

# **Management of Pancreato- biliary Malignancy:**

## **Medical Oncology Perspective**

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# Medical management of pancreato-biliary cancers:

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- Pre-op chemoradiation
  - All potentially resectable tumors or only borderline resectable tumors?
- Post-operative chemoradiation after
  - R0 resection (negative margins)
  - R1 resection (microscopic positive margins)
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- Palliative chemoradiation
  - What is the role and benefit
- Chemotherapy/chemoXRT non-responders
  - Role of second and third line therapies
  - Benefits vs toxicity

# Why Consider Preoperative Therapy?

- Progress using a surgery first approach has been negligible.
  - Poor patient selection.
  - Inadequate local control. (Frequent + surgical margins, or inadequate margin assessment).
  - Leads to treatment of patients with rapidly developing metastatic disease.
  - Marginally effective systemic therapies.
- Pre-operative therapy :
  - Delivers non-surgical modalities to all eligible patients.
  - Provides early treatment of microscopic metastatic disease.
  - Provides a selection mechanism to identify patients most likely to benefit from aggressive surgical intervention.
  - Appears to increase R0 resection rates and decrease local failure rates.
  - Gives us a way to track outcomes for all patients with radiographically resectable disease.

# 20 + years of Upfront Surgery and Adjuvant therapy: Any Progress?

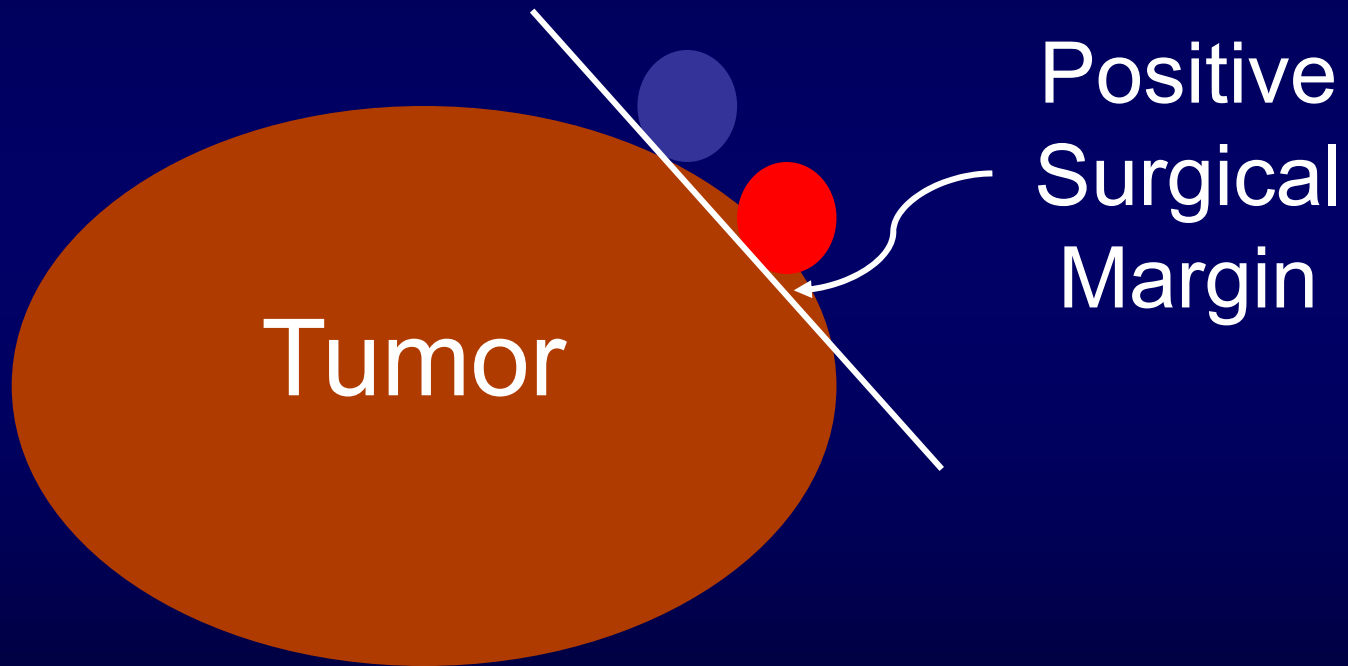
Study (Year)	Number of Patients	Enrolled Patients with R1 Resection (%)	Best Arm	p value	
GITSG (1985)	49	0	21.0	0.035	
EORTC 40891 (1999, 2008)	114*	21	17.1	0.09	Local Failure 34%
ESPAC-1 (2004)	289	18	20.1	0.009	Local Failure 60%
RTOG 9704 (2008)	388+	34	20.5	0.09	Local Failure 25%
CONKO 001 (2008)	368	16	22.8	0.005	Local Failure > 35%

# Pre-Operative Therapy Selects Patients Better than Upfront Surgery

- Avoids surgery in patients with rapidly progressive disease (unfavorable tumor biology).
- Avoids surgery in patients unable to tolerate the stress
- Surgery was avoided in 25-35% of the patients; their median survival was 7-10 mo.
- Local failure occurred in 10-25% of patients undergoing resection; suggesting radiation may have a role in preoperative setting.

MDA	Gem/Cis	90	66%	31 mo
01-341 <sup>^</sup>	Gem/XRT			

# Borderline Resectable Pancreatic Cancer

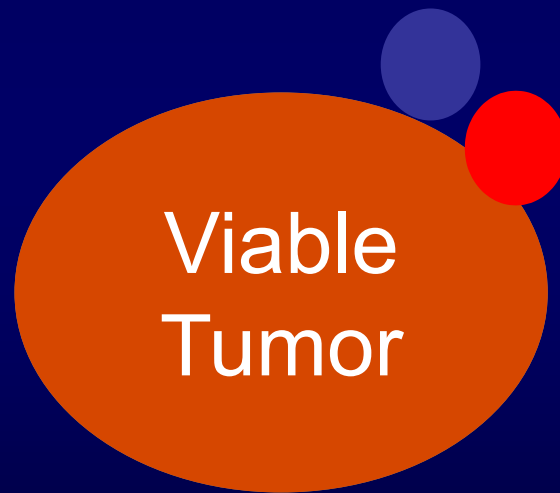


DOOM!!!!!!!!!!!!

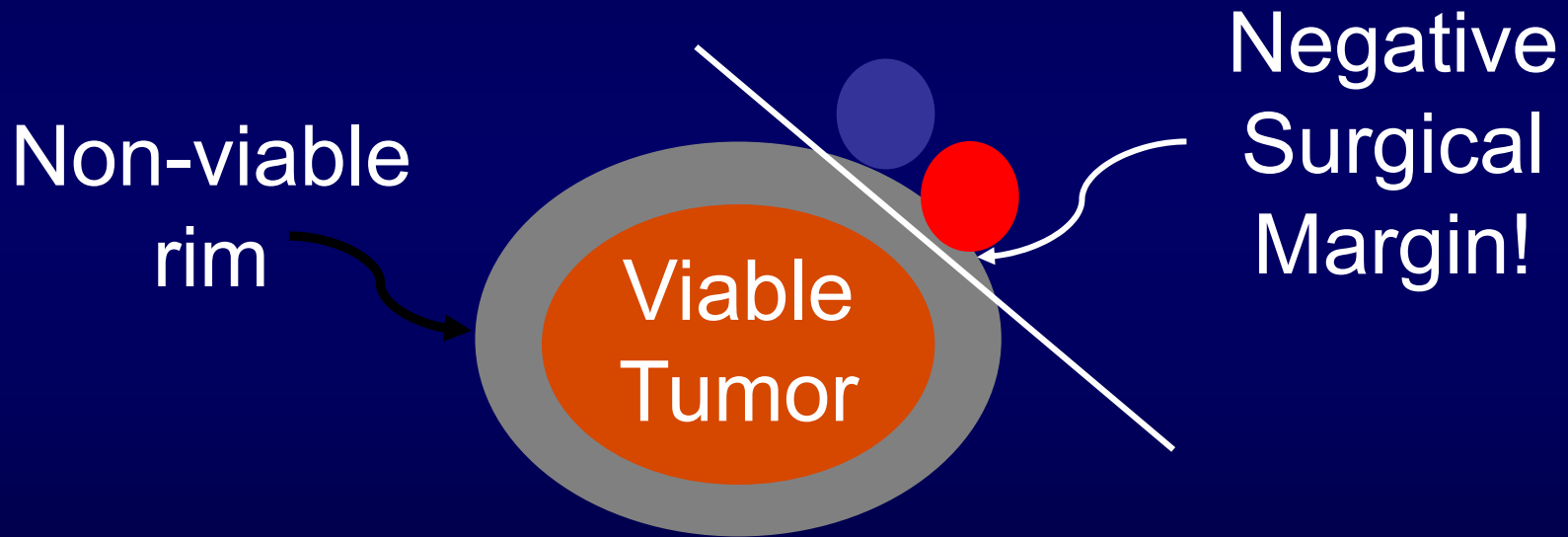
## Margin + Resections are Frequent and Associated with Poor Prognosis

<b>Author - Country</b>	<b>Number of Patients</b>	<b>Margin + Resection Rate</b>	<b>Median Survival</b>	<b>Independent Prognostic Factor</b>
Winter-U.S.	1175	42%	14 m	Yes
Richter-Germany	194	37%	12 m	Yes
Kuhlmann-Netherlands	160	50%	NS	Yes
Takai-Japan	89	47%	8 m	Yes

# Borderline Resectable Pancreatic Cancer



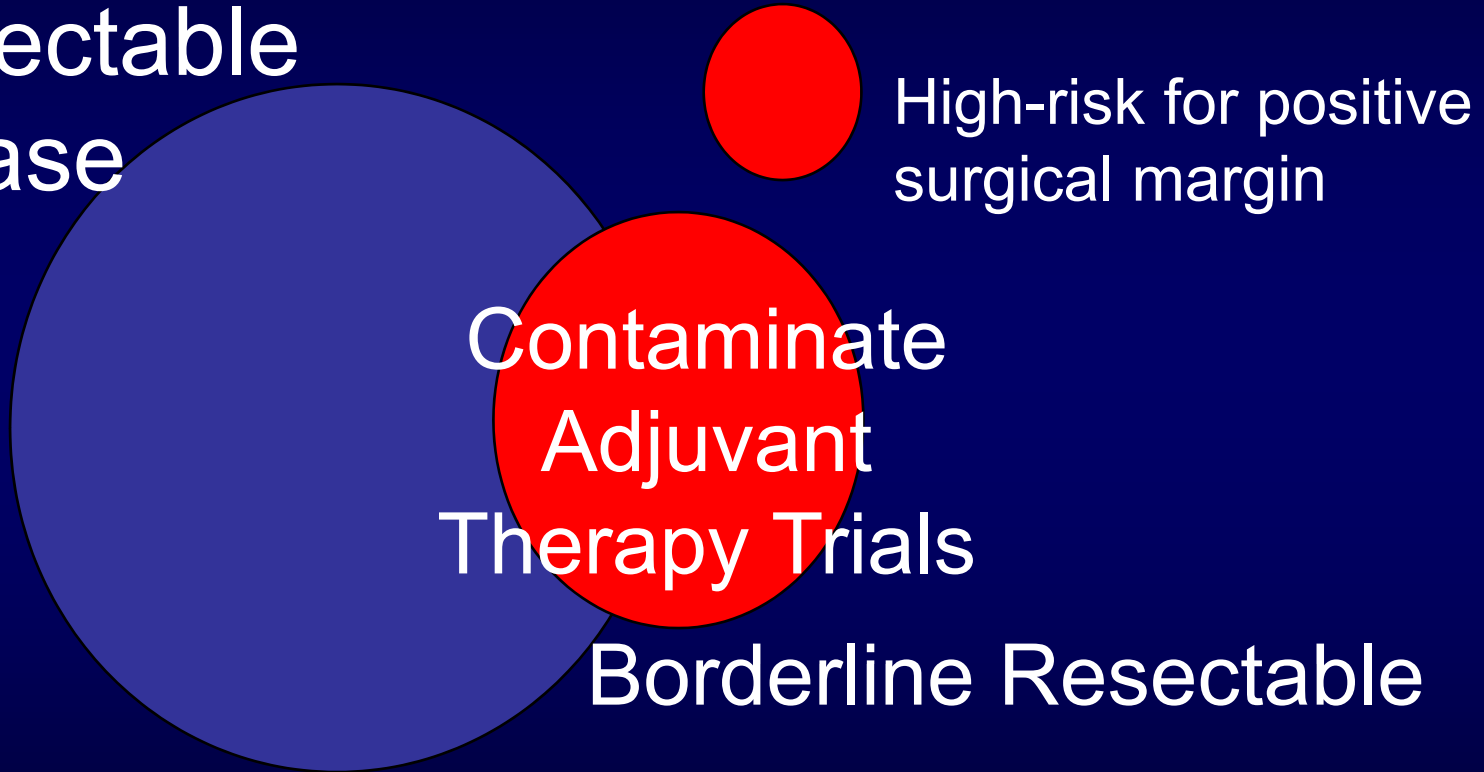
# After Preoperative Chemotherapy and ChemoXRT



YIPPEE!!!!

# MDACC View of “Localized Disease”

Truly resectable  
disease



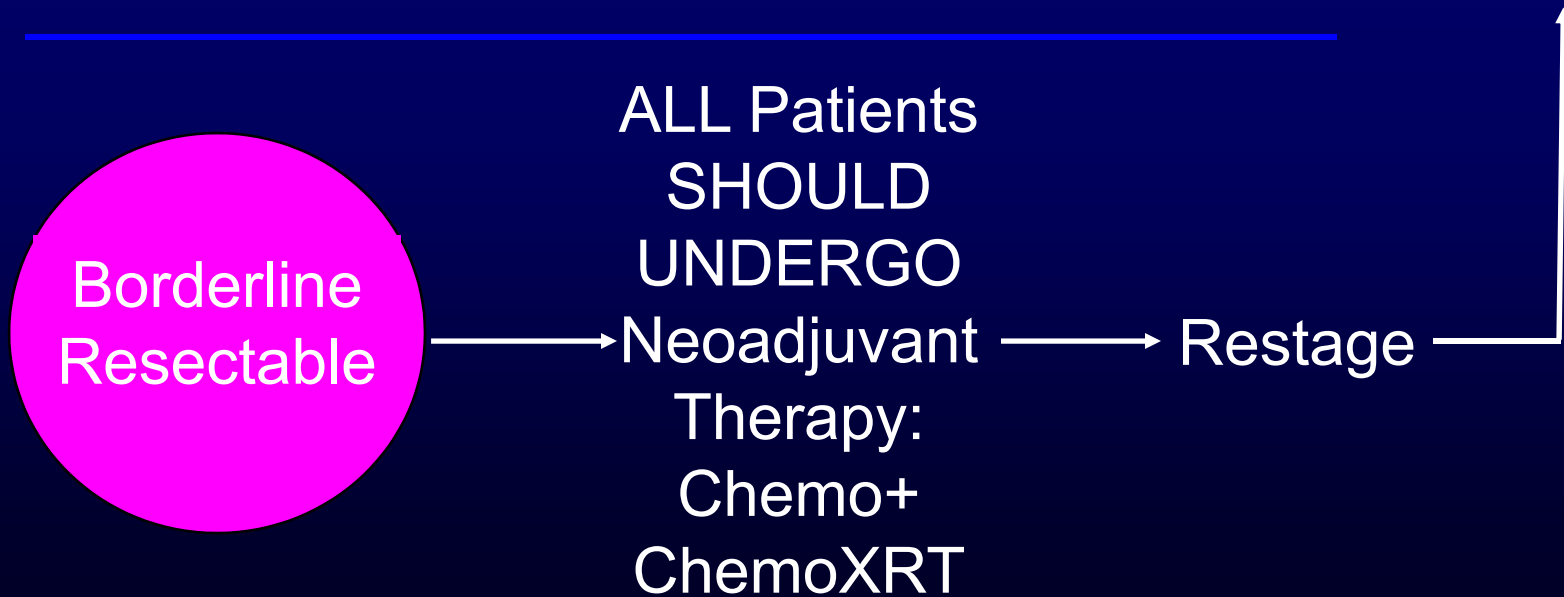
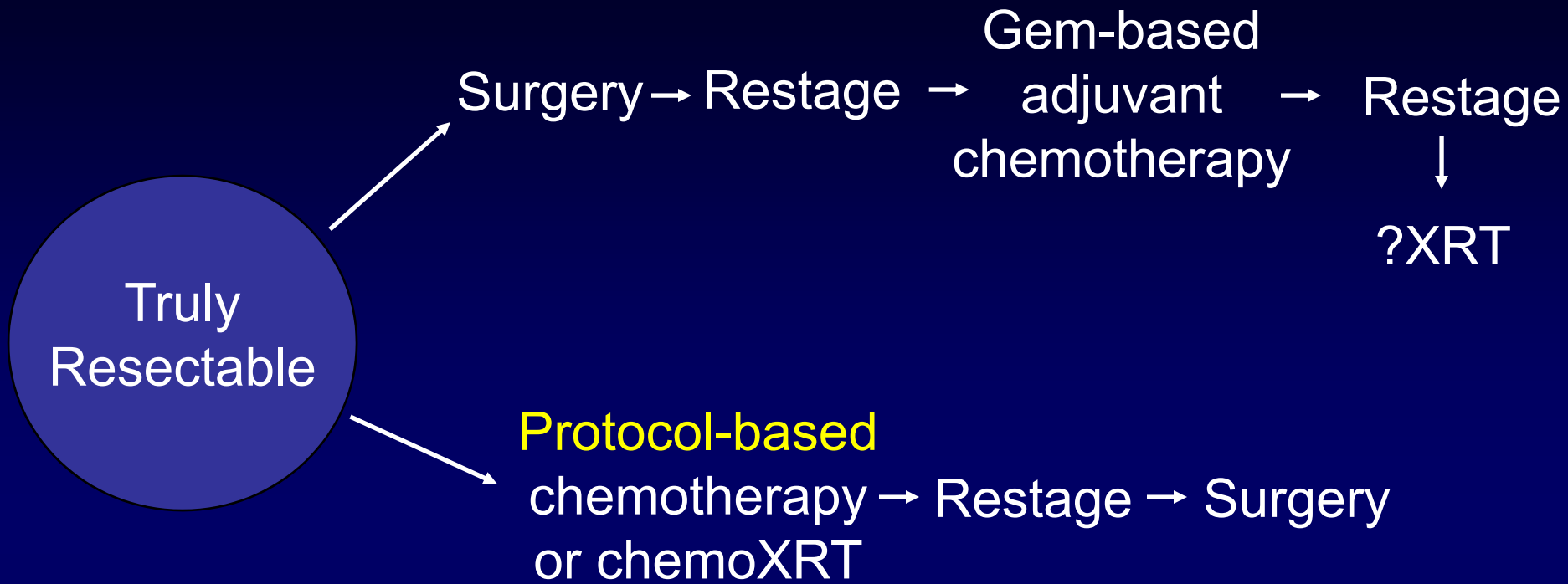
# Staging with High-Quality CT imaging

Resectable Disease

Borderline Resectable

Adjuvant trials in pancreatic cancer have not mandated high-quality preoperative CT imaging nor specified radiographic criteria for resectability!!!!

Higher rate of margin negative resections for both groups of patients!!!



# Medical management of pancreato-biliary cancers:

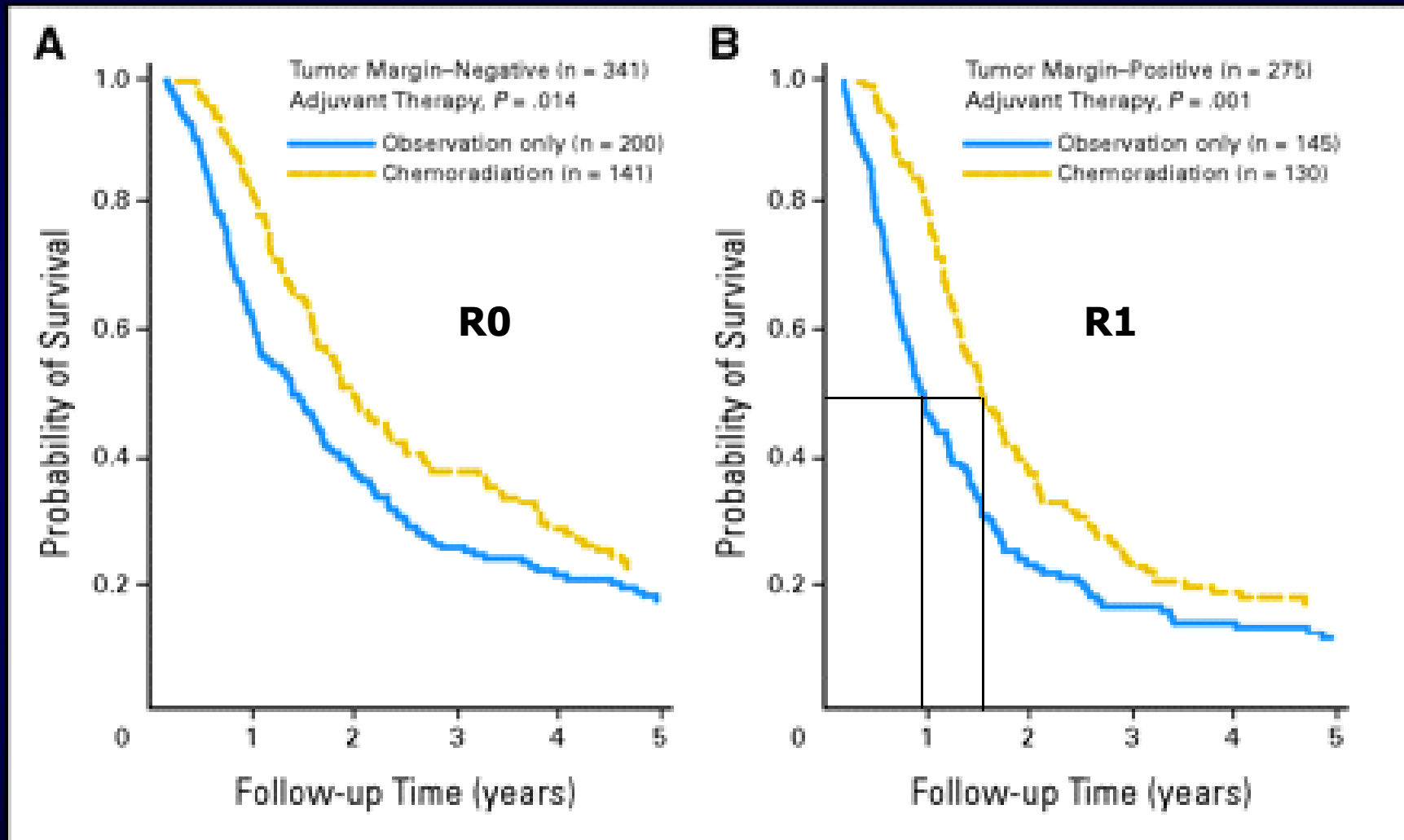
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# Evidence Regarding Post-operative 5-FU-based Chemoradiation (CXRT) for resected pancreatic cancer

Institution	Time Period	# Patients	Median survival CXRT	Median survival No CXRT	P-value
Mayo Clinic	1975-2005	466 (R0)	25.2 Mo	19.2 Mo	0.001
Johns Hopkins Hospital	1993-2005	616 (R0 + R1)	21.4 Mo	14.4 Mo	<0.001

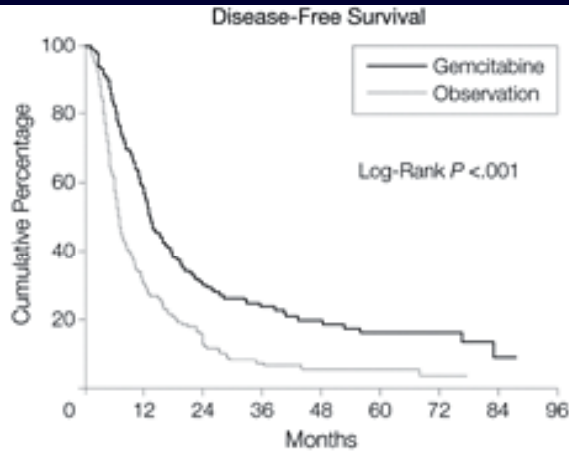
# Hopkins Retrospective Data Adjuvant ChemoXRT vs Obs



# Randomized Trials of Adjuvant Therapy

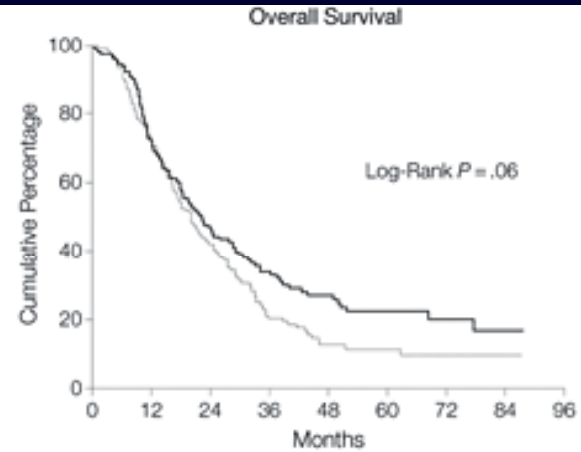
Study (Year)	Number of Patients	Enrolled Patients with R1 Resection (%)	Treatment Assignment Median Survival Months	Treatment Assignment Median Survival Months	p value
GITSG (1985)	49	0	5-FU-based Chemoradiation 21.0	Observation 10.9	0.035
EORTC 40891 (1999)	114*	21	5-FU-based Chemoradiation 17.1	Observation 12.6	0.09
ESPAC-1 (2004)	289	18	5-FU/Leucovorin Chemotherapy 20.1	No Chemotherapy 15.5	0.009
			5-FU-based Chemoradiation 15.9	No Chemoradiation 17.9	0.05
RTOG 9704 (2006)	388 (Head lesions)	34 Unknown in 25%	Gemcitabine then 5-FU/EBRT then Gemcitabine 20.5	5-FU then 5-FU/EBRT then 5-FU 16.9	0.09
CONKO 001 (2007)	368	19	Gemcitabine 22.8	Observation 20.2	0.005
			<del>DFS = 13.4</del>	DFS = 6.9	< 0.001

# CONKO 001: Gemcitabine vs Observation



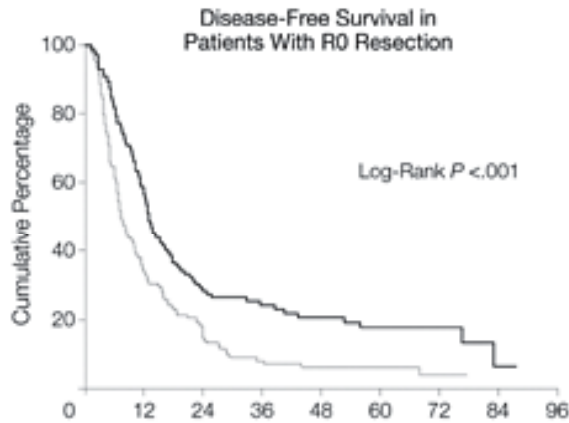
No. at Risk

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



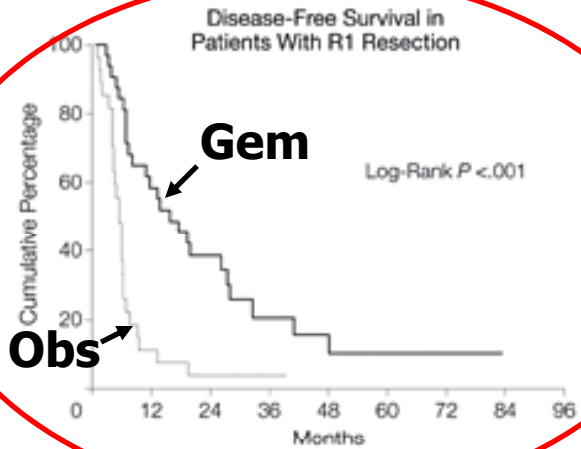
No. at Risk

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



No. at Risk

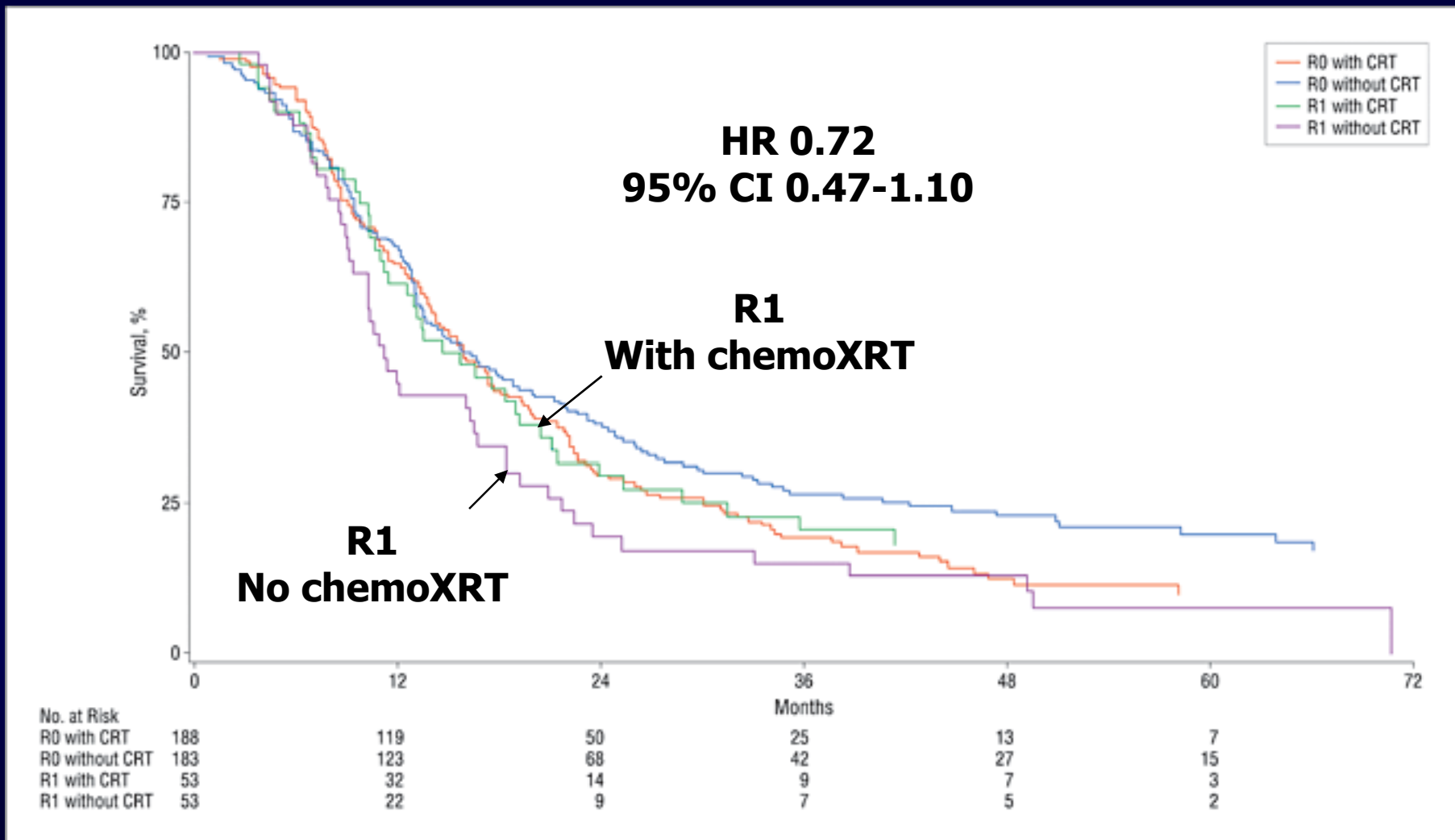
Gemcitabine	145	78	33	21	14	9	6	1
Observation	148	49	23	9	6	6	2	0



No. at Risk

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

# Meta-Analysis of Adjuvant Trials



## So What Should We Do?

- Use high-quality dual phase helical CT imaging to identify patients with truly resectable disease.
  - Patients with a very good chance of having an R0 resection and low probability of R1.
- Assess patients post-operatively for recovery.
  - Restage patient prior to initiating adjuvant therapy with CT imaging +/- CA19-9 level.
  - Tell them whether it is adjuvant therapy or not.
- Deliver systemic therapy (gemcitabine-based) for a few months, restage, and if R1 resection, consider chemoXRT.

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## Palliative chemoradiation

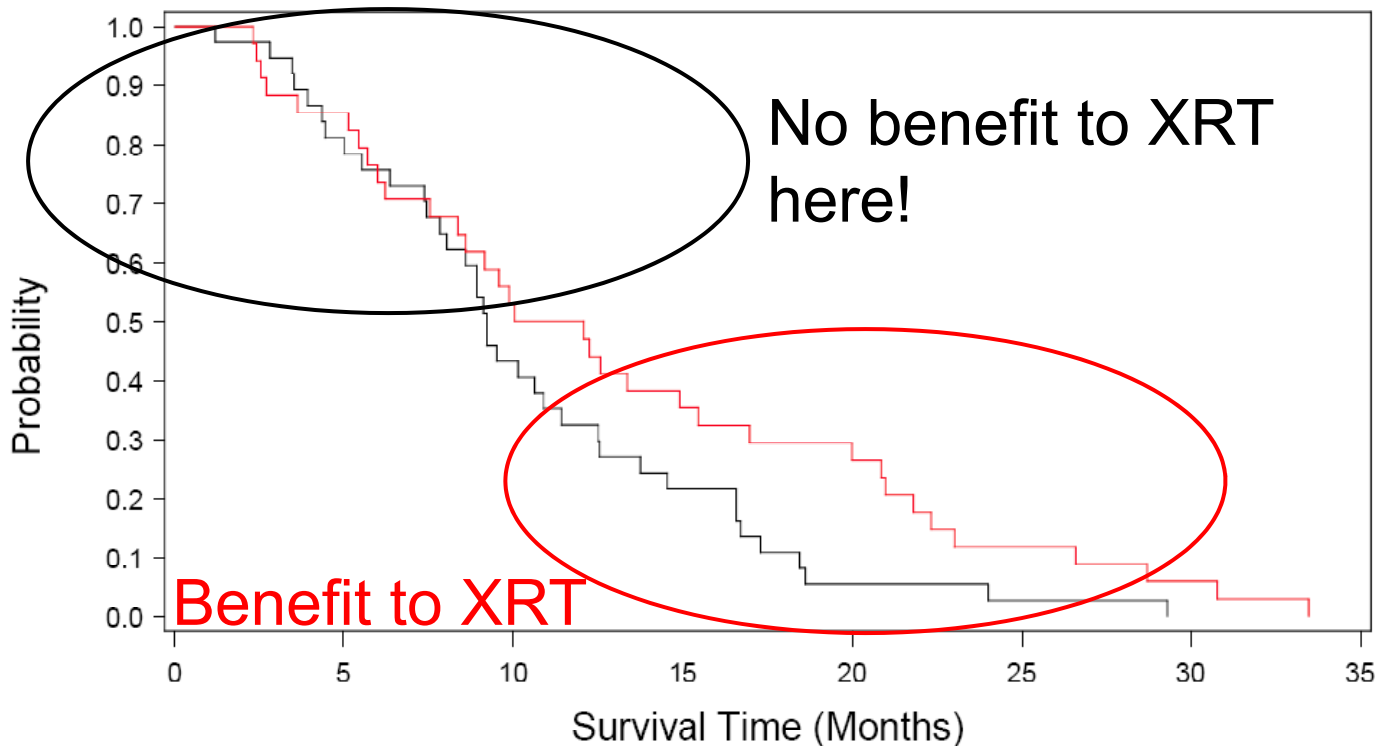
– What is the role and benefit?

- Improve pain
- May provide a survival benefit in patients with good biology

# ECOG 4201: Radiation plus gemcitabine versus gemcitabine alone for patients with locally advanced pancreatic cancer.

## Overall Survival

Figure 1. Overall Survival by Treatment Arm - E4201



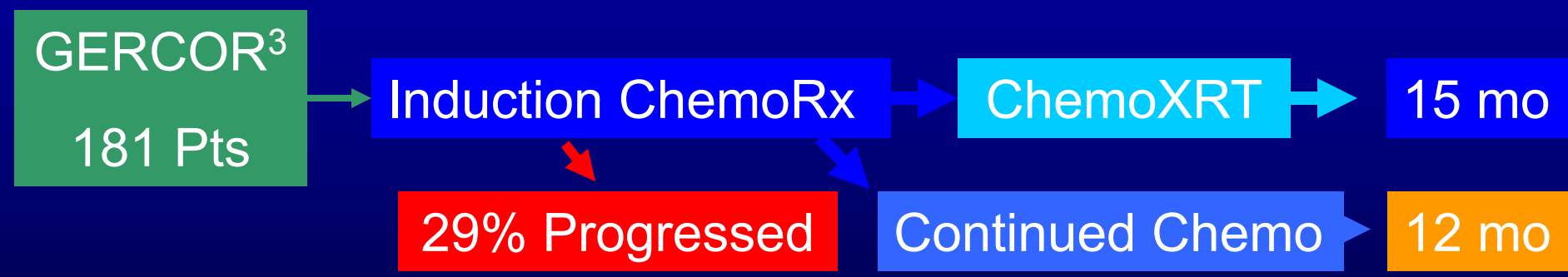
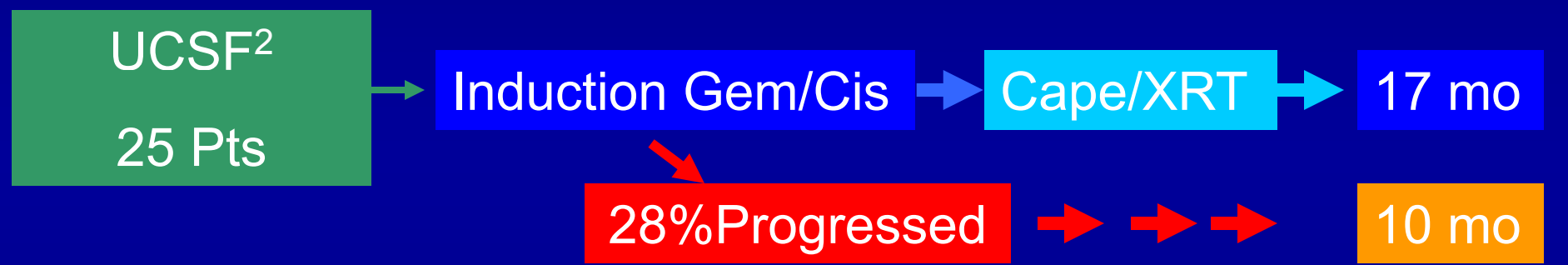
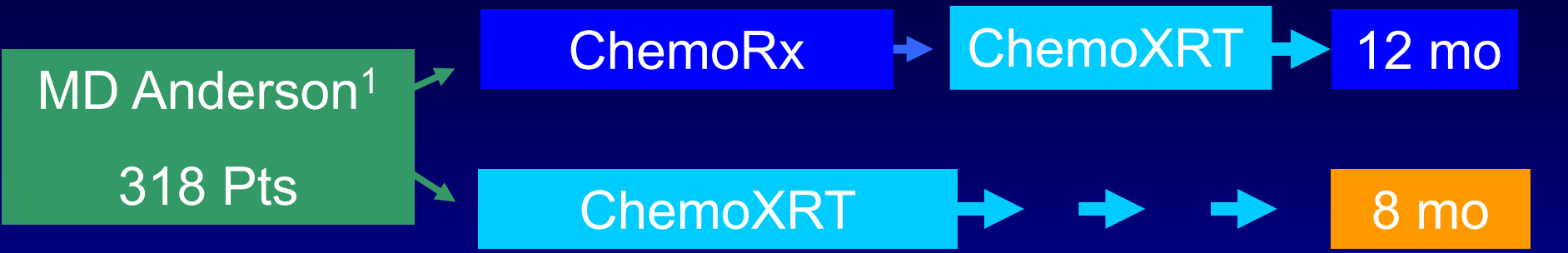
**GEM: Median Survival 9.2 Months (95% CI [7.8, 11.4])** -----

**GEM + Radiation: Median Survival 11.0 Months (95% CI [8.4, 15.5])** - - - - -

# Selection Mechanism

## Tumor behavior (Favorable vs Poor)

- ECOG 4201 demonstrates local control is only relevant in patients with favorable biology.
- In locally advanced disease, chemotherapy can identify patients with poor tumor biology and spare them radiation (unlikely to be effective).

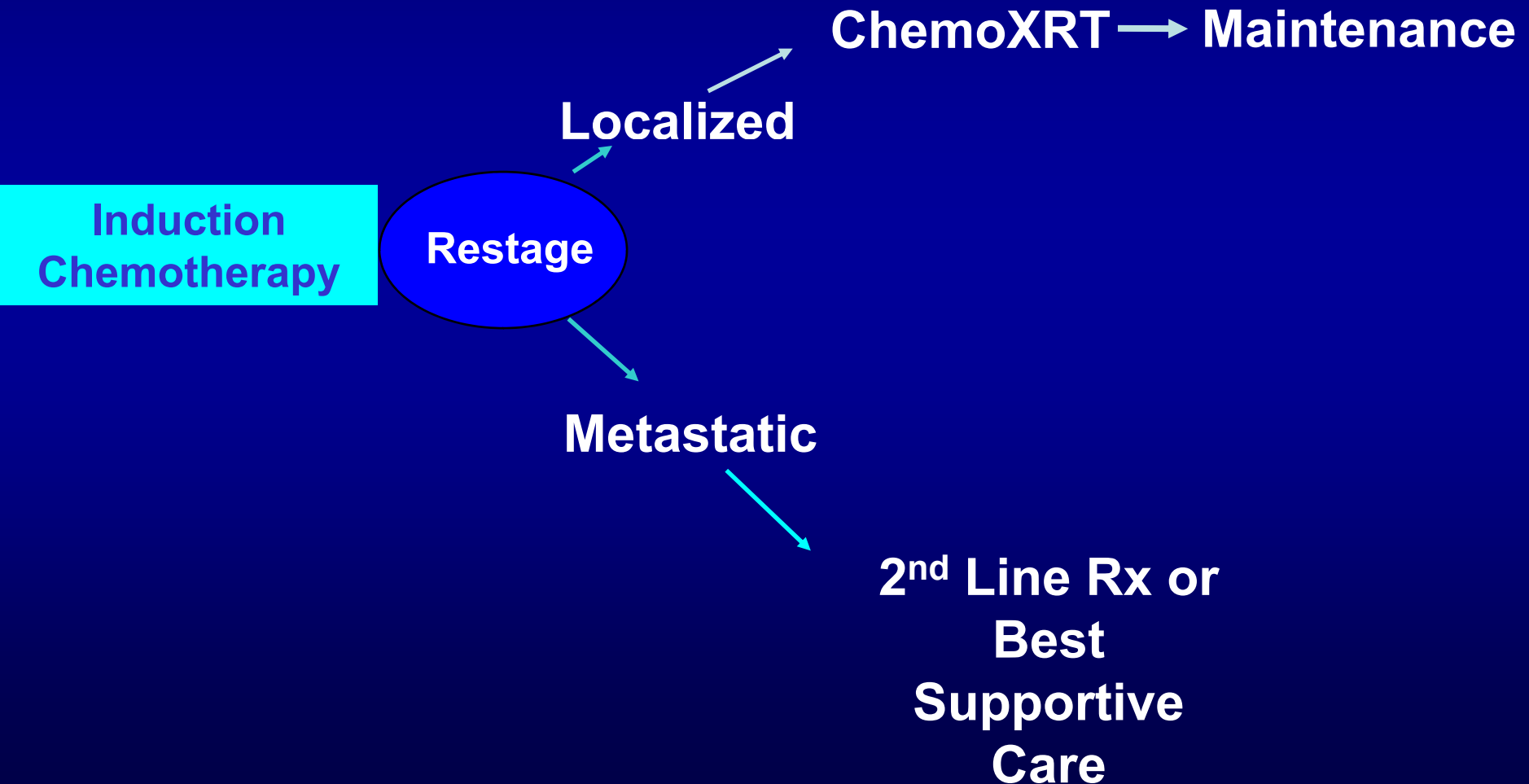


<sup>1</sup>Krishnan S et al. *Cancer*, 2007

<sup>2</sup>Ko A et al. *Int J Rad Oncol Biol Phys*, 2007

<sup>3</sup>Huguet F et al. *JCO*, 2007

# ***Emerging Strategies* for Locally advanced pancreatic cancer**



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- Oxaliplatin, 5FU, Folinic acid "OFF" improves survival over 5FU + Folinic acid in gem failures\*
  - OFF had a median OS of 26 weeks
  - FF had a median OS of 13 weeks
- XELOX after gem failure has median survival of 23 weeks. Most benefit conferred on patients with prior response to chemotherapy.+

\*Pelzer U, et al. ASCO, 2008

+Xiong HQ, et al. Cancer, 2008