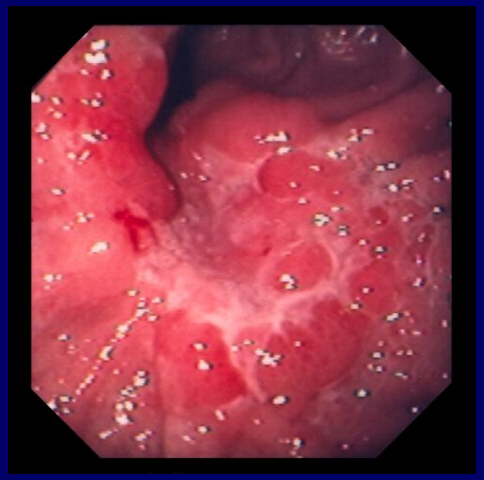
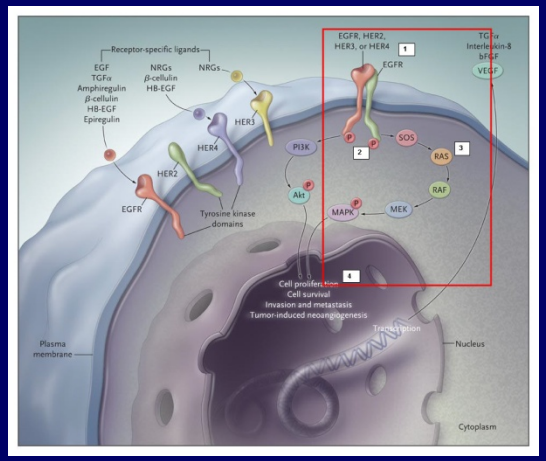
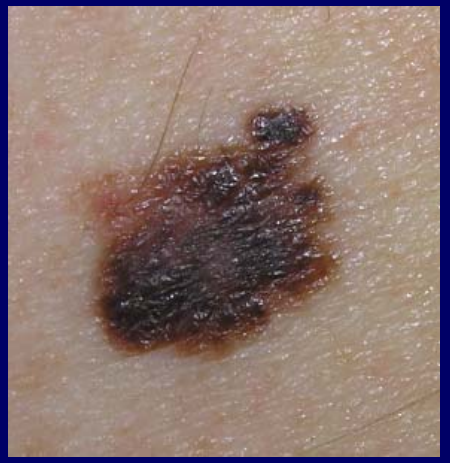
Principles of Cancer Surgery in the Molecular Age



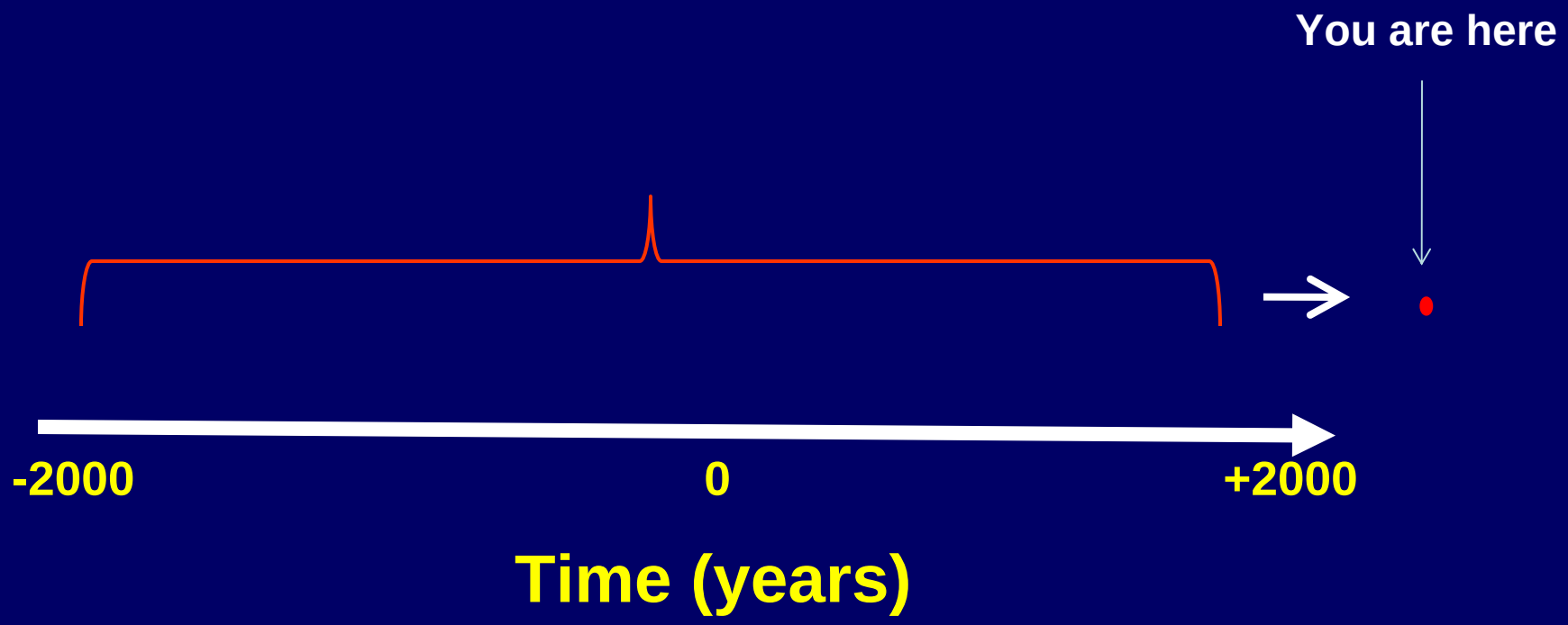




Surgery Grand Rounds
November 15, 2010

Martin McCarter, M.D.
Associate Professor of Surgery
GI Tumor & Endocrine Surgery
University of Colorado Denver

Outline of Today's Presentation



History of Cancer Surgery

Principles of Cancer Surgery

Outline

- The cancer problem
- Tumor staging
- Statistics and prediction tools
- Tumor biology
- Cancer molecules
- Things that make you say huh?
- New therapies for cancer patients

Integrating a Multidisciplinary Approach

Magnitude of the Problem

Leading Sites of New Cancer Cases and Deaths – 2009 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 192,280 (25%)	Breast 192,370 (27%)	Lung & bronchus 88,900 (30%)	Lung & bronchus 70,490 (26%)
Lung & bronchus 116,090 (15%)	Lung & bronchus 103,350 (14%)	Prostate 27,360 (9%)	Breast 40,170 (15%)
Colon & rectum 75,590 (10%)	Colon & rectum 71,380 (10%)	Colon & rectum 25,240 (9%)	Colon & rectum 24,680 (9%)
Urinary bladder 52,810 (7%)	Uterine corpus 42,160 (6%)	Pancreas 18,030 (6%)	Pancreas 17,210 (6%)
Melanoma of the skin 39,080 (5%)	Non-Hodgkin lymphoma 29,990 (4%)	Leukemia 12,590 (4%)	Ovary 14,600 (5%)
Non-Hodgkin lymphoma 35,990 (5%)	Melanoma of the skin 29,640 (4%)	Liver & intrahepatic bile duct 12,090 (4%)	Non-Hodgkin lymphoma 9,670 (4%)
Kidney & renal pelvis 35,430 (5%)	Thyroid 27,200 (4%)	Esophagus 11,490 (4%)	Leukemia 9,280 (3%)
Leukemia 25,630 (3%)	Kidney & renal pelvis 22,330 (3%)	Urinary bladder 10,180 (3%)	Uterine corpus 7,780 (3%)
Oral cavity & pharynx 25,240 (3%)	Ovary 21,550 (3%)	Non-Hodgkin lymphoma 9,830 (3%)	Liver & intrahepatic bile duct 6,070 (2%)
Pancreas 21,050 (3%)	Pancreas 21,420 (3%)	Kidney & renal pelvis 8,160 (3%)	Brain & other nervous system 5,590 (2%)
All sites 766,130 (100%)	All sites 713,220 (100%)	All sites 292,540 (100%)	All sites 269,800 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Staging is All About Real Estate*

The purpose of staging is to provide estimates of expected outcomes

- Facilitates treatment planning
- Allow comparisons between treatment groups

American Joint Commission on Cancer (AJCC)

T = Tumor (size, grade) N = Nodes (number) M = Metastasis

General Classification

Stage I -	Superficial early cancer
Stage II -	Locally advanced - nodes
Stage III -	Regionally advanced + nodes
Stage IV -	Metastatic beyond regional nodes

* The future of staging will lie in the molecular profile of tumor and host

Staging and Estimated 5 year Survival Rates at Diagnosis

Advantages

- Each revision provides more accurate prognosis
- Allows for general estimates of survival

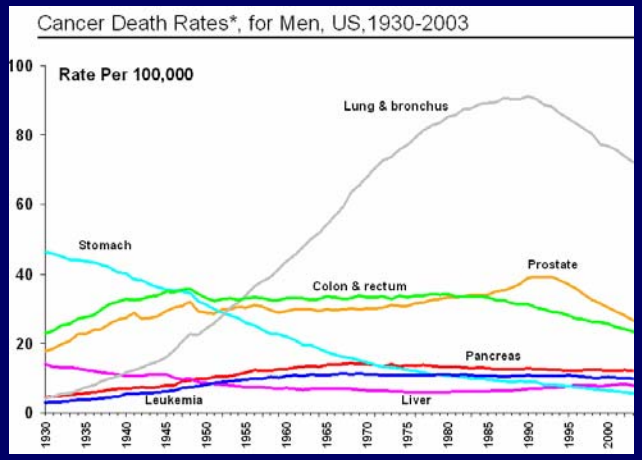
Disadvantages

- Each revision more complex
- Stage shifting over time
- Still lumping cancers by relatively crude descriptive characteristics

Five-year Relative Survival Rates* (%) by Stage at Diagnosis, 1996-2004

Site	All Stages	Local	Regional	Distant	Site	All Stages	Local	Regional	Distant
Breast (female)	88.7	98.1	83.8	27.1	Ovary	45.5	92.7	71.1	30.6
Colon & rectum	64.4	89.7	68.4	10.8	Pancreas	5.1	20.0	8.2	1.8
Esophagus	15.8	34.4	17.1	2.8	Prostate§	98.9	100.0	—	31.7
Kidney†	66.5	89.9	61.3	9.9	Stomach	24.7	60.7	24.8	3.7
Larynx	62.5	80.9	50.2	23.4	Testis	95.5	99.3	95.7	71.1
Liver‡	11.7	23.8	7.7	2.9	Thyroid	96.9	99.7	96.9	57.8
Lung & bronchus	15.2	49.5	20.6	2.8	Urinary bladder	79.8	92.5	44.7	6.1
Melanoma of the skin	91.2	98.7	65.1	15.5	Uterine cervix	71.2	91.7	55.9	16.6
Oral cavity & pharynx	59.7	82.2	52.7	28.4	Uterine corpus	82.9	95.5	67.5	23.6

Statistics for Cancer Patients



- Median follow-up and survival
- Overall survival
- Relative differences vs. absolute differences
- Disease specific survival
- Disease free survival (recurrence free)
- Progression free survival

Guller U. JACS 2004;198:441-58

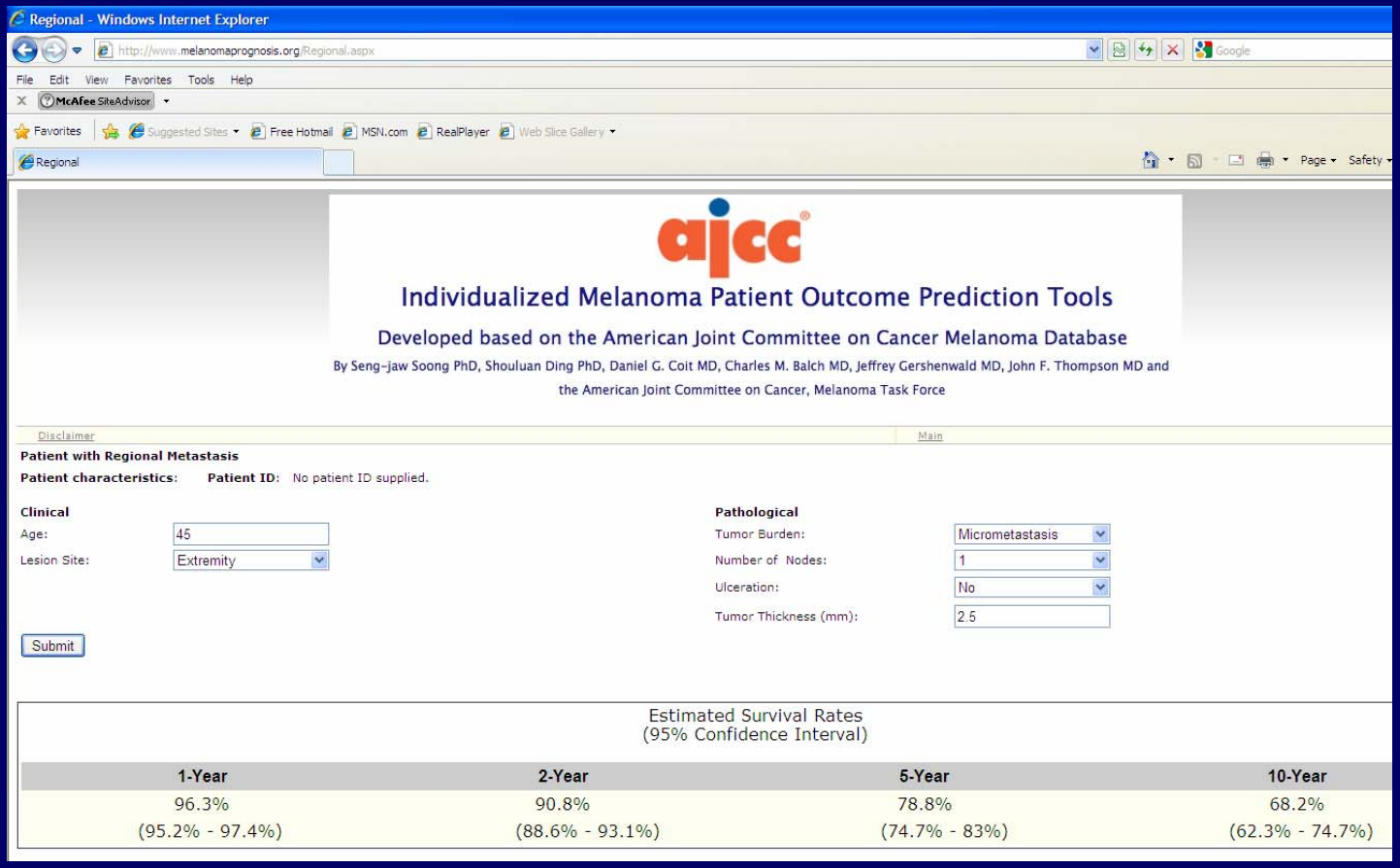
Concept of Relative Conditional Survival

The probability of a cancer patient, who is alive 5 years after the original diagnosis, going on to survive another 5 years.

~ 90% for local disease
~ 85% for regional disease
~ 70% for distant disease

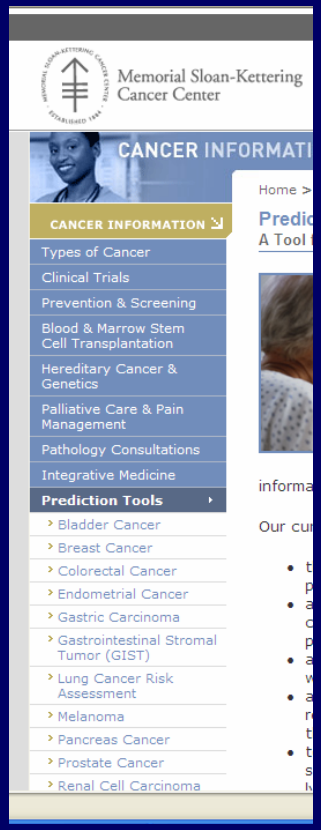
Merrill, RM. Oncologist. 2010;15(8):873-82.

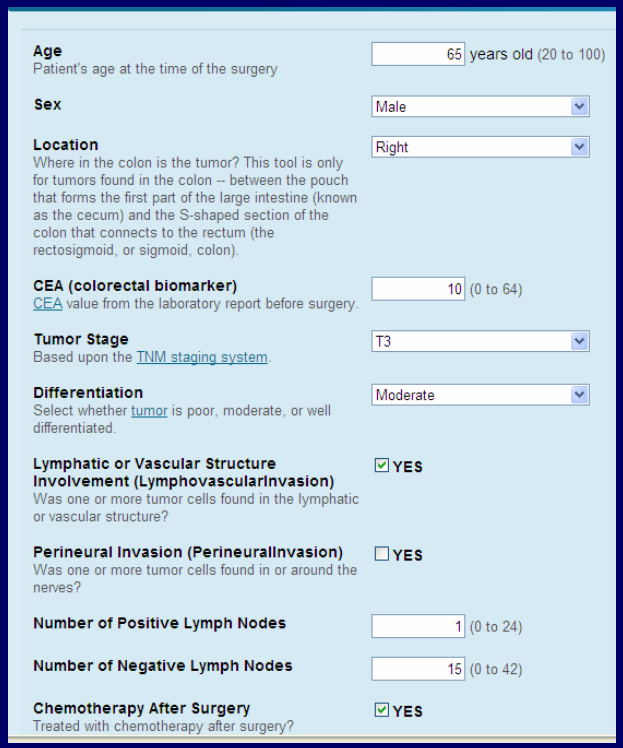
Prediction Tools - Melanoma



http://www.melanomaprognosis.org/Predictiontools.aspx

Prediction Tools





h http://www.mskcc.org/mskcc/html/5794.cfm

Cancer Speak

Terms you have heard but may not know

- **Tumor** = abnormal growth
- **Cancer** = tumor that has the capacity to metastasize
- **Adjuvant therapy** = chemo or radiation therapy added after surgery
- **Neoadjuvant therapy** = chemo or radiation therapy given before planned definitive surgery
- **R0** = complete margin negative resection
- **R1** = complete gross resection, microscopically positive margin
- **R2** = gross disease left behind

Classes of Tumors

General Groupings

Carcinoma = Epithelial tumors

- **breast, melanoma, GI, GU, lung, GYN, H&N**
- **invade lymphatic and vascular structures**

Sarcoma = Connective tissue tumors

- **displace other structures**
- **hematogenous spread**

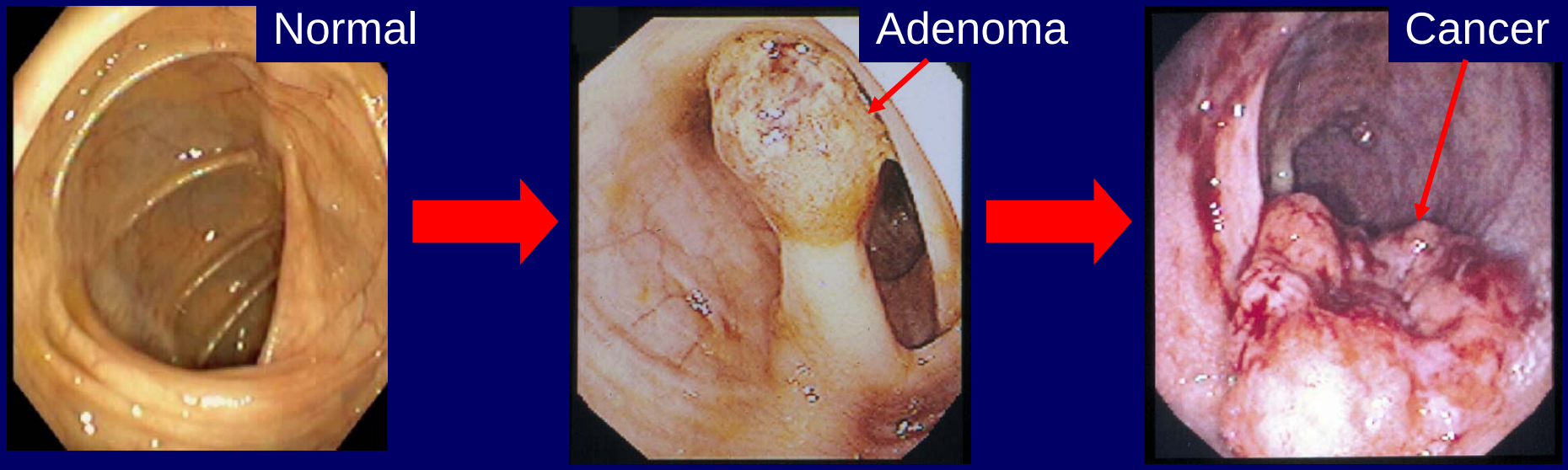
Ovarian

Testicular

Carcinoid tumors = “carcinoma like”

Liquid tumors = leukemia and lymphoma

Tumor Biology



APC loss

K-ras mutation

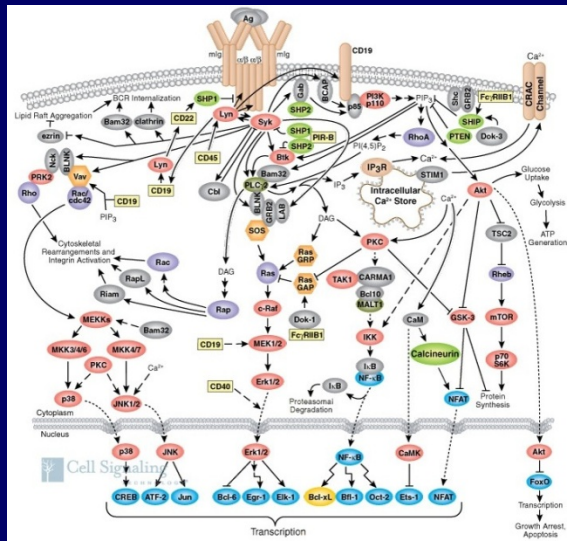
Chrom 18 loss

p53 loss

Normal Epithelium → Hyper-proliferation → Early Adenoma → Intermediate Adenoma → Late Adenoma → Cancer

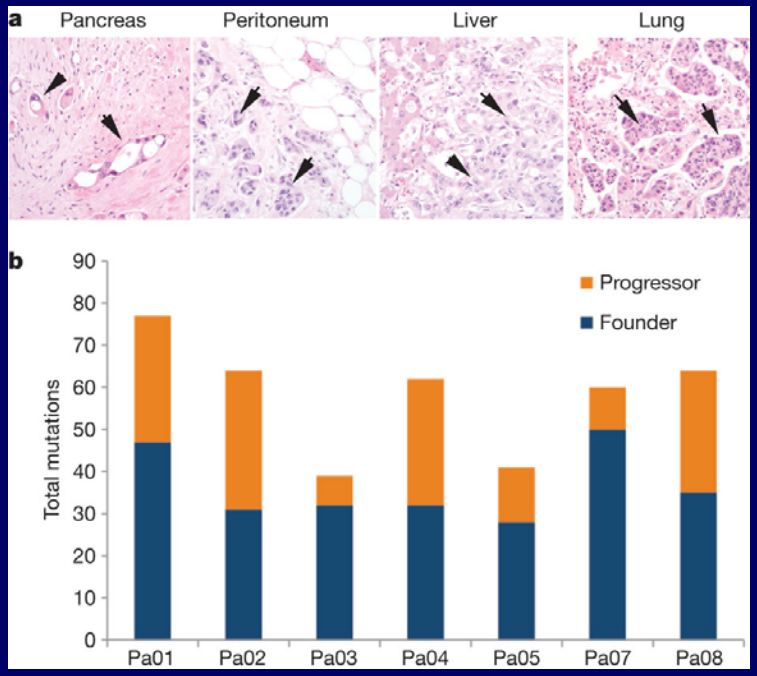
What Does it Take to Make a Tumor?

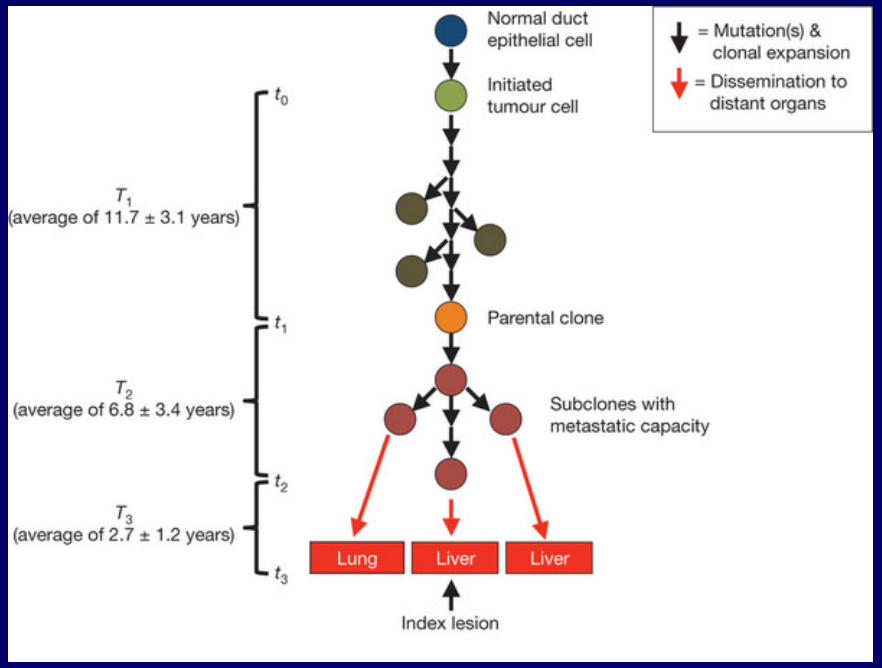
- All tumors have multiple mutations
- Estimated to take at least 10 years from forming a cancer cell to metastasis
- Some mutations are critical for abnormal growth
  - Leukemia – BCR-ABL
  - GIST – cKit
- For most tumors, we haven't found a dominant mutation
- Most mutations are believed to be "passengers"



What Does it Take to Make a Tumor?

- Sequenced the genome of 7 pancreatic tumors and their metastasis
- Classified as Founder and Progressor mutations
- Created evolutionary map





Yachida S. Nature 2010; Oct 28;467(7319):1114-7

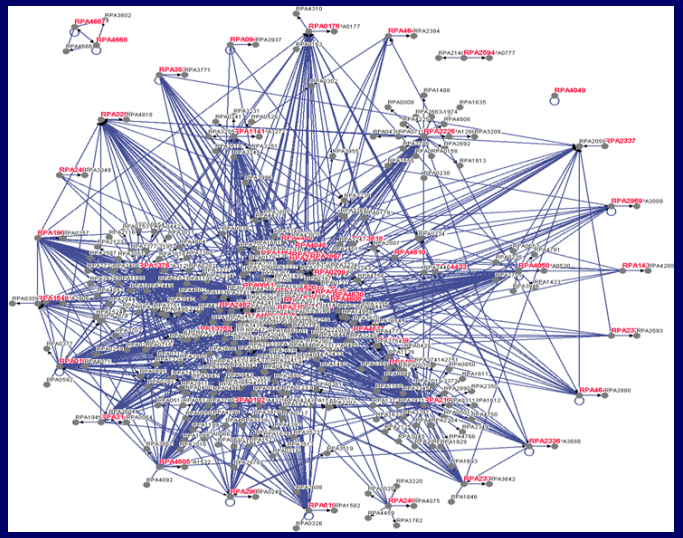
Epithelial to Mesenchymal Transformation (EMT)

Ponder this:

- Much of any tumor mass is stroma (i.e. not cancer epithelium)
    - Fibroblasts, extracellular matrix, myofibroblasts, blood vessels, immune cells
- In tumor xenograft models (human tumor grown in immune deficient mice)
    - Much of the stroma is of mouse origin
- In bone marrow transplant patients who receive bone marrow from the opposite sex and develop CR, Breast, or Gastric cancer
    - Tumor cells are from the host
    - Stroma cells are from the donor!

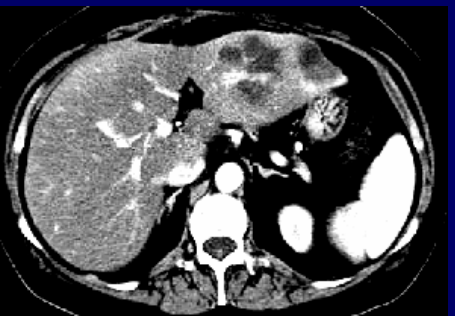
McAllister SS, Weinberg RA. Tumor-host interactions: a far-reaching relationship. J Clin Oncol. 2010 Sep 10;28(26):4022-8. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition J Clin Invest. 2009 Jun;119(6):1420-8

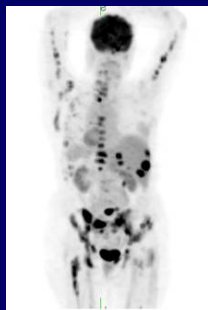
Tumor Biology



Understanding tumor biology is critical for:

- **deciding when to operate**
- **deciding what operation to do**
- **deciding when NOT to operate**





Biology of Cancer Recurrence

some general rules of thumb

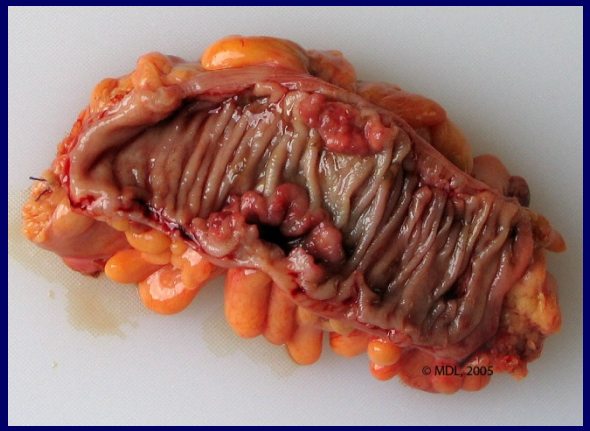
Recurrence of tumor

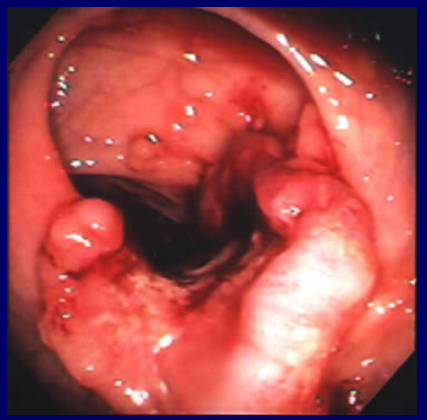
- Tumor environment is a wound that doesn't heal
- ~75% of recurrences occur within the first 2 years of surgery
- 5 year mark for "cure" is arbitrary

- One third local recurrence alone
- One third local plus distant simultaneously
- One third distant alone

Surgery as Curative

- To cure a patient with surgery is still relatively rare
- Some percentage (one third?) may be cured
- Earlier detection is best chance for cure
- Clarify the goal of your operation
  (curative, debulking, palliative, preventative)





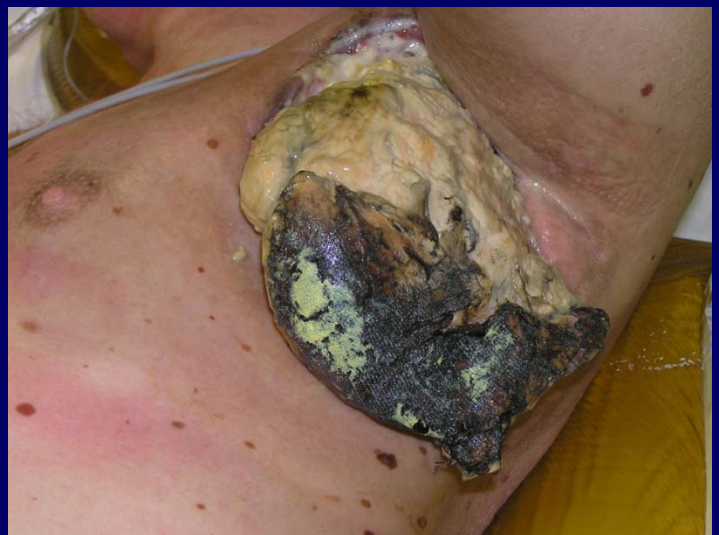
Surgery as Preventative

Prophylactic surgery to prevent cancer development

Disease	Marker	Treatment
FAP	APC	Colectomy
MEN 2	RET	Throidectomy
Familial Breast Cancer	BRCA 1,2	Mastectomy
Familial Ovarian Cancer	?	Oophorectomy

Principles of Surgery for Local Control

- Local control should be a top priority
- First operation is best chance for control
- Apply basic surgical fundamentals to reduce local recurrences
- Salvage surgery to achieve local control is problematic at best



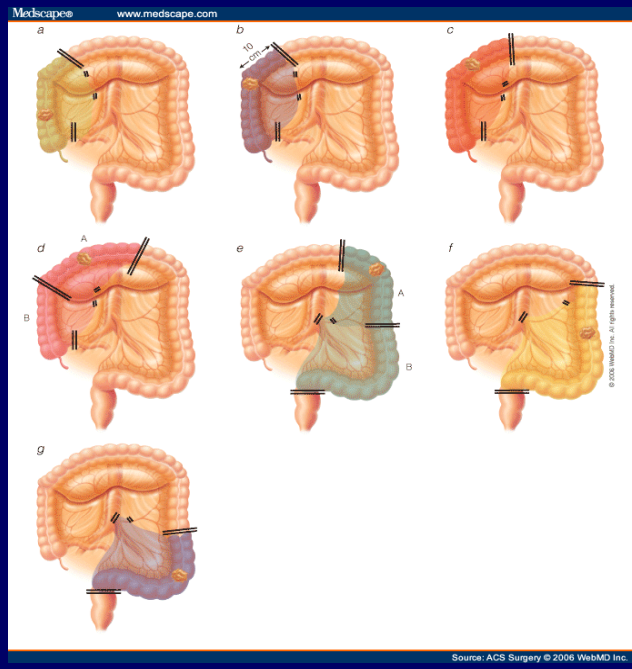
Principles of Biopsies

To biopsy or not to biopsy, that is the question?

Answer:

- Know your tumor biology
- Will it change treatment plan?
- Will biopsy cause tumor spread?
- Biopsy options
  - Aspiration, Core, Incisional, Excisional
- Avoid hematoma
- Plan to excise needle or biopsy site

Principles of Margins



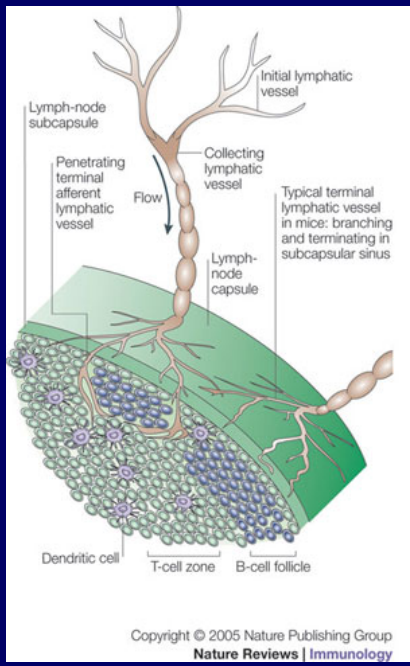
- Factor in tumor biology
- Factor in location
- Factor in other treatments
- In general 1cm gross margin is minimum necessary
- Wider margin preferable if it can be done with minimal additional morbidity
- Goal of margin is reduced local recurrence

Principles of Lymph Nodes

Function of lymph nodes

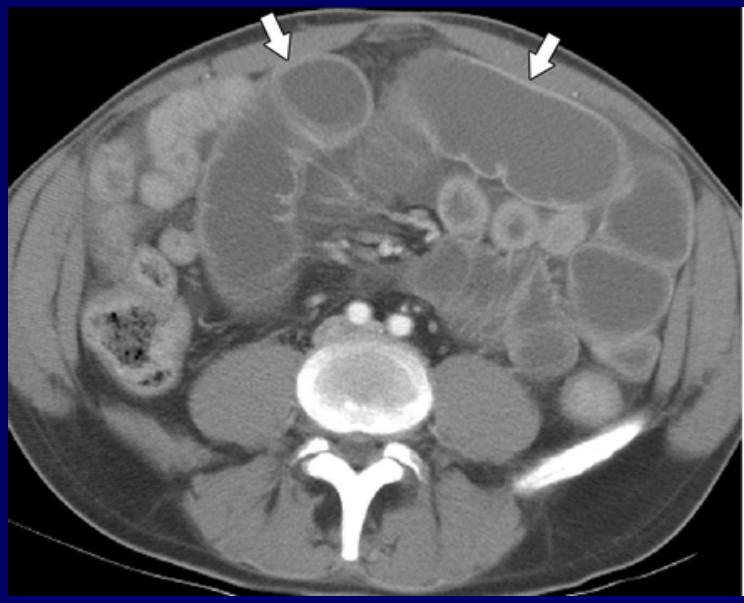
- Primarily for antigen recognition
- Not a filter
- Majority of tumor cells pass through
- Rare tumor cells can grow in lymph nodes
- Lymph nodes are indicators - not governors - of survival
- Therefore the assessment of lymph nodes is a prognostic tool

(that will one day be supplanted by molecular tools)



Principles of Palliative Surgery

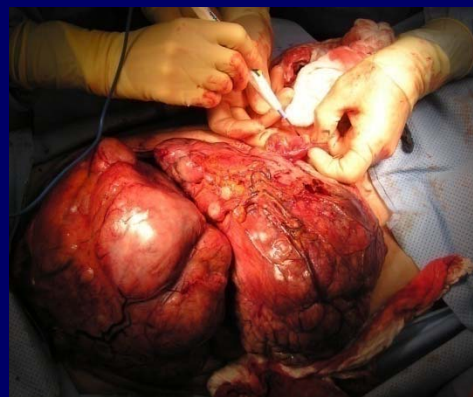
- One cannot palliate asymptomatic cancer patients
- Address the highest priority symptom first
- Manage expectations
- 25% will fail immediately
- 25% will recur with same symptom



Future of Surgical Oncology "Targeted Therapy"

The paradigm of Gastrointestinal Stromal Tumors (GIST)

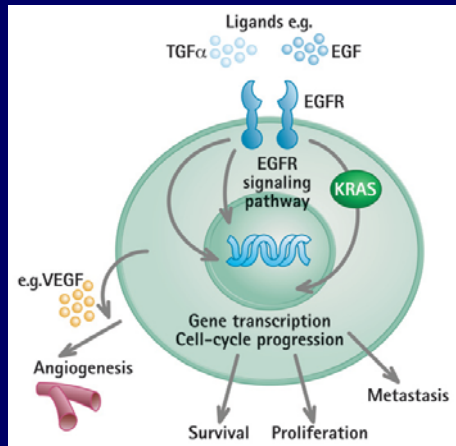
- **cKIT mutation (tyrosine kinase) identified as the activating growth signal**
- **Imatinib (Gleevec) developed as an oral agent to block the activating mutation (ATP binding site)**
- **Indicated in metastatic and high risk resected GIST**
- **Changed the natural history of this disease**



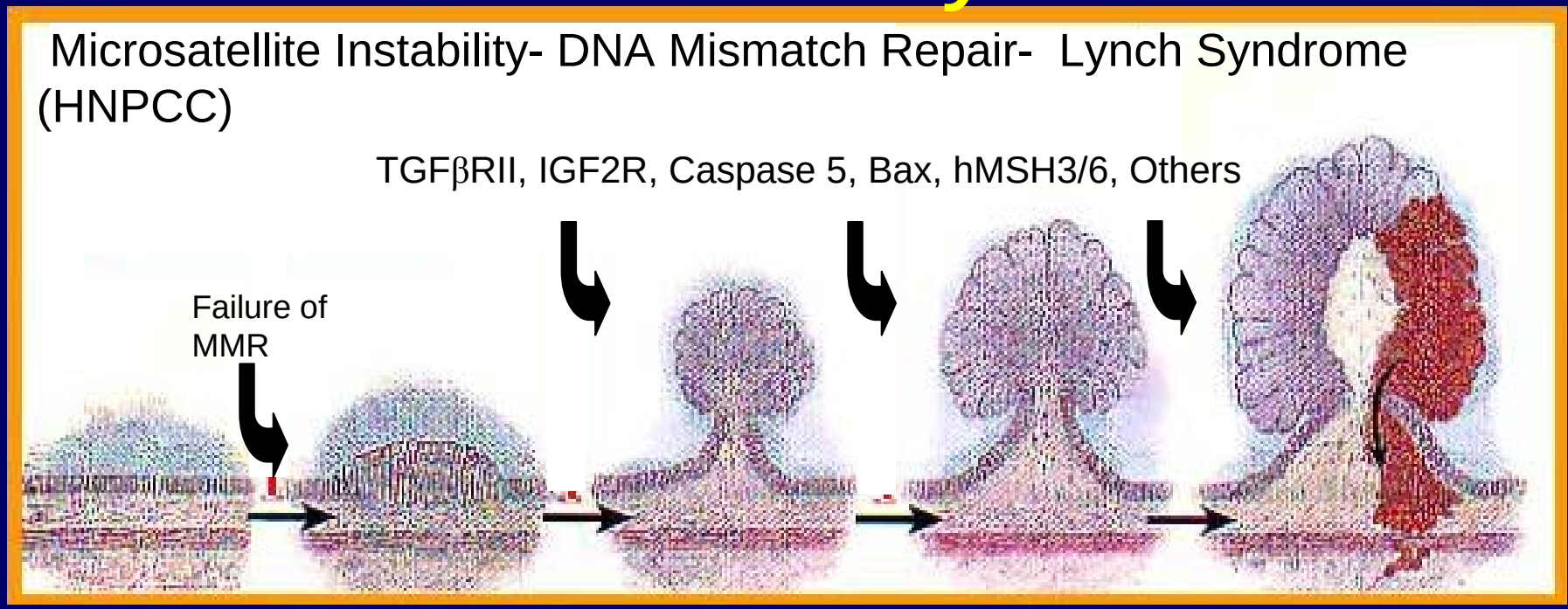
Future of Surgical Oncology "Personalized Therapy"

Example of Tumor KRAS Status in Colorectal Cancer

- Cetuximab (Erbitux) and panitumumab (Vectibix) are monoclonal antibodies directed at the epidermal growth-factor receptor
- Approved for treating metastatic colorectal cancer
- Tumors with a mutation in KRAS (downstream of EGRF) do not respond to EGFR receptor blockade
- Tumor analysis now required to treat with these agents

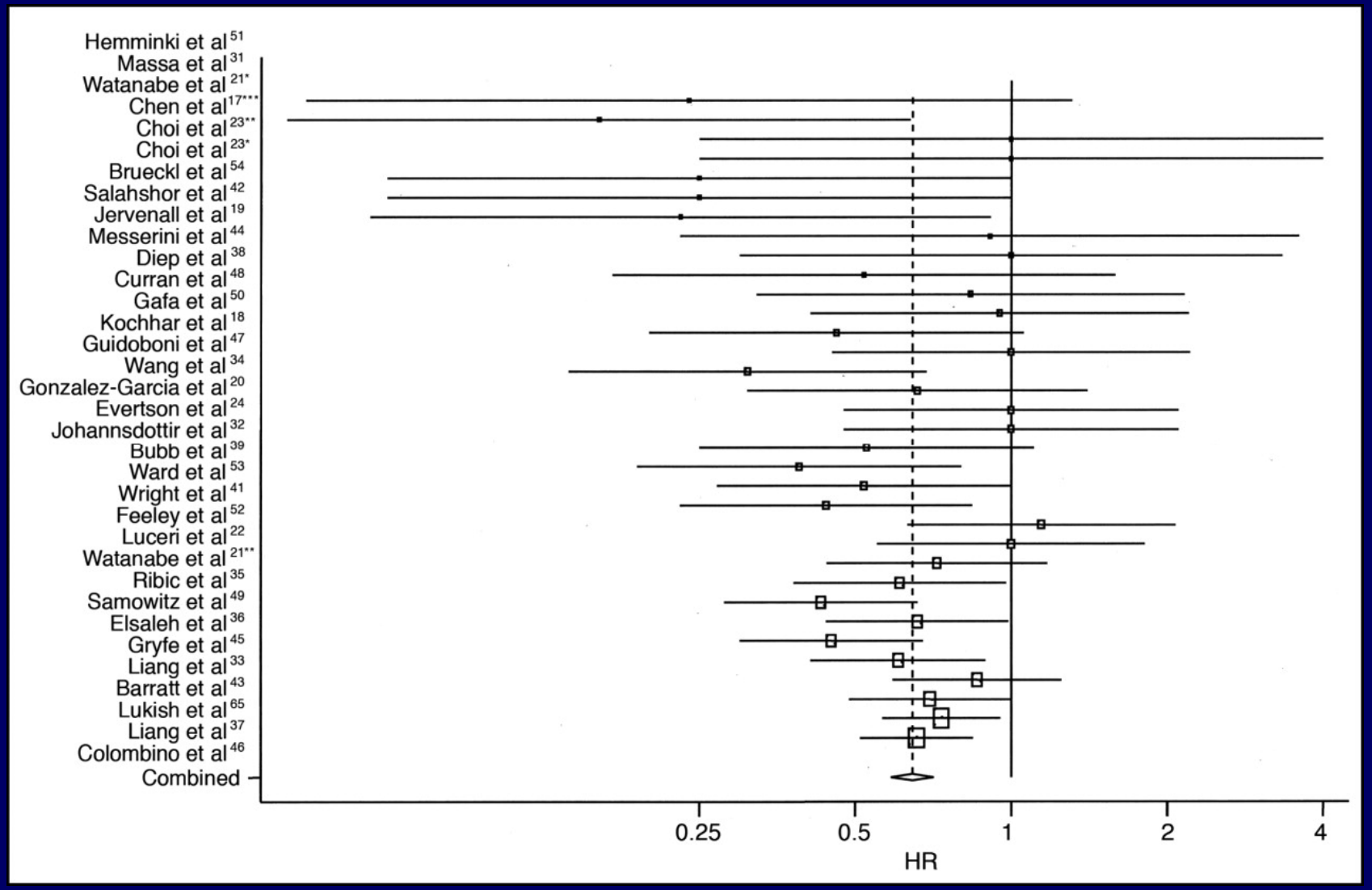


Microsatellite Instability Pathway



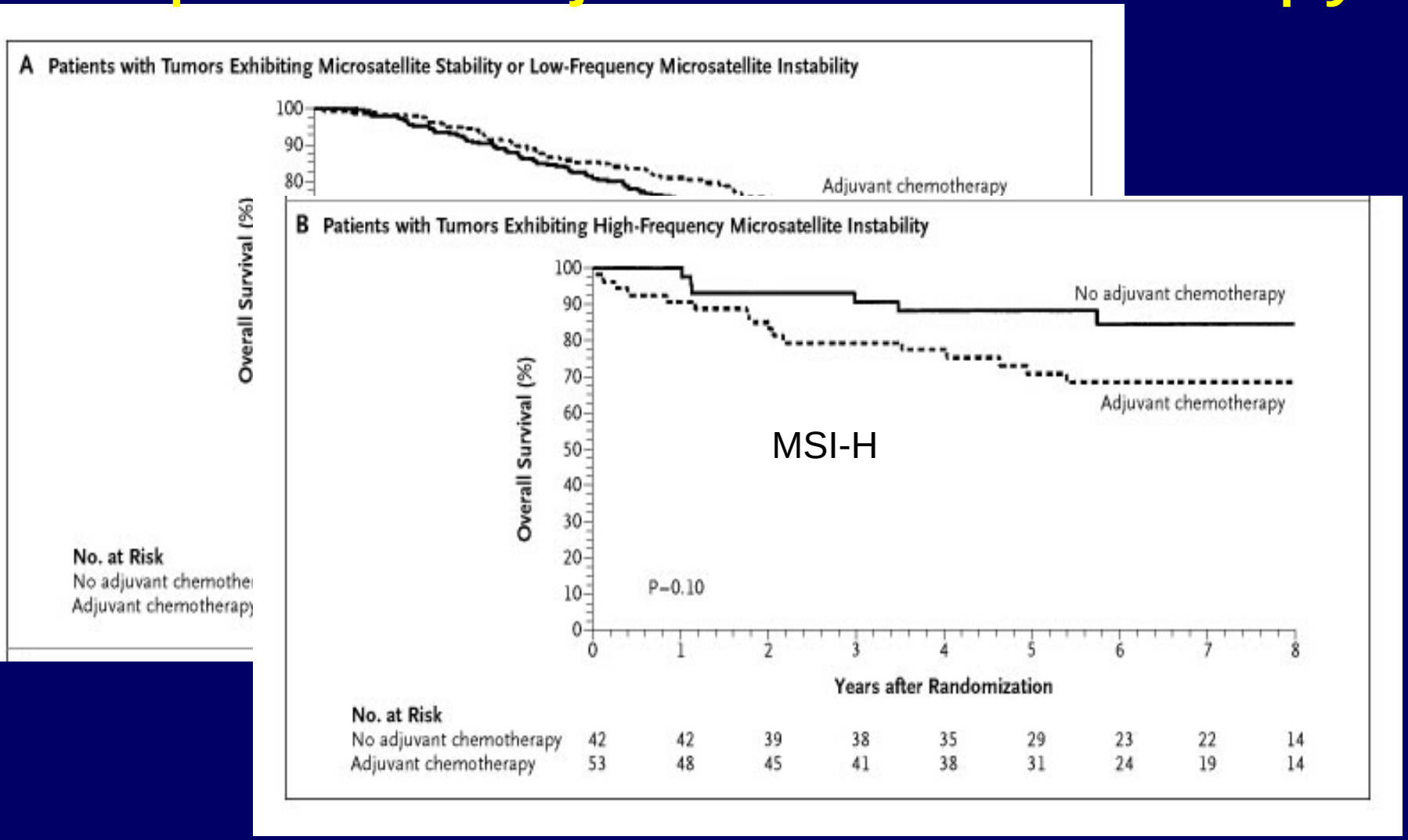
Jänne PA, Mayer RJ. N Engl J Med. 2000;342:1960-8.

Meta analysis of Death- MSI-H vs. MSS



Popat, S. et al. J Clin Oncol; 23:609-618 2005

Microsatellite Unstable CRCs May Not Respond to Adjuvant Chemotherapy

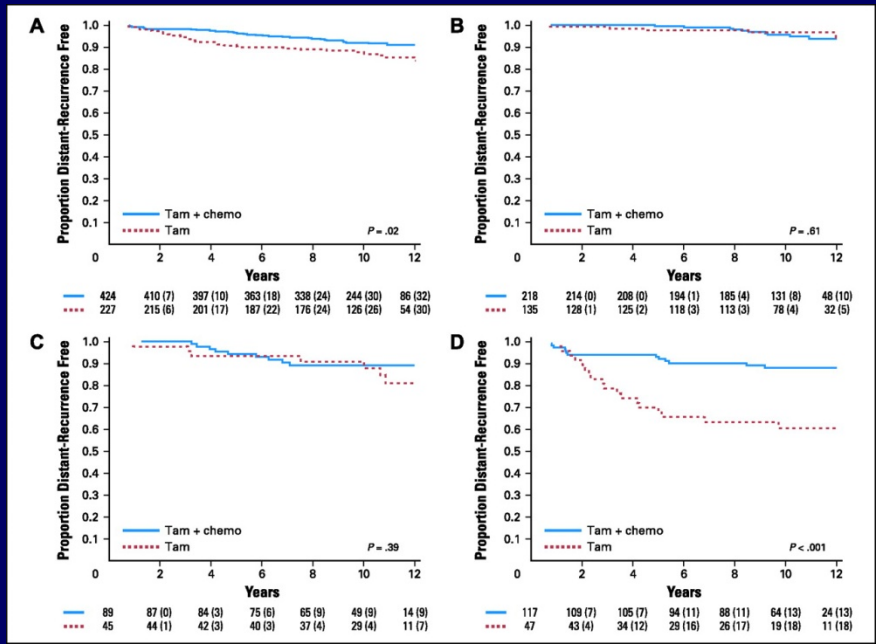


Ribic et al. NEJM 2003

Molecular Diagnostics

Oncotype Dx for Breast Cancer

- 21 Gene PCR on fixed tissue
- Quantifies the likelihood of disease recurrence in early-stage breast cancer
- Assesses the likely benefit from certain types of chemotherapy

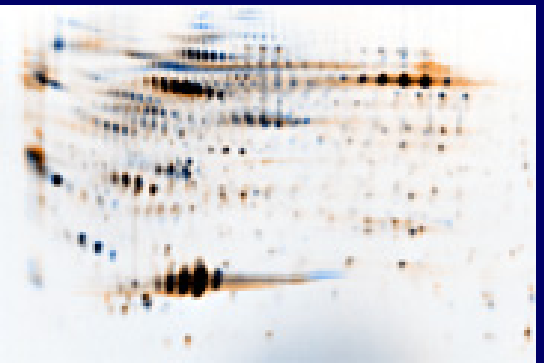


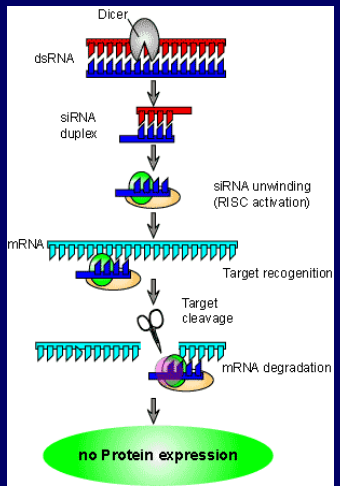
Paik S. J Clin Oncol. 2006;24(23):3726-34

Future of Surgical Oncology Biomarkers

Biomarkers are tumor or circulating molecules that help detect and monitor certain cancers

- **CEA, CA19-9, PSA, CA27-29**
- **Proteomic analysis**
- **microRNA or small interfering RNA (siRNA) analysis**
- **Breath analysis**





Issues of Molecular Marker Detection

Immunohistochemical (IHC) = antibody based assessment

- **Quick and easily adopted by most labs**
- **Strength of staining graded by the pathologist**
- **Examples- Breast – ER/PR, HER2/neu, and GIST – CD117**

Polymerase Chain Reaction (PCR) = Gene or mutation present

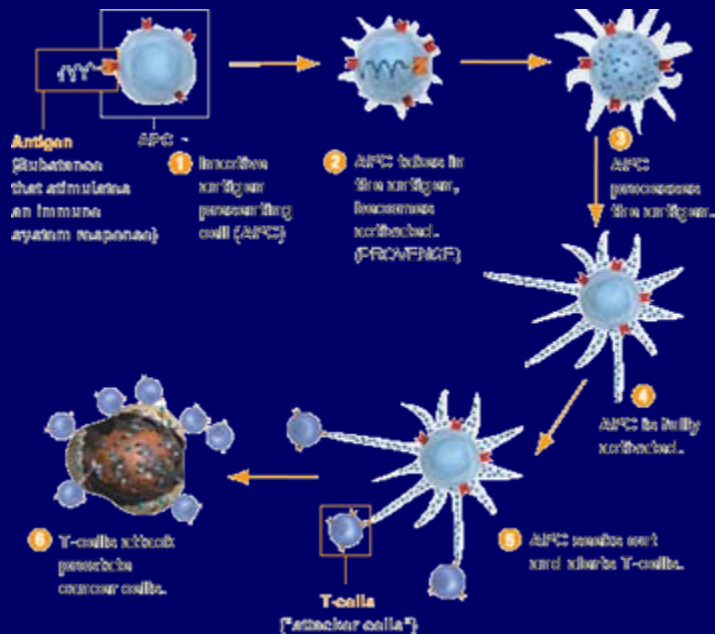
- **Certified lab**
- **Takes days to weeks for results**
- **Examples – Colon cancer KRAS, Melanoma BRAF**

New Immune Therapies

Sipuleucel-T (Provenge)

- FDA approved April 2010 for hormone resistant metastatic prostate cancer
- First therapeutic cancer vaccine to improve overall survival in Phase III trials
- Improved median survival from 21 to 25 months ($93,000)

- Extract antigen presenting cells (dendritic cells) from patient
- Mix with prostatic acid phosphatase (PAP)
- Stimulate with GM-CSF
- Re-infuse to patient three times, two weeks apart



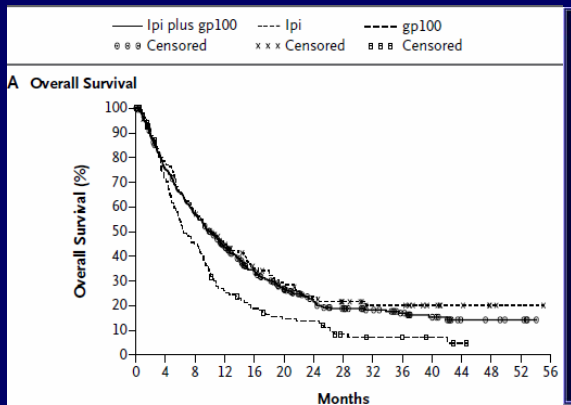
Kantoff PW. NEJM 2010 363: 411–422.

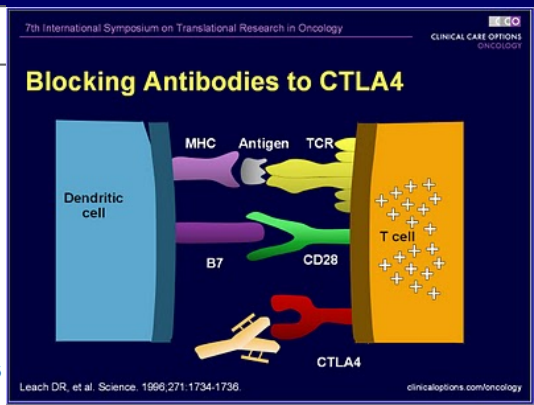
New Immune Therapies

Anti CTLA-4 antibody (Ipilimumab)

- Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) is an immune checkpoint molecule that down-regulates pathways of T-cell activation

- HLA-A2 patients with metastatic disease progressing on therapy
- Randomized to Ipilimumab +/- gp100 vaccine
- Improved overall survival from 6 to 10 months
- Autoimmune major toxicity in 10-15%



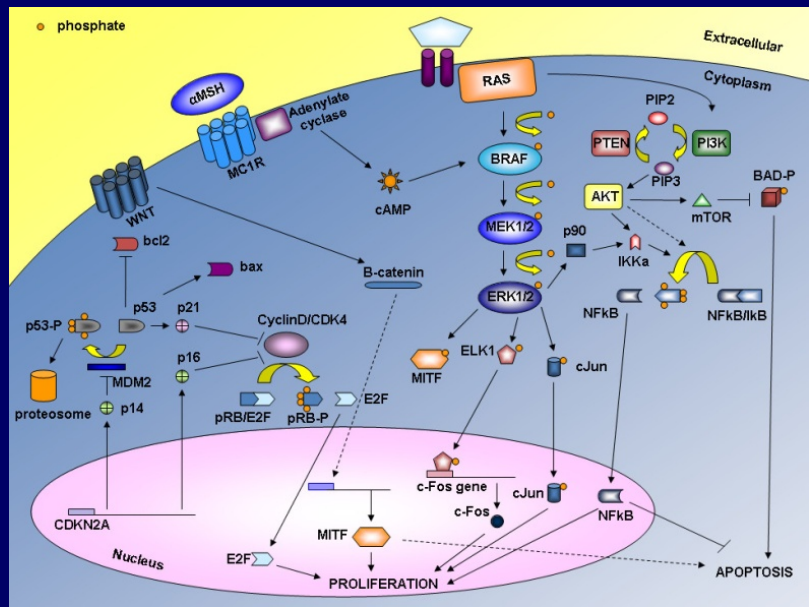


Hodi FS. N Engl J Med. 2010 Aug 19;363(8):711-23

New Targeted Therapies

BRAF inhibitor in Melanoma - PLX4032

- BRAF (V600E) mutation present in about 50% of melanoma
- BRAF mutation activates MAP Kinase pathway
- In phase I trial 26 out of 32 metastatic patients responded
- Phase III trial ongoing



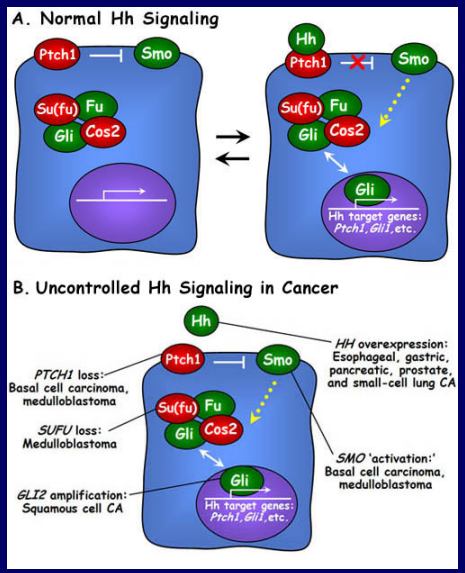
Flarehty KT. N Engl J Med 2010; 363:809-819

New Targeted Therapies

Hedgehog Pathway Inhibitors

- Hedgehog signaling pathway important in embryogenesis
- Regulating adult stem cells
- Involved in maintenance and regeneration of adult tissues

  - Metastatic basal cell carcinoma refractory to conventional chemotherapy
  - Frequently associated with mutations in hedgehog signaling pathway
  - GDC-0449 an inhibitor of smoothened homologue (*SMO*) of hedgehog
  - Phase I trial in which 18/33 patients had a measureable response



Van Hoff DD. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med. 2009 Sep 17;361(12):1164-72

Fundamentals of Surgical Oncology

Biology is King

Selection is Queen

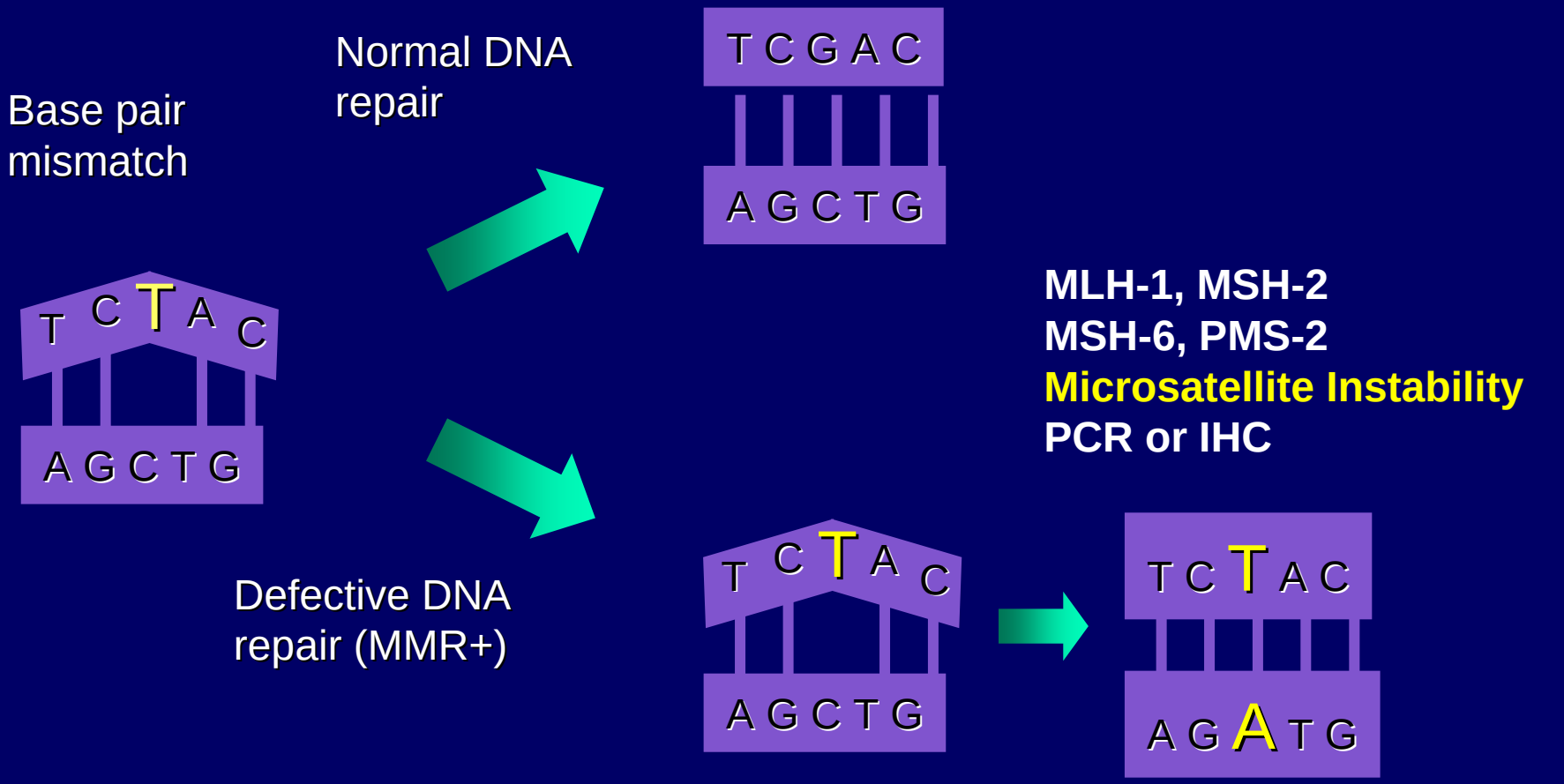
Technical maneuvers are the

Prince and Princess

Occasionally the prince and princess try to overthrow the powerful forces of the King and Queen, sometimes with temporary apparent victories, usually to no long term avail.

Blake Cady, MD

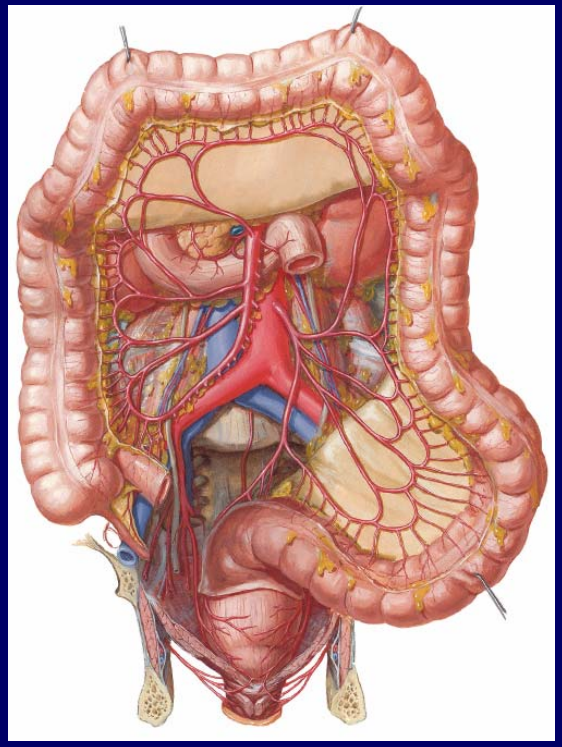
Lynch Syndrome Results From Failure of DNA Mismatch Repair (MMR) Genes



Principles of Surgical Oncology

Colorectal cancer

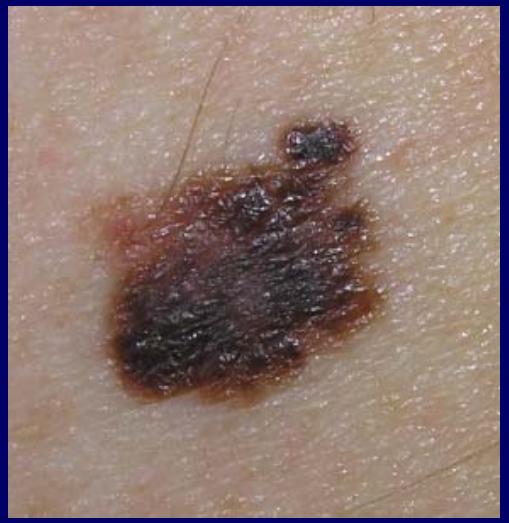
- 5 cm margin when possible
- 1 cm margin for low rectal with XRT
- Take major vascular pedicle at origin along with lymph nodes
- Equivalent cancer outcomes from laparoscopic vs. open



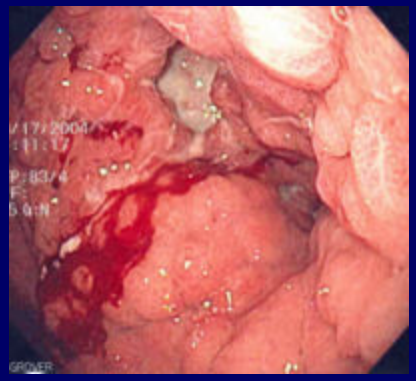
Principles of Surgical Oncology

Melanoma

- 1 cm margin for <1mm deep primary
- 2 cm margin for >1mm deep primary
- Exceptions for hands and face
- SLN biopsy for >1mm deep primary
- Sentinel lymph node biopsy for staging
- Lymph node dissection for metastasis

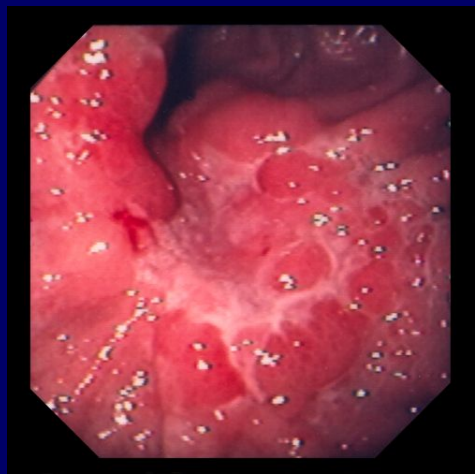


Principles of Surgical Oncology

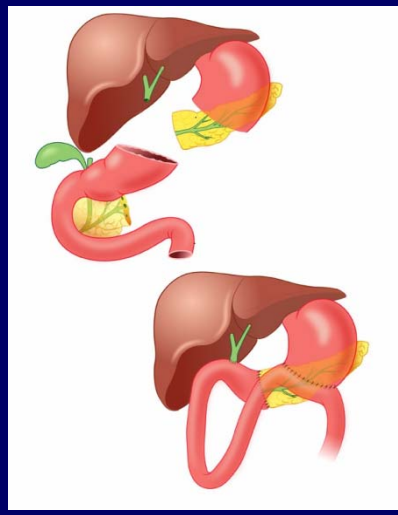


Gastric Cancer

- 5 cm margin when possible
- Take major vascular pedicle with lymph nodes
- Remove lymph node station beyond obviously involved nodes
- Splenectomy generally not indicated
- D2 dissection – no survival benefit

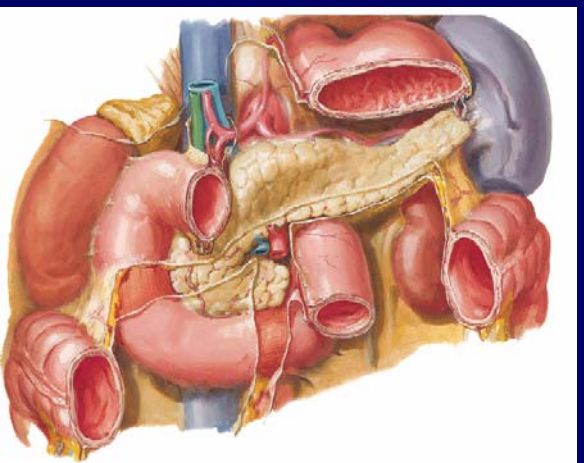


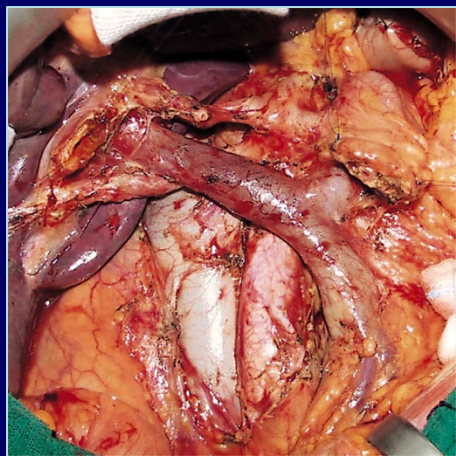
Principles of Surgical Oncology



Pancreatic Cancer

- Resectability is in the eye of the beholder
- Contraindications include Celiac, SMA or Hepatic artery involvement
- Relative contraindications include portal vein or lymph node positive disease

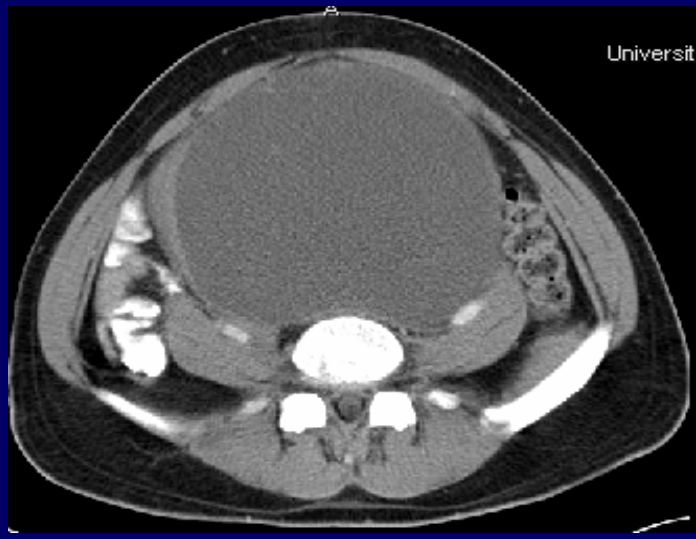




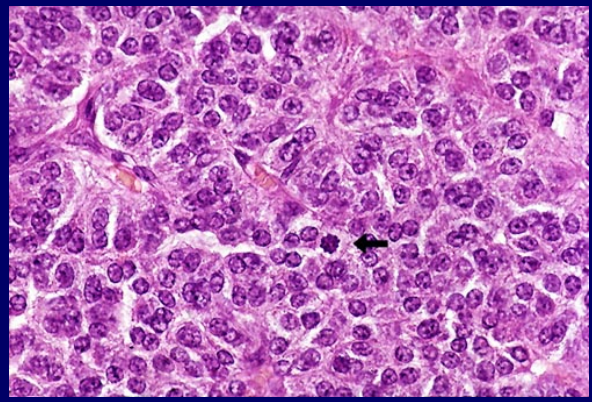
Principles of Surgical Oncology

Sarcoma

- 1-2 cm gross margin
- Preserve neurovascular structures
- No need for lymph nodes*
- Radiation reduces local recurrence
- Chemotherapy of limited value



Principles of Surgical Oncology

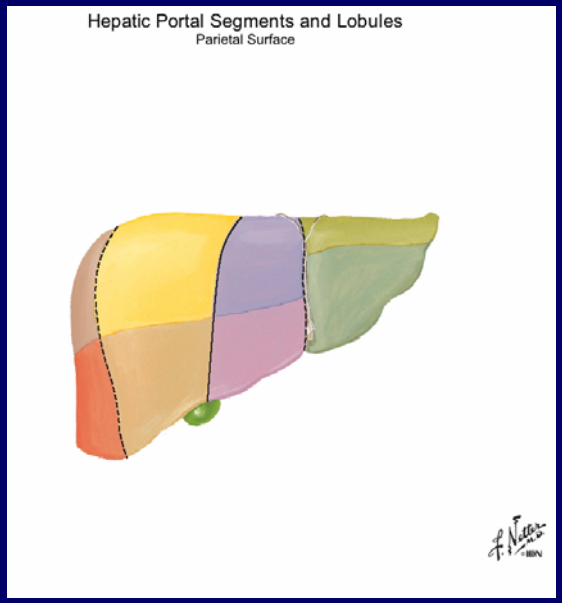


Carcinoids

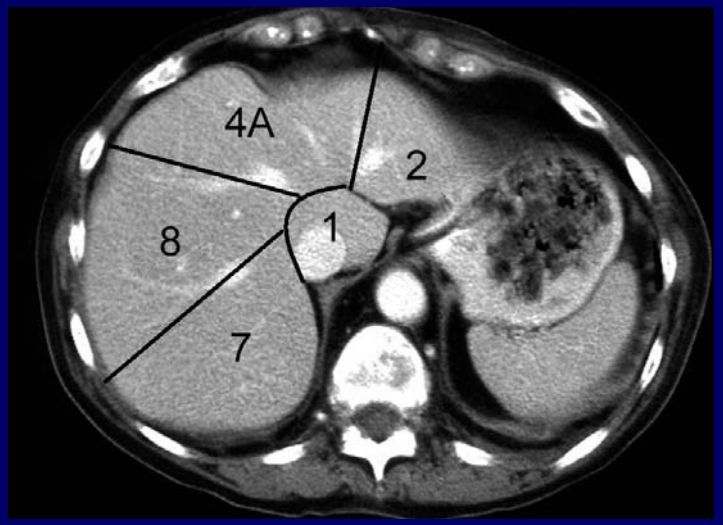
- Slow growing
- Surgery for symptoms – obstruction, hormonal
- Debulking as a goal
- <1 cm – remove tumor only
- >2 cm – remove tumor and lymph nodes
- 1-2 cm – consider removing lymph nodes

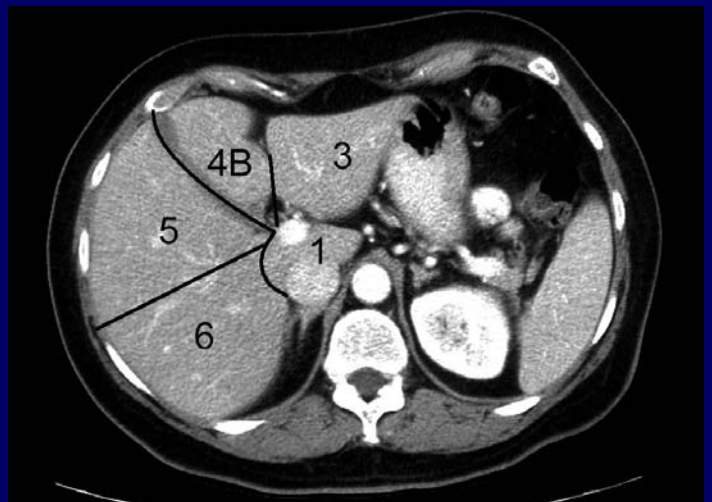
Principles of Surgical Oncology

Liver Tumors



- Primary vs. metastatic
- Resectability
  - Eye of the beholder
  - Real estate
  - Defined by what will be left behind
    (not by what can be removed)



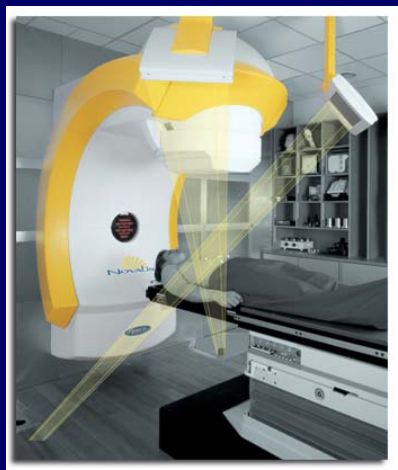


Principles of Radiation Oncology

Radiation Therapy

- Rapidly dividing cells
- Can help reduce local recurrence rate
- Organ preservation (breast, larynx, anal sphincter, extremity)
- Technology and targeting improving

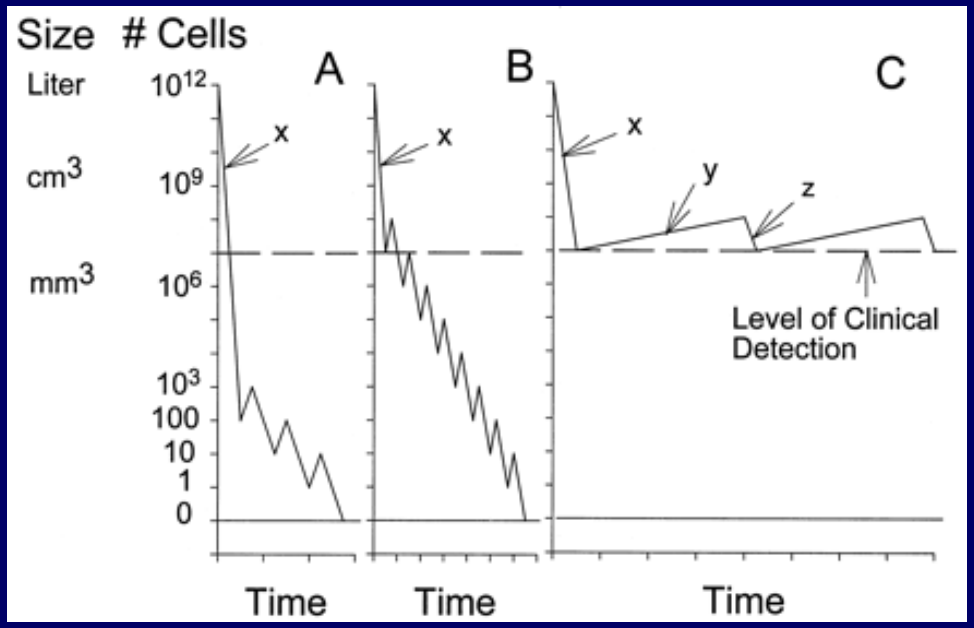
Breast cancer
Prostate cancer
Rectal cancer
Head & Neck
Sarcomas

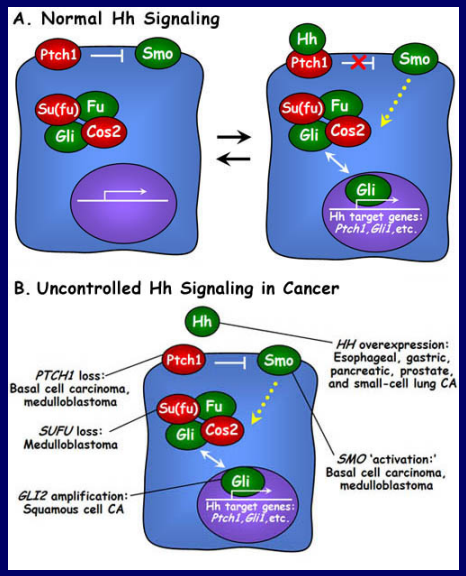


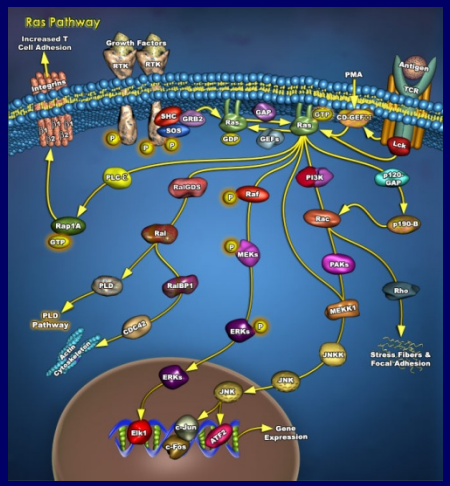
Principles of Medical Oncology

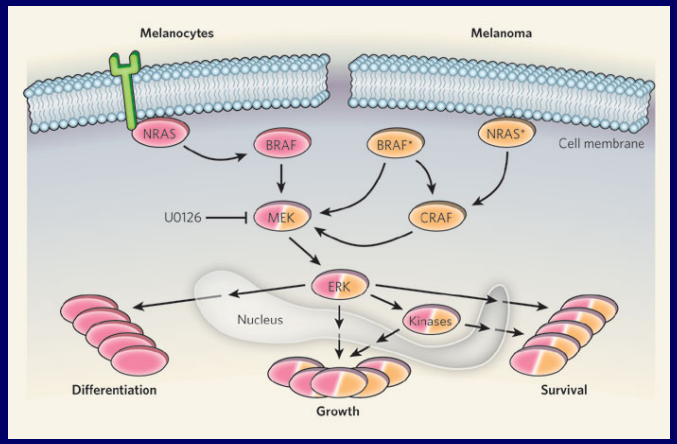
Concepts of Chemotherapy

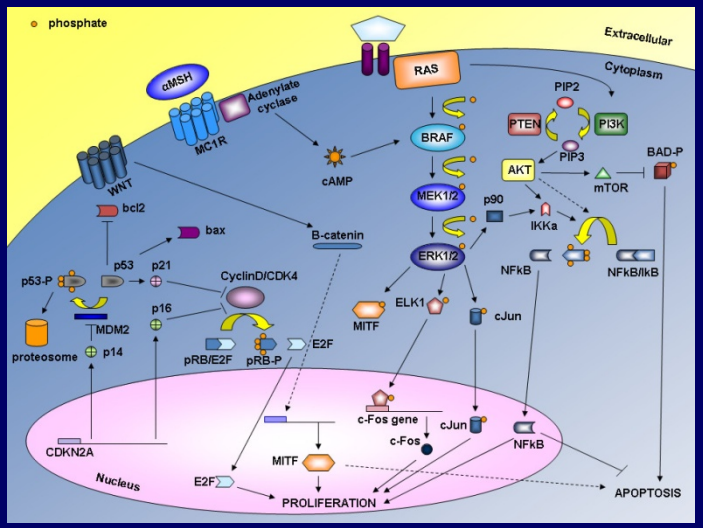
- Tumor doubling time
- Adjuvant vs. Neoadjuvant
- Targeting molecular pathways
- Biologic response indicators
- Drug development – phase I, II, III

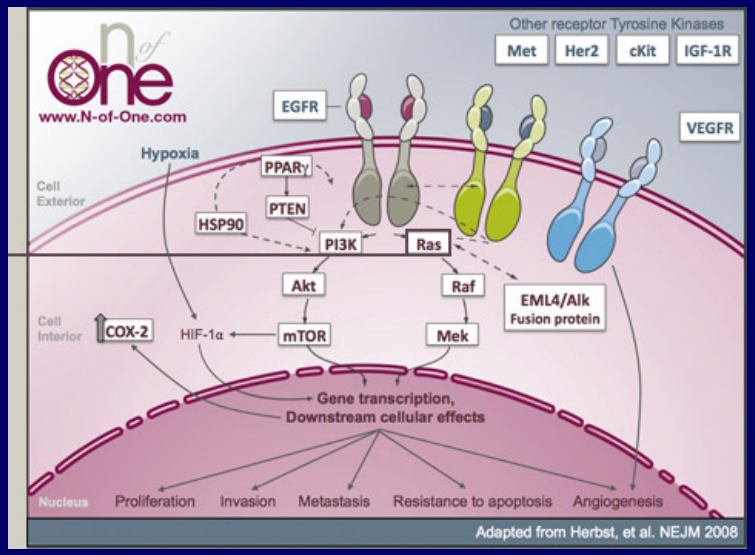


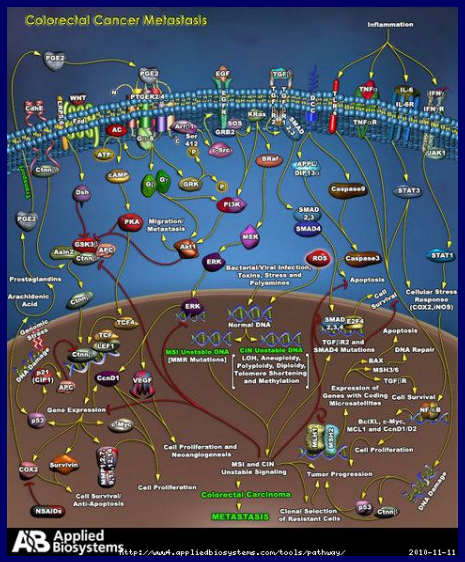

A. Normal Hh Signaling
Ptch1
Smo
Su(fu)
Fu
Gli
Cos2
Hh
Hh target genes:
Ptch1, Gli1, etc.
B. Uncontrolled Hh Signaling in Cancer
PTCH1 loss:
Basal cell carcinoma,
medulloblastoma
SUFU loss:
Medulloblastoma
GLI2 amplification:
Squamous cell CA
HH overexpression:
Esophageal, gastric,
pancreatic, prostate,
and small-cell lung CA
SMO 'activation:'
Basal cell carcinoma,
medulloblastoma

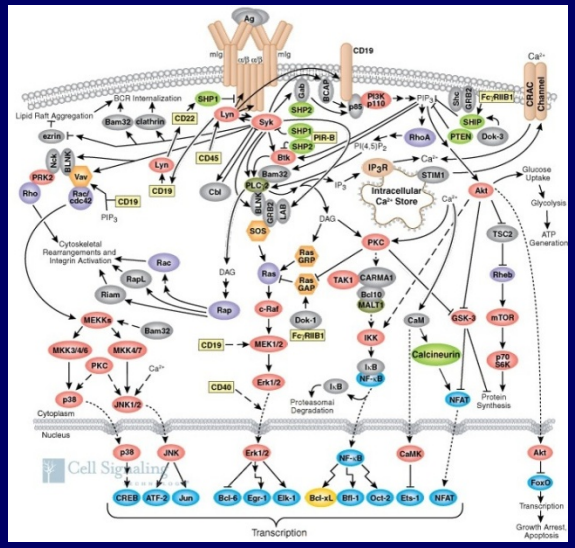

Ras Pathway
Increased T Cell Adhesion
Growth Factors
Integrins
PMA
Antigen
TCR
SHC
GRB2
SOS
GAP
GEFs
Lck
PLC-β
Ras-GDS
PI3K
Raf
Rac
p190-B
Rap1A
Ral
MEKs
PAKs
PLD
RalBP1
Rho
PLD Pathway
CDC42
ERKs
MEKK1
JNKK
JNK
Stress Fibers & Focal Adhesion
Elk1
c-Jun
ATF2
c-Fos
Gene Expression

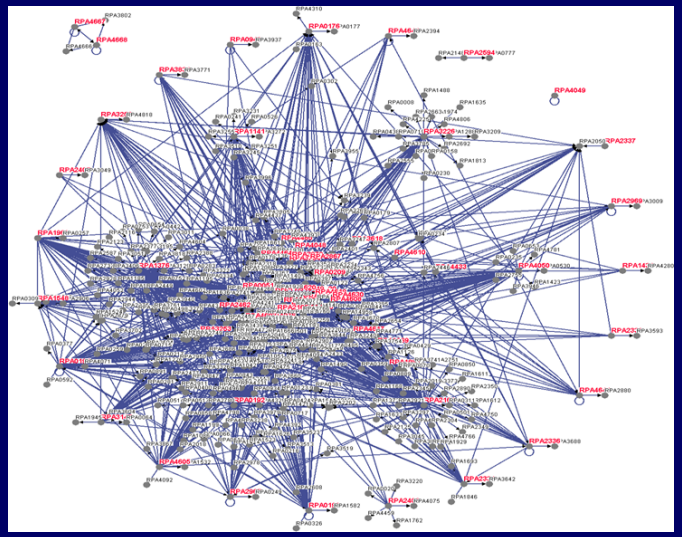

Melanocytes
Melanoma
NRAS
BRAF
BRAF*
NRAS*
Cell membrane
U0126
MEK
CRAF
ERK
Nucleus
Kinases
Differentiation
Growth
Survival


phosphate
Extracellular
Cytoplasm
αMSH
Adenylate cyclase
MC1R
RAS
PIP2
PTEN
PI3K
PIP3
BAD-P
AKT
mTOR
WNT
cAMP
BRAF
MEK1/2
p90
IKKa
bcl2
bax
B-catenin
ERK1/2
NFkB
NFkB/IkB
p53
p21
p53-P
CyclinD/CDK4
ELK1
cJun
MITF
MDM2
p16
proteosome
p14
pRB/E2F
pRB-P
E2F
c-Fos gene
c-Fos
CDKN2A
Nucleus
PROLIFERATION
APOPTOSIS


n of One
www.N-of-One.com
Other receptor Tyrosine Kinases
Met
Her2
cKit
IGF-1R
EGFR
VEGFR
Hypoxia
PPARγ
PTEN
HSP90
PI3K
Ras
Akt
Raf
EML4/Alk
Fusion protein
Cell Exterior
Cell Interior
COX-2
HIF-1α
mTOR
Mek
Gene transcription,
Downstream cellular effects
Nucleus
Proliferation
Invasion
Metastasis
Resistance to apoptosis
Angiogenesis
Adapted from Herbst, et al. NEJM 2008

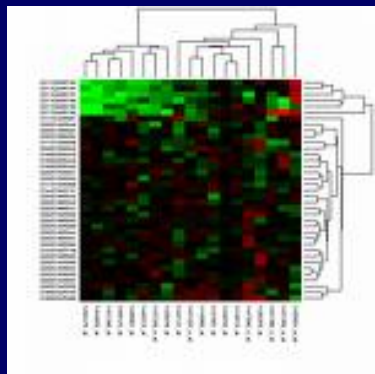

Colorectal Cancer Metastasis
Inflammation
Applied Biosystems
2010-11-11


Ag
CD19
SHP1
Lyn
Syk
SHP2
PIR-B
PI3K p110
PIP3
PIP2
SHP
PTEN
Dok-3
RhoA
Btk
Bam32
PLC-γ2
IP3R
STIM1
Intracellular Ca2+ Store
Glucose Uptake
Glycolysis
ATP Generation
Akt
TSC2
Rheb
mTOR
p70 S6K
Protein Synthesis
SOS
Ras GRP
Ras GAP
PKC
TAK1
CARMA1
Bcl10
MALT1
IKK
I-κB
NF-κB
Proteasomal Degradation
CaM
GSK-3
Calcineurin
NFAT
c-Raf
Dok-1
MEK1/2
Erk1/2
Rap
Rac
RapL
Riam
MEKKs
MKK3/4/6
MKK4/7
PKC
p38
JNK1/2
Cytoplasm
Nucleus
CD45
CD22
CD40
CD19
Fc RIIB1
CRAC Channel
Cytoskeletal Rearrangements and Integrin Activation
Lipid Raft Aggregation
BCR Internalization
CREB
ATF-2
Jun
Bcl-6
Egr-1
Elk-1
Bcl-xL
Bfl-1
Oct-2
Ets-1
NFAT
FoxO
Transcription
Growth Arrest Apoptosis
Transcription



Future of Surgical Oncology

- Growing opportunity
- 1 in 3 diagnosed with some form of cancer
- Aging population
- Increased need for surgical specialists with broad knowledge of cancer treatments
- Integration of multiple therapies
- Field wide open for basic and clinical research
- Intellectually stimulating – rapid progress
- Molecular evaluation of tumor



Rules of Surgical Oncology

Biology is King

Selection is Queen

Technical maneuvers are the

Prince and Princess

Occasionally the prince and princess try to overthrow the powerful forces of the King and Queen, sometimes with temporary apparent victories, usually to no long term avail.

Blake Cady, MD

#1 Rule of Surgical Oncology

When in doubt – consult this man

Future of Surgical Oncology

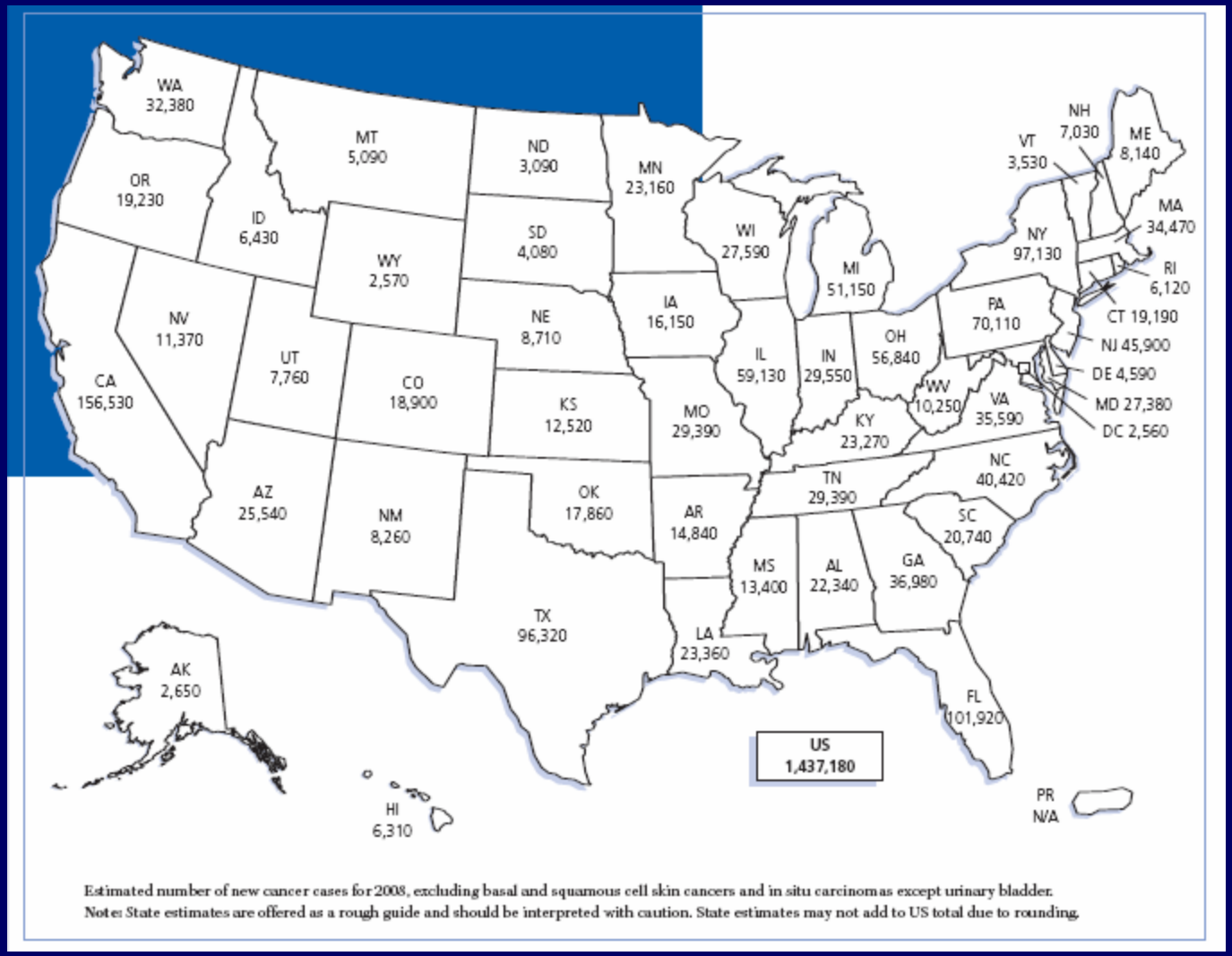
Past	Radical resection
Present	Conservative resection (laparoscopic approaches)
Future	?

Tumor Biology

Tumor Type	Estimated Tumor Doubling Time (days)
Choriocarcinoma	1.5
ALL	4-6
Hodgkin's	38
GI adenocarcinoma	80-130

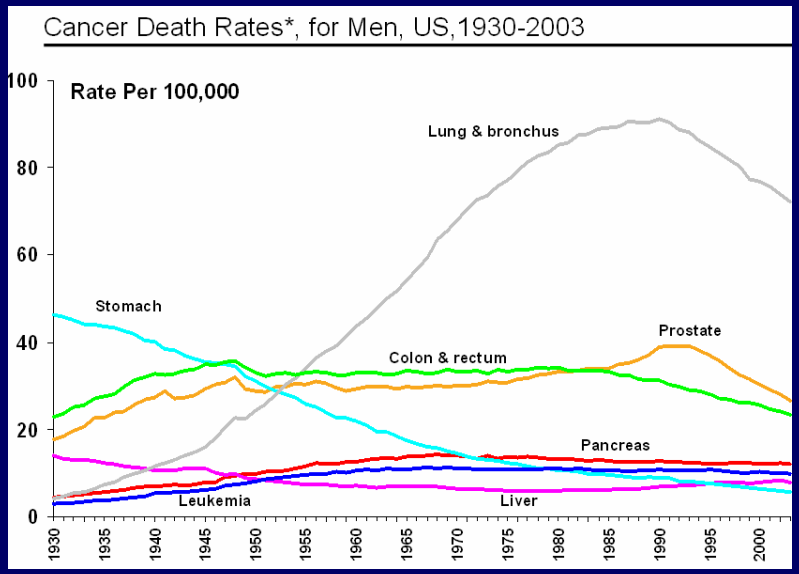
McCarter, M. Ann Surg Onc 2000;8:38-43

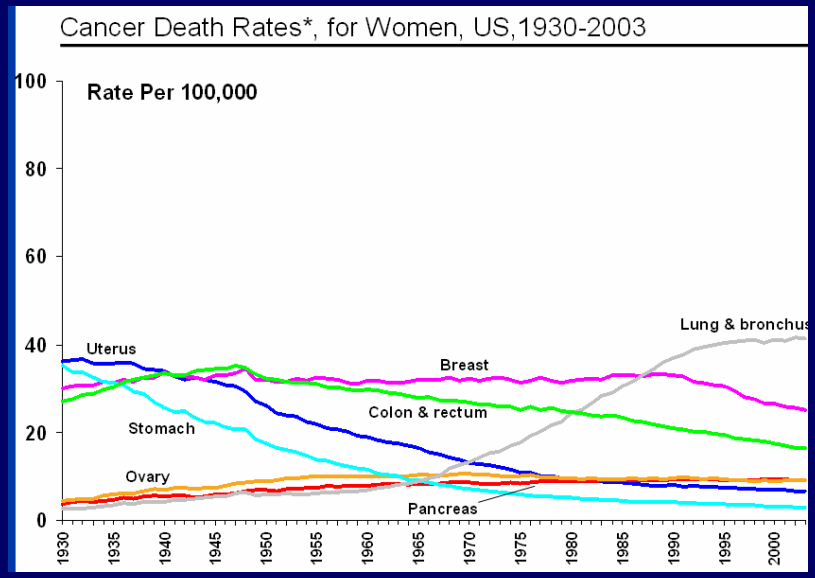
Scope of the Problem

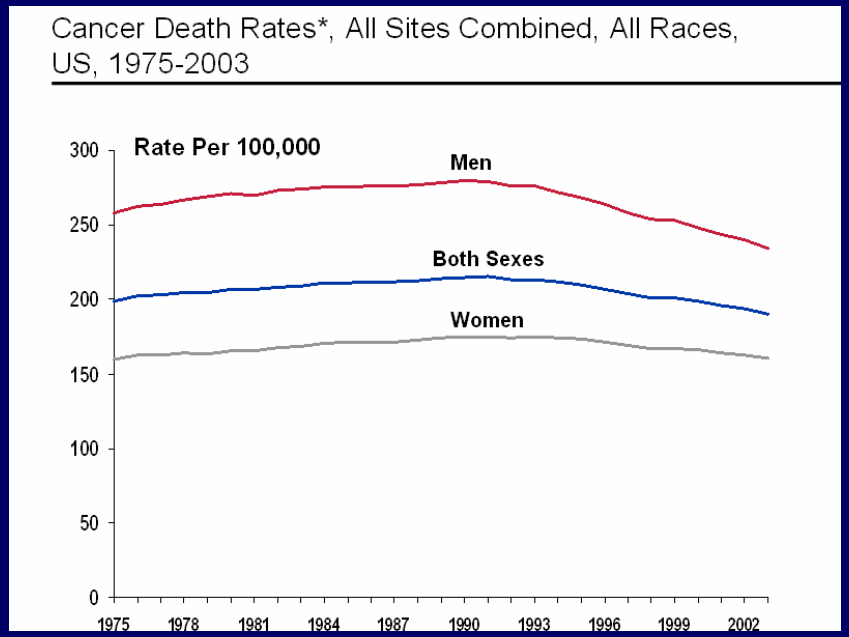


www.cancer.org

Scope of the Problem







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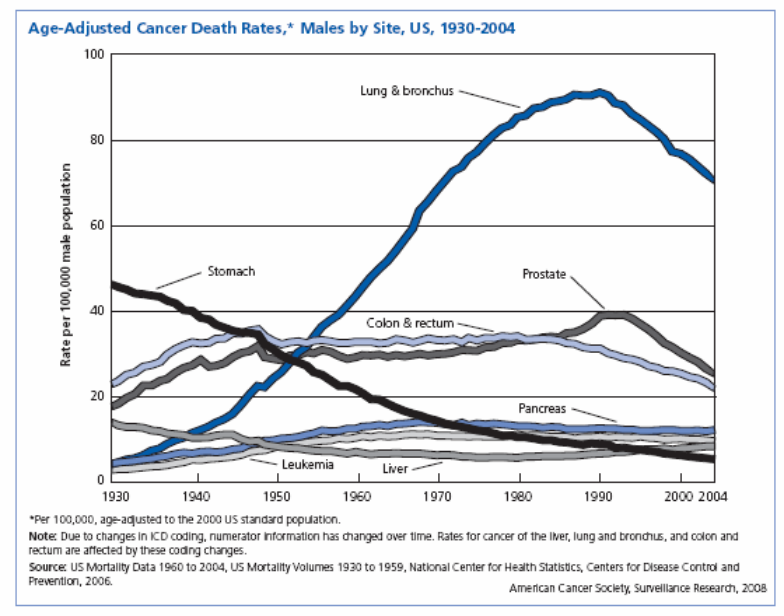
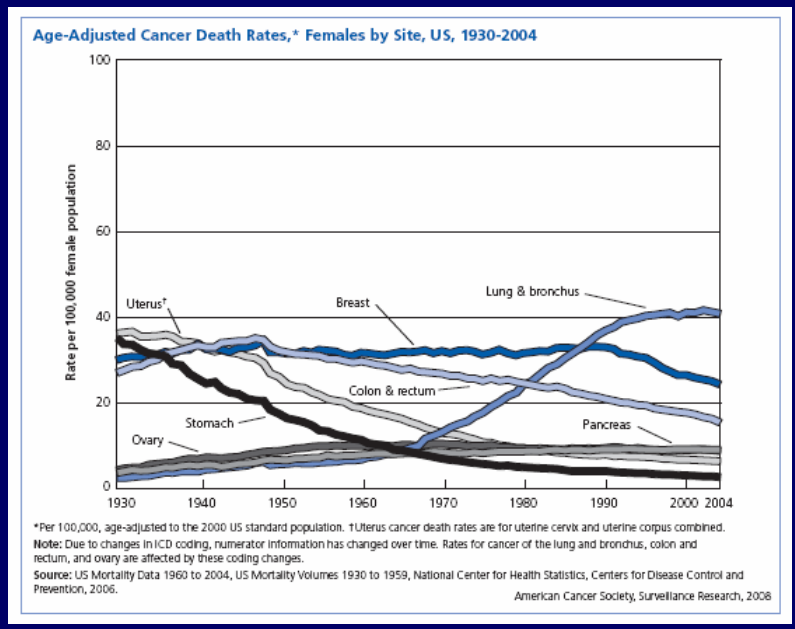
Scope of the Problem





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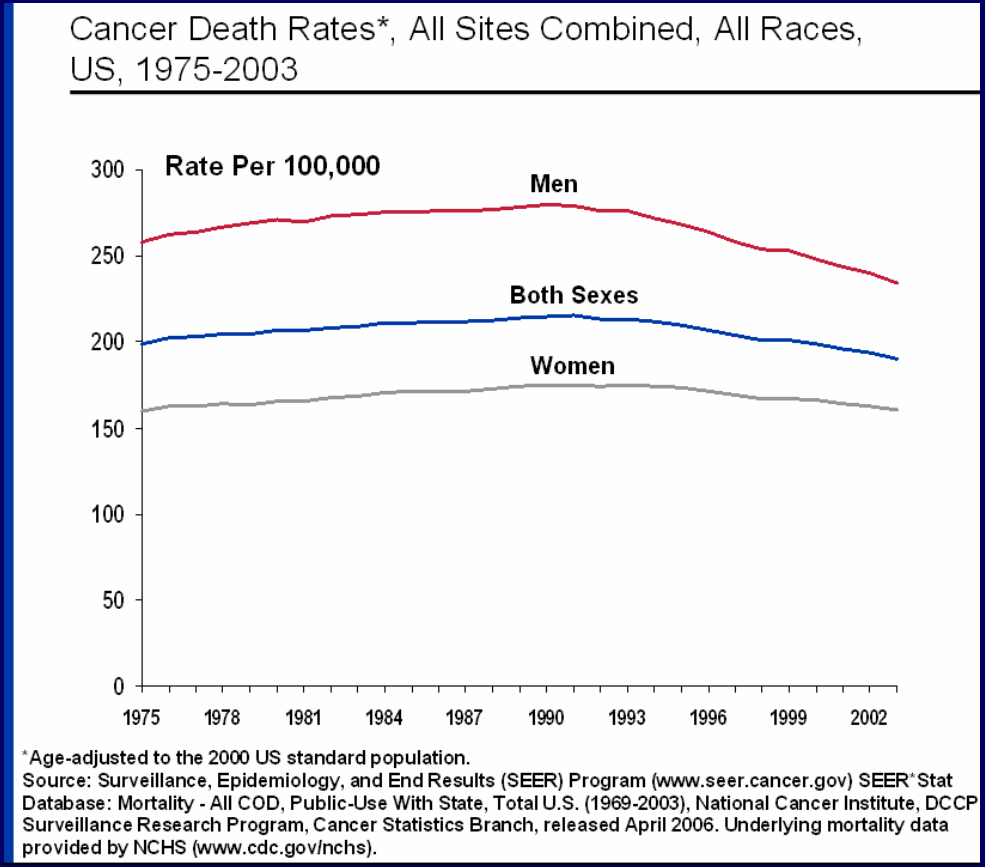
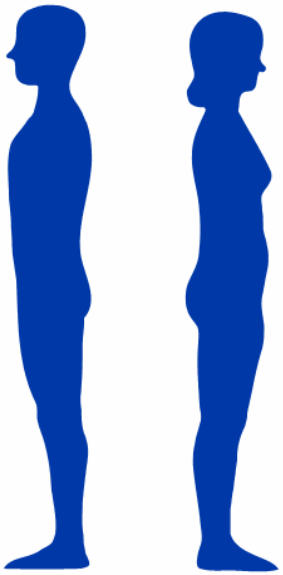
Scope of the Problem



Scope of the Problem

2007 Estimated US Cancer Cases*

		Men 766,860	Women 678,060		
Prostate	29%			26%	Breast
Lung & bronchus	15%			15%	Lung & bronchus
Colon & rectum	10%			11%	Colon & rectum
Urinary bladder	7%			6%	Uterine corpus
Non-Hodgkin lymphoma	4%			4%	Non-Hodgkin lymphoma
Melanoma of skin	4%			4%	Melanoma of skin
Kidney	4%			4%	Thyroid
Leukemia	3%			3%	Ovary
Oral cavity	3%			3%	Kidney
Pancreas	2%			3%	Leukemia
All Other Sites	19%			21%	All Other Sites

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2007.

www.cancer.org

Scope of the Problem

Probability of Developing Invasive Cancers (%) Over Selected Age Intervals by Sex, US, 2003-2005*

		Birth to 39	40 to 59	60 to 69	70 and Older	Birth to Death
All sites†	Male	1.42 (1 in 70)	8.44 (1 in 12)	15.71 (1 in 6)	37.74 (1 in 3)	43.89 (1 in 2)
	Female	2.07 (1 in 48)	8.97 (1 in 11)	10.23 (1 in 10)	26.17 (1 in 4)	37.35 (1 in 3)
Urinary bladder‡	Male	0.02 (1 in 4,448)	0.41 (1 in 246)	0.96 (1 in 104)	3.57 (1 in 28)	3.74 (1 in 27)
	Female	0.01 (1 in 10,185)	0.12 (1 in 810)	0.26 (1 in 378)	1.01 (1 in 99)	1.18 (1 in 84)
Breast	Female	0.48 (1 in 208)	3.79 (1 in 26)	3.41 (1 in 29)	6.44 (1 in 16)	12.03 (1 in 8)
Colon & rectum	Male	0.08 (1 in 1,296)	0.92 (1 in 109)	1.55 (1 in 65)	4.63 (1 in 22)	5.51 (1 in 18)
	Female	0.07 (1 in 1,343)	0.72 (1 in 138)	1.10 (1 in 91)	4.16 (1 in 24)	5.10 (1 in 20)
Leukemia	Male	0.16 (1 in 611)	0.22 (1 in 463)	0.35 (1 in 289)	1.17 (1 in 85)	1.50 (1 in 67)
	Female	0.12 (1 in 835)	0.14 (1 in 693)	0.20 (1 in 496)	0.77 (1 in 130)	1.07 (1 in 94)
Lung & bronchus	Male	0.03 (1 in 3,398)	0.99 (1 in 101)	2.43 (1 in 41)	6.70 (1 in 18)	7.78 (1 in 13)
	Female	0.03 (1 in 2,997)	0.81 (1 in 124)	1.78 (1 in 56)	4.70 (1 in 21)	6.22 (1 in 16)
Melanoma of the skin§	Male	0.16 (1 in 645)	0.64 (1 in 157)	0.70 (1 in 143)	1.67 (1 in 60)	2.56 (1 in 39)
	Female	0.27 (1 in 370)	0.53 (1 in 189)	0.35 (1 in 282)	0.76 (1 in 131)	1.73 (1 in 58)
Non-Hodgkin lymphoma	Male	0.13 (1 in 763)	0.45 (1 in 225)	0.58 (1 in 171)	1.66 (1 in 60)	2.23 (1 in 45)
	Female	0.08 (1 in 1,191)	0.32 (1 in 316)	0.45 (1 in 223)	1.36 (1 in 73)	1.90 (1 in 53)
Prostate	Male	0.01 (1 in 10,002)	2.43 (1 in 41)	6.42 (1 in 16)	12.49 (1 in 8)	15.78 (1 in 6)
Uterine cervix	Female	0.15 (1 in 651)	0.27 (1 in 368)	0.13 (1 in 761)	0.19 (1 in 530)	0.69 (1 in 145)
Uterine corpus	Female	0.07 (1 in 1,499)	0.72 (1 in 140)	0.81 (1 in 123)	1.22 (1 in 82)	2.48 (1 in 40)

* For people free of cancer at beginning of age interval.

† All sites excludes basal and squamous cell skin cancers and in situ cancers except urinary bladder.

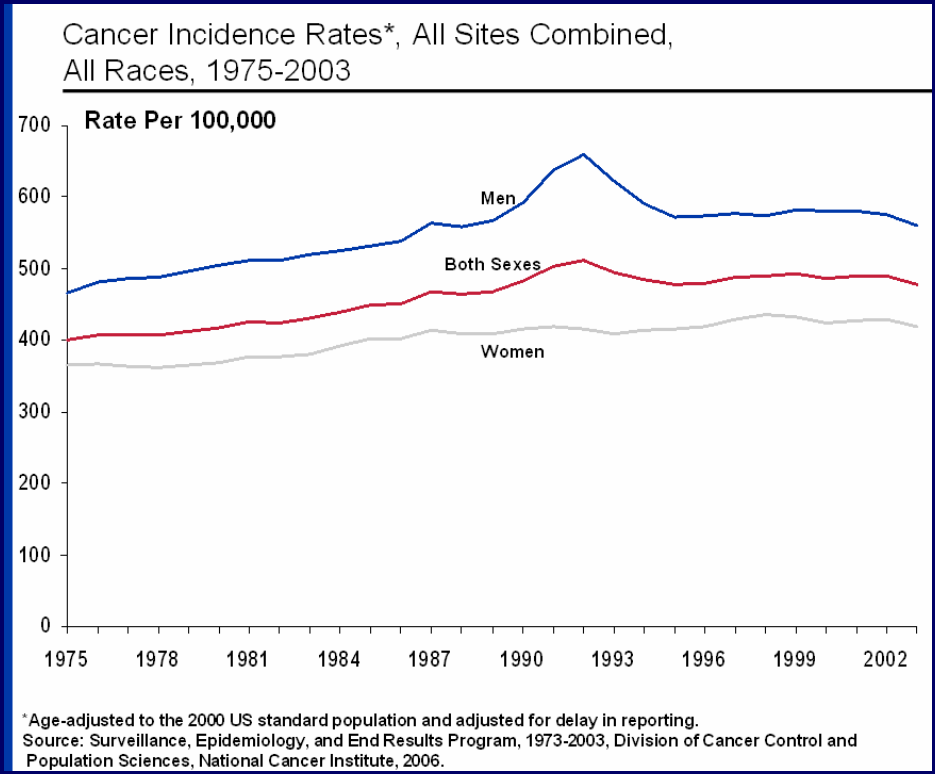
‡ Includes invasive and in situ cancer cases.

§ Statistic is for whites only.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.3.0. Statistical Research and Applications Branch, National Cancer Institute, 2008. srab.cancer.gov/devcan.

American Cancer Society, Surveillance and Health Policy Research, 2009

Scope of the Problem



Scope of the Problem

Five-year Relative Survival (%)* during Three Time Periods By Cancer Site

Site	1975-1977	1984-1986	1996-2002
All sites	50	53	66
Breast (female)	75	79	89
Colon	51	59	65
Leukemia	35	42	49
Lung and bronchus	13	13	16
Melanoma	82	86	92
Non-Hodgkin lymphoma	48	53	63
Ovary	37	40	45†
Pancreas	2	3	5
Prostate	69	76	100
Rectum	49	57	66
Urinary bladder	73	78	82

*5-year relative survival rates based on follow up of patients through 2003.
†Recent changes in classification of ovarian cancer have affected 1996-2002 survival rates.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2003, Division of Cancer Control and Population Sciences, National Cancer Institute, 2006.

Principles of Patient Selection

- Know tumor biology
- Know extent of disease
- Disease free interval
- Clarify goal of operation
  (cure, debulk, palliate)

Patient Selection - Liver Metastasis

Risk Factors

- Node positive primary
- Disease free interval <12 mo
- >1 tumor
- Size >5cm
- CEA > 200ng/ml

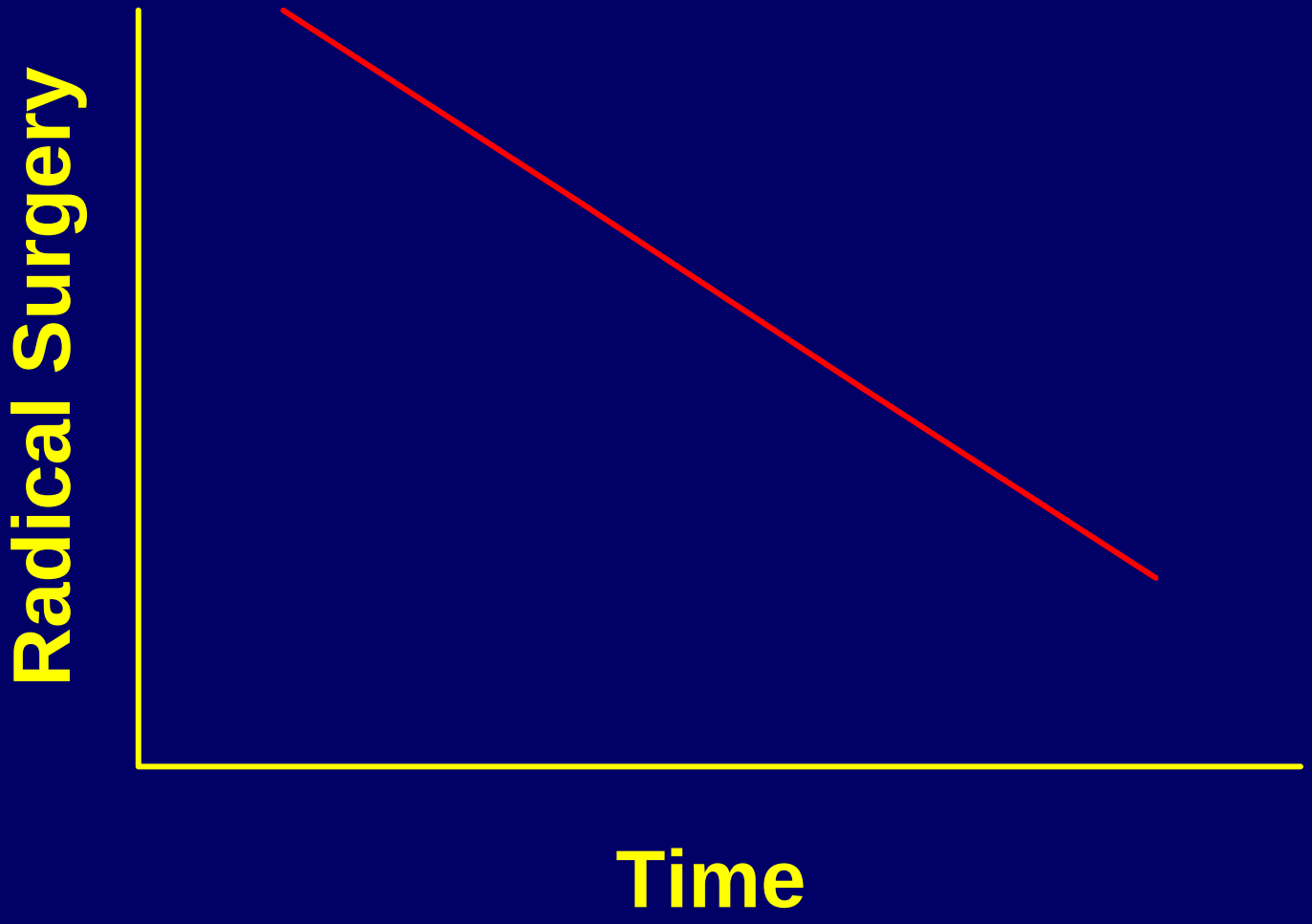
Table 5. CLINICAL RISK SCORE FOR TUMOR RECURRENCE

	Survival (%)					
Score	1-yr	2-yr	3-yr	4-yr	5-yr	Median (mo)
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumor, Size >5 cm, CEA >200 ng/ml.

Fong Y, Ann Surg 1999;230:309-21

History of Surgical Oncology



Scope of the Problem

Lifetime Probability of Developing Cancer, by Site, Women, US, 2001-2003*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 16
Colon & rectum	1 in 19
Uterine corpus	1 in 40
Non-Hodgkin lymphoma	1 in 55
Ovary	1 in 69
Melanoma	1 in 73
Pancreas	1 in 79
Urinary bladder‡	1 in 87
Uterine cervix	1 in 138

* For those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 2001 to 2003.
† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.1.1 Statistical Research and Applications Branch, NCI, 2006. http://srab.cancer.gov/devcan

Lifetime Probability of Developing Cancer, by Site, Men, 2001-2003*

Site	Risk
All sites†	1 in 2
Prostate	1 in 6
Lung and bronchus	1 in 12
Colon and rectum	1 in 17
Urinary bladder‡	1 in 28
Non-Hodgkin lymphoma	1 in 47
Melanoma	1 in 49
Kidney	1 in 61
Leukemia	1 in 67
Oral Cavity	1 in 72
Stomach	1 in 89

* For those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 2001 to 2003.
† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.1.1 Statistical Research and Applications Branch, NCI, 2006. http://srab.cancer.gov/devcan

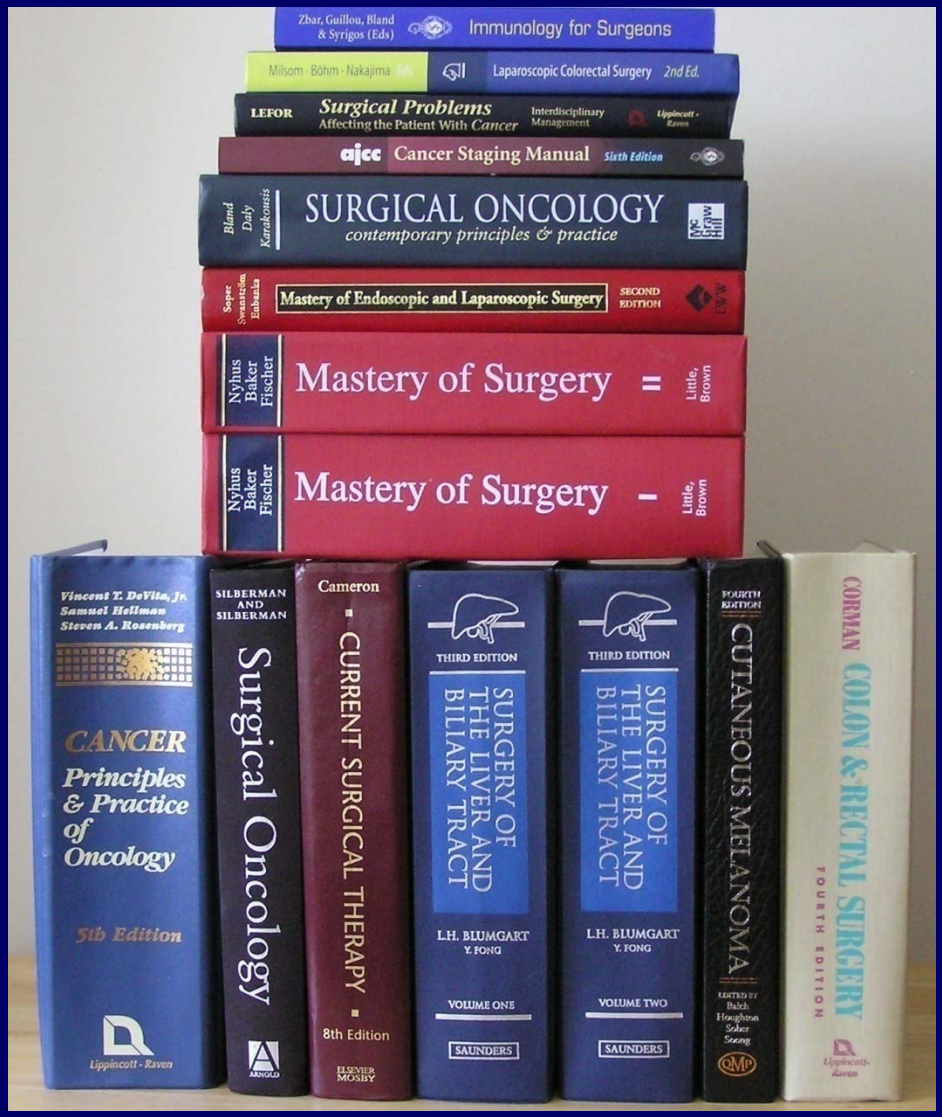
Imaging of Cancer Patients

Pre-op Imaging

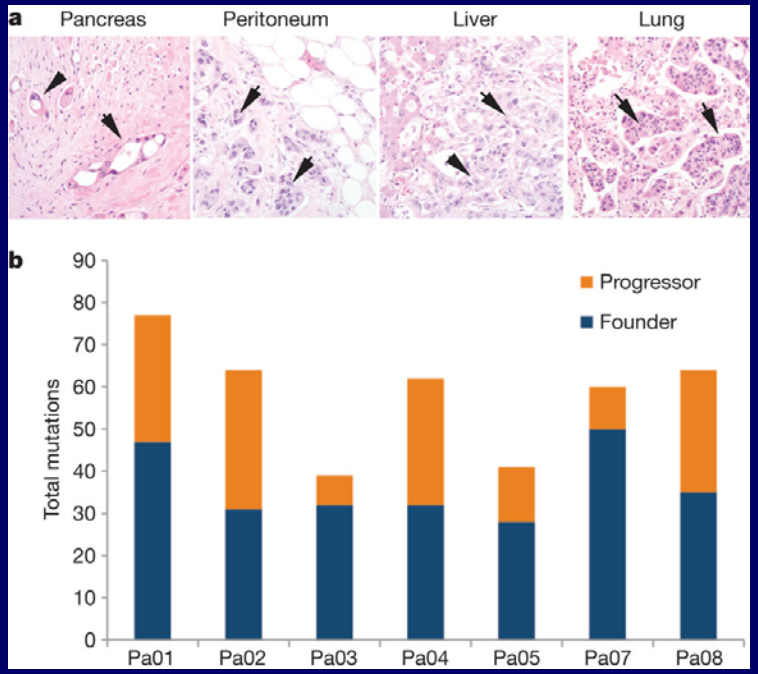
- Apply tumor biology principles
- What would change the type or timing your operation?

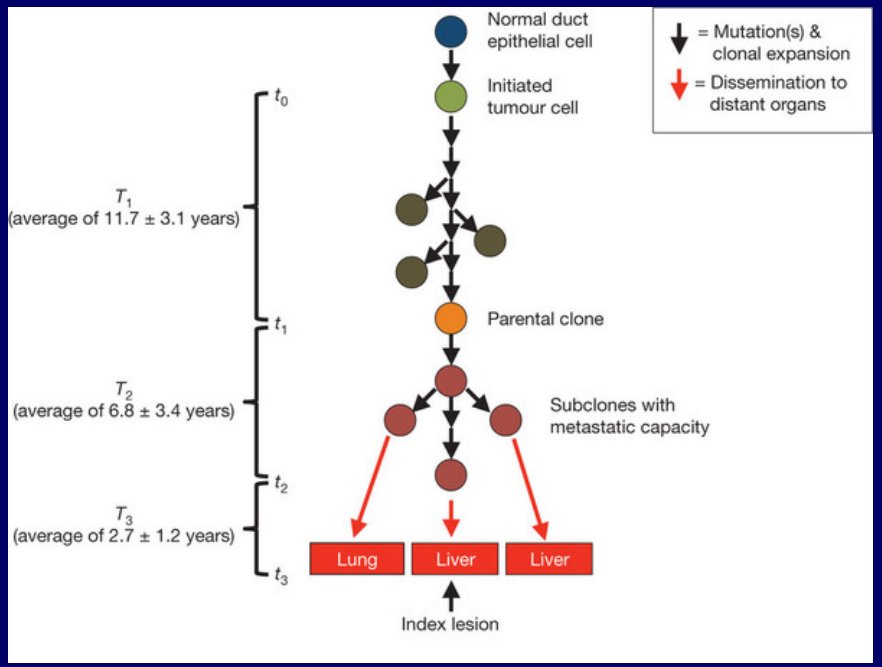
Post-op Imaging

- Selective
- Patient anxiety
- Salvage surgery for recurrence is rare
- No prospective trial for “routine” post-op testing has shown a benefit in survival



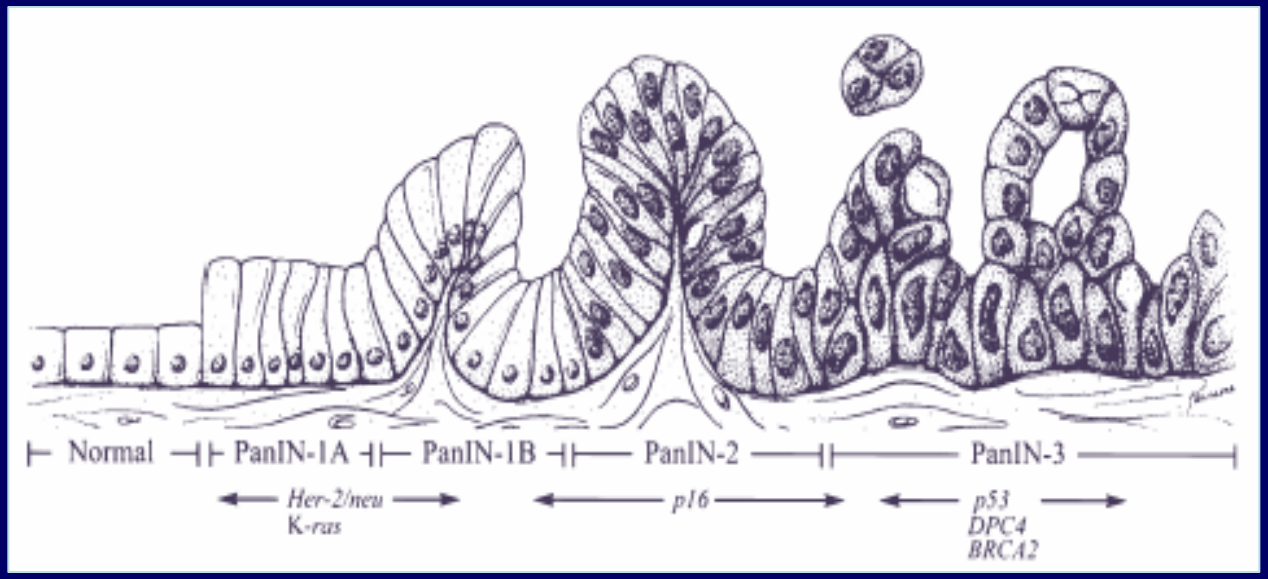
Note – add timeline scale of surgery -500 years experience condensed to 45 minutes





Yachida S. Nature 2010; Oct 28;467(7319):1114-7

Molecular Events in Pancreatic Cancer



- Oncogene activation/overexpression
  - K-ras (85%)
- Receptor tyrosine kinase overexpression
  - HER2/neu
  - EGFR
- Tumor suppressor mutation
  - p53 (50%)
  - SMAD4 (DPC4) (50%)
- Cell cycle regulatory protein silencing/loss
  - p16 (8%)
- Nuclear Transcription Factor Activation

Principles of Lymph Nodes

Lymph node dissection

- Harvest lymph nodes for:
  - 1 staging
  - 2 local control
  - 3 interrupt metastatic cascade
- Factor in risk/benefit ratio