

10th International Kidney Cancer Symposium Chicago, October 14-15, 2011

Reporting by Joyce Wilcox Graff, Director of Wellness, VHL Family Alliance

Foreword:

As ever, the Kidney Cancer Symposium is stimulating and educational.

While we are always impatient with the speed of progress, it is amazing how far we have come in a short time. Progress is astounding. Ten years ago the standard of care was open radical nephrectomy. Five years ago we were moving toward partial nephrectomy but still had only IL-2. Today we have kinder, gentler surgical approaches and a growing selection of new drugs, though we are still learning how to apply them most beneficially. Imagine what the next five years will bring!

People with early stage tumors are recovering from treatment and living full lives. People with later-stage tumors have a much more difficult course of treatment and a much less certain future. One major component of lessening the suffering and death from kidney cancer is learning how to find kidney cancer at earlier stages. Still today most kidney cancer tumors are found after they become symptomatic and metastatic, though there is a rising number of “incidental findings” of earlier stage tumors. This is certainly fortuitous, but it would be even better if there were biomarkers to identify the presence of cancer and the need for follow-up screening during a routine doctor’s visit.

I appreciate the opportunity to hear this rich series of talks, and to report on the proceedings for the patients who were not able to attend. I will convey here my impression of the key points of the sessions I am reporting. Others will cover the remaining sessions.

Videos of the full talks are available on the KCA website. <http://www.kidneycancerassociation.org>

The complete agenda and slides from many presentations are available at:
<http://kca.omnibooksonline.com/chicago2011>

Contents

10 th International Kidney Cancer Symposium Chicago, October 14-15, 2011.....	1
Management of Small Renal Masses	4
Clinical Epidemiology of the small renal mass: contemporary trends and implications for patients, by David C. Miller MD (University of Michigan, Ann Arbor)	4
Case Presentation, by Dr. Samuel Klempner (Beth Israel Deaconess, Boston)	5
Ablation, by Dr. Thomas Atwell (Mayo Clinic)	5
Robert Uzzo (Fox Chase, Pennsylvania) argued for no treatment for this patient, but Active Surveillance instead.	6
Paul Russo (Memorial Sloan Kettering, New York) arguing for nephron-sparing surgery	6
Dr. Houston Thompson (Mayo Clinic): Ischemia time in Nephron Sparing Surgery.....	6
Robotics in RCC Surgery, Gennady Bratslavsky (SUNY Upstate Medical University, Syracuse)	7
Summary: Dr. Christopher Wood (MD Anderson Cancer Center, Houston)	8
Eugene P. Schoenfeld Memorial Lecture: Progress against Kidney Cancer: the best is yet to come, <i>by Robert Motzer (Memorial Sloan Kettering, New York)</i>	9
Young Investigator Award Presentations	11
A detailed structural and functional analysis of VHL mutations and their effects on hypoxia- inducible factor-alpha(HIF α) in sporadic ccRCC – Lucy Gossage, MD, Cancer Research UK, London	11
SETD2, a histone methyltransferase, is misregulated in advanced ccRcc, by Dr. Thai Ho, MDACC ...	12
Serum Proteomics classifies outcome in RCC patients receiving Sunitinib and Erlotinib, Kyle Robinson, MD, Oregon HSU	12
Impact of target therapy on overall survival in advanced RCC: a population based analysis of the national surveillance epidemiology and end results (SEER) registry database. – Herna Vakayala, MD, Wayne State Univ.....	13
Distinguished Lecture: Andrew C. Novick Memorial Lecture: Genetic Basis of Kidney Cancer: A metabolic disease, <i>by W. Marston Linehan, M.D. (Chief of Urology Oncology, U.S. National Cancer Institute, Bethesda)</i>	14
Future Strategies to Overcome Resistance, moderated by Michael Atkins (Beth Israel Deaconess Medical Center, Boston)	17
Mechanisms of Resistance to Renal Cell Carcinoma therapy, by Dan George (Duke University)	17
Current Strategies to overcome resistance, by Tom Hutson (Baylor Sammons Cancer Center, Dallas)	18

Novel Immunotherapies: David McDermott (Beth Israel Deaconess Medical Center, Boston)..... 19

Novel Angiogenesis inhibitors, by Gary Hudes (Fox Chase Cancer Center, Philadelphia) 19

Intermittent VEGF inhibition: rationale and current data, by Viktor Gruenwald (Hannover Medical School, Hannover, Germany) 20

Novel P13K/TOR pathway inhibitors, by Dan Cho (Dana Farber/Harvard Cancer Center, Boston) ... 21

Novel combinations, by Roberto Pilli (Roswell Park Cancer Institute, Buffalo, NY) 21

Summary, by Michael Atkins..... 21

Discussion: 22

Management of Small Renal Masses

Dr. Christopher Wood (MD Anderson Cancer Center, Houston) filled in for Dr. Leibovich. He began by asking everyone to take a moment of silence in honor of the passing of Dr. Horst Paul Zincke, 1937-2011, former Chief of Urology at the Mayo Clinic, who recently passed away. He described Dr. Zincke as “one of the legendary figures in our field.”

Dr. Wood presented a case study, a 54-year-old woman with vague abdominal complaints. CT of chest and bone scan were negative, other tests were “unremarkable”. Imaging found a mass on her right kidney. How would you manage this patient?

The series of presenters in this section of the program presented possible therapeutic options for a patient like this one with a small renal mass. The audience was asked to decide how best to treat her.

Clinical Epidemiology of the small renal mass: contemporary trends and implications for patients, by David C. Miller MD (University of Michigan, Ann Arbor).

Dr. Miller defined a “small renal mass” (SRM) as one less than 4 cm. While 80% are malignant, 60% are confined to the kidney. 50-60% of all kidney tumors fall into this category. The incidence of such tumors has been rising over the last two decades.

58% of these patients have pre-existing high blood pressure, 60% have diabetes, both significant risk factors for kidney cancer. Mortality (risk of death) may be increasing for patients with tumors confined to the kidney. He focused the discussion on the following goal:

How can we reduce death and suffering for patients with small renal masses (SRM)? He outlined four primary tasks:

- Distinguish more precisely those pts who actually need treatment
- Reduce treatment-related morbidity and mortality
- Develop better treatments for patients whose tumors progress despite local therapy
- Improve palliative care for patients with incurable disease

In earlier times, one would have removed the entire kidney with Open Radical Nephrectomy. In most cases, this would fix the problem. It is an operation which can be performed competently by most urologists, even in small practices, and it is cost-effective.

So why would we move away from open radical nephrectomy? We have learned that for best quality of life, it is best to preserve as much healthy kidney tissue; reduce the pain and risk associated with incisions; shorten hospital stays (to lessen cost and risk of infection), and provide easier recovery. If it is possible to fix the problem without open surgery, then we should look at those alternatives.

In fact we have been moving away from open nephrectomy toward partial nephrectomy, and toward increased use of laparoscopic treatment. By 2005 at least 50% of urologists in the United States had performed at least one laparoscopic procedure.

Have the benefits been realized? Have there been any unintended consequences?

In a recent population-level comparative effectiveness of laparoscopic vs open radical nephrectomy compares ICU admission, prolonged length of stay (LOS), and hospital readmission, laparoscopic surgery does have better recovery, but also paradoxically has a higher in-hospital mortality. (Tan et al, Cancer, 2011) When correlated with “surgeon volume,” there are no differences in the open radical data, but distinct differences in laparoscopic outcomes. It is clear that the experience level of the surgeon performing a laparoscopic procedure is key to a successful outcome.

Dr. Miller is concerned about the risks involved in introducing other complex new surgical technologies. How are we going to train physicians in the proper use of these technologies, and in the management of complications that can arise?

For patients, it will be important to choose a center and a surgeon with a strong track record of successful laparoscopic partial nephrectomies. In some hands an uncomplicated radical nephrectomy may be a better choice than a partial nephrectomy.

Case Presentation, by Dr. Samuel Klempner (Beth Israel Deaconess, Boston)

Dr. Klempner presented a 65 year-old man with an enlarging renal mass (2.3 x 3.3 cm). Three years before this mass was only 10mm. Should this man be treated with open or laparoscopic partial nephrectomy? or simply watched? or treated with radio frequency ablation (RFA) or cryoablation (cryo)?

This patient chose laparoscopic partial adrenalectomy. Once removed, the tumor measured 2.3 x 2.1 x 1.6 cm with negative margins.

Ablation, by Dr. Thomas Atwell (Mayo Clinic)

Dr. Atwell discussed the pros and cons of Radio Frequency Ablation versus Cryoablation. Both are minimally invasive procedures with potential benefits for patients. Because they can be performed through 2 or three small slits in the abdomen, rather than the broad incision required for open surgery, they offer less incision to heal, less risk of infection, quicker recovery, and fewer adhesions. However each one has limitations that need to be carefully considered as well.

The AUA guidelines (2009) for use of RFA call for evaluation of

- Size, and potential risk of metastasis
- Position:
- care must be taken to protect the ureter. prevent provoking an adrenal crisis, and ensure adequate space between the bowel and the ablation field, to prevent injury to the bowel
- Tumors on the outer edges of the kidney do well, but central tumors are less successful because of the risk of damage to the veins or collection system.
- There are also risks of injury to nerves which may cause post-treatment pain, and there is a small risk of bleeding.

RFA can usually be done quickly (8-10 minutes of heat to the tumor), but it does not treat large tumors effectively and cannot be tracked with imaging during the procedure as easily as cryo

RFA is easy to use, fast (8-10 min of thermal), but unable to treat large tumors effectively and can't track with imaging as we can with cryo. Tumors larger than 3 cm should not be treated with RFA.

Cryoablation is effective in dealing with larger tumors due to the combined use of multiple probes. Nonetheless it has risks of its own:

- bleeding, longer time to treat
- durability of results are less than with RFA
- higher rate of complications in patients who were not well
- central tumors 92-97% success vs 60-81% success with RFA

These ablative techniques are particularly interesting for people who have additional complications or who are older or less healthy.

Robert Uzzo (Fox Chase, Pennsylvania) argued for no treatment for this patient, but Active Surveillance instead.

Dr. Uzzo and his colleagues at Fox Chase have assembled a "nomogram" or computerized calculation of risk factors to help them determine the best method of treatment for a patient. They evaluate pathology, patient age and wellness, and the likelihood that this tumor may be slow or fast growing. How soon might this tumor become metastatic? Given his age, we would expect him to live another 10-12 years. At this rate, his risk of dying of something other than RCC is 80%.

Similarly, the treatments themselves carry risks. In this type of patient there is a 36% risk of complications, 25% of them minor and 11% of them major.

The 5 year mortality from this cancer is 55, and 30% from other causes.

On balance, Dr. Uzzo would recommend Active Surveillance for one year, after which he would only treat the tumor if it were growing.

See his predictive tool at <http://cancernomograms.com>

Paul Russo (Memorial Sloan Kettering, New York) arguing for nephron-sparing surgery

Dr. Russo noted that both RFA and cryoablation result in considerable scarring which makes subsequent surgeries more challenging. In a patient where we anticipate we may need to do additional surgeries in future, ablation is less desirable.

Partial nephrectomies have more complications than open radical nephrectomies. As long as the right level of surgical experience and expertise are available, partial nephrectomy offers easier recovery to the patient. Dr. Russo recommends partial nephrectomy for tumors under 7 cm, and larger if they are technically feasible. The technique is less important than the safety of the patient.

Dr. Houston Thompson (Mayo Clinic): Ischemia time in Nephron Sparing Surgery

We used to believe that a kidney could be safely clamped for up to 55 minutes, shutting off the blood supply to the kidney to reduce blood loss during the surgery. Clamping also means that the cells of the

kidney are not receiving the oxygen they require to live and reproduce successfully. This artificial reduction in oxygen to the cells of the kidney is known as “ischemia”, and duration of clamping is known as “ischemia time”).

Mayo and Cleveland clinic pooled their patients and looked at people with only one kidney to evaluate what impact this period of ischemia might have on kidney function:

They reviewed the cases of 362 patients with ischemia time greater than 20 minutes, looking for:

- acute renal failure
- new onset stage IV chronic kidney disease during follow-up median 1.6 months
- each minute increase in warm ischemia increased risk of failure for 5%, GFR <15 odds
- acute renal failure: optimal <25 min
- acute GFR: optimal <25 min
- new onset chronic kidney disease: optimal <25 min

Compared with patients with no ischemia, the odds of these serious complications was many times greater. Patients with ischemia time greater than 20 minutes were

- 3 times more likely to have acute renal failure
- 6 times more likely to have acute GFR
- 3 times more likely to have new onset chronic kidney disease

See their published paper, “Every Minute Counts”

No ischemia preserves renal function better than warm ischemia or cold ischemia

kidney quality and quantity are strongly associated with ultimate renal function

keeping warm ischemia <20-25 min improves short- and long-term renal function

In summary, quantity, quality, and quickness of resection are the most important in preserving renal function.

Robotics in RCC Surgery, Gennady Bratslavsky (SUNY Upstate Medical University, Syracuse)

Dr. Bratslavsky posed the question: Is there a future for robotics in partial nephrectomy?

There are now 300 articles in PubMed evaluating the use of robotics, especially in the management of small renal masses, particularly when multifocal or genetic. Partial nephrectomy helps to preserve renal function, and loss of renal function increases the odds of mortality. Robotic surgery results in significantly less pain, blood loss, risk of infection, etc.

Comparing robotic to laparoscopic surgery, both are preferable to open surgery where possible. The size and location of the tumor will be major factors in choosing the technology to use. Both will give similar margins and will help to preserve renal function.

Patient selection is the key. Warm ischemia is still a concern. People who are likely to have multiple surgeries will benefit most from robotic surgery. He joked that performing robotic surgery without clamping calls for “a stress test before surgery for both the surgeon and the patient” and showed a video to demonstrate the bleeding during surgery that this implies. It is important to have an able assistant clearing the visual field, and to be prepared to replace at least five pints of blood.

Summary: Dr. Christopher Wood (MD Anderson Cancer Center, Houston)

In 2000, most patients received open radical nephrectomy. In 2011, most patients receive partial nephrectomy. Our goals are

1. to take care of the cancer
2. to spare as many healthy nephrons as possible
3. to use a minimally or non-invasive technique if possible

He asked the audience to vote on which technique to use for a 60 year old woman with a 3 centimeter tumor, and then discussed the choices with members of the panel:

1. Partial Nephrectomy. She is relatively young (60) and the tumor has been there for 10 years. As the tumor grows, even if it is benign it could destroy the kidney. There are complications, but she is young and healthy so her risk factors are low.
2. Active Surveillance is not a good strategy with potentially 30 years life expectancy. There is uncertainty in biopsy, as there is so much variation within the tumor, so he would be unwilling to take that chance in a young patient. Biology may also change over time. Better to do a partial nephrectomy, preferably robotically.
3. If the patient were 84, would Dr. Uzzo use biopsy? Uzzo replied that did a partial nephrectomy on an 84-year-old last week on whom he did not do a biopsy.
4. Is there a role for ablation? At her young age, ablation is not a good option. If she were older or with co-morbidities, he would have used RFA
5. Bratslavsky would not remove all these healthy nephrons. Would do Partial Nephrectomy with clamp open.

There was a question about biopsy: is there not a danger of “seeding” or spreading the cancer through the needle track? This has been a question for a long time, but there is only one documented case of seeding in the wall and that was in a patient with a recurrent ccRCC. It is felt that seeding is not an issue.

In surgeries following ablation, what is the success of Partial Nephrectomy? Often people are referred for ablation because it's a difficult partial. Ablation often costs more nephrons than Partial Nephrectomy. We have not yet proved that ablation has changed the biology of the tumor and truly disabled the cancer. Ablation is now used for fewer and fewer tumors.

Dr. Russo noted that in the last 15 yrs, BMI has drifted upward and GFR downward in the general population. The population is sicker. There is some driving carcinogenic element that we do not yet understand.

There was a question about a European study that concluded that partial nephrectomy was not as effective in long-term control as radical nephrectomy. The panel pointed out that the patients were accrued for that study 1990-2002, when partial nephrectomy was very early and not widely used. The fact that there is 9 year follow-up data and 400 patients is good data, but is to a certain extent historical, not current. The panel believes that if that same study were done using patients accrued in the following decade, the outcome would have been very different.

Eugene P. Schoenfeld Memorial Lecture: Progress against Kidney Cancer: the best is yet to come, by Robert Motzer (*Memorial Sloan Kettering, New York*)

We have made a great deal of progress in kidney cancer, and there are many choices of surgical and chemical treatment. Many trials have completed accrual, and are awaiting completion of the data and analysis. Meanwhile we are faced every day with treatment challenges:

- What is the optimal first-line treatment?
- What is the best sequence of agents?
- What about combinations of agents?
- How do the targeted agents integrate with surgery? (before or after surgery?)

There are a number of trials going on to evaluate the use of adjuvant therapy with drugs given before surgery in an effort to control and shrink the tumor, making it more amenable to successful surgery. It is an exciting prospect. However, we must remember that to date:

- There are few complete responses
- Continued treatment required
- Disease resistance develops
- There is always the issue of refractory patients – what to do when the drug simply does not work for this patient?

He described three such cases to stimulate thinking:

Case 1 – A 47-year-old man who came in for a persistent cough. On scans he had a large kidney tumor and metastatic disease. He died within three months.

Case 2 – A 41-year-old man who came in with abdominal pain. A CT showed a 20cm right renal mass. Pathology revealed it to be sarcomatoid carcinoma, chromophobe, very aggressive. Chromophobe tumors are usually indolent, but with sarcomatoid features it can be very aggressive. They tried two drugs, no response, the patient died within six months.

Case 3 – A 51-year-old woman with unclassified RCC and a KPS of 70. After 4 weeks on temsirolimus the disease continued to progress; after another 4 weeks on bevacizumab the disease continued to progress; she died after 6 months.

The Kidney Cancer Association gathered a Think Tank of young investigators for a one-day retreat to consider the question: “Now it is time to reassess our research future – what should our focus be? Dr.

Motzer chaired the retreat. The senior investigators were Eric Jonasch (MDACC), David McDermott (DFHCC), James McKiernan, and James Hsieh (MSKCC)

Young investigators included among others Haifeng Yang, Dan Cho, Toni Choueiri, and Gennady Bratslavsky.

They considered three categories: surgery, advanced disease, and translational research

There were Five questions for discussion:

What are the most important kidney cancer research accomplishments in the last 10 years?

- Defining RCC subtypes
- nephron-sparing surgery and minimally invasive
- discovery of role of VHL gene and therapeutic targets
- Improved patient outcomes

What are the major unmet needs in RCC treatment and research?

- Non-ccRcc management
- role of biopsy of renal masses
- partial vs radical
- predictive ability to determine best treatment
- new drug categories
- integration of surgery and systemic therapy

What should our research priorities be?

- Define risk factors and screening for RCC
- develop pt-selection models for surgery and med therapy using tumor-specific biomarkers
- identify novel targets and therapies
- establish a central multi-center tissue bank

What resources will we need?

- funding
- organized data-collection strategy within kidney cancer community
- national tumor registry
- clinical trials consortium
- integration efforts between academia, industry, government and clinicians

What role should the KCA play in the future of kidney cancer research?

- Encourage patient participation in clinical trials
- lead effort toward a national tissue collection strategy

- . %%
- .

next steps:

- publicize findings of this symposium – KCA website and distribution
- begin discussions among potential partner organizations on feasibility of:
- funding opportunities
- multi-center collaboration
- tumor registry

The retreat was sponsored by:

- Gavin Anderson, former board member
- William Perry, former board member

organized by Carolyn Konosky

Paul Larson, documentation and writing

Dr. Motzer hopes that we will all review the findings of the retreat and help to realize its goals. He left us with these three reminders:

- Perspective
- Unmet need
- The future

Young Investigator Award Presentations

Dr. Bukowski chaired four presentations by awardees of the KCA Young Investigator Awards

A detailed structural and functional analysis of VHL mutations and their effects on hypoxia-inducible factor-alpha(HIF α) in sporadic ccRCC – Lucy Gossage, MD, Cancer Research UK, London

VHL is a multifunctional protein. Missense mutations (30%) are distributed throughout the VHL gene. There is currently no way to predict their behavior. VHL plays a role in angiogenesis and glucose uptake and other non-HIF dependent functions less well understood.

RCC risk seems to correlate to the degree to which HIF is dysregulated.

- Half the mutations interfere with the ability of VHL to bind with elongin.
- Others interfere with HIF-alpha binding and/or degradation.
- Others disrupt interactions with other binding partners: e.g. cullin-2, p53

She set out to study the differential effects on the function of pVHL caused by the different mutations in the gene.

She performed in vitro biophysical experiments on wild-type and mutant pVHL, using 600 archived ccRCC samples to construct tissue microarrays, looking for mutations, promoters, methylation and change.

VHL alone is unstable, VHL+elongins is more stable. Wild-type (WT) pVHL degrades over about 40 minutes. Some mutants degrade more rapidly, others are more persistent. Stable mutants retain the ability to bind with HIF-1 α . Can the unstable mutants retain the ability to bind with HIF-1 α ? Stable vs unstable mutants have varying abilities to down-regulate Glut-1. WT pVHL downregulates VEGF α , different mutants have different capabilities in this.

Conclusions:

Most unstable mutants fail to downregulate Glut-1 and VEGF α to the same extent. There is a great deal more work to be done. There are many different mutations, and their methods of pathogenesis are quite different. Binding for HIF-1 α and HIF-2 α is the same binding pocket, but the two have different functions. HIF-2 α is thought to be the most important one in kidney cancer.

SETD2, a histone methyltransferase, is misregulated in advanced ccRcc, by Dr. Thai Ho, MDACC

Dr. Ho studied the role of epigenetics in ccRCC. Epigenetic mechanisms modify gene expression without altering DNA sequence.

Loss of VHL function alone is insufficient to promote tumorigenesis. A systematic sequencing of RCC reveals inactivation of histone modifying genes.

His hypothesis: Loss of SETD2 histone methyltransferase activity promotes tumorigenesis

SETD2 should reduce the methylation; is there decreased H3K36 trimethylation? He explored the frequency of SETD2 loss of heterozygosity (LOH) in advanced ccRCC. He found that LOH is an early event in the creation of a tumor. Advanced ccRCC tumors have decreased H3K36 trimethylation compared to adjacent unaffected kidney. LOH of chromosome 3p >> loss of SETD3 >> loss of pVHL

VHL, PBM1, and SETD2, all contribute to genetic stability. If all are knocked out a tumor grows.

Serum Proteomics classifies outcome in RCC patients receiving Sunitinib and Erlotinib, Kyle Robinson, MD, Oregon HSU

EGFR upregulation is associated with RCC proliferation. There is a Phase II study currently going on to study sunitinib and erlotinib, with 37 patients enrolled who have measurable disease and have had no prior treatment. So far, at 8 months, progression-free survival (PFS) = 95%.

He explored the utility of the Veristat serum proteomic assay in RCC patients. These patients were evaluated using the Veristat testing to stratify them into “good” or “poor” risk of PFS and overall survival (OS). 2/3 were classified as good, 1/3 as poor, and 1 was indeterminate. Those classified as “good” had average PFS=38.5 months, those classified as “poor” 11.6 months. Overall response was 66%. All 4 of the patients who had progressive disease had been classified as “poor”.

Only one sample was taken from each patient at pre-treatment. There could be much variability depending on when and how the blood was drawn, and how it was stored. It might also be helpful to take multiple samples at different periods during treatment.

Impact of target therapy on overall survival in advanced RCC: a population based analysis of the national surveillance epidemiology and end results (SEER) registry database. – Herna Vakayala, MD, Wayne State Univ.

Has targeted therapy made an impact on overall survival?

Dr. Vakayala studied the SEER database for deaths during since 1990 to compare the overall survival in the regional and distant RCC cases in the SEER registries across two different time frames:

- 2000-2003
- 2004-2008

Overall, from 1990 to 2006 there is only a 6.7% improvement in RCC survival.

Looking at age, race, nephrectomy status, and patient characteristics, there is very little change in the data in these two different time periods. Median survival improved by 5 months (5.6%); 3 yr survival rose from 13% to 16%.

Conclusions:

There is no statistically significant difference in age, race, or histology. Supportive care has not changed significantly. Nephrectomy continues to be an important determinant of OS in advanced kidney cancer

Improvement was predominantly see in non-AA population. It is not clear whether this is because of some difference in response to treatment, or access to care.

Patients with distant stage disease (metastasis) and those without nephrectomy appear not to have benefitted.

**Distinguished Lecture: Andrew C. Novick Memorial Lecture:
Genetic Basis of Kidney Cancer: A metabolic disease, by W. Marston Linehan,
M.D. (Chief of Urology Oncology, U.S. National Cancer Institute, Bethesda)**

Dr. Bukowski introduced Dr. Linehan as “most prominent urologist to date. In the past 20 years, Linehan and his group have described the multiple syndromes involved in RCC.”

Dr. Linehan remembered that Andrew Novick was passionate about his patients, “Whenever I operate on a patient,” he said, “Andy Novick is at my side”

“Genetic Basis of Kidney Cancer: A metabolic disease”

In the early 1980’s, we thought RCC was a single disease. Now we know RCC is a set of different diseases:

- Clear cell – the VHL gene
- papillary type 1 – the Met gene
- chromophobe and oncocytoma – the BHD gene
- papillary type 2 – the FH gene
- granular/clear – the SDHB gene

In our experience, RCC is primarily a metabolic disease.

We set out to find a kidney cancer gene, and found consistent loss of chromosome 3 in most tumors. Al Knudson suggested studying families to find the gene. He advised us to set up a hereditary kidney cancer program and used the power of genetics to trace genes in these families.

We have so far identified five types of inherited kidney cancer:

VHL – bilateral, multifocal, early stage kidney cancer, up to 600 tumors per kidney, and 1300 cysts

- 684 (now nearly 800) patients seen, some for more than 25 years
- For a tumor to grow from 0-2 cm may take 25 years. We do Active Surveillance until 3 cm, then surgery
- We have not had a single VHL patient develop mets using this approach
- We gathered samples from 4321 patients
- We mapped the gene to short arm of chromosome 3
- We published these results with Maher’s team in Cambridge, UK, as Latif et al, 1993
- We identified the alterations in all 161 families

We did find one family with an inherited translocation that we call the “3-hit model”.

Example: 52yo man with familial ccRCC, with a translocation from chromosome 3 to 8 – 3hit model, later onset disease:

- inherits the translocation

- loss of entire chromosome 8
- leaves one copy of VHL gene
- random mutation event to mutate the second copy of the VHL gene

It took us 10 years to find the VHL gene. Was this the gene for the common form of RCC? We found the VHL gene to be altered in a high number (88%) of sporadic RCC. When we first did this analysis we included all cell types. When we confined the search to clear cell RCC, we found that as many as 98% of ccRCC were altered. Thus we feel that it is safe to say that VHL is the clear cell kidney cancer gene.

VHL is a classic Knudson 2-hit gene. It combines with elongin-a and elongin-b. CULLIN-2 was found to be an additional component of the VHL complex by Arnim Pause. HIF α is targeted for degradation by pVHL in normoxic, but not in hypoxic cells. VHL is in essence an oxygen sensor.

If VHL is altered, then it cannot bind HIF and HIF accumulates in the cell. If the alteration is in the alpha domain it does not bind HIF; if in the beta domain, it does not bind with other elements.

Non-Clear Cell

Hereditary Papillary RCC (HPRC) autosomal dominant

- at risk of multiple tumors, always type 1 papillary, up to 1000 tumors per kidney
- when smaller than 3 cm, active surveillance, then surgery
- HGF or hepatocyte growth factor
- Clinical trial of Foretinib (dual MET and VEGFR inhibitor). The trial is recruiting sporadic type2 papillary, closed to accrual, analyzing the data

Birt-Hogg-Dube (BHD)

- cutaneous fibrofolliculomas, hair follicle tumors
- pulmonary cysts, 30% will have spontaneous pneumothorax
- Kidney cancer runs in these families, bilateral, multifocal, can metastasize
- various histologic types: oncocytomas, chromophobe, or hybrid oncocytic tumors
- up to 3000 chromophobe/hybrid oncocytic tumors per kidney
- identified the gene: short arm of chromosome 17, FLCN protein
- 175 families, detected mutation in 95% of families
- somatic mutations in tumors from a single BHD patient
- loss of function tumor-suppressor gene
- FLCN is in the LKB1/AMPK/mTORC1 pathway. This changed our entire thinking about kidney cancer. AMPK is the energy-sensing super-highway in the cell. When FLCN is knocked out, mTOR does not function properly
- Treated BHD mice with rapamycin (targeting TORC1), and got a dramatic effect
- We are looking at a drug targeting mTORC1 and mTORC2

HLRCC

- cutaneous leiomyomas (muscle tumors in the skin)
- 90% of women with HLRCC have uterine leiomyomas (fibroids)
- This is a unique form of RCC, similar to papillary type 2
- HLRCC is a very aggressive type of kidney cancer that can spread early. We have seen a lymph node met with a primary tumor less than 0.5 cm.
- It does respond to aggressive surgical resection – not simple enucleation, but an aggressive cancer surgery.
- HLRCC can occur early – we should begin imaging at 8 years old, and image them every year
- Surgical management should not be delayed in HLRCC.
- Fumarate Hydratase (FH) gene, mutations in all parts of the gene. We have identified the mutation in 98% of the families in this group
- How does a Krebs Cycle enzyme lead to cancer? HLRCC is a Classic example of the Warburg model. When the FH gene is knocked out, Krebs cycle becomes linear rather than a cycle. The cells live on glucose. They do not get energy as usual. They are sucking in glucose, and glycolysis is way up. They take up no oxygen, they make a whole lot of lactate. Metabolism is very high.
- When FH altered, Fumarate increases, the Krebs cycle is broken, Fumarate targets PHD as the agent for VHL to target HIF- α . It poisons PHD, and creates a VHL-independent mechanism for dysregulating HIF1 α , VEGF up, GLUT up
- AMPK goes up when the cell is short of energy. An altered glucose metabolism in FH-deficient RCC leads to decreased activation of AMPK. Decreased AMPK activity leads to an abnormality in iron sensing.
- We are targeting AMPK in FH-deficient kidney cancer with Metformin/AICAR. Metformin activates AMPK, and can crush this aggressive form of kidney cancer.
- PET scans light up, every organ is high in glucose.
- We are targeting VEGF/EGFR in HLRCC
 - bevacizumab suppresses VEGF

Succinate Dehydrogenase Subunit B (SDHB)

- If you see young people with kidney cancer, think about genetic causes!
- Do not delay treatment for SDHB. This is a highly metastatic disease.
- We followed one family 11 years. We knew they did not have VHL, but they certainly had familial kidney cancer. Eventually we found a germline SDH mutation and a carotid body tumor, which was positive for the SDH mutation.
- In the cell it works similar to FH. When succinate is altered, interferes with Krebs cycle, targets PHD, etc.

Each of these genes is on the same pathway – a response to environmental nutrients, oxygen, iron, and citric acid (energy sensing). MET, TSC1,2, SDH, FLCN, FH, VHL.

Future Strategies to Overcome Resistance, moderated by Michael Atkins (Beth Israel Deaconess Medical Center, Boston)

Mechanisms of Resistance to Renal Cell Carcinoma therapy, by Dan George (Duke University)

Today the standard of care for kidney cancer is monotherapy (treatment with a single drug) in sequence with mTOR inhibitors and other VEGF/VEGFR targeted therapy. 20-30% of patients do not respond. Others respond for a time, and then the tumor develops “resistance” to the action of the drug.

Patterns of resistance:

- no tumor shrinkage, followed by rapid progression
- minor tumor shrinkage, followed by progress and new lesions
- dramatic and prolonged tumor regression, followed by slow, mixed progression

Symptoms that define resistance: The patient may experience...

- pain
- constitutional symptoms (weight loss, anorexia, fever)
- visceral symptoms (constipation, diarrhea)
- skeletal defects

Resistance in VEGF-targeted therapy exhibits:

- inadequate target inhibition
- upregulation of on-target proangiogenic genes and proteins
- upregulation of off-target proangiogenic genes and proteins
- tumor biology not limited by growth factor-mediated angiogenesis

Angiogenic-driven resistance, or “angiogenic escape,” is driven by other angiogenic factors

- patients with high HGF levels had a poorer outcome
- patients with IL-6 had a better outcome
- patients with high VEGF-C had a worse outcome
- anemia and performance status are predictors of poor outcomes
- a sarcomatoid variant is associated with poor outcomes (especially greater than 20%)

He discussed the concept of Reversible epithelial to mesenchymal transition and acquired resistance to sunitinib in patients with RCC. A quick aside to help put this into context: During embryogenesis and early development, cells switch back and forth between different cellular phenotypes via mesenchymal-epithelial transition (MET) and its reverse process, epithelial-mesenchymal transition (EMT).

Developmental METs have been studied most extensively in embryogenesis during development of the kidney (nephrogenesis), but also occurs in development of the heart and liver. While the mechanism in

which MET occurs during development of each organ is similar in that epithelium-associated genes are upregulated and mesenchyme-associated genes are downregulated, each process has a unique signaling pathway to induce MET and these changes in gene expression profiles. It is now recognized that cells go through a similar 2-way change during the progression toward metastasis. In particular, Dr. George noted that kidney cancer mesenchymal cells...

- implanted into a mouse, grow back as an epithelial cell tumor
- these tissues may change in both directions depending on the environment of the cells

In Summary, he stressed that we need to do more research to discover which group of patients is likely to benefit most from VEGF-targeted therapy, and how to avoid or overcome development of resistance so that the drug will continue to constrain tumor growth.

Current Strategies to overcome resistance, by Tom Hutson (Baylor Sammons Cancer Center, Dallas)

RCC is heterogeneous – types are defined by histology, prior therapies, and grade

What can we do when resistance occurs?

- Use a higher dose of the same drug (to overcome, or delay resistance)
- Switch to another VEGF pathway blocker (axitinib, sunitinib after bevacizumab, axitinib after sorafenib)
- Take a Drug Holiday (go off the drug for up to 6 months, then go back on); sometimes there is better response than originally
- Switch to an mTOR inhibitor (everolimus alone or with a VEGF inhibitor)

There are new trials of drugs to treat the Angiopoietic axis (development of new blood and lymphatic vessels): AMG-386 and CVX-060

See <http://clinicaltrials.gov/ct2/show/NCT00982657>

CVX-060 is a recombinant humanized monoclonal antibody fused to two angiopoietin-2 (Ang2) binding peptides. In preclinical studies, CVX-060 is antiangiogenic and decreases tumor proliferation.

or <http://clinicaltrials.gov/ct2/show/NCT00467025?term=amg-386&cond=kidney+cancer&rank=3>

AMG 386 is an anti-angiopoietin peptibody^{*1} discovered by Amgen. AMG 386 targets the angiopoietin axis by blocking the interactions between angiopoietins -1 and -2 (Ang1 and Ang2) and their receptor Tie2. Ang1 and Ang2, types of cytokines^{*2}, each play a significant role in the growth and stabilization of neovascular vessels. Angiogenesis, the formation of neovascular vessels, is necessary for tumor growth and metastasis. By inhibiting Ang1 and Ang2 from binding to Tie2 receptors, AMG 386 ultimately produces anti-tumor effects.

Novel Immunotherapies: David McDermott (Beth Israel Deaconess Medical Center, Boston)

Immunotherapies are those which target the immune system. The body's immune system is designed to turn ON and OFF in response to bacteria and viruses. By targeting the OFF switch, drugs can get the immune system to work on cancer. As one example, CTLA-4 in melanoma targets the brakes on the T-cells.

There are a number of clinical trials currently going on for immunotherapy in lung cancer. Understanding the mechanisms of anti-tumor immunity, and identifying target antigens, will likely improve these therapeutic strategies not only for lung cancer but for other cancers as well.

PD-1 agents are in development -- hopefully we can get these companies to work on kidney cancer

Programmed Death 1, or **PD-1**, is a Type I membrane protein of 268 amino acids. PD-1 is a member of the extended CD28/CTLA-4 family of T cell regulators. The protein's structure suggests that PD-1 negatively regulates TCR signals. PD-1 is expressed on the surface of activated T cells, B cells, and macrophages, suggesting that compared to CTLA-4, PD-1 more broadly negatively regulates immune responses.

Novel Angiogenesis inhibitors, by Gary Hudes (Fox Chase Cancer Center, Philadelphia)

Fibroblast growth factor (FGF) is another element in the process of angiogenesis that is a potential target for therapy.

There are a number of new drugs designed to target specific the production or reception of signals along the angiogenic pathway.

VEGFR TKIs (tyrosine kinase inhibitors (TKI) that target the VEGF receptor) – tivozanib and axitinib

Axitinib –

- Side effects: hypertension, fatigue, and gastrointestinal upset
- Phase II studies, almost approved.

Tivozanib AV-951

- Side effects: hypertension, little else
- Phase II randomized discontinuation study nearing completion
- Might be more active than existing VEGF TKIs

Ramucirumab (IMC-1121B)

- fully human IgG, MAb to BEGFR=2, blocks BEGF binding
- Phase I studies: 8 mg IV 1-hr infusion 2-3wk recommended
- merits future investigation

VEGF-Trap (Aflibercept)

- Phase II
- binds tightly VEGF to Kd and PIGF1 and PIGF2

So far most TKIs develop resistance after 9-12 months. It initially blocks the VEGF receptor and causes tumor shrinkage, but then the tumor begins to grow again. Some new strategies are being tried to develop second-line or third-line therapies for use once the tumor becomes resistant to the initial drug.

Dovitinib (TKI258) = VEGFR and FGFR tyrosine kinase inhibitor

- trial for metastatic RCC (mRCC) refractory to other therapies (3d line)
- binds to FGFR and VEGFR
- being studied at U Penn

Angiopoietins/Tie-2 and angiogenesis

- Ang-1 and Ang-2 ligands compete for Tie-2 receptor binding
- this should teach us whether targeting angiopoietins is a good strategy

TGF-beta targeting – can upregulate Smad

- PF-346962 (Pfizer)
- ACE-041 (Accerlaron)
- both drugs are in Phase 1 studies

should we be going back to cytotoxic drugs?

- perhaps we need to study the phenotypes of these tumors, and take the antibody for the cell type

Summary – are these new drugs better? safer? Can resistance be circumvented? Angiopoietins and bone marrow derived cells are interesting new targets

Intermittent VEGF inhibition: rationale and current data, by Viktor Gruenwald (Hannover Medical School, Hannover, Germany)

VEGFR-TKI upregulated will lead to tumor progression

What is the biological relevance of the gene alterations during TKI treatment? Are changes reversible or a sign of clonal evolution? He studied the outcome of treatment discontinuation in patients with metastatic kidney cancer (mRCC) and no evidence of disease following targeted therapy, with and without surgical removal of the metastatic tumors.

Sunitinib is the gold standard in Europe. Nonetheless, most patients developed recurrence during follow-up.

Conclusions:

- compete clearance of tumor burden is rare
- tumor relapse was 67% after 7 months, but long-term progression-free survival (PFS) may occur in individual patients (up to 31+ mo)
- clinical predictors of prolonged PFS could not be determined

Novel P13K/TOR pathway inhibitors, by Dan Cho (Dana Farber/Harvard Cancer Center, Boston)

Can we improve on the current mTOR inhibitors? (everolimus, temsirolimus)

- Only a small subset of patients respond
- Strategies to improve should focus on the shortcoming and methods of resistance

TORC1 and TORC2

- TORC1 is sensitive to agents
- We are beginning to understand how they work
- If you inhibit TORC1, it activates a feedback loop and enhances TORC2, leads to loss of Grb10 feedback loop, activates other pathways such as MAP-1.
- Is TORC1 the correct target in renal cancer? Does HIF-2 α work better?
- Is blocking TORC2 enough?

Potential strategies: dual inhibition of PI3-Kinase and mTOR. There are new drugs that inhibit both.

- preclinical studies confirm that this might work, eg NVP-BEZ235 vs Rapamycin
- more: Novartis, genentech, Pfizer, GSK, et al

Conclusion:

- PI3kinase /AKT is a viable therapeutic target

Novel combinations, by Roberto Pilli (Roswell Park Cancer Institute, Buffalo, NY)

Dr. Pilli suggests targeting tumor endothelium

- mTOR inhibitor + vascular disrupting agent
- delta-like 4 inhibitor + VEGF inhibitor (Notch blockade)
- VEGF inhibitor+
- looking at anti Delta-like 4 Ab and Sunitinib = significant inhibition of tumor growth
- Flavinoid tumor DVA – significant inhibition ASA404 and Everolimus
- combination of mTOR and DVA inhibitor being tried
- cMET overexpression may be related to resistance
- Crizotinib + axitinib

Summary, by Michael Atkins

ccRCC therapy model:

VEGFR inhibitor, then Axitinib or everolimus or rechallenge with same agent.

Clinical trials:

- novel
- more potent VEGF
- intermittent VEGF
- targeting factors associated with resistance
- PI3Kinase inhibitors

Resistance to VEGF blockage

Understanding treatment, based on

- mechanisms of resistance
- drug studies in relevant animal models
- moved early into benchmark

Imaging: measuring response relative to the baseline tumor

- degree of baseline perfusion may be a marker for benefit
- eventually resistance involves the ability for the tumor to grow in an hypoxic environment.

Intermittent dosing leads to slowed tumor progression (3 days out of 7)

- shown in Arterial Spin Labeling imaging (Bhatt)

We need to study those with late progression and the best responders to understand how to predict before treatment how well someone is likely to do on a specific therapy. Characteristics such as:

- tumors that lack other mutations
- tumors that express HIF1, HIF2
- tumors that have physiological mechanisms of resistance related to prolonged hypoxia.
- A598 model with later resistance

Which patients should get immunotherapy first?

- Both IL2 response and PD1 Ab response appear to be associated with upregulation of B7H1

The key to moving forward is translational research

Conclusion: This is a complex problem, we have the tools, and will find the best ways to benefit patients

Discussion:

Most patients do not benefit from mTOR inhibitors. How can we predict?

Should we use a more potent inhibitor after a less potent inhibitor? – Dr. Atkins thinks it's better to use the stronger one first.