

Adjuvant Therapy of Pancreas Cancer

Jordan Berlin, M.D.

Associate Professor, Medicine

(Presented by Mace L. Rothenberg, MD)



Vanderbilt-Ingram **Cancer Center**

A Comprehensive Cancer Center Designated by the National Cancer Institute

Objectives

- Review the data on established trials
- Review current status of new trials
- Speculate on the future a bit

- All the while I promise to remain as cynical as ever
 - Hmm, I wonder what Jordan meant by that?



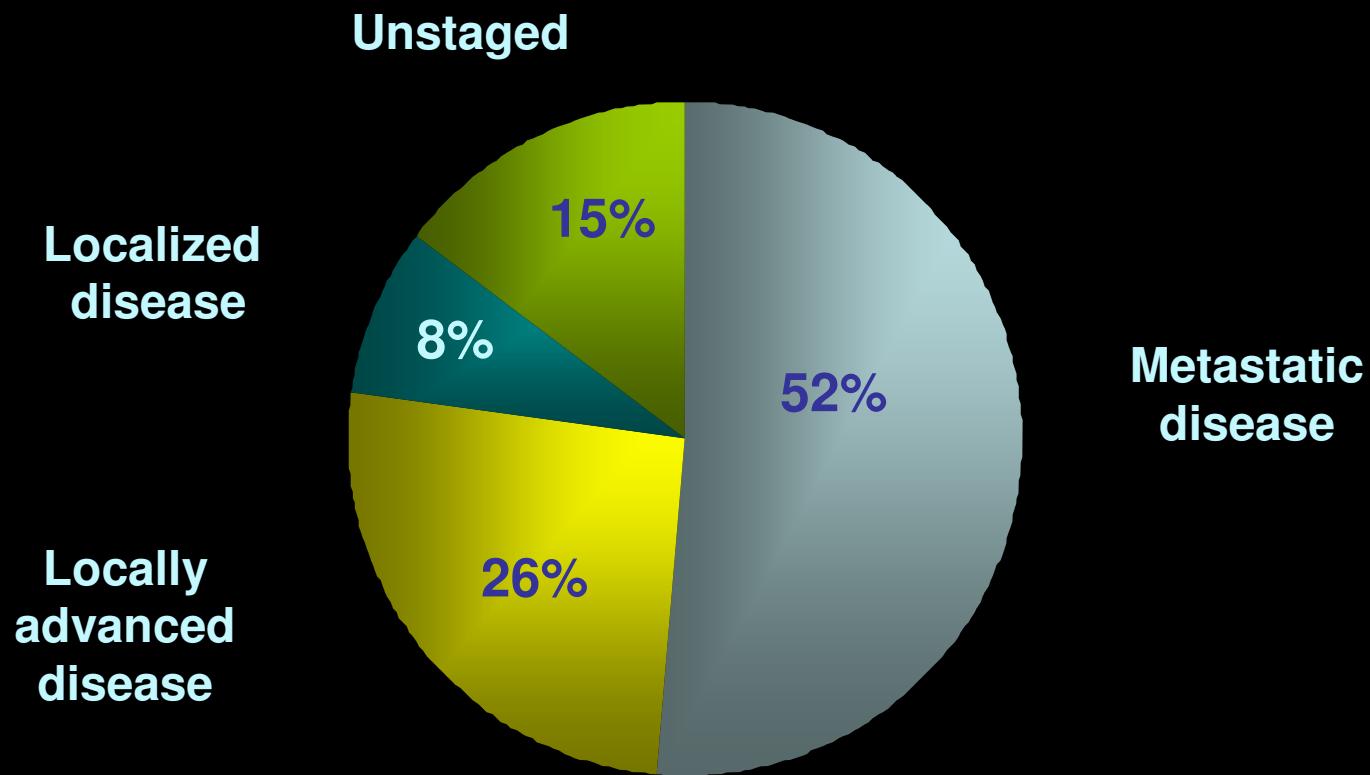
**Which group of patients are we
talking about?**

Pancreatic Cancer Demographics

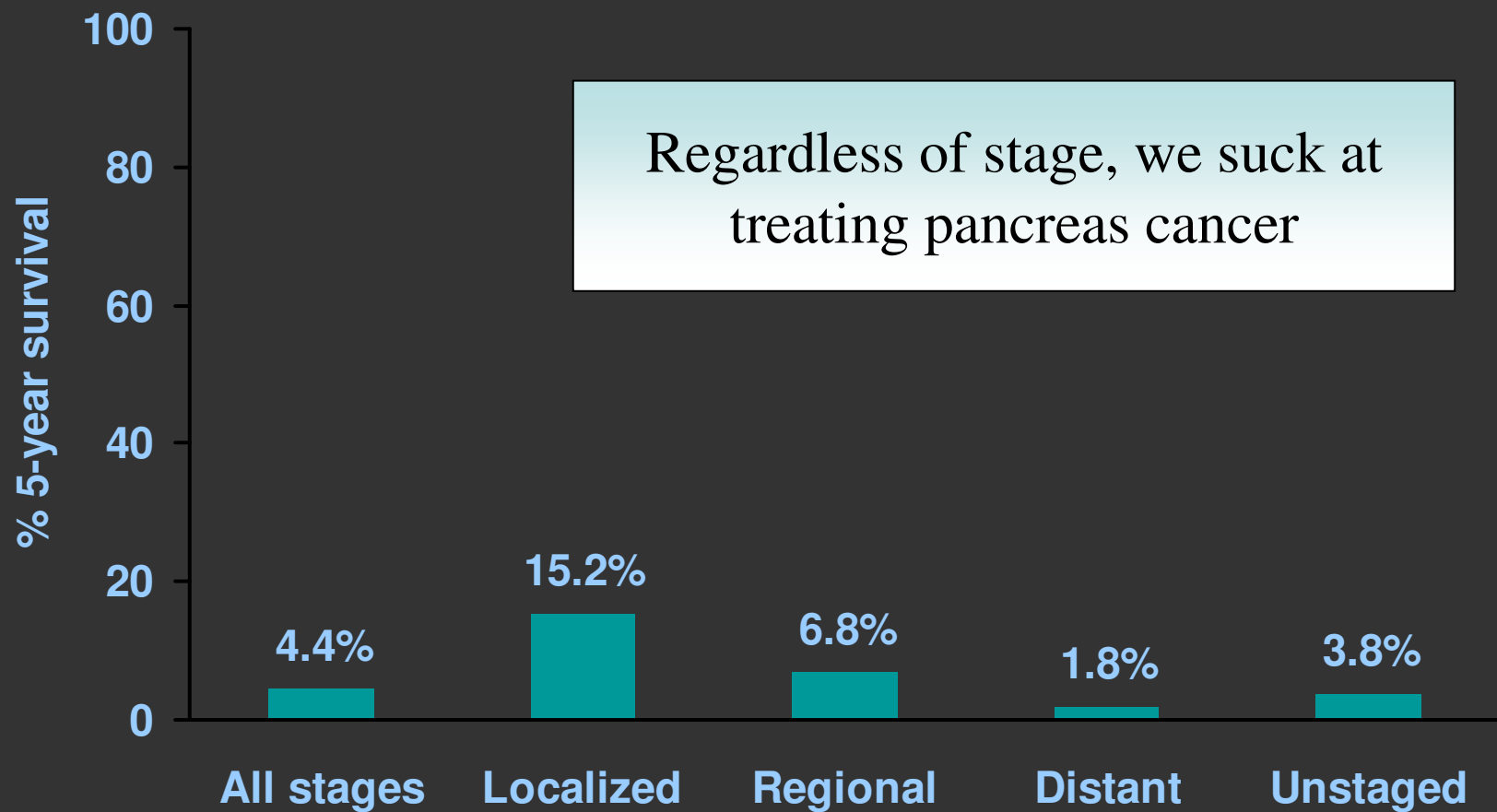
- **In the United States there are over 33,000 new cases per year and nearly as many deaths from pancreas cancer**
- **Pancreatic cancer accounts for approximately 2% of malignancies in men and women in the United States**
- **Fourth leading cause of cancer death in the United States**



Pancreatic Cancer: Stage at Diagnosis



Pancreatic Cancer: 5-Year Survival by Stage

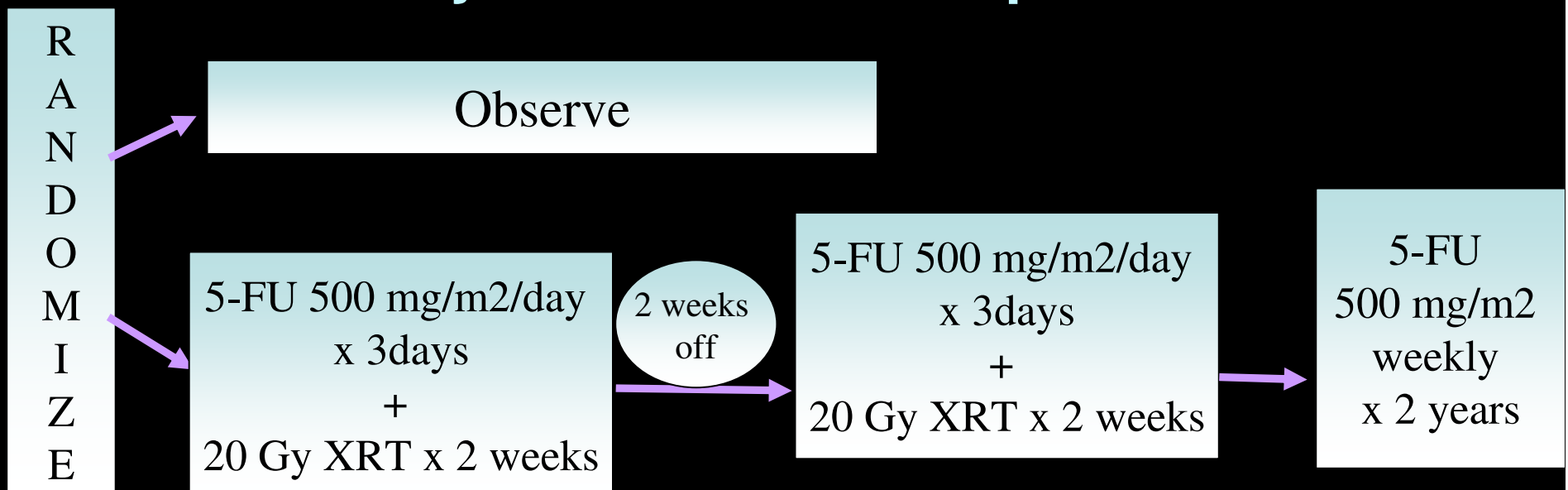


**Have we ever justified any
adjuvant therapy?**

GI Tumor Study Group

- **Randomized Trial**

- **Primary endpoint: survival**
- **Took 8 years to accrue 43 patients**



GI Tumor Study Group Results

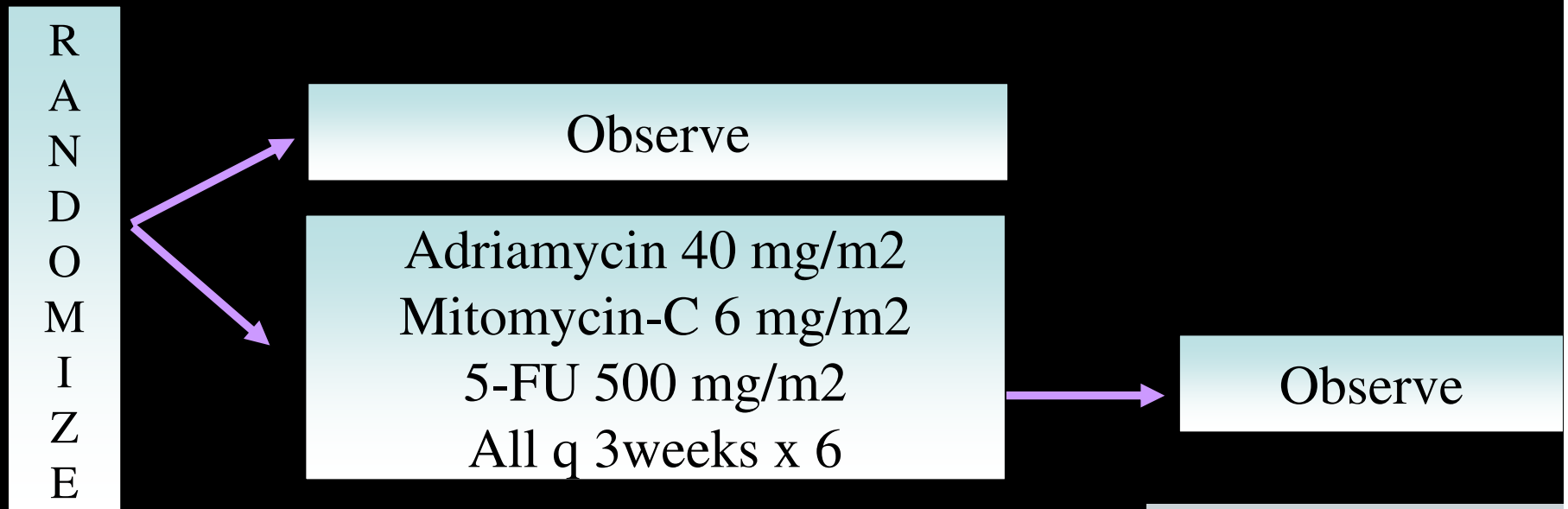
- 43 patients enrolled over 8 years
- Median follow-up 5.5 years
 - Survival: 20 vs 11 months, $p = 0.035$, unadjusted
 - DFS: 9 vs 11 months, p not given
 - 19 dead vs 15 dead
- Treatment Compliance was a disaster
- This trial is of historic interest only
- If you believe it was truly positive, was it the radiation with almost no compliance or the chemo, only completed in 1 patient?



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%

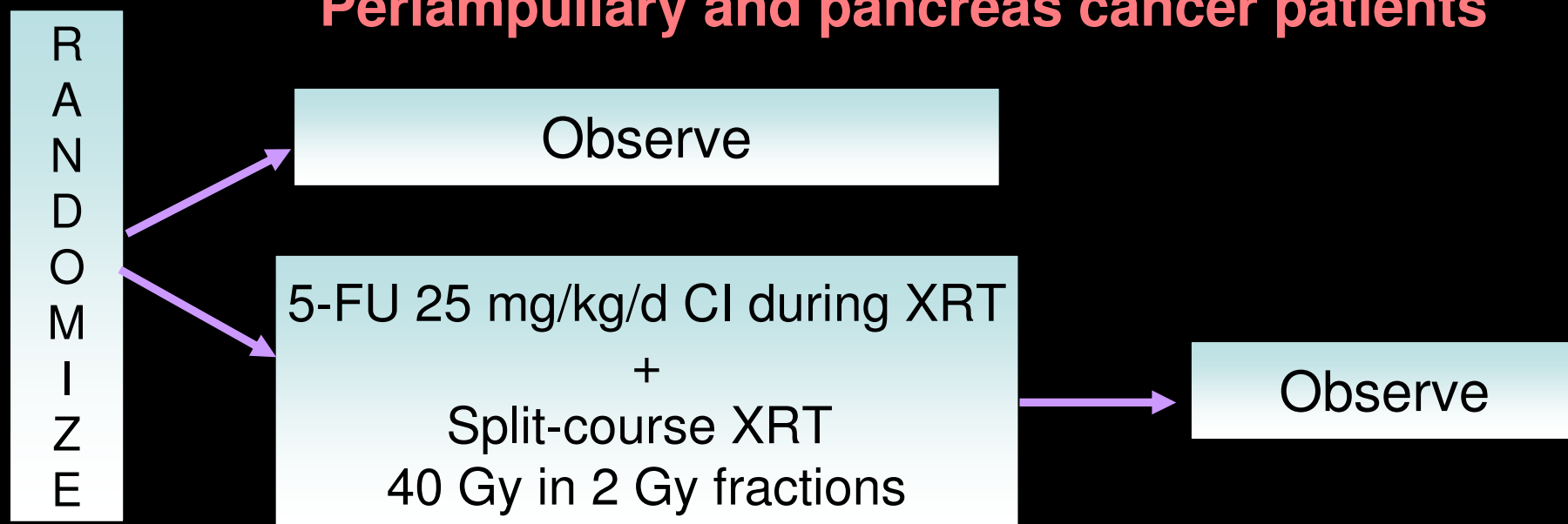
Only 24 of 30 randomized to treatment received it

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



EORTC

Periampullary and pancreas cancer patients



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 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



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?**



European Study Group for Pancreatic Cancer (ESPAC-1)

Observation	Chemotherapy	No Chemo- radiotherapy
Chemoradiotherapy	Chemoradiotherapy → Chemotherapy	Chemo- radiotherapy
No Chemotherapy	Chemotherapy	

Neoptolemos et al: Lancet 2001;358:1576-1585
Neoptolemos et al: NEJM 2004;350:1200-1210



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 vs no 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: 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**

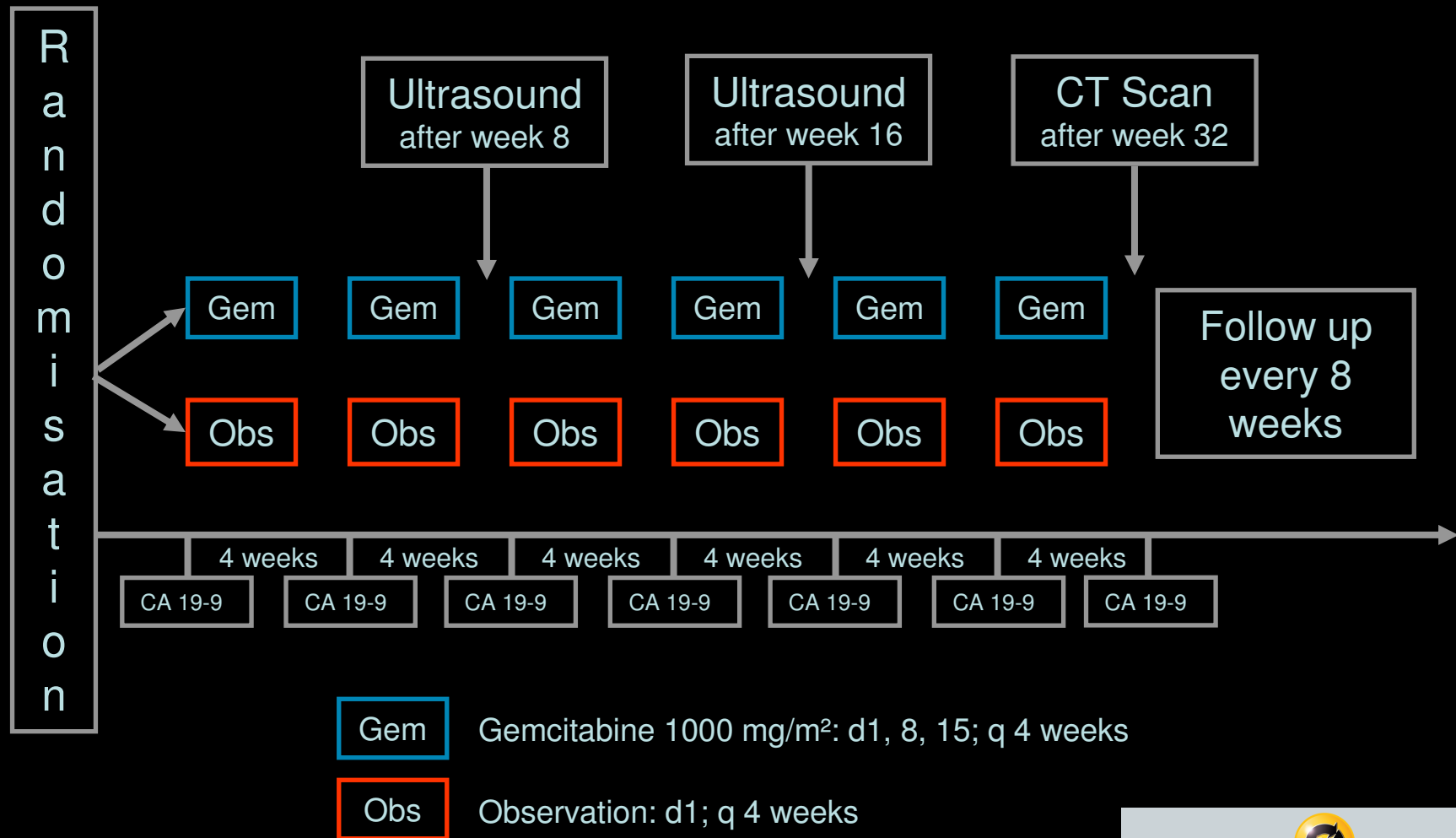
- **Of 147 patients randomized to chemotherapy** (Choti MA NEJM 350:1249-51, 2004)
 - **33% of 122 for whom data is available did not complete chemotherapy**
 - **17% of 122 for whom data is available did not receive any chemotherapy**
 - **2x2 was not powered to evaluate the individual boxes**
 - Stepwise 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**



CONKO-001: Trial Design



Oettle H, et al JAMA 297:267-77, 2007



More info on trial design

- **Intent-to-treat analysis**
 - **Primary endpoint Disease free survival**
 - **Secondary endpoint Overall survival**
- **Pre-planned “qualified” analysis**
 - **This analyzed only those patients who went through at least 1 cycle of chemo**
 - **Same endpoints**

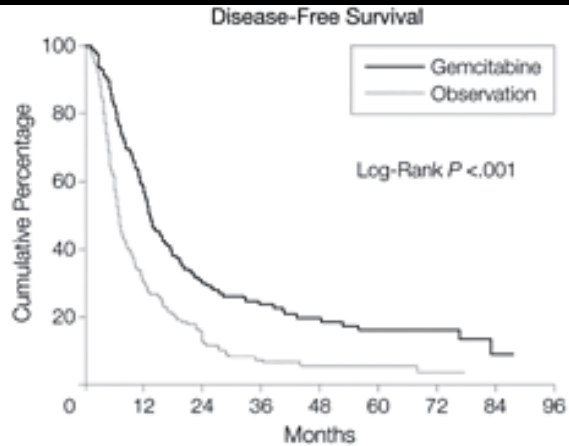


CONKO-001: Results

	Intent-to-Treat Gem vs obs	Qualified Gem vs obs
DFS (months)	13.4 vs 6.9 P < 0.001	13.7 vs 6.9 P < 0.001
Median OS (months)	22.1 vs 20.2 P = 0.06	24.2 vs 20.5 P = 0.02
5-year Survival	22.5% vs 11.5%	N/A

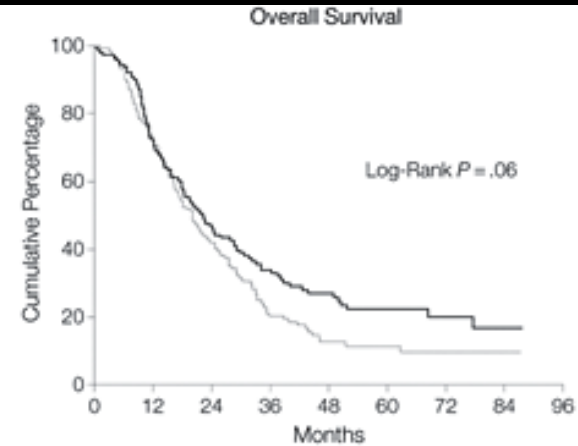


CONKO-001: DFS Curves



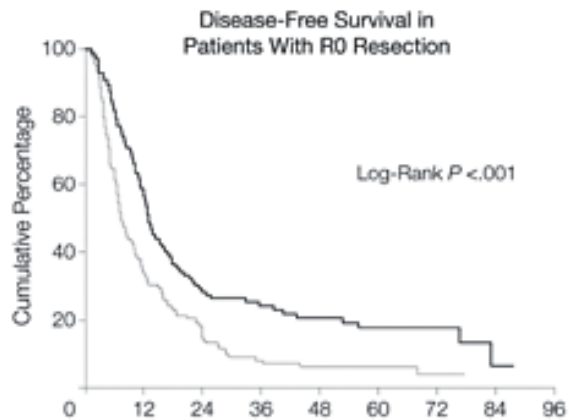
No. at Risk

Gemcitabine	179	96	43	25	17	11	8	1
Observation	175	52	24	10	6	6	2	0



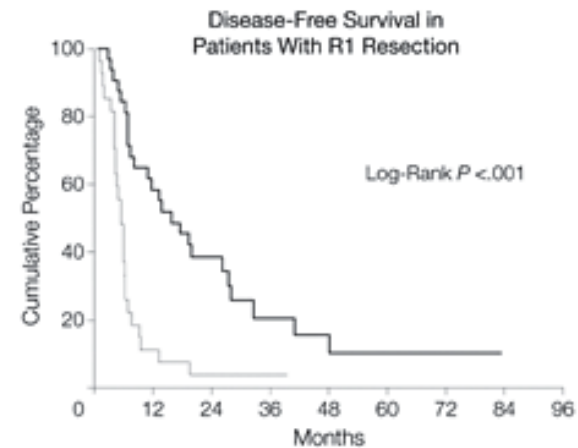
No. at Risk

Gemcitabine	179	128	73	36	23	14	9	2
Observation	175	126	64	25	12	8	4	1



No. at Risk

Gemcitabine	145	78	33	21	14	9	6	1
Observation	148	49	23	9	6	6	2	0

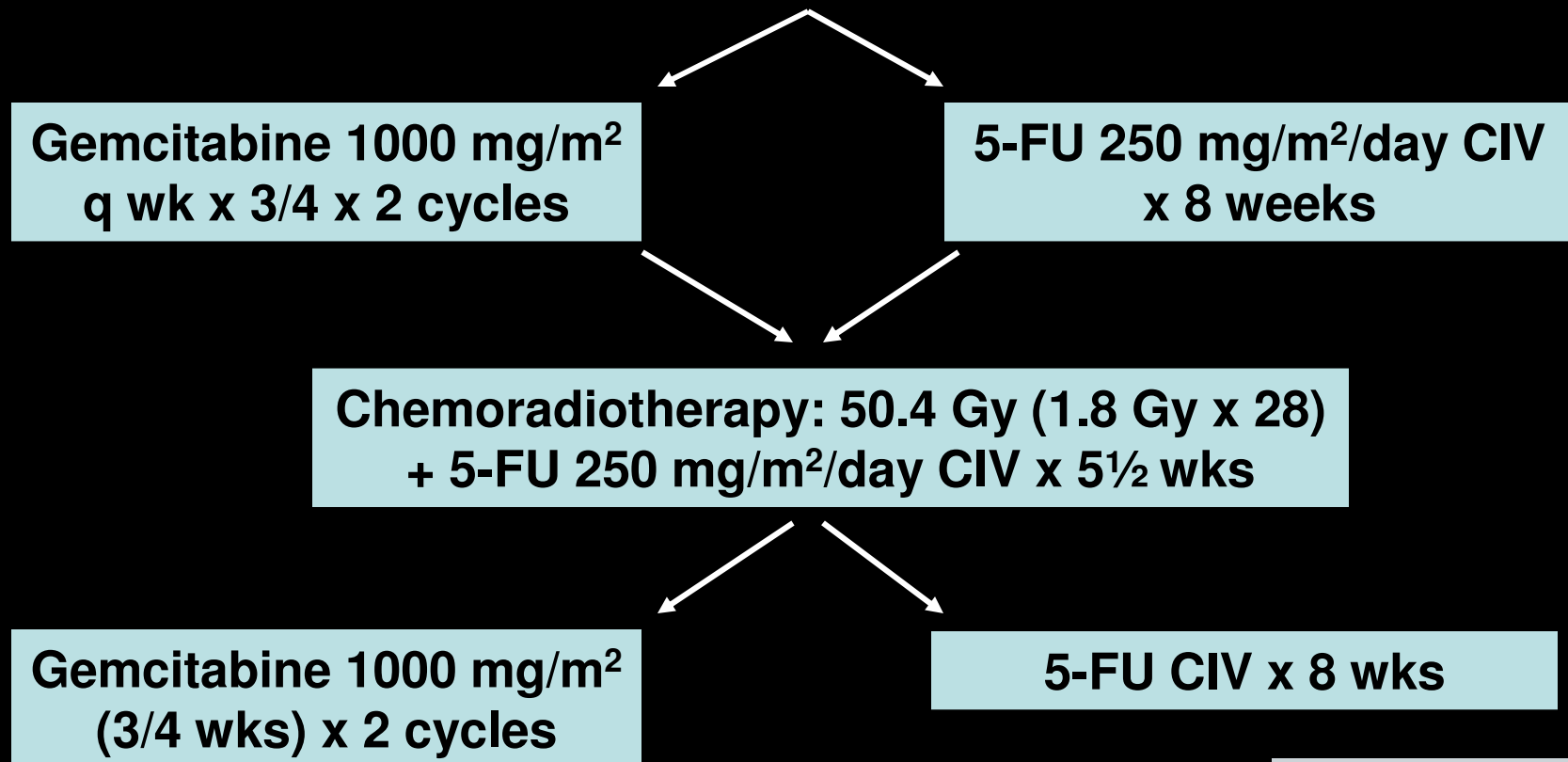


No. at Risk

Gemcitabine	34	18	10	4	2	2	2	0
Observation	27	3	1	1	0	0	0	0

RTOG 9704

Gross Total Resection Stage I-III Pancreatic Cancer



Regine et al: Proc ASCO 2006;24:180s (abst #4007)



Vanderbilt-Ingram Cancer Center

RTOG 9704 Trial

Key Study Characteristics

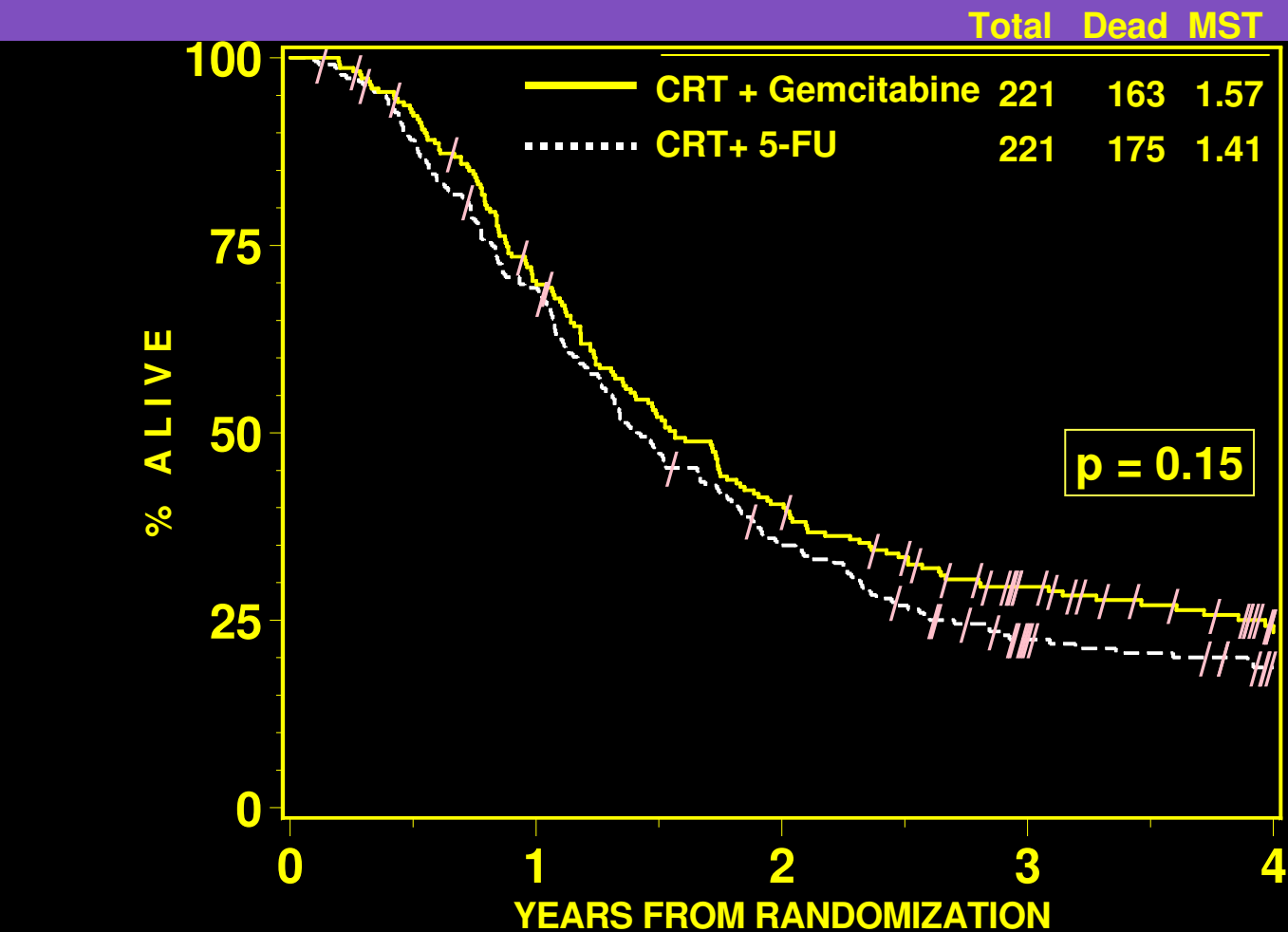
- **Primary endpoint:**
 - Survival of all patients
 - Survival in pts with pancreatic head tumors
- **Secondary endpoints: DFS, toxicity, correlation of CA19-9 with outcome**
- **Original accrual goal: 330 pts. Due to rapid accrual, goal increased to 518 pts.**
- **85% power to detect a death hazard ratio of 0.71 in the experimental arm at the 5% level of significance (2-sided) and 80% power to detect this difference in the pancreatic head group**
- **Non pancreatic head lesions: 15-20%**

Regine et al: Proc ASCO 2006;24:180s (abst #4007)



RTOG 9704

Overall Survival – All Eligible Patients



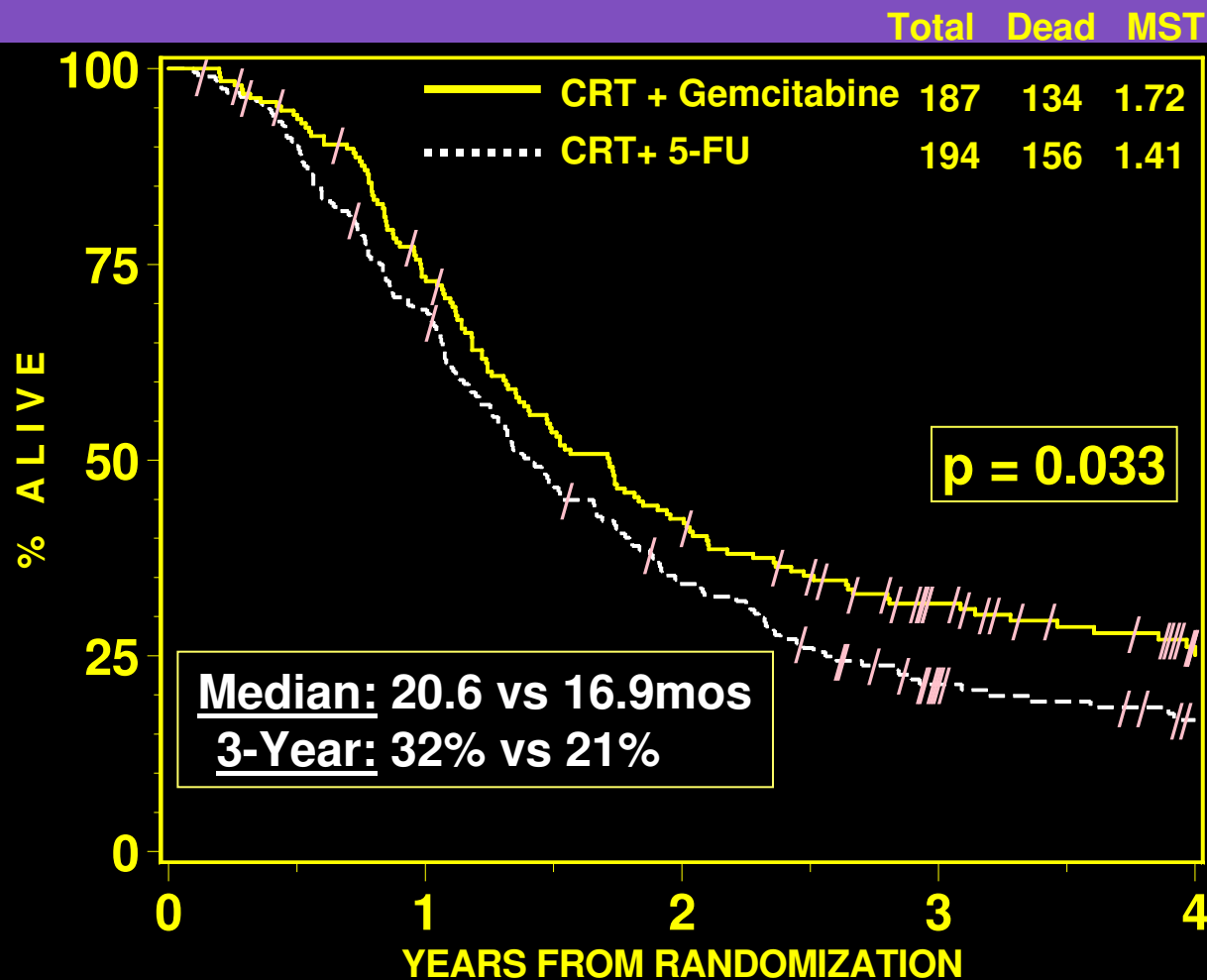
Patients at Risk

RT + GEM	221	152	87	52
RT + 5FU	221	151	74	39



RTOG 9704

Overall Survival – ‘Pancreatic Head’ Pts Only



Patients at Risk

RT + GEM	187	134	77	46
RT + 5FU	194	132	63	31

24
19

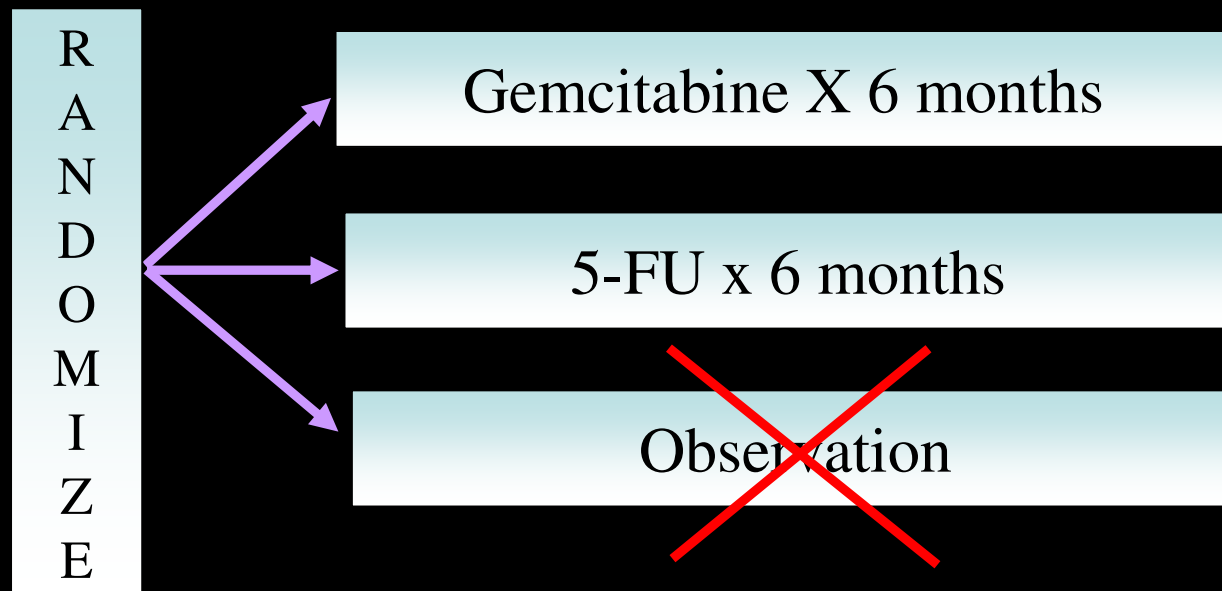


Conclusions about Phase III trials as a whole

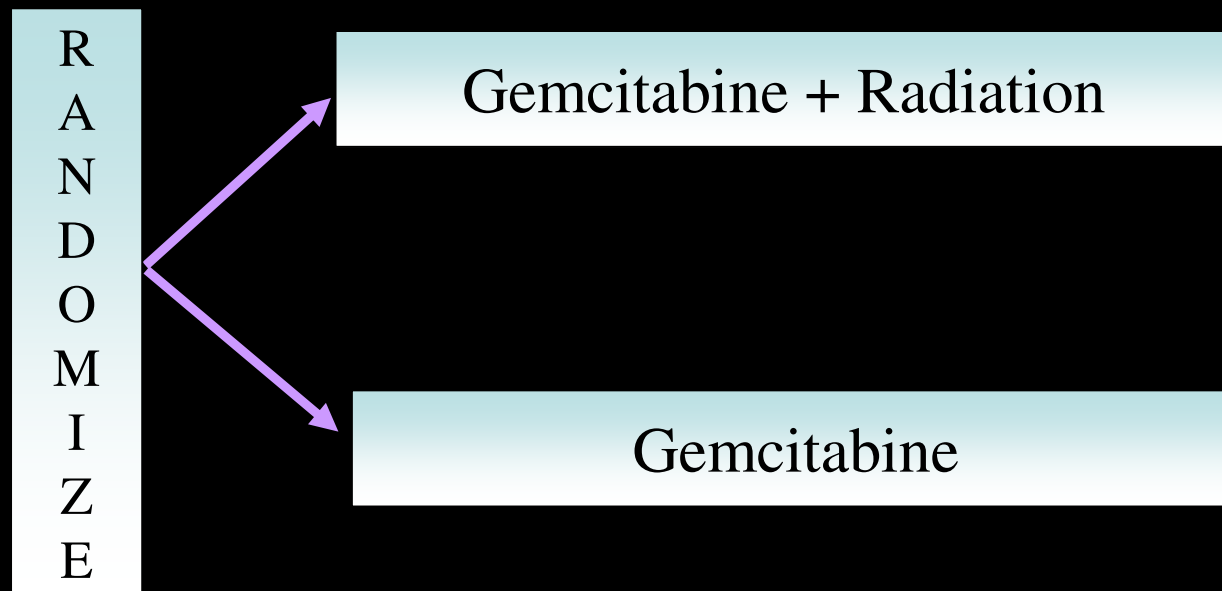
- **Two trials (ESPAC and CONK) suggest benefit from adjuvant chemotherapy**
 - Both suggest this is true for both + and – margins
- **The only trial that shows benefit to chemoradiation (GITSG) is suspect at best and was the only trial disproven by ESPAC-1**
- **R9704 definitely does not prove benefit 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

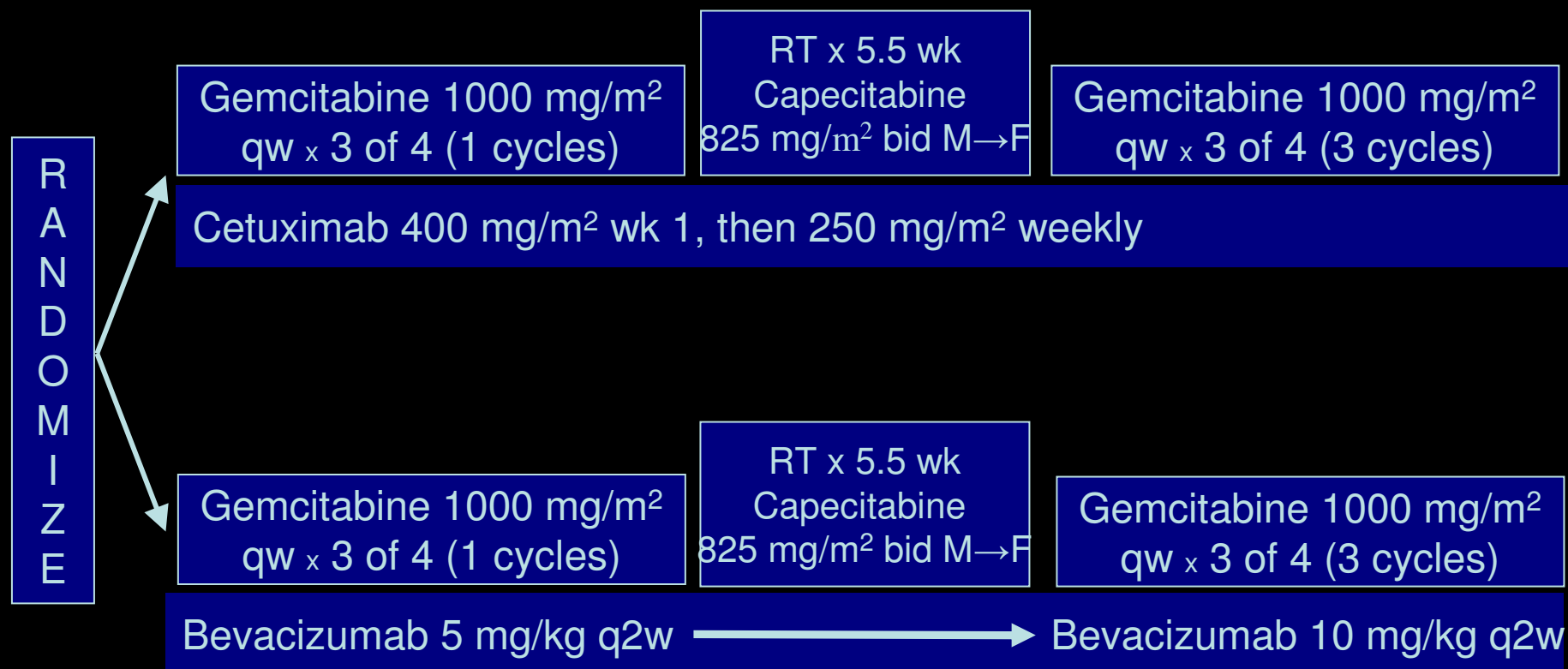


Picozzi Regimen

- **Phase II trial**
 - 43 patients
 - Treated with 54Gy XRT +
 - Cisplatin 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 but estimated ~ 6 years
 - 1,2 and 5-yr actuarial survival: 95%, 64%, and 55%, respectively
 - **Conclusion: Should be evaluated further**
 - ACOSOG trial has completed accrual. Results pending



E2204 Schema



- **R0 or R1 resection allowed; tissue requested**
- **Standardized margin definitions given**
- **Serum for TGF alpha obtained**



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 prophecy



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 results may 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**
 - **Either chemo or chemoradiation may be used in this setting**

