

## Neoadjuvant Therapy in the Management of GI Tract Cancers

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## Objectives

- List at least 3 clinical and biologic reasons for administering therapy in the neoadjuvant setting
- Identify the gastrointestinal malignancies for which studies unequivocally support the use of chemotherapy, radiation, or both in the neoadjuvant setting
- Describe other GI malignancies for which the use of neoadjuvant therapy has been evaluated but remains controversial or unproven

## Definition of neoadjuvant therapy

- Per National Cancer Institute:

“Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given... includ(ing) chemotherapy, radiation therapy, and hormone therapy.”

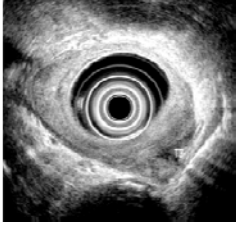
## Neoadjuvant therapy: pros and cons

POTENTIAL ADVANTAGES	POTENTIAL DISADVANTAGES
Earlier eradication of occult metastatic disease	Delay of potentially curative operation
No need to wait for postoperative recovery	Major treatment-associated side effects may weaken patient's condition prior to surgery
Primary lesion still present and evaluable	Obscuring accurate surgical pathologic staging
Downstaging/downsizing of tumor	
Previously undetectable metastases may become evident, sparing some patients from undergoing unnecessary operation	

## Case presentation #1

- A 60 year old man with longstanding reflux symptoms has progressive dysphagia symptoms over the past 3 months, and is found on upper endoscopy to have a distal esophageal tumor extending into the gastroesophageal (GE) junction. Biopsy reveals a well-differentiated adenocarcinoma.

Case presentation #1 (cont'd)



Further staging workup includes an endoscopic ultrasound, suggesting a T3 lesion with some enlarged peri-esophageal lymph nodes; and a CT/PET which does not reveal any distant metastases.

(Audience response question – case #1)

What do you recommend for initial therapy?

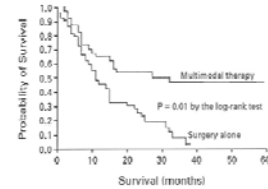
- A. Surgery (Ivor-Lewis resection)
- B. Cisplatin/infusional 5-FU x 2 cycles
- C. Radiation (5,040 cGy) over 5.5 weeks
- D. Radiation plus concurrent low-dose weekly carboplatin/paclitaxel

Esophageal and gastroesophageal cancer

- Mounting evidence supports the use of neoadjuvant therapy prior to surgical resection
- Trimodality therapy (chemoRT → surg) vs. preoperative chemotherapy alone?
- Lump or split?: esophageal ↔ GE junction ↔ gastric cancer
- GE junction/distal esophageal adenocarcinomas significantly increasing in the U.S. – esp. amongst Caucasian males (Cook, Chow, and Devesa, *Br J Cancer* 2009;101:855)

A comparison of multimodal therapy (CDDP/5-FU/XRT x 2 cycles → surgery) vs. surgery alone for esophageal adenocarcinoma (Walsh, *NEJM* 1996; 335:462-7)

- Median survival difference = 16 vs. 11 months (p=0.01)
- 3-yr survival 32 vs. 6%
- Criticisms:
  - Small sample size (113 evaluable patients)
  - Insufficient staging methods (no EUS) -- ? imbalance in treatment arms
  - Much poorer than expected outcomes in surgery-only arm



CALGB 9871

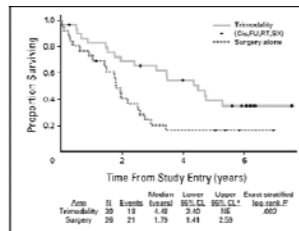
(Tepper, J. et al. *J Clin Oncol*; 26:1086, 2008)

Preop regimen: Cisplatin + 5-FU (2 cycles) + concurrent XRT 5,040 cGy

- 475 patients planned; only 56 enrolled

- Despite small sample size, significant improvements in median survival (4.5 vs. 1.8 years), 5-yr survival (39% vs. 16%), and median PFS (3.5 vs. 1 yr)

- 10/25 patients receiving preop chemoXRT had path C.R.



The CROSS trial: moving away from cisplatin/5-FU

Chemoradiation regimen

- XRT 41.4 Gy over 23 fractions (1.8 G/fx)
- Carboplatin (AUC 2) + paclitaxel (50 mg/m2) weekly x 5 concurrent with RT

	Surgery alone	CRT + surgery
N	188	175
R0 resection rate	67%	92.3%
Path complete response	N/A	32%
Med survival	26 months	49 months
1-year survival	70%	82%
3-year survival	48%	59%
Anastomotic leakage	25%	22%
In-hospital mortality	3.8%	3.4%

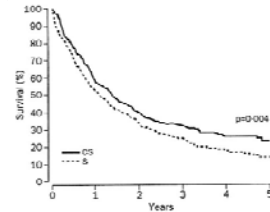
Gaast, *J Clin Oncol* 28, 2010 (suppl; abstr 4004)

Summary of neoadjuvant chemoRT studies in esophageal/GEJ cancer

Author	# patients (multimodality/ surgery alone)	Preop regimen	Overall survival diff? (median)
Walsh, 1996	58/55 (adenoca only)	CDDP/5-FU + XRT	Yes (16 vs. 11 months)
Urba, 2001	50/50	CDDP/5-FU/ vinblastine + XRT	No (16.9 vs. 17.6 months)
Burmeister, 2005	128/128	CDDP/5-FU + XRT	No (21.7 vs. 18.5 months)
Tepper, 2008 CALGB 9871	30/26	CDDP/5-FU + XRT	Yes (4.5 vs. 1.8 years)
Gaast, 2010 CROSS	175/188	Carboplatin/ paclitaxel + RT	Yes (49 vs. 26 months)

What about preoperative chemotherapy alone?: Medical Research Council Oesophageal Cancer Working Party (*Lancet* 359:1727-33, 2002)

- Largest randomized study to date: 802 patients (both adenoca and SCC)
- Multimodal arm: preop chemo = CDDP/5-FU C.I. X 2 cycles → surgery
- 9% of patients also received XRT
- Median survival difference 16.8 vs. 13.3 months



Summary of neoadjuvant chemo alone (no RT) studies in esophageal/GEJ cancer

Author	# patients (multimodality/ surgery alone)	Preop regimen	Overall survival diff? (median)
Kelsen, 1998 (INT 0113)	213/227	CDDP/5-FU	No (14.9 vs. 16.1 months)
MRC Oesophageal Cancer Working Party, 2002	400/402	CDDP/5-FU	Yes (16.8 vs. 13.3 months)
ACCORD07/FFCD 9703	113/111	CDDP/5-FU	Yes (5 yr surv rate, 38 vs. 24%)

Meta-analysis: survival benefit from neoadjuvant chemoradiation vs. chemotherapy

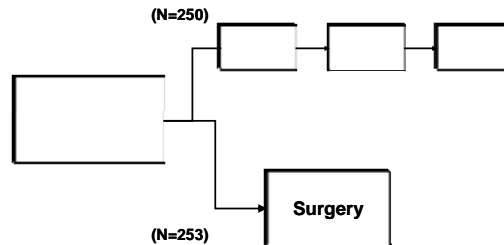
	NEOADJUV CHEMOXRT	NEOADJUV CHEMO
Number	10 studies, total n = 1209	8 studies, total n = 1724
HR for all-cause mortality	0.81 (p=0.002)	0.90 (p=0.05)
Absolute survival difference at 2 years	13%	7%
Comments	Similar results for SCC and AC	Benefit only in AC, not SCC

Gebski, *Lancet Oncol* 2007; 8:226-34.

Pathologic response to preoperative chemo/chemoRT

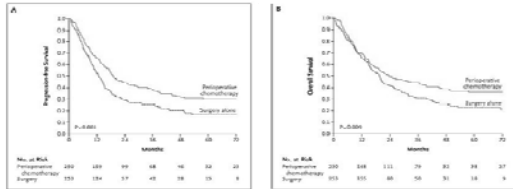
Study	Preop regimen	Pathologic C.R.
<b>CHEMORT</b>		
Walsh, 1996	CDDP/5-FU + XRT	25%
Bosset, 1997	CDDP + XRT	26%
Urba, 2001	CDDP/5-FU/ vinblastine + XRT	28%
CALGB 8741	CDDP/5-FU + XRT	40%
<b>CHEMO ALONE</b>		
Kelsen, 1998 (INT 0113)	CDDP/5-FU	2.5%
MRC Oesophageal Cancer Working Party, 2002	CDDP/5-FU	4%
ACCORD07/FFCD 9703	CDDP/5-FU	< 3%

What about true gastric cancers: the MAGIC study demonstrates a therapeutic alternative to postoperative 5-FU-based chemoRT



Cunningham et al. *N Engl J Med.* 355:11, 2006.

MAGIC trial demonstrates survival benefit of perioperative chemotherapy for resectable gastric cancer  
(Cunningham et al, *N Engl J Med* 2006, 355:11)



Progression-free survival  
HR 0.66 (p<0.001)

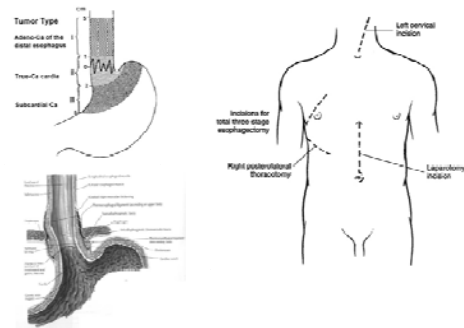
Overall survival  
HR 0.75 (p=0.009)  
5 yr survival **36.3%** vs.  
**23.0%**



MAGIC trial: additional points to note...

- One-third of patients assigned to perioperative ECF **did not** receive any of the planned postoperative chemotherapy
- Patients assigned to perioperative chemotherapy had smaller tumors at surgery (T1-2) and less advanced nodal disease (N0-1), suggesting downstaging with initial chemotherapy
- No differences in perioperative complication rate vs. patients undergoing surgery alone

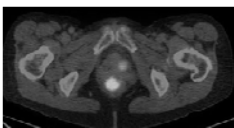
Where do **GE junction tumors** fit in classification schemes?



Case presentation #2

- A 48 year old gentleman with unremarkable past medical history reports a 6-month history of intermittent bright red blood per rectum. In recent months he also noted a thinner caliber to his stools (which he describes as "pencil-like") and mild pelvic discomfort.
- Laboratory studies indicate an iron deficiency anemia, with a Hct of 34%. A colonoscopy reveals a partially obstructing mass in the rectum, approximately 7 cm from the anal verge, biopsy-proven to represent a well-differentiated adenocarcinoma.

Case presentation #2 (cont'd)



- Endorectal ultrasound confirms a mid-rectal mass extending through the muscularis with enlarged perirectal lymph nodes.
- CT/PET demonstrates FDG-avidity of the rectal mass with no evidence of distant metastases.

(Audience response question – case #2)

What do you propose as the first step of this patient's treatment?

- Sphincter-sparing operation (low anterior resection), if possible
- Short-course radiation (25 Gy over 5 days)
- mFOLFOX chemotherapy for 4-6 cycles
- Radiation (5,040 cGy) over 6 weeks with concurrent infusional 5-FU

### Neoadjuvant therapy for rectal cancer

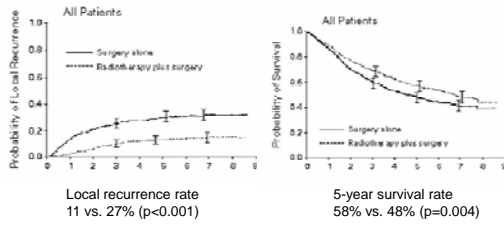
- High rates of locoregional failure (up to 50+ % for stage III disease) suggest important role for radiation
- Downstaging may permit sphincter preservation (avoid need for permanent colostomy)
- Differences in toxicity and efficacy when treatment is given pre- rather than post-operatively
- Questions:
  - Is there single best approach to delivering preoperative therapy?
    - Short-course vs. conventional fraction RT
    - Chemotherapy, concurrent and/or sequential? Or is it even necessary?
  - What about the timing of surgery relative to preoperative therapy?

### Early studies evaluating preoperative XRT for rectal cancer

TRIAL	XRT dose	5-yr OS	Local recurrence rate
EORTC (1988)	34.5 Gy over 15 doses	69% vs. 59% (NS)	14 vs. 28%
Stockholm I and II (1995-96)	25 Gy over 5 days	NS in Stockholm I; 46 vs. 39% in Stockholm II (p < 0.03) **	17 vs. 32%
Swedish rectal cancer trial	25 Gy over 5 days	58 vs. 48% (p = 0.004)	11 vs. 27% (p < 0.001)

\*\* In combined Stockholm studies, rectal cancer-specific mortality reduced from 47 to 32% (p < 0.001). However, increased risk of pelvic fx, DVTs, fistulas seen with preop XRT group.

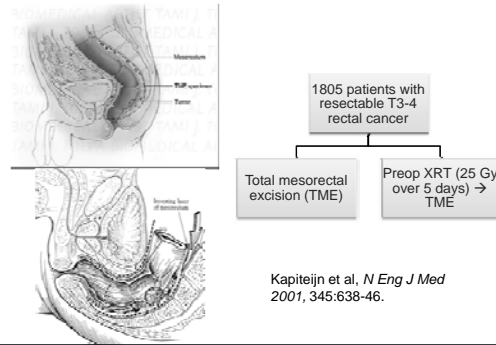
### Swedish Rectal Cancer Trial (n=168): short-course RT preoperatively reduces local recurrence rate and improves long-term survival



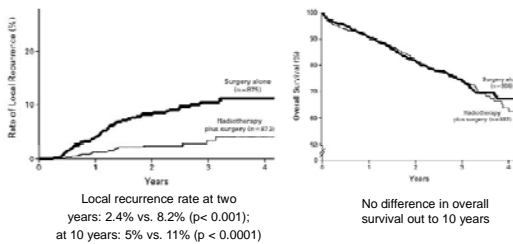
Swedish Rectal Cancer Trial, N Engl J Med 1997;336:980-7  
N Engl J Med 1997;336:980-7.



### Dutch TME rectal cancer trial



### Dutch TME rectal cancer trial

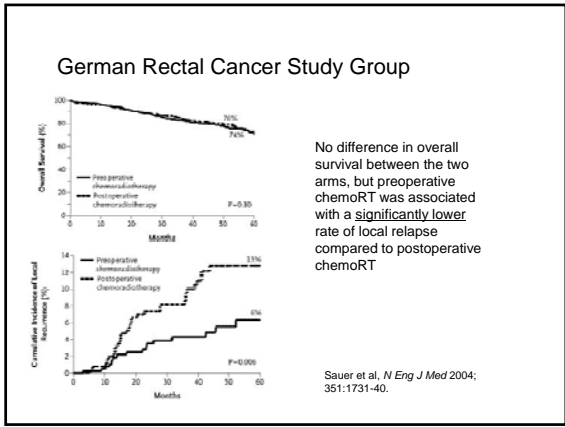
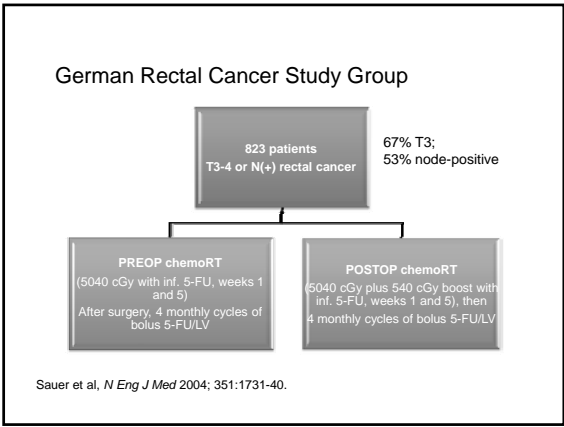
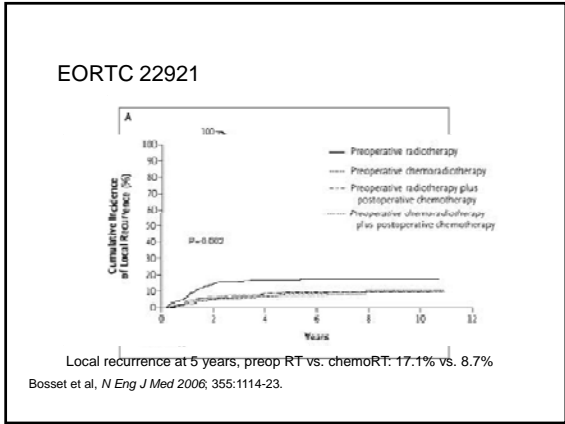
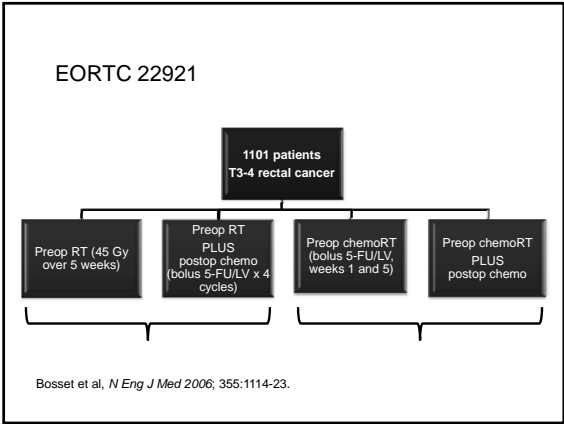


Kapiteijn et al. N Eng J Med 2001, 345:638-46.  
van Gijn et al. Lancet Oncol 2011, 12:575-82.



### Preoperative chemo plus RT for rectal cancer

- Early reports of preoperative 5-FU-based chemoRT suggest less acute toxicity when compared to postoperative rx (Minsky et al, J Clin Oncol 1992;10:1218-24)
- Higher rates of pathologic C.R. and local control compared to RT alone (FFCD 9203 trial, Gerard et al, J Clin Oncol 2006;24:4620-25)
  - ... although unclear whether ypCR translates into improved survival (Capirci et al, Int J Radiat Oncol Biol Phys 2008;72:99-107)



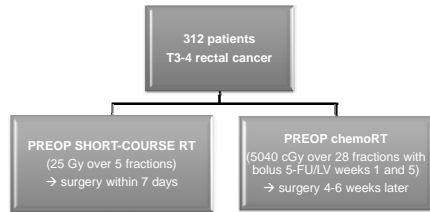
**German Rectal Cancer Trial: additional advantages of preoperative treatment**

	PREOP	POSTOP	P value
Downstaging effects (T1 vs. T3-4)			
Stage I	25%	18%	
Stage II	7%	7%	
Stage III	25%	40%	
Thought to require APR by surgeon; able to undergo sphincter-sparing operation	45/116 (39%)	15/78 (19%)	0.004

**German Rectal Cancer Trial: additional advantages of preoperative treatment**

	PREOP	POSTOP	P value
POSTOP COMPLICATIONS	36%	34%	NS
ACUTE TOXICITIES			
Any grade 3-4	27%	40%	0.001
Grade 3-4 diarrhea	12%	18%	0.04
Grade 3-4 dermatologic	11%	15%	0.09
LONG-TERM TOXICITIES			
Any grade 3-4	14%	24%	0.01
Grade 3-4 gastrointestinal	9%	15%	0.07
Grade 3-4 anastomotic stricture	4%	12%	0.003

Randomized trial comparing preop short-course RT or conventionally fractionated chemoRT

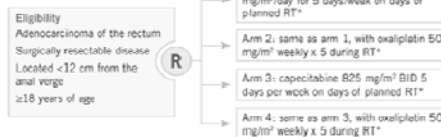


NO differences between the two arms in rates of local recurrence, overall survival, or late toxicity

Bujko et al, *Br J Surg* 2006; 93:1215-23.

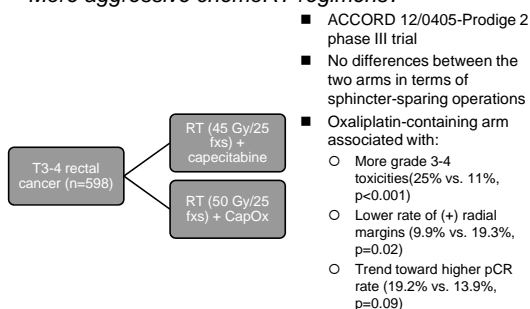
Neoadjuvant therapy for rectal cancer, unanswered questions:  
*More aggressive chemoRT regimens?*

Protocol ID: NSABP-R-04, NCT00058474  
Target accrual: 1,606



\* 4,500 cGy in 25 fractions over five weeks with a 540 cGy boost in three fractions for nonfixed tumors or a 1,080 cGy boost in six fractions for fixed tumors

Neoadjuvant therapy for rectal cancer, unanswered questions:  
*More aggressive chemoRT regimens?*

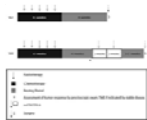


Neoadjuvant therapy for rectal cancer, unanswered questions:

*What is the optimal timing for surgery after neoadjuvant chemoXRT?*

- In most series, patients undergo surgery 4-6 weeks after completion of preoperative therapy
- Scandinavian/Dutch approach (5 x 5 Gy followed by immediate surgery): average interval is 10.5 days
- Some, but not all, studies, suggest higher rates of tumor response and clinical downstaging with longer interval between chemoRT and surgery

Neoadjuvant therapy for rectal cancer, unanswered questions:  
*What is the optimal timing for surgery after neoadjuvant chemoXRT?*



- Median time to surgery:
  - SG1 = 40 days
  - SG2 = 77 days
  - SG3 = 106 days
- Path CR:
  - SG1 = 18%
  - SG2 = 25%
  - SG3 = 31%
- No difference in AEs or surgical complications

Garcia-Aguilar et al, *Annals of Surg* 2011, 254:97-102; ASCO 2011, abstr 3514.

Case presentation #3

- A 62 y.o. female presents with several months of decreased appetite and intermittent epigastric pain, accompanied by obstructive jaundice symptoms and early satiety over the last several weeks. CT scan reveals a pancreatic mass with non-circumferential involvement of the distal superior mesenteric vein (SMV), invasion of the proximal portal vein, but no involvement of the superior mesenteric artery (SMA) or hepatic artery. There is no evidence of distant metastases.

### Case presentation #3 (cont'd)



Lall C G et al. *AJR* 2007;189:1044-1050

### (Audience response question – case #3)

What would you recommend for initial treatment of this patient?

- A. Surgical exploration with curative intent, including PV/SMV resection if needed
- B. Biliary decompression followed by FOLFIRINOX chemotherapy
- C. Biliary decompression followed by RT plus concurrent capecitabine

### Summary of phase III postoperative adjuvant therapy trials for resectable pancreatic adenocarcinoma: What progress have we really made?

**Table 5.** Previously Reported Phase 3 Postoperative Adjuvant Therapy Trials for Pancreatic Adenocarcinoma: Summary Results of Adjuvant Therapy Groups

	GITSG <sup>1</sup>	EORTC <sup>2</sup>	ESPAC-1 <sup>3,4</sup>	CONKO-001 <sup>5</sup>	RT05	
					Chemoradiation + Fluorouracil	Chemoradiation + Gemcitabine
No. total (% of patients)	0	20/104 (19) <sup>6</sup>	19/147 (13)	34/179 (19)	75/230 (33)	72/221 (33)
Microscopically positive margins	0	20/104 (19) <sup>6</sup>	19/147 (13)	34/179 (19)	75/230 (33)	72/221 (33)
13 or 14 disease	NA	0	NA	124/179 (69)	182/230 (79)	178/221 (81)
Lymph node–positive disease	6/20 (30)	22/104 (21)	22/117 (19)	127/179 (71)	148/230 (64)	151/221 (68)
Local recurrence rate, % (No./total)	17 (7/40)	51 (24/47) <sup>7</sup>	83 (36/156) <sup>8</sup>	37 (84) <sup>9</sup>	28 (61/178)	22 (50/156)
Median survival, mo	21	17.1	20.1	22.1	18.9	20.8
2-Year survival, %	24	20	30	34	22	31
5-Year survival, %	10	20	21	22.5	NA	NA

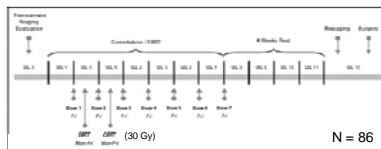
<sup>1</sup>Regina, W. F. et al. *JAMA* 2008;299:1019-1026.



### What about neoadjuvant (preoperative) therapy for resectable disease?

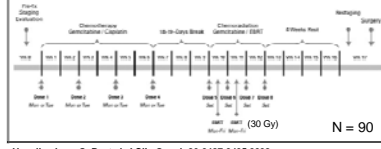
- **Theoretical advantages over postoperative treatment**
  - Improved rate of obtaining negative surgical margins
  - Do not need to worry about prolonged postoperative recovery before administering treatment
    - *In older postop studies, ~20-25% of patients intended for adjuvant therapy do not end up receiving it*
  - Patients who manifest with distant metastases on restaging studies are spared the morbidity associated with surgery
  - Allows radiation to be performed on well-oxygenated cells prior to surgical devascularization
- **Major concern: delay of only potentially curative option (surgery)**

### Neoadjuvant treatment for resectable pancreatic cancer: the M.D. Anderson experience



- All 86 completed rx  
 - 73 (85%) taken to surgery  
 - 64 (74%) had successful operation  
 - Median OS for entire study population: **22.7 months**  
 - Median OS for pts undergoing successful Whipple: **34 months**

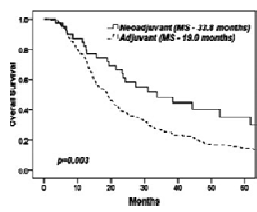
Evans, D. B. et al. *J Clin Oncol*; 26:3496-3502 2008



- 79 (88%) completed rx  
 - 62 (69%) taken to surgery  
 - 52 (58%) had successful operation  
 - Median OS for study population completing preop rx: **18.7 months**  
 - Median OS for pts undergoing successful Whipple: **31 months**

Varadhachary, G. R. et al. *J Clin Oncol*; 26:3487-3495 2008

### Neoadjuvant vs. adjuvant therapy for resectable pancreatic cancer



- Retrospective analysis from Calif. Cancer Surveillance Program, L.A. County, over 20-year period using SEER data
- 458 patients -- comparison of those receiving neoadjuvant (8.5%) vs. adjuvant (91.5%) therapy

Artinyan et al. *Cancer* 2011;117:2044-9.

Resectable vs. borderline resectable pancreatic cancer: Expert consensus statement (AHPBA/SSAT/SSO)

- |  |   |
|--|---|
| <p>■ <b>RESECTABLE</b></p> <ul style="list-style-type: none"> <li>○ NO distant metastases</li> <li>○ NO radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement</li> <li>○ Clear fat planes around the celiac axis, hepatic artery, and SMA</li> </ul> | <p>■ <b>BORDERLINE RESECTABLE</b></p> <ul style="list-style-type: none"> <li>○ NO distant metastases</li> <li>○ Venous involvement of the SMV/portal vein demonstrating tumor abutment +/- impingement and narrowing of the lumen, encasement of the SMV/portal vein but no encasement of the nearby arteries, or short segment venous occlusion 2o to either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction</li> <li>○ Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis</li> <li>○ Tumor abutment of the SMA not to exceed &gt;180° of the circumference of the vessel wall</li> </ul> |
|--|---|

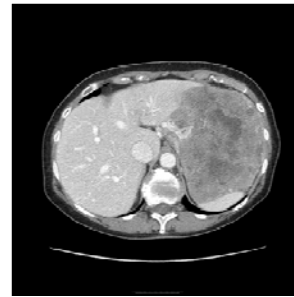
Optimal treatment approach for borderline resectable pancreatic cancer: where's the data?

- ECOG 1200: randomized trial preop gem/RT vs. gem/5-FU/cisplatin → 5-FU/RT – closed early due to poor accrual (n=21) (Landry et al, *J Surg Oncol* 2010;101:587-92)
- Mostly retrospective series suggest that patients with borderline resectable disease able to undergo successful resection (after preoperative chemo +/- RT) have similar outcomes to those with initially resectable tumors (Allendorf et al, *J Gastrointest Surg* 2008;12:91-100; Brown et al, *Am J Surg* 2008;195:318-21; Stokes et al, *Ann Surg Oncol* 2011;18:619-27)
- Sequence and duration of chemotherapy vs. RT remain undefined
- Cooperative group trial specific to borderline resectable disease planned using neoadjuvant FOLFIRINOX

Case presentation #4

- A 73 year old woman presents with a 3-month history of progressively worsening left abdominal pain radiating to the shoulder, accompanied by some palpable swelling in the LUQ.
- CT scan of the abdomen demonstrates a large 14 cm mass in the LUQ appearing to arise from the anterolateral surface of the gastric fundus, effacing the left hepatic lobe and displacing the spleen.
- Percutaneous biopsy reveals a CD117-positive spindle cell neoplasm c/w GIST (gastrointestinal stromal tumor), with 10 mitotic figures per 50 hpf.

Case presentation #4 (cont'd)

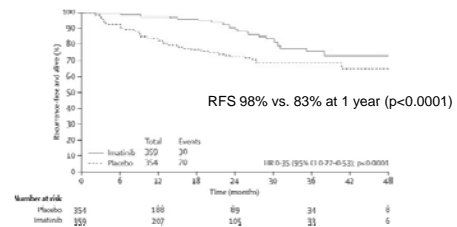


(Audience response question – case #4)

What do you recommend as the initial step in this patient's management?

- A. *En bloc* resection by a surgical oncologist
- B. Imatinib 400 mg daily
- C. External beam radiation

Adjuvant (postoperative) imatinib improves recurrence-free survival after resection of 3+ cm GIST (ACOSOG Z9001)



Dematteo et al, *Lancet* 2009, 373:1097-104.

