New Developments in GI Malignancies

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Developments

- I. New techniques and procedures
  - EUS -- NOTES
  - Robotics -- SIRT
- II. New approaches to older procedures
  - Staged hepatectomy
  - Portal vein embolization
- III. Evolution of philosophy
  - Expanded indications for hepatectomy
  - The intact primary

I. Technical Advancements

Endoscopic Ultrasound

- Diagnosis: good for pancreas
- T stage: esophagus, stomach, rectum
- N stage: able to biopsy
- Cancer therapy

Gene Mediated Cytotoxic Immunotherapy for Pancreatic Adenocarcinoma

- Phase I clinical trial
  - Arm A: resectable
  - Arm B: locally advanced
- Intratumoral injection of HSV-thymidine kinase vector followed by anti-herpetic prodrug in conjunction with:
  - Arm A: surgery
  - Arm B: chemoradiation

Gene Mediated Cytotoxic Immunotherapy for Pancreatic Adenocarcinoma

- Diagnosis confirmed by EUS
- Virus injected by EUS into tumor followed by 2 weeks of Valacyclovir
- Arm A: surgery with repeat injection of virus into resection bed
- Arm B: repeat intratumoral injection during chemoradiation

Gene Mediated Cytotoxic Immunotherapy for Pancreatic Adenocarcinoma

- 24 patients treated
- Toxicities
  - Grade 3: 5 patients (pain, azotemia)
  - Grade 4: none
- 2 patients on Arm A alive at nearly 2 years
- 6 patients on Arm B alive at 5-34 months

NOTES

- Natural Orifice Transluminal Endoscopic Surgery
- No skin incisions
- Useful for identifying occult metastases or obtaining tissue from suspicious lesions

Minimally Invasive Surgery

Preoperative Considerations

- Site of tumor
- Tumor size/invasion
- Obesity
- Previous surgery
- Must be able to find tumor/polyp
- Possibility of converting to open

Data

What difference does it make?

Laparoscopic Colectomy

- **Return of bowel function 1-2 days sooner**
- **Less need for narcotics**
- **Quicker return of lung function**
- **Length of stay ~1 day less**
- **May be influenced by biased expectations**

Laparoscopic Colectomy

- Return to work and quality of life
  - No statistical difference
  - Anecdotally improved
- Cost
  - Equipment costs and OR time are greater
  - May be balanced by shorter hospital stay
- Operative Time – 30-60 minutes longer

COST Trial

Clinical Outcomes of Surgical Therapy Study Group

- 872 patients with colonic adenocarcinoma
- Recurrence
  - 16% laparoscopic
  - 18% open
- Survival
  - 86% laparoscopic
  - 85% open
- Post-operative stay
  - 5 days laparoscopic
  - 6 days open

N Engl J Med 2004;350:2050-9

COST Trial

Clinical Outcomes of Surgical Therapy Study Group

- 5 year data
- Disease-free 5 year survival
  - 68.4% Open
  - 69.2% Laparoscopic
- Overall survival
  - 74.6% Open
  - 76.4% Laparoscopic
- Recurrence
  - 21.8% Open
  - 19.4% Laparoscopic

Ann Surg 2007;246:655-64

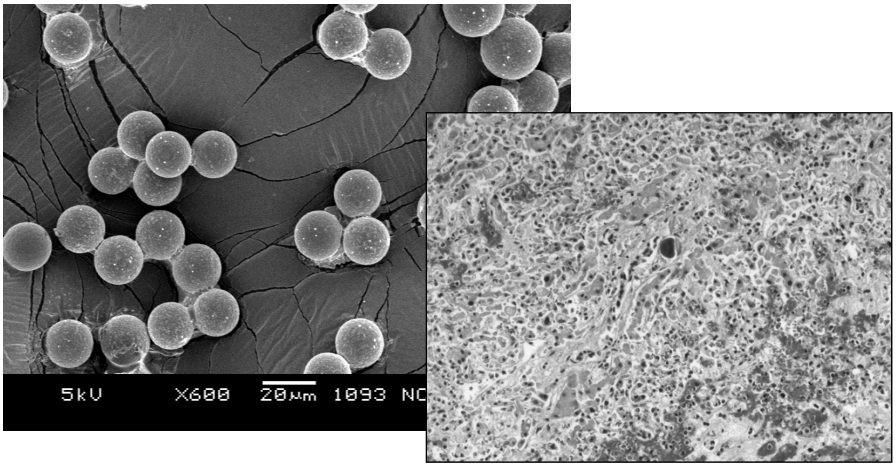
Robotic Surgery

No Surgery?

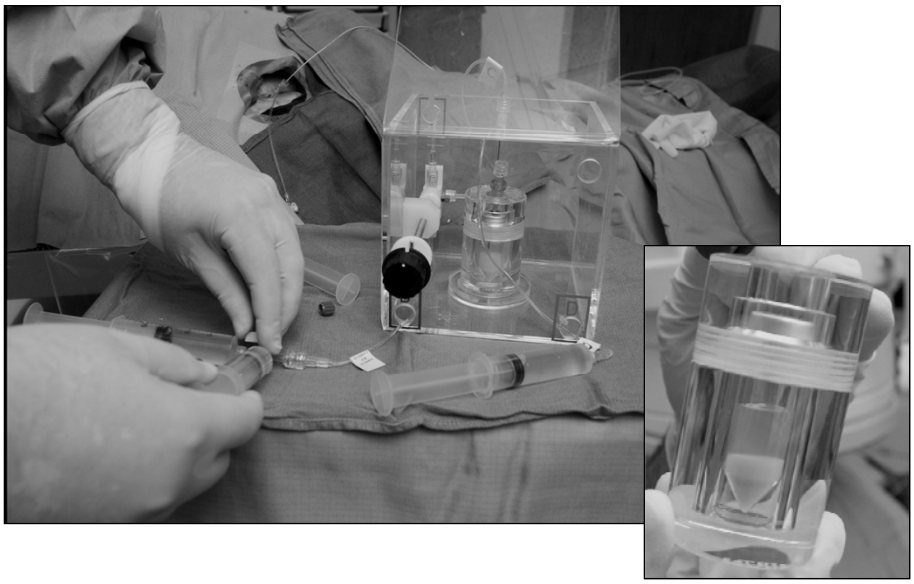
Selective Internal Radiotherapy (SIRT)

- Radiolabelled particles (Y^{90})
  - TheraSpheres® - MDS Nordion (HCC)
  - SIRSpheres – SIRTex (CRC)
- Injected through hepatic artery
- High dose radiation to tumor
- Low dose radiation to liver
- β particle emission
  - 2-3mm of penetration

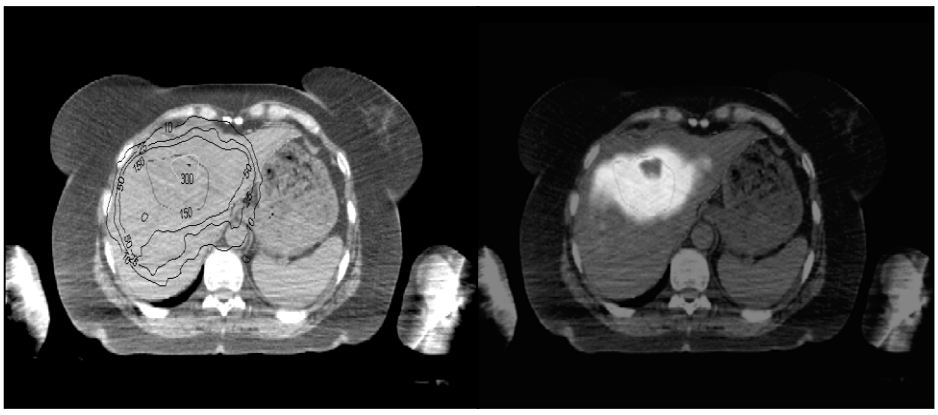
Microspheres



Delivery of Microspheres



Radiation Dose Deposited



II. New Approaches

2-Stage Hepatectomy

- 16 patients with bilobar disease
- Major resection at 1st stage in 8 (no deaths)
- Chemotherapy pre- and post-operative
- 3 patients progressed (1 intra- and 2 extra-)
- Major resection at 2nd stage in 8 (2 deaths)
- 4 liver recurrences (3rd resection in 3)
- Median survival 31 months from 2nd and 44 months from 1st resections

Adam et al. Ann Surg 2000

2-Stage Hepatectomy

- 33 patients with "unresectable" CRCM
- 1st stage: clearance of left-sided disease
- Right PVE ± segment IV
- 2nd stage (5-8 weeks): major hepatectomy
- No deaths
- 2 stages completed in 28 (progression in 5)
- 3-yr survival from 2nd stage 54%, median not reached

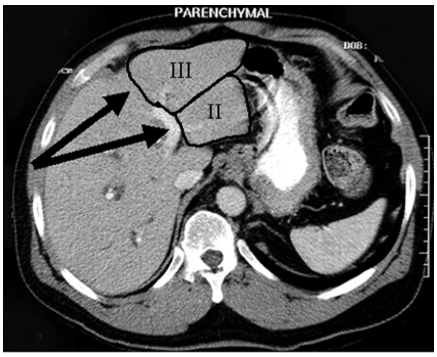
Jaeck et al. Ann Surg 2004

Portal Vein Embolization

- First described in 1990
- Occlusion of blood flow to all tumor-bearing liver
- Hypertrophy of future liver remnant (FLR)
- Atrophy of embolized segments
- Recommended if FLR <20% in healthy liver (<30% if heavily pretreated)

Preoperative Volumetry

- **3-D reconstruction of CT images**



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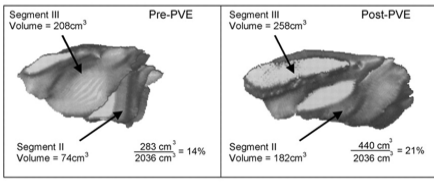
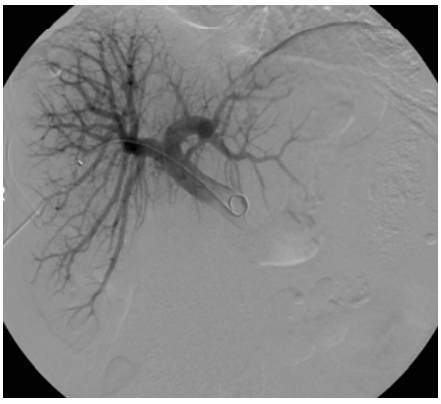
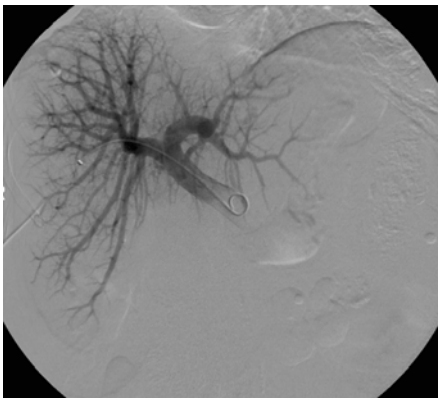


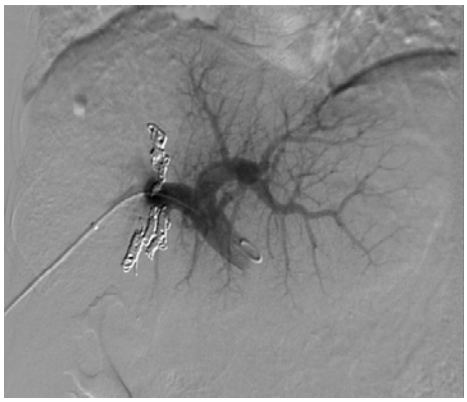
c.

Portal Vein Embolization

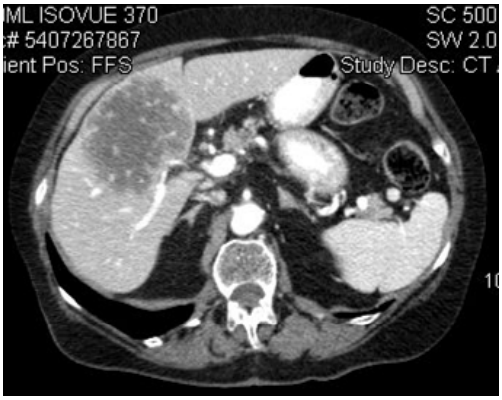


Portal Vein Embolization





Portal Vein Embolization



Portal Vein Embolization

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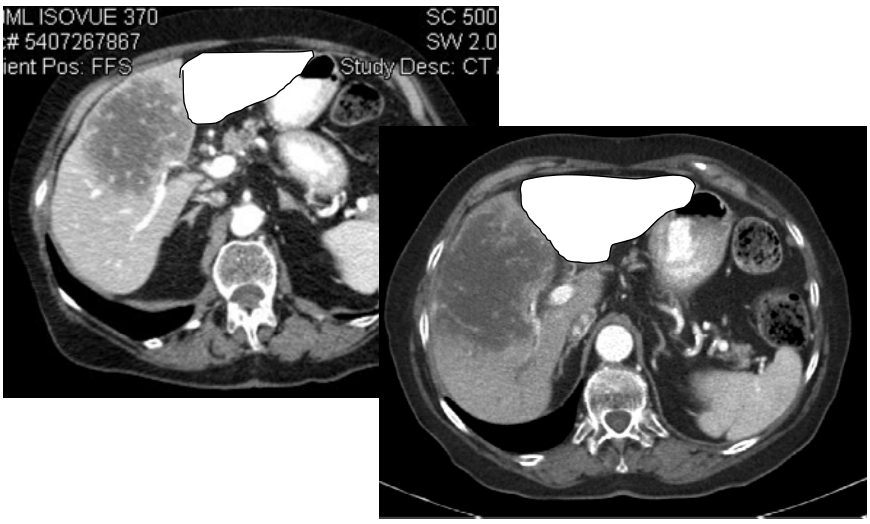
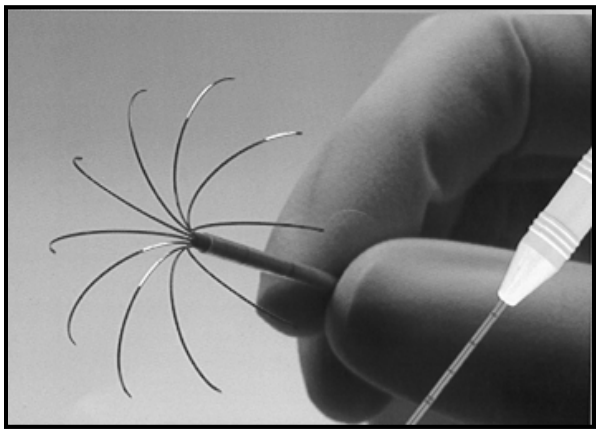
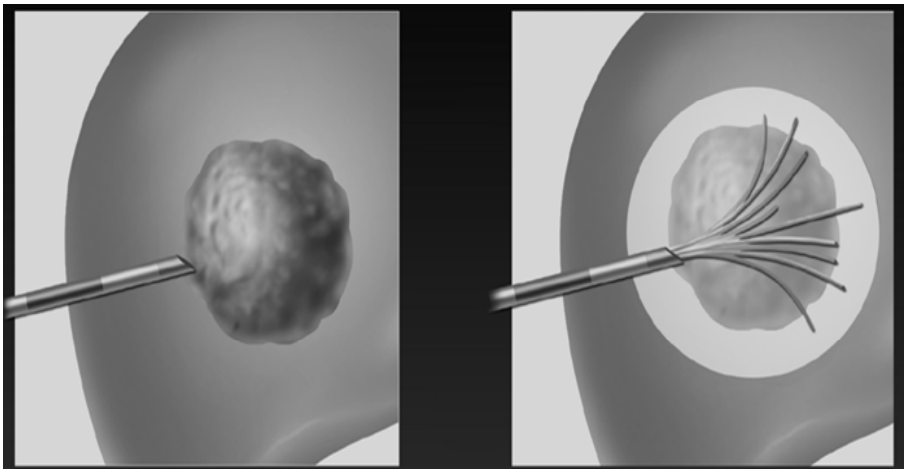


Radiofrequency Ablation





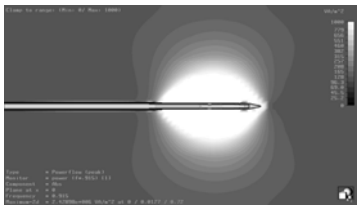
RFA

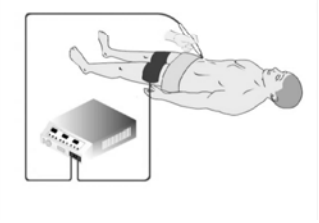
- Limited damage to surrounding liver
- Can be done in OR or radiology
- Limited by tumor size
- User-dependent
- Higher local recurrence rates (vs. resection)
- Efficacy: open > laparoscopic > percutaneous

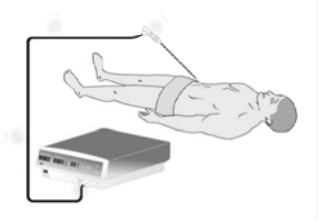
Role of RFA

- Adjunct to resection
- Few, small unresectable tumors
- Unfit patient

Microwave Ablation








THE OSUMC
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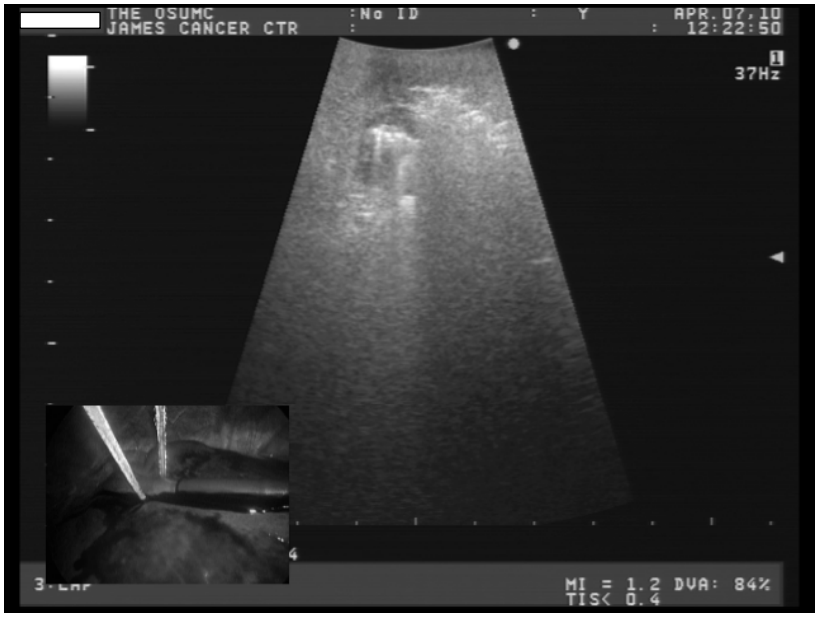
MI = 1.2 DVA: 84%
TIS< 0.4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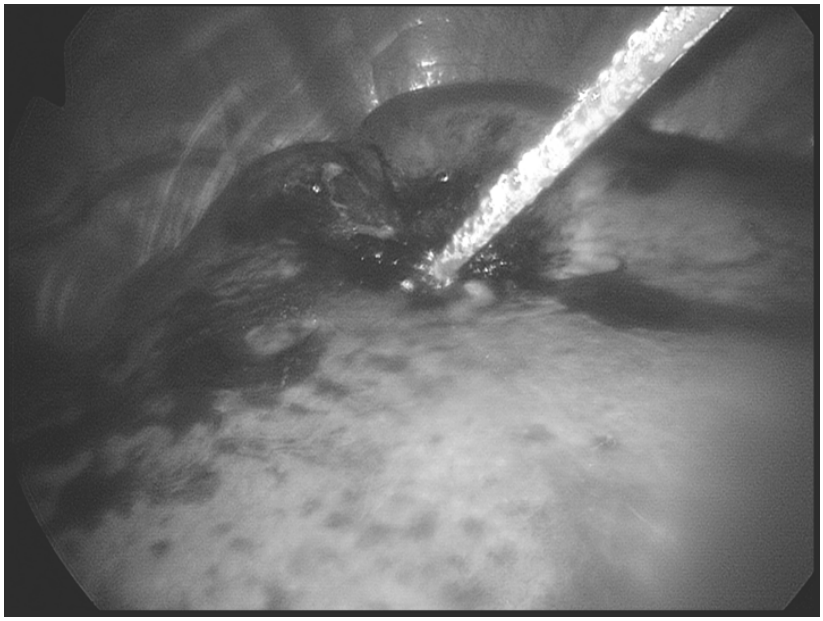

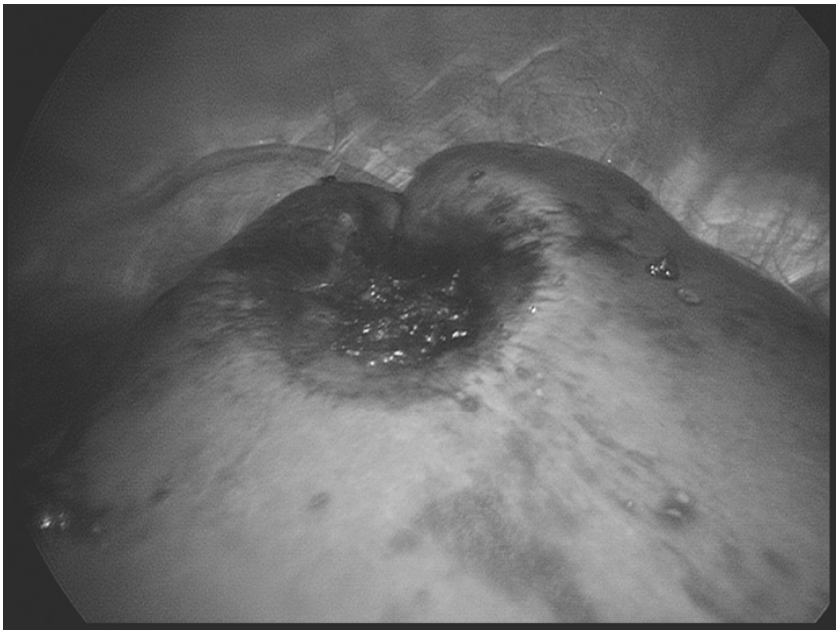

III. Philosophic Evolution

What does "operable" mean?

- Defined in relative terms
  - Based on expertise, resources, attitude
- "High-risk surgery"
  - Knowledge of internal liver anatomy
  - Operative techniques
  - Mortality 20% (1980s) → <5% (2000s)
- "Poor outcomes"
  - Better imaging (spiral CT, MRI, PET, I/O U/S)
  - Better patient selection
  - Better chemotherapy

Traditional Dogma

- **Definitions of inoperable disease**
  - **Bilobar disease**
  - **>4 lesions**
  - **Extrahepatic disease**
  - **Lesion >5 cm**
  - **Synchronous disease**

Debunking Dogma

Bilobar Disease

- Tomlinson et al. 2007
  - Actual 10+ year survivors (N=102)
  - 25% had bilateral disease resected
    - 29% for 2-5 and 5-10 year survivors (P=NS)
- Bolton et al. 2000
  - Simple (N=121) vs complex (N=44) resections
  - 98% of complex had bilobar disease (vs 0%)
  - Similar perioperative mortality (9% vs. 5%)
  - Similar survival (36% 5-yr, median 43 months)

Bilobar Disease

- Fong et al. 1999
  - 1001 resections
  - 40% bilobar disease
  - 5-yr survival 29% vs. 38%
  - Not predictive by multivariate analysis (p=0.4)

Traditional Dogma

- Definitions of Unresectability
  - Bilobar disease
  - >4 lesions
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Traditional Dogma

- Definitions of Unresectability
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Tumor Number

- Pawlik et al. 2006
  - 159 patients with ≥4 lesions
  - Median 5 lesions (4 – 14)
  - Resection ± RFA in 94%
  - Overall survival: median 62 months, 5-yr 51%
- Kornprat et al. 2007
  - 98 patients with ≥4 lesions
  - Median 5 lesions (4 – 15)
  - Overall survival: median 41 months, 5-yr 33%

Traditional Dogma

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Traditional Dogma

- Definitions of Unresectability
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Extrahepatic Disease

- Elias et al. 2005
  - 308 resections, 84 (27%) with EHD
  - EHD not predictive of survival
    - 5-yr survival 34% vs. 28%
- Kornprat et al. 2007
  - Multiple liver mets, 18% with EHD
  - Predictor of poor outcome
  - Median survival 32 months

SSO/AHPBA/SSAT Consensus

"The presence of extrahepatic disease should no longer be considered an absolute contraindication to hepatic resection provided …. complete resection of both intra- and extrahepatic disease is feasible."

Traditional Dogma

- Definitions of Unresectability
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  - ~~>4 lesions~~
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Traditional Dogma

- Definitions of Unresectability
  - ~~Bilobar disease~~
  - ~~>4 lesions~~
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  - Lesion >5 cm
  - Synchronous disease

The Modern Era of Liver Surgery for CRC Metastases

New Rules

- Complete resection a must
  - Negative liver margins
  - All extrahepatic disease
- Preservation of 2 contiguous segments
- Preservation of vascular inflow, outflow, and biliary drainage
- Preservation of adequate future liver remnant (>20% in healthy liver)

Asymptomatic Colorectal Primary

Traditional Dogma

- Must resect primary
  - Risk of obstruction
  - Risk of bleeding
  - Nidus for more metastases

Unresected Primary CRC

- 233 patients with stage IV CRC and intact primary tumor
- All received modern chemotherapy
- 89% never required intervention
- 7% required emergency surgery
- 4% required other intervention (eg stent)

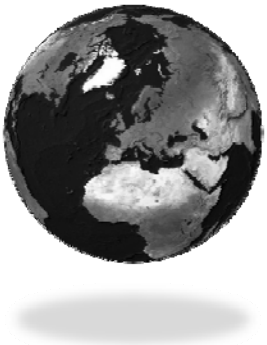
Poultsides et al. JCO 2009

Updates On Gastrointestinal Malignancies

Tanios Bekaii-Saab, MD
Medical Director, Gastro-intestinal Cancer Program
Division of Medical Oncology
Department of Pharmacology
OSUCCC – Arthur James Cancer Hospital

Gastrointestinal Malignancies

- **Lung (1.4 million deaths)**
- **Stomach (740 000 deaths)**
- **Liver (700 000 deaths)**
- **Colorectal (610 000 deaths)**
- **Breast (460 000 deaths)**



http://www.who.int factsheet N°297 February 2011

Courtesy of Florian Lordick, MD

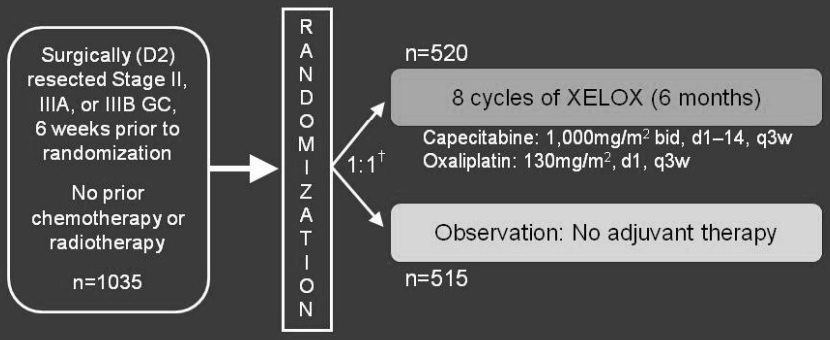
Gastric and Gastro-Esophageal Cancers

Introduction: Epidemiology

- 35,000 new cases a year with 25,000 deaths
- 3 entities:
  - Squamous cell carcinoma of the esophagus
  - Adenocarcinoma of the distal esophagus, GE junction and proximal stomach
  - Adenocarcinoma of the distal stomach
- Esophageal cancer is the most rapidly growing cancer in the USA and is affecting middle aged Caucasian males mostly. Its incidence rate is 6 times, and its mortality 7 times what it was in the 1970s.

Early Stage Disease

CLASSIC study design



- Primary endpoint: 3-year DFS‡
- Secondary endpoints: overall survival and safety profile

†Stratified by stage and country with age, sex, and nodal status as covariates
‡GASTRIC project: 3-year DFS and 5-year overall survival are strongly associated, Burzykowski et al. ASCO 2009

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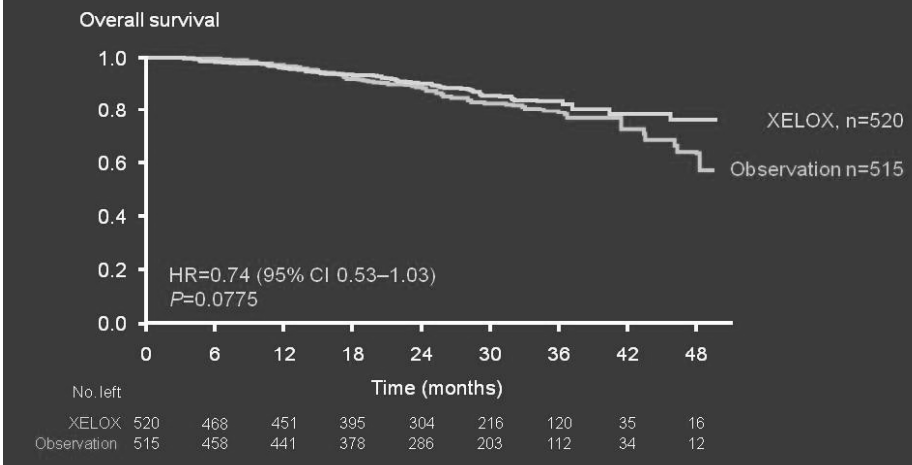
Overall survival at interim analysis



ITT population
Median follow-up 34.4 months (range 16–51)

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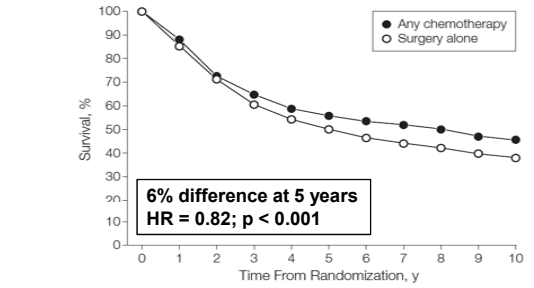
GASTRIC Group Meta-analysis

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



No. at risk
Any chemotherapy 1924 1688 1385 1217 1080 929 709 526 390 297 243
Surgery alone 1857 1568 1300 1092 952 782 583 407 267 172 138

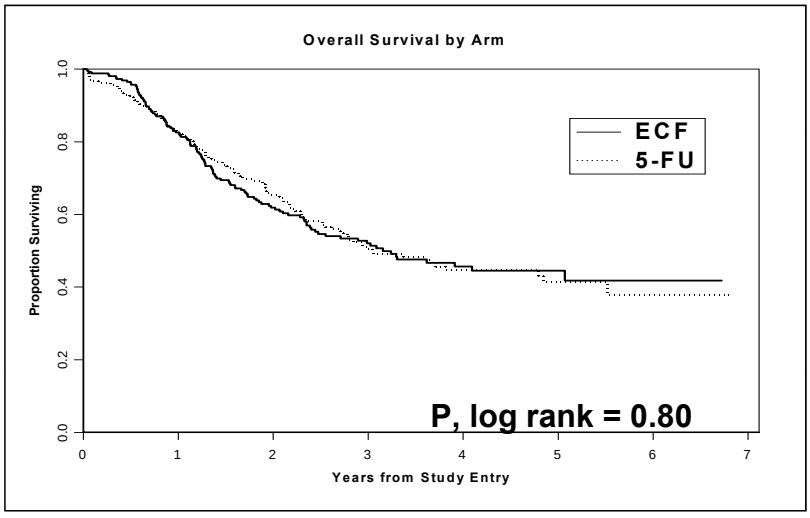
The Gastric Group. *JAMA* 2010; 303: 1729-1737

Postoperative adjuvant chemoradiation for gastric or GE junction adenocarcinoma using ECF before and after 5-FU/radiotherapy compared to bolus 5-FU/LV before and after 5-FU/radiotherapy: Intergroup trial CALGB 80101

CS Fuchs, JE Tepper, D Niedzwiecki, D Hollis, HJ Mamon, RS Swanson, DG Haller, T Dragovich, SR Alberts, G Bjarnson, CG Willett, PC Enzinger, RM Goldberg, AP Venook, RJ Mayer

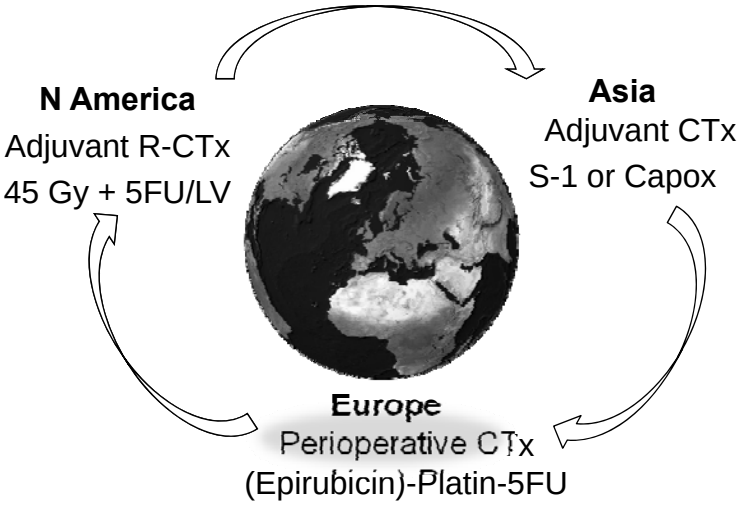
CALGB

CALGB 80101 – Overall Survival

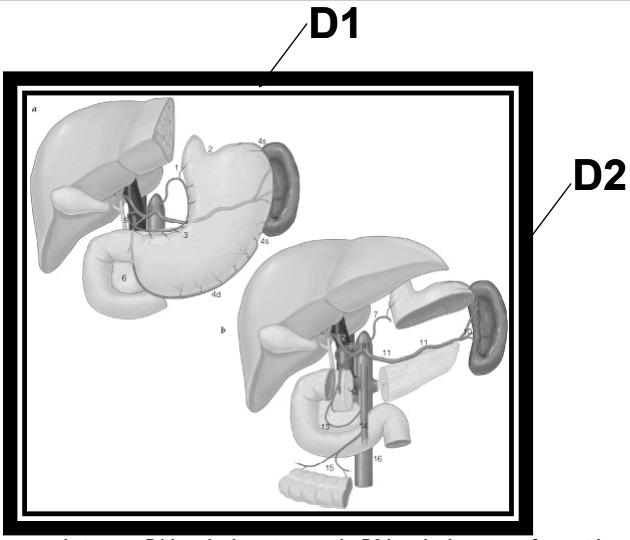


Fuchs et al , ASCO 2011

Adjuvant Gastric Cancer in 2011



Courtesy of Florian Lordick, MD



Illustrated are the differences between a D1 lymphadenectomy and a D2 lymphadenectomy for gastric cancer. (a) A D1 lymphadenectomy is accomplished by removing the perigastric lymph nodes with the resection specimen; these nodes include those along the right and left cardia (1, 2), those along the lesser curvature (3), those along the greater curvature (4), the suprapyloric nodes (5), and the infrapyloric nodes (6). (b) A D2 lymphadenectomy involves a more radical resection specimen, which includes nodes along the left gastric artery (7), the common hepatic artery (8), the celiac artery (9), the splenic hilum (10), the splenic artery (11), the hepatoduodenal ligament (12), the posterior pancreas (13), the root of the mesentery (14), the transverse mesocolon (15), and the aorta (16).

D2 Resection rates across studies

Classic
D2 Resection 100%
Median 42 lymph nodes examined (range 9-127)

D2 Resection rates across studies

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US INT 0116 (SWOG 9008) Macdonald et al. 2001	
D2-Resection	10%
D1-Resection	36%
D0-Resection	54%

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D1-Resection	36%
D0-Resection	54%

UK MAGIC Cunningham et al. 2006	
D2-Resection	41%
D1-Resection	19%
Other Resections	40%

What have we learned about localized gastric/GE cancers?

- Surgical approach determines the optimal adjuvant treatment strategy
  - Asia: Radical resection (D2)
    - Adjuvant chemotherapy
  - U.S.: Sub-radical resection (≤ D 1)
    - Adjuvant chemoradiation

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- Awaiting data on adjuvant CRT vs. chemotherapy
  - ARTIST (capecitabine/cisplatin compared with resected gastric cancer with D2 nodal dissection trial - when surgery is controlled, is adjuvant radiation necessary?

What have we learned about localized gastric/GE cancers?

- Is a neoadjuvant approach feasible and better?
  - Neoadjuvant much more likely to receive therapy (SAKK)
  - EORTC 40954 – 3 months neoadjuvant chemo trends towards better
  - No randomized neoadjuvant CRT gastric studies reported yet
    - Attempts have been aborted secondary to low accrual

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  - No randomized neoadjuvant CRT gastric studies reported yet
    - Attempts have been aborted secondary to low accrual
- Data with targeted therapies, more aggressive chemotherapy
  - MAGIC 2 – ECF +/- bevacizumab

Gastro-esophageal Cancers : Advanced disease

- Marginal differences between doublets and triplets that perhaps do not justify the differences in toxicities.
- Trastuzumab should be considered as an option added to a platinum and 5FU in the presence of Her-2 overexpression
  - LOGIC Trial
    - Rand Ph III, HER 2+ gastric cancer
    - Capecitabine + oxaliplatin +/- lapatinib
- 2nd line Irinotecan has a proven benefit in advanced gastric cancer and should be offered to patients with a PS 0-2 (Park et al Abs 4004, ASCO 2011 and Thuss-Patience P. *Eur J Cancer*; 2011)

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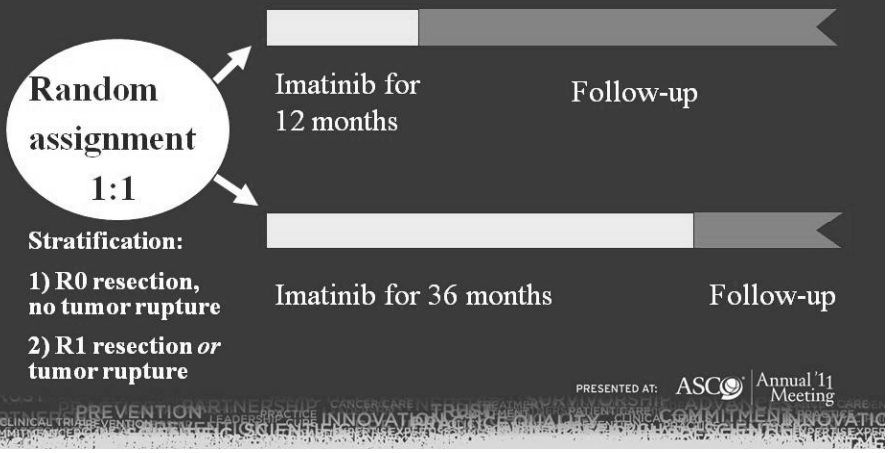
GIST

SSGXVIII: Study design

An open-label Phase III study



Stratification:

1) R0 resection, no tumor rupture

2) R1 resection *or* tumor rupture

PRESENTED AT: ASCO Annual '11 Meeting

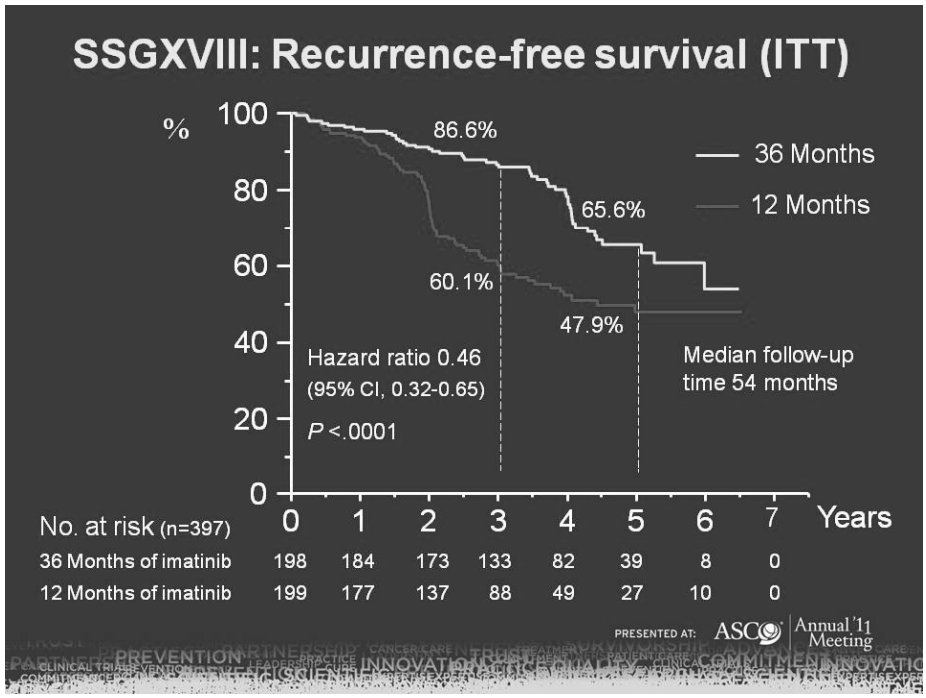
SSGXIII: Key inclusion criteria

- Histologically confirmed GIST, KIT-positive
- High risk of recurrence according to the modified Consensus Criteria*:
  - Tumor diameter >10 cm *or*
  - Tumor mitosis count >10/50 HPF** *or*
  - Size >5 cm and mitosis count >5/50 HPFs *or*
  - Tumor rupture spontaneously or at surgery

*Fletcher CD et al. Hum Pathol 2002; 33:459-65

**HPF, High Power Field of the microscope

PRESENTED AT: ASCO Annual '11 Meeting

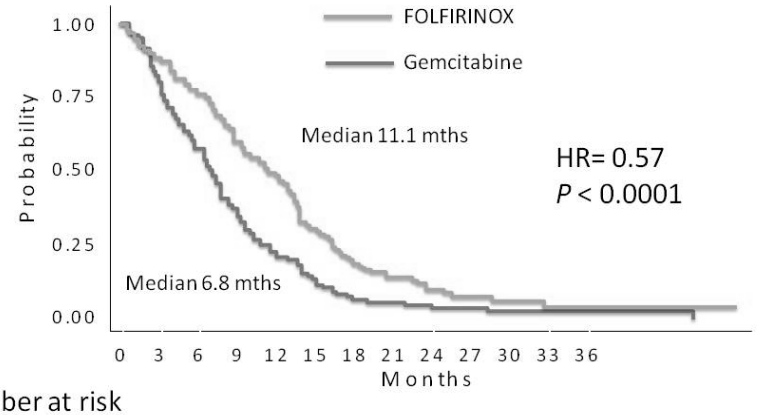


Conclusions: Adjuvant GIST

- **3 years adjuvant imatinib is better than 1 year in high risk patients**
  - **Well tolerated**
  - **Cost benefit?**

Pancreas Cancer

FOLFIRINOX vs Gemcitabine: Overall Survival



Number at risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2

Conroy TJ. NEJM, 2011

Conclusions: Pancreas Cancer

- Pancreas cancer has consistently been the most lethal cancer
  - Less than 5% of patients diagnosed with it actually survive it.

Conclusions: Pancreas Cancer

- Pancreas cancer has consistently been the most lethal cancer
  - Less than 5% of patients diagnosed with it actually survive it.
- Adjuvant:
  - Gemcitabine or 5FU remain the standard for treating patients with resected pancreas cancer based on best Level 1 evidence!!
  - The role of radiation remains unanswered.

Conclusions: Pancreas Cancer

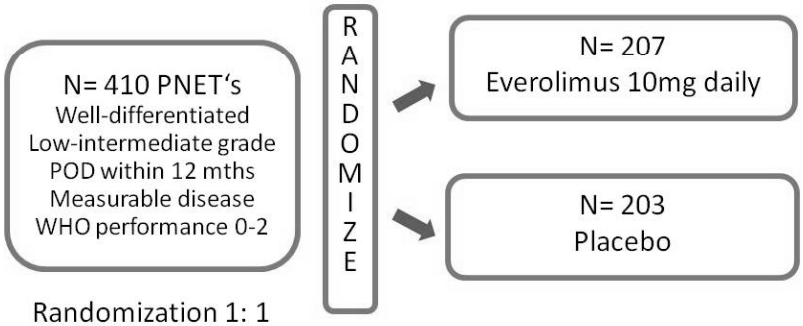
- **Advanced disease (First Line):**
  - **Gemcitabine combinations remains a SOC for most patients with PS 0-1. Fluoropyrimidines?**
  - **Novel taxanes seem to hold promise. No role for abraxane in pancreas cancer for now, awaiting phase III studies**
  - **FOLFORINOX can be considered an option for excellent PS patients with no biliary obstruction?**
    - **FOLFOX or FOLFIRI ?**
    - **Neo-adjuvant ?**
    - **Confirms the need to move to non-gemcitabine backbones**

Pancreas Neuroendocrine Tumors (PNET's)

- Rare malignancies
  - 1.3% of all pancreas malignancies
  - 2-4 per million
  - 1,000 yr new diagnoses US, rising incidence
- Variable natural history, median OS with metastases > 2 yrs
- FDA drug approvals
  - 1982 Streptozotocin (+/- 5FU, doxorubicin)
  - 1998 Somatostatin (symptomatic NET's)

Yao, JC. Ann Surg Oncol, 2007. Moertel, CG. NEJM, 1980. Jensen, RT. Cancer, 2008

RADIANT-3:
Phase III Everolimus vs Placebo



Randomization 1: 1

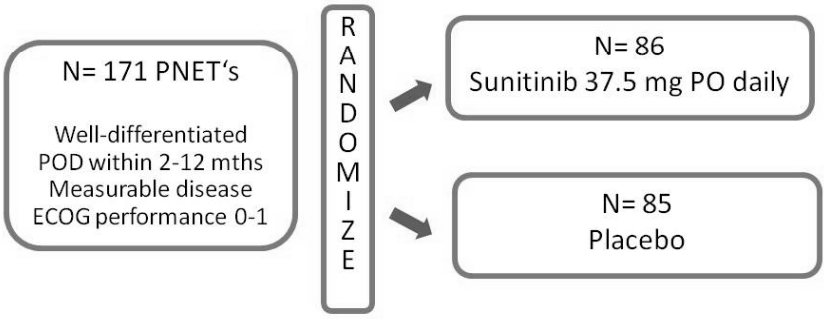
Stratification

- Prior chemotherapy Y vs N
- WHO performance status 0 vs 1-2

Option for cross-over from placebo arm on POD

Yao, JC. NEJM, 2011

Randomized Phase III Sunitinib vs Placebo
SUN 1111



Randomization 1: 1, balanced by country/region

No other stratification factors used

Raymond, E. NEJM, 2011

Efficacy of Sunitinib and Everolimus: Pancreatic NET Randomized Trials

	Sunitinib (n=171)	Everolimus (n=410)
Median PFS	11.4 mos *(vs. 5.5 mos in placebo arm)*	11.0 mos *(vs 4.6 mos in placebo arm)*
Overall Response Rate (RECIST)	9.3%	5%
Partial Response or Stable Disease	72%	78%
Survival Advantage Demonstrated?	No*	No*

**Pts on placebo in either study received study drug following progression*

Raymond et al, NEJM 2011; 364: 501-513; Yao et al, NEJM 2011; 364: 514-523

Adverse Events in Sunitinib and Everolimus Treatment Arms: Pancreatic NET Phase III Trials

SUNITINIB				EVEROLIMUS		
Event	All Grades (%)	Grade 3-4 (%)		Event	All Grades (%)	Grade 3-4 (%)
Diarrhea	59	5		Stomatitis	64	7
Nausea	45	1		Rash	49	1
Asthenia	34	5		Diarrhea	34	3
Vomiting	34	0		Fatigue	31	2
Fatigue	32	5		Infections	23	2
Hypertension	*26*	*10*		*Pneumonitis*	*13*	*5*

Raymond et al, NEJM 2011; 364: 501-513; Yao et al, NEJM 2011; 364: 514-523

What should the Sequence of Therapy in Symptomatic Pateints with PNET be?

- Initiating targeted therapy is reasonable in most patients with symptoms , clinically significant tumor burden, or PD on chemotherapy

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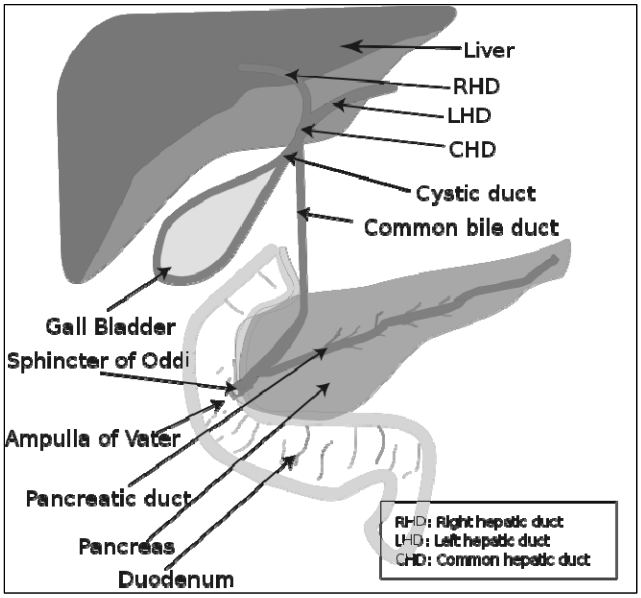
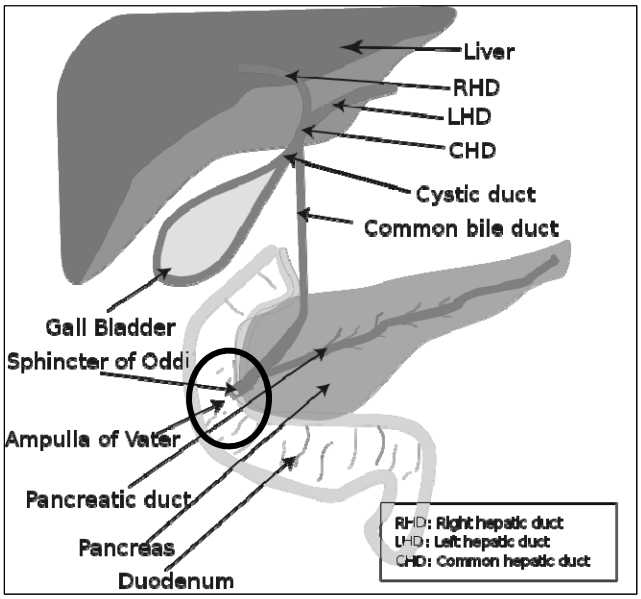
- Streptozocin or TMZ-based therapy considered where tumor response is required or patients had PD on targeted therapy

What should the Sequence of Therapy in Symptomatic Pateints with PNET be?

- Initiating targeted therapy is reasonable in most patients with symptoms , clinically significant tumor burden, or PD on chemotherapy
- Streptozocin or TMZ-based therapy considered where tumor response is required or patients had PD on targeted therapy
- Future studies will consider options such as new targets and combination studies.

Ampullary Cancer


Liver
RHD
LHD
CHD
Cystic duct
Common bile duct
Gall Bladder
Sphincter of Oddi
Ampulla of Vater
Pancreatic duct
Pancreas
Duodenum
RHD: Right hepatic duct
LHD: Left hepatic duct
CHD: Common hepatic duct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(Peri-)Ampullary ESPAC-3: Trial Design

Patients with adenocarcinoma of the ampulla of Vater undergoing 'curative' resection
Target N= 300

RANDOMISE

OBSERVATION
Target N= 100

5FU/ FA
5-FU 425mg/m² & FA 20mg/m² for 5 days every 28 days for 6 cycles
Target N= 100

GEMCITABINE
1000mg/m² once a week for 3 of 4 weeks for 6 cycles
Target N= 100

Ampullary: 300 patients (200 chemotherapy and 100 observation) would provide 80% power to detect a 15% 5y survival difference, p<0.05

Other periampullary to add to power

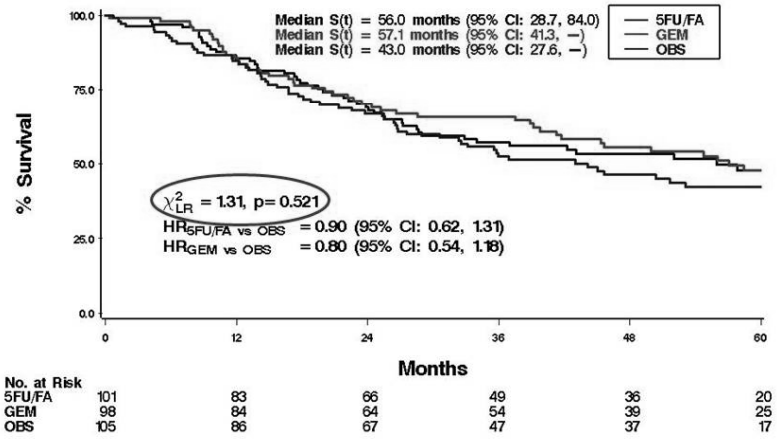
LCTU
Liverpool Cancer Trials Unit

Trial opened July 2000

CANCER RESEARCH UK

Neoptelemos et al Abs 4006 , ASCO 2011

Ampullary overall survival:
5FU/FA vs Gemcitabine vs Observation



No. at Risk						
5FU/FA	101	83	66	49	36	20
GEM	98	84	64	54	39	25
OBS	105	86	67	47	37	17

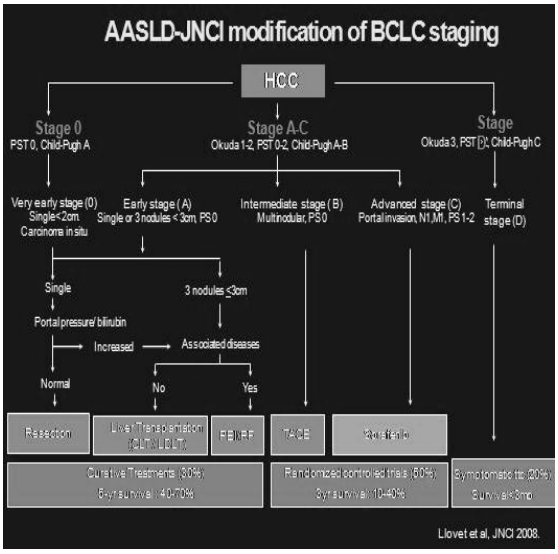
LCTU
Liverpool Cancer Trials Unit

CANCER RESEARCH UK

Neoptelemos et al Abs 4006 , ASCO 2011

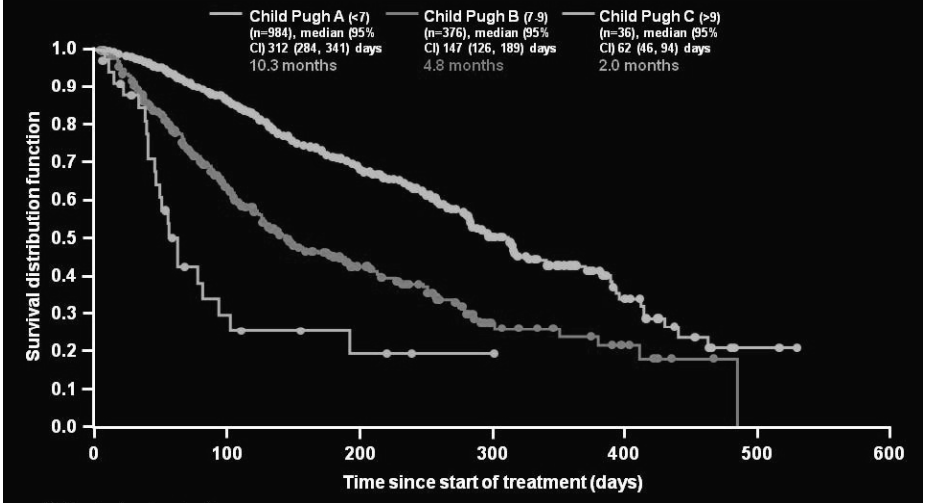
Hepatocellular Cancer (HCC)

Introduction: HCC



- **5th most common cancer worldwide**
- **3rd leading cause of mortality worldwide**
- **Sharp rise in the USA and the rest of the world because of a hepatitis C epidemic.**
- **Sorafenib in Child's Pugh A patients is SOC in advanced disease**

Preliminary overall survival by Child-Pugh status[a] at study entry



[a]207 patients not evaluable
CI, confidence interval

16

SUN1170 HCC – Study Design

Enrollment Criteria
- Advanced histologically confirmed HCC
- No prior systemic chemotherapy
- ECOG PS 0–1
- Child-Pugh group A

Stratification
- Region (Asia vs Ex-Asia)
- Prior TACE (≤3 vs. >3 courses)
- Tumor invasion (presence vs absence of vascular invasions and/or extrahepatic spread)

RANDOMIZATION

N=1,200

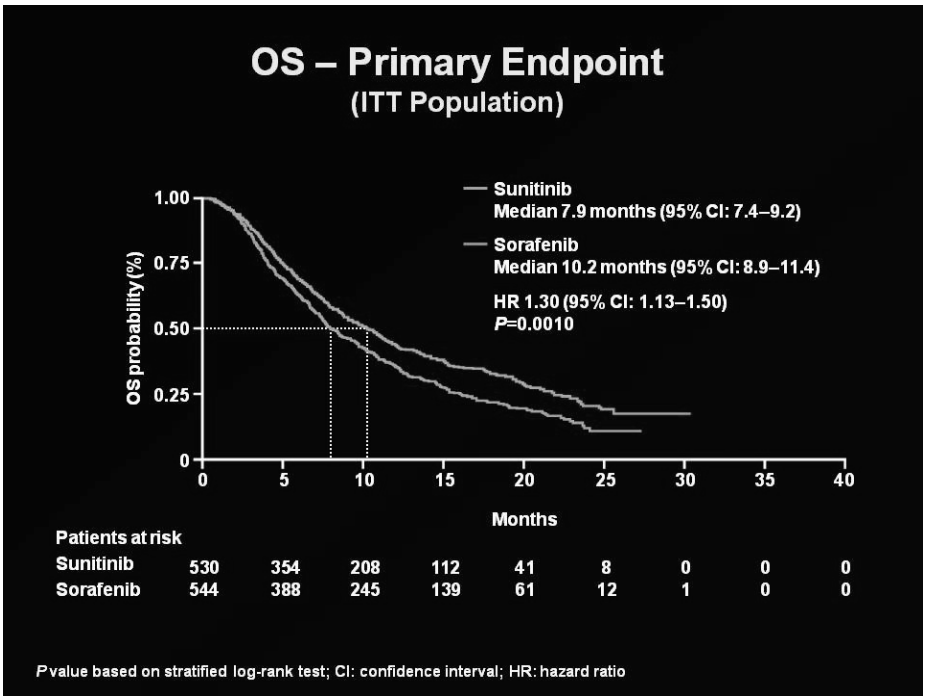
Sunitinib 37.5 mg/day CDD (N=600)

Sorafenib 400 mg BID (N=600)

Endpoints
- Primary: OS
- Secondary
  - PFS
  - TTP
  - Safety

Statistics
- Superiority/ non-inferiority design
- Hypothesis: increase in median OS from 10.7 to 13.3 months
- Non-inferiority boundary of median OS (9.5, 11.5 months)
- 1-sided log-rank test; α=0.025, 90% power

BID: twice daily; CDD: continuous daily dosing; ECOG PS: Eastern Cooperative Oncology Group performance status; PFS: progression-free survival; TACE: transarterial chemoembolization



Conclusions: HCC

- **Sorafenib remains the SOC for treating patients with advanced HCC for patients with Child's Pugh A**
  - **Sorafenib can be used with relative safety in the C-P B HCC population. Optimal dose remains to TBD.**
  - **No data in CP-C**

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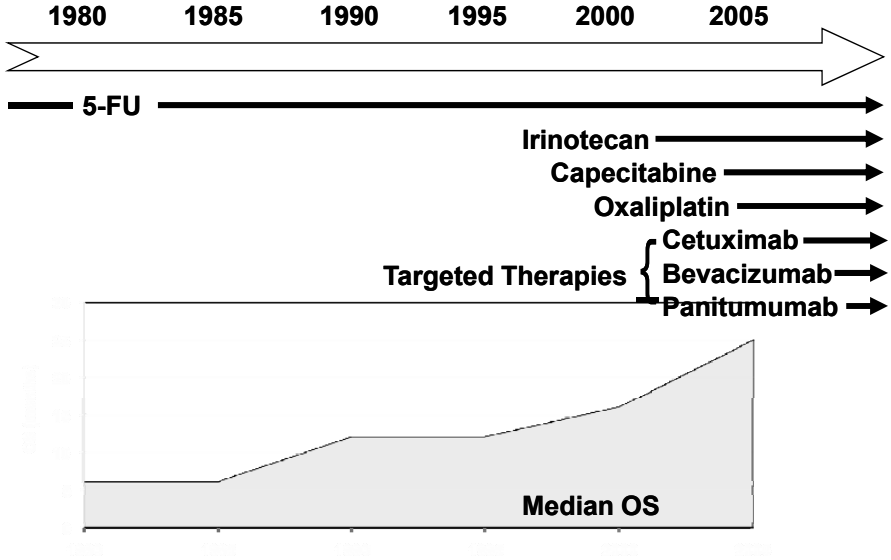
  - The superiority of sorafenib over sunitnitb in HCV infected patients raises interesting questions about non-VEGFR-related activities of sorafenib
- A better tolerated VEGFR agent would be welcome
  - Sunitinib does not fill this role
  - Others may, including bevacizumab
  - Studies of brivanib and linifanib vs. sorafenib continue

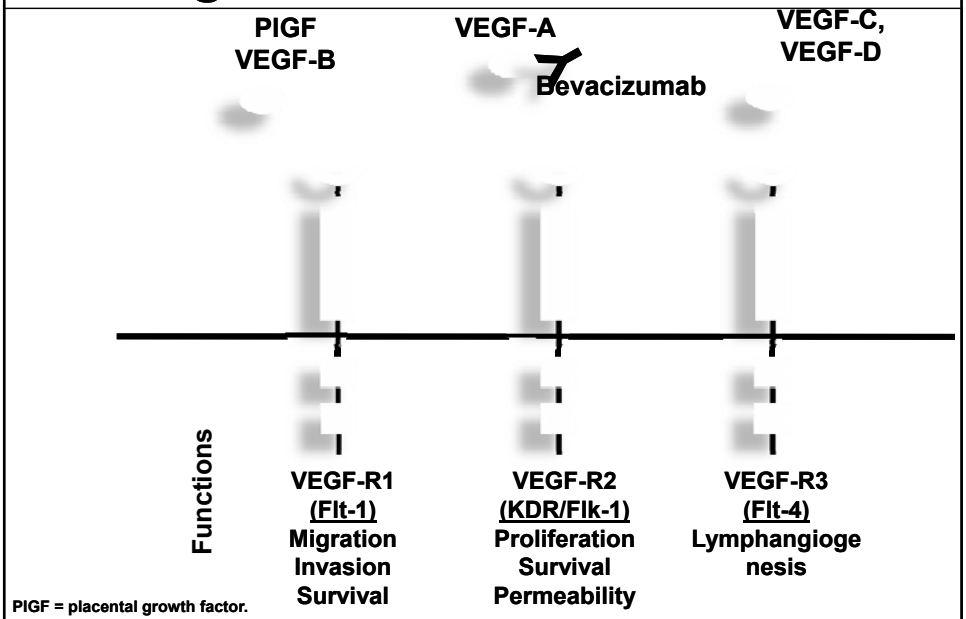
Colorectal Cancer

Advances in the Treatment of Stage IV CRC



5-FU = 5-fluorouracil; OS = overall survival.
McRee & Goldberg, 2011.

Large Molecule VEGF Inhibitors



PIGF = placental growth factor.
Holash et al, 2002; Roy et al, 2006; Ghosh et al, 2000.

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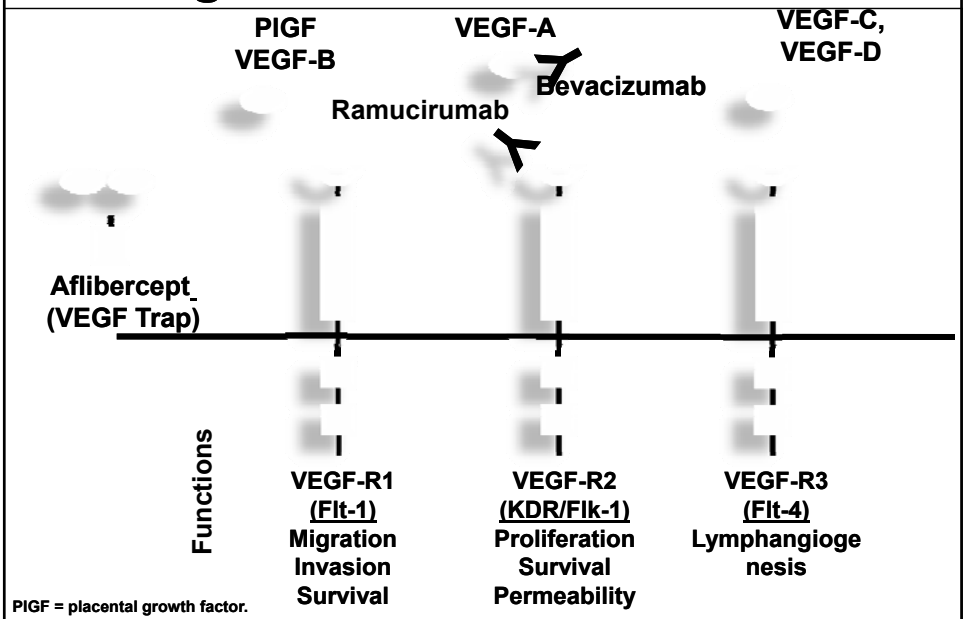

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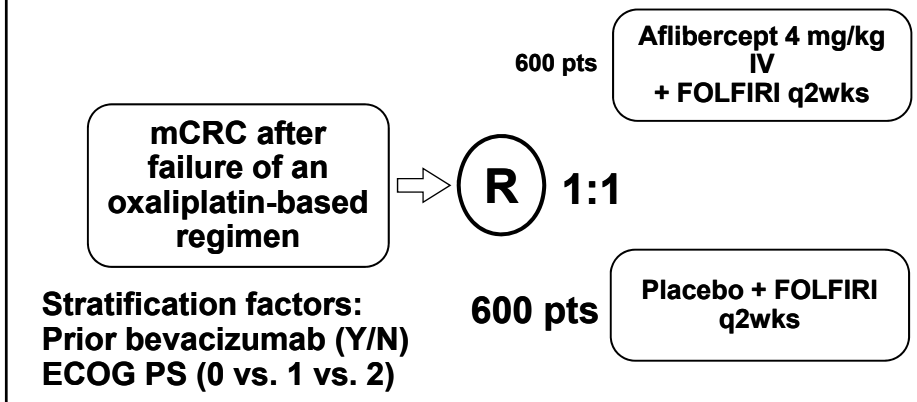
EFC10262: VELOUR Phase III Trial Second-Line FOLFIRI +/- VEGF-TRAP (aflibercept)



ECOG = Eastern Cooperative Oncology Group.
US NIH, 2011a.

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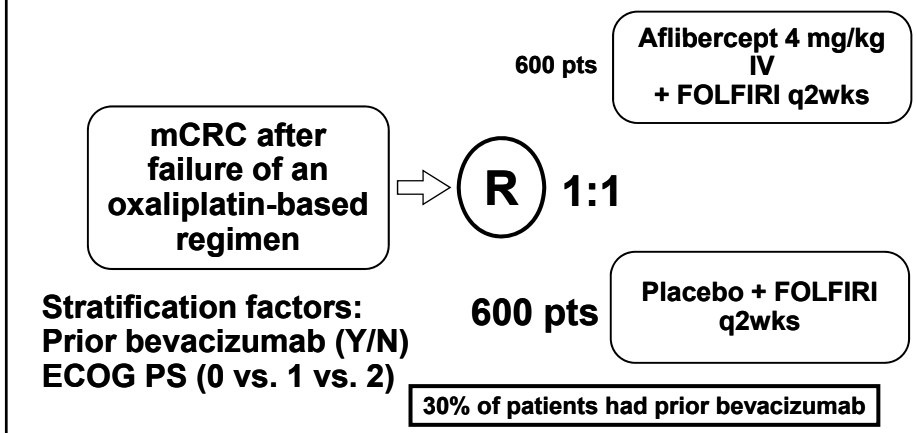

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US NIH, 2011a.

Safety – Most Frequent AEs, With ≥ 5% Difference in Incidence Between Treatment Arms, Excluding Anti-VEGF Class Events

Safety Population, % of patients	Placebo, N = 605		Aflibercept N = 611	
PT, SOC, HLT*	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Diarrhea	56.5	7.8	69.2	**19.3**
Neutropenia**	56.3	29.5	67.8	36.7
Complicated neutropenia		2.8		**5.7**
Asthenic conditions (HLT)	50.2	10.6	60.4	**16.9**
Stomatitis & ulceration (HLT)	34.9	5.0	54.8	**13.7**
Thrombocytopenia**	33.8	1.7	47.4	3.3
Infections (SOC)	32.7	6.9	46.2	**12.3**
Decrease appetite	23.8	1.8	31.9	3.4
Weight decreased	14.4	0.8	31.9	2.6
Palmar plantar erythrodysaesthesia	4.3	0.5	11.0	**2.8**
Skin hyperpigmentation	2.8	0	8.2	0
Dehydration	3.0	1.3	9.0	4.3

*** PT = preferred term; SOC = system organ class; HLT = high level term.**
**** From lab.**
Van Cutsem, 2011.

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Skin h				0
Dehyd				4.3

AEs leading to treatment discontinuation:
AFL: 26.6%
PL: 12.1%

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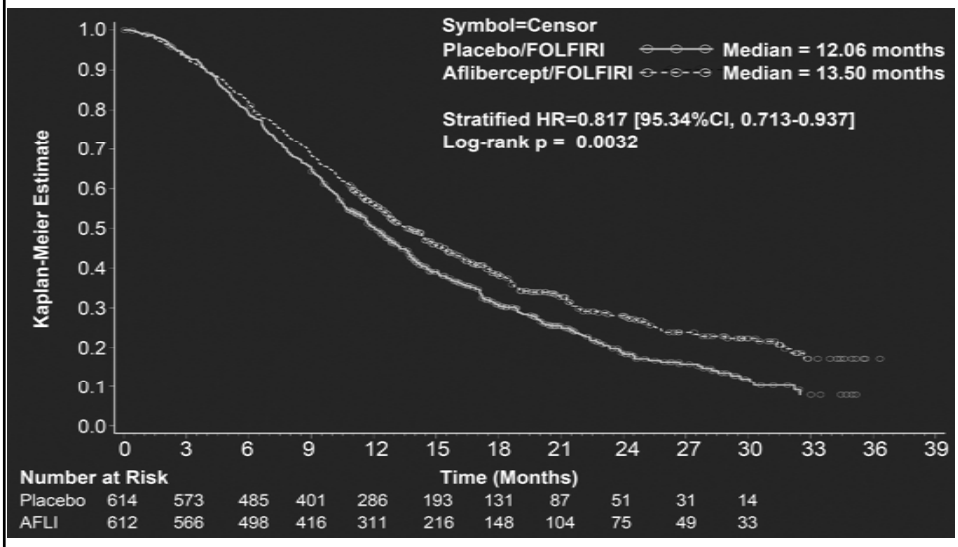
**** From lab.**
Van Cutsem, 2011.

OS: ITT Population



Cut-off date = February 7, 2011; Median follow-up = 22.28 mos

Van Cutsem et al, 2011.

Optimized Medical Therapy of Advanced CRC

1. Identify the goal of therapy
   - RR only matters for
     - Conversion therapy of liver metastases or
     - If patient is symptomatic from his tumor burden
   - For most patients gain of time and maintaining QOL is more important
2. Treat to progression – and perhaps beyond?
   - Be mindful about toxicities, stop oxaliplatin before neurotoxicity develops
   - Some select patients can have CFI

CFI = chemotherapy-free intervals.
NCCN, 2011.

Optimized Medical Therapy of Advanced CRC (cont.)

3. Expose patients to all potentially active agents
   - These agents are the oncologist's tools to keep patients alive
   - Use fluoropyrimidine-based combinations as default backbone, reserve sequential single agent therapy for select patients
4. Reutilize chemotherapeutic agents (in different combinations?) in the course of the therapy
   - Continuum of care vs. distinct lines of therapy

NCCN, 2011.