Management of Hepatic Metastases

Updates on the Management of
Gastrointestinal Malignancies

Natural History
Untreated Hepatic Colorectal Metastases

- Annual no. patients 65,000
- Median survival-untreated 5-10 m
- Five year survival 0

- Death with only liver mets 38%

Review of Hepatic Resection for Metastatic Disease

- 99 institutions
- 14 years
- 168 resections
- 5-year Survival = 20%

Foster J.H., Am J Surg 135:389, 1978

Hepatic Resection for Colorectal Metastases

Long Term Follow-up

- 1960 - 1992
- Erlangen University Hospital
- 469 resections

	Survival (%)
5-year	39
10-year	24
20-year	18

Scheele et al., World J Surg 19,59, 1995

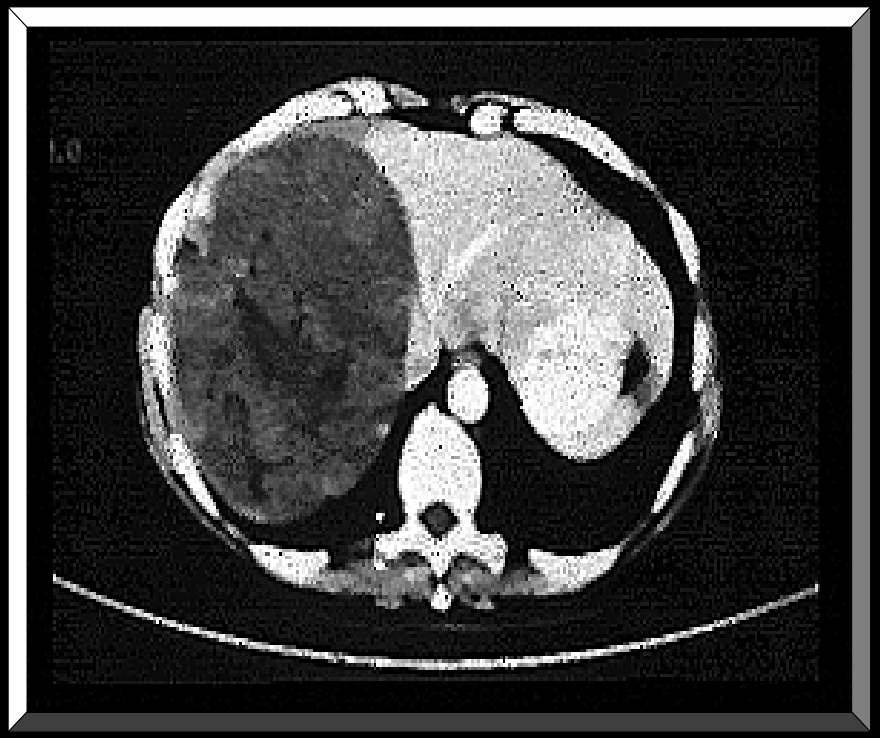
Hepatic Resection for CRC Metastases: Past Studies

Study	n	Mortality	5-yr Surv
Hughes, 1986	607*	NS	33
Scheele, 1991	219	6	39
Rosen, 1992	280	4	25
Gayowski, 1994	204	0	32
Scheele, 1995	469	4	39
Fong, 1995	577	3	38
Nordlinger, 1995	1568*	2	28
Iwatsuki, 1999	305	0	32
Fong, 1999	1001	3	37

***multi-institutional reviews**

How Should We Classify Patients with Hepatic Colorectal Metastases?

- All are stage 4 by TNM classification
- Resectable disease behaves like stage III colorectal cancer
- Better classification needed
  - Selection for chemotherapy
  - Stratification for clinical trial
  - Comparison of various studies



Solitary
4 Year disease-free interval
Node negative primary

Multiple
Bilateral
Synchronous
Node positive primary

Hepatic Resection for Colorectal Metastases

Prognostic Factors

Study	Age	Stage	Synch	Size	Number	Bilobar	Satellite	Margin	CEA
Foster	—	N	N	Y	Y	—	—	—	—
Adson	—	Y	N	N	N	N	—	__	—
Fortner	N	Y	—	N	N	—	—	—	N
Butler	N	Y	N	N	N	—	—	N	—
Iwatsuki	N	Y	N	Y	Y	—	—	—	—
Hughes	—	Y	Y	Y	Y	Y	—	Y	Y
Nordlinger	—	N	N	N	N	—	—	—	—
Coburn	—	N	N	—	Y	—	N	—	—
Schlag	—	—	Y	—	—	—	—	—	—
Doci	N	Y	N	N	N	N	—	—	N
Younes	—	N	N	Y	Y	—	—	—	Y
Scheele	N	Y	Y	N	N	N	Y	Y	—
Rosen	—	N	N	N	N	—	Y	N	N

Resection for Colorectal Metastases
Multivariate Analysis

	p	Hazard
Positive Margin	0.004	1.7
Extrahepatic Disease	0.003	1.7
Number >1	0.0004	1.5
CEA >200	0.01	1.5
Size >5 cm	0.01	1.4
Primary LN Status	0.02	1.3
Presentation < 12 mo	0.03	1.3
Bilateral Tumor	0.4	0.9

Fong et al., Ann Surg, 230:309, 1999

Clinical Risk Score

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

1 point for each criterion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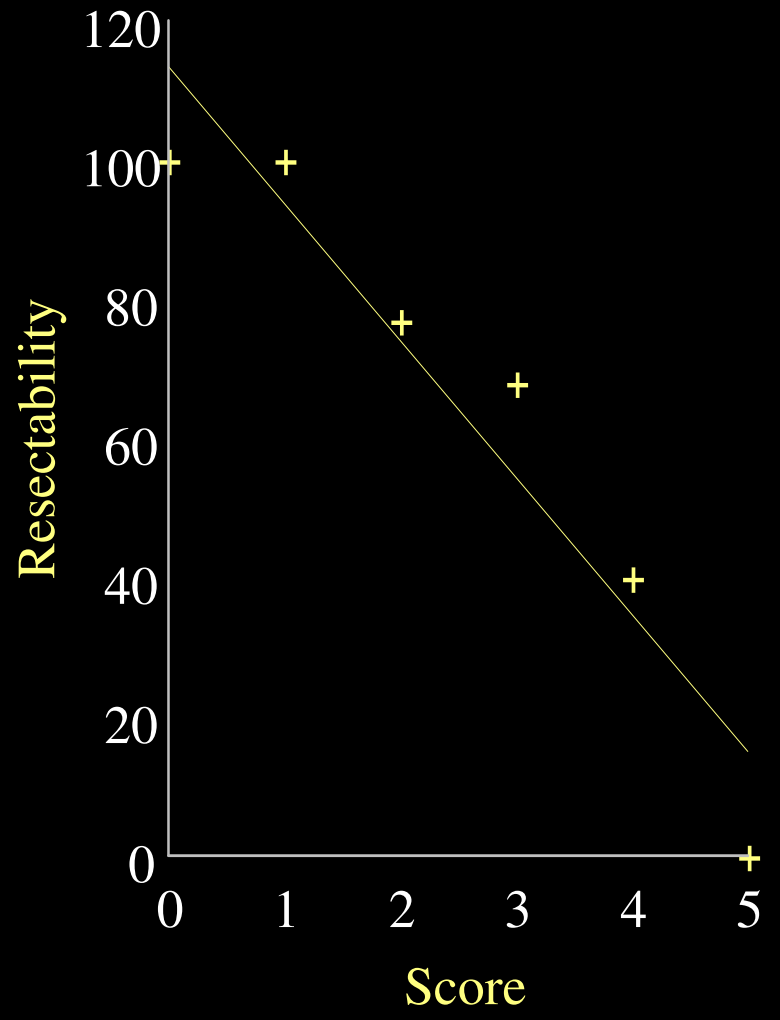
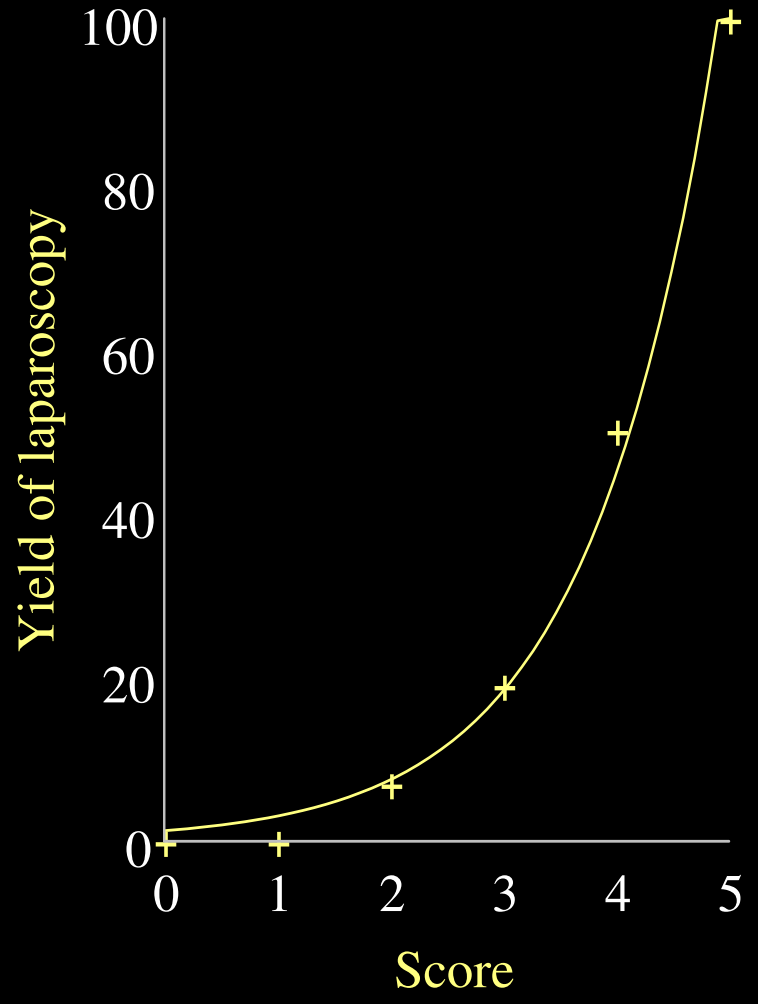
Clinical Risk Score Predicts Resectability and Yield of Laparoscopy

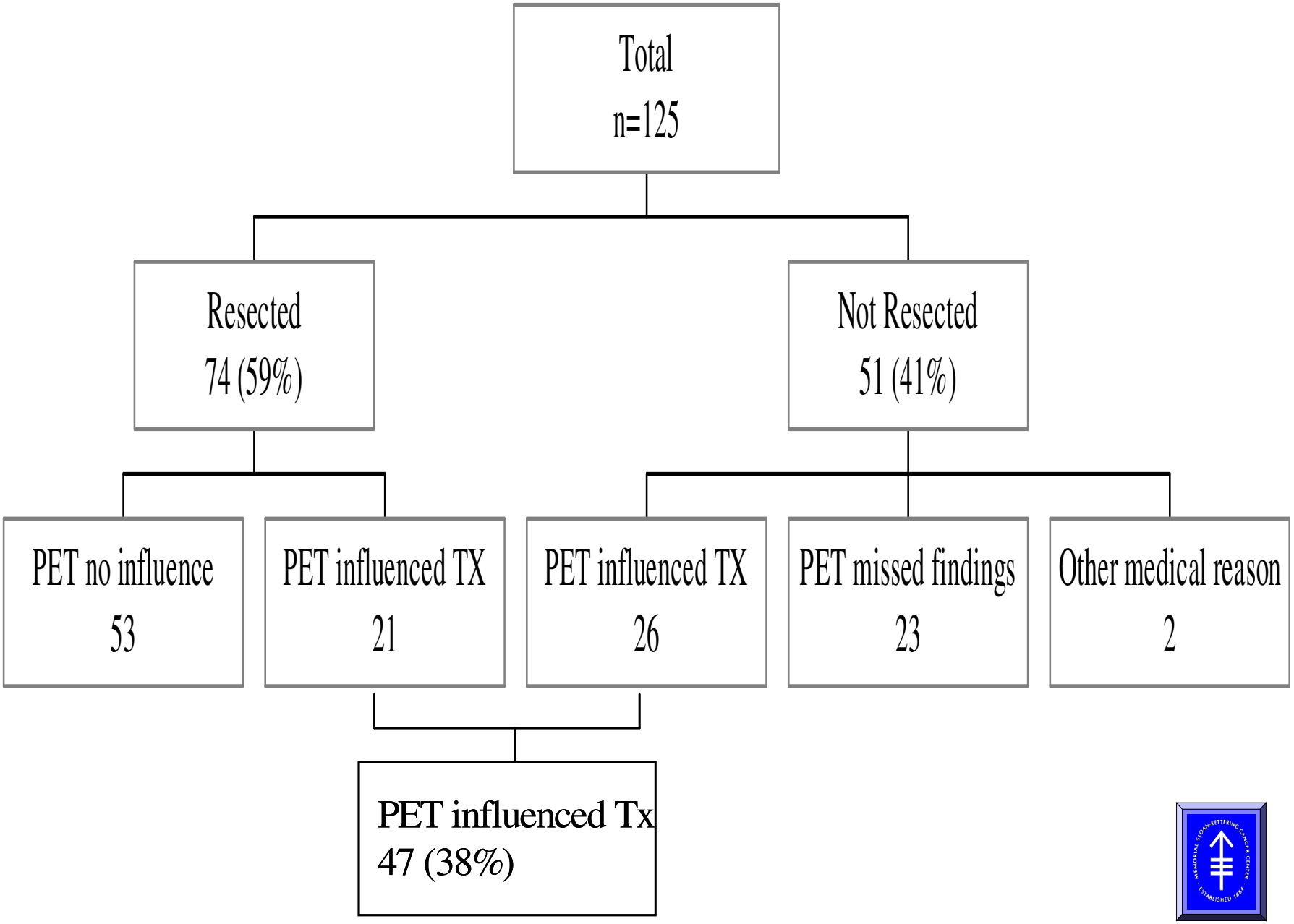




^{18}F-FDG PET Scanning

- Many patients found at laparotomy to have unresectable disease
- Two-thirds of patients will recur due to metastatic disease undetected at original resection

Yield of PET in Patients with Hepatic Metastases

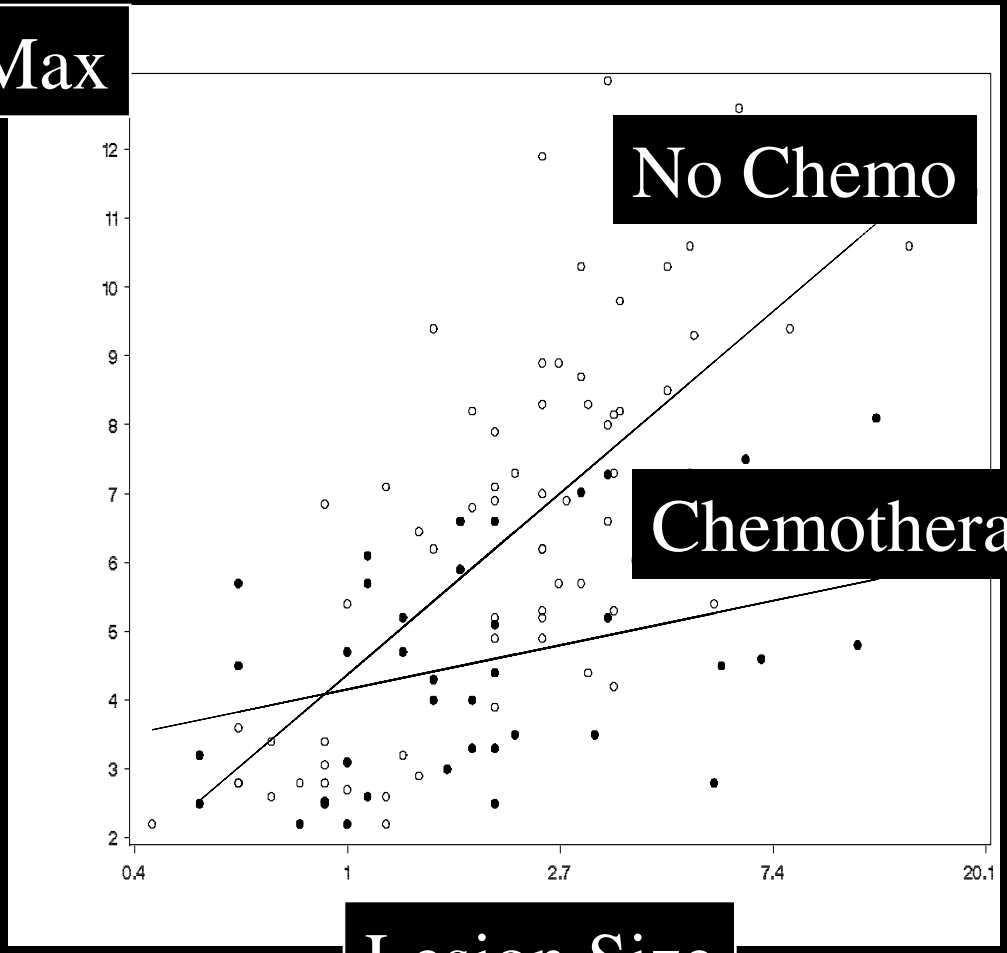


Yield of 18F-FDG PET for Liver Metastases

	PET+	PET-	Total	%
<1 cm	2	22	24	8
1-2 cm	28	7	35	80
2-3 cm	17	1	18	94
>3 cm	32	1	33	97
Total	79	31	110	72

Treatment with Chemotherapy Effects FDG- uptake

SUV Max

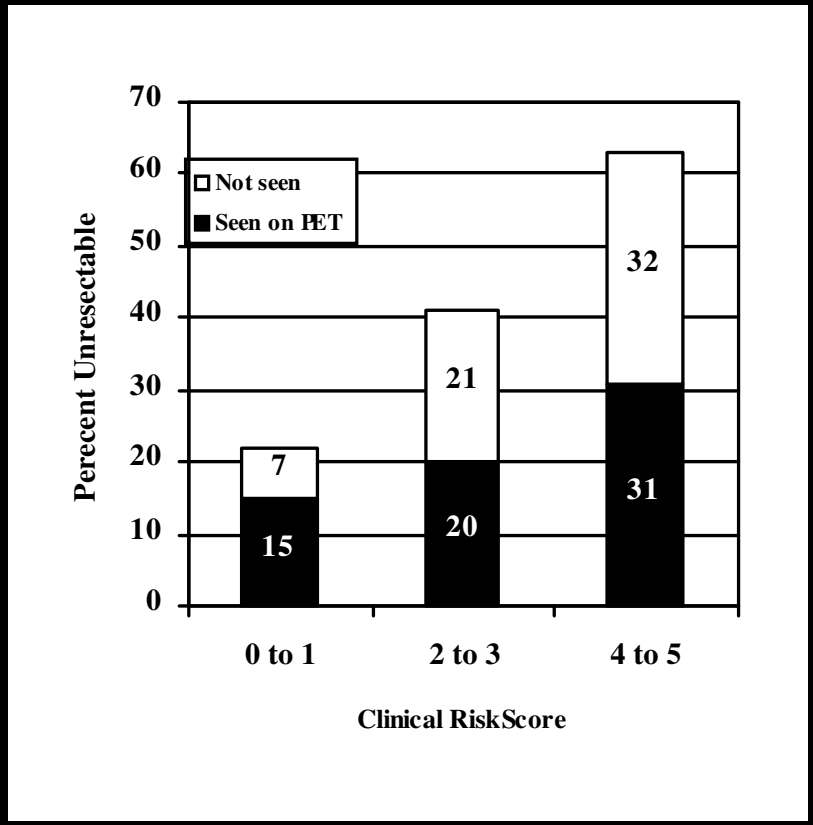


Lesion Size

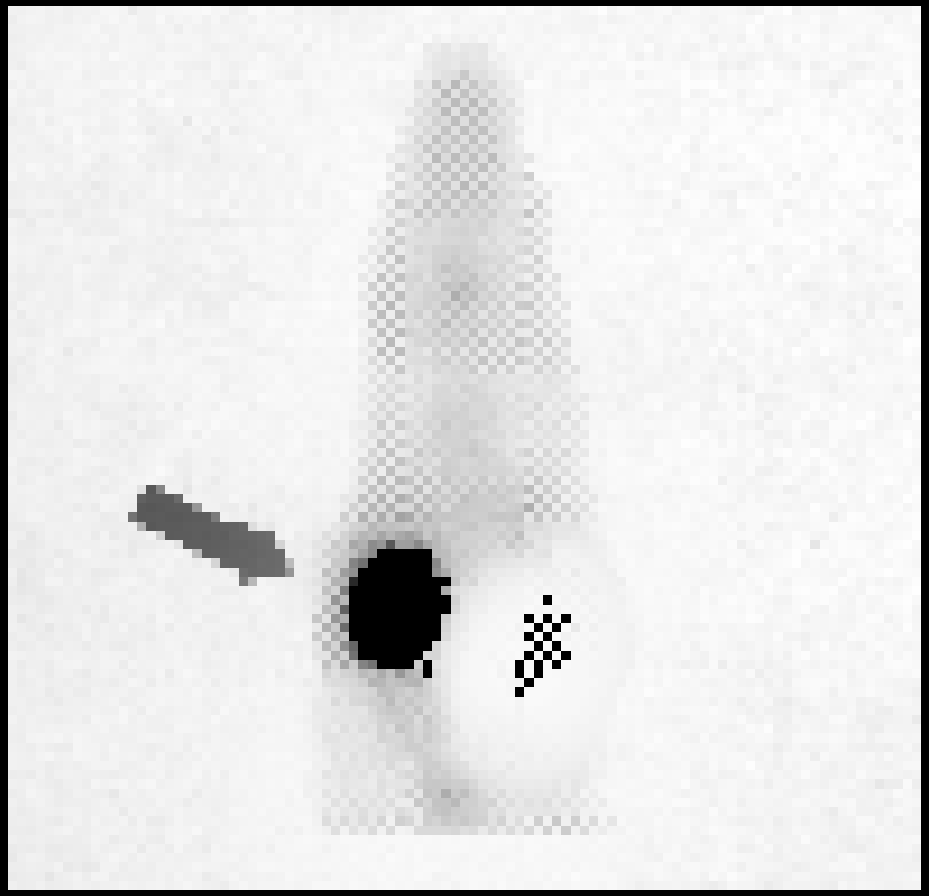
Akhurst et al., J Clin Oncol, 2005

FDG-PET Yield and Clinical Risk Score

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



PET Image of Liver Tumor after Injection of ^{124}IUDR



Biologic Imaging

◆ Glucose metabolism	FDG
◆ Proliferation	IUDR, FLT
◆ Apopotosis	Annexin V
◆ Hypoxia	Fluoroetanidazole
◆ Angiogenesis	$^{15}H_2O$, ^{11}CO, functional MRI
◆ Phosphorous metabolism	MR spectroscopy

1995: Drugs for Colorectal Cancer

- Fluorouracil (5FU)
- Floxuridine (FUDR)

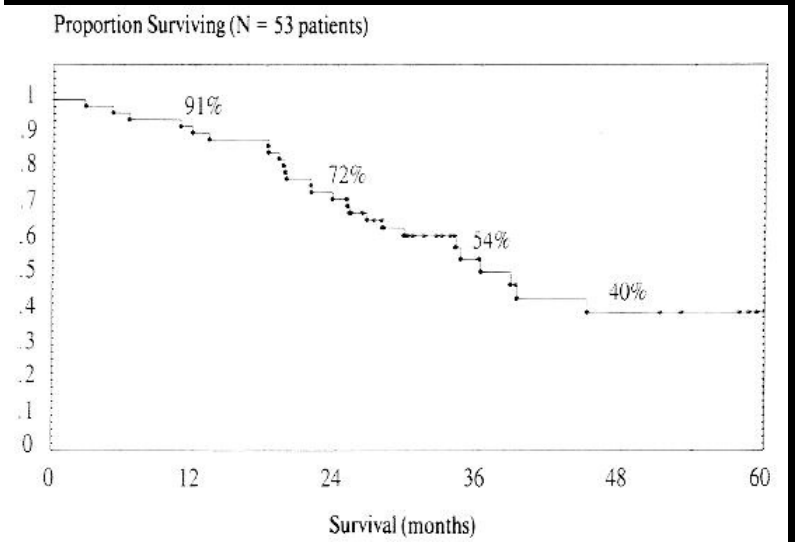
2007: Drugs for Colorectal Cancer

- Fluorouracil (5FU)
- Irinotecan (CPT-11, Camptosar)
- Oxaliplatin (Eloxatin)
- Capecitabine (Xeloda)
- Floxuridine (FUDR)

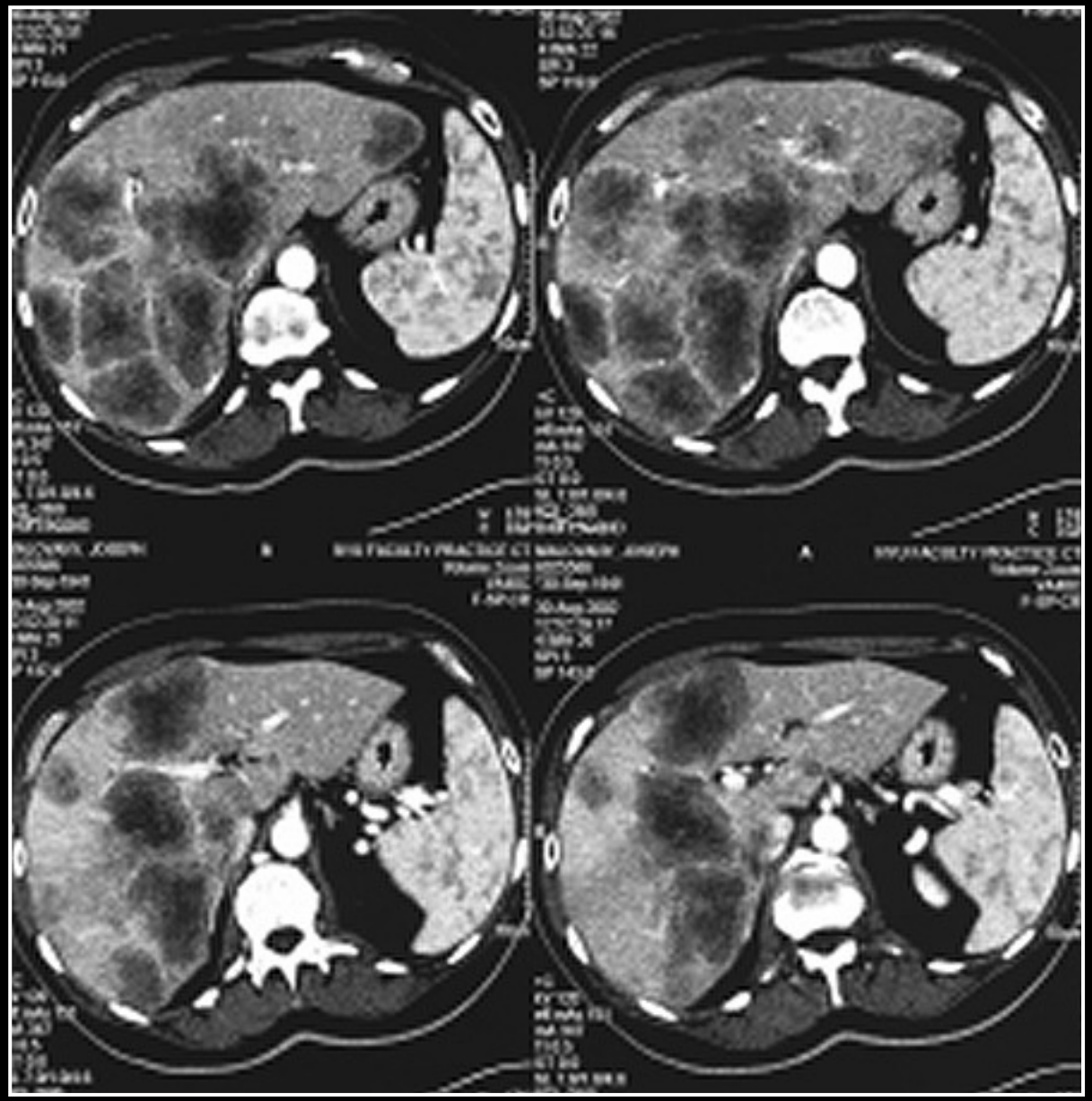
- Cetuximab (C225, Erbitux)
- Bevacizumab (Avastin)

Downstaging Using Systemic Chemotherapy

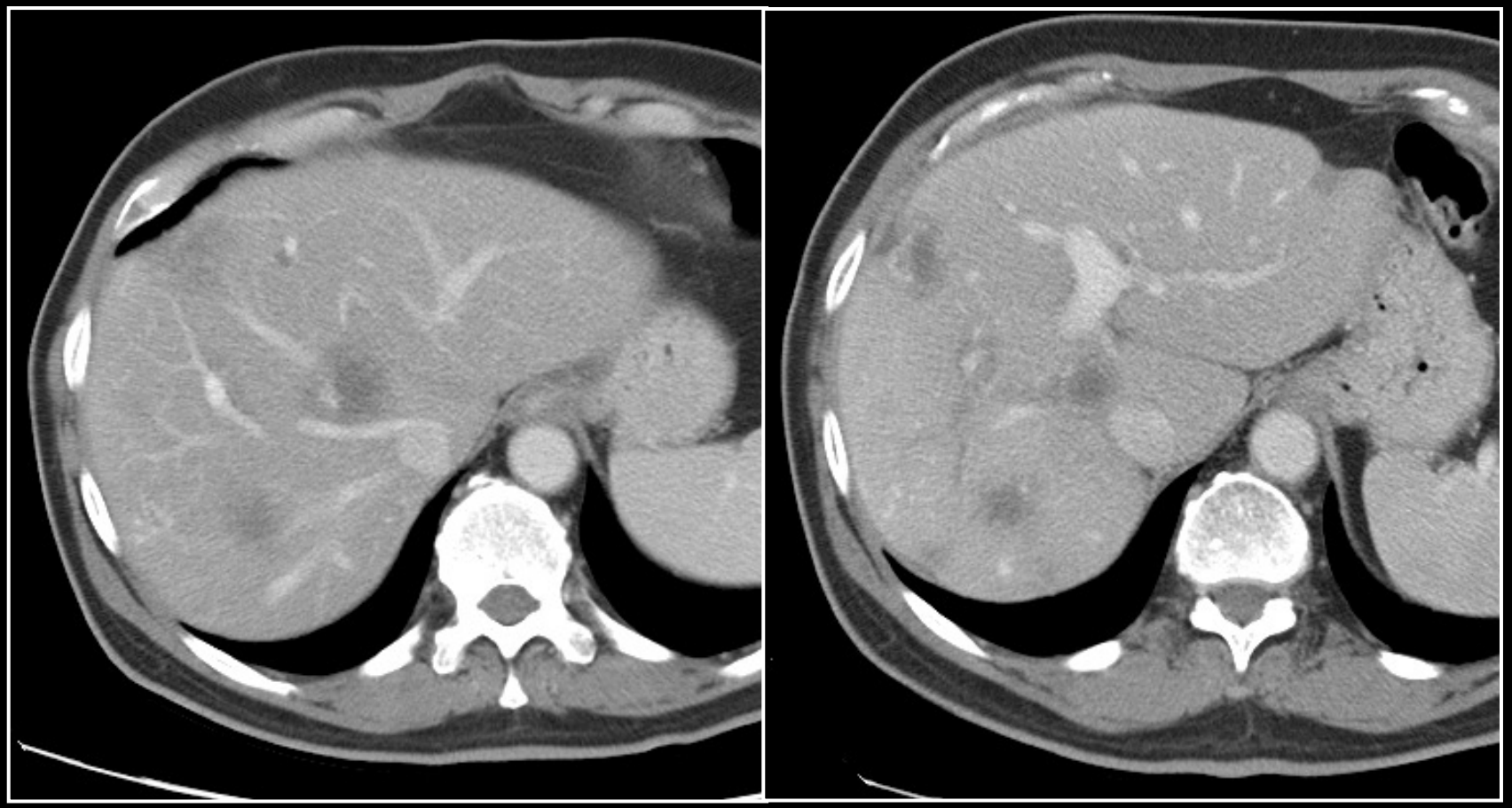
- 434 patients seen
- 104 resected; 330 not resected
- 53 patients converted to resectable
  - 8 ill-located; 8 large; 24 multinodular; 13 extrahepatic
- 5FU, folinic acid, oxaliplatin
- 54% and 40% survival at 3 and 5 years



Bismuth et al., Ann Surg, 224:509, 1996



After 5FU/Oxaliplatin

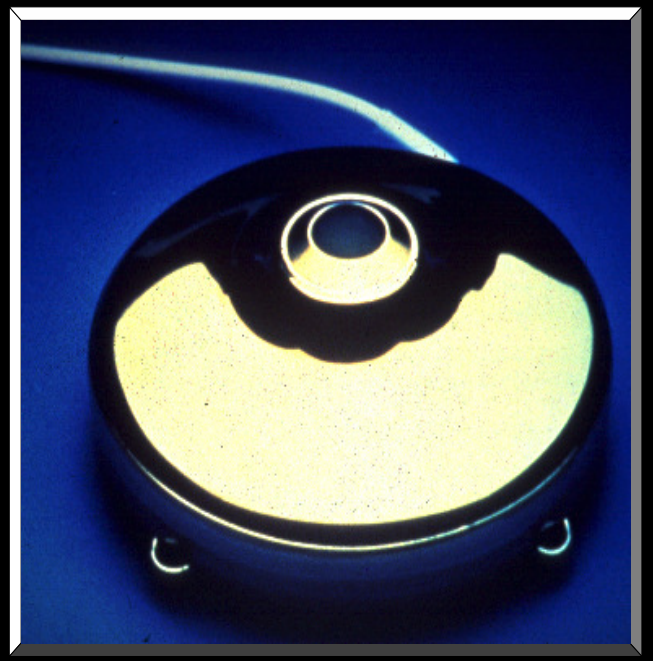


Second Line Therapy
Metastatic Colorectal Cancer

Sys	# PT	% Response	1 Year Survival
CPT-11	205	11 %	46 %
CPT +C225	218	23 %	---
Folfox	289	20 %	40 %
Folfox + Bev	290	---	55 %
CPT +C225 + Bev	45	35%	---

Downstaging by Regional Chemotherapy

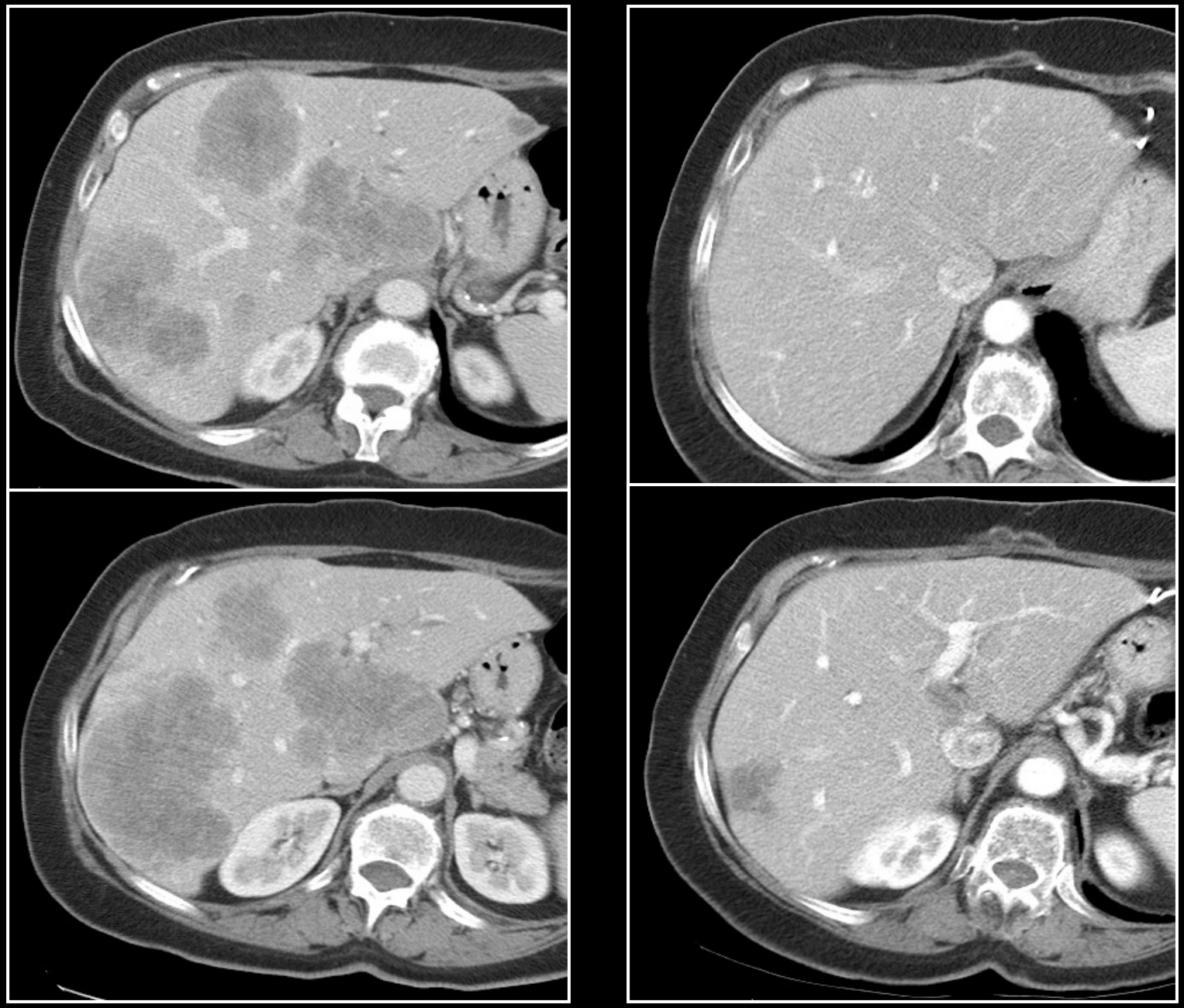
- 23 patients with unresectable hepatic CR metastases
- Floxuridine (0.2mg/kg/d x 14 d)
- 6 (26%) were converted to resectable



Clavien et al., Surgery 131:433, 2002

Before

After



Combined HAI FUDR / Systemic CPT-11 and Oxaliplatin

- N=22
- Un-resectable
- 20 previously treated
- 16 previously treated with CPT-11
- 19 (86%) response
- 9 (41%) converted to resectable
- 2 with no viable tumors

J Clin Oncol, 2004

Second Line Therapy
Metastatic Colorectal Cancer

Sys	# PT	% Response	1 Year Survival
CPT-11	205	11 %	46 %
CPT +C225	218	23 %	---
Folfox	289	20 %	40 %
Folfox + Bev	290	---	55 %
CPT +C225 + Bev	45	35%	---
HAI + Sys			
FUDR + CPT-11	56	74%	84%
FUDR + Oxali +CPT	34	86%	87%

Neo-adjuvant Chemotherapy

- Helps select chemotherapy after resection or ablation
- Treat microscopic disease
- Shrink tumors to improve ease of resection
- Shrink tumors to improve completeness of ablation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Costs of Neoadjuvant Chemotherapy

- Patient with CRS=3, no previous chemotherapy (synchronous)
- Risk of recurrence 80%, response rate 50%

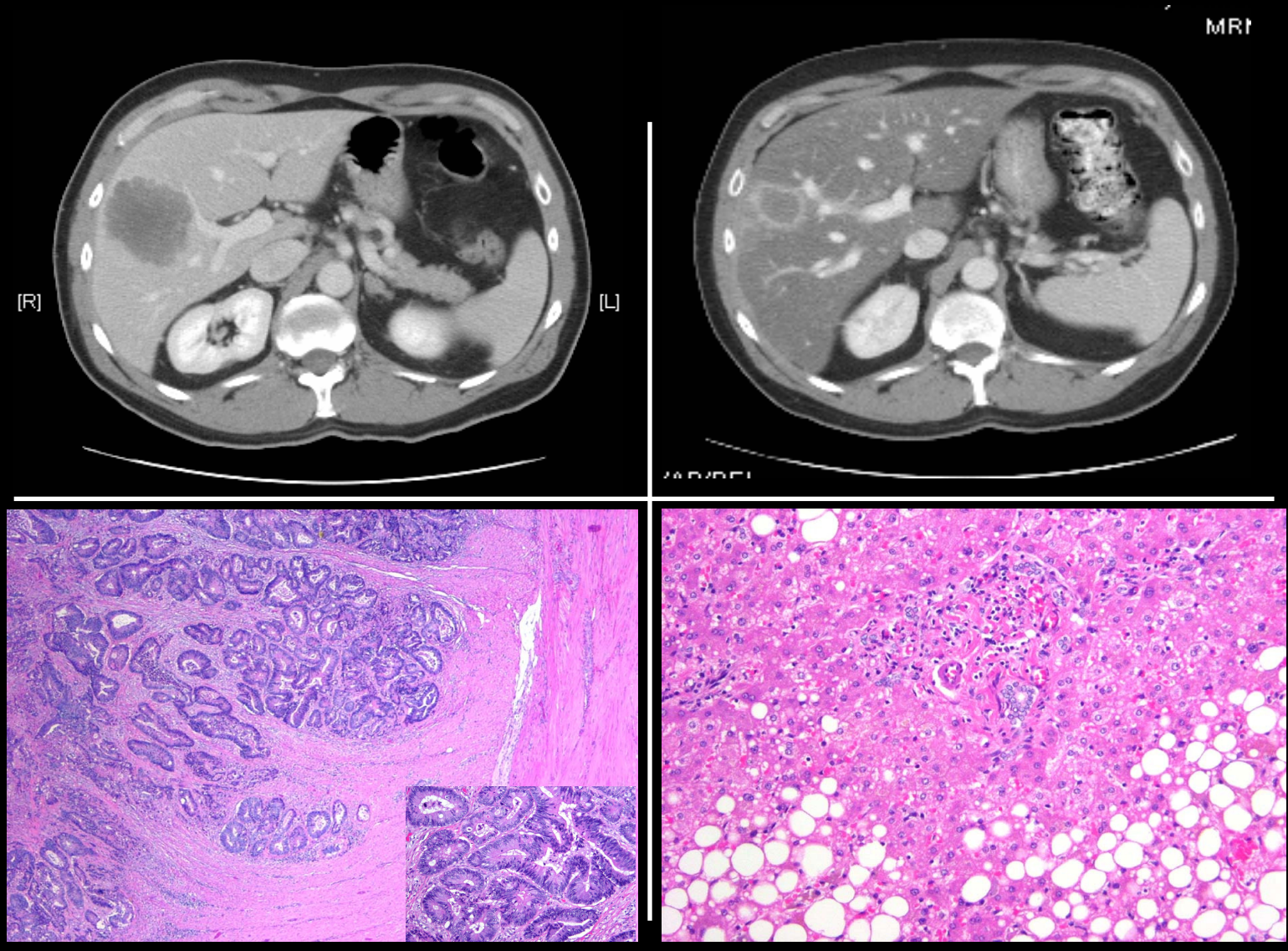
- For every 100 patients
  - .5 (response) X .8 (at risk) X100 = 40 patients benefit
  - 60 patients received chemo with no benefit
  - 2 deaths from chemo
  - (50K X 80) + (150K X 20) = 10 million dollars
  - For 65,000 patients = 6.5 billion

Costs of Neoadjuvant Chemotherapy

- Patient with CRS=0, previous chemotherapy
- Risk of recurrence 40%, response rate 20%

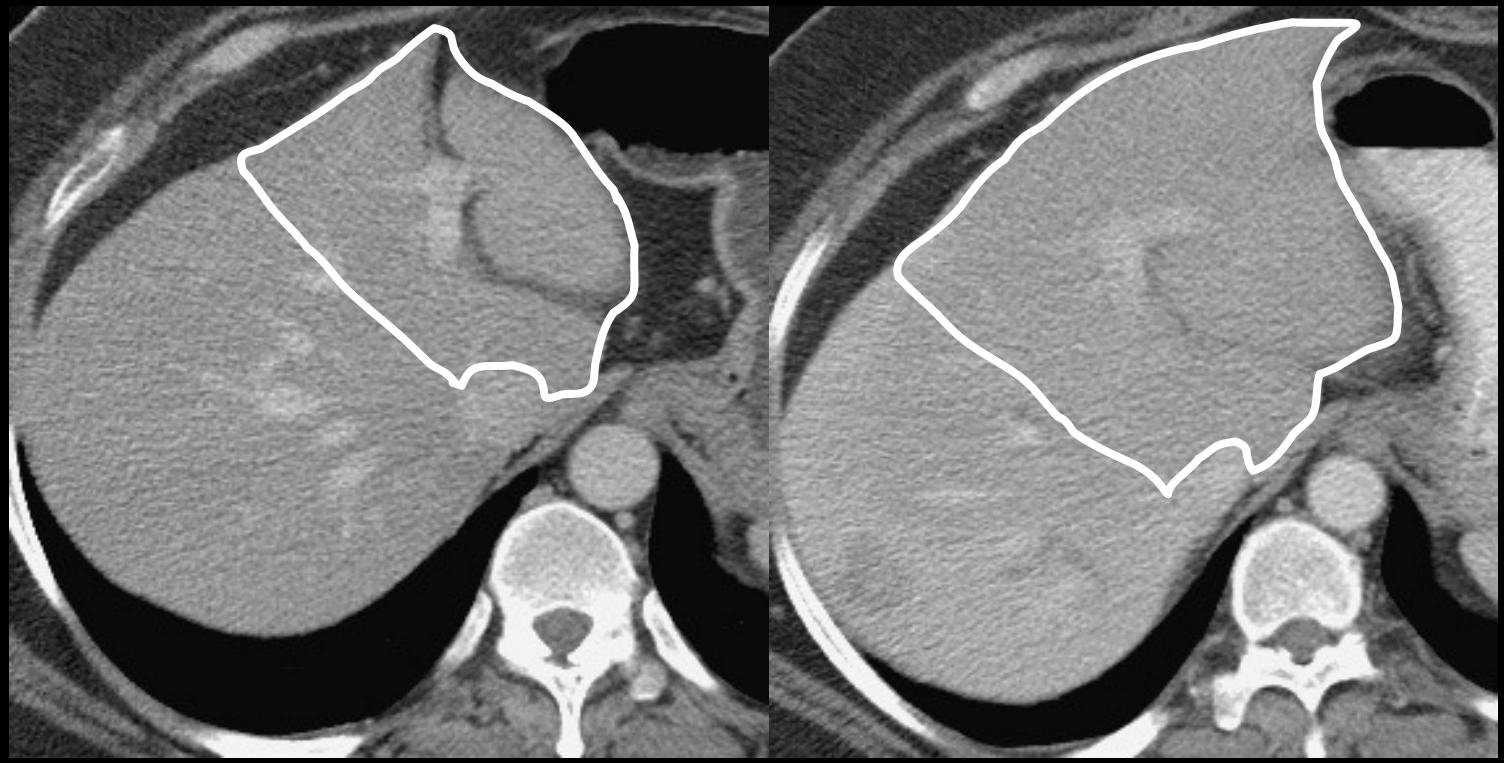
- For every 100 patients
  - .2 (response) X .4 (at risk) X100 = 8 patients benefit
  - 92 patients received chemo with no benefit
  - 2 deaths from chemo
  - (50K X 80) + (150K X 20) = 7 million dollars
  - For 65,000 patients = 4.6 billion

Chemotherapy Associated Steatohepatitis (CASH)



Fong and Bentrem, Ann Surg, 2005

Liver Growth after Contra-lateral Portal Vein Embolization



4 weeks

8 weeks

First suggested for resection of Hilar Ca
Makuuchi et al., Surgery 1990

Combined PV Embo with Neoadjuvant Chemotherapy Unresolved Questions

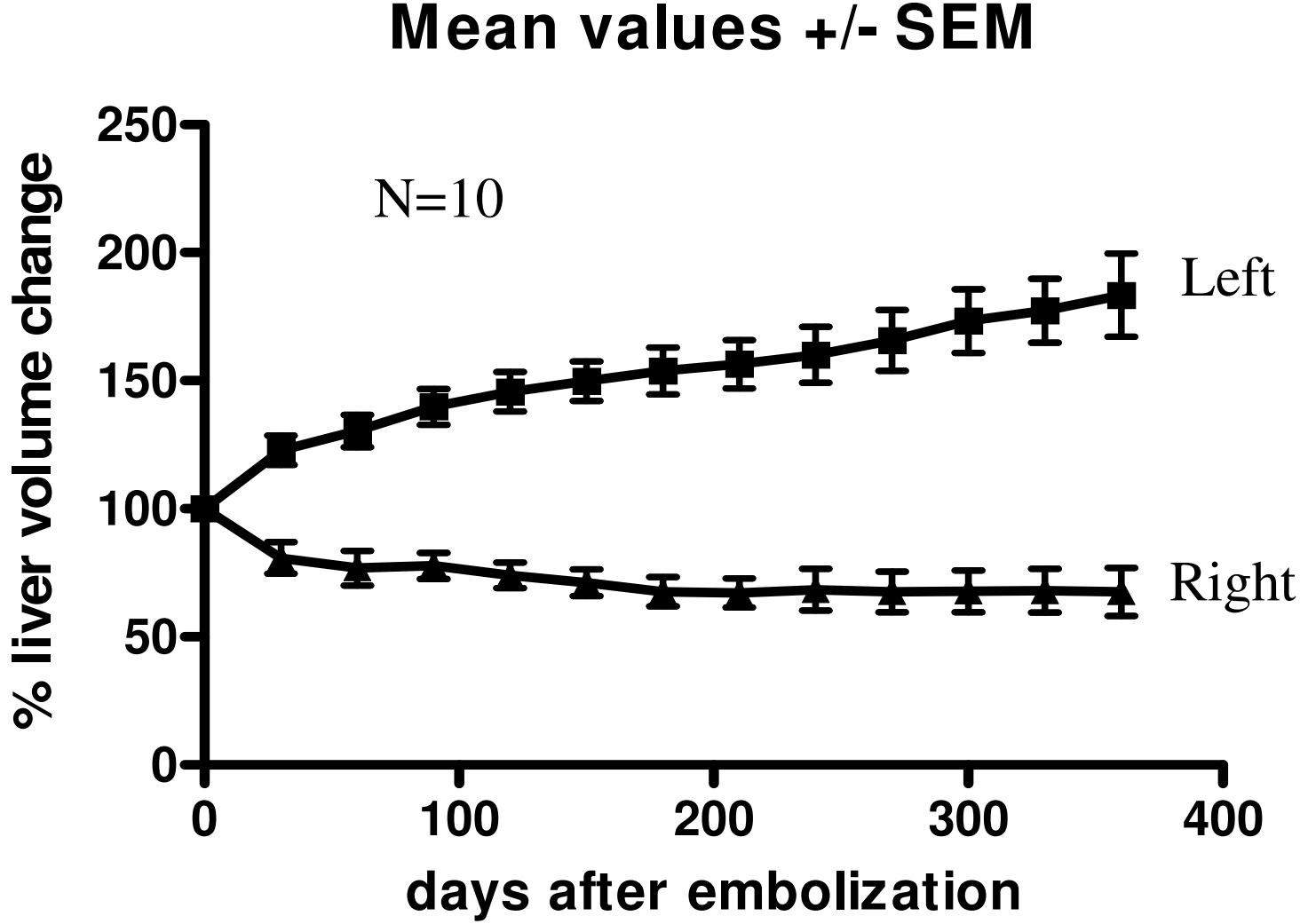
- Will the liver grow in response to portal vein embolization during chemotherapy?
- Will portal vein embolization improve the recovery from extended hepatectomy for patients with non-cirrhotic livers after extensive chemotherapy?

Growth of Liver After PV Embolization During Chemotherapy

	No Chemo (n=57)	Chemo (n=43)	P
Number with <5% growth	6	4	NS
Liver growth @ 30±2 days	26±3% 26 (0-86)	22±3% 22 (0-58)	NS
Contralateral atrophy	-14±3% -22 (0-52)	-15±3% -24 (0-41)	NS

N=100

Hypertrophy and Atrophy after Right Portal Vein Embolization



Combined Neoadjuvant Chemotherapy and Portal Vein Embolization

- Requires extensive resection:
  - lobectomy or more
- High risk patient
  - Synchronous disease
  - Clinical risk score >2
- Has not failed all systemic chemotherapy
- Neoadjuvant chemotherapy
- Portal vein embolization after 1st cycle
- Resection after 2 cycles if progression or stable
- Resection after 6 months if regression