

THIRD ANNUAL

*Update on the Management
of Gastrointestinal
Malignancies*

*October
20-22, 2006*

**Estancia La Jolla Hotel & Spa
LA JOLLA, CALIFORNIA**

Chairman:

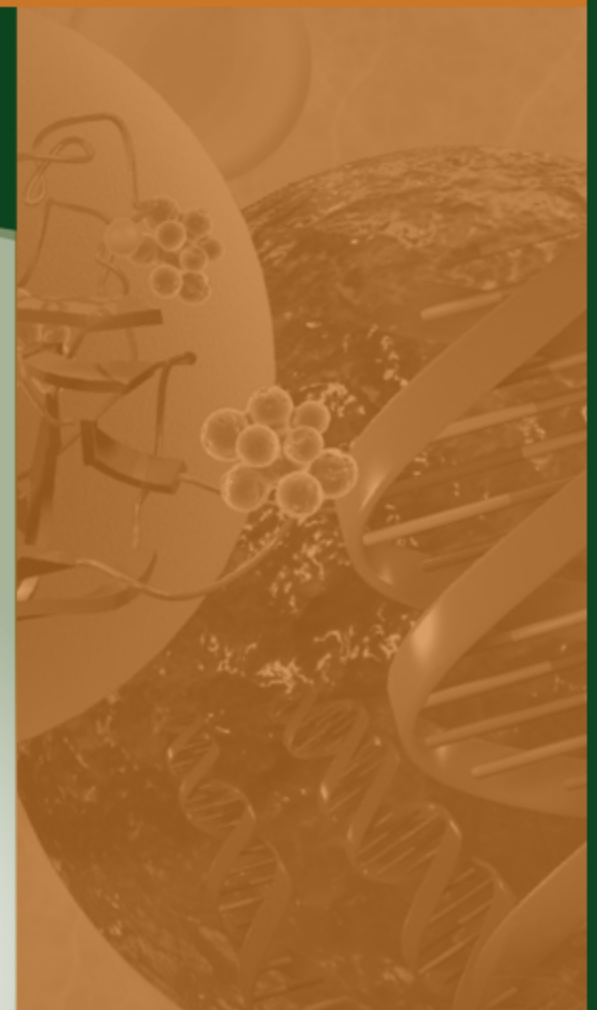
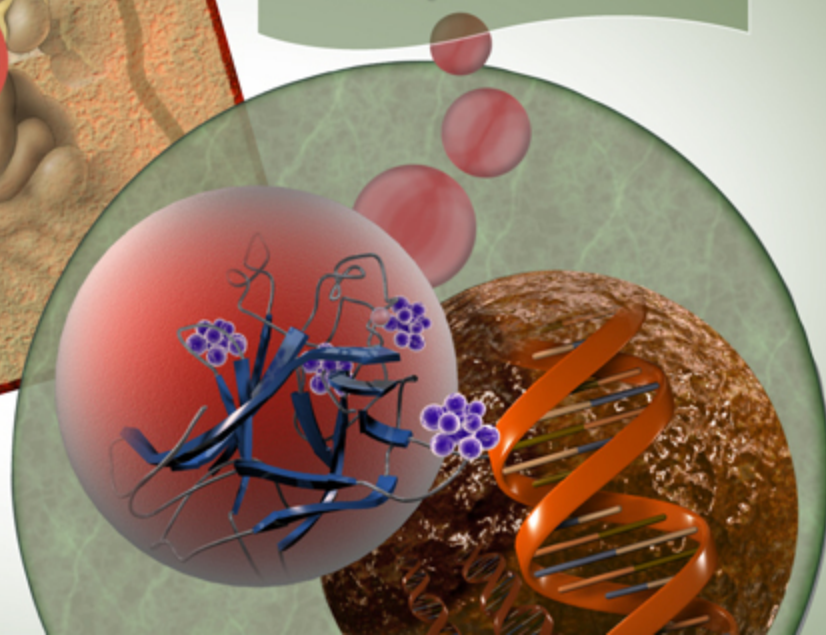
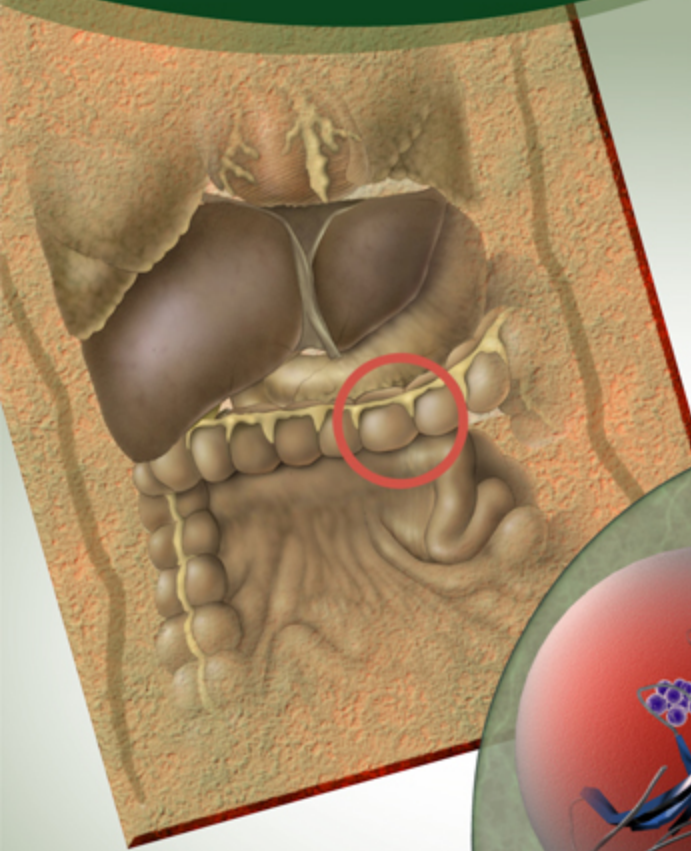
Mace L. Rothenberg, MD

Ingram Professor of Cancer Research

Professor of Medicine

Director, Phase I Drug Development Program

Vanderbilt Ingram Cancer Center



MEDICAL EDUCATION CONFERENCES

Developing Medical Paradigms Through Education™

Adjuvant Therapy of Pancreas Cancer: Where are we?

Jordan Berlin, M.D.

Associate Professor, Medicine



Objectives

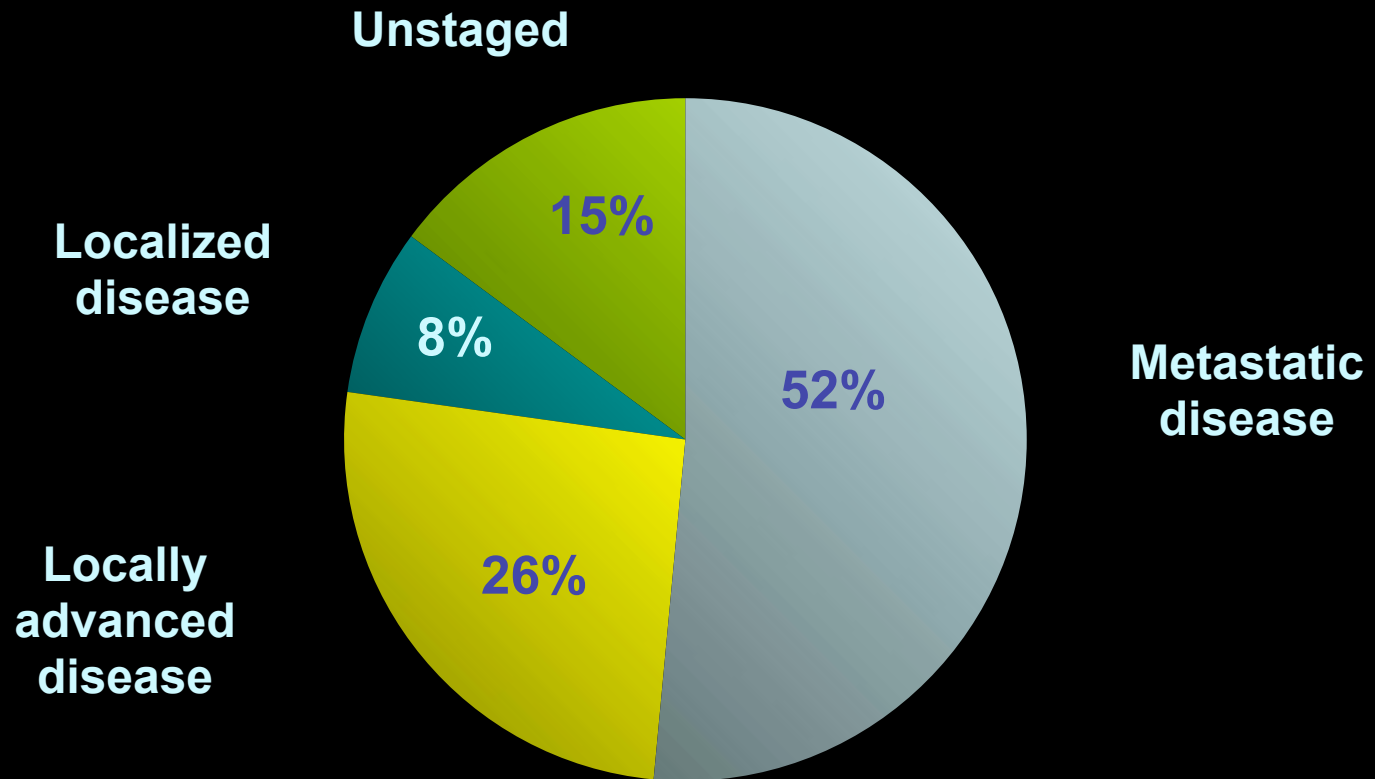
- Review surgical results
- Consider the adjuvant therapy data thus far
- Discuss the role of targeted therapies
- Right or wrong, I tend to editorialize

**Which group of patients are we
talking about?**

Pancreatic Cancer

- In the United States in 2005, there will be an estimated 32,180 diagnosed cases of pancreatic cancer and 31,800 deaths from this disease
- Pancreatic cancer accounts for approximately 2% of malignancies in men and women in the United States
- Fourth leading cause of cancer death in the United States

Pancreatic Cancer:



TNM Staging Guidelines for

- The TNM staging system provides only 1 system for both radiographic and pathologic staging
- Pathologic staging can only be applied to patients undergoing pancreatectomy
 - Without surgery, histologic status of regional lymph nodes cannot be

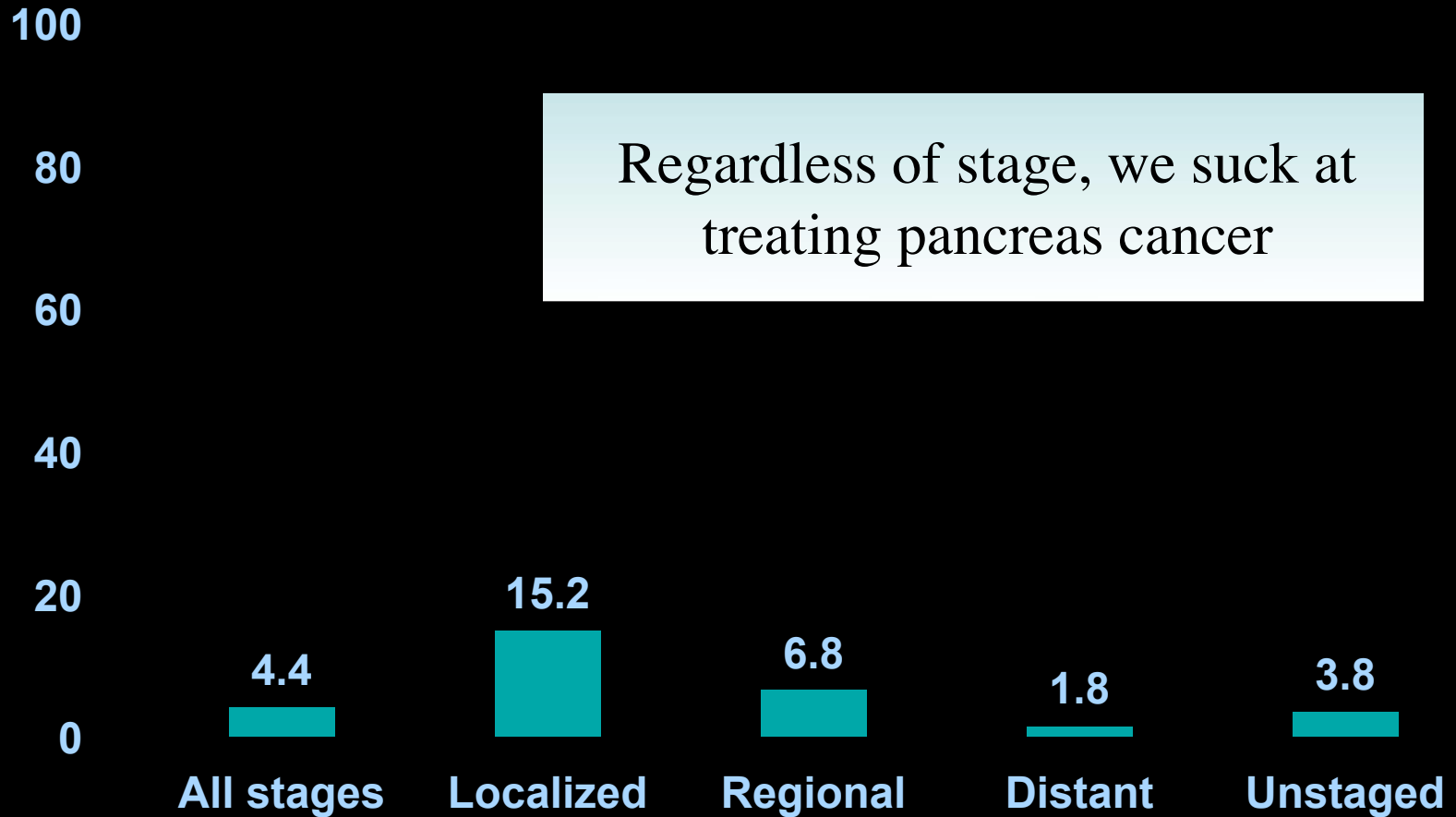
Stage I	$T_{1-2}N_0M_0$	Tumor ≤ 2 cm in greatest dimension, no lymph, no metastasis
Stage II	$T_3N_0M_0$	Tumor extends directly to duodenum, bile duct, or peripancreatic tissues, no lymph, no metastasis
Stage III	$T_{1-3}N_1M_0$	Regional lymph node involvement, no metastasis pN1a: single regional lymph node pN1b: multiple regional lymph nodes
Stage IVA	$T_4N_{Any}M_0$	Tumor extends directly to stomach, spleen, colon, or adjacent large vessels; involvement of 1 or more regional lymph nodes
Stage IVB	$T_{Any}N_{Any}M_1$	Presence of metastatic disease

Staging-Real World

- Localized, resectable
- Locally Advanced, Unresectable
- Metastatic

- Location
 - Head -80% (more likely to be resectable)
 - Other -20%

Pancreatic Cancer:



**With those numbers should we
even do surgery?**

Surgery

- For resectable disease

- Best results (Yeo, et al) have <1% perioperative mortality for Whipple
 - 5-year survival was 20% (most patients received adjuvant chemoradiation)
- Options for surgery
 - Head:
 - Whipple, pylorus-preserving procedure
 - » Randomized trial demonstrated no difference in efficacy, morbidity, dumping syndrome, etc
 - Body, tail
 - Distal or total pancreatectomy

Defining Resectable

- Lines are blurred now
 - SMA or celiac artery involvement are clearly unresectable
 - SMV, portal vein can be resected with vein reconstruction
 - Do we help by doing this?
 - Resectability is defined by
 - Surgeon, first and foremost
 - EUS and CT scan do not always agree
 - Can we reconstruct the veins?
 - Should we reconstruct the veins?
 - Above all else, treatment decisions should be made by a multidisciplinary team
 - Treatment planning is complex
 - If the team does not communicate, it's not a team

Surgery

- Who does the surgery matters
 - Several databases demonstrate that high volume institutions (> 10 Whipple procedures per year) and high volume surgeons have
 - Longer survival
 - Less perioperative morbidity and mortality
 - Low volume MD, low volume hospital ~15% perioperative mortality
 - High volume MD, high volume hospital <3% perioperative mortality

Surgery Conclusions

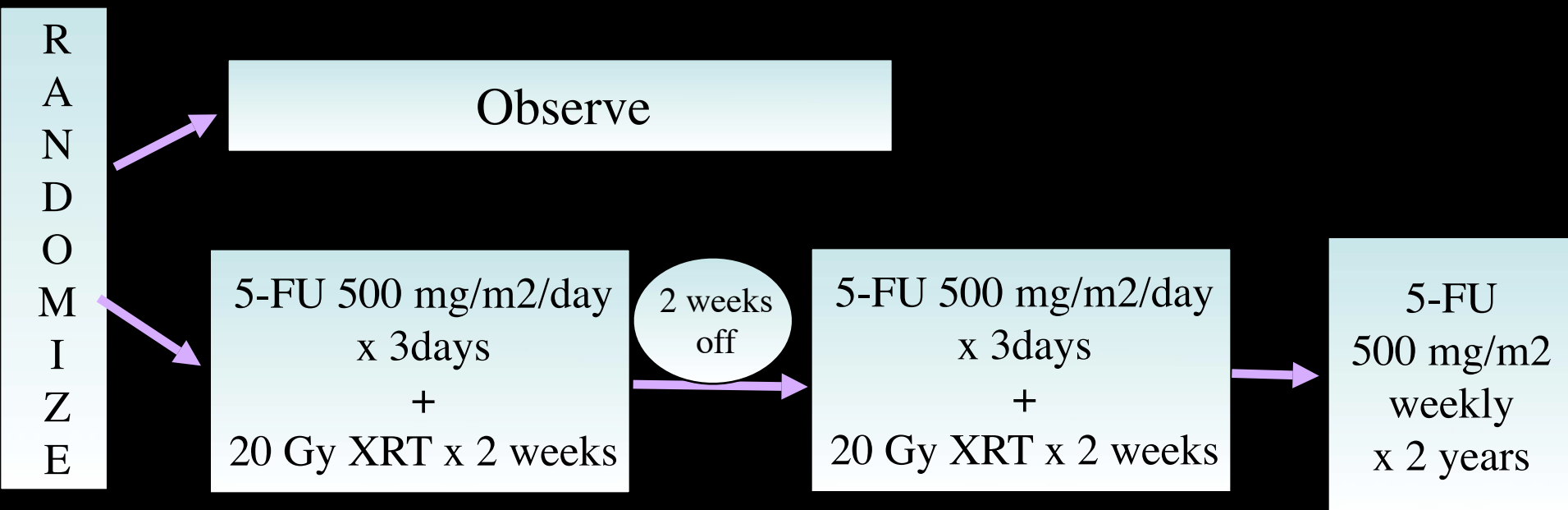
- Our surgical results are not pretty, but this is the only way to achieve long-term survival
 - Surgery is justified, but not by every surgeon or at every hospital
 - Training programs need to take the experience factor into account and train surgeons to have the experience by the time they are done
 - Surgeons without the volume need to accept this and refer patients on

**Have we ever justified any
adjuvant therapy?**

GI Tumor Study Group

• Randomized Trial

- Primary endpoint: survival
- Took 8 years to complete accrual



GI Tumor Study Group Design

- **Stratifications**

- Type of surgery (partial vs full pancreatectomy)
- Degree of differentiation
- Stage
- Location (head vs body or tail)

- **Statistics**

- Log rank test, one sided analysis
- No specific accrual goal, but
- 50 patients per arm was required to provide a 90% power to detect a doubling of survival time at the 0.05 level with a one-sided test

GI Tumor Study Group Results

- 43 patients enrolled over 8 years
- Median follow-up 5.5 years
 - Survival: 20 vs 11 months, $p = 0.035$, unadjusted
 - DFS: 9 vs 11 months, p not given
 - 19 dead vs 15 dead
- Treatment Compliance
 - 6 pts had wrong radiation, but 19/21 had the tumor bed included in XRT port
 - 2 completed 2 years of chemo
 - 11 were on chemo until recurrence
 - 3 completed 17 months
 - 4 had < 1 year
 - 1 never started

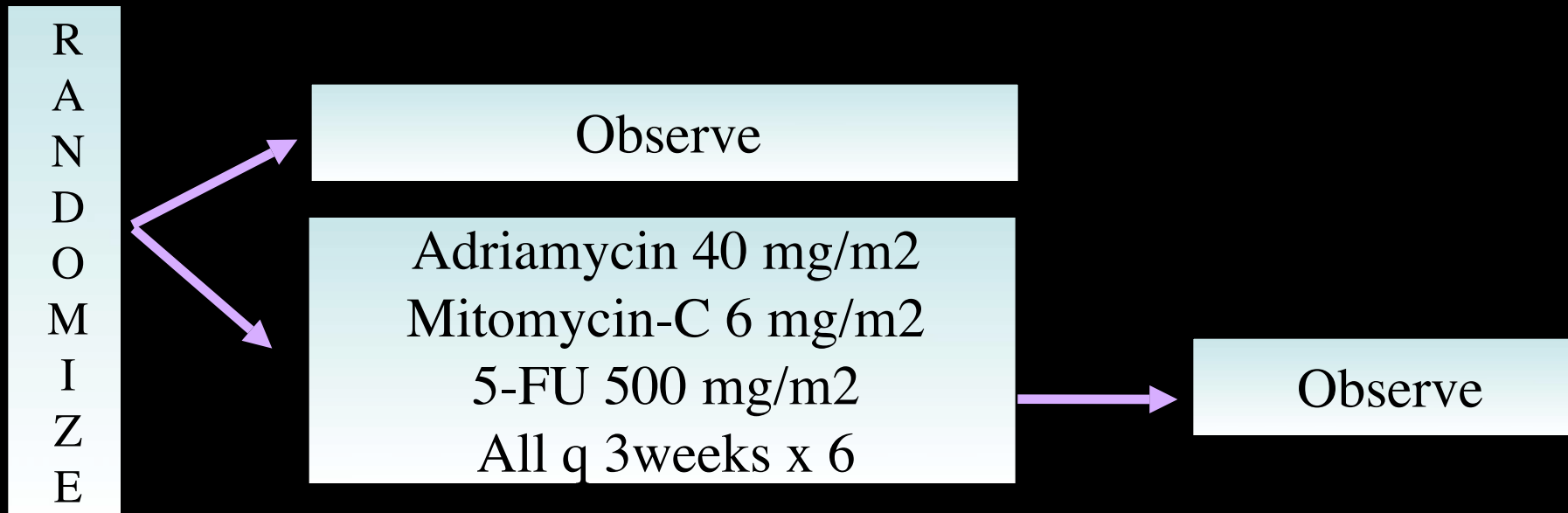
GI tumor study Group: Issues

- Long accrual time
- No discussion of margins
- Radiation is “sub-standard”
- My issue:
 - Design would have required at least 50 patients per arm to have seen the difference so it is unclear how this led to a significant difference

Norwegian Trial

- Randomized trial

- 61 patients : 47 pancreas, 14 periampullary



Norwegian Trial: Results

	Control	Treatment
# of patients	31	30
Med Survival	11 months	23 months (p, 0.02)
Yearly survival		
1	45%	70%
2	32%	43%
3	30%	27%
5	8%	4%

Only 24 of 30 randomized to treatment received treatment

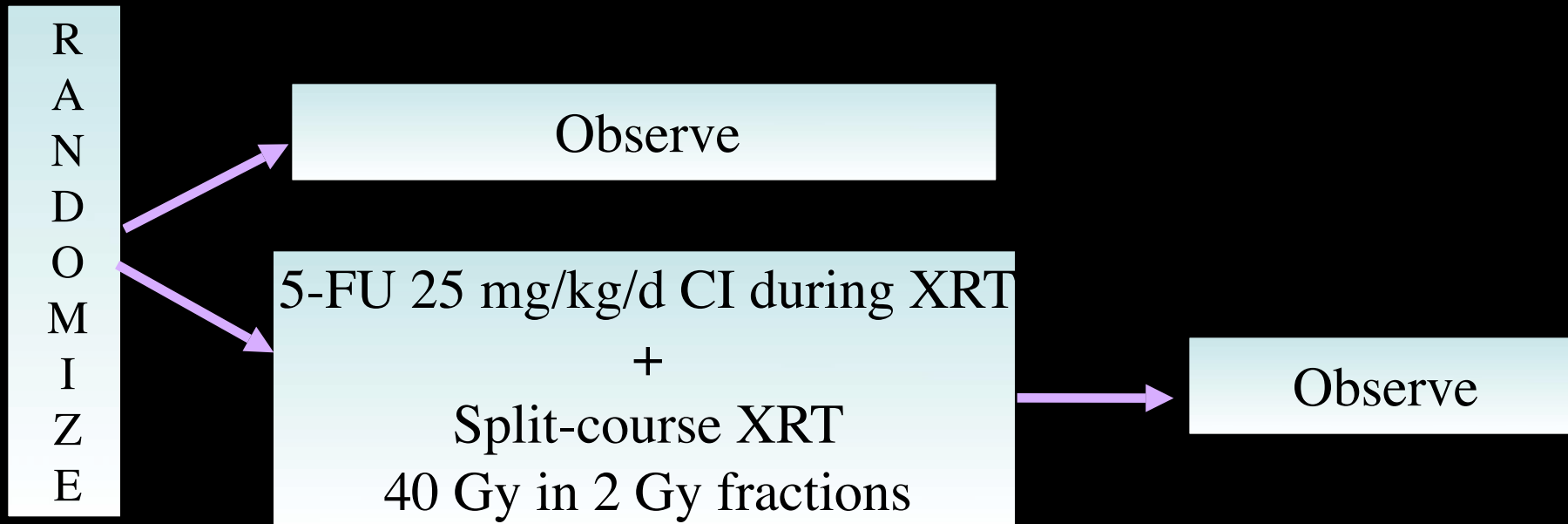
Authors concluded that chemotherapy delayed recurrence, but didn't prevent it.

EORTC

• Randomized Trial

- Pancreas + Periapillary
 - Periapillary = common bile duct, ampulla of vater, duodenum
- Chemoradiation vs observation after surgical resection
- Central pathology review
- Quality assurance on XRT

EORTC



Primary Endpoint: 2-year survival

110 deaths needed to detect a 20% increase in 2-yr survival with 2-sided log rank, power of 80%

EORTC Treatment

- 29 patients did not receive treatment in the adjuvant arm
- Of the remaining 81 patients, evaluated with intent to treat
 - Treatment administration
 - 93% of 81 who started XRT completed
 - Median 90% of dose of 5-FU given (range: 50 – 122%)

EORTC Results

	Observation	Chemoradiation
Median Survival	19 months	24.5 months
2-year survival	41%	51% (p,0.208)
5-year survival	22%	28%
Med Survival, Pancreas only	12.6 months	17.1 months (p, 0.099)
Med Survival, periampullary	40.1 months	39.0 months

EORTC Issues

- Split-Course radiation not considered ideal
- Combined periampullary with pancreas despite significantly different outcomes
- Pancreas group is a subset analysis
- Positive: No chemo after chemoradiation makes the analysis of treatment more pure

ESPAC-1

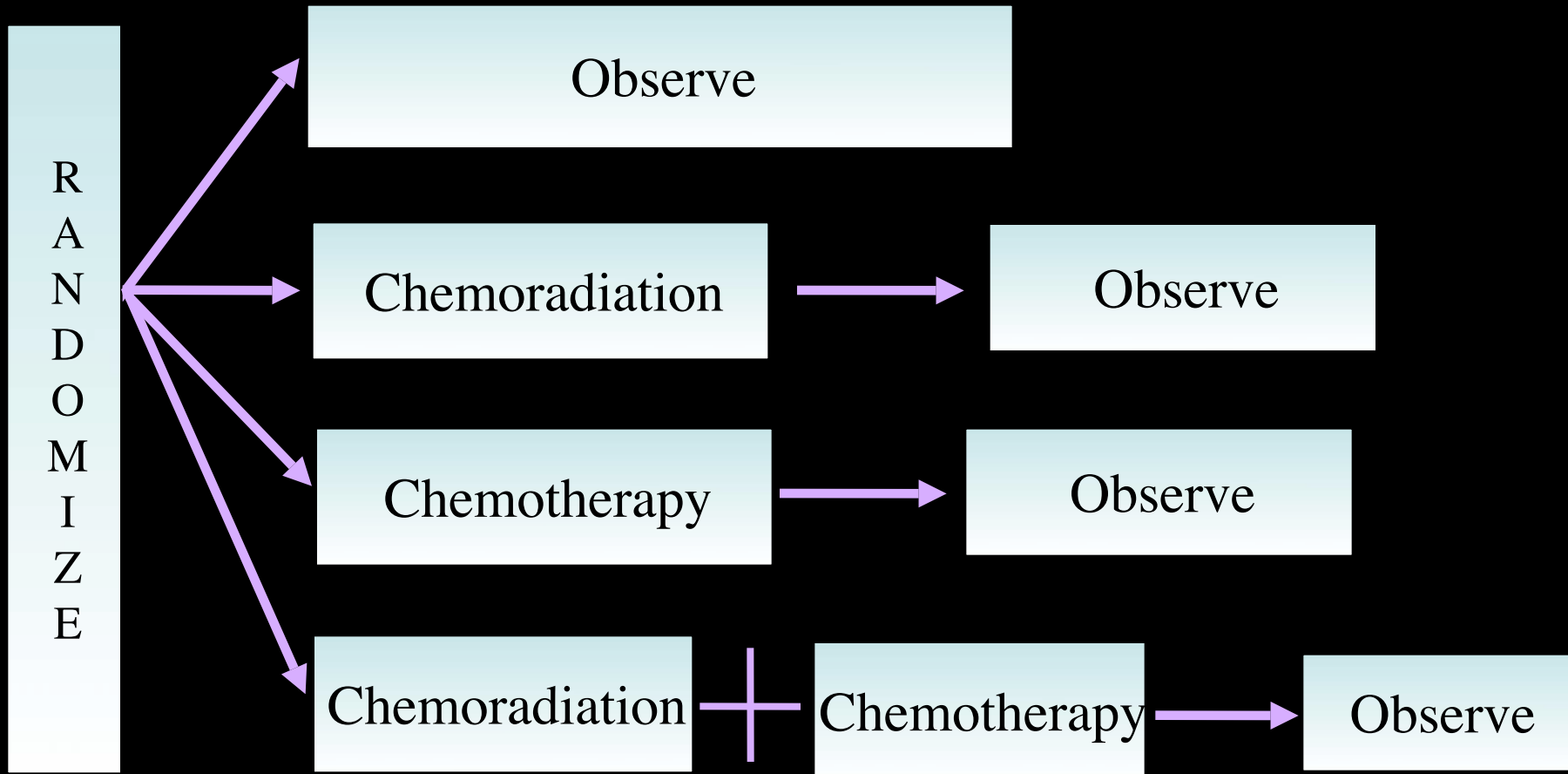
• Publications

- Neoptolemos JP, et al Digestion 58:570-7, 1997
- Neoptolemos JP, et al. Lancet 358:1576-85, 2001
- Neoptolemos JP, et al. Ann Surg 234:758-68, 2001
- Neoptolemos JP, et al NEJM 350:1200-10, 2004

Randomization

- Planned 2 x 2 design
 - Randomization 1:
 - Chemoradiation vs no chemoradiation
 - Chemoradiation = 40 Gy in split-course (20 Gy x 2 weeks with 2 week break) with chemotherapy 500 mg/m²/d x 3 days at beginning of each 2 week XRT course
 - Randomization 2:
 - Chemotherapy vs no chemotherapy
 - Chemotherapy = 5-FU 425mg/m² x 5 days q 28 days x 6
 - Allowed sites to choose one of the two randomizations rather than both to help accrual?

ESPAC-1: Arms

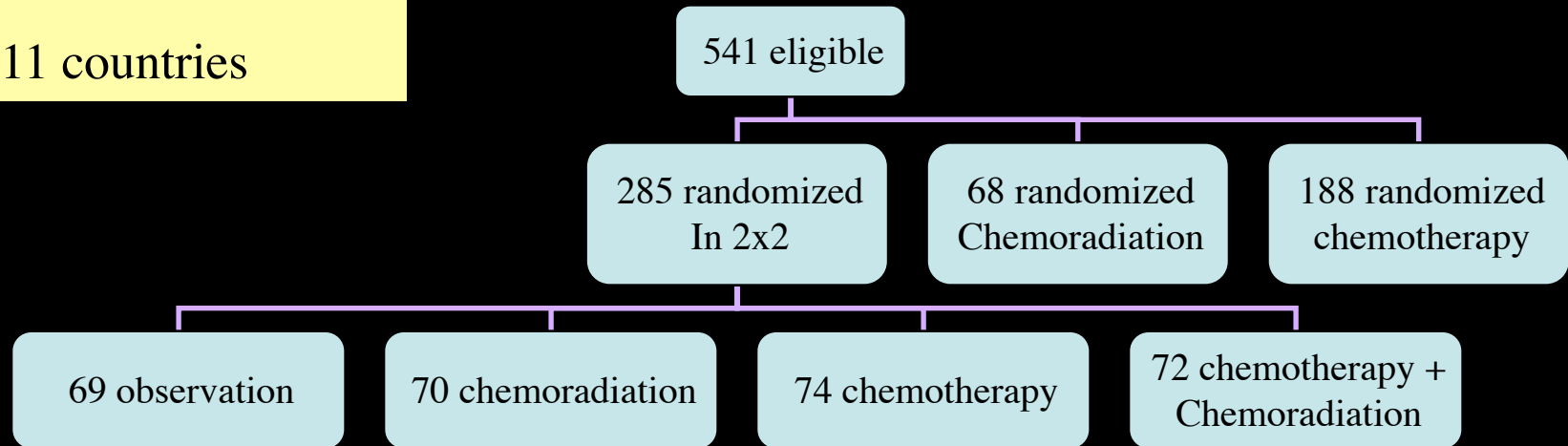


ESPAC-1 Design

- “The purpose of this study is to compare the three principal options for adjuvant therapy versus a control arm.” --Not exactly
 - Improvement of 20-40% 2-year actuarial survival with negative margins, and
 - 1-20% in patients with positive margins
 - $\alpha = 0.05$ and power of 90%, requires
 - 220 margin negative patients
 - 60 patients with positive margins
 - Overall, 280 patients in trial would be minimum
 - Elective randomization of peri-ampullary and non-ductal pancreas cancer was added later, but these patients are analyzed separately and not included in the 280

ESPAC-1: Patient Distribution- (pancreas only)

61 centers
11 countries



68 randomized chemoradiation only
35 assigned no chemoradiation
33 assigned chemoradiation

188 randomized chemotherapy only
96 assigned no chemotherapy
92 assigned chemotherapy

ESPAC-1: Final Results of 2x2

- Chemoradiation vs no chemoradiation

- Median Survival:

- Hazard Ratio 1.28 (0.99-1.66), p =0.05

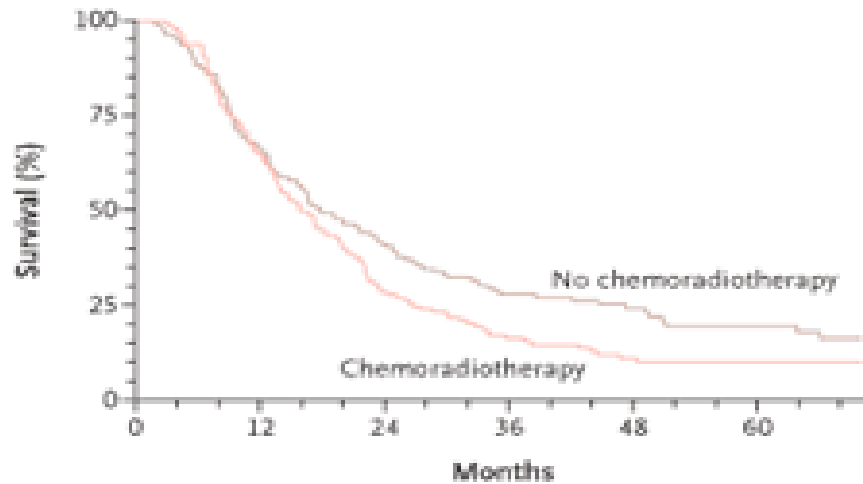
	Chemo-XRT	No Chemo-XRT
Overall Survival	15.9 m	17.9 m
2-year survival	29%	41%, ns
5-year survival	10%	20%, ns

ESPAC-1: 2x2 Final Results

- **Chemotherapy**
 - Median Survival
 - Hazard Ratio 0.79 (0.55-0.92), $p = 0.009$

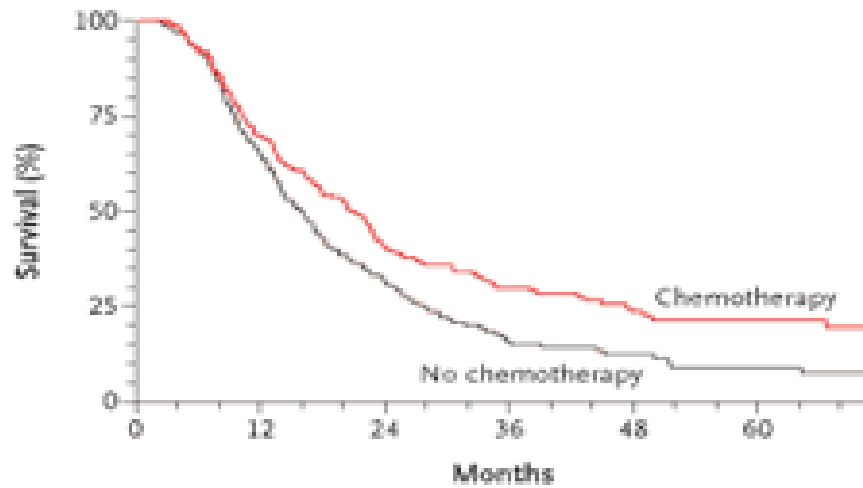
	Chemo	No Chemo
Median Survival	20.1 m	15.5 m
2-year survival	40%	30%
5-year survival	21%	8%

ESPAC 1: 2x2 Survival



No. at Risk

No chemoradiotherapy	144	94	57	36	22	13
Chemoradiotherapy	145	94	40	20	11	5



No. at Risk

No chemotherapy	142	89	41	18	11	7
Chemotherapy	147	99	56	38	22	11

NEJM 350:1200-10, 2004

ESPAC-1: 2x2 Final Results

• Recurrence

– Site of recurrence (n =158 recurrences)

- Local Only 56 (35%)
- Distant Only 53 (34%)
- Local + distant 43 (27%)
- Unknown 6 (4%)

– Time to recurrence

- Chemo vs no chemo 15.3 vs 9.4 months (p, 0.02)
- ChemoXRT vs no chemoXRT 10.7 vs 15.2 months (p, 0.04)

ESPAC-1: Conclusions

- **Conclusions by authors**
 - Chemotherapy with 5-FU improves the outcome for patients with resected pancreas cancer
 - Chemoradiotherapy “reduces survival when it is given before chemotherapy.”
 - Chemoradiotherapy did not appear to affect local recurrence rate

ESPAC-1: 2x2 Issues

• Editorial

- Of 147 patients randomized to chemotherapy (Choti MA NEJM 350:1249-51, 2004)
 - 33% of 122 for whom data is available did not complete chemotherapy
 - 17% of 122 for whom data is available did not receive any chemotherapy
 - 2x2 was not powered to evaluate the individual boxes
 - Stepwise treatment makes it more important to be able to perform a box by box analysis

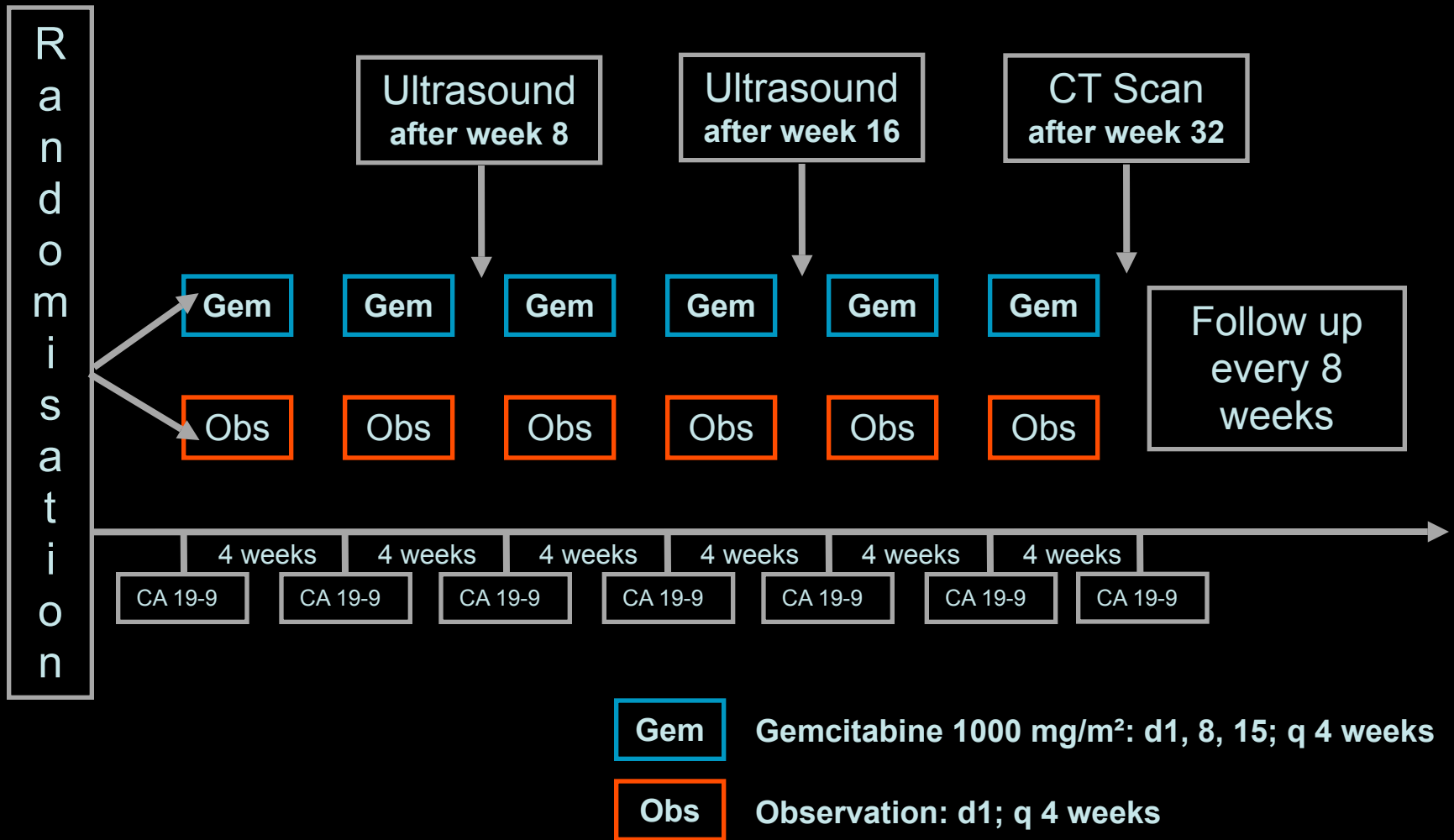
• Other

- No radiation quality controls
- No control on the dose (could go to 60Gy)
- Still don't know how to analyze the other patients not listed in the NEJM article

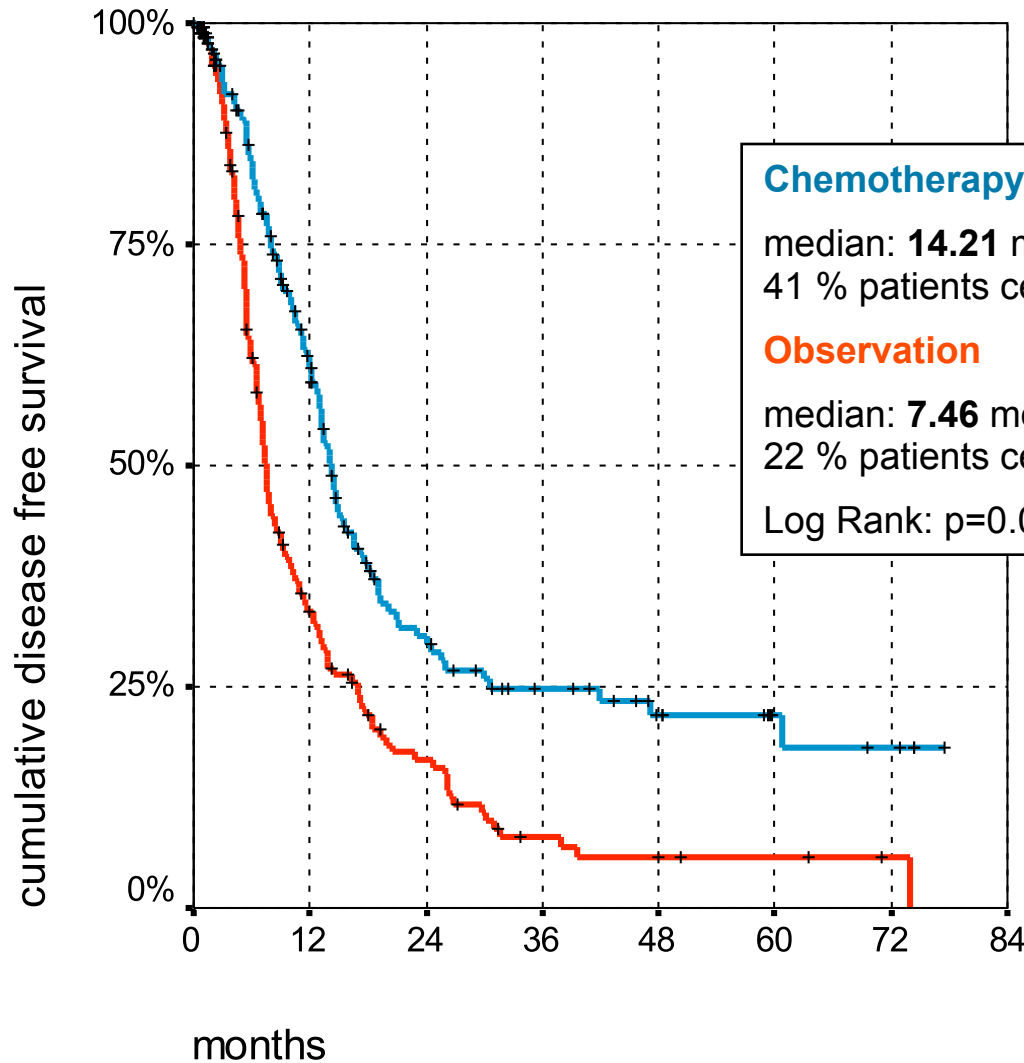
Editorial Should have asked...

- Was this paper worthy of the top tier journal in clinical research?
 - NO
 - P-value on primary endpoint (2-year survival) never reported
 - Patients enrolled on the trial, though not part of the primary analysis, were not included in the report
 - Not the first report of the data
 - Poorly conducted trial for one of the two endpoints (chemoradiation)
 - No quality controls
 - Outdated therapies
 - Yes
 - Could be practice changing

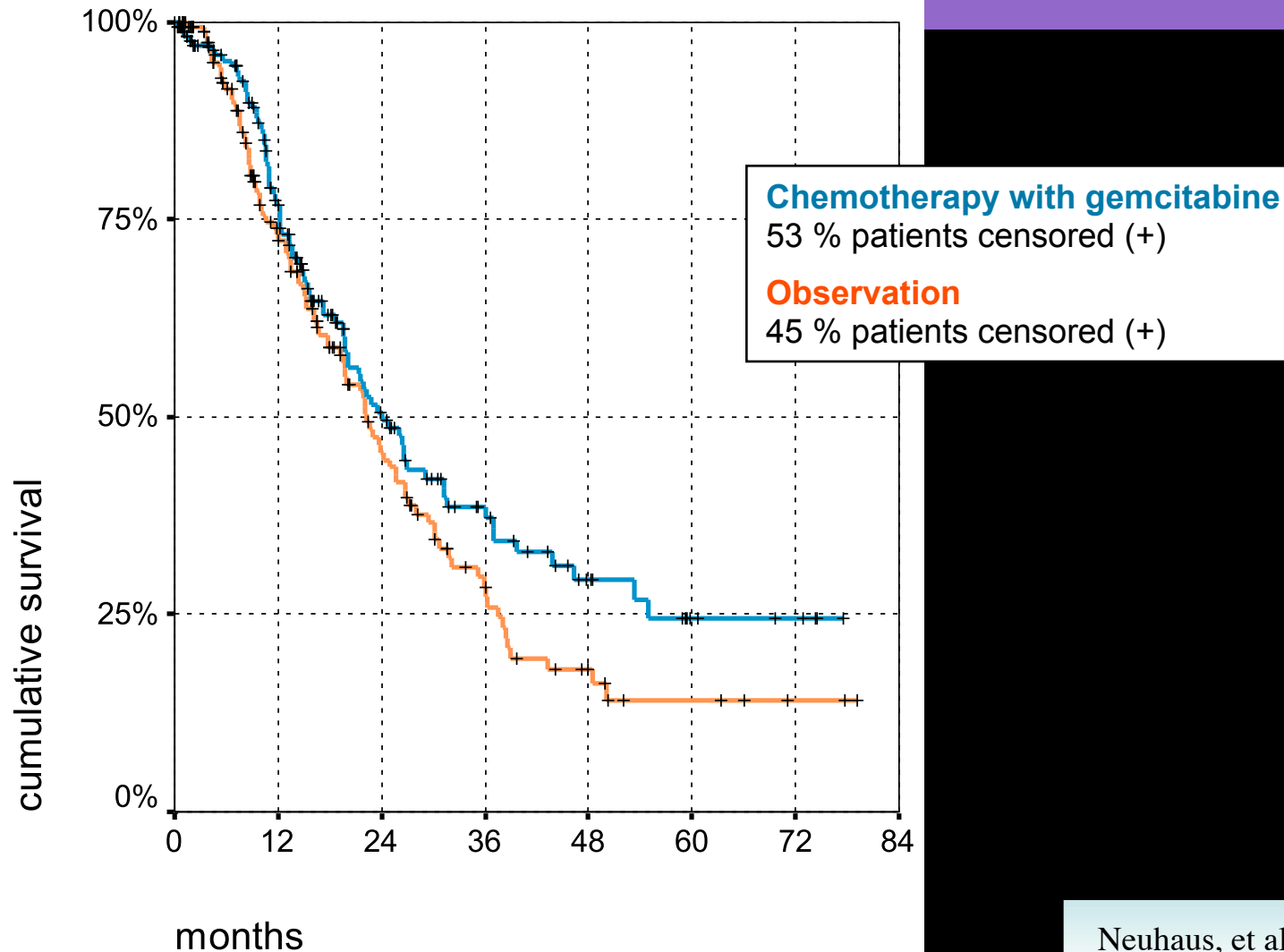
CONKO-001 Disease



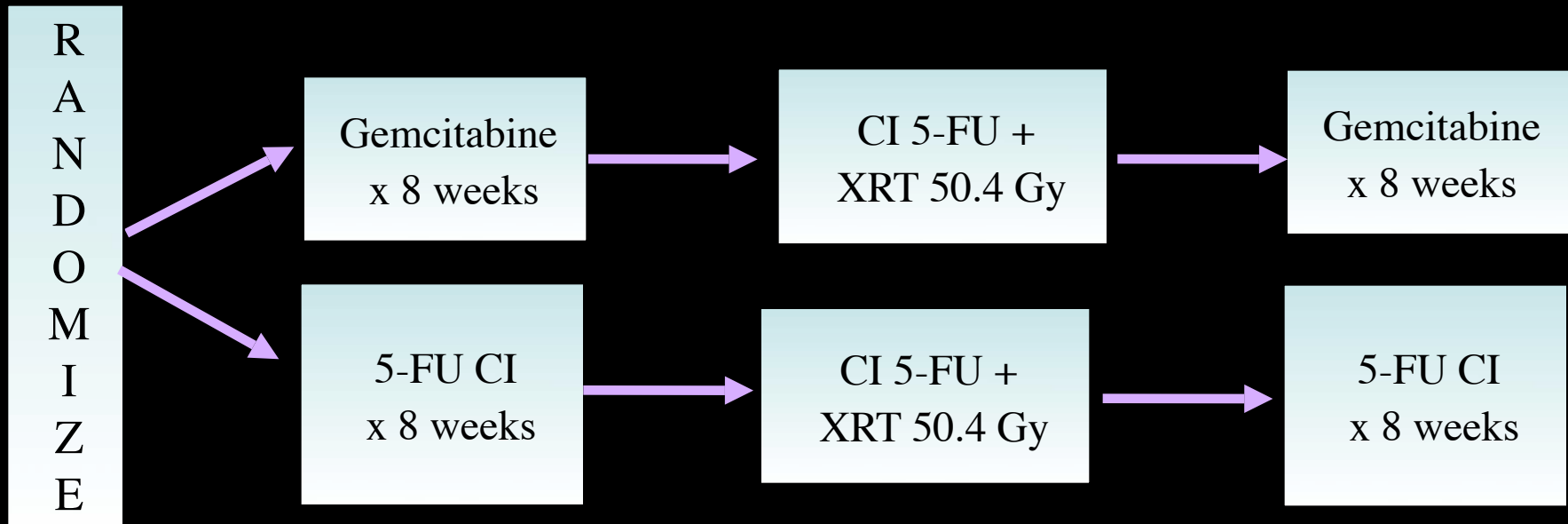
CONKO-001 Kaplan Meier



CONKO-001 Kaplan Meier



R-97-04



Regine, et al ASCO 2006

R9704

	Median Survival	3-year survival
Gemcitabine arm	18.8 months	31%
5-FU arm*	16.7 months	21%
ESPAC-1 5-FU arm	20.1 months (half had XRT)	40% at 2 years 20% at 5 years

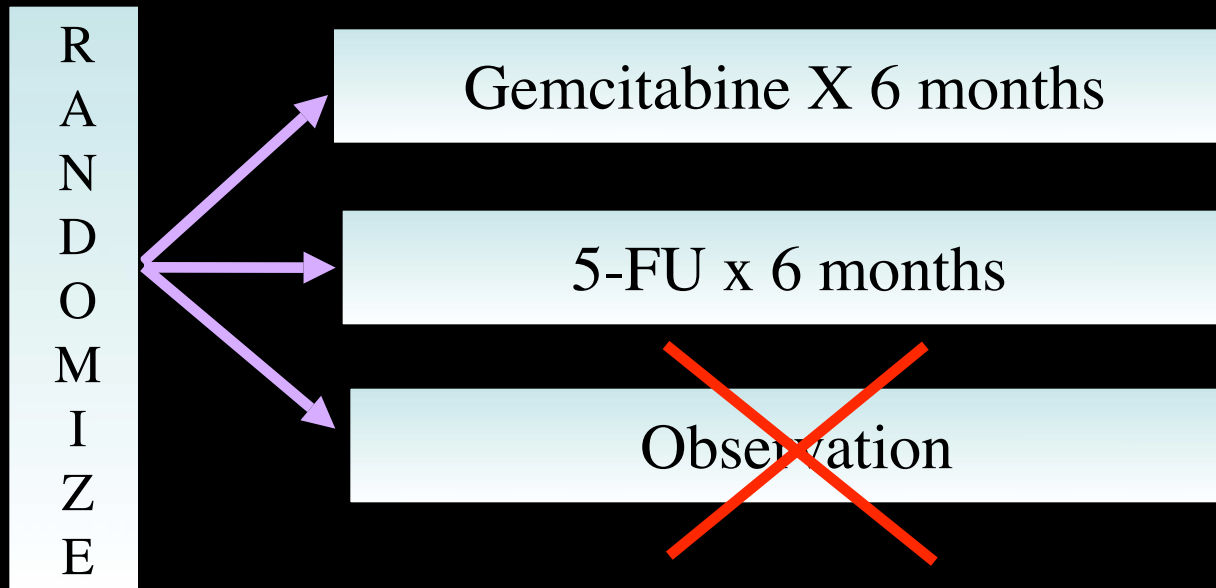
*R9704 data is for pancreatic head carcinoma only

**Hazard Ratio 0.79, $p = 0.47$, favoring gem arm

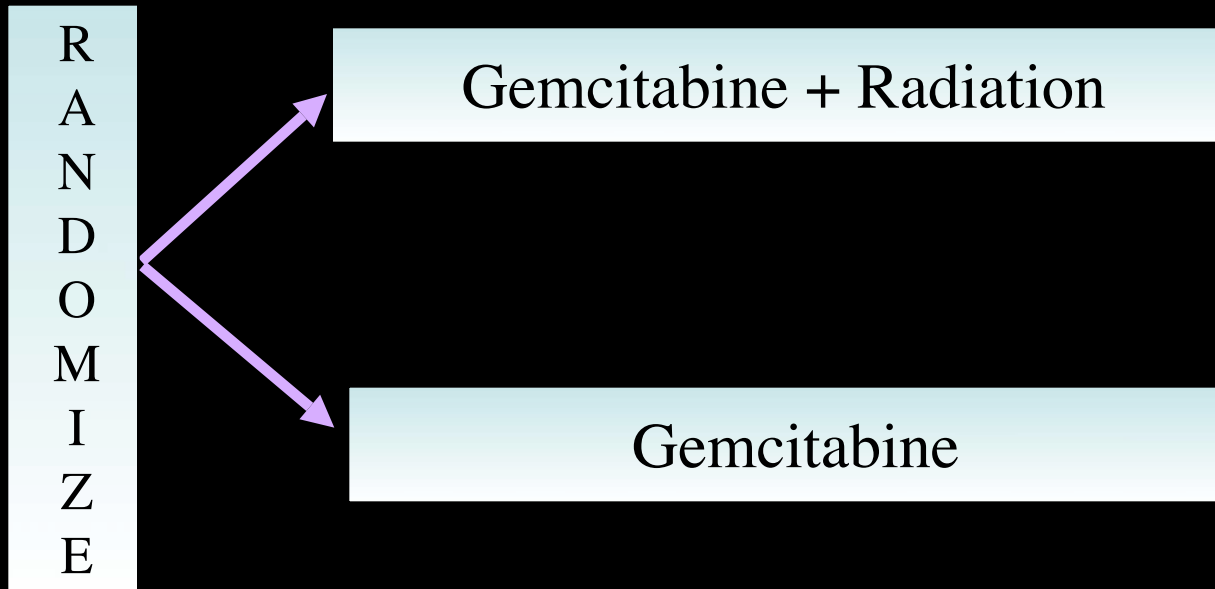
Conclusions about Phase III trials as a whole

- Two trials (ESPAC and CONK) suggest benefit from adjuvant chemotherapy
 - Both suggest this is true for both + and – margins
- The only trial that shows benefit to chemoradiation (GITSG) is suspect at best and was the only thing disproven by ESPAC-1
- R9704 definitely does not prove benefit to radiation, nor does it disprove it
- Borrowing from Descartes, “I can neither prove nor disprove the utility of adjuvant radiation”
 - Nor has XRT been proven—lack of proof against a therapy is not adequate for its continued use
 - Adjuvant radiation should be considered experimental

ESPAC-3 Study Design



EORTC Study Design



Picozzi Regimen

- Phase II trial

- 43 patients
- Treated with 54Gy XRT +
 - Cisplat 30 mg/m²/week + CI 5-FU 200 mg/m²/d + interferon 3,000,000 units/d
 - Followed by 5-FU 200mg/m²/d x 6 weeks repeated x1 (total + 2 cycles)
- Results
 - 42% hospitalized, no deaths
 - Median survival not defined
 - 1,2 and 5-yr actuarial survival: 95%, 64%, and 55%, respectively
- Conclusion: Should be evaluated further
 - ACOSOG Trial is repeating this trial with careful monitoring

New Agents

- Most chemotherapy agents have not added a lot to gemcitabine therapy
 - Some may still be good radiation sensitizers
- Targeted agents may have promise
 - Need to be tested in metastatic setting
 - EGFR and VEGF inhibitors have both shown some promise when combined with gemcitabine
 - Inhibitors of both EGFR and VEGF preclinically are good radiation sensitizers

Metastatic Pancreas Cancer

- Adenocarcinoma of pancreas
- No prior chemotherapy
- Measurable or non-measurable disease
- EGFR status not an eligibility criteria

Stratified by:

- Center
- PS (0/1 vs 2)
- Stage of disease

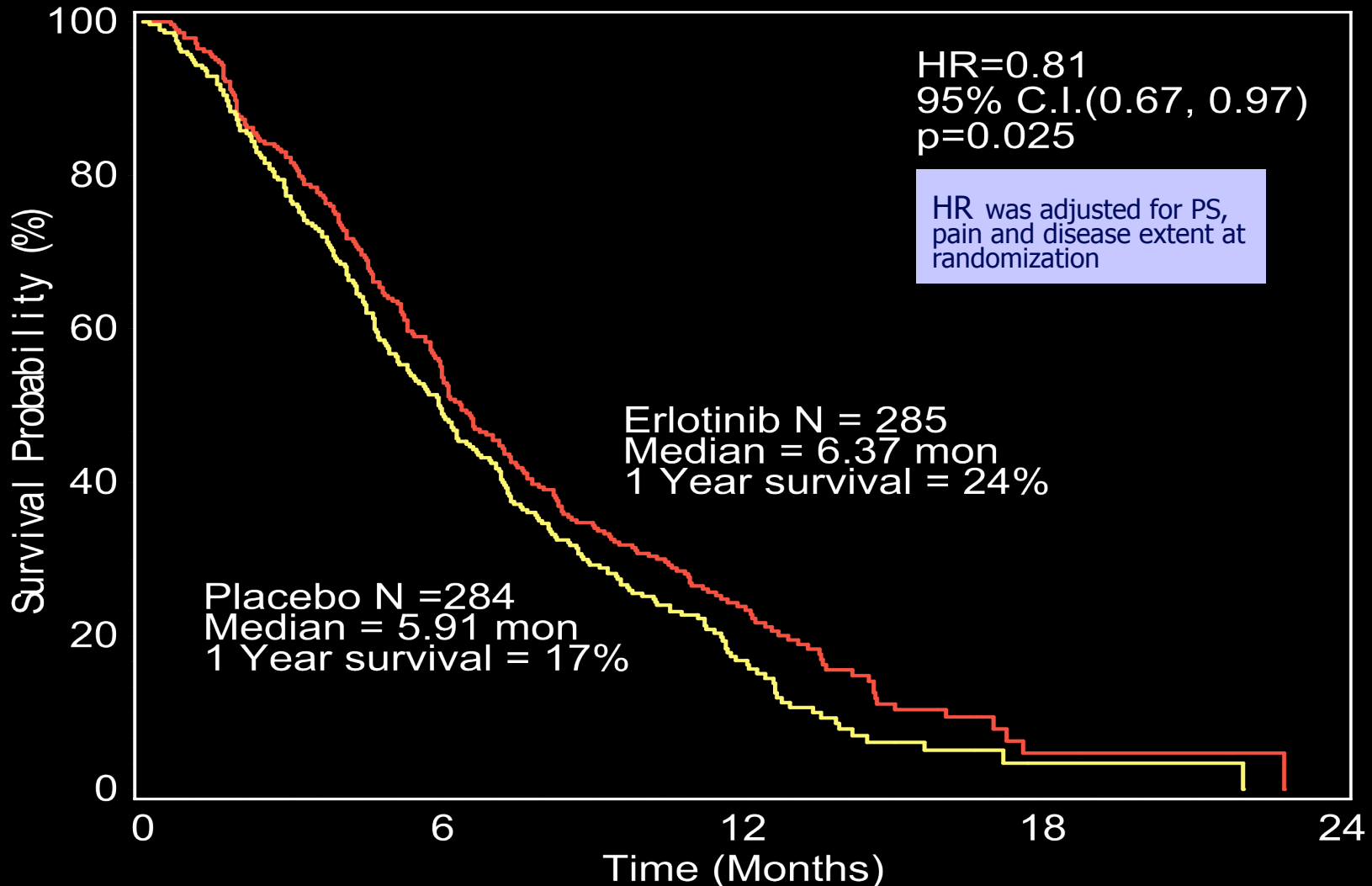
R
A
N
D
O
M
I
Z
E

Gemcitabine 1000 mg/m² IV
+
Erlotinib 100 / 150 mg
p.o. daily
N = 285

Gemcitabine 1000 mg/m² IV
+
Placebo 100 / 150 mg
p.o. daily
N = 284

Primary Endpoint: Survival

Metastatic Pancreas Cancer



SWOG Trial: Monoclonal antibody

One phase II trial of cetuximab + gemcitabine had median survival of 7.1 months and 1-year survival of 32%, leading to:

R
A
N
D
O
M
I
Z
E

Opened 2004: Accrual > 700

Gemcitabine

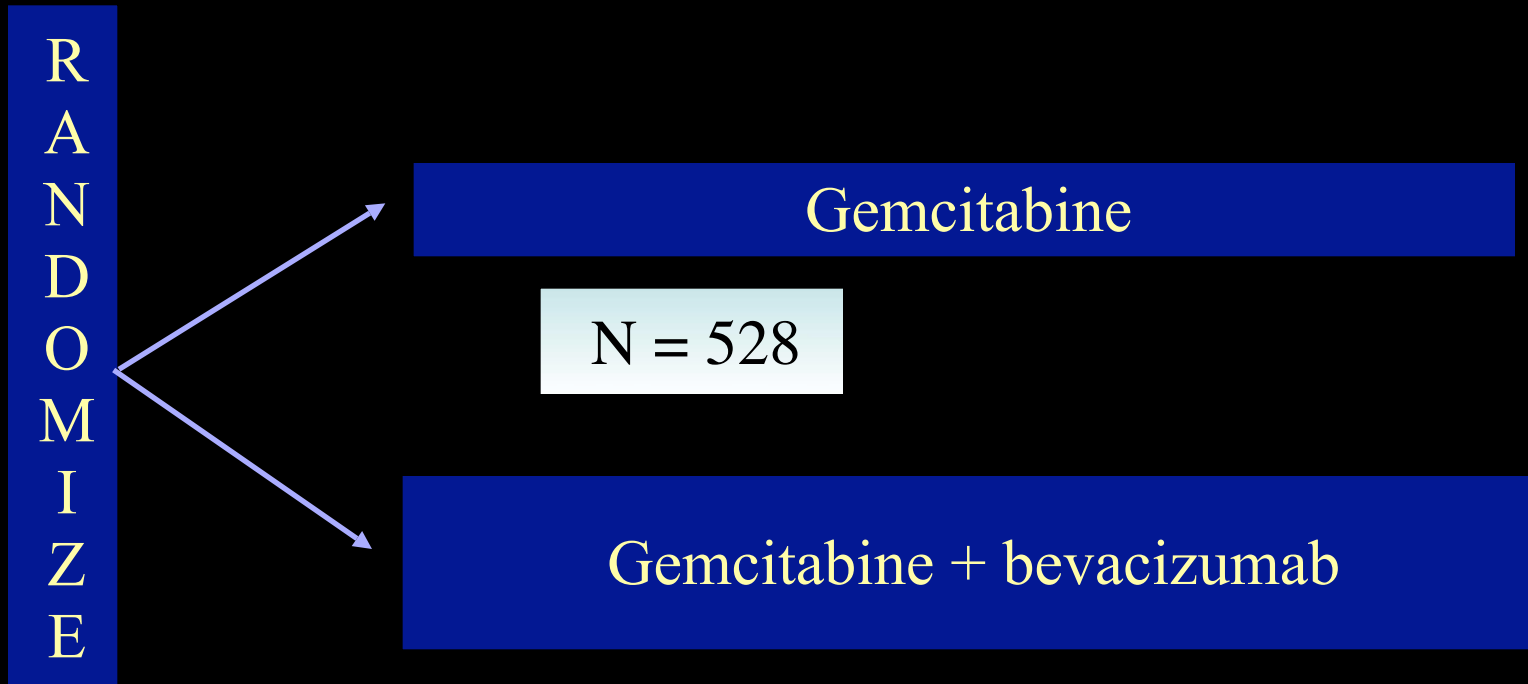
Gemcitabine +
cetuximab

CALGB Trial: Monoclonal antibody to VEGF

Phase II trial in 42 patients:

Med survival: 8.7 months

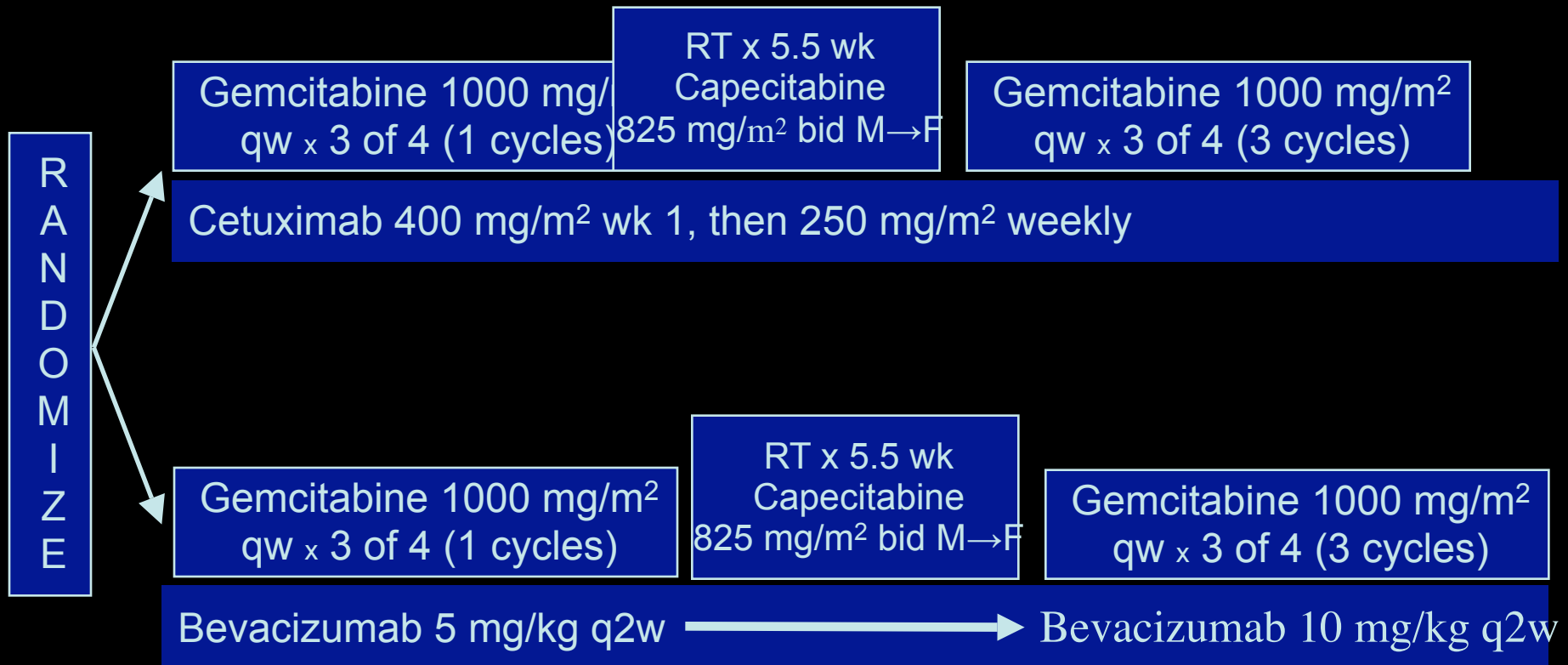
TTP: 5.8 months



Targeted Agents in Adjuvant Therapy

- Clearly with such large trials, both cetuximab and bevacizumab may statistically significantly add to the effects of gemcitabine alone
 - Both agents have unique side effects
 - Bevacizumab has resulted in wound healing problems, though not if given >28 days after surgery
 - Concern was raised about the peri-operative safety of these agents in pancreas cancer where perioperative recovery is not as rapid
 - Of note, at ASCO 2005, VEGF expression appeared to predict for outcome in adjuvant therapy of pancreas cancer

E2204 Schema



- R0 or R1 resection allowed; tissue requested
- Standardized margin definitions given

E2204

- Best to get safety data on a smaller trial than get a surprise on a large phase III trial
- Best to be completely prepared
 - ie whichever monoclonal antibody wins (if any) we are ready
 - If chemoradiation wins in EORTC, we are ready
 - If chemotherapy wins in EORTC, we can just drop the chemoradiation portion without harm
 - If 5-FU wins in ESPAC-1...
 - Well, we can't have every contingency ready

Neoadjuvant Therapy

- Rationale

- At most, 10-15% undergo resection
 - Up to 80% have R0 resection (Neoptolemos, et al)
- Many who undergo surgery never receive post-operative therapy
 - All randomized trials have had 8-20% never receive therapy
 - On ESPAC-1 25-32% of patients enrolled had post-op complications (Lancet article)
- Pre-operative therapy would allow treatment first
 - Higher percentage of patients would receive therapy
 - Possibly increase the number of R0 resections
 - Possibly make unresectable disease, resectable
 - Would select out a better group of patients---ie self-fulfilling

Neoadjuvant Therapy

- **Several neoadjuvant trials**
 - Most involved 5-FU, bolus or infusional
 - Radiation dose ranges from 30 Gy to 50.4Gy
 - Resectable patients range from 12.5- >60%
 - Survival range up to 45 months for resected patients
 - It is unclear if this increases the R0 resection rate
 - At ASCO, analyses were presented that showed good survivals, but
 - Many of these analyses skipped the patients who did not receive surgery
 - So result smay be a product of patient selection

Conclusions

- **Surgery helps a select few**
 - Surgery should be performed by high volume surgeons at high volume hospitals
- **Adjuvant chemotherapy appears to improve the outcomes from surgery**
- **Adjuvant radiation (or chemoradiation) is still possibly helpful**
 - It is incumbent on us to better evaluate this issue
 - We have left it up to Europe to get this done

The Chair would like to thank the following companies for their generous support of this CME activity.



Bristol-Myers Squibb Company



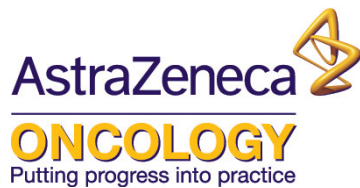
sanofi aventis

L'essentiel c'est la santé.

AMGEN®

(osi)[™] pharmaceuticals

Lilly Oncology



Roche Oncology

THIRD ANNUAL

*Update on the Management
of Gastrointestinal
Malignancies*

*October
20-22, 2006*

**Estancia La Jolla Hotel & Spa
LA JOLLA, CALIFORNIA**

Chairman:

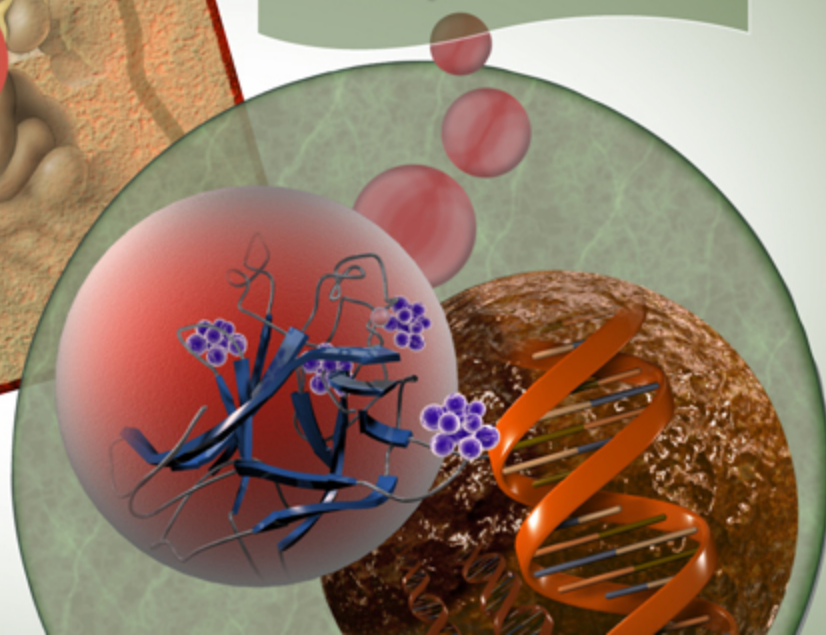
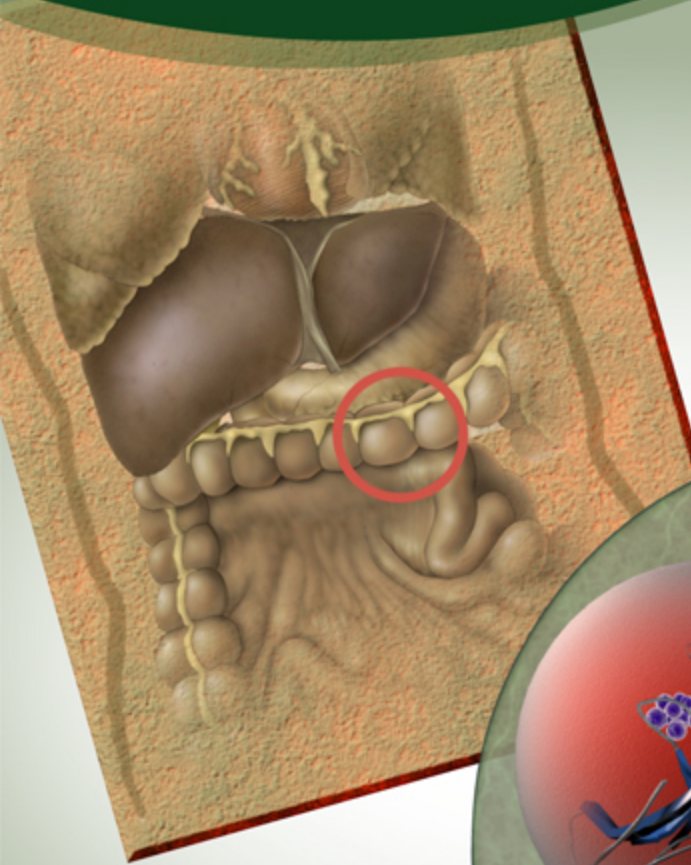
Mace L. Rothenberg, MD

Ingram Professor of Cancer Research

Professor of Medicine

Director, Phase I Drug Development Program

Vanderbilt Ingram Cancer Center



MEDICAL EDUCATION CONFERENCES
Developing Medical Paradigms Through Education™