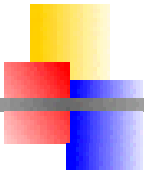


**Metro New York**  
**Carcinoid Support Group**  
**Newsletter**

May 2008

[www.carcinoid.us](http://www.carcinoid.us)



**Well-Deserved Recognition**

The peace and calm of the April 13<sup>th</sup> lectures were interrupted with long overdue thanks. On behalf of the Metro New York Carcinoid Support Group, Dr. Warner was given a plaque for his dedication of a lifetime of work for carcinoid and NET patients. Dr. Warner has been a pioneer in the field, and is often referred to as "the guru" by other experts in the field.

He has been the driving force behind much of the research and education that is taking place today. This has resulted in longer and better lives for patients. He has also been instrumental in setting up the Carcinoid Cancer Foundation, which turned 40 years old in 2008.

When presented on the stage, Dr. Warner received a standing ovation from everyone there.

The Carcinoid Cancer Foundation was also recognized for their 40 years. Think about that...it is a long time. In 1968 the Beatles just filmed "Yellow Submarine", then recorded their last album the next year. The Cincinnati Bengals football team was formed in 1968, and they have not won a Super Bowl yet. Rowan & Martin's Laugh-In started, and ran only until 1973. The musical "Hair" opened on Broadway, and closed 4 years later. The US flew two Apollo missions to the moon that year, but neither landed on the moon.

*Continued on page 2*

**Carcinoid Cancer Foundation Lecture**

In what has become an annual event, hosted by the Carcinoid Cancer Foundation, approx. 160 "noids" and medical students made the journey to Mt. Sinai Hospital to hear the latest information. This year, however, it was not raining torrents. This was the eleventh lecture hosted by the Foundation in recent years.

This day of lectures was opened by Bob Wahmann,



*Dr. Warner*



*Dr. Herbert Chen*

President of the Carcinoid Cancer Awareness Network, Inc. Bob was the Master of Ceremonies for the day. Dr. Warner followed with Opening Remarks, including an overview of some of the current strategies being used to treat carcinoid and NETs.

Dr. Herbert Chen, Chief, Section of Endocrine Surgery,

*Continued on page 4*

**PCCAN / CCAN Lectures**

Approx. 130 attended the Pennsylvania Carcinoid Cancer Advocacy Network / Carcinoid cancer Awareness Network, Inc. lecture on Saturday, April 26<sup>th</sup>. The all-day event was held at the Harrisburg Hilton Hotel. The day was dedicated to "The Loving Memory of Donna Gibson" and her husband, Kevin, was there for the day.

The morning started with an overview of Carcinoid by Dr.

Harold Harvey from Milton S. Hershey Medical Center. The topic then turned on to one of the newest technologies with a session by Dr. James Pingpank, National Cancer Institute. Dr. Pingpank has been working with Delcath Systems, Inc. on a method that allows delivery of higher doses of chemotherapy agents directly to the liver, while reducing the side effects and

*Continued on Page 3*

**Upcoming Dates**

**May 4<sup>th</sup>, 2008** – New Jersey Chapter meeting at Crossroads Christian Fellowship. Union, NJ, 1:30 PM. Contact Jim Weiveris at 609-812-9294 or [Caring4Noids@aol.com](mailto:Caring4Noids@aol.com)  
**Next NJ meeting is June 8<sup>th</sup>**

**May 18<sup>th</sup>, 2008** - Long Island, NY Chapter meeting at Bellmore Library. Verify dates at [www.carcinoidaware.org](http://www.carcinoidaware.org) or call 516-781-7814.

**September 24, 25 & 26 2009** - 2009 National Conference, New Orleans, LA. Details will be published as they become available.



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 For newsletter questions & submissions please contact: Jim Weiveris  
 Phone/Fax: 609-812-9294  
[Caring4Noids@aol.com](mailto:Caring4Noids@aol.com)  
 Mailing address is:  
 9 Maplewood Dr.  
 Little Egg Harbor, NJ 08087

# Recognition

*Continued from Page 1*

The Carcinoid Cancer Foundation has been the reason behind the many patient support groups today. As little as 8 years ago, there were no support groups as we know them now. The only two websites with Carcinoid information were the Foundation and Susan Anderson's.

In 2001, the Foundation began helping support groups get off the ground. One of those was the Metro New York Carcinoid Support Group, which also became the seed and the example for some other groups around the US.

At the Tampa conference, Sue had a list running for anyone interested in starting a group in their area. That list resulted in several of the groups that are active today, some of them becoming, in turn, the parent to others in their area.

The support group movement

has even spread to Europe, where doctors groups (ENETS) are well founded, but patient groups are sadly lacking.

With the awareness raised by support groups, Carcinoid is becoming "more common", and patients are able to live better lives with the information the group shares. Without the support information of the Foundation, these groups may never have happened.

Also recognized was Monica Warner. Monica is the engine behind the foundation and many of it's events, such as the conferences at Mt. Sinai. Without her time, energy and determination, many of the events and much of the work of the Foundation would not be done.

To Monica, Dr. Warner and the Carcinoid Cancer Foundation, we all owe an infinite debt of gratitude.

can tailor information to your area, for you. You also get your copy sooner, rather than waiting for the information to be passed along.

There is no charge to get our newsletter.

## Are You Missing Out?

If you are not on our mailing list, you may be missing out on some of what we can offer.

If you have an e-mail address, please send an e-mail to [Caring4Noids@aol.com](mailto:Caring4Noids@aol.com) to be added. Please include your name and address, as we often find e-mail addresses change frequently. We do not "spam".

If you don't have e-mail, just drop a note that you want to be included. Send it to: MNYCSG, 9 Maplewood Dr., Little Egg Harbor, NJ 08087.

All information is kept confidential and is not shared. By being on our direct list, we

## NJ June Meeting Reminder

Don't forget that the NJ Chapter meeting will be June 8<sup>th</sup>, not June 1<sup>st</sup> (the first Sunday) because of a schedule conflict. Same time and place. See the website, [www.carcinoid.us](http://www.carcinoid.us), for directions and details.

# Our Sister Groups

**Arizona Carcinoid Team** – Meets in Phoenix, For information contact, James at [act\\_mail@yahoo.com](mailto:act_mail@yahoo.com)

**Northern CA - NCF** meets in Fairfield. For information contact, Kathy at [karbanis@yahoo.com](mailto:karbanis@yahoo.com)

**Carcinoid One on One** meets in Orange, CA. For information contact, Terri at [Terris12@att.net](mailto:Terris12@att.net)

**SEA (Support Education & Awareness for Carcinoid Patients)** *Not affiliated with CalCF.* Meets in SanGabriel/San Fernando Valley area. For information contact, Nickolette at [sea4carcinoid@msn.com](mailto:sea4carcinoid@msn.com)

**South Bay Carcinoid Fighters (LA)** Meets in Redondo Beach, CA. Pat [carcinoidfighter@yahoo.com](mailto:carcinoidfighter@yahoo.com)

**Connecticut Carcinoid Initiative** - Meets in Glastonbury through this summer. Contact, Pat [PStrongLaw@aol.com](mailto:PStrongLaw@aol.com)

**Capital Area Carcinoid Survivors** (Washington, DC) – For information visit the group's web site, <http://hometown.aol.com/cacs/ya/>

**Florida** (informal group) Pam [prpowell@cfl.rr.com](mailto:prpowell@cfl.rr.com)

**Chicagoland Carcinoid Fighters** Meets in Gurnee, IL contact pending

**Boston Area** –At the Dana-Farber Cancer Institute - contact Sarah Murphy, LICSW at 617-632-6463 or the New England Carcinoid Connection (NECC)at [www.carcinoid-newengland.org](http://www.carcinoid-newengland.org)

**Michigan** - Meeting place may rotate. Contact Dave at [Day2005@earthlink.net](mailto:Day2005@earthlink.net)

**Minnesota Carcinoid Peer**

**Support Group**, contact Jan Jackson [jaxon7@msn.com](mailto:jaxon7@msn.com), also covering western WI and surrounding areas

**Arkansas**– Meets near Hot Springs. Contact Kathy, [terris12@cablelynx.com](mailto:terris12@cablelynx.com)

**Central Pennsylvania** - (Harrisburg/Hershey), For information contact, Teresa [CarcinoidSupport@juno.com](mailto:CarcinoidSupport@juno.com).

**Pennsylvania / Philadelphia** (Informal group) Contact Anne [StJohns56@aol.com](mailto:StJohns56@aol.com)

**Dallas, Texas** Contact Carol-Anne for information [CarolAnne52@gmail.com](mailto:CarolAnne52@gmail.com)

**Houston, TX** Contact Jan Peine, [carcinoid@comcast.net](mailto:carcinoid@comcast.net)

**Austin, TX** - For information contact, Ann Meyer [ameyer@swrcc.com](mailto:ameyer@swrcc.com)

Carcinoid NeuroEndocrine Tumour Society Canada - For information contact Maureen C. [maureenc@sympatico.ca](mailto:maureenc@sympatico.ca) or <http://www.cnetscanada.org/>

**Oregon Chapter of Pacific Northwest Group** - contact Kari at [Kbrendtro@yahoo.com](mailto:Kbrendtro@yahoo.com)

**Washington (state) Chapter of Pacific Northwest Group** - For information contact, Corie at [cadean@NATPIPE.COM](mailto:cadean@NATPIPE.COM)

For the latest list of support groups visit the Foundation's web site ([www.carcinoid.org](http://www.carcinoid.org)), our web site ([www.carcinoid.us](http://www.carcinoid.us)) or Susan Anderson's web site (<http://www.carcinoidinfo.info/>).

*To list your group or update a listing, please send us a note*

*Telephone numbers and personal addresses are not normally included for the security of those listed, whose information becomes "searchable" data through any Internet search engine, such as Google.*

# PCCAN / CCAN Lectures

*Continued from Page 1*



complications.

The delivery system is called Percutaneous Hepatic Perfusion (PHP) and is currently in Phase II and Phase III trials. NET trials are Phase II and the system is hoped for availability to NET patients near the end of the year. They are currently using Melphalan as the chemotherapy agent, but it is expected later use will expand the drugs and items that can be delivered.

The system inserts a catheter into the groin, which is then snaked into the liver. Another catheter is inserted near the neck. A balloon on the catheter is then inflated, blocking off blood flow and shunting it into a closed loop outside the body, but encompassing and treating the entire liver. It is through one side of this loop that they can inject ultra high doses of chemotherapy agents.

It is through the other end of this loop that they can filter out the chemotherapy agents and return the blood to the body, not flooding the body with the chemo drug. Drug levels in the target area (liver) can be as much as 100 times the normally allowed dose in traditional methods.

An activated charcoal filter is used to remove the chemo agent from the blood. Since the heart is not part of the loop, a pump is used to facilitate moving blood through the loop. The filters remove almost all of the

chemo agent before returning it to the body, thus avoiding damage to the heart and other organs. The average hospital stay lasts about 3 days.

One of the problems in chemotherapy is delivering enough drug to kill the tumors, but not too much to damage other organs. NETs participating in the trial had a 79% response to the treatment. There were 36 Carcinoid patients and 12 Islet Cell patients involved. The trial also encompasses several other cancers and is expected to take on other diseases affecting the liver. The procedure can be repeated.

Delcath is a development stage company, with headquarters in New York City. They have been working with the National Cancer Institute for research and approval and have been granted fast track status for development. Trials are ongoing and open.

The lectures then continued with Dr. Matthew Kulke,



*Dr. Matthew Kulke*

Dana-Farber Cancer Institute. Dr. Kulke noted that in bronchial carcinoids, it is important to focus on the histology (typical or Atypical), as this will determine course of action. He also mentioned that most stomach Carcinoids are "nearly benign". There is also



*Dr. Harold Harvey*

a difference in response to chemotherapy treatments between Carcinoids and Pancreatic NETs. This results in NETs being divided into two groups, Carcinoid or Pancreatic NET

Dr. Kulke did not feel that Sandostatin was effective in treating anything more than



*Dr. Thomas O'Dorisio*

symptoms, but noted that it did work well for secretory diarrhea. Chromogranin A is more sensitive for monitoring tumors than 5-HIAA. Surgical resection and liver transplantation remained viable options.

VEGF (signal pathways) remain very promising, with newer drugs available (such as Avastin, Sutent, or Nexavar) or others soon to be available. Trials of RAD001 have been promising, with low toxicity, but all will need further study.

The next lecturer was Dr. Thomas O'Dorisio, University of Iowa, who took a three hour trip over two days to arrive (airlines and bad weather don't mix it seems).

Dr. O'Dorisio spoke about the history of Carcinoid and then began to touch on some very current information.

56% of all NETs are carcinoids, with 38.4 new cases, per year, per million in the US (just over 11,000 new cases per year). The prevalence of the disease is MUCH higher due to the chronic nature of the disease. That is a significant increase over past studies. Only Ileal carcinoids are being shown to have an actual increase in disease, the rest from better diagnosis and awareness.

Ki-67 is not the only determining factor to aggression and not all Ki-67 tests are equal. Not all labs are equal, with many labs using different assays, thus producing different results that can not be translated between each other. Pancreastatin is proving to be a better indicator of tumor activity that Chromogranin A and it may be helpful as a predictor of malignancy. Even short term, low dose PPI use can raise CgA levels.

95% of all NETs have



*Dr. James Pingpank*

Somatostatin receptors. Octreotide and Lanreotide is not just palliative - it is therapeutic. Whenever practical, remove the primary - It is seeding other tumors as long as it is there. Just taking Octreotide has doubled survival, it also improves the Quality of Life. Samatostin analogues should be started

*Continued on Page 4*

# PCCAN / CCAN Lectures

*Continued from Page 1*

right after a diagnosis is made.

The session closed with a Question and Answer period. Some of the points brought out were: Treat metastases, even if primary is not known. Treatment may be to monitor, if patient is doing well (risks to almost all procedures). The dangers of SSRIs to NET patients has not been evidenced in clinics.

Different scans look at different things: CT scan is like an X-Ray, PET Scan looks at sugar uptake,

Octreoscan looks at Octreotide uptake. If there is a risk of recurrence, the time to follow should be over 5 years. We should be treating metastases, even if the primary is not known.

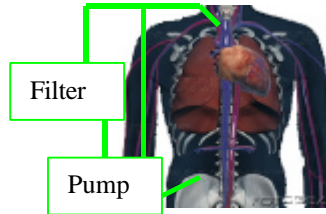
Many thanks to the Hershey (PCCAN) group, the Carcinoid Cancer Awareness Network, inc. and the Delaware Valley Group (Philadelphia) for their work on putting together the program.

Lecture notes begin on page 7

# PHP, Over Simplified

Using methods similar to a chemoembolization, catheters are placed into the hepatic artery, inferior vena cava, and jugular. Two balloons along the catheter are then inflated, isolating the liver while a lumen allows blood flow directly past the isolated area to continue flow to the body.

Contrast media is pushed to



the now-isolated liver to confirm isolation of the liver vessels. Ultra-high dose of chemo can be sent to the liver for approx. 30 minutes.

The drug is allowed to bathe the tumors in doses higher than normally allowable.

The drug is collected by the catheter and sent to the filter for removal. The filtered blood is then sent back into the body via the jugular.

Once completed, the balloons are deflated and the catheters removed. The procedure can be repeated (usually 4 to 6) at one month intervals.

# Carcinoid Cancer Foundation Lectures

*Continued from Page 1*

Department of Surgery, University of Wisconsin, Madison, WI spoke about the exciting use of "Notch 1 as a Therapeutic Target for Carcinoid". Dr. Chen has spoken at prior conferences and lectures on this topic, which appears to hold much promise. The Carcinoid Cancer Foundation and the Doctor's Cancer Foundation have both supported the research of Dr. Chen with grants.

Notch 1 therapy basically allows a pathway to be activated or turned off by using the Notch 1 protein within cells. The on/off can be controlled at varying levels, not simply a black or white presence. Dr. Chen's research has found that in traditional cancers, the Notch 1 protein is present in higher amounts. In NETs, the Notch 1 protein is either not present, or in very small amounts. By raising the level, they can watch (and

cause) the tumors to reduce, or stop, production of hormones that are harmful. Chromogranin A results were shown, using Western Blot testing. With the activation of Notch 1, CgA levels could be made to drop to zero in NETs.



*Dr. Kennedy*

The research team has been using Valproic Acid (VPA), which has long been prescribed for epilepsy, to activate the Notch 1 protein.

The doses are far below that used to treat epilepsy, or trigger traditional cancers. Notch 1 levels work in reverse of traditional cancers form NETs. In traditional cancers, Notch 1 levels are high, while in NETs, Notch 1 levels are low.

They are also currently investigating some several thousand additional drugs that may have a similar effect. The treatment is also expected to produce results with Medullary Thyroid Cancers. Dr. Chen is currently conducting trials on Carcinoid patients with lung or gastrointestinal primary tumors.

Dr. Andrew Kennedy, Co-Medical Director, Wake Radiology Oncology, Cary, NC was the next lecturer. His talk, "From Grade School to Graduate School: Becoming an Expert in Radioembolization" showed the results of the current Yttrium 90 (Y<sup>90</sup>) treatments in the US. The procedure has become very popular recently, because of the success and longer lasting results in

palliative care of liver metastases.

Despite the recent popularity, the first procedure of this type was done in the US in the late 1960's, only a couple years after Intra Hepatic Artery delivery was conceived. The doctor who did the first was Dr. Richard Warner, with an amazing success rate, treating four or five patients at that time.

One of the myths cleared up by Dr. Kennedy was regarding the potential danger of radiation to others who are near a patient from a Y<sup>90</sup> procedure. Y<sup>90</sup> is a Beta emitter, with a short range. It does not radiate outside of the body. Part of the myth may be fueled by regulations in other countries, and that when they first began testing, Dr. Kenny initiated the "3 feet for 3 days" rule. After they became more familiar with the procedure, and its effects, they found this rule to be unnecessary.

The Y<sup>90</sup> procedure is shown to

*Continued on Page 5*

# Carcinoid Cancer Foundation Lectures

Continued from Page 4

have a longer time until disease progression within the liver than bland or chemoembolization. The treatment can also be found to be reducing hormone levels long after it is completed.

Patents must be pre-tested prior to the Y<sup>90</sup> procedure, to make certain that there are no blood shunts (flow) to undesired organs, such as stomach and lung. This is done by injecting albumen, chopped up to the same size as the microspheres, and watching the flow path. If a shunt is found, they can often close it by introducing a coil or "shaving" into the vessel to

form a clot, which closes the vessel. Collateral vessels can still supply enough blood to the organ.

The popular Question and Answer Session allowed patients to submit their questions to the assembled panel of experts. Questions need not be on just the topics discussed, since the panel consists of additional experts, from additional fields.

Some of the items covered included the role of Sandostatin, which is not given just for symptom control (the original FDA approval). Also, if Serotonin is high, Sandostatin helps to

control it, and Serotonin is what is causing heart valve damage.

Some of the other questions brought out answers to what is the recommended followup for a Y<sup>90</sup> procedure. While other facilities may use other criteria, Dr. Kennedy uses imaging at 6 week and 12 week intervals for evaluation. There is currently a Seneca Valley Virus that is being tested in Phase 1 trials for use in NET cases.

The day was capped off (after refreshments, of course) with four patients being able to speak about their experiences on their "journey" to the group. Bea Lehming, Grace Mulligan, Charles Prinz and Valerie Leitman each recounted some of their varied, yet often common,

ride on the roller coaster.

Monica Warner also gave a five minute history of the Carcinoid Cancer Foundation, which celebrates it's 40<sup>th</sup> year in 2008.

Also, the Foundation has contracted for these lectures to be videotaped and they are expected to be available on-line in a very short time. Check the Foundation website at [www.carcinoid.org](http://www.carcinoid.org) to see if they are there (they may even beat publication of this newsletter).

Our thanks to the Carcinoid Cancer Foundation for assembling such a fine list of lecturers and for funding and putting together such an excellent program.

Notes from the lectures are below this article.

## Carcinoid Cancer Foundation Lecture Notes

Please note that these edited and cryptic records are those taken by one person and that not all points of any lecture are covered. Due to the possibility in error or interpretation, it is highly advised to seek a professional medical opinion before relying on treatments from these notes. These notes are provided only to give you some insight in to which ideas you may want to seek further follow-up information & discuss with your doctor

### Introductory Remarks

**Dr. Warner, Mt. Sinai School of Medicine**

#### Medical Treatments

Supportive: includes diet, etc.

#### Radiation Treatments

External Beam Radiation

Internal targeted therapies (Y<sup>90</sup>) - typically for liver metastases

Systemic: PRRT, Lu<sup>177</sup>, or Y<sup>90</sup>

#### Biological Antitumor Treatments

Octreotide

Alpha Interferon

Anti Angiogenesis Agents

Virus (attacks only NET cells)

Vaccine

#### Chemotherapy

Cytotoxic

Specific-target drugs

Current state of the science and art is to customize a multi-modal approach with appropriately chosen and sequentially administered options

### Notch 1 as a Therapeutic Target for Carcinoid

**Dr. Herbert Chen, University of Wisconsin**

By understanding the biology of NETs, we can develop treatments

Need for palliative treatment for symptoms caused by excess hormones

Government funding for NET research is small

#### Research Hypothesis

NETs use different signal pathways or use them differently than traditional cancers

Traditional cancer thinking may not apply

NETs may respond in an exact opposite manner as traditional cancers

RAS Pathway causes growth in most traditional cancers, but inhibits growth in NETs

Notch 1 is this type pathway

Notch 1 is a protein in cells

Using fly (think house fly) for research tests

Normal Notch level = normal sensory hair on fly back

Too much notch = no hair on back

Too little notch = much hair on back & oddly grown

1999 Islet Cell research in mouse

Too much Notch eliminated all the Islet Cells in Pancreas

No notch resulted in over development of Islet Cells in Pancreas

In research, turning on Notch stopped NETs from growing

Use a chemical "switch" to regulate Notch to reach complete stop of NET growth  
Slowing NET growth slows hormone production This is shown through Western Blot tests for hormone levels such as CgA, which were reduced

In traditional cancers, increasing Notch increases the cancer  
Problem is to be able to activate Notch in humans  
VPA (Valproic Acid) is commonly used to treat epilepsy  
Increasing VPA increases the Notch level present in the cell  
Gastro & lung Carcinoids have been tested  
VPA is the same as giving the gene for Notch  
Histone Deacetylase Inhibitors (HDAC)  
VPA is part of that class  
Vorinostat is used for treatment of other cancers  
Do HDAC inhibitors suppress NETs? - Tests in mouse show it suppresses NET growth and drug levels used were far below dosing for epilepsy treatment  
Currently researching other drugs to activate Notch  
Also testing on Medulary Thyroid Cancers (MDC)

**From Grade School to Graduate School:  
Becoming an Expert in Radioembolization  
Dr. Andrew Kennedy, Wake Radiology Oncology**

Why use radiation?  
No cross-resistance (chemorefractory tumors)  
Long history of success with solid tumors  
Improved understanding of liver tolerance to radiotherapy  
Unmet clinical need  
Can develop liver failure because of overradiation and other causes  
Increased anemia & Ascites  
Radiation does not damage liver cells as much as it damages the delicate cells that line the blood vessels of the liver  
Radiation is most effective when there is plenty of Oxygen present - Oxygen helps make radiation changes more permanent  
There are as many as 200 times more blood vessels in tumors as in normal liver tissue - allows blood delivery systems to concentrate on the tumors  
As tumors get larger, the centers die off  
Not seeing angiogenesis in irradiated areas  
Glass spheres can hold more metal (radioactive element)  
None is unilaterally better than another, glass vs resin  
One may work better in a particular case  
Post treatment tumors become a non-cellular liquid  
No fears about being around family & friends - post treatment  
Beta emitter  
Does not emit outside of the body  
Many "myths" abound  
CgA levels will fall for months, or years, after treatment  
Median survival is 70 months and is better than bland or chemoembolization  
MRI is superior for liver imaging  
Zone of damage to normal liver tissue is 1 mm or less  
Systemic radiotherapies do not have much of an effect in the liver

**Question and Answer Session  
Drs. Zachs, Kennedy, Chen, Warner**

Seneca Valley Virus is the virus being Phase 1 trials for NETs  
Y<sup>90</sup> does cause scarring, but it is limited amount  
Notch 1 trials are open for patients with G.I. or Islet Cell NET  
Y<sup>90</sup> followup imaging is usually at 6 weeks & 12 weeks  
Some teams use different schedules  
Tumors tend to respond slowly & swelling of tumor can be misinterpreted as tumor growth  
Some cases may take longer for response  
VPA trial - must be at least 4 weeks post other treatment, will monitor liver & liver function  
"If no symptoms, should I stop taking Sandostatin LAR?"  
Original FDA approval was for symptom control, bit it has been shown to have some, limited anti tumor inhibition effect  
If no significant side effects, continue it  
If Serotonin is elevated, continue to avoid heart valve damage  
Heart damage is caused by Serotonin, which scars inner lining and valves of the heart, usually right side. If left side damage, then tumors are in lung and/or there is a right/left connection between heart sides, allowing blood to flow between the sides  
Actual tumor spread to heart is approx. 5% and Chemo and radiation have good treatment effect  
"How does manipulating Notch 1 not allow other cancers to grow?"  
VPA can be used for manipulation & can be regulated to avoid doses large enough to be a problem.  
Notch 1 is not the only force driving other cancers  
After Y<sup>90</sup> treatment, there is no need to avoid pets, family, or children  
Often confused with other radiation treatments that use different materials (emitters) and higher doses  
Protocols may be different in other countries  
Kennedy initially stated "3 feet for 3 days" rule - this was until they learned more about it and research had proven it to be not needed  
US hospitals must scan you for radiation before discharge and can't release you if you are not safe  
Seasonal allergies should have no effect on tumor markers  
"Can a patient have Lu<sup>177</sup> treatment after two Y<sup>90</sup> treatments?"  
Must be evaluated on case by case basis  
Must watch total liver lifetime radiation dose  
SPECT99 or LU<sup>177</sup> is "trial run" before Y<sup>90</sup> to make sure that there is no blood shunt (flow) to undesired areas  
Instead of glass or resin spheres, albumen is chopped to same size as spheres and injected  
Octreotide and SOM230 both have tendency to increase blood sugar  
If shunt to stomach, they can insert a "coil" or "Shaving" to cause a blood clot in the shunt vessel that closes it off.  
Body has enough redundancy to still function  
Finding primary tumor is important, as it helps decide the best course of treatment

# Hershey/Harrisburg PA Lecture Notes

Please note that these edited and cryptic records are those taken by one person and that not all points of any lecture are covered. Due to the possibility in error or interpretation, it is highly advised to seek a professional medical opinion before relying on treatments from these notes. These notes are provided only to give you some insight in to which ideas you may want to seek further follow-up information & discuss with your doctor

## **High Dose Intra Arterial Melphalan Dr. James Pingpank, National Cancer Institute**

Delcath Double Balloon Catheter used  
Drug use is still "off label"  
Non-Functional Pancreatic NET  
At diagnosis, 60% already have liver metastases  
Median diagnosis to death is 1.4 years  
Carcinoid Tumors  
38.4 cases/million & increasing  
Presence of metastatic disease varies with tumor size  
Hepatic metastases will occur in 30% to 50% of patients with tumors > 2cm  
Hepatic resection is a VERY viable option  
75% five year, plus, survival  
Study by Dr. Chen (2006) shows resected patients have better survival than conservative therapies  
OSU study - Hepatic Arterial Chemoembolization  
Median survival is 33.3 months  
Progression free survival is 10 months  
Regional Chemotherapy  
Done if there are too many tumors to resect liver  
Regional therapy allows dose escalation to the cancer bearing organ while reducing systemic toxicity  
Current imaging does not show small metastases, so the assumption is that they exist  
Need to deliver enough drug to kill tumors, but not too much that it kills organ (liver) or body  
Liver is good candidate because of unique vascular properties  
Percutaneous Hepatic Perfusion  
Catheter into Hepatic artery through groin & neck/clavicle vessel  
Creates loop to outside body when balloons are inflated  
Gives chemo & loop has charcoal filter to remove chemo  
Treatment is repeatable  
Overall patient response was 79%  
Average length of hospital stay is 3 days  
One patient (of 23) had a reaction to the Melphalan  
Side Effects to PHP  
Some drug "leaks" into body  
Similar to chemo regimen (bone marrow function)  
3 deaths during study (of 160 patients), one each: hepatic insufficiency, gastric perforation, HA pseudoaneurysm  
Hepatic progression free survival after PHP is 39 months  
Protocol  
Calls for one treatment, followed by another after 4-5 weeks  
Interval evaluation is done at 8 - 10 weeks  
Repeat cycle of two treatments and re-evaluate  
Preliminary Trials  
Inclusion criteria: non-resectable liver masses; limited,

treatable extra-hepatic disease; adequate hepatic reserve  
Neuroendocrine tumors were included as part of the trial, represented by 23 patients  
2 had a complete response  
13 had a partial response  
showed reduction in hormone levels  
increased survival

### conclusions

High-dose Melphalan, delivered via Intra-Arterial administration, is effective against hepatic metastases from NETs  
Tumor reduction from PHP routinely results in durable control of hormone related symptoms  
Moving toward Phase III trial, possibly by late 2008

## **Update on the Diagnosis and Treatment of Neuroendocrine Tumors**

### **Dr. Matthew Kulke, Dana-Farber Cancer Institute**

Bronchial Carcinoids comprise 2% of all primary lung tumors  
Often central in location  
May cause Carcinoid syndrome, including Cushings  
Important to focus on Histology (typical/Atypical=1/3 of cases)  
Typical can often be cured with surgery  
Most stomach carcinoids are "nearly benign"  
Response to chemo shows difference between Carcinoids and Pancreatic NETs  
Testing tumors for MGMT can help determine what drugs will work best  
NETs are subcategorized into Carcinoid or Pancreatic Neuroendocrine Tumors  
Both tumors have variable, but indolent biologic behaviors  
For patients with localized disease, surgery alone is often curative  
Somatostatin analogues are effective at symptom control, they are rarely associated with tumor control  
Proton Pump Inhibitors are effective in controlling gastric hypersecretion, but may complicate diagnosis  
Gastrinomas should be suspected in cases of non-healing peptic ulcer and fasting gastrin level over 100 pg/ml  
VIPomas are generally greater than 1 cm and Somatostatin analogues can be effective in controlling secretory diarrhea  
15-25% of gastric carcinoids are sporadic  
Small bowel Carcinoid tumors make up 1/3 of small bowel tumors in surgical series  
Approx. 5-7% of small bowel carcinoids will present with syndrome, most have abdominal pain or obstruction  
In cases of liver metastatic disease, liver function tests are not reliable indicators of disease  
The uptake of radiolabeled Octreotide (Octreoscan) can be

predictive of treatment response with Octreotide  
 5-HIAA is usually specific to Carcinoid but not particularly sensitive to changes  
 Chromogranin A is more sensitive than 5-HIAA but should be used with caution in patients on Octreotide therapy, which reduces CgA levels  
 Surgical options include surgical resection, liver transplantation  
 Hepatic Artery Embolization is used for palliative care where surgery is not recommended, duration of response can be brief, lasting from 4 to 24 months (note: bland embo)  
 Radio Frequency Ablation and Cryoablation have not been well studied  
 Somatostatin Analogues are used for symptom control and may be used for "breakthrough symptoms"  
 Alpha Interferon has the ability to control the secretion of tumor products. Low dose therapy has results in approx. 40% of cases  
 The combination of Somatostatin and Interferon is controversial for a cytostatic effect  
 Cytotoxic Chemotherapy studies have been relatively limited, with nearly identical survival rates regardless of agent(s)  
 Pancreatic endocrine tumors may be more responsive to chemotherapy  
 External beam radiation is beneficial to patients with bone metastases  
 Radiolabelled Octreotides have shown encouraging results, especially Y<sup>90</sup> and Lu<sup>177</sup>. In<sup>111</sup> has had low response  
 Inhibition of VEGF pathways suggests this pathway may be involved in the development of NETs. Preliminary results for Avastin has shown 95% of patients to be progression free after 18 weeks; Sutent studies show the median time to tumor progression is as long as 42 weeks (depending upon tumor type); Nexavar has shown 6 months progression free in 40% to 60% of patients, depending upon tumor type  
 RAD001 has had low toxicity and showed partial responses in 11% to 13% of patients, when used with Octreotide  
 Conclusion  
 Future trials with NETs are likely to build on these promising observations

**Current Neuroendocrine Tumor Therapies: Current State of the Art**

**Dr. Thomas O'Dorisio, University of Iowa**

56% of all NETs are carcinoids  
 38.4 new cases, per year, per million in the US (just over 11,000 new cases per year)  
 Prevalence of the disease is MUCH higher due to the chronic nature of the disease  
 One problem with markers in the US is that there are too many different labs, many using different assay tests, with varying reliability and no ability to convert levels  
 Ki-67 is not the only consideration to determine tumor aggression  
 Results may vary from tumor to tumor  
 Pathology has not standardized how to cut a tissue sample block  
 Pancreastatin is a better marker

It is a product of CgA  
 Reflects "total" tumor burden better  
 Due to extreme sensitivity, small changes should be ignored  
 1997 Modlin publication shows that Ileal carcinoids are on the rise, but not from increased awareness  
 NET patients are at higher risk for other Thyroid and Oropharyngeal cancers  
 95% of all NETs have Somatostatin receptors  
**Octreotide and Lanreotide is not just palliative - it is therapeutic**  
**Remove the primary - It is seeding other tumors as long as it is there**  
 Just taking Octreotide has doubles survival  
 Also improves the Quality of Life  
 Y<sup>90</sup> Phase I study - survival went from 12 months to over 5 years  
 57% of patients improved with treatment  
 Progression free survival was 29.3 months, if stable disease after Y<sup>90</sup> treatment  
 40-50% of NETs produce substances that  
 As hormones have very powerful clinical side effects  
 As blood markers reflect tumor burden  
 Even short term, low dose Proton Pump Inhibitors (and modest renal insufficiency and hypertension) can raise CgA results  
 Pancreastatin may aid in predicting malignancy  
 Prevalence of Carcinoid Syndrome  
 7.7% regardless of tumor site  
 19% in all carcinoids with metastases  
 35% of small intestine carry highest risk of causing syndrome  
 Somatostatin analogues should be started right after a diagnosis is made

**Question and Answer Session**

If there is a risk of recurrence, following time and frequency is case by case, probably over 5 years (Kulke)  
 Use Pancreastatin, not CgA (O'Dorisio)  
 Treat metastases, even if primary is not known. Treatment may be to monitor, if patient is doing well (risks to almost all procedures) (Kulke)  
 If you find the primary, take it out. This is interpretative from Modlin survey which shows "not specified" (=unknown, thus not removed primary) has lower survival rates (O'Do)  
 Dangers of use of SSRIs have not been seen in clinics (Kulke)  
 Octreoscan kit has cut the amount of radioactive material since it was originally designed. Scan after 24 hours. Scans after that will show material as it begins to recirculate for excretion  
 Different scans show different things  
 CT - Like an X-Ray  
 PET - sugar uptake  
 Octreoscan - Octreotide uptake and concentration  
 Supplemental/Alternative medicine is fine when your metabolism is healthy and working normally. People with illness need additional care