

Recent Advances Carcinoid/NETs

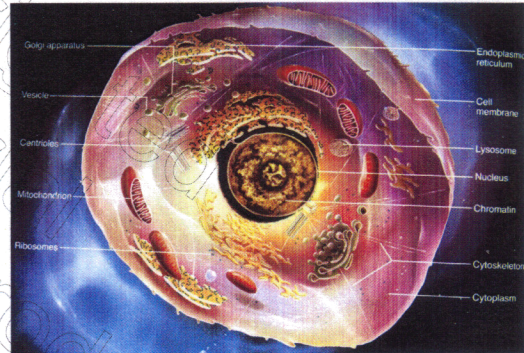
Richard R. P. Warner, MD

OUTLINE

- Basics
 - The Cell
 - Growth Signaling Pathways- mTOR
- Diagnosis
 - Gallium 68 scan
 - NETest
 - Double and single balloon enteroscopy
 - Recognition of Familial carcinoid
 - Advances in surgery-multitasking, resecting primary,,etc.
- Treatment
 - PROMID Study
 - CLARINET Study
 - everolimus
 - sunitinib

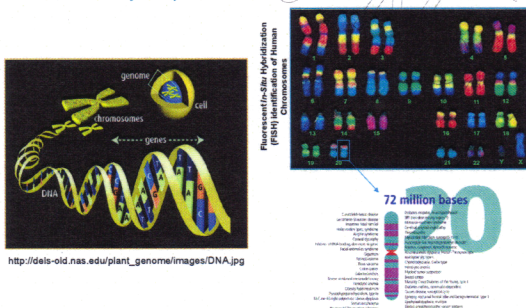
OUTLINE (cont.)

- Drug combinations
 - CapTem
 - Folfox
 - Everolimus/Sandostatin
 - PRRT
 - Molecular profiling

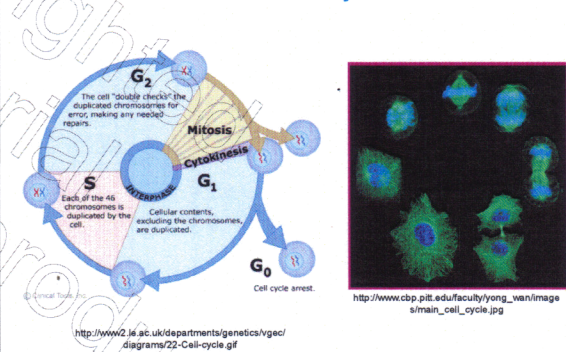


Genes and chromosomes

- The genes are the coded messages in a cell that guide its behavior; they are packed in bundles called chromosomes



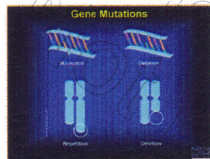
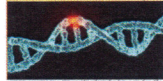
Normal cell cycle



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Errors during the cell cycle

- Sometimes, mutations occur. Mutations are changes in the genes that result in the cells changing their behavior.
- These changes can involve losses, alterations or gains in the important cell control systems related to growth, interaction with other cells and even cells' life span
- Once damage occurs, it can be:
 - Reversed
 - Removed
 - Tolerated



<http://www.cancer.gov/PublishedContent/images/images/Document/20060704-020-4a52-ba30-a05720ee414cancer10.jpg>

Mutations



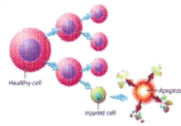
Apoptosis (Programmed Cell Death)

Some times, when the damage is significant and it cannot be repaired or removed, the cell goes through a process of programmed cell death called apoptosis

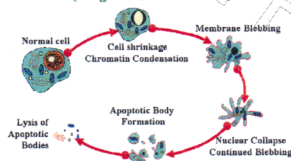
Apoptosis: A normal, genetically regulated process leading to the death of cells and triggered by the presence or absence of certain stimuli, as DNA damage

www.dictionary.com

Normal Cell Division



Apoptosis
(Programmed Cell Death)



<http://www.microbiologybytes.com/virology/kaimakoffbaculovirus/apoptosis.gif>

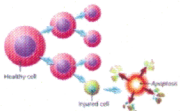
How does cancer develop?



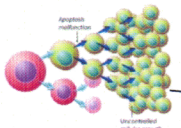
When a mutation cannot be repaired and the abnormal cells continue to multiply and become resistant to death (apoptosis), cancer occurs

Different cancers behave differently depending on the type of cell involved and the degree of uncontrolled cell growth

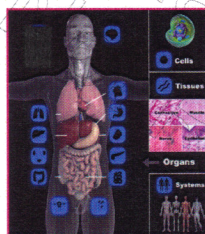
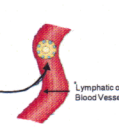
Normal Cell Division



Cancer Cell Division



Metastatic Spread



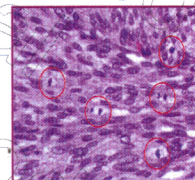
Disseminated Disease

http://www.beliefnet.com/healthandhealing/images/Cancer_cell_division.jpg

Looking at degrees of cell growth

Mitotic count

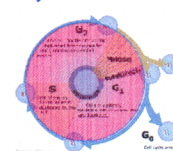
- How many cells are undergoing mitosis (cell division)



http://www.gistupport.org/media/Understanding_Pathology_Report/misases-marked-575pix.jpg

Ki-67

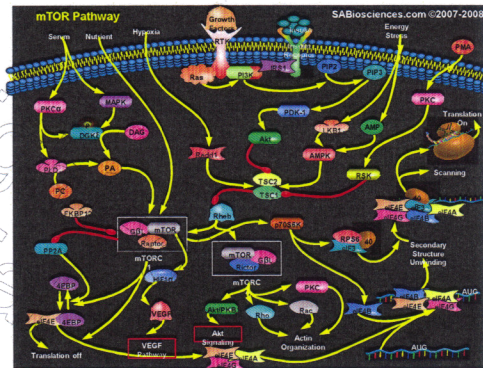
- Immunohistochemical stain that identifies cells in any non-resting stage of the cell cycle (anything but G₀). The result is given as the percent of cells that have entered the cell cycle.



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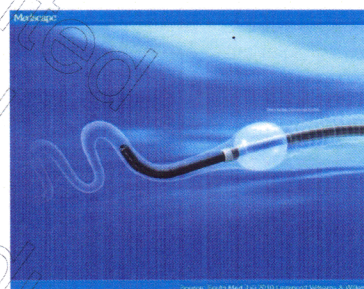
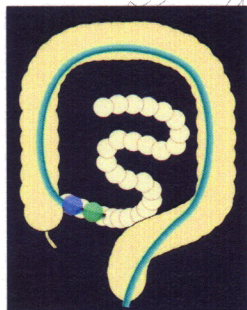
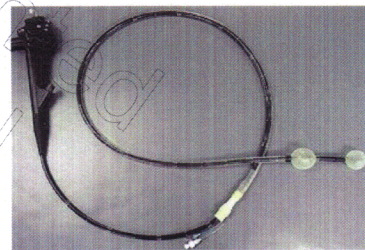
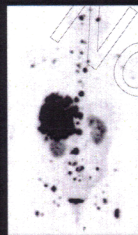
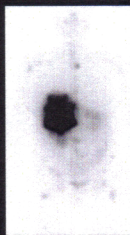
Genetic Familial Syndromes

- MEN-1
- von Hippel-Lindau
- Neurofibromatosis-1
- Tuberous sclerosis
- Familial Carcinoid?

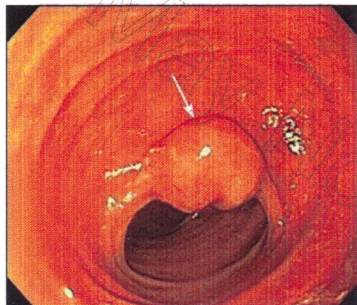


On the horizon: Gallium 68 Somatostatin PET/CT

• 68Ga-DOTA-TOC or 68Ga-DOTATATE



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NETEST Wren Lab-2013

- Diagnosing the presence and severity of any type NET, by genomic technique (PCR), measuring the quantity of 51 different gene fragments of NETs in the Blood.

FAMILIAL CARCINOID

- Rare familial clusters of small intestinal carcinoid cases.
- NIH studied 33 families with at least 2 cases each.
- Screened undiagnosed asymptomatic relatives.
- Sporadic small intestinal carcinoids and familial S I carcinoids are indistinguishable except that familial are usually multiple.
- 34% of symptom free relatives >50 yrs found to have occult carcinoid tumors-cured by surgery.
- Mutation of the gene inositol polyphosphate multikinase (IPMK) was found in all the familial carcinoid patients and in 17 of 35 asymptomatic family members.
- This mutation inhibits apoptosis.
- The researchers speculate that this gene defect might account for 12-35% of cases considered sporadic!

PROMID

Placebo controlled, double blind, Prospective Randomized study on the effect of Octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine MIDgut tumors. Demonstrated a benefit in time to progression. (2009)

CLARINET

Controlled study of Lanreotide Antiproliferative Response In Neuroendocrine Tumors demonstrated a similar benefit in PFS for patients with both PNETS and extrapancreatic NETS. (Not dependant on + or - on Octreoscan).

EVEROLIMUS

Inhibitor of mTOR. FDA approved for PNETS in 2014 usually used with octreotide LAR. Also effective for midgut NETs (carcinoids) but not yet FDA approved for this. RADIANT-3 Trial.

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SUNITINIB

- Inhibits TK VEGF pathway
- FDA approved for PNETs 2011
- Often used with somatostatin analogue (SMSA)

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

- NETTER 1 STUDY
- Lu177 DOTATOC compared to LAR alone-favorable outcome
- Advanced small bowel Carcinoids
- Under consideration by FDA-approval pending

Recognition of increased efficiency of drug combinations

- Octreotide / alpha interferon
- Capicitibine / temozolamide (CAPTEM)
- FOLFOX (leukovorin/5FU/oxaliplatin)
- Octreotide/everolimus

New treatment for SCLC/ G3

Duke Univ School of Medicine

- Sunitinib-Double blinded clinical trial
- 144 patients, 78 treated with active drug-34 with beneficial response (CR,PR or SD)
- Folfox-Eric Baudin, France.
- 2nd line treatment, 20 G3 patients
17 evaluable: 29%-PR
35%-SD
35%-PD

Molecular Profiling

- Use of genomic and IHC (staining) techniques to determine the unique molecular chemical signature of an individual tumor.
- This may show weak points in tumor cell's signaling growth pathways. Vast research has identified many of the sites on these pathways that are targets for specific drugs.
- Examples:
 - everolimus (Afinitor) inhibits the mTOR pathway.
 - sunitinib (Sutent) inhibits a tyrosine kinase enzyme that activates VEGF and VEGFR which promote angiogenesis.
- Recognizing the importance of molecular profiling ASCO has initiated the nationwide TAPUR Study (Target Agent and Profiling Utilization Registry).

Conclusion

The last 5 years have been more productive of diagnostic and treatment modalities than were the preceding 2 decades. The future is increasingly promising for the Carcinoid/ NET patient.