DO WE NEED RADIATION THERAPY IN PANCREATIC CANCER?

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Dr. Raben does not have any relevant financial relationships with commercial interests to report.

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Objectives

- Review current algorithms for pancreatic cancer management
- **Discuss issues and controversies related to adjuvant radiation**
- SBRT? What is it and does it have a role in this disease?
- New science – after all – lets be honest – this is a systemic disease!

Diagnostic tests and Work-up

- Endoscopic US (alone or with ERCP) with biopsy of suspicious nodes if feasible
- CT Abdomen/Chest but I prefer a PET-CT scan
- Labs: please include Ca 19-9 pre-op!! (sensitivity – 90%, specificity- 75% and good marker for follow-up if elevated)
- Laproscopy: optional but I think helpful to prevent unnecessary resections; helps in looking for peritoneal seeding or liver mets

TREATMENT ALGORITHM
NEWLY DIAGNOSED ADENOCARCINOMA OF PANCREAS

Confirm histologic diagnosis (CT or EUS guided needle aspiration)

↓

Staging evaluation: CA 19-9 & liver chemistries; Rule out intra-abdominal and chest metastases with CT abdomen/pelvis, possible laparoscopy, chest x-ray

↓

Exploratory laparotomy; resection if possible
(no encasement of the celiac/superior mesenteric vessels)

Resectable

Standard:
EBRT + 5FU or Gemzar based chemo

Evaluate:
Neoadjuvant RT + chemo

Unresectable or Borderline Resectable

Standard:
EBRT+ 5FU or Xeloda or Gemzar based chemo

Evaluate:
Neoadjuvant EBRT + chemo
New therapies:
– EGFR, VEGF Inhibitors, mTor inhibitors, Src kinase inhibitors, Akt inhibitors

Adjuvant RT or CRT in pancreatic cancer

So what are we really talking about here?

- ~28, 000 cases per year
- ~15% of those are resectable so…~**4200 cases in the US each year**
- Out of those, at least 15% will have developed metastasis at the time of restaging..**so down to ~3600 cases left**
- ~80% of the resected cases will have regional nodal spread and/or positive margins (3000 cases)…so not big numbers here!

Resected Pancreatic Cancer

- High Risk For Local Failure + Distant Metastases

Has adjuvant CRT been effective in other diseases??

- Breast cancer – YES
- Gastric Cancer – YES
- Head and Neck Cancer – Yes
- Lung Cancer – controversial but most say YES in N2 disease
- Rectal cancer – YES (for LC)
- Brain – YES
- Prostate - YES

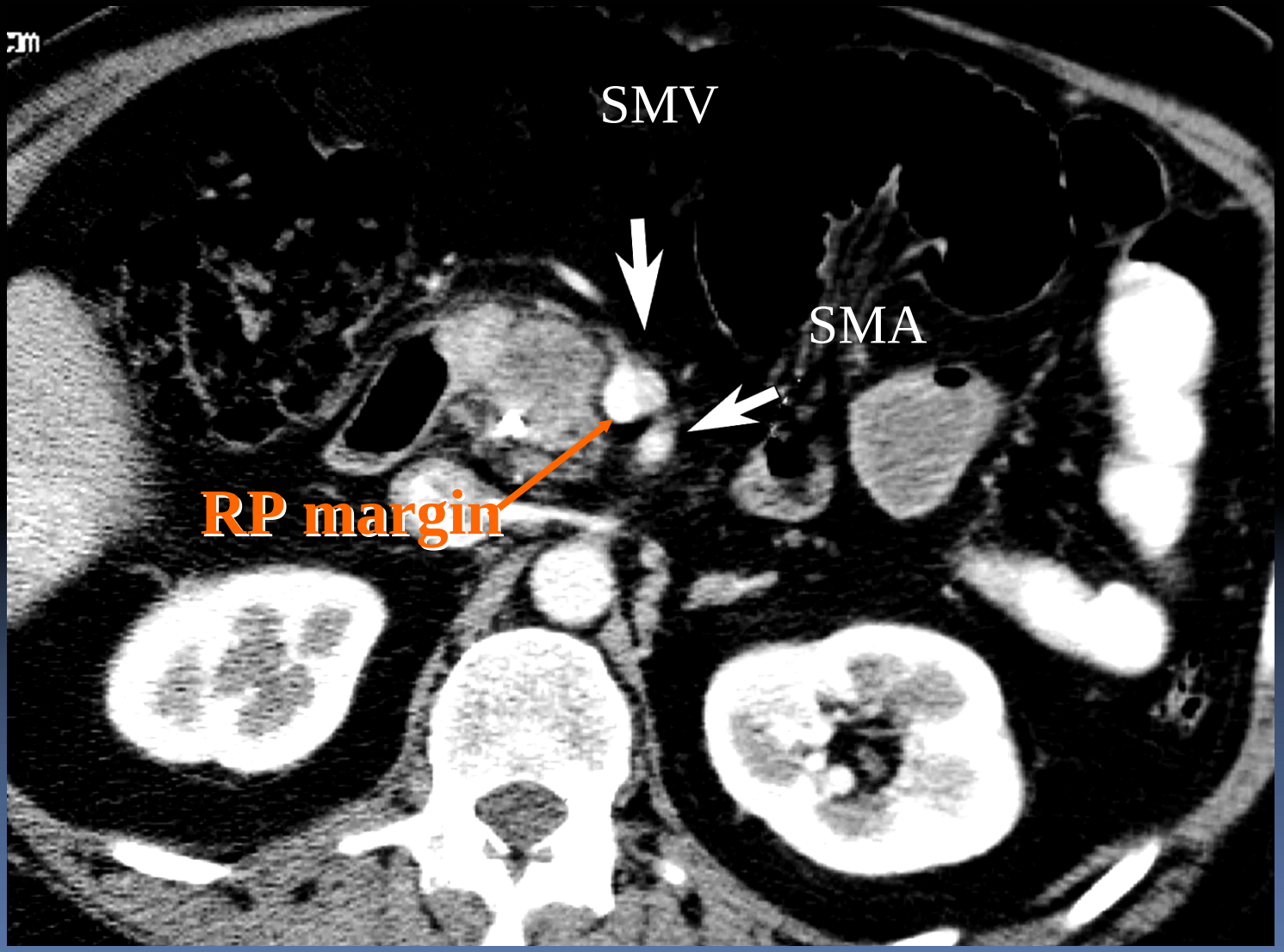
What do the Europeans say? Dr. Neoptolemos on RT for Pancreatic ca

- Ann Surg (2002): Espac 1 has clearly and unequivocally rejected the survival value of adjuvant chemoradiotherapy
- Clinical Gastroenterology (2002): Adjuvant chemoradiotherapy is of no benefit.
- Expert Opinion (2002): It is not necessary to give chemoradiotherapy when chemotherapy provides as good, if not better results.
- J Surg Oncol Clin N Amer (2004): The standard treatment for pancreatic cancer is now resection and adjuvant chemotherapy
- Br J Ca (2005): Routine use of chemoradiotherapy is not warranted

Here's the Problem: Patterns Of Failure After Surgery

Study	# Pts.	**Local (%)**	Peritoneal (%)	Liver (%)
Tepper	26	**50**	-	-
Griffin	36	**53**	31	44
Whittington	29	**85**	23	23
Ozaki	14	**86**	36	79
Westerdahl	74	**86**	-	92

Retroperitoneal margin a major problem



Pancreas Ca: Patterns of Failure After Surgery

MGH: 72 Patients Underwent Resection of Pancreatic Head Carcinoma:

- 37/72 Patients (51%): Tumor Extension to Margins (Retroperitoneum-27, Pancreatic Transection-14, Bile Duct-4)

Intergroup (RTOG 97-04) Trial

Crude data on 538 patients

SURGICAL MARGINS	RT + 5-FU	RT + Gemzar
Negative	45%	39%
Positive	32%	34%
Unknown	**23%**	**26%**

What about around the world?
Pancreatic Adenocarcinoma
Positive Margin Resection

Author (YR)	N	Margin	Med S
Neoptolemos (2001)	101	R1	11
Benessai (2000)	15	R1/2	9
Sohn (2000)	184	R1/2	12
Millikan (1999)	22	R1	8
Nishimura (1997)	70	R1/2	6
Sperti (1996)	19	R1/2	7
Nitecki (1995)	28	R2	9
Yeo (1995)	58	R1/2	10
Willett (1993)	37	R1/2	12

Local Failure After Resection

- A Significant Clinical Problem:
- Pain, Obstruction (Biliary, Gastric), and Bleeding

Efforts to Improve Local Control

- Postoperative RT+ChT
- Preoperative RT+ChT

For the surgical residents: Two Important GITSG Studies (1985): The Beginning!!

Resected Pancreatic Ca

n=43

- Observation
- **RT + 5-FU**

Resected Rectal Ca

n=227

- Observation
- RT
- 5-FU + MeCCNU
- **RT + 5-FU/MeCCNU**

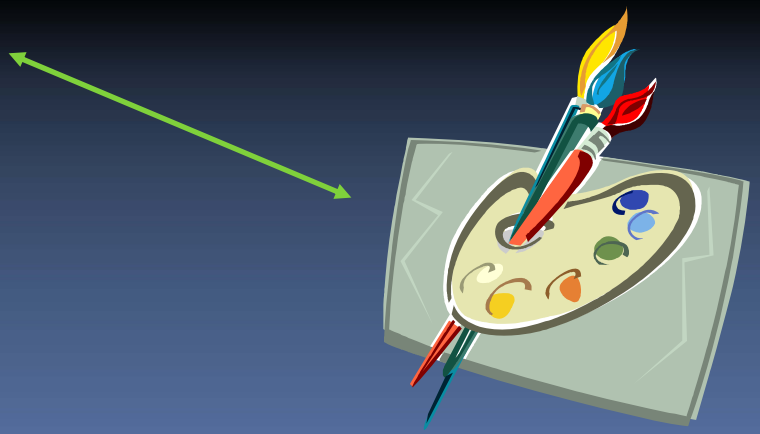
Lessons from Rectal Ca Trials (1985-2004)

LC + S Improved by:

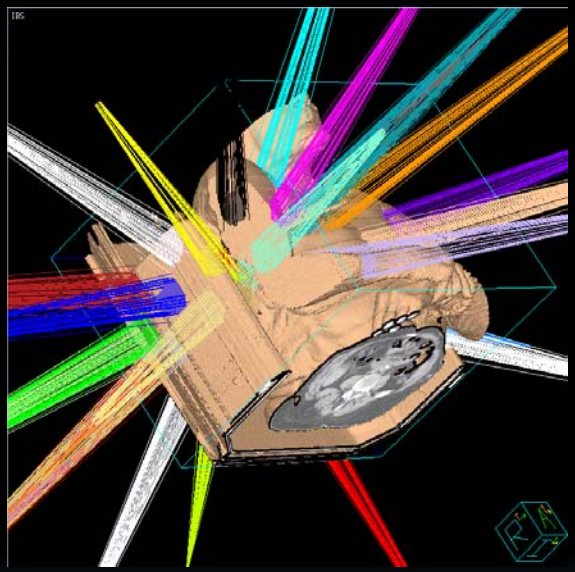
- Combined Modality Tx (RT + ChT)
- Modern Tx: Continuous + Higher Dose RT (50-54 Gy) vs Lower Dose (40 Gy)
- PVI vs. Bolus 5-FU with RT
- Sequence: Preop > Postop
- More QA not Less (RT, ChT, Path, Surgery)
- Now using IMRT based approaches with image guidance

Surgeons view of radiation oncology

IMRT and IGRT are becoming standard



Modern Technological Innovations



- Stereotactic targeting
- 3-D conformal avoidance
- IMRT
- 4-D motion assessment
- Motion control
- Image guidance
  - ALL FACILITATING STEREOTACTIC ABLATIVE AND HYPOFRACTIONATED RADIOTHERAPY

Adjuvant Pancreatic Ca Trials

Table 1: Phase III-studies for adjuvant therapy

Group - Study Year	Patients (n)	Inclusion criteria Resection-Status	Treatment arms	Median overall survival (Months)	*p*-value	Preoperative imaging
GITSG-1985[18]	49	R0	CRT Observation	21.0 10.9	0.005	No
EORTC-1999[22]	114*	R0	CRT Observation	17.1 12.6	0.099	No
ESPAC-1-2004[17]	289#	R0 or R1	Cx No Cx&	21.6 16.9	Not available	No
CONKO-001-2007[19]	368	R0 or R1	Cx Observation	22.1 20.2	0.06	Yes
RTOG 9704 2008[20]	442^	R0 or R1	CRT + GEM CRT + 5-FU	20.6 16.9	0.033	Yes

GITSG (1974): 40 Gy (SC) + Bolus 5-FU

Path QA: Yes

RT QA: Yes

EORTC (1987): 40 Gy (SC) + 5-FU

Path QA: Yes

RT QA: Yes

ESPAC 1 (1996): 40 Gy (SC)+ Bolus 5-FU

Path QA: No

RT QA: No

Adjuvant Pancreas Ca: GITSG (1985)

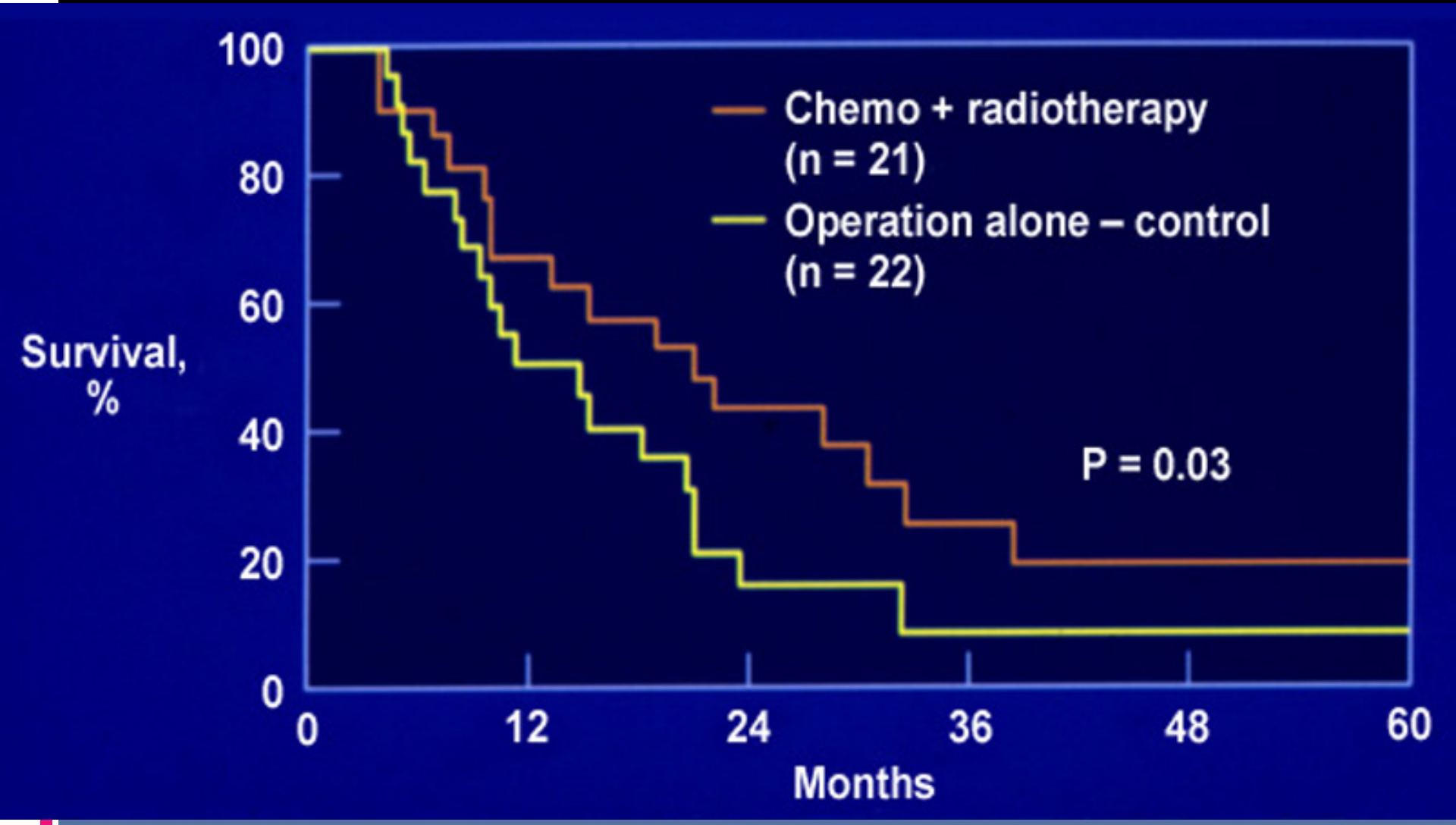
Resected Pancreatic Ca

RT (40 Gy-SC) + 5-FU

Observation

Tx	# Pts	MS (mo)	2 Yr. S
40 Gy/5-FU	21	20	**43%**
Observation	22	11	**18%**

Pancreas Adjuvant – GTSG Phase III Study
Probability of Survival by Treatment Group



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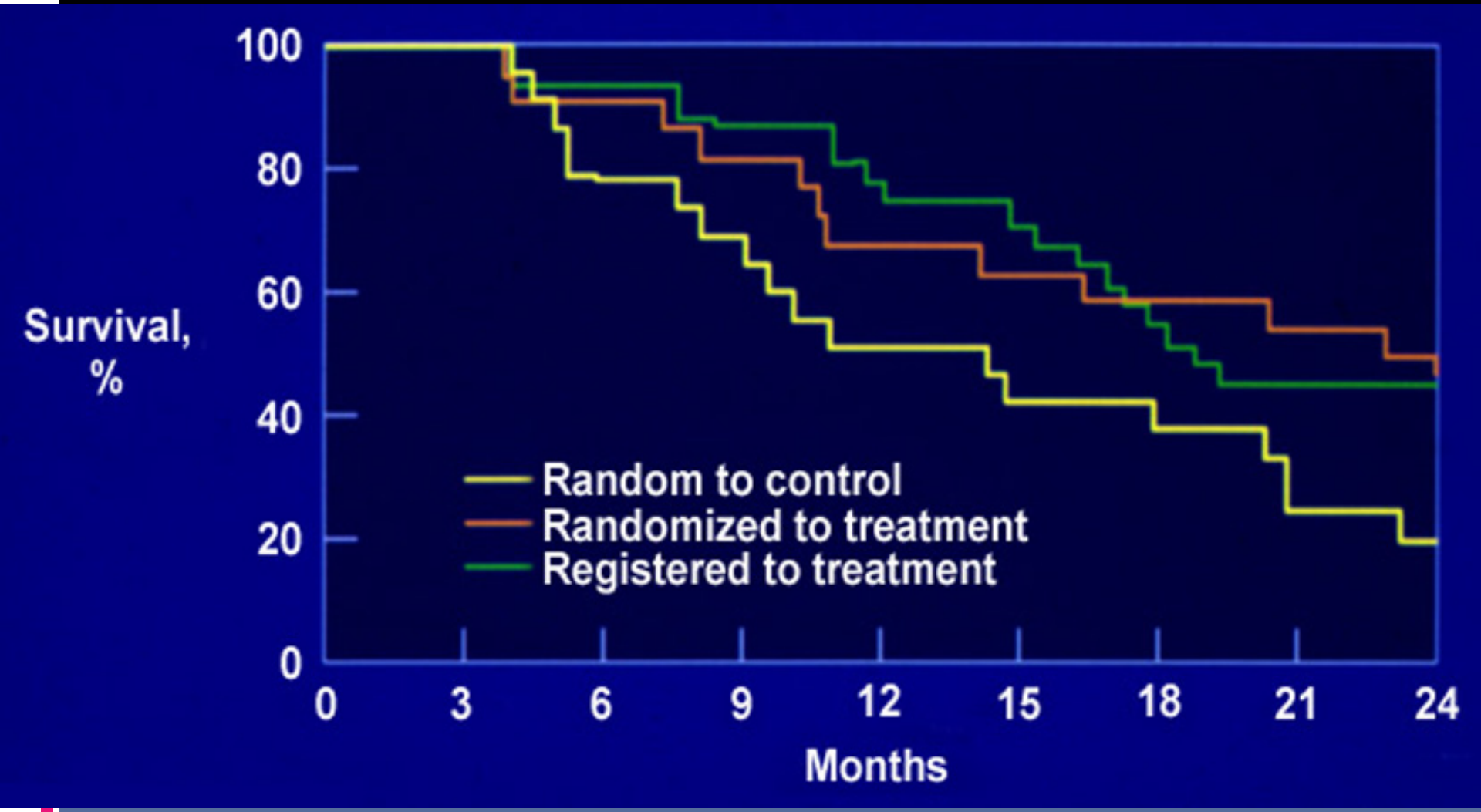


Cancer 59:2006, 1987

Adjuvant Pancreas / Periampullary Ca: EORTC (1999)

Resected Pancreas/Periampullary Ca

→ **RT (40 Gy-SC) + 5-FU**

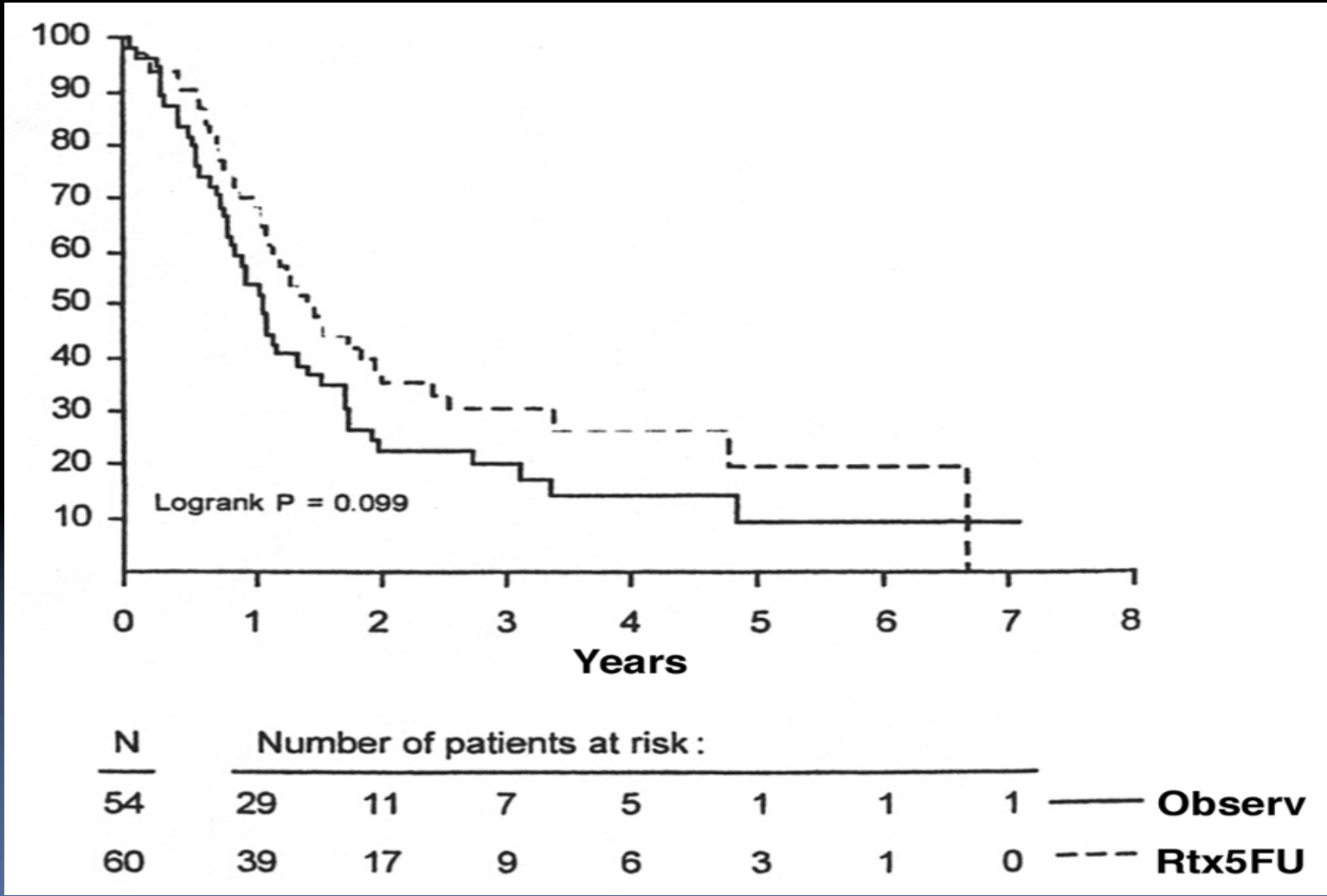
→ Observation

		Median S (mo)	5 Yr. S (%)
Pancreatic Ca			
RT/5-FU	(n=60)	**17.1**	**20**
Observe	(n=54)	**12.6**	**10**

P=0.099

PANCREAS CANCER: EORTC PHASE III TRIAL

Survival – Surgery ± EBRT + 5FU



Klinkenbijl et al, Ann Surg 230:776, 1999

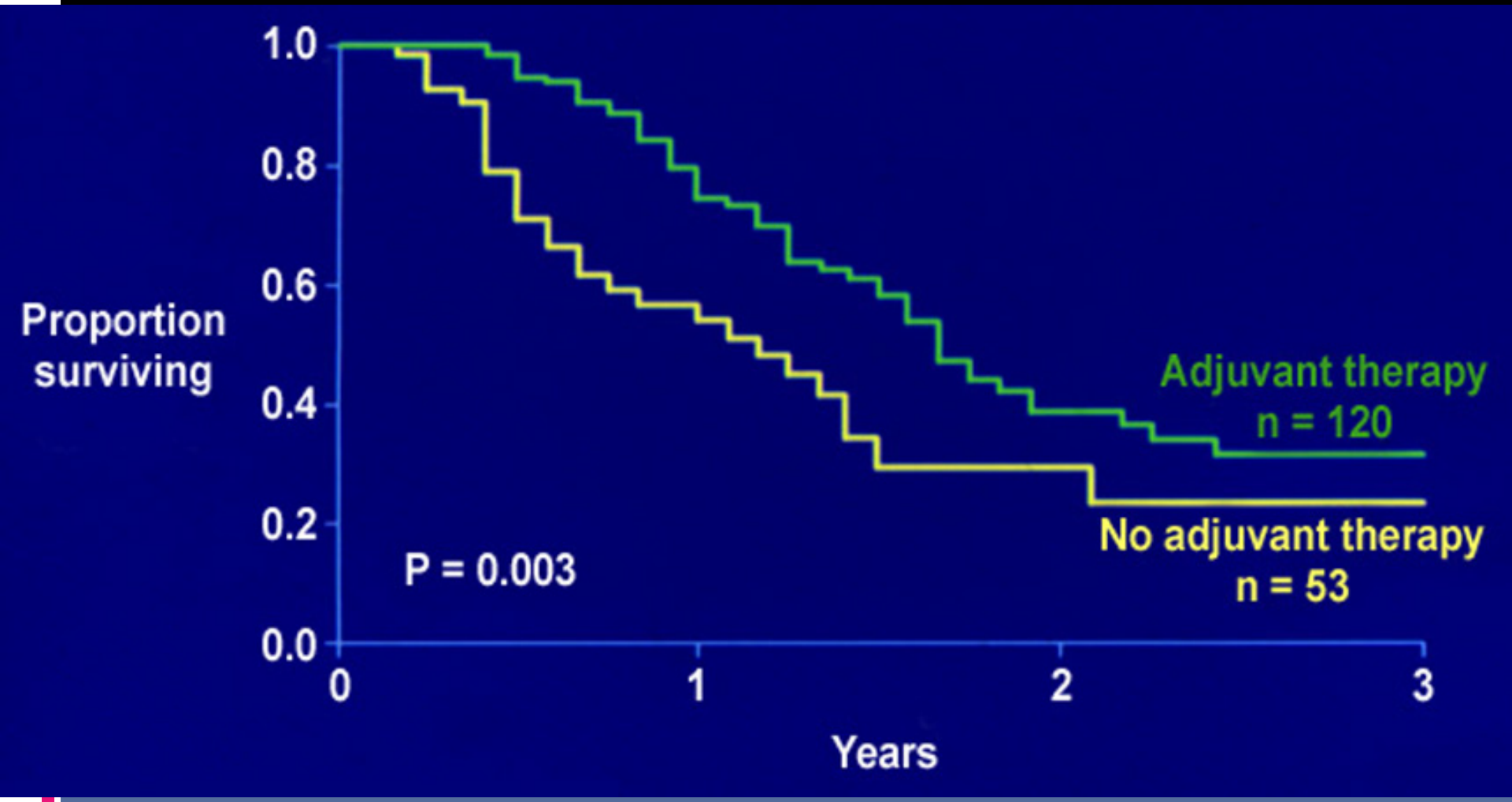
EORTC (1999): Conclusions

- Pancreas Ca: Trend to Improved S with Adjuvant Tx

Caveats:

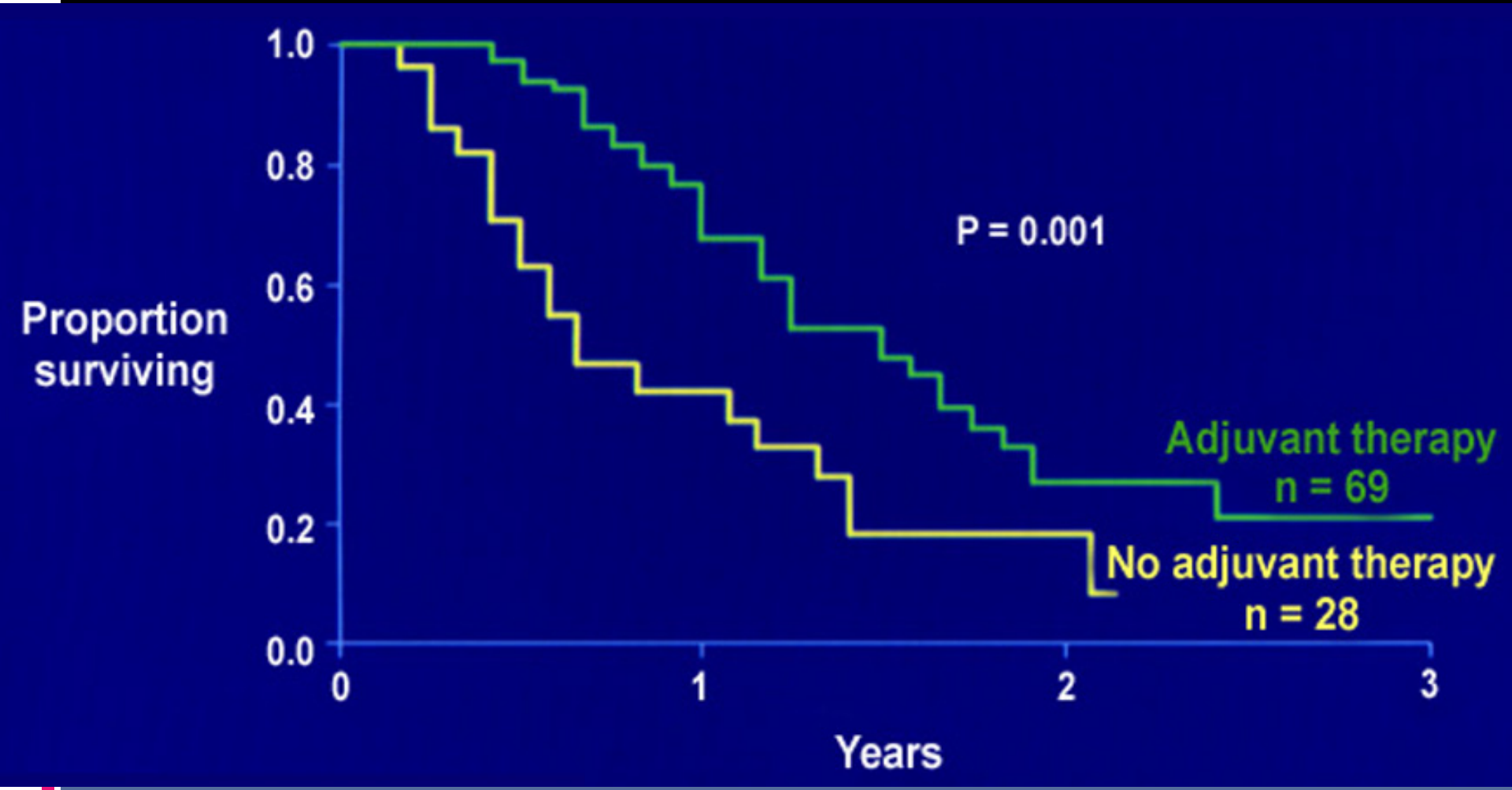
- No Maintenance ChT
- 20% of "Tx Patients": **No Tx!!**
- Underpowered Study

Pancreas Adjuvant – Johns' Hopkins
Survival – Surgery ± Postop EBRT + 5-FU



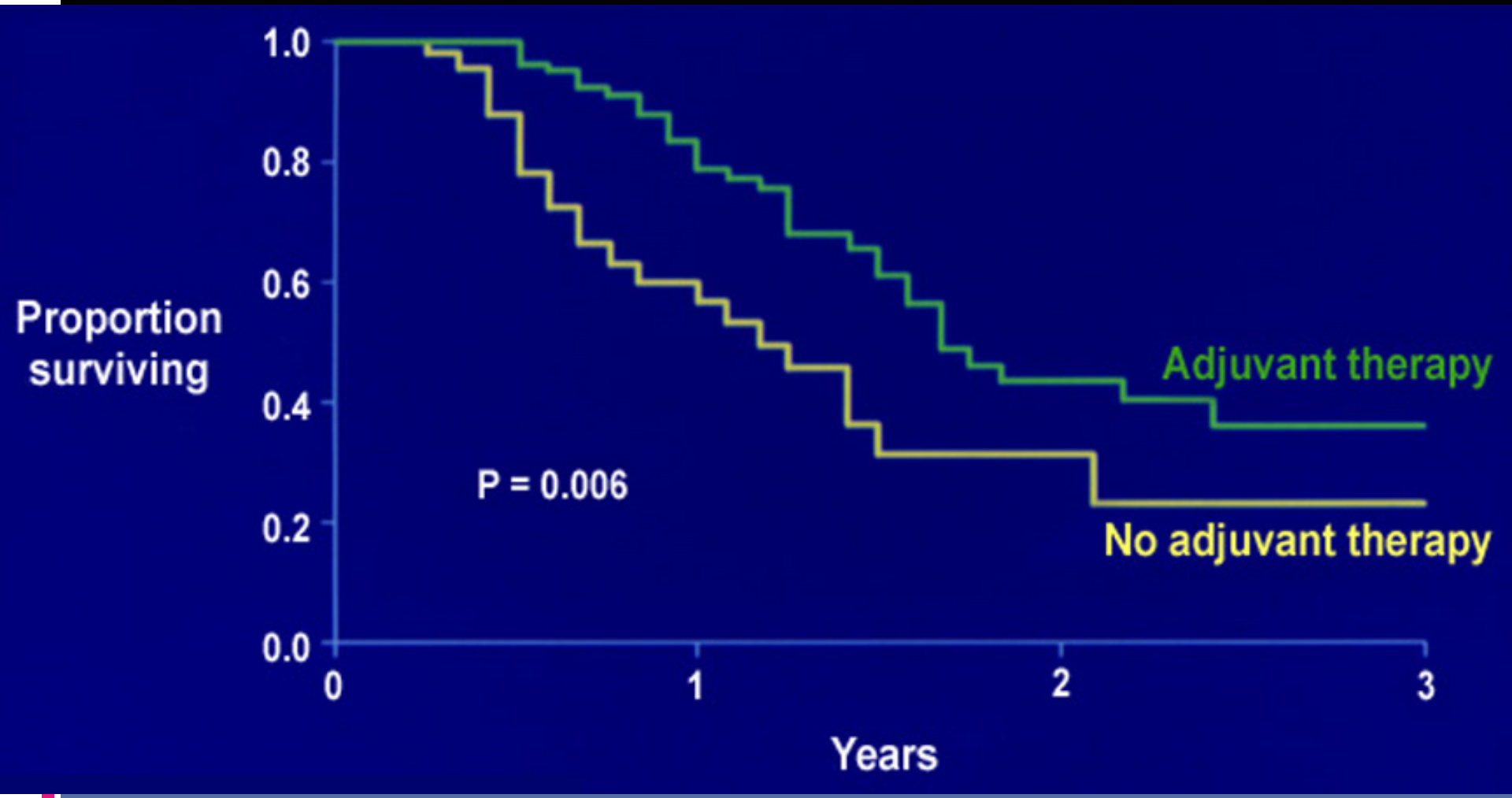
Yeo C et al., Ann Surg 225:621-36, 1997

Pancreas Adjuvant – Johns' Hopkins
Survival – Surgery ± Postop EBRT + 5-FU
Tumors ≥3 cm



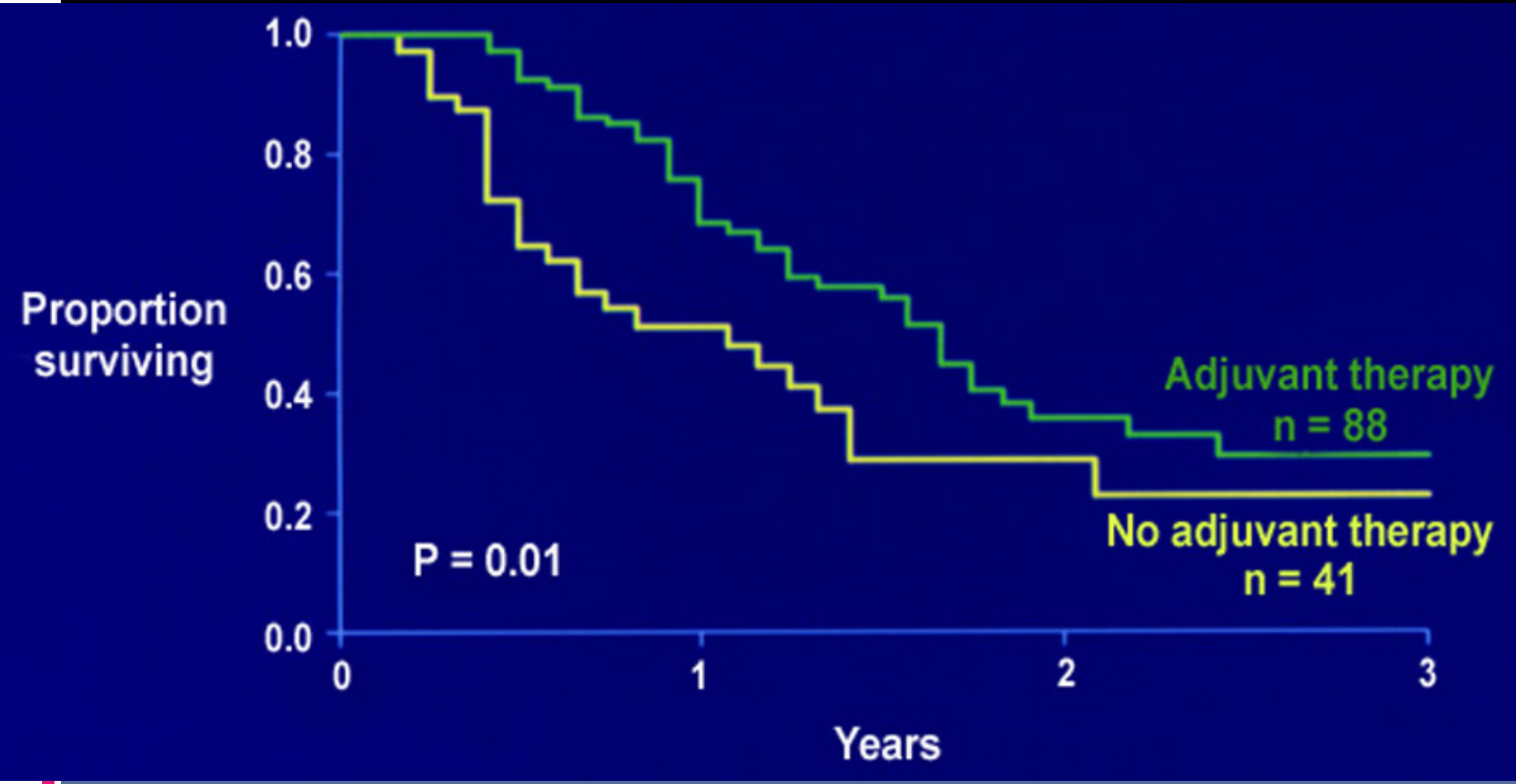
Yeo C et al., Ann Surg 225:630, 1997

Pancreas Adjuvant – Johns' Hopkins
Survival – Surgery ± Postop EBRT + 5-FU
Margin-Negative Patients



Yeo C et al., Ann Surg 225:631, 1997

Pancreas Adjuvant – Johns' Hopkins
Survival – Surgery ± Postop EBRT + 5-FU
Node-Positive Patients



Yeo C et al., Ann Surg 225:631, 1997

ESPAC-1: European Adjuvant Trial

- 541 Pts. With "Macroscopically Resected" Pancreatic Cancer
- Eleven Countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Spain, Sweden, Switzerland, UK
- 61 Centers

ESPAC-1: European Adjuvant Trial

Two Main Tx Questions:

- ChemoRT vs. No ChemoRT
- ChT vs. No ChT

ESPAC-1 PHASE III PANCREAS TRIAL: SURGERY ± ADJUVANT

- Randomization methods: 3 separate trials, evaluated as single trial
  - 2x2 factorial (N=285)
    - Surgery alone, EBRT+5FU, 5FU/Leuc, or both
  - Chemoradiotherapy vs none (N=68)
    - Background tx allowed (21/68-unknown)
  - Chemotherapy vs none (N=188)
    - Background tx allowed (61/188-unknown)
- Restaging studies - not performed

Neoptolemos JP et al Lancet 358:1576-85, 2001

Restaging CT Study: Critical Prior to Study Entry

- Verify Quality of Surgery: R0 / R1 vs R2

R Designation	Gross Resection	Microscopic Margin
R0	complete	negative
R1	complete	positive
R2	incomplete	positive

- Identify patients (25%) who develop metastatic disease after CT restaging

PANCREAS CA: ESPAC-1

Randomization Method, 3 Trials

541 eligible patients: Bx (+) ACA pancreas; gross total resection

Physician Selection

285 pts randomized for both chemoRT and adjuvant chemo (2X2 factorial)

68 pts randomized for chemoRT only; **(record background chemo or not)**

188 pts randomized for adjuvant chemo only **(record background chemoRT or not)**

ESPAC-1: Pooled Data Results

- Improved MS in Pts. Receiving 5-FU/Leuc (19.7 mo) vs Pts. Not Receiving ChT (14.0 mo)
- No Difference in MS Between ChT/RT Pts. (15.5 mo) and Non-ChT/RT Pts. (16.1 mo)

Neoptolemos JP et al Lancet 358:1576-85, 2001

ESPAC-1 PHASE III PANCREAS ACA TRIAL Patient Group and Randomization Methods*

- Eligible patients: ACA pancreas, gross total resection
- Randomization methods: 2x2 factorial design (N=289)
  - Surgery alone (N=69)
  - Postop EBRT+5FU (N=73)
  - Adjuvant 5FU/Leucovorin (N=75)
  - EBRT+5FU, 5FU/Leucovorin (N=72)
- Statistical analysis: Analyzed by intent to treat
  - Adjuvant chemotherapy (N=147) vs none (N=142)
  - Postop EBRT+5FU (N=145) vs none (N=144)

Neoptolemos JP et al , NEJM 350:1200-10, 2004

PANCREAS CA: ESPAC-1

Randomization Method, 3 Trials

541 eligible patients: Bx (+) ACA pancreas; gross total resection

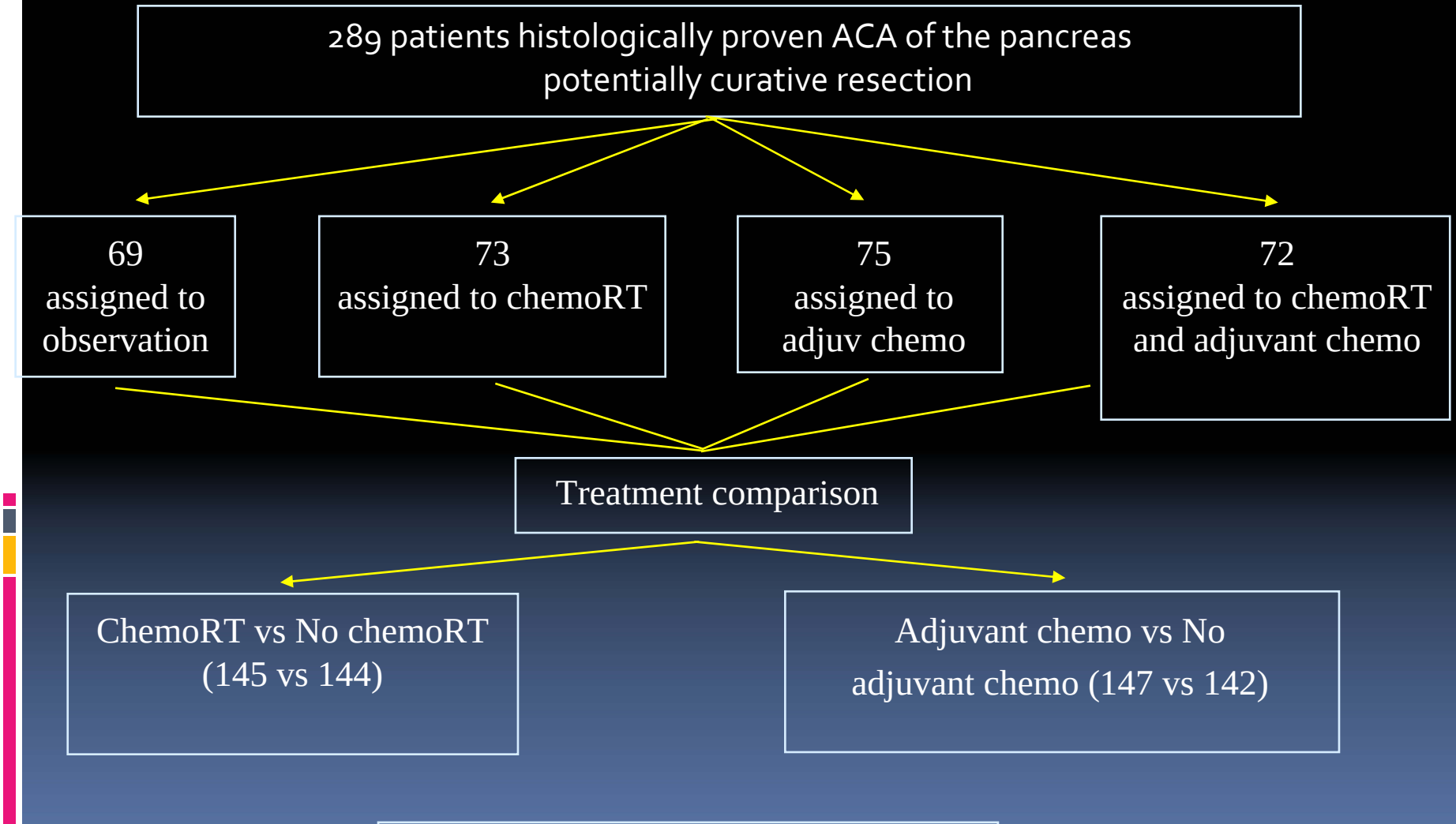
Physician Selection

289 pts randomized for both chemoRT and adjuvant chemo (2X2 factorial)

68 pts randomized for chemoRT only; **(record background chemo or not)**

188 pts randomized for adjuvant chemo only **(record background chemoRT or not)**

PANCREAS CANCER: ESPAC-1 TRIAL
2x2 Factorial Design



Neoptolemos et al, NEJM 350:1202, 2004

ESPAC-1 PHASE III PANCREAS ACA TRIAL*
Tx Methods – Surgery & Adjuvant Therapy

- Surgery
  - Pancreatico-duodenectomy (head lesions) or total pancreatectomy
  - Positive resection margins, 18% of patients
- Adjuvant chemotherapy
  - 5FU (425 mg/m^2) Leucovorin (20 mg/m^2)
  - 5 consecutive days every 28 d for 6 cycles
- EBRT+5FU
  - 40 Gy/6 wks split course
  - No defined fields, no central audit !!! (dealer's choice)
  - Each center used its own QA standards
  - Concurrent bolus chemo, 5FU 500 mg/m^2 d 1-3, wk 1 and 3 EBRT

*Neoptolemos JP et al, Lancet 358:1576-85, 2001; NEJM 350:1200-10, 2004

ESPAC 1: ChemoRT vs. No ChemoRT

	# Pts	MS (mo)	2 Yr S (%)	5 Yr. S (%)
ChemoRT	145	15.9	29	**10**
No Chemo RT	144	17.9*	41	**20**

ESPAC 1: ChT vs. No ChT

	# Pts	MS (mo)	2 Yr S (%)	5 Yr. S (%)
ChT	145	20.1*	40	**21**
No ChT	144	15.5	30	**8**

ESPAC-1

- 2x2 factorial 289

Chemo	147
data available	122 (83%)
received all chemo	**61 (41%)**
received < 6 cycles	40
received none	21
ChemoXRT	145
data available	128 (88%)
received 40 Gy	**90 (62%)**
received +/- 40 Gy	27
received none	11

Protocol Compliance

	German Rectal CAO/ARO/ AIO-94 (n=421)	Espac-1 ChemoRT (n=145)	Espac-1 ChT (n=147)
Unavailable Data	**< 2%**	12%	17%
RT Dose per Protocol	**92%**	62%	-
ChT per Protocol	**89%**	-	41%
No Tx	**3% RT 4% ChT**	7% RT	14% ChT

Local Recurrence: The Unexplained Problem

- First site of recurrence local = *62%*
  - 35% Local
  - 27% Local + distant
- No QA: path, surgical, RT, diagnostic imaging
- Margins + reported to be 18% overall

ESPAC-1/Neoptolemos, NEJM, 2004

ESPAC-1 PHASE III PANCREAS ADJUVANT
Major Flaws in Study Design

- Randomization methods:
  - 3 separate trials, evaluated as single trial
  - Background therapy allowed 2 of 3 trials
- Restaging studies - not performed
- EBRT+5FU
  - 40 Gy/6 wks split course
  - No defined fields, no central audit
  - Each center used its own QA standards

Neoptolemos JP et al Lancet 358:1576-85, 2001; NEJM 350:1200-1210, 2004

Pancreas Ca: Adjuvant Phase III Trials

Study	Efficacy of 40 Gy (S.C.) + 5-FU	Comment
GITSG (1985)	Yes	- Small #'s - Slow accrual
EORTC (1999)	No	- Underpowered - Periampullary - 20% Not tx
ESPAC 1 (2001, 2004)	No	-Flaws in Trial Design

PANCREATIC CANCER
Phase III U.S. GI Intergroup Adjuvant Trial

- RTOG was the Coordinating group of the Intergroup Phase III postop study:

RTOG 9704

5-FU ⇒ Chemo RT (5-FU) ⇒ 5-FU

vs

GEM ⇒ Chemo RT (5-FU) ⇒ GEM

RESECTED PANCREATIC CANCER

Phase III U.S. GI Intergroup, RTOG 9704

- Initial accrual goal of 330 pts was increased due to excellent accrual (11/mo)**; 538 pts accrued from Jul 98-Jul 2002**
- Restaging studies were performed after recovery from surgery
- Chemoradiation (CRT)
  - EBRT, 50.4 Gy in 28 Fx over 5.5 wks, boost after 45 Gy
  - PVI 5FU, 250 mg/m2/d during EBRT
- Pre and Post-CRT Chemotherapy
  - Arm 1: 3 wks of PVI 5-FU (250 mg/m2/d) before CRT and 2 cycles after CRT (cycle = 4 wk PVI 5FU 250 mg.m2/d; 2 wk rest)
  - Arm 2: 1 cycle of gemzar before CRT and 3 cycles after CRT (cycle = 3wks of gemzar @ 1000 mg/m2; 1 wk rest)

Results of RTOG 97-04

- On multivariate analysis **3 parameters** reached statistical significance:
  - treatment arm (p = 0.025),
  - nodal status (p = 0.003)
  - maximal tumor diameter (p = 0.03).
- Benefits with Gem seen in HOP cancers
- Compared to ESPAC-1, RTOG 97-04 included patients with a more **unfavourable distribution of risk factors** (resection status, pN-category and largest tumor diameter) but nevertheless resulted in longer survival.

RTOG 9704 2008[20]	442^	R0 or R1	CRT + GEM CRT + 5-FU	20.6 16.9	0.033

Oh…and one more thing

- The improved radiotherapy technique employed in the RTOG trial is reflected in the reduction of local recurrence rates being
  - **25%** in the RTOG trial compared to
  - **47%** in the GITSG trial
  - And **62%** overall in the ESPAC-1 trial.

- In other words …when we do our job correctly, use IMRT and image guidance, we have less toxicity and better outcomes

Adjuvant Therapy: Pancreas Ca

- The value of postoperative EBRT 40 Gy (S.C.) with concurrent ± maintenance 5-FU: Conflicting Results

Adjuvant Therapy: Pancreas Ca

Given this data, what is appropriate tx for patients with potentially resectable pancreatic cancer?

Rationale: Adjuvant Radiation Therapy + ChT

- LF - Significant clinical problem: Effective Tx is critical
- Locally Advanced Pancreas Ca: 3 Positive Trials for EBRT+ChT
- Well Conducted Adjuvant Trials in Gastric and Rectal Ca: Improved LC and S
- Trials: Contemporary Techniques and Doses (EBRT+ChT)

Pancreas Ca: Adjuvant Tx

Study	# Pts.	EBRT (Gy)	ChT	5 Yr.S (%)	LC (%)
Virginia Mason (2003)	43	45-54	5-FU CDDP Interferon	55	-
Hopkins (2000)	366 132	40-57.6 -	5-FU ± L -	20 9	-
Mayo (1993)	29 89	45-54 -	5-FU -	17 4	93
U. Penn (1991)	20 53	>45 -	5FU+Mit-C -	43 # 35 #	75 15

Resectable Pancreas Cancer

Phase II/III Trials: Optimize Local Control by Integrate EBRT (Contemporary Techniques and Doses) with Newer Cytotoxics and Target Agents

EORTC (40013-22011): Adjuvant Pancreas Phase II Trial

Resection:

- Gemcitabine + EBRT (50.4 Gy) with Gemcitabine
- Gemcitabine

- Better local control with CRT after Gem, only RO patients entered, good QA

- **RTOG 0848/EORTC Phase III study** will seek to clarify the role of adjuvant CRT, following delivery of full-course gemcitabine-based chemotherapy.

Selected Adjuvant Pancreatic Protocols

Study	Design	Arms
GI Intergroup	Randomized phase II (Adjuvant/ Post-op)	Gem + C-225 Cape + C-225 + XRT (50.4 Gy / 5.5 weeks)* Gem + C-225
		Gem + Bev Cape + Bev + XRT (50.4 Gy / 5.5 weeks)* Gem + Bev
ACOSOG Z05031	Phase II	XRT (50.4 Gy / 5.5 weeks) + PVI 5-FU + IFN + CDDP weekly
ACOSOG	Phase II (Neoadjuvant/ Pre-op)	Gem + Bev Surgery Cape + XRT (45 Gy / 5 weeks) + Bev

Summary

- GITSG/EORTC/ESPAC: Conflicting Results
- Strong Rationale and Support for Adjuvant RT and ChT (Concurrently and Maintenance)
- Phase III Trials: Results Pending
- Dr. Neoptolemos (2005): "There may be scope for future studies to investigate more modern chemoradiation techniques"…ya think!!

Neoadjuvant CRT – can't we just get along??

- Kill the microscopic areas of the cancer, get more RO resections and decreased LN metastasis
- Don't have the problems related to hypoxia and long post-op delays
- Less injury as we aren't worried about surgical anastomosis
- Better selection of patients, imaging, biomarkers to tell us which way to go (ca 19-9)

Pancreas Ca: NeoAdjuvant Tx

Study	# Pts.	EBRT (Gy)	ChT	4 Y.S (%)	LC (%)
MDAH (2002)	20	30/10 Fx	Paclitaxel	28	100
MDAH (1999)	35	30/10 Fx	5-FU	23	90
MDAH (1996)	39	30-50.4	5-FU	17	93
F.C.C. (1995)	11	50.4	5FU+Mit-C	40	91

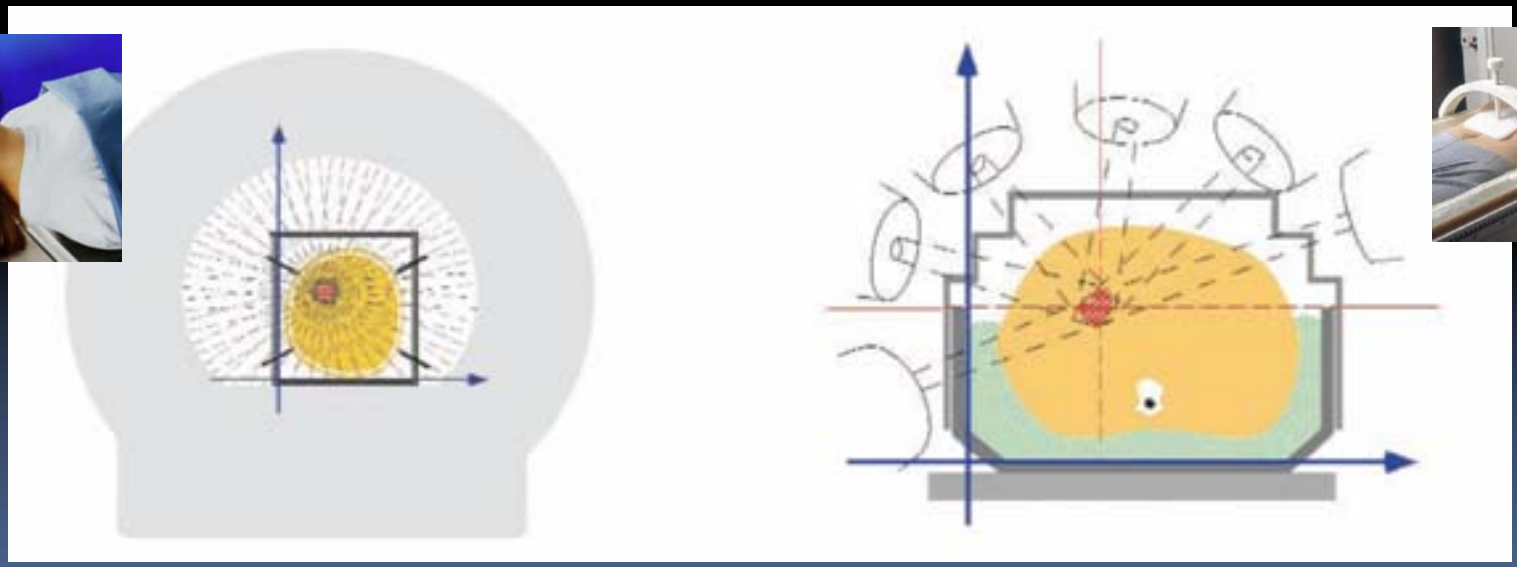
Stereotactic Body Radioablation or SBRA (or SBRT) for LAPC

Reality of Stereotactic Ablation

- Historically, rarely feasible
  - Requires very high dose delivery
  - Toxicity would typically prohibit ablation
  - Only BRACHYTHERAPY techniques
- Historically, required a special circumstance
  - Inherent uptake of iodine by thyroid-like tissue
  - Implantable tumors
- **Ablation with radiation was NOT feasible – simply didn't have the "soft" or "hard" technology (or QA and expertise not there…aka..ESPAC!!)**

SBRT: operational definition

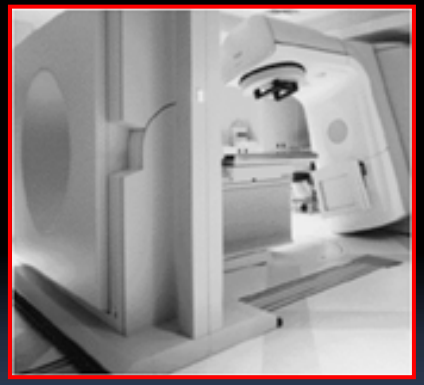
- *Stereotactically* localized, ultra-high-dose radiotherapy
  - Given to discrete tumor nodules in *extracranial* locations
  - Within a *hypofractionated* regimen (1-5 treatments)
    - Unlike typical 6-7 week course of radiotherapy
  - Analagous to cranial stereotactic radiosurgery (SRS)



Head frame-based cranial SRS

Body frame-based cranial SRS

SBRT-friendly systems now widely available



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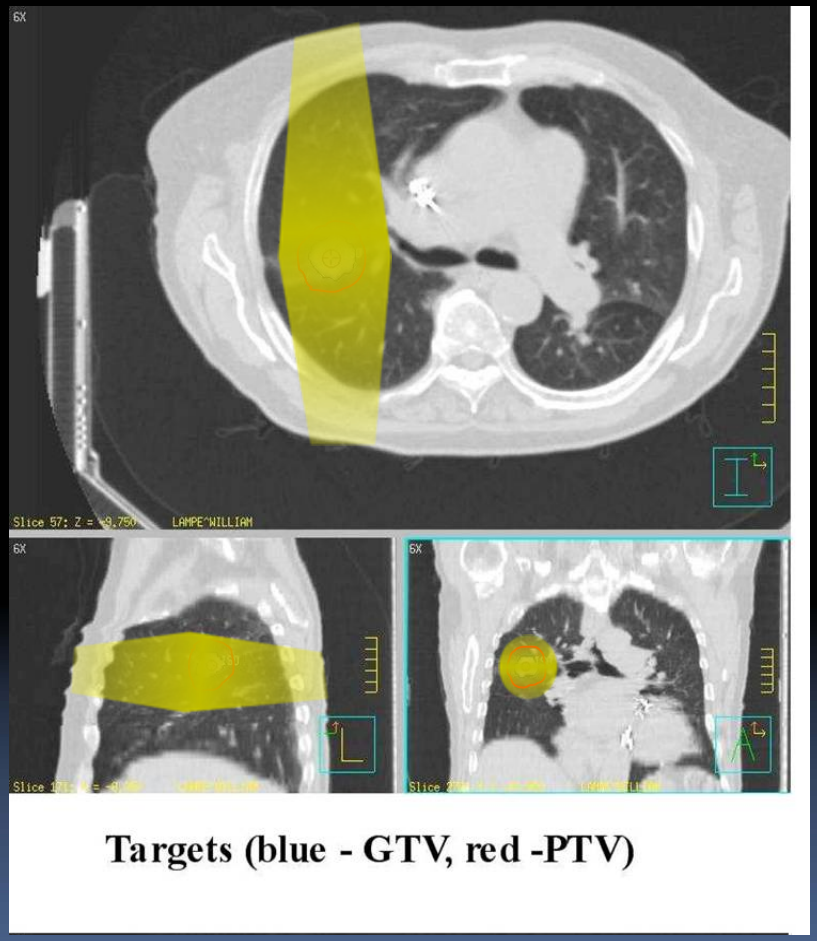
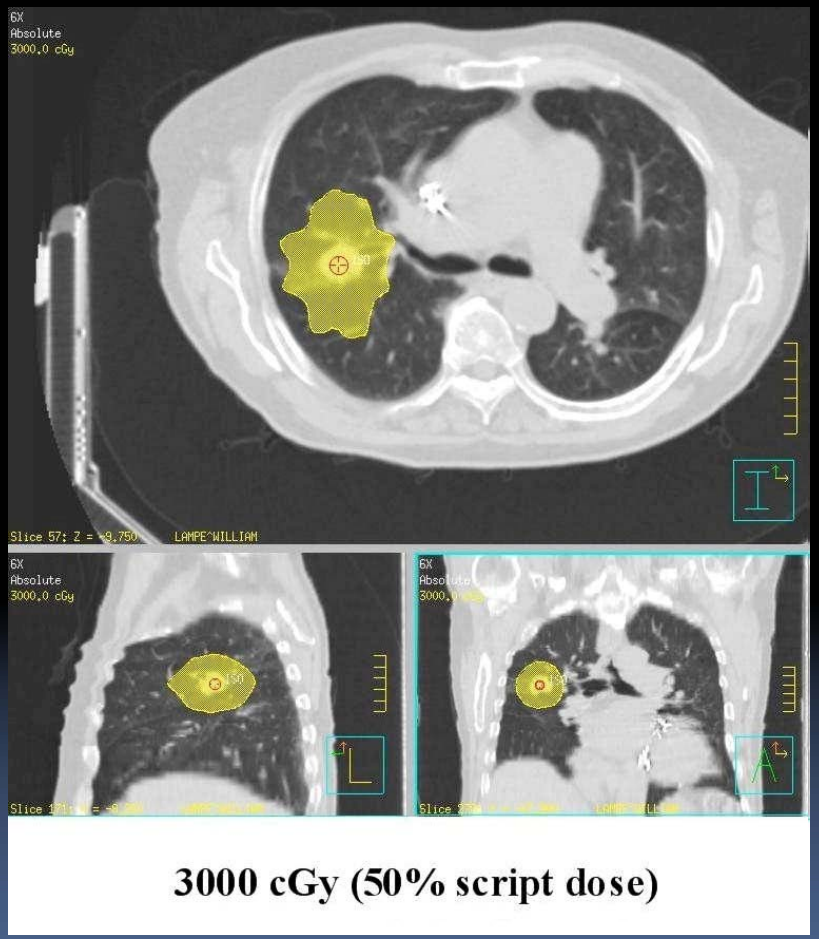
Spectrum of potential applications of SBRT

- Intensified treatment to a primary cancer
  - Stage I lung cancer
  - Primary HCC
  - **Pancreas cancer**
  - Prostate cancer
- Palliation/control for challenging sites of recurrence
  - Spinal
  - Retroperitoneal
  - Previously irradiated volumes
- Adjuvant systemic cytoreductive therapy
  - "Radical" treatment for isolated liver, lung, spine, and other mets

High Dose: Conventional Radiation vs. SABR



Targets (blue - GTV, red -PTV)



3000 cGy (50% script dose)

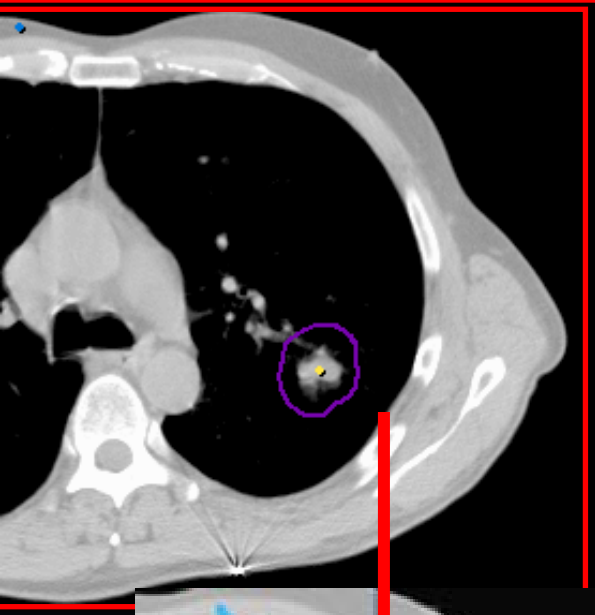
Postage Stamp

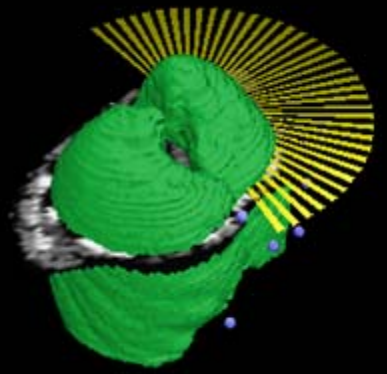
SABR

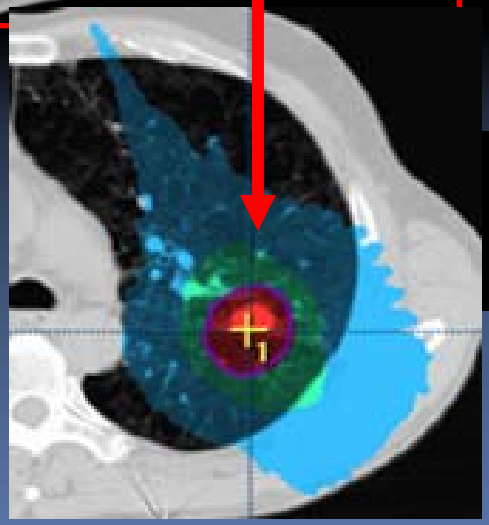
6000 cGy (script dose)

THIS IS A PARADIGM CHANGING DIFFERENCE

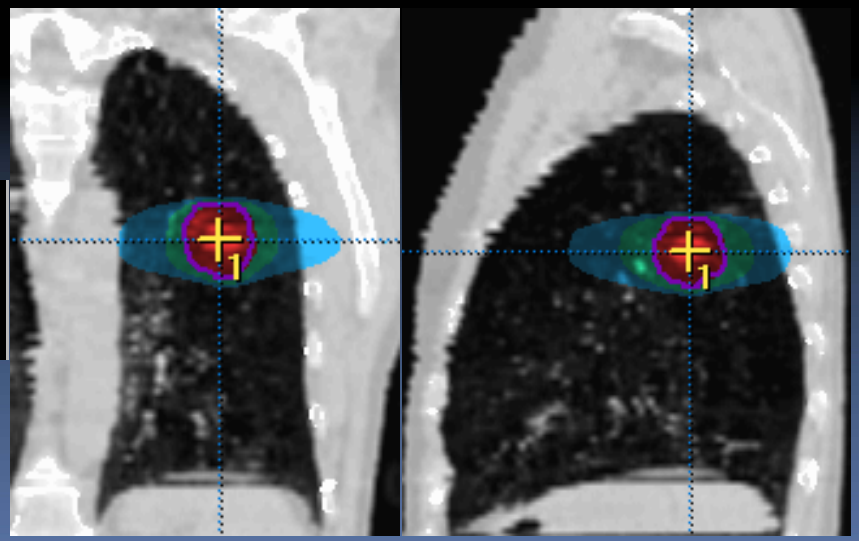
Treatment: 60 Gy/3 fractions



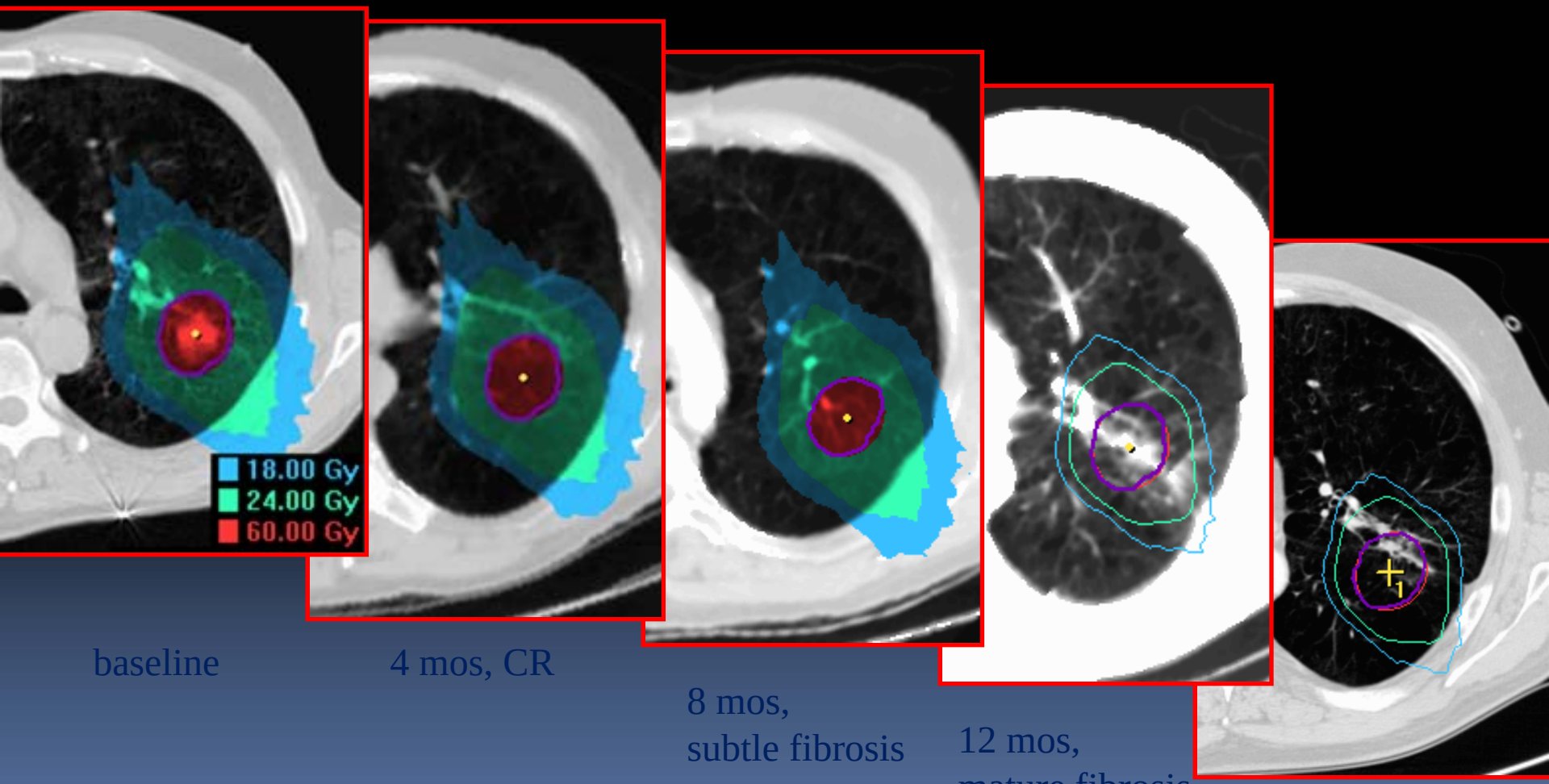




15.00 Gy
30.00 Gy
60.00 Gy



Characteristic radiographic findings



baseline

4 mos, CR

8 mos,
subtle fibrosis

12 mos,
mature fibrosis

18 mos, NED

Benefits of Stereotactic Ablative Radiotherapy

Outpatient

20-60 Minutes Per Treatment

Entire course of Rx in 1-2 weeks

No Sedation or Anesthesia (painless)

1-5 Treatments qd or qod

Immediate Return To Activities

Can we do this with LAPC?

Stereotactic Radiotherapy for Unresectable Adenocarcinoma of the Pancreas

Daniel T. Chang, MD[1], Devin Schellenberg, MD[2], John Shen, BS[1], Jeff Kim, BS[1], Karyn A. Goodman, MD[3], George A. Fisher, MD, PhD[4], James M. Ford, MD[4], Terry Desser, MD[5], Andrew Quon, MD[6], and Albert C. Koong, MD, PhD[1]

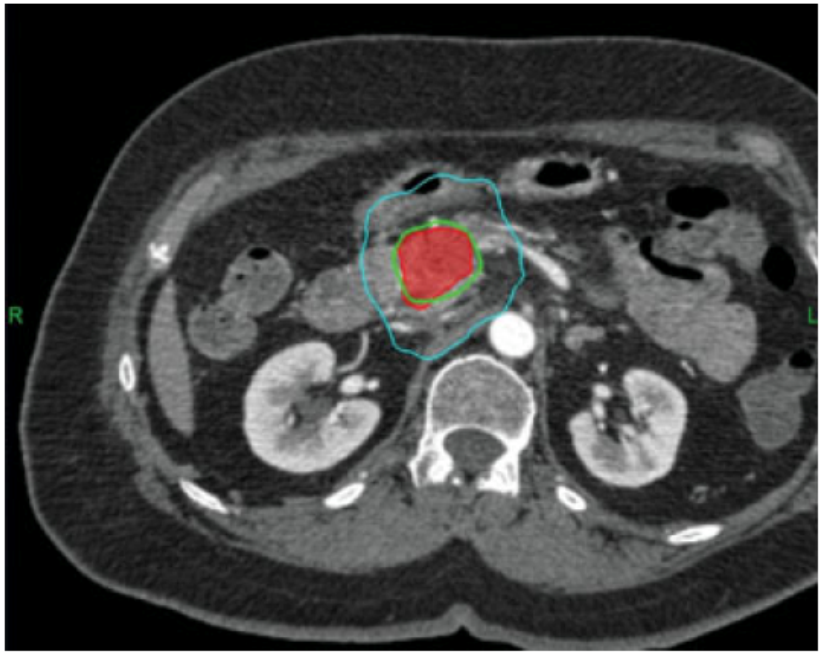


FIGURE 1. Typical isodose distribution for patients receiving stereotactic body radiotherapy. Twenty-five grays (Gy) are prescribed to the line that completely encompasses the planning target volume. The 12.5-Gy line is kept away from the distal wall of the duodenum and stomach.

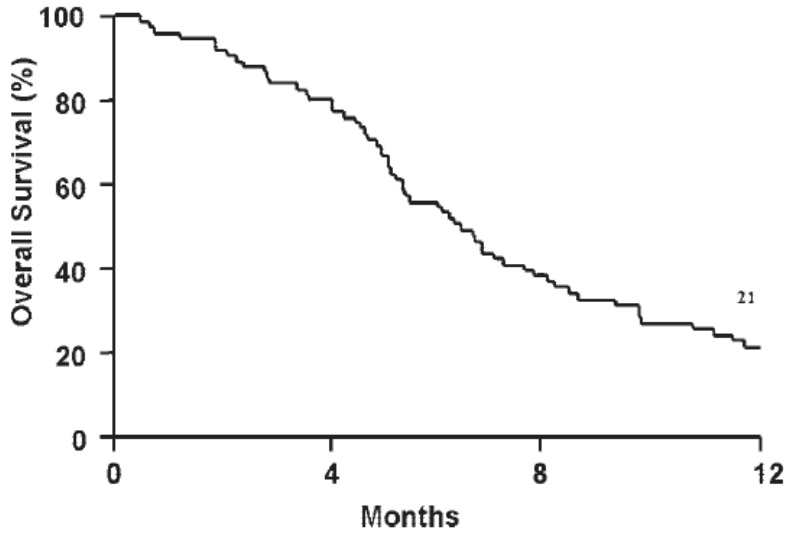


FIGURE 3. Actuarial curve of overall survival calculated from date of stereotactic body radiotherapy.

Can it be done safely?

	No. of Patients (%)			
Toxicity	Grade 2	Grade 3	Grade 4	Total
Acute				
Small bowel ulcer	2	0	0	2 (3)
Gastric ulcer	0	1	0	1 (1)
Pain	1	0	0	1 (1)
Late				
Small bowel ulcer	3	0	0	3 (4)
Gastric ulcer	0	3	0	3 (4)
Duodenal stricture	0	1	0	1 (1)
Biliary stricture	0	2	0	2 (3)
Small bowel perforation	0	0	1	1 (1)
Total	6 (8)	7 (9)	1 (1)	14 (18)

Cancer February 1, 2009

Bottom line – volume of duodenum getting high dose is the key!

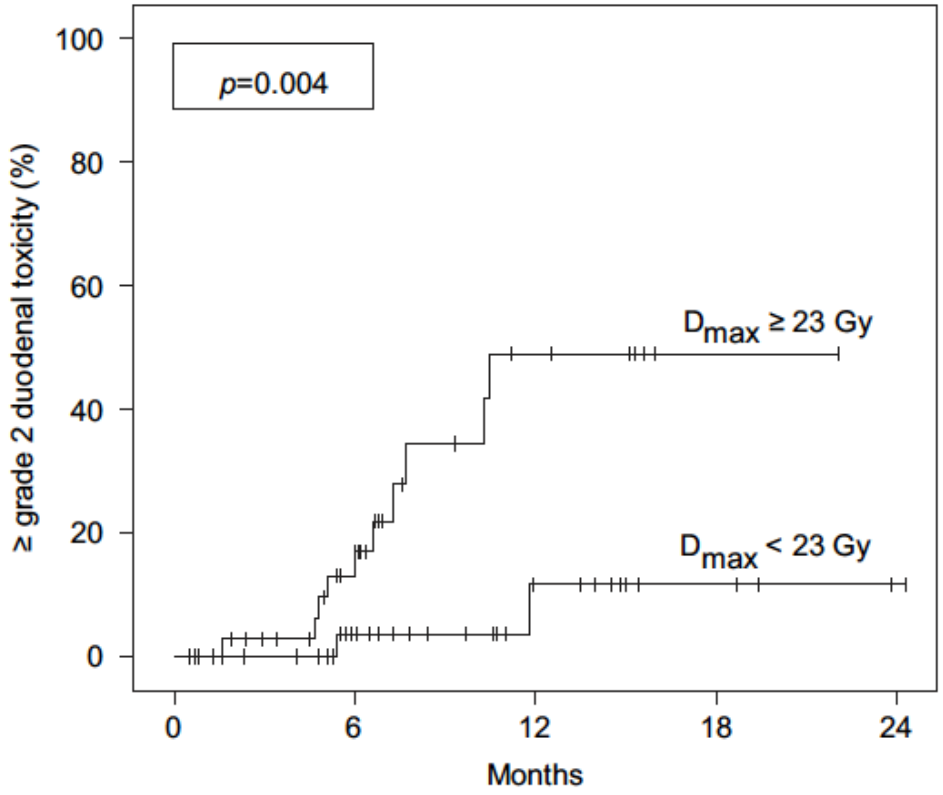


Fig. 3. Maximum dose predicts duodenal toxicity. Kaplan-Meier analysis of toxicity according to the maximum dose to 1 cm^3 of duodenum (D_{max}).

Adapt based on location of cancer

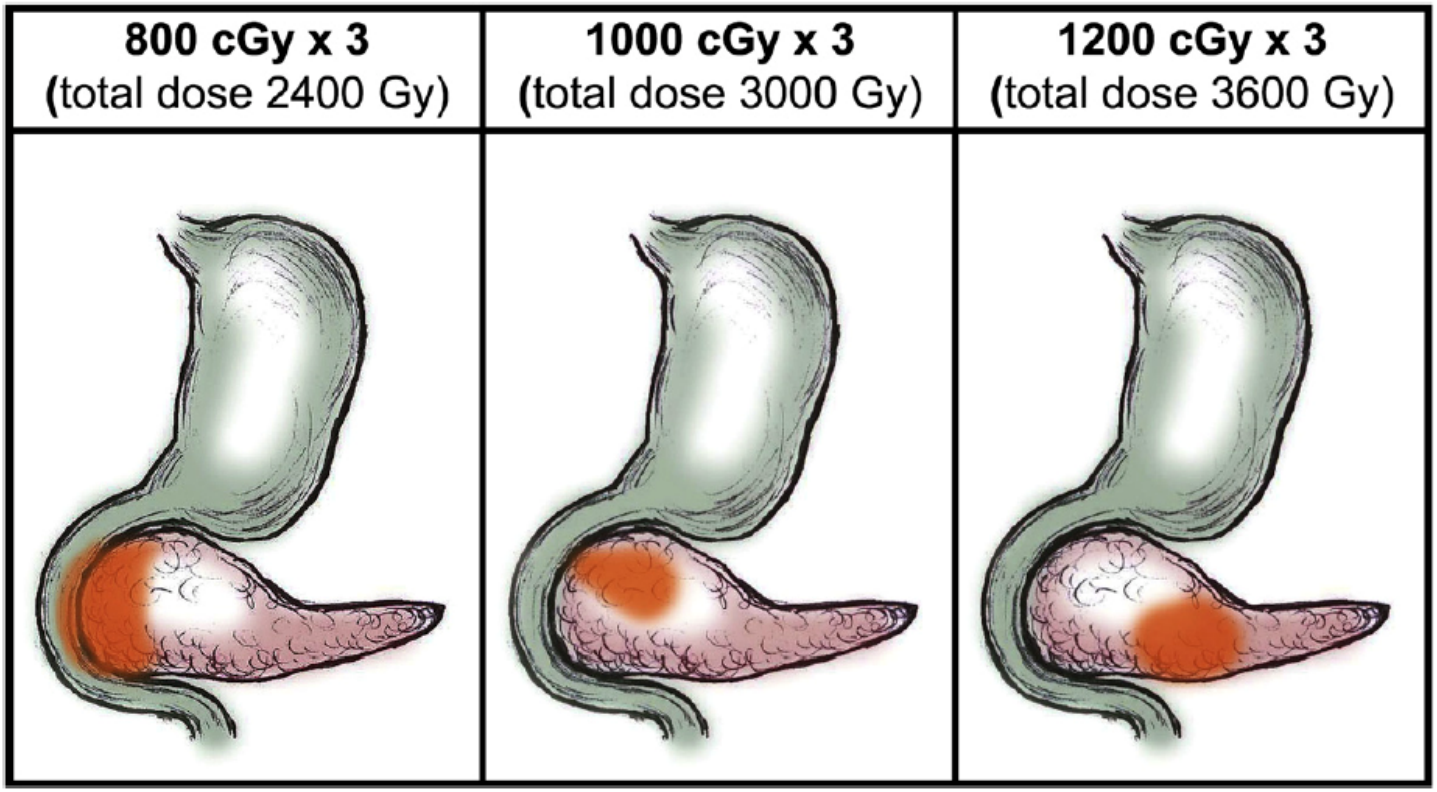
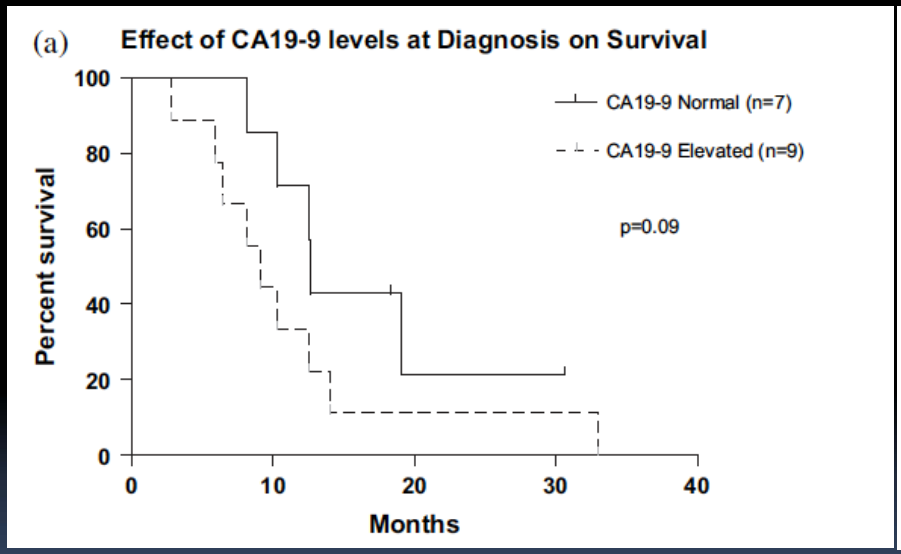


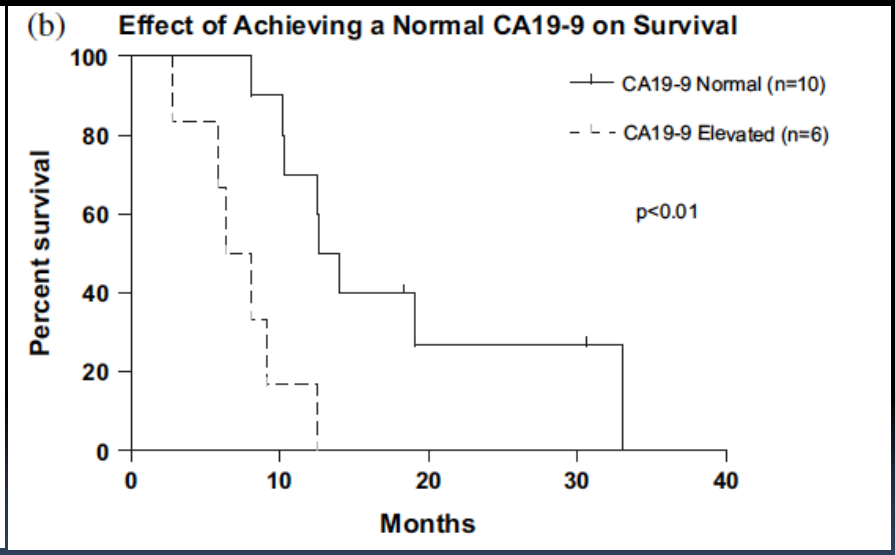
Fig. 1. Adaptive tolerance-based stereotactic body radiotherapy dose prescription showing graphic depiction of relationship between duodenum and pancreatic tumor (red) used to determine each of three prescribed doses.

ANAND MAHADEVAN, M.D.,

Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 3, pp. 735–742, 2010

Can we use Ca-19-9 after SBRT?





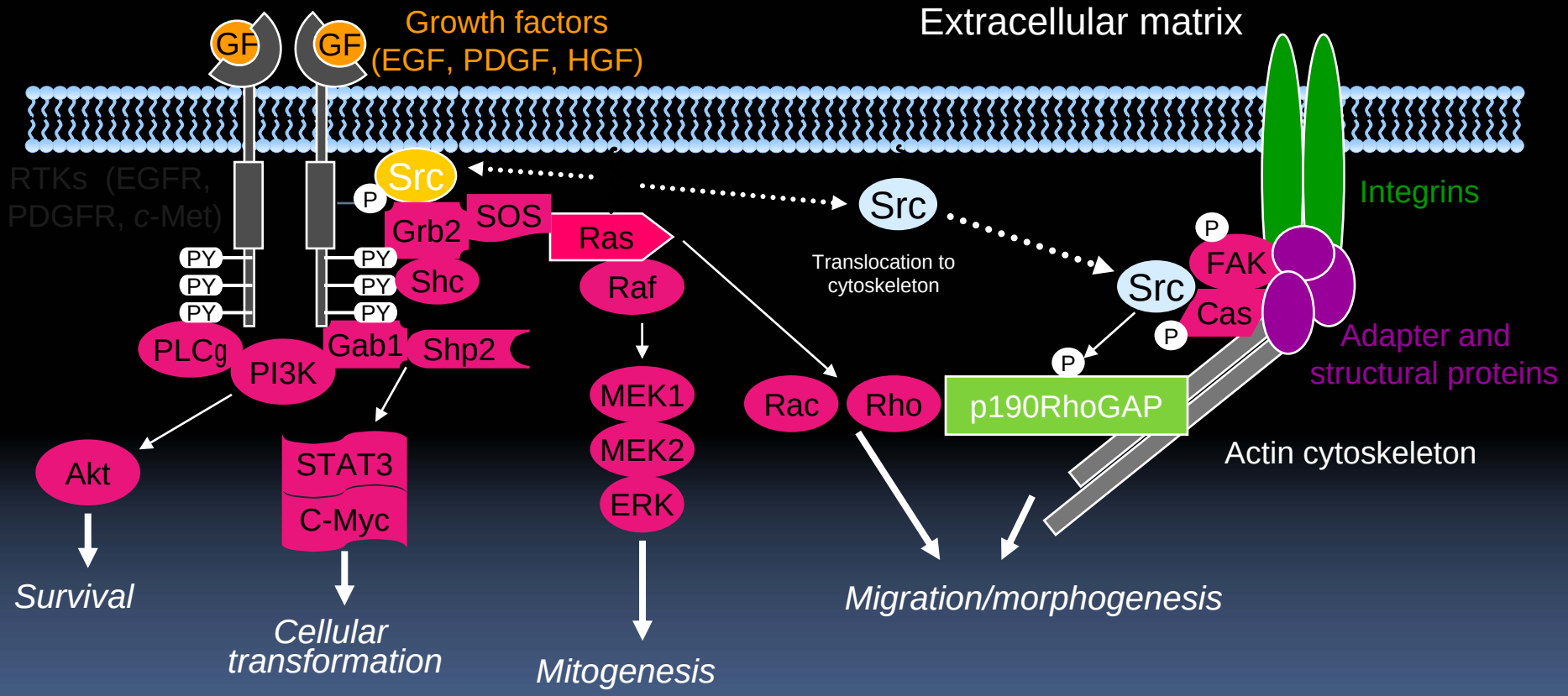
DEVIN SCHELLENBERG, M.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 3, pp. 678–686, 2008

And finally…where does biologics come in to play?

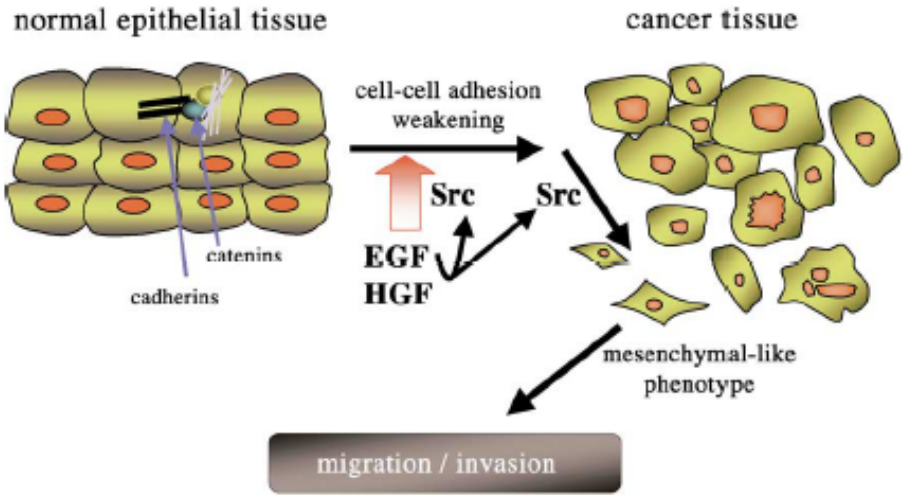
- Tarceva FDA approved with gemzar – not very active
- Src kinase inhibitors
- mTOR inhibitors
- DNA repair inhibitors (PARP)
- Protease inhibitors
- Akt/PI3-K inhibitors

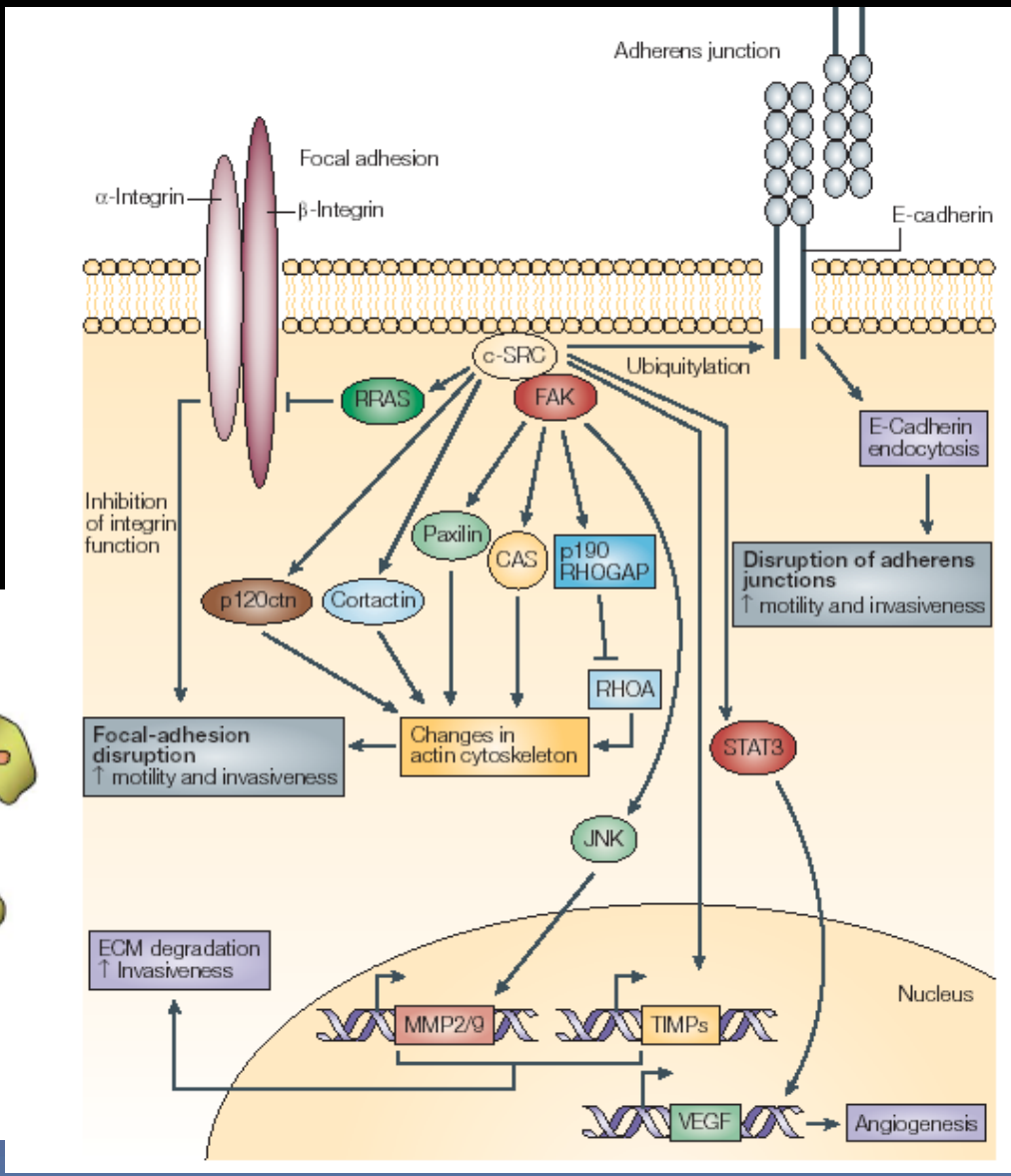
SRC-family kinases in signal transduction



SFK roles in cytoskeletal function

Central role of c-Src in cellular morphology, motility, adhesion, membrane ruffling, and invasive phenotype ('epithelial-to-mesenchymal transition')





Dasatinib, a src kinase inhibitor blocks metastatic process

Table 2. Effects of c-Src Targeted siRNA or the Src Family Kinase Selective Inhibitor BMS-354825 on *In Vivo* Growth and Progression of Pancreatic Adenocarcinoma Cells

	Primary Pancreatic Tumors				Metastases	
	Incidence	Mass (mg)			Lymph Node	Liver
		Mean	Median	Range		
Vehicle	9/9	1486	1634	(570-2600)	5/9	3/9
BMS-354825	7/7	754*	606	(370-1900)	1/7*	0/7*

L3.6pl cells were injected into the pancreas of nude mice (5 x 10^5 cells/mouse) on Day 0. On Day 14, 200 μl BMS-354825 (15 mg/kg) or an equal volume of citrate buffer vehicle was administered by oral gavage. Treatments continued daily for 28 days. Mice were sacrificed on Day 42 and evaluated for primary pancreatic tumors and liver and lymph node metastases.

* = $P<0.05$, relative to controls

from Trevino, et al. Cancer Res 2005

… so does the AZD Src inhibitor

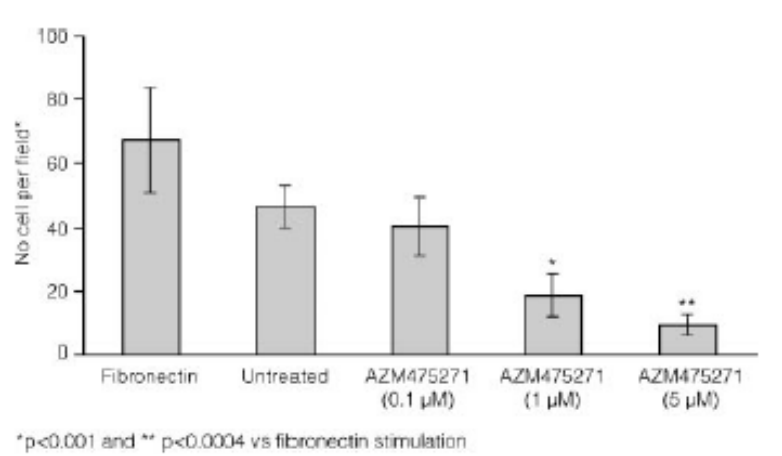


Fig. 7 Dose-dependent inhibition of L3.6pl human pancreatic cancer cell migration by AZM475271 (modified Boyden chamber assay). *, $P < 0.001$; **, $P < 0.0004$ (*versus* fibronectin stimulation).

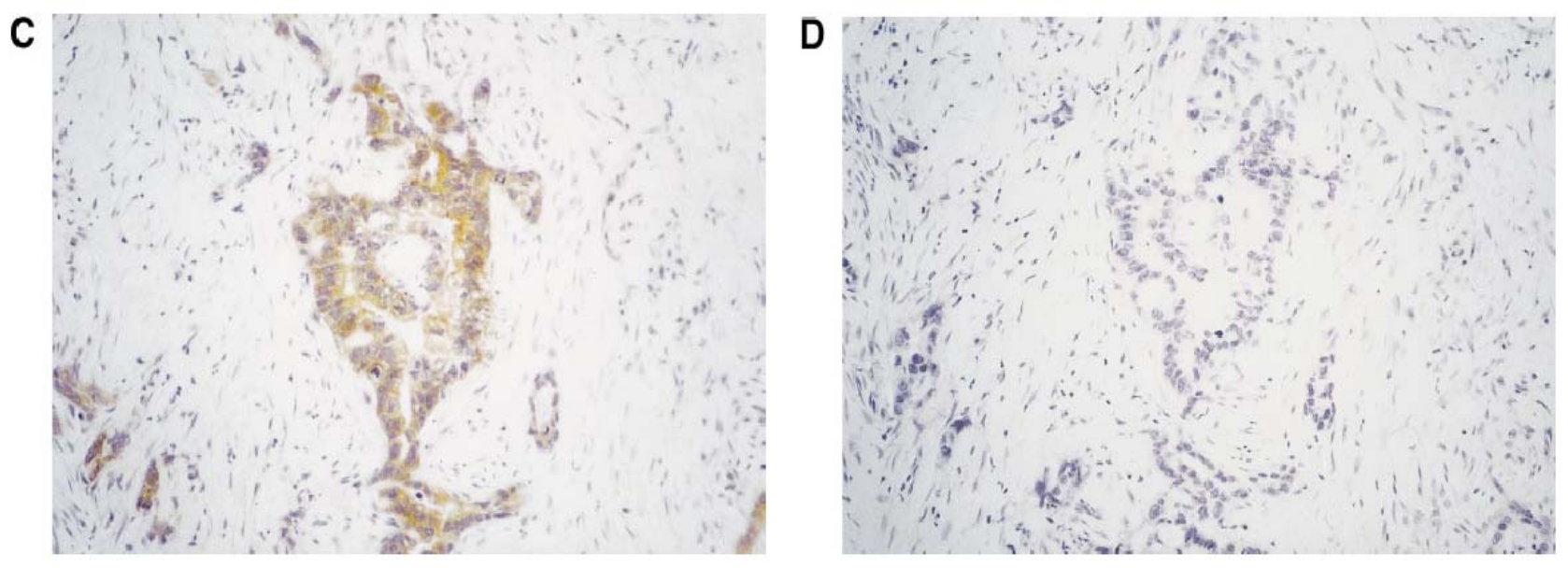
From Yezhelyev MV, et al. Clin Cancer Res 2004

Table 1 In vivo Efficacy of AZM475271 +/- Gemcitabine for Human Pancreatic Cancer in Nude Mice

Treatment	Pancreatic tumor: Tumor incidence * (N)	Pancreatic tumor: Median (range) tumor volume (mm^3)	Metastases† (*N*): Lymph node	Metastases† (*N*): Liver	Median (range) body weight (g)
Saline (control)	5/5	1359 (921–1989)	5/5	3/5	24 (21–25)
Gemcitabine (twice weekly, 100 mg/kg)	5/5	393 (297–471); $P < 0.0004$ ‡	2/5	1/5	23 (20–23)
AZM475271 (50 mg/kg/d)	9/9	827 (603–879); $P < 0.002$ ‡	9/9	0/9	22 (22–24)
AZM475271 (50 mg/kg/d) + gemcitabine (twice weekly, 100 mg/kg)	8/8	124 (63–363); $P < 0.0001$ ‡; $P < 0.002$ §	0/8; $P < 0.001$‡	0/8	18 (17–21)

* Data represent number of mice with tumors/number of mice receiving injections.
† Data represent number of mice with metastases/number of mice receiving injections.
‡ Compared with controls.
§ Compared with gemcitabine alone (unpaired Student's *t* test).

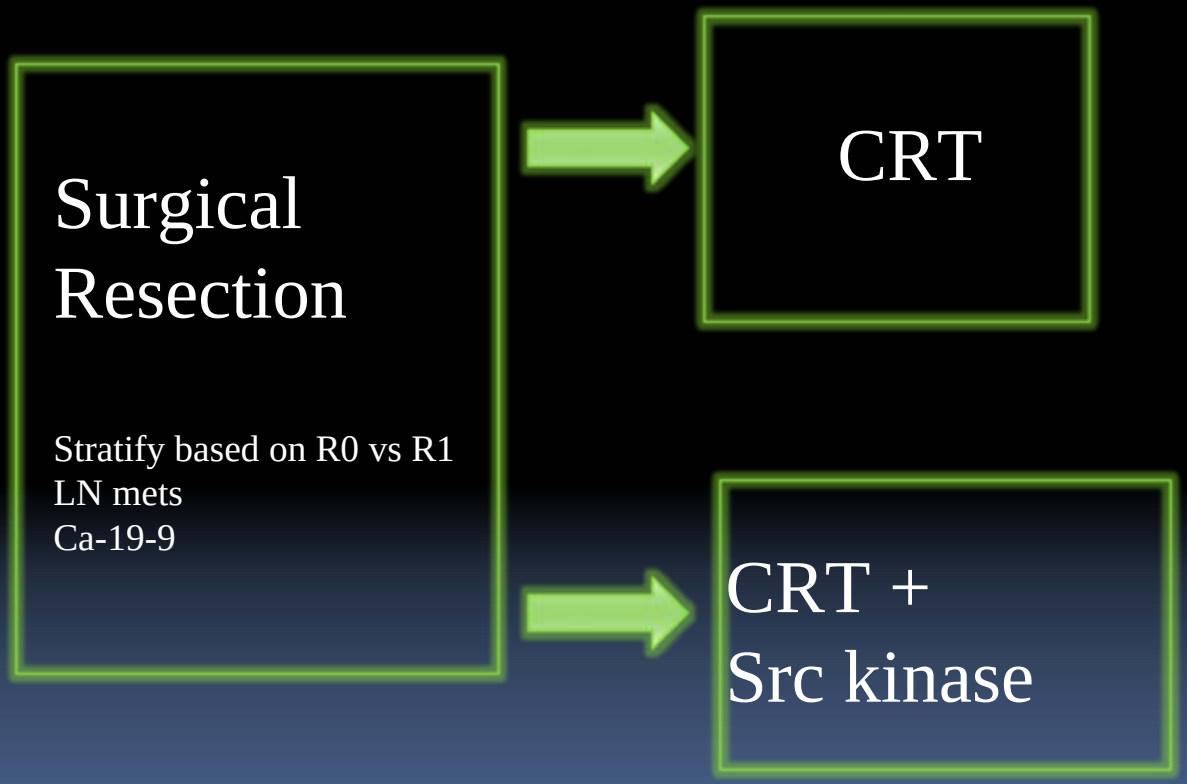
Src expressed in pancreatic cancer



c-Src overexpression was found in 13 of 13 clinical samples of pancreatic cancer (but not in normal tissues) and in 14/17 cell lines

Lutz MP, et al. Bioch Biophys Res Comm 1998

So…how could we use it?



Still a ways to go – but he who dares…wins!
Thanks

Impossible is nothing