this patient post-surgery? Therapy not in the setting of a clinical trial in this case would be problematic, as he would be hard to follow closely. Getting him onto a clinical trial would be good; however a positive margin causes ineligibity for clinical trials.

At 11 months post-op this patient presents with liver and lung mets. Metastatic disease occurrence after 11 months is a bad prognostic sign; The options were considered: Is there a solitary or multifocal tumors that can be removed? What drug therapy would be best to offer; the panel preferred either pazopanib or sunitinib and recommended that the attending oncologist choose the drug. He was put on Pazopanib .



The Protracted Process of Drug Development. Once a candidate drug(s) has been identified (see the blue panels in this figure the company or companies developing them must get permission to test them in humans. This is done by filing an investigational new drug application (IND) with the FDA. A successful IND allows the candidate drug(s) to be tested in patients in clinical trials (olive Phase 1, 2, and 3 rectangles). Clinical trials are multi-year assessments of the safety and efficacy of drugs, requiring increasing numbers of patients in subsequent phases If a compound is successful in treating a given cancer, the company then files for a new drug application (NDA), at which time the FDA will review the application and either approve or reject the drug based on the results of the clinical trials; in some cases, the FDA will require further testing before approval can be granted (green FDA review rectangles). If the drug is granted approval, a market authorization is given, and the company can begin marketing and selling the drug (green FDA review rectangles), once they have produced enough of the drug to meet patient demand (green scale-up rectangle). Once a drug is on the market, physicians and patients are encouraged to report any adverse reactions so that they can be tracked by the FDA and further investigation may be required; this is the post-marketing surveillance period, also known as pharmacovigilance (gold post-marketing surveillance rectangle). Adapted from pharma.org.

American Association for Cancer Research 2012 Progress Report p.25

A Dedication to Andrew C. Novick, M.D.

Excerpts from the Dedication page of :
Guideline for Management of the Clinical Stage 1 Renal Mass

For many, Andy Novick's career was both the quintessence of leadership and the embodiment of the best in academic urology. Andy's clinical and intellectual contributions in the fields of kidney transplantation and renovascular surgery provided the underpinning upon which surgical and functional renal preservation in cases of kidney cancer is based. He brought forward many of the concepts and techniques for nephron-sparing surgery. Perhaps most importantly, Andy facilitated the recognition that nephron-sparing surgery was safe, feasible and oncologically sound through the systematic study and publication of his work as well as thoughtful review of the work of colleagues.

In the midst of all this, he mentored hundreds of students, residents and fellows, cared for thousands of patients and developed one of the premier urologic programs in the world.
Andy had an enormous set of expectations of himself and those around him, recognizing that great achievements are within each of our own capacities.
Andy engendered loyalty not to himself, but to the best within one's self.

Andrew C. Novick, MD

1948-2008

Chairman of the Cleveland Clinic Glickman Urological and Kidney Institute

THE 2012 NOVICK AWARD LECTURE:

The Future of Multi-disciplinary Care for Metastatic RCC

by award recipient Michael Blute

Introduction by R. Houston Thompson, M.D.: Dr. Blute is now Chair of Urology at Massachusetts General Hospital, Boston. Of his papers, 71 have been cited a minimum of 71 times; one of a handful of surgeons to have this distinction. He is one of the original publishers of papers on survival with Partial Nephrectomy; and been instrumental in pioneering the management of thrombus and of lymph node dissection. He was a football linebacker and football coach. Dr. Thompson summed up his introduction by stating: "Operating with Dr. Blute is like operating with Dick Butkis. He is the best surgeon I have ever operated with."

Sept, 2010 - Michael L. Blute, MD, invested as the Mary C. DeFeudis Chair of Cancer and Research at the University of Massachusetts
Pictured from left: UMass President Jack M. Wilson,
Mary C. DeFeudis, Dr. Blute and Chancellor Michael F. Collins
Photo Credits: John Gillooly, *Professional Event Images*

Dr. Michael Blute (U Mass): The Future of Multi-disciplinary Care for Metastatic RCC

RCC facts: 60,000 people diagnosed each year with RCC, 10-15% of which are already metastatic. Mortality from RCC continues to rise.

Dr. Blute was invited to talk about the FAILURE of multi-disciplinary care – but it's not all bad, so he changed the title. He sees an integration of surgery and targeted therapy in patients with metastatic RCC (mRCC).

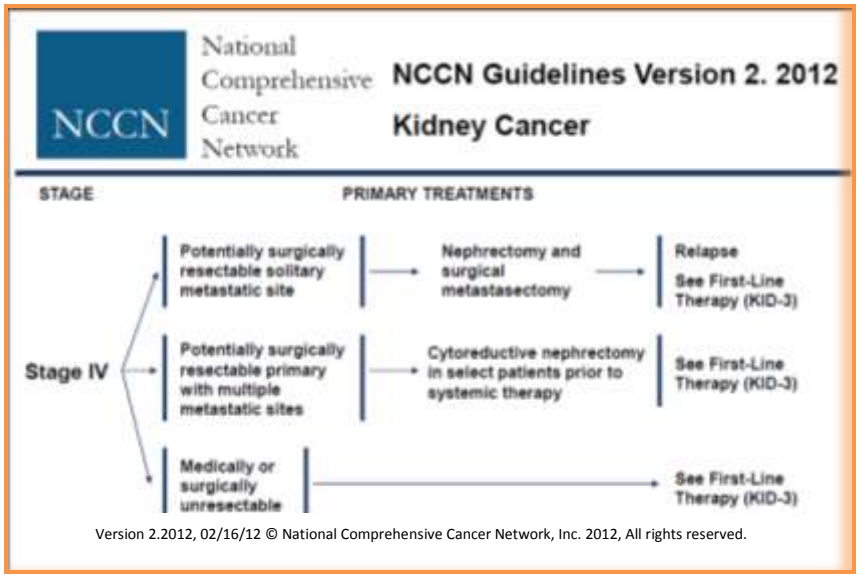
We have to look, not just the outcome, but at the quality and effectiveness of surgery. It is clear that most people do better with cytoreductive partial nephrectomy, which is now routine practice in the United States. However most of the evidence published to date is based on retrospective evidence and has bias.

The CARMENA *(Clinical Trial to Assess the Importance of Nephrectomy*) trial now underway in France is gathering data on the value of surgery and the sequencing. These trials will not tell us the value of achieving a tumor-free status.

What is the value of consolidated therapy? Most trials have been done in highly nephrectomized patients. The SEER data also shows benefit from surgery: without nephrectomy, there is a 2.5-time increased overall mortality, and a 2.5-times increased overall cancer mortality.

Unless the tumor is unresectable, patients should have cytoreductive nephrectomy. Those who received targeted therapy alone:

- were poor surgical candidates
- had non-clear cell histology
- had poor risk disease features



One major predictor of poor survival: no surgical history. Metastatic RCC treated with targeted therapy without cytoreductive nephrectomy shows a 10% survival at the end of 5 years.

Resecting the primary tumor and the mets yields 50% 5y survival

A study from MSKCC shows that complete resection of mets was more important than the number of mets. Survival varied based on the location of the mets:

- lung: 40%
- bone: spine, pelvic, femur, humerus, 5 y survival 35%
- liver : 15%
- lymph nodes : 12%, metachronous 30%
- isolated pancreas, adrenal : 60%

Case: 45yo male, one episode of gross hematuria (blood in urine)

CT shows a chest lesion in the left lower lung, and a smaller one in the left upper lobe

- did nephrectomy
- lymph node dissection (negative) – may change management
- treat lung mets like primary tumors

Within 28 days, this patient was tumor free.

Control for surgical standardization and risk adjustment

- catch relapse quickly
- 3 yrs later had a left chest lesion,
- post-op year 7, met to appendix
- now 10 years since original nephrectomy, long-term survivor

Where are we going?

- pre-surgical targeted therapy followed by debulking surgery
- risk of major surgical complications is not much greater than without targeted therapy
- 30-40% of these patients will progress
- up to 25% will progress during a surgical break
- In addition to CARMENA, there are 22 phase II trials of neo/presurgical TKI in progress

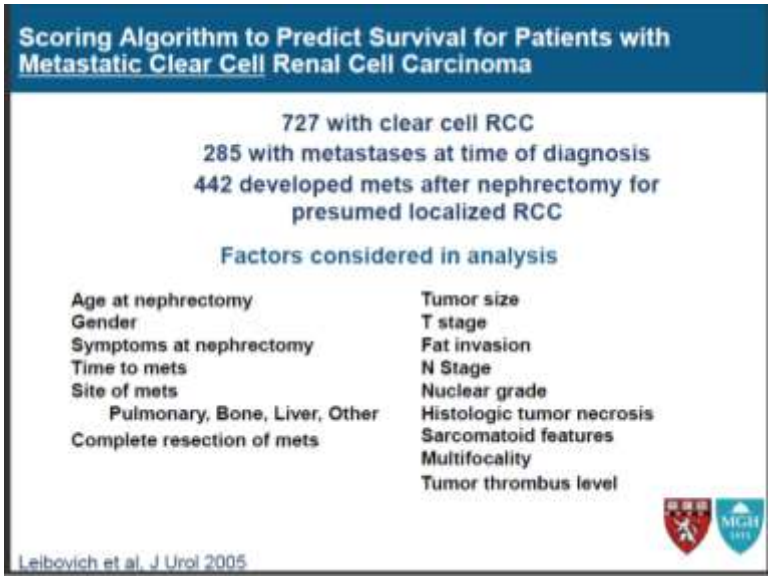
Case: 23 cm tumor, 50 lb weight loss

- mass from kidney to diaphragm
- perhaps pre-surgical therapy, 2 cycles of sutent, tumor regressed
- local regional met to diaphragm, became surgically resectable
- patient is tumor free and doing well
- time off targeted therapy is important

The number of patients eligible for this will increase

performance status > is tumor resectable? > resect if possible > targeted therapy

If the patient is not a candidate for surgery, then use first-line therapy. It may reduce the tumor to the point where it is resectable.



We agonize over patients with metastatic kidney cancer and whether or not surgery is going to provide value to them; it's not just the outcome that we have to look at, we have to look at the quality and the safety of our surgical procedures

The indolent nature of this disease has to be recognized. Some people will have a chronic rather than a rapid progression of their disease.

If you are going to subject people to the resection of a metastases then surgeons and medical oncologists need to adopt dynamic surveillance models so that we can catch relapse in the situation where the tumor burden is low so that surgical intervention can be more effective.

Kidney Cancer is one of those unique solid tumors where... surgery plays an important role in every stage of the disease.

MICHAEL BLUTE, M.D.
University of Massachusetts Memorial Health Care, Inc.
Worchester, MA

Renal cell carcinoma is a highly invasive disease. The most predominant type, clear-cell, accounts for 75 to 80% of the total cases.

Because it is such a metastatic and invasive disease, circulating tumor cells are of particular interest in this cancer.

BENJAMIN P. CASAVANT, M.D.
University of Wisconsin
Carbone Cancer Center
Madison, WI

Invited Abstracts from Young Investigators

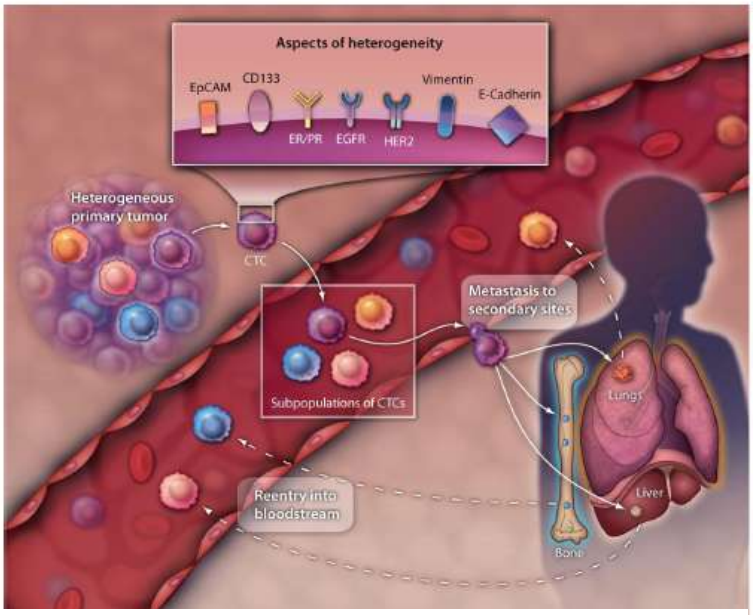
Dr. Benjamin P. Casavant (U Wisconsin): Isolation of RCC Cells

Dr. Casavant is an inventor with a patent application pending. He presented his invention, VerIFAST, for our consideration: an integrated system for flexible isolation and analysis of circulating tumor cells. Cancers shed cells into the bloodstream which can then be trapped by this device and used to diagnose cancer. These cells are part of the metastatic cascade, so we need to look more into the nature of them.

VerIFAST uses oil to exclude any object not bound to magnetic particles (PMPs). It isolates Circulating Tumor Cells (CTCs), achieving >70% purity in a single traverse. It is used in prostate cancer.

The device will process 5-50 ml blood and isolate the CTCs for study, which can be used to diagnose cancer. This work was funded in part by the Department of Defense through the Congressionally Directed Peer-Reviewed Medical Research Program.

Circulating Tumor Cells



Lang, Casavant, and Beebe Sci Trans Med

Kritti Mittal, M.D., (Cleveland Clinic), Detection of Circulating Tumor Cells

Dr. Mittal uses immunomagnetic enrichment to tag the CTCs, and microfilters capture these larger cells, or Ben's method above. She does immunohistochemical staining. Cellsearch or Veridex assay finds cells that express EpCAM (epithelial cell adhesion molecule). Only 21% of patients demonstrated EpCAM expression, so it is clear that the Veridex method is not ideal.

Microfilter size based capture is an effective method of detecting circulating tumor cells in metastatic RCC patients. However it detected cells in only 50% of patients. We don't yet know whether CTCs are released at a steady rate or in spurts, so this partial success might be attributable to flaws in the technology or to this spasmodic release of CTC's.

Circulating Tumor Cells can be as rare as one In 100 million or one in 1 billion

Isolating CTCs is a challenging concept

Tumor cells are larger than other cellular elements

KRITI MITTAL, M.D.
Cleveland Clinic
Taussig Cancer Institute
Cleveland, OH

Martin Voss, M.D., (MSKCC)

We found that understanding treatment response in the molecular and genetic level is very complex

It gives us a flavor of how complicated biomarker discovery is going to be moving forward with next-generation sequencing

Next-Generation Sequencing

Dr. Voss evaluated patients treated with sunitinib (VEGF inhibitor), everolimus, temsirolimus (mTOR inhibitors)

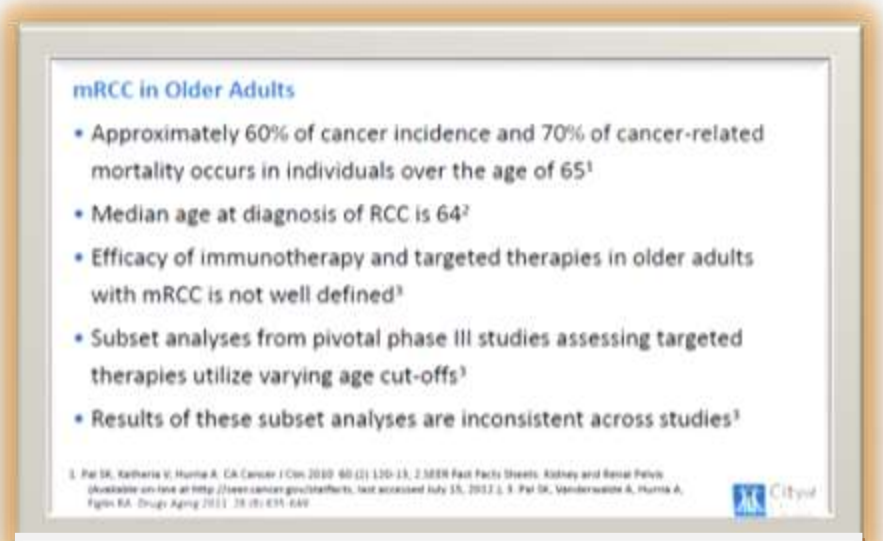
There were four patients who did not respond to sutininib. They used IMPACT: *Integrated Mutation Profiling of Actionable Cancer Targets*, which analyzes 230 genes of interest in the IMPACT panel. It provides information on single base substitutions or bigger deletions, including some with *gain of function* (GOF) status.

They looked for the concept of clonal convergence = inter-tumor heterogeneity with convergence within a single pathway. Were there changes in groups of genes that all appear along the same pathway?

There may be oncogenomic causes for exceptional treatment response that can be identified in some, but not all patients. It is important to do a comprehensive analysis in order to examine the complexity of genomic background to treatment response. Identification of mutations alone is not sufficient; one must also investigate their biologic effects.

Despite intratumoral heterogeneity, targeted therapy can be successful due to clonal convergence.

Sumanta Pal, M.D.
City of Hope Comprehensive Cancer Center, Duarte, CA



Impact of Age on Treatment Trends and Clinical Outcomes

As the population ages, we are seeing more mRCC in older adults. Approximately 60% of cancer incidence, and 70% of cancer-related mortality, occurs in individuals over 65. The mean age at diagnosis of RCC is age 64. The efficacy of immunotherapy and targeted therapies in older adults with mRCC is not well defined.

Dr. Pal charted people on the trial, date they began, discontinuation for various reasons, clinical outcomes. Most were clear cell tissue type (82%), some chromophobe (6%).

The most common reason for discontinuation of treatment among people over 75 was toxicity.

Age range	Progression-free survival
<55	25.2 months
65-74	23 months
>75	12.5 months

Older patients exhibited similar clinical characteristics, received no systemic therapy more frequently. Only 20 of 219 patients were age >75. Data on co-morbidities is still being collected.

Future directions: expand efforts to characterize clinical outcomes in older adults. Frailty needs to be characterized and may be relevant. There is, for example, a Comprehensive Geriatric Assessment (CGA).

Because more older people have cancer, this work is important.

A Story of Survivorship:

Ed's experience with cancer began in 1998, when, at age 69, he was diagnosed with bladder and kidney cancer. After a nephrectomy and treatment for his bladder cancer, Ed went back to his life as a retiree and busy grandfather. But in 2004, cancer returned – this time invading his pancreas. He had surgery on his pancreas and a series of treatments followed; today, Ed is in good health, overall, though still coping with his disease. He is on a drug regimen, which is currently keeping his tumor growth in check.

We Have Kidney Cancer: Survivors Stories (2012) p.15

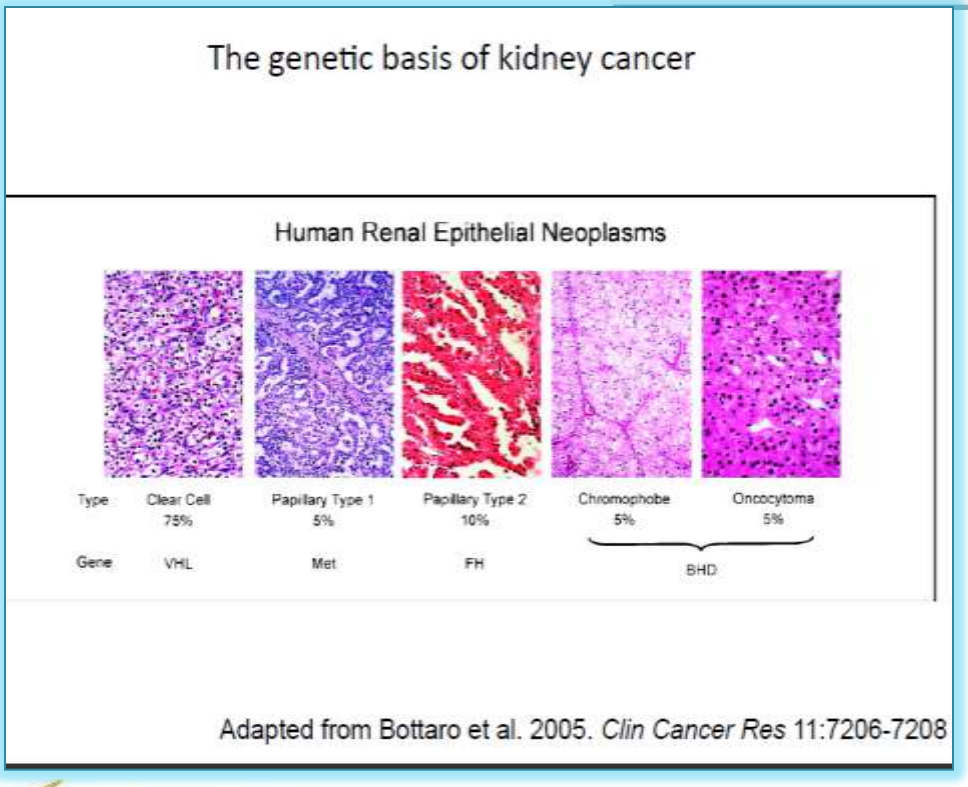
Tumor Suppressor Screens of 3p Chromatic Modulators
Link BAPI Mutations to Poor Clinical Outcomes in ccRCC
Abraham Hakimi, M.D., (MSKCC)

We have known for a long time that genetic alteration of the VHL gene in kidney cancer tumors is an important prognostic marker. It is lost in more than 90% of kidney cancer tumors. PBRM1 is the second most frequent genetic event in We have known for a long time that genetic alteration of the VHL gene in kidney cancer tumors is an important prognostic marker. It is kidney cancer (40%), followed by SETD2 and BAPI. All of these genes are tumor suppressors, and all of them are found on the short arm of chromosome 3 (3p).

In fact all of 3p is lost in a very high percentage of kidney cancer. When there are mutations in more of these additional points, the outcome for the patient is poorer. Loss of SETD2 is associated with tumor recurrence. BAPI and SETD2 are associated with worse survival.

Further investigation is needed.

There are several risk factors associated with the development of kidney cancer. These include: smoking, which almost doubles one's risk; obesity; and exposure to toxic chemicals such as asbestos, cadmium and petroleum by-products (gasoline, for example). Having family members with kidney cancer also increases one's risk.
WE HAVE KIDNEY CANCER (2012) p.13

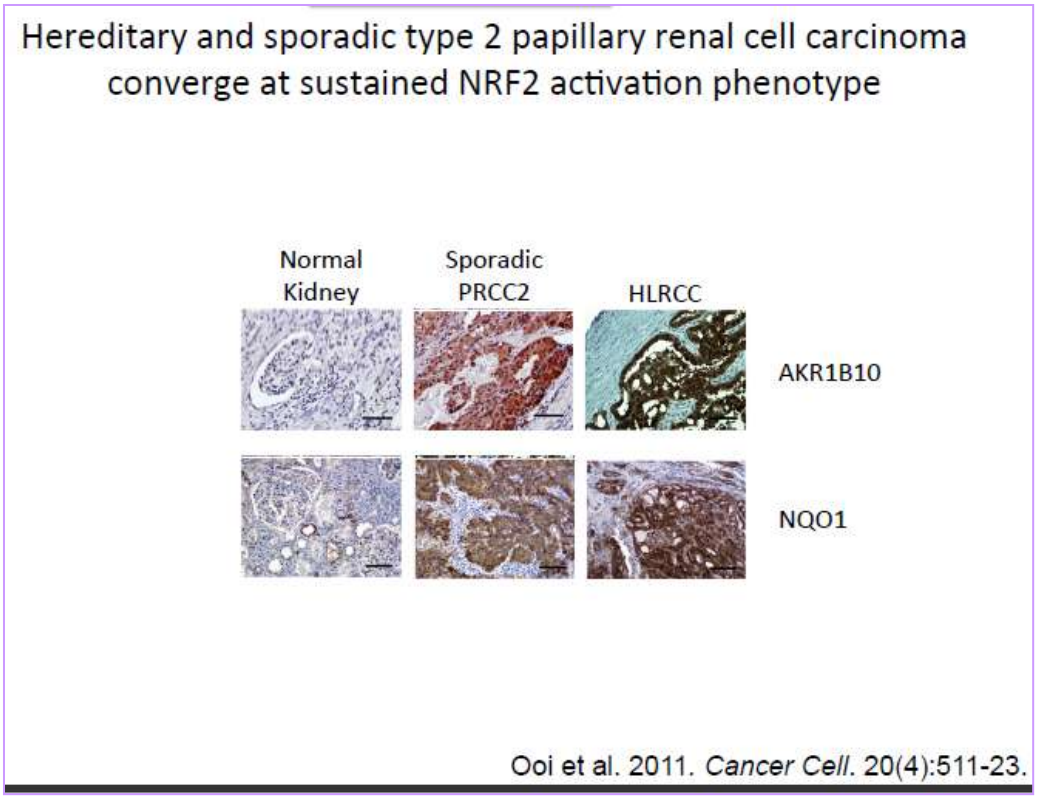


Recent Insights into RCC Biology

Does Hereditary and Sporadic Type 2 Papillary RCC Converge at Sustained NRF2 Activation Phenotype?

Aikseng Ooi, Ph. D., (Van Andel Research Institute, Singapore)

The FH mutation is the hallmark of HLRCC, and causes papillary type 2 kidney cancer. Both FH and VHL mutations cause upregulation of HIF. NRF2 transcription-activation is a convergence point of these two tumor subtypes.



What is NRF2? – it drives transcription of several genes involved. It forms a complex with CUL3, Keap2, Rbx1, E2, and occurs in papillary type 2 RCC.

Hereditary and sporadic type 2 papillary RCC converge at sustained NRF2 activation phenotype. Somatic gene mutation is a mechanism of NRF2 activation in sporadic type 2 papillary RCC. They are doing exome and transcriptome sequencing to study its mechanism of action. They are seeing NRF2 gain of function mutations in 5 cases, which causes glutamate to be converted to glycene. There is CUL3 loss of function in 2 cases. Similar transcription reprogramming is observed in hereditary type 2 papillary RCC. NRF2 is at the core of the function of papillary type 2 RCC. It is a very aggressive tumor.

We need to design a drug that could be bioactivated, controlled by NRF2.

Charles Swanton, M.D., (Univ College London):
The Challenges of Genetics Heterogeneity
to RCC Translational Research

Is there evidence that heterogeneity is important to the success of targeted therapy?

Most tumors are heterogeneous. 52-75% of somatic mutations are heterogeneous. A biopsy may not capture and profile all the mutations in a single tumor. They exhibit a "branched evolution" – one change happens first, then others, in a kind of cascade of events.
VHL and PBRM1 mutations were in the trunk of the tree (first). SETD2 loss of function can further compound the picture.

Diversity itself may be a biomarker – that is, the more diverse a tumor, the greater the risk of treatment failure. He used three trees as analogies for the complexity of the branching: a palm tree, a chestnut tree, and a baobab tree. The baobab tree configuration would be the most likely to fail. The driver of tumor growth may not always be in the trunk. One biopsy is unlikely to find them all.
The treatment may need to adapt to challenges of targeting trunk and branch drivers that may be diverse from patient to patient, and may be spatially separated within one tumor. Spatially separated drivers can outnumber common drivers: does this contribute to resistance to targeted therapeueitcs?

He concludes that genetic heterogeneity does indeed contribute to functional diversity and drug resistance. The dominance of branched driver events may be enriched during tumor adaptation. Should we be adapting trials to address this need? We will need international initiatives to identify and exploit tumor convergent features.

Drug resistance is one of the greatest challenges we face today in cancer treatment. Most tumors that are not completely eliminated will, over time, become resistant to a given therapy and continue to progress.

Resistance generally falls into two categories: acquired resistance, which develops during the course of treatment in response to the therapy; and innate resistance, which is inherent at the outset of treatment.

Diversity among the cancer cells within a single tumor is what ultimately drives insensitivity to treatment with cytotoxic and molecularly based therapeutics alike. For example, within a given cancer, some cells may be actively proliferating, while others are not. Since many cytotoxic therapies destroy only rapidly dividing cells, some cells within a cancer escape these treatments. In addition, the unstable and error-prone genome in a cancer may create a mutation in the drug target itself, rendering the drug useless in a subpopulation of cells.

American Association for Cancer Research: Cancer Progress Report 2012 p. 49

Pankaj Seth, Ph.D. (Beth Israel, Boston), Inhibiting RCC Metabolism

In addition to the VEGF pathway, VHL also performs a function in control of metabolism, specifically the Warburg effect, which shifts energy production from oxidative phosphorylation to fermentative glycolysis. The more lactate is present, the less pyruvate is available to metabolism.

Loss of VHL increases HIF1 activity, which further facilitates production of lactate.

Instead of targeting VHL, HIF, etc, perhaps we should be targeting TCA. Multiple cancers express multivate to lactate. HLRCC is different from other cancers in that it is primarily dependent upon this cycle. Isaac (2005) showed that LDH-A is dramatically up-regulated in tumor cells of HLRCC patients.

Imaging can be used as a surrogate to evaluate fermentative glysolysis. He showed pictures of MR imaging of implanted tumors in mice, and metabolic imaging with hyperpolarized 13C pyruvate.

James W. Mier, M.D., (Beth Israel, Boston):
P53 inactivation as potential target in TKI Resistance

Angiogenesis inhibition leads to reduced O2, glucose, which then leads to

- HIF activation
- AMPK activation, leads to autophagy, selective translation
- P53 activation
- UPR (unfolded protein response) PI3-K, NF-kB, Nrf2 leads to autophagy

These are also seen in injury, the tumor uses nothing new

P53 is regulated by HDN2 and HDMX, which may lead to P53 actually functioning as a transcription factor.

HDM2 blockade – in nearly all RCCs, the P53 gene is intact. Expression of p53 dependent genes is lost with the emergency of resistance and is temporally discordant with that of HDMX. Early during treatment, the increase in p53 is noted.

If you use HDM2 blockade, the tumor does not figure out a way around the TKI.

Myriad actions are kicked off by P53. HIF is also an RNA binding protein and influences Translation.

p53 activation is essential for a robust response to VEGF-targeted therapy. Sanofi MI-319 maintains P53.

Dr. Elisabeth Henske, Beth Israel Deaconess/ Dana Farber/ Harvard

New Targets for the Non-CC RCC (Birt-Hogg-Dube)

Rare genetic syndromes can advance our understanding of sporadic cancers. Just as VHL has helped us to understand clear cell RCC (90% of all kidney cancer), so too Birt-Hogg-Dubé syndrome (BHD) is helping us understand chromophobe kidney cancer (about 5% of all kidney cancer).

The VHL syndrome (familial) increases the risk of tumors of the retina, hemangioblastomas of the CNS (brain, spinal cord, inner ear), kidney cancer, pancreatic neuroendocrine tumors, and adrenal (pheo/para) tumors.

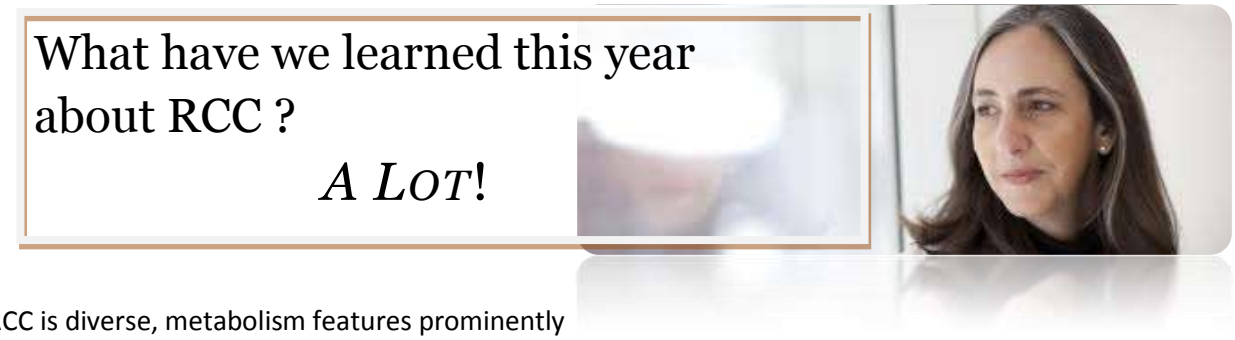
The BHD Syndrome (familial) increases the risk of kidney cancer, fibrofolliculomas, and lung cysts which often lead to spontaneous pneumothorax.

15-30% of people with BHD develop kidney cancer, most of which is chromophobe (34%) or an chromophone/oncocytic hybrid (50%). The BHD gene encodes folliculin (FLCN), a 64 kDa protein with unclear function.

FLCN interacts with AMPK through FNIP1, and negatively regulates mTORC1. FLCN is also a positive regulator of mTOR.

FLCN interacts with p0071 to regulate cell adhersion, Rho activity, and cell polarity. This understanding is leading us to potential targets for therapy for all people with chromophobe kidney cancer.

W. Kimryn Rathmell, M.D., Ph. D., (U North Carolina), Future Directions in RCC Translational Research



RCC is diverse, metabolism features prominently

ccRCC features 3p loss, associated mutations, few other classic mutations

ccRCC itself is genetically heterogeneous.

RCC is interlinked with metabolism (Linehan 2012); All the RCC's are linked in one way or another

We are now looking at metabolic properties of RCC subsets – aspects important for tumor maintenance. We are leveraging the current momentum of tumor metabolic research in RCC, finding innovative ways to target renal tumor metabolism.

Identification and understanding of the common mutations are critical. What do these mutations do, both within and across tumors. Tumors are transcriptionally and clinically heterogeneous.

Is there a future for biomarkers? – don't know, but hope so.

Is looking at sequence everything? – There is a theory that they may not be all that different from each other. RNA, miRNA, other?
Can we use primary tumor disease biology to inform risk of recurrence?

We need to understand diversity and how it influences tumor behavior or response to therapy, and to understand the mechanisms contributing to new diagnostics.

Discussion

We need to understand the challenges of resistant disease.

Mets are not necessarily monoclonal – there may be many more clonal events.

There are too many targets to say that any one of them will be the magic bullet. It is probably best to go after the fundamental processes. Some of the inhibitors of the protein folding mechanism would likely to a good job. Tackle the fundamental problem of how cells deal with hypoxia. These are normal signaling events. But there will likely be many. There are seven that were found to be relevant in GIST.

Transcription factors may also be the result. Modify the epigenetic cells and the cell will modify its behavior. If we find some of these, they might be able to solve the problem.

TCGA data is at Nature awaiting review, and should be out in due course.

Next steps? We need unlimited money but also **unlimited** samples. We need more subsample tumors and metastases, and to understand the genetic events in the mets.

Patient Management Issues

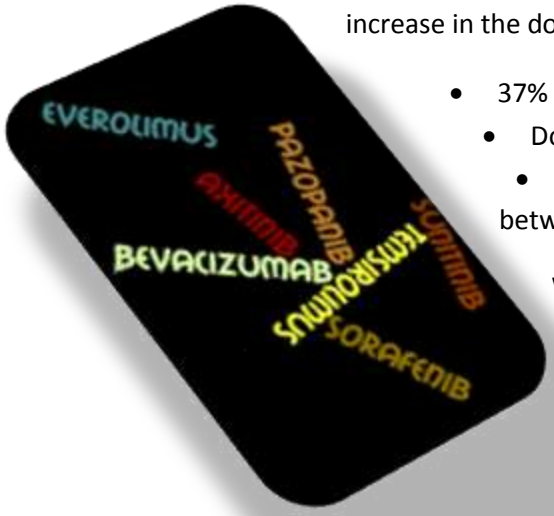
Elisabeth Heath, M.D., (Karmanos Cancer Institute, Wayne State Univ, Michigan) Importance of Dose in RCC Therapy,

The Renal EFFECT trial (RP2D) is designed to evaluate dosing methods for Sunitinib

- 50 mg orally daily 4 weeks on/2weeks off vs 37.5 mg orally daily continuously
- Median time to tumor progression is 9.9 months vs 7.1 months

Axitinib is a second generation oral TKI

- 5 mg twice daily, vs sorafenib 400 mg twice daily
- median PFS 6.7 mo (A) vs 4.6 mo (S)
- treatment discontinued 4% (A) vs 8% (S)
- dose escalation allowed only in axitinib arm (7 mg and 10 mg twice daily)



PFS survival vs Exposure: Retrospective analysis of Phase II RCC data – an increase in the dose enhanced the PFS.

- 37% A pts increased; 20% increased but then decreased
- Dose reduced in 25% of patients on axitinib
- overall incidence of AEs not signifiantly different between groups

What we need now is a Prospective study: Axitinib 6 mg BID 4 wks. Depending on how they do, proceed on Axitinib alone, or add another agent.

Sorafenib – would increasing dosage (1st generation drug) the improve results?

There are two trials in which patients escalated to 600 mg for one month, if continuing well 800 mg twice daily. 74% were escalated to 800 mg. 64% with prolonged PFS > 6 mo, tolerable toxicity

Pazopanib should be administrered to patients in a fasting stage to minimize variability in systemic exposure. Some foods with enhance the action of the drug (essentially raising the effective dose). In most other meds, it doesn't matter.

PISCES study: What do patients prefer? Patients took one of Pazopanib or Sutent for 10 weeks, then 2 weeks off, then 10 weeks on the other drug. At 22 weeks, patients were asked, and 70% favored pazopanib, 22%sunitinib, 8% no preference. Reasons were improved quality of life and less fatigue.

There is a model of tumor growth dynamics using serial measurements of the sum of the longest tumor diameter from patients on the RECORD-1 trial.

Evaluating Everolimus, oral inhibitor of mTOR at 10 mg daily vs 5 mg daily. 10 mg daily dose shrinks target lesions more compared to 5 mg daily, although there is still antitumor activity.

Now 3rd generation drugs:

TIVO-1 trial evaluating tivozanib (T) vs sorafenib (S) in mRCC. Better response with lower dose and lower side effects. Dose and schedule do matter

Changing dose and schedule need to be discussed with the doctor. We are evolving clinical trials to maximize efficacy and minimize toxicity. We need better tools to guide dose and schedule decisions.

Patient preference and quality of life need to be considered.

Dr. Michael Jewett (Princess Margaret Hospital, Toronto)
Collaborating to Improve Survivorship Care

Dr. Jewett is a surgeon. He has lately been learning the importance of survivorship issues. Not enough attention has been paid to this important topic in the past. The push is coming from our survivors, including Kidney Cancer Canada.
In Canada the surgeon discharges the patient to the general physician, with a survivor care plan. They did a survey to determine how well the urologist's perceptions and those of the patient were in synch. They saw a significant gap: the surgeon might think the patient understood, but the patient in fact did not understand.

Survivorship is important, is underappreciated by professionals, is underfunded and should be fostered by both survivors/caregivers and their health care professionals.

Additional information on the survey in Dr. Jewett's presentation is discussed in
A *Closing Note for Consideration: Gap Between Urologist and Survivor Perceptions?* on page

One way you can increase your odds of survival after a diagnosis of kidney cancer is by becoming a strong self ~advocate in all phases of your care.

Remember that you and your family have options and rights ~ as well as responsibilities ~ at every step of the way as you deal with your cancer. By exercising your options, rights, and responsibilities, you will become empowered and be able to make sound decisions. And your peace of mind will increase

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Disparities in RCC Therapy, Dr. Ulka Vaishampayan (Karmanos, Wayne State, Michigan)

Patients over 65 do respond, but not to temrisolimus. Overall, age as an isolated factor is unlikely to lead to therapeutic disparity. Co-morbidities affecting performance status and delivery of therapy continue to have an impact.

	age 20-59	60+
African American	4.46%	4.35%
White	2.87%	3.6%

With every $10,000 increase in income, the prevalence of radical nephrectomy increases 7%. Pts without insurance and with Medicare were less likely to have radical nephrectomy than those with private insurance.

DR. ULKA VAISHAMPAYAN
Karmonos Cancer Institute
Wayne State University
Detroit, MI

Young black patients had a higher rise in incidence and poorer outcomes. Is this because of the greater use of radical nephrectomy among lower-income patients and at community hospitals?

With every $10,000 increase in income, the prevalence of radical nephrectomy increases 7%. Pts without insurance and with Medicare were less likely to have radical nephrectomy than those with private insurance.

Patients treated at community hospitals were 48% more likely to have radical nephrectomy than those treated at teaching hospitals.

Race related disparities: the gap is widening in targeted therapy era. Minimal impact of targeted therapy in the African American patients with distant disease. Nephrectomy still remains a major determinant of OS outcome.

Age adjusted incidence rates have remained essentially the same

- Pre-targeted therapy era: years 2000-2003
- Targeted therapy era: years 2005-2008

SEER does not collect data about which therapy, so these year ranges were used to differentiate

If no nephrectomy, there is no change between the two time periods.

Population access to care is significantly different. Impact of targeted therapy is minimal in the African Amerian population with metastatic RCC.

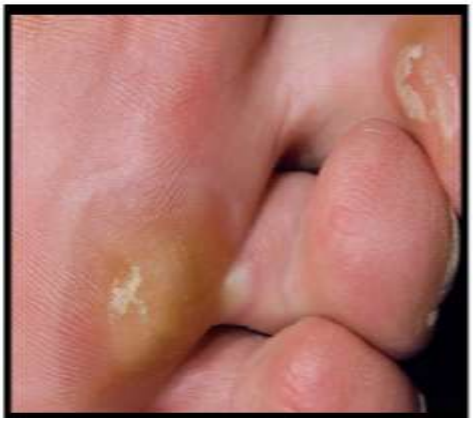
Overall outcomes in kidney cancer are improving, but the disparity gap is widening. Improving access to care is urgent. Multidisciplinary expertise is needed in targeting higher risk patient populations. There should be a clinical trial emphasis on recruiting minorities into clinical trials.

Dr. Naomi Haas (U Penn)
Does Adjuvant Therapy Produce Toxicity Concerns?

There have been concerns about cardiac related adverse events. In one clinical trial the one patient who had a serious cardiac event was in fact on placebo.

Patients who developed hypertension did better throughout, whether or not they had HBP therapy.

Hypothyroidism as a predictive marker – yes



Hand/foot syndrome – as a marker of action? These patients did seem to have a better outcome.

Increase in cholesterol predicts survival advantage in RCC with temsirolimus.

Is the incidence of type of toxicity different in the adjuvant setting than in the metastatic setting?

Toxicity vs Tolerability – unpleasant but less medically relevant issues (17% hand/foot, 7% fatigue)

Patients who discontinued due to hand/foot 22%, fatigue 14%. One doctor noted that complaints about these issues decreased once the patient saw evidence of tumor shrinkage on the scans.

What is your advice about finding the right medical team?

What do you say to other patients who have just been diagnosed?

Bob: I really lucked out with the doctors. I've had some great ones. But having talked to other people and seeing other situations, your doctor is basically your treatment, so take care in choosing. It's critically important. I had a great team. I think building a trusting, open relationship with your doctors is the key. From a patient perspective, don't be afraid to ask questions. And if you're not happy with the questions and the answers that you're getting, find another doctor.

Carol: And also don't go by yourself to the doctor. Take somebody with you because you're going to hear something, and they're going to hear something, and in between you'll find what really was said. You have to listen together. And that has been super important for us.

Bob: It's critical. Your doctors are your lifeline.

WE HAVE KIDNEY CANCER: SURVIVORS STORIES (2012) p.14

Special Session

Results of the BeST Trial (Bevacizumab, Sorafenib, Temsirolimus)

Keith Flaherty, M.D., Massachusetts General. Boston)

The hypothesis is that targeting multiple growth and survival pathways in vascular endothelial cells will result in suppression of escape mechanisms to angiogenesis resistance.

There is a randomized phase II trial, of the most active 2-drug therapy:

- single-agent bevacizumab chosen as control (Arm A) because it is the most selective
- bevacizumab/temsirolimus (Arm B)
- bevacizumab/sorafenib (Arm C)
- sorafenib/temsirolimus (Arm D)

The goal was to find a 67% improvement in median PFS compared to the control arm (median 9 vs 15 months)

Full information would exist when 104 of 160 eligible patients on a pair of arms had progression or death.

Disease progression was the most common reason for stopping therapy.

No combination arm was superior to single-agent bevacizumab for the PFS endpoint, all 3 arms had a response rate >20%

Some severe toxicities were expected.

Clinical trials have been largely responsible for important advances in the treatment of kidney cancer in recent years. The key to their success is finding suitable human volunteers. By participating, you can obtain access to innovative treatments while helping advance researchers' understanding of kidney cancer. Volunteers in clinical trials play an essential role in the ongoing quest to find a cure for the disease.

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Rational Combination Therapy for RCC,
Bernard Escudier, M.D, Institut Gustave-Roussy France

The combination of mTOR inhibitors and TKI's is toxic:

- sunitinib + temsirolimus = impossible
- sutent = everlimus = impossible
- sorafenib + temsirolimus = impossible
- sutent + bevacizumab = impossble at full dose

mTOR + bevacizumab combination

- recommended for further testing
- dream strong enough to proceed, BUT
- mirage confirmed. temsirolimus + bevacizumab or interferon + bevacizumab = just the same

is everolimus a better partner?

- no chance here
- everolimus + bevacizumab vs Interferon + bevacizumab = PFS went down
- everolimus after TKI vs bevacizumab after ev? = don't bother

The best would be to combine drugs with two different mechanisms of action:

- vaccines and VEGF targeted agents
- TKIs and ab against other targets
- combination which prevents resistance
- not too expensive

Risks of combination

- must have good data before starting
- Phase 3 MAILSAIL trial – 50 patients looked good, decided to go forward, went to 1000 pts, worse outcome

Some exciting combinations

VEGF +PD1

tremelimumab plus sunitinib – much toxicity

What combinations are ready for Phase III? –

- bevacizumab + low-dose Interferon, 147 pts, PFS 15.6, OS 30.7
- maybe put this one into trial.

What we want when combining drugs is synergy. The ideal rationale for combination would be based on mechanism of action, good in vitro data, and convincing clinical data.

The ideal combination would induce Complete Responses, and would be more active than the two drugs sequentially, and would not be toxic.

The goal should be: 40% increase in PFS, or don't continue.

There should be a good safety profile with long term follow up

The bottom line is: two drugs are not necessarily better than one

BERNARD ESCUDIER, M.D
Institut Gustave-Roussy
Villejuif, France

Surgery – The Setting of Metastatic Disease

Moderator: Dr. Andrew Wagner, Beth Israel Deaconess, Boston

Stephen Culp, M.D., PhD, (U Virginia),
Cytoreductive Nephrectomy and its Role in Metastatic RCC

People who use cytoreductive surgery tend to be younger, have better insurance, and may be those who do more research in self-advocacy. Newer therapies may result in primary tumor regression. Using neadjuvant therapy, most patients had little or no change in the primary tumor. In fact there is now significant evidence that the primary tumor will not respond in the neoadjuvant setting.

Cytoreductive nephrectomy is the term used for removal of the primary tumor from the kidney, through total or partial nephrectomy. This eliminates the main source of new metastatic cells floating through the blood or lymphatic system looking for a new place to implant.

Complete responses are non-existent in the era of targeted therapy. Most people with the best responses have been those who have had a previous nephrectomy. In a Sutent trial evaluating Sutent with or without a prior nephrectomy, patients with nephrectomy did better.

People with a performance score of KPS <80% also did less well.

Cytoreductive nephrectomy (CN) should remain the paradigm of choice. The residual tumor is still a source of morbidity and metastatic progression.

It's also not for everyone – elderly, non-ccRCC histology, T4 disease, increased risk for these patients, but some might benefit. People with performance scores <3 benefitted more; 4+ benefitted less

CN palliates local symptoms, and the primary tumor does not respond predictably to therapy

Nephrectomy has become an integral part of the management of patients with metastatic kidney cancer. In the past, nephrectomy was performed in this setting only in certain circumstances – sometimes to relieve pain or as a response to intractable bleeding from the kidney. But indications that some patients had spontaneous regression of their metastatic disease following nephrectomy, and the fact that the primary tumor rarely, if ever, responded to systemic therapy, prompted more widespread integration of nephrectomy into the management of patients with metastatic disease. Patients respond better to systemic therapies, particularly immunotherapies, if the kidney is removed.

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Role of Neoadjuvant Medical Treatment
Dr. Eric Jonasch (MDACC)

Today the standard of care is cytoreductive surgery + targeted therapy

In 2012 the role of neoadjuvant therapy:
- an alternate therapeutic paradigm that requires validation
- a discovery platform to detect new targets

Presurgical therapy is safe – bevacizumab delayed healing some, but the others do not

Presurgical therapy can act as a litmus test: restaging after 6-8 weeks, evaluate for cytoreductive surgery
- 6 patients on bevacizumab did not have surgery, rapid change in performance status, progressive disease
- 7 patients on sunitinib did not go to surgery, progressive disease or declining performance status. Primary tumor did shrink in some cases, but that was not the governing issue

We can shrink the primary tumor, although modestly
- after 4 bevacizumab treatments
- after 2-3 cycles of sunitinib
- did not change surgery
- need something to really downstage the tumor, which we do not have this year

Presurgical treatment also changes the way that we collect the tissue. It changes the microenvironment of the tumor so that the tissue is different when you operate.

We are designing a trial so that acquired tissue that informs of:
- Pre-treatment biopsy, do some –omics (several different biological studies of tissue), derive a predictive biomarker
- when you do a biopsy, there is tumor heterogeneity, so we don't always get a good handle on the tissue type. Surgery gives you a bigger chunk of the tumor so you can evaluate whether the biopsy was truly informative.
- genomic information – determine targets

The current agents target endothelium, and we still don't know much about it. The biopsy alone will give us -omics info, however incomplete. We need omics of the renal mass and mets, of protein and tissue phenotype.

In 2012 the role of neoadjuvant therapy is twofold:

An alternate therapeutic paradigm that does require and is actively undergoing prospective validation

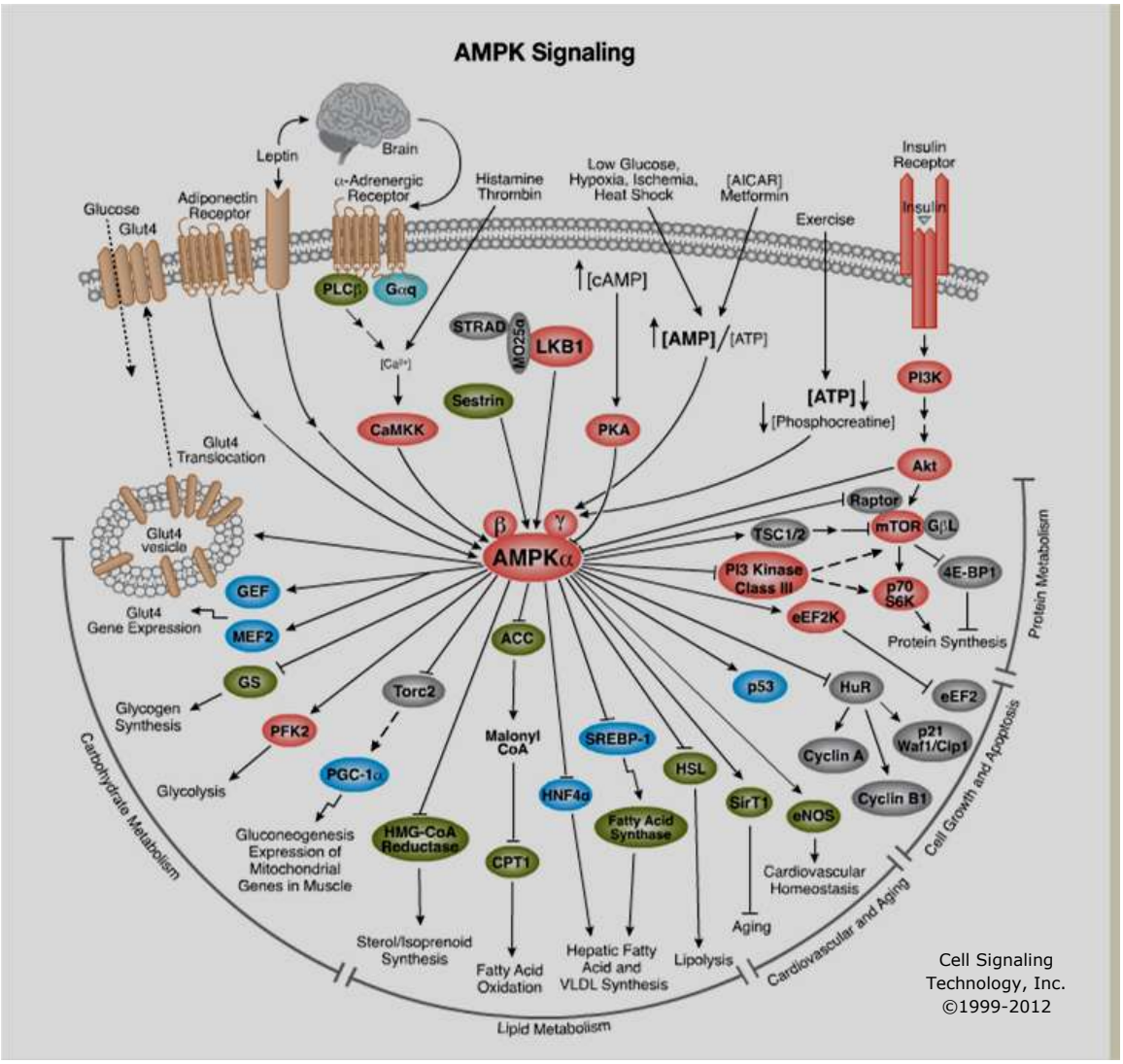
Part of a discovery platform that allows us to integrate genomic information with unique biological observations that provides us with the best opportunity to detect new targets

Hopefully as our therapy evolves our ability to modify both the primary tumor and metastases, as well as the circulating tumor microenvironment will change the paradigm of surgery and therapy to some degree

It is clear that the only way we're going to come up with new treatments in the next 5 to 10 years is by studying treated as well as untreated tissue to change our paradigms

ERIC JONASCH, M.D.
University of Texas,
M. D. Anderson Cancer Center
Houston, TX

Having the post-treatment renal mass gives us information about how things change, so we can evaluate the results – did the drug actually achieve its target and make a difference?



A higher total AMPK level is associated with better PFS

(AMP-activated protein kinase (AMPK) plays a key role as a master regulator of cellular energy homeostasis.)

In the Next Few Years We Need To Gain Information On:

- Distinct baseline molecular phenotypes that predict for response to specific classes of agents (does not require presurgical model)
- Mechanism of therapy resistance:
  - Can only be accomplished using treated tissue.
  - Characterize changes in endothelium, stroma and epithelium as a result of therapy.
  - Need to acknowledge multiparametric aspect of this research endeavor and develop tools to accomplish.

Hierarchy of Tissue Collection

Biopsy alone: Omics information

Renal mass/metastasis: Omics, protein, tissue phenotype at baseline

Posttreatment renal mass/metastasis: Omics, protein, tissue phenotype – identify resistance mechanisms.

Role of Metastastectomy, Stephen Boorjian, M.D. (Mayo clinic)

What is the role of surgical resection of mets? does it help?
How to integrate it into the total treatment plan?
RCC does not respond to radiation,
traditional chemotherapy, minimally responsive to cytokines
While targeted responses are achieved, only 3% (or less) achieve complete response.

Removing mets offers potentially curative treatment for mRCC. It avoids the side effects of the drugs, and can make a patient NED (no evidence of disease); It can be useful for palliation – it can alleviate spinal cord compression, fix pathologic fractures.

Does it help with cancer control? yes, cancer control is feasible, beneficial

We have most experience with pulmonary mets –
surgery is well tolerated, 10% incidence of surgery-related complications.

In the bone: palliative benefit, 35% 5yr survival, 10% complications
pancreas: 66% 5y survival
adrenal: 60% 5yr survival, severe complications rare
renal fossa recurrence 30% 5yr

What is the impact on survival? we don't really know, all data is retrospective. Complete resection of mets seems to yield additional 5 yr survival. Mayo retrospective review indicates that complete resection of mets yields 50% reduction in death. Conversely, lack of resection of mets = 2.7x increase risk of all-cause mortality. Most of the patients in these studies have had one primary site of metastatic disease.

A retrospective study at Mayo of 887 pts with multiple mets, 15% underwent resection, median followup 3 yrs, yielded 4-5 yrs overall survival benefit. With lung mets, the benefit was 73%, but even with other sites the benefit was 32%. With no surgery, there was a 3x risk of death from all causes.

The question with retrospective data is: are the observed results reflective of a benefit to surgery, patient, or other variables not obvious?

A favorable candidate for surgery is one with a single metastatic site, prolonged time since nephrectomy (>2 yrs), but even when not an ideal candidate, it does still have benefit.

Your own doctor can be one of the best sources of information about your disease and its treatment. Doctors who specialize in treating cancer are known as oncologists. After an initial diagnosis is made, don't be afraid to ask your doctor many questions. You should also consider getting a second opinion from another doctor who is a kidney cancer specialist. If you do not know the name of a specialist, you may obtain names from the Kidney Cancer Association (email the request via the Association's website at www.kidneycancer.org or by calling 1-800-850-9132).

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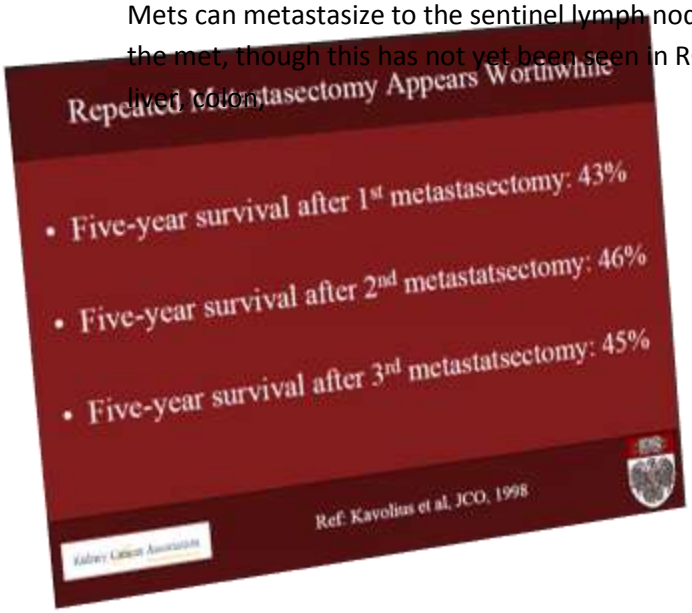
Scott Eggener, M.D., (U Chicago),
Summary of surgical options for metastatic disease

Cytoreductive Nephrectomy (CN) – randomized trials in the cytokine era showed median survival benefit of 6 months. Most trials for current systemic agents show benefit.

Laparoscopic CN speeds time to targeted therapy when patient is a good candidate for it.
Mets can metastasize to the sentinel lymph nodes in the area around the met, though this has not yet been seen in RCC. In melanoma, the standard of care is resection. In lived colon, cervical, pulmonary, pancreatic cancer, resecting mets yields 5yr survival is 5+ years.



According to a study by MSKCC, repeated met surgery is also worthwhile. Percutaneous ablation (RFA, Cryo) can also be helpful in people who are not good surgical candidates. Nonetheless patient selection leads to bias. In order to prove the value we would need a prospective trial. A randomized prospective trial of people with stage IV melanoma has recently been completed and should be public soon.

In sum, CN and surgical excision of mets has a role in management of mRCC. About 20-30% of patients qualify for percutaneous treatment.

What is the value of lymph node dissection? CN is usually done open at Mayo because they also do LND. They employ close collaboration with thoracic surgeons, and form a joint decision among oncologist, thoracic and urology, as to whether to start with systemic therapy or to begin with surgery.

In melanoma, we have seen that the treatment changes the pattern of disease. They are now seeing small bowel disease and pancreas disease in people who have undergone treatment for melanoma. The Betsy Plymouth paper looks at patterns of progression. Recurrent disease tends to occur in new organ sites.

CN is good for SOME patients, especially those with a large primary and one met, and with an ECOG status 0-1 (healthy).

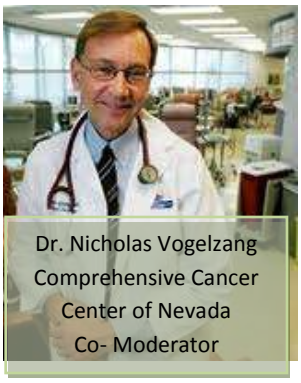
Q&A On Surgery and The Setting of Metastatic Disease

Blute: We are redesigning our approach to cancer patients.

Jonasch: Anyone who goes off these agents will have some rebound. Will it be a problem? In the Sutent neoadjuvant study, where we stopped the agent and did surgery, we saw that some patients had brain mets that were not there 3 months before.

Health care access is a major problem. We have patients who are qualified for surgery, but who cannot get surgery for various reasons. We need to educate the public and the doctors.

Is there a different perspective on CN for non-clear-cell vs ccRCC? So far we have very little data. We just don't know.



Dr. Nicholas Vogelzang
Comprehensive Cancer Center of Nevada
Co- Moderator

Options for the treatment of the naïve patient

"Treatment naïve" is the term used to describe a patient who has not yet received any drugs for treatment of their cancer. Use of any one of the drugs will have had some effect on the cancer, changing the microenvironment of the cancer in some way, and probably therefore affecting how the next drug will work on that same tumor.

Joaquim Bellmunt, M.D.
Hospital De Mar,
Barcelona, Spain
Co-Moderator

Case presentation, Dr. Allison Ackerman, BIDMC

59 yo woman with no symptoms is found to have a left renal mass. CT showed pulmonary nodules. A nephrectomy was recommended for the 6 cm RCC. The patient felt well, exercised regularly, but had an anxiety disorder which required a standing order for clonazapam, and would not agree to surgery.

Treatment options:

- a VEGF inhibitor, (sutent vs pazopanib)
- an mTOR inhibitor (but she would not tolerate IV or hospital admission due to her anxiety)
- Immunotherapy (IL-2)

She was started on Sutent, at a reduced dose, for 4 weeks. At that point the disease had progressed. After progression, she went on Axitinib, and felt so well that she went to Vegas. We increased her dose until she reached grade 2 hypertension and tumor response. She was still asymptomatic, feels better. Today Dr. Acknerman would have put her on pazopanib.

Case for Moving Axitinib into the Front Line,
Dr. Brian Rini, Cleveland Clinic

Rini feels axitinib is now the standard of care. RCC is fundamentally VEGF driven. Potent inhibition of VEGF will produce the most robust clinical effects, and should be applied as soon as possible.

Axitinib is doing well. The trial design starts patients off with 4 weeks at 5 mg, evaluated to see if their reactions were okay, if not, continue at 5 mg, if yes, half the patients received a raised dose (titrated based on their side effects), half not. If their blood pressure had not risen, they were assumed not to have achieved a sufficiently high level of drug in the bloodstream so their dosage was increased until they achieved suffient elevation of blood pressure.

Most Common Adverse Events[a]

	Axitinib (N=213)	
Event, n (%)[b]	All grades	Grade 3/4[c]
Hypertension	135 (63)	61 (29)
Diarrhea	123 (58)	15 (7)
Fatigue	102 (48)	13 (6)
Dysphonia	85 (40)	2 (1)
Decreased appetite	74 (35)	7 (3)
Hypothyroidism	72 (34)	0
Nausea	70 (33)	5 (2)
Hand–foot syndrome	65 (31)	7 (3)
Proteinuria	61 (29)	3 (1)

[a] As of March 23, 2012
[b] All-causality adverse events reported in >25% of patients
[c] There was 1 grade 4 diarrhea AE and no grade 4 hypertension AEs

For those on the optimal dose, PFS 14.5 mo – Arm C = 16.4, 60% response

For those on Arms A + B (inadequate dosing), 14.5 months median PFS, response rate of 43%

Axitinib is the most effective first-line treatment with long PFS. It could be that other TKIs are being under-dosed. We do not know whether they would do better at a higher dose. There is no directly comparable data across all drugs, but axitinib is doing very well and should be considered for front-line status,

Is blood pressure an indication of blood levels? sometimes. Should we measure blood levels rather than inferring it from Blood Pressure? easier to measure BP, and the blood levels tend to vary depending on the timing of the dose.

Why did they not let the sorafenib side also have dose escalation? The patients did not tolerate higher levels of sorafenib, and did not seem to benefit. That trial tried to escalate everyone, and that is not going to work. It is necessary to escalate thoughtfully.

Our dramatically increasing knowledge of cancer biology at the molecular level is beginning to transform the standard of care from a one-size-fits-all approach to personalized cancer medicine, also called molecularly based medicine, precision medicine or tailored therapy.

With this type of medicine, the molecular makeup of the patient and the tumor dictate the best therapeutic strategy. The overall goal is to increase survival and quality of life for most cancer survivors.

AMERICAN ASSOCIATION FOR CANCER RESEARCH -- CANCER PROGRESS REPORT 2012

Dr. Camillo Porta (Pavia, Italy, San Matteo Univ)
How Does Recent Pazopanib Data Impact Our Prescription Paradigm?

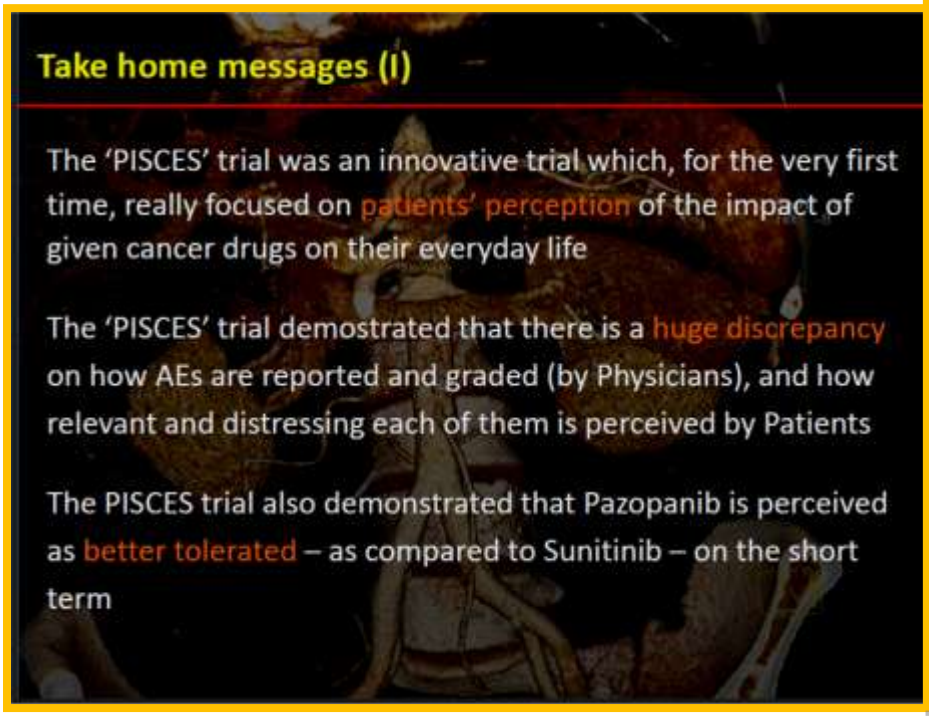
The PISCES trial consists of 10 weeks of Pazopanib or Sutent / 2 wks off / then switch to the other drug another 10 weeks. At that point (22 weeks), they asked the patients which drug they preferred. Patients preferred Pazopanib due to better quality of life and less fatigue, less foot and mouth soreness. It demonstrates better tolerability.

The actual effects as measured by the physician are very comparable, if not slightly better for Sutent.

However the patient experience is very important, and the effects of Pazopanib are less draining.
Is there bias in the PISCES study? 10 weeks is ¼ or 1/5 of the suggested course of treatment. The timing of the question might have influenced patient responses. More fatigue was reported in all consecutive treatment cycles.
More fatigue was reported in first segment, less fatigue noted on day 1 of the second cycle (after the break). The end of week 22 is the worst possible day for toxicity in Sutent.

Were patients told that side-effects are an indicator of efficacy?
Did that change their attitudes about them?

PISCES demonstrated the huge discrepancy between the physicians' rating, and the patients' rating of the quality of life effects of the two drugs.



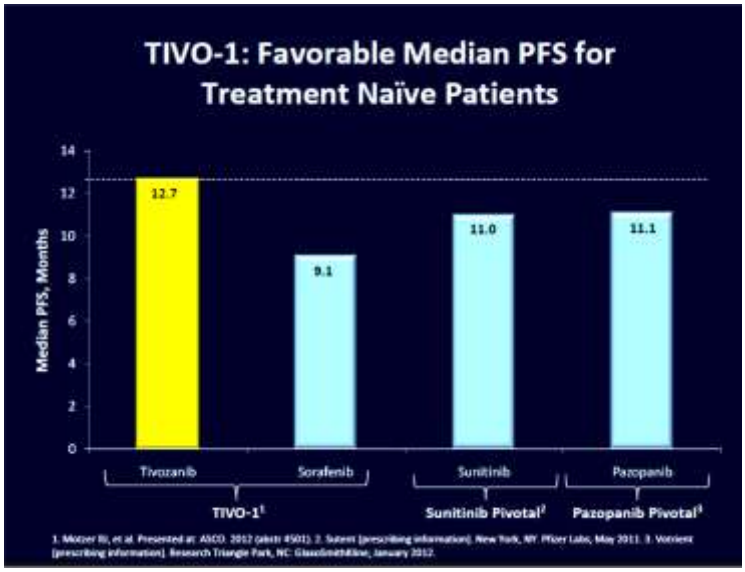
Let's come back to the main message in my mind; the discrepancy between the physicians and the patients for adverse events as reported by the physicians. There was essentially no difference in the fatigue between the two drugs. But: one of the two most important reasons for patients preferring pazopanib over sunitinib was less fatigue. Quality of life surveys filled out by patients clearly indicated this; the other most important reason was *no single reason* meaning that patients were simply not able to explain the exact reason for their choice.

CAMILLO PORTA, M.D.
IRCCS
San Mateo University Hospital
Pava, Italy

Tivozanib as First-line Therapy for mRCC, Dr. Robert J. Motzer, MSKCC

Dr. Motzer said that Tivozanib is showing efficacy, safety, and tolerability. Tivozanob targets VEGFR.

Most of the currently approved first-line therapies have a PFS of 11 months of less.



Safety is a big issue for our patients – they are looking for tolerability and good quality of life (QoL)

Tivozanib inhibits VHGFR types 1, 2, and 3. It's a once daily dosing schedule, 3 weeks on, 1 week off. It has no interaction with CYP3A4 inhibitors, so it would have been okay for our patients with the anxiety disorder. It has good safety characteristics.

TIVO-1: is a phase 3 study of Tivo vs sorafenib as first-line targeted therapy for mRCC. Tivo demonstrated 26 mo vs 9-11 PFS for other drugs. After one year the OS = 77% for tivo, 81% sorafenib, need longer data. Tivo is very safe, tolerable, should be a candidate for first-line therapy

A Survivor Speaks

The size of the tumors eventually started to increase and at that time, the doctors started me on one of the newer drugs for kidney cancer. In the meantime, I was having some trouble with my vision, so I went in for an MRI of my brain. And it turned out that I had three lesions in my brain. So my next treatment was to have gamma-knife surgery. This was successful in removing the lesions. I continued with the drug treatment for the lungs and liver at the medical center, but I was having a hard time with side effects, including very high blood pressure, coughing up blood and on top of that, it didn't work. [Laughs] At that time I was offered the opportunity to participate in a clinical trial. I would be a part of a group testing what was a new drug at that time. Given prior results, I was happy to consent.

Interviewer: And are you on that drug now?

Billy: Yes – I take it every night and have been on it for three years.

Interviewer: And what is the status of your tumors?

Billy: Some of the tumors have reduced in size since the beginning of this, which was an unexpected result.

Interviewer: And how are the side effects for this one?

Billy: Well, at first, they started at a fairly high dosage, I guess, and I was getting more side effects. But over time we got that adjusted.

Interviewer: What was it doing to you?

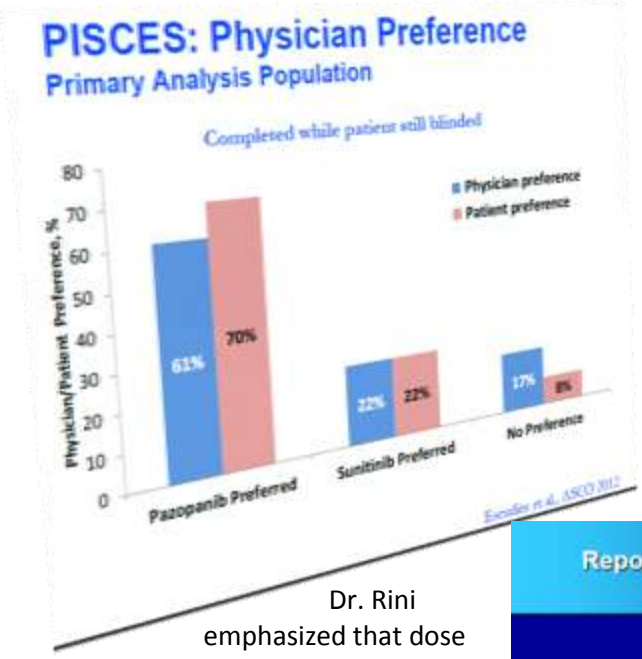
Billy: Well, I couldn't eat. Everything tasted horrible. My stomach was hurting every time I ate something, fatigue would set in and I had a sore on the bottom of one of my feet caused by the medicine. With the sore on my foot I would put a salve recommended by the doctors and a foot patch on to cushion it…

WE HAVE KIDNEY CANCER: SURVIVORS STORIES (2012) p. 46-47

Dr. Tim Eisen, Univ of Cambridge, England Does Emerging Data Justify a Change in the Standard of Care for Treatment of Naïve Patients?

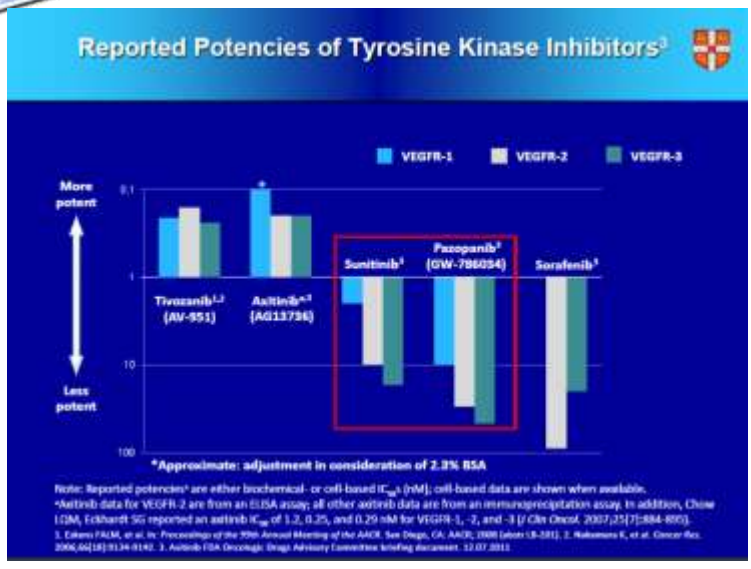
Are the data credible? can we choose? which drug is best for which patient?

Tivozanib and axitinib and 2x more potent than sutent, sorafenib. Disease assessments are not optimal in the studies. High Blood Pressure, hypothyroidism, and dysphonia (disturance of vocal function) are on-target effects, indicating that the drug is working. There are other off-target side effects.



Pazopanib did worse in liver function tests and weight loss. Fatigue, skin toxicity, and dermatitis were also reported. Pazopanib is great, but he advised its pharmaceutical company to "make hay while the sun shines" because Tivozanib is close behind and is showing much more dramatic improvements.

If one of these drugs was less expensive, would your opinion change? If sunitinib would reduce its price by 25% would they use it in the UK? Yes. One currently has to apply for permission to use a second-line treatment in the UK.



Dr. Rini emphasized that dose titration is essential because without appropriate drug levels the patient does not have a chance to respond.

pazopanib – contra-indicated for liver problems, but otherwise doctor and patient are making the decision every week, attitudes about side effects often change once they see tumor shrinkage.

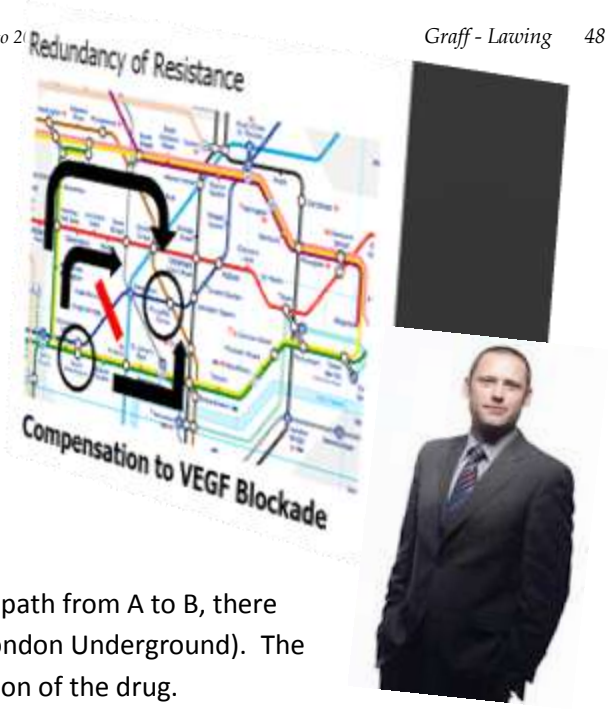
There is dramatic impact to survival with this third generation of drugs. The data is confounded because many patients did not have access to second-line drugs. Only targeted drug showing improvement is temsirolimus. Dr. Motzer is looking for improvement in OS, and especially to PD-1.

Be careful in over-interpreting retrospective data.

Therapy for the VEGF Resistant Patient

Biologic Mechsnisms of Resistance,

Dr. James Larkin (Royal Marsden Hospital, London)



Anti-VEGF drug resistance

- is inevitable
- patients die because of resistance
- can be dynamic and reversible?

The issue is that while the drug blocks the primary path from A to B, there are many other compensatory routes (similar to London Underground). The tumor figures out a way to grow in spite of the action of the drug.

We sample the tissue at the time of disease progression in order to understand what may have changed. There are a number of challenges to biopsying progressive metastatic sites in trials. Not only is the tumor heterogeneous (and you might not get the relevant bit in your biopsy), but the patient may not be available, may not give consent, and there are issues of logistics and cost.

In RCC there is significant preclinical literature, but relatively little is known about resistance.

Possible solutions:

- Detect the presence of rare subcategories during pre-treatment
- Use sensitive non-invasive methods to detect and characterize resistance early
- Combining targeted drugs will just delay the emergence of resistance, not prevent it.
- Try immunotherapy

Intra-tumor heterogeneity – is the chunk of the tumor you are analyzing representative of what you need? 68% of tumors are heterogeneous and the relevant bit is not in the biopsy

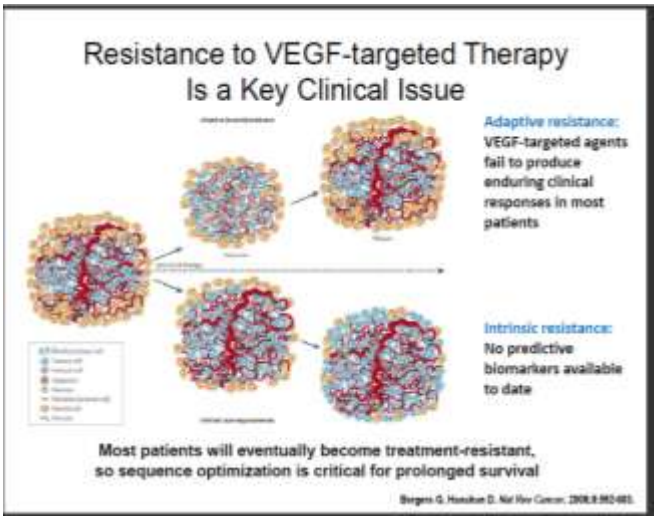
Resistance and Sensitivity are intrinsically linked. There is likely a genetic connection here, but we do not yet know how to test for it. We are still learning about the mechanisms of VEGF resistance.

We need a great deal of tumor tissue in order to study this process. A longitudinal study of patients from initial diagnosis to metastatic disease and progression on treatment is needed. Such studies are difficult (but possible).

A-PREDICT is a trial among patients presenting with metastatic RCC NOT suitable for debulking nephrectomy as part of routine care. The nephrectomy becomes the biopsy, and it is also important to have tissue from metastases. This study is being conducted UK-wide. Will tumors always be one step ahead of us? We may need post-mortem studies as well.

Anti-VEGF Drug Resistance: the Problem

- Is inevitable whether intrinsic or acquired
- Our patients die because of resistance to therapy
- Can be dynamic and reversible (? drug therapy as selective pressure on tumour subclones)
- Activation of compensatory pathways e.g. FGF, IL-8 is likely; myeloid-derived suppressor cells may be important; variation between patients
- Angiogenesis is complex and redundant; no single drug can block all pathways



Is Understanding Resistance Tractable?

- We can never sample all sites of metastatic disease apart from with postmortem studies
- Will tumours always be one step ahead because of their ability to evolve under the selective pressure of therapy?

We agree with the requirement for postmortem studies to characterize heterogeneity at multiple sites of metastatic disease and to reveal evolutionary bottlenecks that may govern both the clonal evolution from localized to metastatic disease and the acquisition of drug resistance by tumors. Such studies face numerous regulatory and ethical challenges and will require close collaboration with patient-advocacy groups.

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Cancer Research UK London Research Institute
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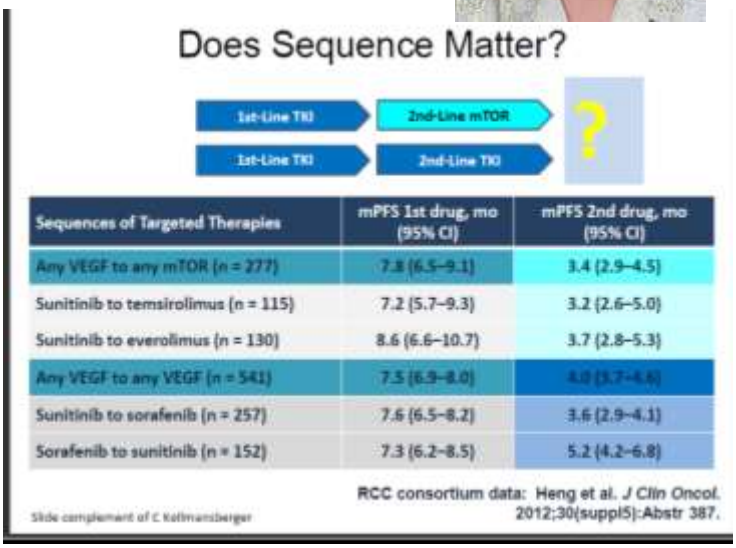
Gerlinger *NEJM* 2012 (correspondence)

Existing Clinical Data in VEGF Resistant Disease
Jennifer Knox, M.D., (Princess Margaret Hospital, Toronto)

Does the sequence of treatements matter?

TKI followed by an mTOR inhibitor?

TKI followed by a 2nd line TKI?



Sequences of Targeted Therapies	mPFS 1st drug, mo (95% CI)	mPFS 2nd drug, mo (95% CI)
Any VEGF to any mTOR (n = 277)	7.8 (6.5–9.1)	3.4 (2.9–4.5)
Sunitinib to temsirolimus (n = 115)	7.2 (5.7–9.3)	3.2 (2.6–5.0)
Sunitinib to everolimus (n = 130)	8.6 (6.6–10.7)	3.7 (2.8–5.3)
Any VEGF to any VEGF (n = 541)	7.5 (6.9–8.0)	4.0 (3.7–4.6)
Sunitinib to sorafenib (n = 257)	7.6 (6.5–8.2)	3.6 (2.9–4.1)
Sorafenib to sunitinib (n = 152)	7.3 (6.2–8.5)	5.2 (4.2–6.8)

RCC consortium data: Heng et al. *J Clin Oncol.* 2012;30(suppl5):Abstr 387.

Slide complement of C Kollmannsberger

Among the people who did not gain significant benefit from 1st line therapy, there were very poor outcomes. What should we do following tumor progression on a VEGF-inhibitor TKI? Follow with..

Everolimus vs placebo
Strongly favored everolimus
4.9 months
Placebo control shows that everolimus is indeed active

at

The study found toxicity due to mTOR, which was not worse depending which 1st line therapy was used. = sutent 4.6 mo. Those people who did not tolerate TKI treatment had similar results.

The AXIS trial demonstrates that not all 2nd line TKIs are the same: axitinib seems better than sorafenib

The INTORSECT study compared temsirolimus vs sorafenib following sutent for at least 4 weeks. The primary end point was PFS, which was similar (4.3 mo), but sorafenib (16.6 mo) did better than temsirolimus (12 mo). Is there some biology favoring the VEGF TKI? PFS does not predict for overall survival in these trials.

Some patients believe that information about kidney cancer is presented in complicated medical terms they won't be able to understand. But a great deal of information is specifically written for patients in easy-to-read language that requires no specialized training to understand. Doctors and nurses will be very willing to answer your questions, because the more you understand, the better you will be able to participate as an active member of your health-care team.

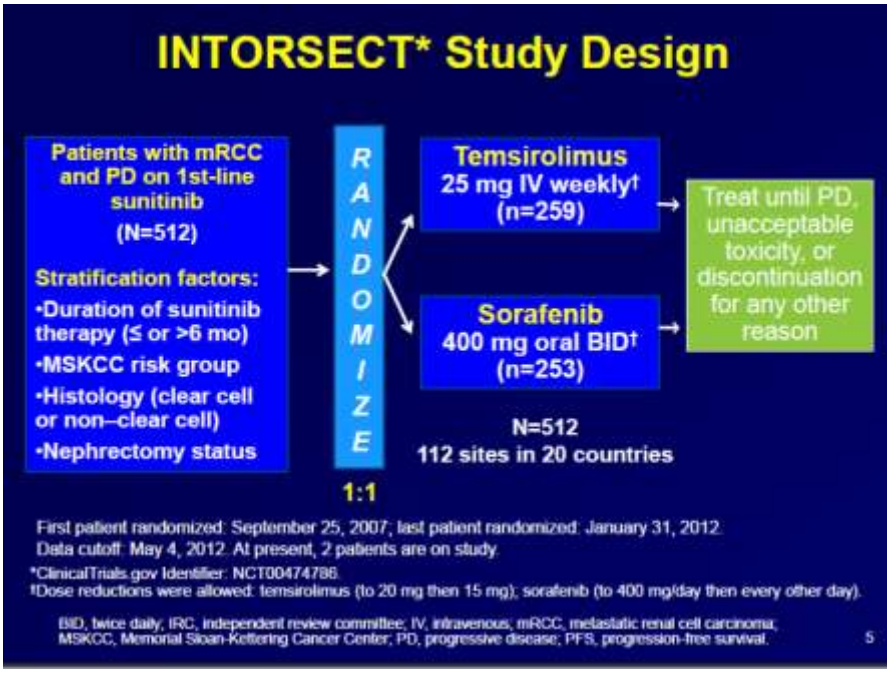
We think that learning more about the disease and your treatment choices will help you. History has shown that assertive patients who actively work to overcome cancer often increase the odds of survival, live longer, and enjoy life more. You can be a passive victim or an active fighter. The choice is yours.

Our recommendation is to fight. Don't surrender! *WE HAVE KIDNEY CANCER (2012) p. 47*

VEGF vs mTOR – How does the Wyeth 404 result impact Decision making?
Dr. Thomas Hutson (Texas Oncology, Dallas)

The results of this trial were presented at ESMO the previous Monday October 1, 2012 so the audience had not yet seen it. Temsirolimus was approved with only a narrow indication in Europe, so Wyeth launched another trial to broaden the indication.
Does sequence matter?

The INTORSECT trial enrolled 512 people in 20 countries, patients who had progression of disease on sunitinib. These people were randomized to temsirolimus or sorafenib based on their time on sunitinib. They excluded people who has mets to the central nervous system, or who had to discontinue sunitinib due to intolerance. 90% of these patients had received a prior nephrectomy (radical or partial), 80% had clear cell. One-third of the patients were on sunitinib less than 6 months, two-thirds for more than six months.



The Progression-free survival (PFS) for the temsirolimus group was 4.28 months vs. 3.91 months for sorafenib. The objective response by RECIST criteria was equal. Thirty days after the trial 54 patients went on to third-line therapy, while others went on to radiation and surgery. Overall survival on temsirolimus was 12.27 months, and on sorafenib 16.64 months.

One of the "confounders" (elements providing confusion) might have been access to third-line therapies. Not all the patients in the trial were eligible for a third-line therapy which might have extended their overall survival.

The patients experienced progression at approximately equivalent time periods. The number of deaths during this trial were approximately equal on both sides. PFS by duration of prior sunitinib: the numbers favored temsirolimus over sorafenib slightly, but the difference was not statistically significant.

Is this a true effect? or statistical? false positive? different tumor biology? dose delivery? Is previous VEGF therapy modifying the biology of the disease? The longer the patients remained on the initial therapy, the longer they lived.

Sequential therapy remains the standard of care, with second line therapy including bevacizumab and axitinib. The optimal sequence remains to be defined. What we really need are biomarkers to guide us.

Audience dialogue

Kaelin: why not combination therapy to manage resistance? Just because they have not worked to date doesn't mean that there might not be a combination in future. In the 1990's Kaelin worked with the drug companies to try VEGF inhibitors; they said that medical therapy had never worked in kidney cancer and therefore never would. Combination therapy has been the answer is many other diseases, why not in kidney cancer?

Larkin: it would delay resistance, but probably not cure the patient. Combinations don't seem to be tolerable. We need rational combinations based on their biology.

We drop-off of patients as we go forward: 50% go on to 2nd line, 25% go on to third line

All PFS may not be equal, some may be worse, and may influence survival.

Not all patients have access to 2nd and 3rd line therapies everywhere in the world. Are we preventing personalization? Payers are an increasing part of the problem. It's a decision for the society to determine what's right for the society.

Atkins: what about taking a break and continuing on the same drug? We need to explore this possibility.

Sutent re-challenge data indicates that might work.

Jessica is an energetic 25-year-old from a small community about an hour north of New York City. Naturally athletic, she recently earned a bachelor's degree in psychology and took time off after graduation to snowboard – one of her great passions – in Utah.

Jessica was a junior in college when she learned of her diagnosis – but the diagnosis itself didn't emerge easily. She estimates that she saw at least six doctors before the kidney cancer was discovered. While doctors early on suspected a kidney stone or cyst, she intuitively thought it might be more serious and kept pressing her doctors to be more proactive. Jessica underwent no additional treatment for her kidney cancer after a partial nephrectomy, though she has had several other surgeries for other health problems. Like many patients, she has become active in the community of kidney cancer survivors, interacting with others at the Kidney Cancer Association website and its Facebook page.

Jessica's story illustrates how difficult it can be, in some cases, to detect kidney cancer definitively – and why it's a good idea to be your own advocate. As she puts it, "advocating for myself, in my case, literally saved my life."

Emerging new agents

Once we determine that VEGF is no longer a valid target, what else is there?

PI3K, Dr. Dan Cho (Beth Israel, Boston)

Allosteric inhibitors of TORC1 (torisel, RAD001) have shown activity in mRCC. TORC1 is sensitive to the rapalogues, cells can get around it pretty easily. Inhibiting TORC1 can drive TORC2 and Mak Kinase, another negative effect.

Dependence on the HIFs by TORC 1 or 2 activitiy. HIF2 is the more relevant, and is almost completely dependent on TORC2. Several drugs are available which inhibit mTOR, and there are dual inhibitors of PI2K and mTOR.

A Trial was conducted using GDC-0980 vs everolimus in patients with advanced RCC (who have failed up to 2 TKIs). There has also been a Phase II trial of MK2206 vs everolimus.

What is the relevant target? PI3K or mTOR? Preclinical models say that so far mTOR may be the more relevant target in RCC. Clinically, the active site in mTOR inhibitors and PI3K/mTOR inhibitos appear to have similar toxicity profiles.

Predictive biomarkers:

- only a small subset of patients derive significant clinical benefit
- mechanism of antitumor response may reside in the tumor cells
- pre-treatment tumor activation – mutation, epigenetic analysis. Surrogates of activation: phospho0Akt, -S6, -PRAS40

Mechanistic biomarkers:

- HIF-1 expression
- eIF4E overexpression
- Serum LDH

What rational combinations should we try?

- VEGF signaling antagonists like BKM120 + everolimus
- other combinations

Your doctor does not work alone in keeping you healthy. He or she relies on you to discuss any problems you have. If you experience any of the following problems, be sure to call them to your doctor's attention: weight loss, loss of appetite, weakness, headache, changes in your mental status, fevers or high temperature, abdominal or skeletal pain, cough, shortness of breath, enlarged lymph glands, or blood in your urine. Be careful. Do not dismiss symptoms of illness as unimportant. Your doctor will not criticize you for being cautious.

WE HAVE KIDNEY CANCER (2012) p.39

cMET as a target in RCC: cabozaninib,
Dr. Toni Choueiri (Dana Farber, Boston)

MET and VEGFR cooperate to promote tumor survival through angiogenesis, invasion/motility, proliferation, survival.
Cabozantinib (XL184) characteristics:

- dual VEGF and MET inhibitor
- ALLIANCE/CALGB trial, Cabo vs Sunit (N=150)
- untreated ccRCC with poor risk and bone mets, randomize to Cabo vs
- Papillary RCC
- oncogenic events in PRC are largely unknown, but do not involve the VHL-HIF-VEGF axis
- Activating mutations of the MET gene have been identified in hPRC

Foretinib (XL880/GSK) characteristics

- used for papillary RCC (PRCC)
- 80% previously untreated
- 13.5% of participants had 18.5 mo duration of response, ORR 88%

MET is an interesting target in ccRCC. Evidence points to dual control of VEGF/MET
Cabozantinib seems to be the leading compound in cRCC.
We need more refinements in our understanding of papillary RCC.

Novel Angiogenesis inhibitors: beyond VEGF (SK, and-2, etc),
Dr. Rupal Bhatt (Beth Israel Boston)

S1P is elevated in the blood of RCC patients. The company LPATH has an antibody which has activity even in the presence of VEGF inhibition, and may have additional activity with mTOR inhibition.
Resistant tumors show presence of TGF-beta. Dr. Bhatt tried adding ALK-1 inhbition to VEGRF inhibition

- treated mice with sunitinib
- adding ALK-1 stabilizes the tumors (Acceleron Pharma)
- If failure on one, follow with axitinib + ALK-1

Angiopoietin2 is a known angiogenic target, inhibitors being tried. In a subset of people, Ang2 increased when the tumor progressed.
Cathepsin B is highly upregulated at the time of resistance

- treated mice 3 days, almost complete abolition of blood flow
- searching for an inhibitor

How Should You Choose Second-line Therapy for mRCC,
Dr. Jorge Garcia (Cleveland Clinic)

What is the biologic or molecular data? What are the goals of care? How should we interpret the existing clinical data to choose?

Second-line therapy is a moving target: sutinitinib vs pazopanib vs interferon/bevacizumab vs high-dose IL-2 vs tivozanib. We do not know enough at this point about the underlying biological mechanisms to choose among these options in a smart way. The reasons why the drug does not work for a given patient may be biological (the cell type is not responding) or may be physiological (the patient is not reacting well to the drug). Even the patients entering Phase III studies of second-line therapy are widely heterogeneous.

Really all we can do at this point is the use the existing Phase II data to maintain the patient's quality of life. We can use one or more of the existing scales to evaluate the histology and risk.

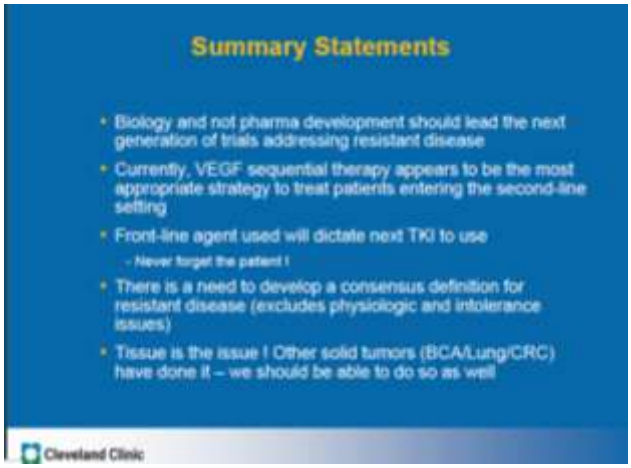
How should we define Progressive Disease (PD)? The AXIS trial redefined PD during first-line therapy. Cytokine resistance (35% is not the same as VEGF resistance. The INTORSECT trial defined PD by RECIST criteria or clinical Progression of Disease. There were no clear correlations between the prior treatment and the subsequent PFS, and PFS may not correlate with OS.

Possible 2nd line treatment options:

sutent/pazopanib/tivozanib > axitinib > mTOR inhibitor

The protocol for treatment should be:

- renal mass > diagnostic biopsy for molecular characterization
- surveillance / rfa/ nephrectomy – adjuvant drug? – then rebiopsy as the microenvironment may have changed.
- metastatic disease – measure of AUC or biomarker for study



Summary:

- Biology and not pharmaceutical development should lead the next generation of trials addressing resistance
- Currently VEGF sequential therapy appears to be the most appropriate strategy to treat patients entering 2nd line
- Front-line agent used will dictate the next TKI to use
- Tissue is the issue!

Schoenfeld Lecture: Science-Driven Kidney Cancer Clinical Trials

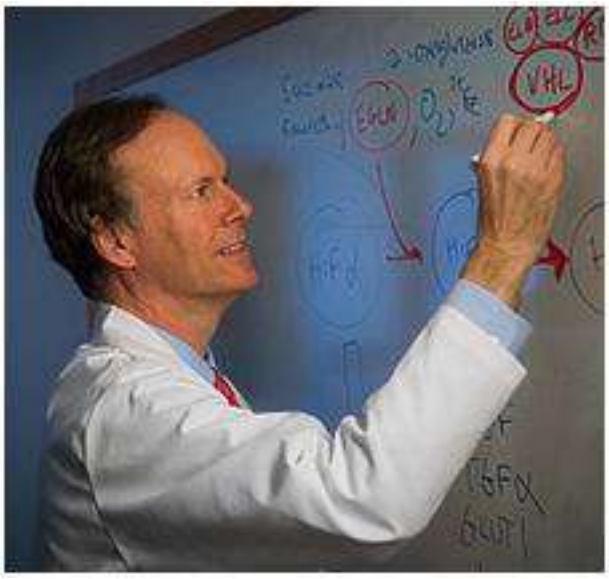
In 1989 Eugene Schonfeld was diagnosed with kidney cancer. What he accomplished within the span of a few short years afterwards is quite remarkable. When Gene was diagnosed he found there was nothing useful at the patient level available about his diagnosis of kidney cancer. His physician challenged him; his exact words were: "Gene if it bothers you so God damn much – do something about it." And Gene did. He gathered at his kitchen table with that physician and three other patients and shortly thereafter the forerunner of today's Kidney Cancer Association was formed. Gene was a visionary; he was convinced that the Internet was the future of society and that someday it would be a great source of information for patients.

We have grown from an organization with three employees that reached a few thousand people in the United States to one that reaches more than 70,000 people in 102 countries – still with a full-time staff of three people.

This award is named for someone who demonstrated great capacity, intellectual curiosity, someone who was driven and someone who has made a real difference ultimately in the lives of patients who are affected by this disease. The recipients of this award are passionate about their work and of whom their patients can be proud.

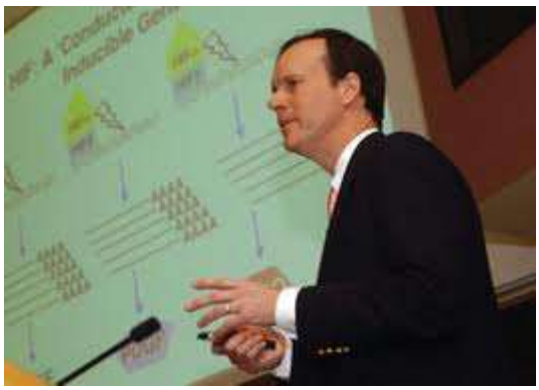
Introductory Comments by William P. Bro, CEO – Kidney Cancer Association

Award Presentation and Speaker Introduction by Dr. David McDermott



Bill Kaelin is the "Chief Resident in Kidney Cancer" – he has provided leadership, and better outcomes for people not only with cancer but also stroke and myocardial infarction. "When your slides begin with VHL> HIF > angiogenesis ... that's the work of his lab. Also as a good chief he sets high standards. No one can find the weaknesses in a plan than Bill, but he is also right there to help you fix it." He has helped in the growth and development of many of the members of the Harvard team – Rupal, Toni, Sabina Signoretti, and a long list of others.

William G. Kaelin Jr. M.D., - Dana Farber Cancer Institute, Boston, MA - Schoenfeld Lecture



Cysts that have become null for VHL (VHL-/-), will grow to become VHL RCC's. While this mechanism plays a pivotal role, it is not sufficient. In sporadic RCC, VHL loss is an early gatekeeper event. This is important because of the heterogeneity within the tumor, you can rely on the fact that the VHL loss is an early event in those changes.

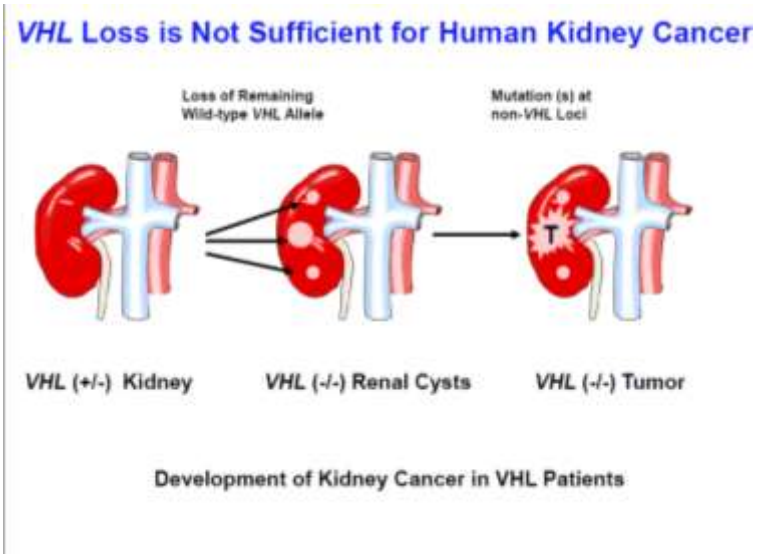
The most common event in ccRCC is loss of chromosome 3p -- not just VHL, but all of 3p and 14q, which contains the genes for HIF1-alpha, HIF2alpha, HIF3alpha. The oncoprotein is HIF2alpha, HIF1 is a tumor suppressor on 14q, and the process gets rid of HIF1alpha altogether.

HIF1a is on 14q, and frequently we see loss of the entire arm of 14q. There are multiple relevant genes on 14q. We also see increased expression of 51 amplicon Genes – abundance of those transcripts, 60+ genes, especially SQSTM1/P62 which activates NRF2, NFkB, mTOR, all of which have a role in the development of ccRCC.

Is this functionally relevant? The knockdown of SQSTM1 inhibits ccRCC growth in vivo. To prove this his lab did a rescue experiment, where they reintroduce SQSTM1 which does not have the binding site for the hairpin, and it does rescue the tumor.

SQSTM1 could be some housekeeper gene, needed to test for overexpression of SQSTM1, which promotes ccRCC in soft agar growth, and promotes tumor formation.

The genes most commonly mutated in ccRCC are VHL, PBRM1, SETD2, BAP1, mTOR. Four of these are on 3p. When you lose 3p, you lose multiple tumor suppressor genes relevant to kidney cancer.



Other genes found to be mutated: PTEN, PI3KCA, TP43, ATM, MLL3, NRF2, ARID1A. Several of these are on the mTOR pathway.

Kaelin is seeing too many of what he calls "Emperor's new clothes" trials – outcomes that show very small differences, and yet are treated as success. Companies can make milliions on very small differences between their drug and another—it creates a sociology that we should end.

The process goes like this: preclinical > phase i > phase II > big randomized Phase 3 trial (big bucks)

You don't want a false negative in phase 2, so you do the phase 3, bypassing phase 2. You don't want to be the guy at the pharmceutical who approved the phase 3 that failed – you would be out of a job. Thus a lot of things get killed in phase 1 or 2. Every new transformative drug had to have a champion who worked to get it through.

In the 1990's there was a trial of PTK787, a drug that inhibited both KDR and PDGFR. Dan George remembers this painfully well. Many patients had stable disease (57%), central necrosis, measured blood flow, PFS 655 days, -- it looked great. However, this might have been due to patient selection, and if you do a big trial, it might fail. The company was convinced that since drugs had never before worked in kidney cancer, they never would. They decided to do a big phase 3 trial in colorectal cancer, but the drug withered on the vine.

Genentech did a 3-arm randomized trial for bevacizumab and it worked.

Kaelin proposes that we do preclinical studies, phase i (single arm), and then a randomized phase II (not so big). If you can't see a difference in phase 2, you are not going to see them later.

What he thought the end game was, was to find a combination of 3-4 active drugs, each given at or near full dose, with distinct mechanisms of action, that are non-cross resistant. It has worked in TB, ALL, childhood leukemia, etc.

What we have used so far are different selectivity profiles of kinase inhibitors. Sunitinib is a multi-targeted kinase inhibitor. By contrast, PTK787 was more specific, Sorafenib has 3-4 targets.

- HIG is inhibited by rapamycin-like drugs
- VEGF is inhibited by Avastin
- KDR is inhibited by sorafenib or sunitinib

All three are inhibiting the same pathway, and if resistance arises, they are all out of business

Rapamycin-like drugs actually promote other kinases, so they are probably counter-productive.
If you hit the VEGF pathway hard enough, you will create cardiac issues.

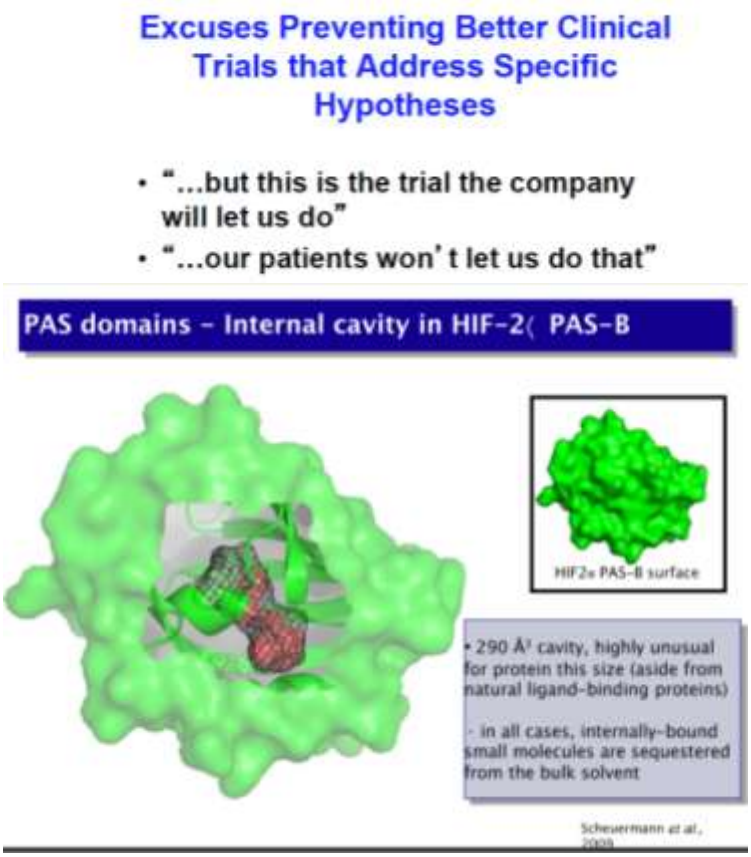
VHL regulates HIF [and C-MET] which regulates VEGF and PDGF and TGFalpha, and EGFR. We have known this since 1999. In the setting of lung cancer, MET activation is a path to resistance. That might also be true in human kidney cancer, emitting signals that are leading to resistance.

Mouse HGF does not engage the human cMET receptor.
But it may not be getting the full signal because the mouse model does not energize it.

Another possible target: IL-8. Several articles looked at IL-8 across many cell lines.
ccRCC has high levels of IL-8. The IL-8 SNP might be a biomarker.

Other combinations worth pursuing:

- VEGFi plus anti-PD1
- VEGFi plus METi
- VEGFi plus IL8i
- VEGFi plus anti-DC105 (endoglin)
- PI3K
- Torc1/Tor2
- Cdk4/6



- specific histone methyl transferases,
- histone methyl demethylases

targeting histone methylation

- EZH2 is drugable
- MEN1 is part of an H3K4 methyltransferase complex
- loss of RBP2 is protective in MEN-1 defective pancreatic islet cell tumor model

If I had a magic wand, I would target HIF2alpha (not druggable), but Kevin Gardner at UTSW has found a pocket, an internal cavity in HIF-2 which might make it druggable after all.

Excuses preventing better clinical trials that address specific hypotheses:

- "...but this is the trial the company will let us do"
- "...our patients won't let us do that."

A clinical trial is a clinical experiment. We need tissue to verify the action of the drug. It takes work and good communication skills.

Q&A Preclinical models will be important
VHL does more than HIF. What about the other branches?
If you turn off HIF2alpha you would be well on your way to inhibiting tumor growth.
Many of the other pathways are not so easily druggable.

Emerging Therapeutic approaches

Experimental Immunotherapy, Vaccine Strategies
Dr. Robert A. Figlin (Cedars Sinai, Los Angeles)

immune system plays an imporant role in controlling tumor growth: suppressor cells, tumor escape, microenvironment are all mechanisms which contribute to immune suppression

dendritic cell approaches: ideal T-cell peptide target should be present on the tumor; you get a better immune response with more T-cells. There is a trial of regulatory T-cells to alter the regulation of T-cells, consisting of 17 vaccinations over 9 months. A reduction in absolute Treg levels is induced by single dose.

IMA901 RCC Phase II trial shows a survival benefit. Myeloid-derived suppressor cells are measured. MDSC4 and 5 correlate with overall survival

Sunitinib inhibits immunosuppressive cell populations clinically. IMA901 plus GM-CSF + sutent, vaccination phase 4 months, follow up for PFS every 12 weeks, to a maximum of 19 months, and then every 3 months for up to 8 years.

AGS-003 fully personalized immunotherapy, RNA-loaded dendritic cell immunotherapy, provides all 3 signals required for adaptive immune response.

- intracellular activity
- not all VEGF-TKIs are created equal: Sunitinib
- reduces MDSC's
- Imroves Th1 response
- diminishes Treg function
- 21% intermediate prognosis, 8% poor prognosis, OS 30 months

ADAPT trial, opening at 60 centers across the US,

- RCC with medium to poor prognosis, presenting with mets, vaccination vs Sutent alone
- standard of care is the 42 months length of study

Conclusion: Novel vaccine strategies, when combined with tumor mocroenvironment modifiers (e.g. Sunitinib), may lead to new treatment options for both levels of risk and may become the international standard of care.

PD-1/PD-L1 Blockade
David F. McDermott, M.D. (Beth Israel Deaconess, Boston)

Immunotherapy is important and we need to work on improving immune responsiveness and to improve responsiveness through possible potential combination therapies. we need to implement even earlier therapy focusing on the immune response. We are looking at the PD1 antibodies in combination with dendritic cell vaccines which makes sense. Perhaps most important is patient education and selection: how do we find them early so they can get the full benefit of immunotherapy?

Co-stimulation of immune checkpoints, with required positive and negative signals can block CTLA-4 in melanoma, the first drug that has improved survival in melanoma. Less toxic than IL-2, it still has toxicity, but impacts the tail of the curve, in remission for years after therapy.

They designed a study to investigate the clinical activity and safety of anti-programmed Death (PD-1) (BMS-936558/MDX-1106/ONO-4538). The study design included outpatient injections every 2 weeks, could come off if confirmed Complete Response (CR).

Baseline for RCC patients, 34 patients, 40% of whom had received 3 or more prior therapies, for a total of 304 patients in multiple cancers. Key safety results: discontinuation in only 6% of patients, 3 treatment-related deaths (2 lung, 1 colon).

This drug is more active in humans than in mice: 10 major responders, 9 stable disease >24 weeks, 3 with disease progression. Those who continued on treatment, eventually became responders. RECIST criteria may not be the best measurement of response in this method of treatment.

He showed a chart showing the shifting of the treatment paradigm in RCC. Several had response at 6 weeks, 140 weeks, and there may even have been some complete remissions. Partial regression of mRCC

- poorly differentiated kidney tumor, near complete response, still quiet after 3 years
- PD-1 manageable side effects
- anti-tumor response observed in RCC patients, new trials in biomarker, dose finding, combination with pazopanib and sunitinib
- management requires a multi-disciplinary team, inclujding a rheumatologist

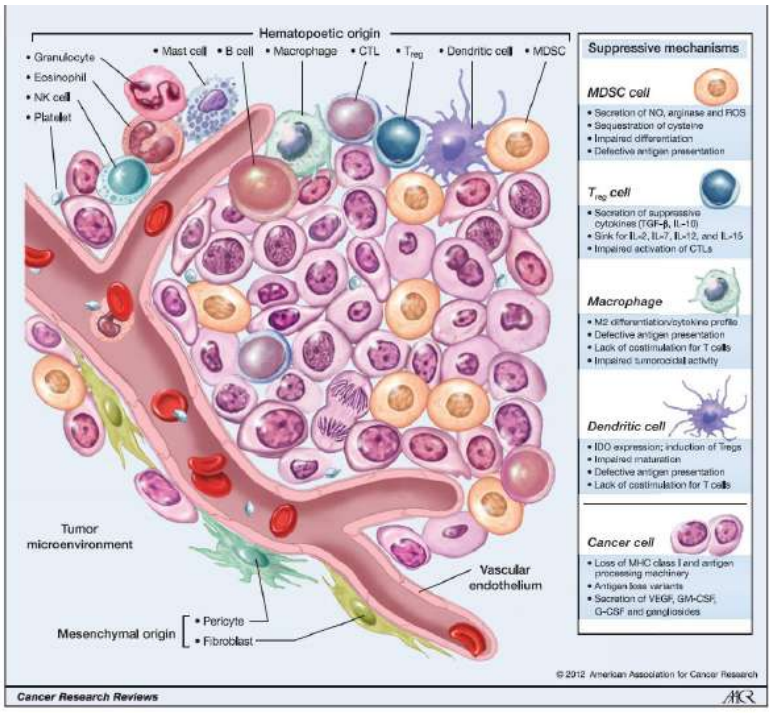
No tumor type is responding better than RCC. Toxicity seems manageable, combinations may be possible. Biomarkers PDF-L1/L3 might predict for a response to IL-1 and are more likely to respond to IL-2. Negative immune regulators preventing the immune system from attacking, “inflamed phenotypes.”

There is a Phase III trial going on now, hoping to move this agent into the first line as quickly as possible. Consider adjuvant therapy. Many PD-L1 pathway agents are in development.

Role of Tumor Microenvironment in RCC
James H. Finke, M.D. Cleveland Clinic

PDL-1 (B7-H1) expession by RCC and its suppression of T cell function. They modified the tumor microenvironment through the use of Sunitinib.

In mouse models, using the melanoma vaccine, the combination is much more robust. The combination improved the T cell response.



Cellular Constituents of Immune Escape within the Tumor Microenvironment
Kerkar SP, Restifo NP.
Cancer Res. 2012 Jul 1;72(13):3125-30. Epub 2012 Jun 21. Review

Clinical trials with sunitinib plus immunotherapy are going on now under the aegis of Argos, Immatics Biotechnology.

In sum: Tumors are composed of both malignant and non-malignant cells that promote tumor growth and block immune destruction. The different histological sites all have similar immune characteristics

AT ANY TIME, THERE MAY BE DOZENS OF CLINICAL TRIALS FOR KIDNEY CANCER.

You or your doctor can get a list of current clinical trials by calling 1-800-4-CANCER, or you may look at descriptions of clinical trials at the National Cancer Institute website, www.cancer.gov.

The Kidney Cancer Association website **www.kidneycancer.org** offers a free service that will connect you with various other websites offering information about clinical trials. The lists provide a description of each trial, the eligibility criteria, and the name, address, and phone number of the doctor conducting the clinical trial. To find out about a specific trial, have your doctor contact the doctor or nurse conducting the trial – or you may call the study site directly.

Immune Checkpoint Inhibitors, Biomarker Development, Rational Combinations, Charles Drake, M.D., Ph. D., (Johns Hopkins)

Why immunotherapy? mRCC presents an array of diverse and moving targets – phylogenetic relationships of tumor regimens. Can the immune system hit the target(s)? – yes

In the most current trials, there have been 2 complete responses, colorectal cancer, 3 doses, watched 2 years, brain lesion, and there is still response.

Interaction between the T-cells and the tumor cells is important. T-cell needs 2 signals: B7-CD28 normally, but in tumors this is hijacked. Anti-tumor activity results in -itis's (inflammation). Other activity turns off the action of apoptoses.

Not all tumors express PD-L1 -- >5% for membrane expression of PD-L1. Lack of PD-L1 expression correlates with lack of response to PD-1 blockade. Some T-cells recognize tumor cells, upregulated PD-L1, turned off T-cells.

Orthotopic RENCA model is hypoxic, gets a nice combined treatment effect. Inside the tumor,

- IL-2 + CD4 in DLN
- IFN+ CD8 in DLN

Combinations are synergistic. They looked for transcriptional targets that are upregulated in PD-1. PD-1 and LAG-3 are co-expressed on tumor infiltrating lymphocytes. PD-1 is the dominant checkpoint. LAG-3 doesn't cure anything. The combination is synergistic.

Future of Medical Therapy for RCC

Dr. MIchael Atkins (Georgetown Comprehensive Cancer Center)

The following chart summarizes recommendations based on papers published 2006-2008, and is the current standard of care:

Current Standards for Clear Cell RCC Therapy			
Setting		**Phase III**	**Alternative**
1st-line Therapy	good or intermediate risk*	sunitinib	HD IL-2
		bevacizumab + IFNalpha Pazopanib	
	Poor risk*	Temsirolimus	Sunitinib
2nd-line Therapy	Prior cytokine	Sorafenib Pazopanib	Sunitinib or Bevacizumab
	Prior VEGFR inhibitor	Everolimus Axitinib	Clinical Trials

*MSKCC risk status

The PISCES and COMPARZ trials showed that Pazopanib was preferred by patients over Sunitinib. However the therapeutic results of the two agents were very similar, and half the patients on each agent required dose reductions due to side effects. 20% (Sunitinib) and 24% (Pazopanib) of the participants had to discontinue therapy due to serious adverse effects.

By contrast, in the Tivozanib trial, only 12% of patients needed dose reductions, and 4% discontinued therapy. The most commonly reported side effects of Tivozanib were: high blood pressure (44%), diarrhea (22%), dysphonia (voice problems, 21%), fatigue (18%), weight loss (17%), all of which were mild (grade 1 or 2). The most commonly reported side effects reported for Sorafenib were: hand/foot syndrome (54%), of which high blood pressure (34%), diarrhea (32%), hair loss (21%), and weight loss (17%). Hand/foot syndrome was particularly annoying.

We understand that hypertension seems to be a biomarker for action of drug, but it is still hard to manage. Careful management of hypertension is essential to maintain health. Treating hypertension does not affect the effectiveness of the drug.

Axitinib study – will titration help? – the plan is yes.

VEGF pathway inhibitors have a diverse spectrum of biochemical, clinical, and toxic effects. Axitinib and Tivozanib appear to be “cleaner” drugs, and therefore exhibit a greater therapeutic index than currenty approved first-line agents.

mTOR inhibitors help some patients more. We should limit the use of mTOR inhibitors to patients whose tumors are driven by mTOR pathway

Combination therapy? Neither vertical blockade (too toxic) nor horizontal blockade (sequence or combination) are significantly better than single agent anti-VEGF therapy. We should aim to combine agents inhibiting processes involved with resistance (IL-8, Met, Ang2, Alk1, HIF2, maintenance of P53) OR blocking secondary molecular changes

Novel immunotherapy: PD1 antibodies show high response rates and durable responses in patients. How do we enhance the efficacy of PD1 directed therapy? Patient selection (those who have tumors expressing PDL1)

Combination with other immunotherapies (IL-2, ipilimuab, lag-3, etc) OR combination with anti-VEGF therapy

How do we move these treatments to the first line?

Vision of the future:

- treatment more personalized
- immunotherapy first
- VEGF therapy is driven by therapeutics
- smaller trials to show benefit

Atkins proposed a new RCC Therapy Algorithm for 2012:

RCC Therapy Algorithm: 2012		
Setting	**Tumor Markers**	**Treatment choice**
1st-line therapy	PDL1 expression	Anti-PD1 based therapy
	PDL1 - /VHL null, BAP-1 WT	Selective VEGF inhibitor
	PDL1- /VHL null, BAP-1 mutant	VEGF inhibitor + agent "X"
	mTOR activation, high LDF	TOR inhibitor
	Other mutation	specific inhibitor
2nd-line therapy	Not necessary	

Refs: Future leaders of RCC investigation

- If there is a BAP-1 or other mutation, use an inhibitor that is specific.
- 2nd line therapy – not needed

How do we get from here to there?

- translational research
- teamwork
- courage

Group discussion

Blocking IL-8 would reduce your ability to fight off infection. Keeping the neutrophils out of tumors might be a good thing. Need to do small trials for proof of concept.

Editorial Addenda:

A Closing Note for Consideration: by Michael B. Lawing

Gap Between Urologist and Survivor Perceptions ?

Tips for Survivors and Caregivers

Interesting statistics were released in the American Association for Cancer Research *Cancer Progress Report* earlier this year. The report states that in 2012 there will be approximately 13.7 million cancer survivors in the United States; that is a drastic increase in survivors from the 3 million in 1971 when the US Congress passed the National Cancer Act.

In 2005 a report was issued by the Institute of Medicine of the National Academies entitled *From Cancer Patient to Cancer Survivor: Lost in Transition*. This landmark report suggested that dialogue be established between cancer survivors and their medical teams. Among other things a general discussion of survivorship, quality of life issues, and similar items were recommended. In addition to those recommendations palliative care was defined as "treatment of symptoms associated with the effects of cancer and its treatment;" palliative care as well as end-of-life discussions were also encouraged in this report. A link to an online video on this topic by the Institute of Medicine is at the end of this article. In addition to an increase in the number of cancer survivors the length of survivorship is increasing as well. The AACR estimates that 64% of today's survivors were diagnosed with cancer five or more years ago and some 15% were diagnosed 20 or more years ago. Fully 50% of the current survivor population is 70 years or older in age and only 5% of survivors are younger than 40.

Because of these facts it may be appropriate to revisit some of the material contained in the presentation, *Collaborating to Improve Survivorship Care* by Dr. Michael A. S. Jewett of Princess Margaret Cancer Centere, The University of Toronto, Canada. Dr. Jewett presented a slide in his presentation that listed the Institute of Medicine recommendations to healthcare providers from the 2005 report. He also presented material based on a Kidney Cancer Survivorship Survey entitled *Gap between Urologist and Survivor Perceptions* which was conducted by Kidney Cancer Canada. This material had been presented as an unmoderated poster during the 67th Annual Meeting of the Canadian Urological Association earlier this year. Data was obtained through comparable online surveys that were sent to patients/ caregivers and also to urologists. The surveys were available throughout Canada; 40 urologists, 276 kidney cancer patients and 45 caregivers of kidney cancer patients responded. The patients and caregivers that responded had been diagnosed from stage I to stage III of the disease. As a result of this relatively small sampling that indicated a gap between the perceptions of Canadian urologists and of the survivor /caregivers, both groups are seeking to find ways to support the development of a kidney cancer survivorship care plan that will assist in alleviating the differences noted. Some of the information in Dr. Jewett's presentation follows:

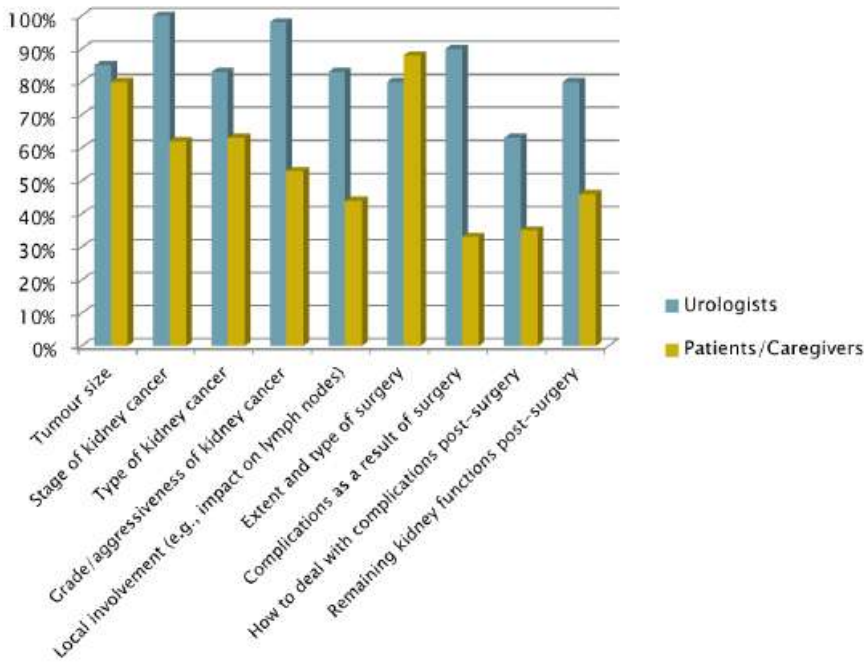
1. Patients Desire More Information Post-Surgery

- Most urologists indicate they provide their patients with detailed and clear information about their kidney cancer following surgery
- Patients/caregivers wish their urologist gave them more detailed information (i.e. pathology report, surgery report etc.).

On this question 73% of the doctors that responded strongly agreed they gave their patients clear information whereas 38% of the patients strongly agreed and 22% somewhat agreed that they wished for more clear information about their kidney cancer after surgery.
36% the patients strongly agreed that they should have had more detailed information from the pathology etc. and 22% somewhat agreed; 68% of the doctors stated they provided detailed information.

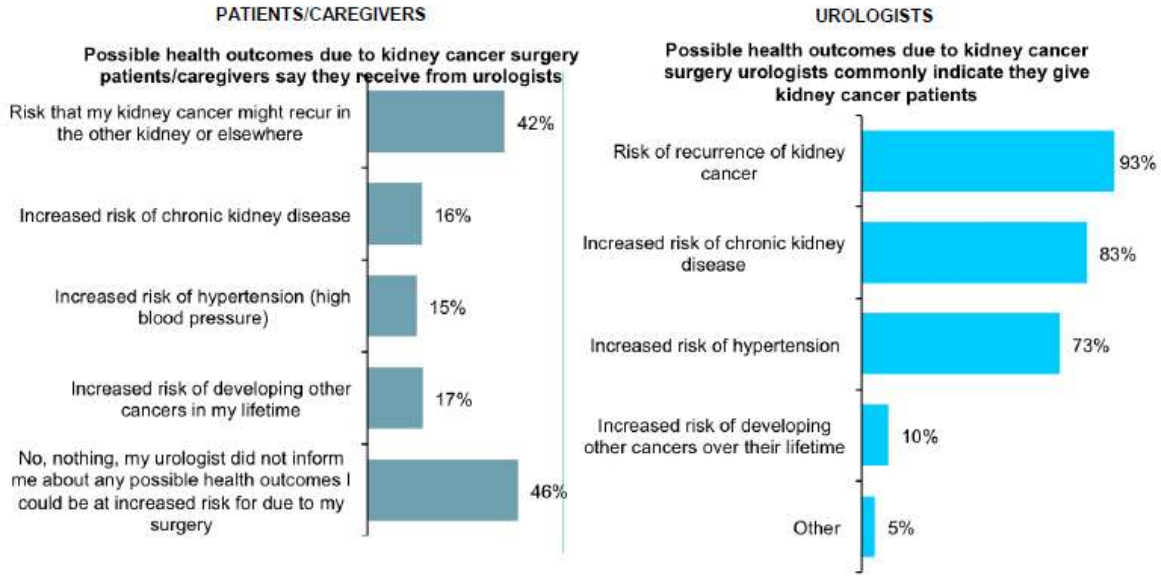
2. Disconnect Between Information Given by Urologist/Recalled by Patient

- Urologists and kidney cancer patients/caregivers do not agree on what cancer details and survivorship information are given post-surgery.



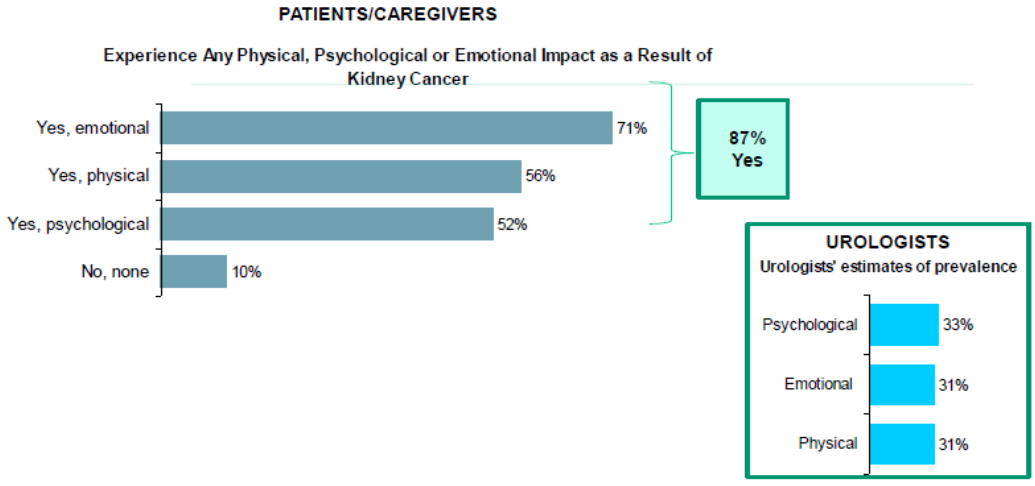
3. Patients Do Not Recall Information on Late-Term Effects

- There is also discordance between urologists and kidney cancer patients/caregivers perceptions of what information is provided about possible health outcomes due to kidney cancer surgery.



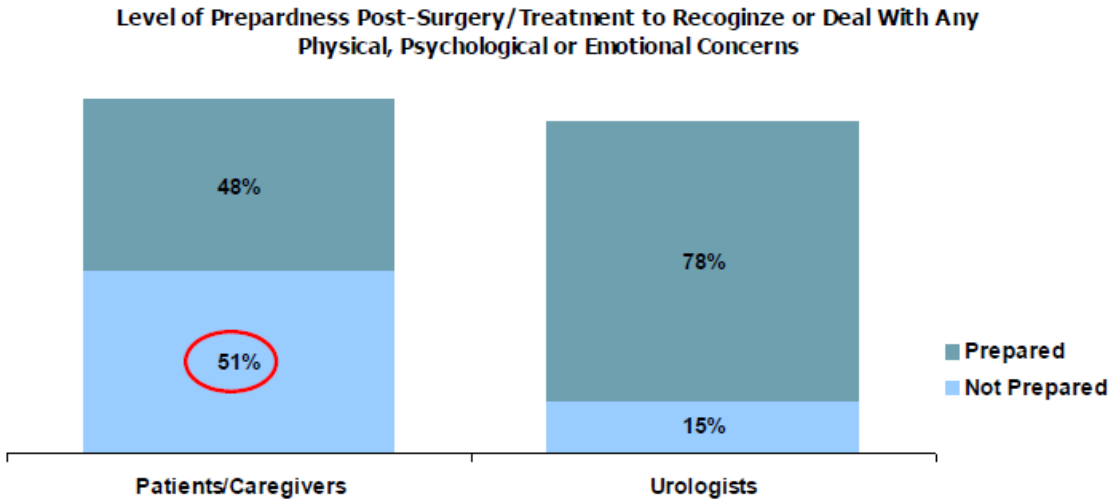
5. Patients Experience Significant Emotional/Physical/Psychological Effects

- The majority of patients/caregivers indicated that the patient was dealing with emotional, physical, and psychological impacts as a result of their experience with kidney cancer. Interestingly, urologists may be underestimating the prevalence of these issues among patients.



6. Patients Not Prepared for Post-Surgery Concerns

- Half of those affected by kidney cancer say they were *not prepared* after their surgery/treatment to recognize or deal with any physical, psychological or emotional concerns.
- However, most urologists believe their patients feel prepared post-surgery to recognize or deal with these concerns.



It should go without saying that the surveys listed above are from a very small group of individuals with no control as to how many are patients of any particular care facility or how large a practice the urologists have. Nevertheless the disconnect between what the patients and the doctors perceive appears to be significant.
When considering the comments made by Dr. Porta of the Pisces trial and take-home messages the surveys take on additional significance. Portis said of the Pisces trial the main message in his mind was the discrepancy between the physicians and the patient's perception of adverse events.

In these presentation notes we have attempted to list some of the information that was presented in such a way as to be beneficial to cancer patients, caregivers, and families and friends affected by this disease. It is imperative that all of us as survivors seek to learn the basic survival skills in dealing with cancer. They include as much as possible a healthy diet, adequate exercise and rest, the ability to be as free of stress as possible; often becoming involved in support groups that are conducive to deriving the most from life that is possible. Another essential skill that is so important is the ability to communicate and to record significant and pertinent information from your medical care team. Overcoming the reluctance to ask questions, to tell of fears, concerns, side effects, pain, and other issues can have a significant positive impact on survivorship. ML