The evolution of rectal cancer therapy

Hagen Kennecke MD MHA FRCPC

Western Canada Consensus Conference

September 5, 2014

Objectives

- Identify standard therapy: stage II/III rectal cancer
- Update recent adjuvant trials
- Discuss current and planned innovative rectal cancer studies

Where are we now?

- Low Locoregional relapse rates: 3-8%
  - 50-70% with LRR have Distant Relapse
- Poor DISTANT Disease Free Survival Rates
  - 5-Year DFS in modern trials: 56-74%
- Poor compliance with post-operative chemo
  - 60-70% in phase III studies
- DELAY of post-op systemic therapy
  - due to pre-op chemoXRT and surgery

Bosset NEJM 06,Sauer NEJM 04
Allegra ASCO 2014, Aschele ASCO 2009, Gerard ASCO 2009, Roh ASCO 2011

Radiation Benefits & Issues

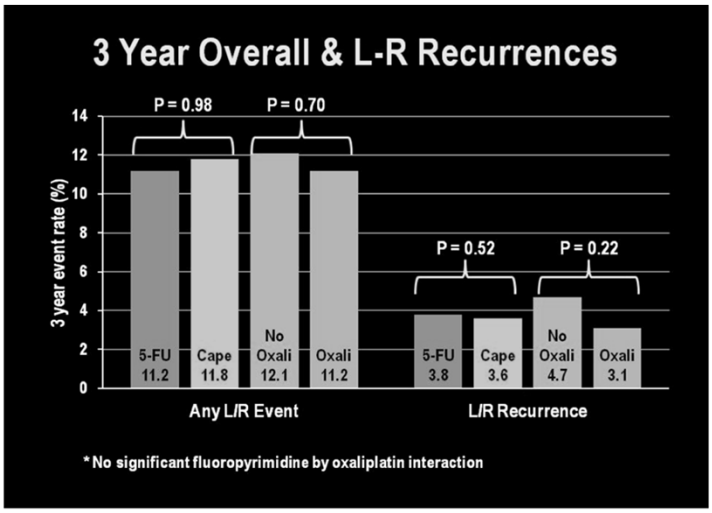
- 60% reduction in LRR
- Acute & Chronic Toxicity:

  5 Y Incontinence: XRT 62 % vs. no XRT 38%
  5 Y Severe Incontinence: XRT 14% vs. no XRT 5%
  Sexual Dysfunction – men

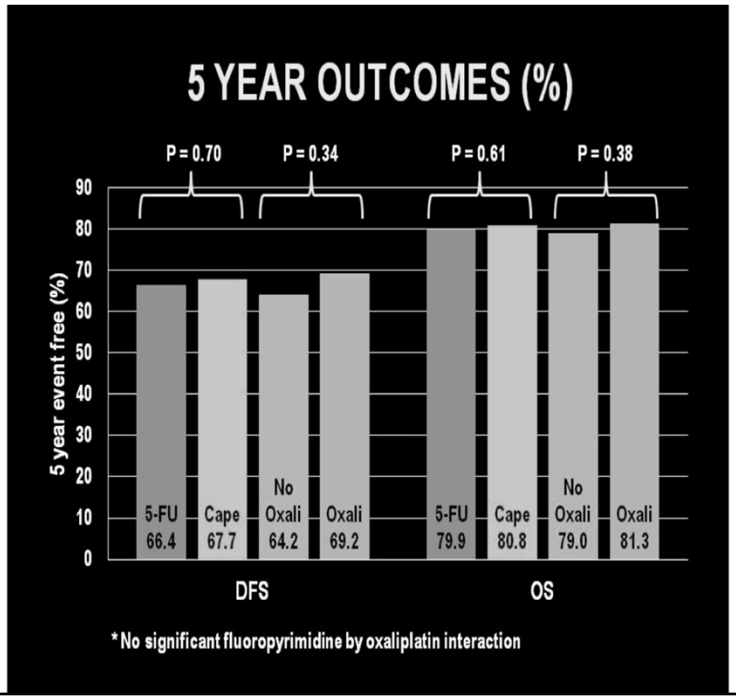
  Toxicities maintained at **14 years**
- Lack of effect on distant disease – no DFS in modern studies OS

Glimelius Acta Oncologica 2003, Marijnen JCO 2005, ESMO 2014, Peeters JCO 05, Bosset NEJM 06,Gerard JCO 06

NSABP R04



Allegra GI ASCO 2014



Current Questions in Rectal Cancer

All 3 modalities needed for stage II/III disease?

- Surgery ✔**?**
- Radiation **?**
- Chemotherapy **?**

When is the best time to introduce therapy?

- Radiation – Pre-Op ✔
- Chemotherapy – Post-Op vs. Pre-Op**?**

Are we satisfied with patient outcomes?

- Short term (LR) ✔
- Long term (OS) **X**

Objectives

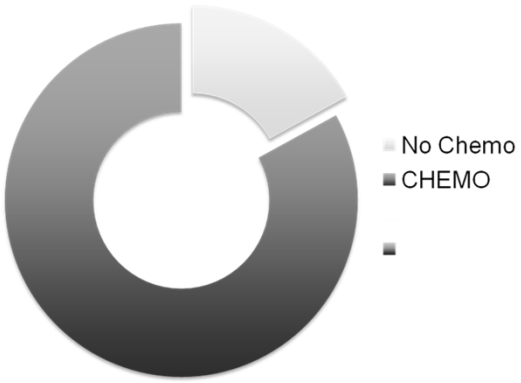
- Identify standard therapy: stage II/III rectal cancer
- Update: recent adjuvant trials
- Review recent phase II/III rectal trials
- Discuss innovative rectal studies

Adjuvant Chemotherapy in Rectal Ca

NCCN Database:
2005-10, N=1193

Stage II/III Rectal

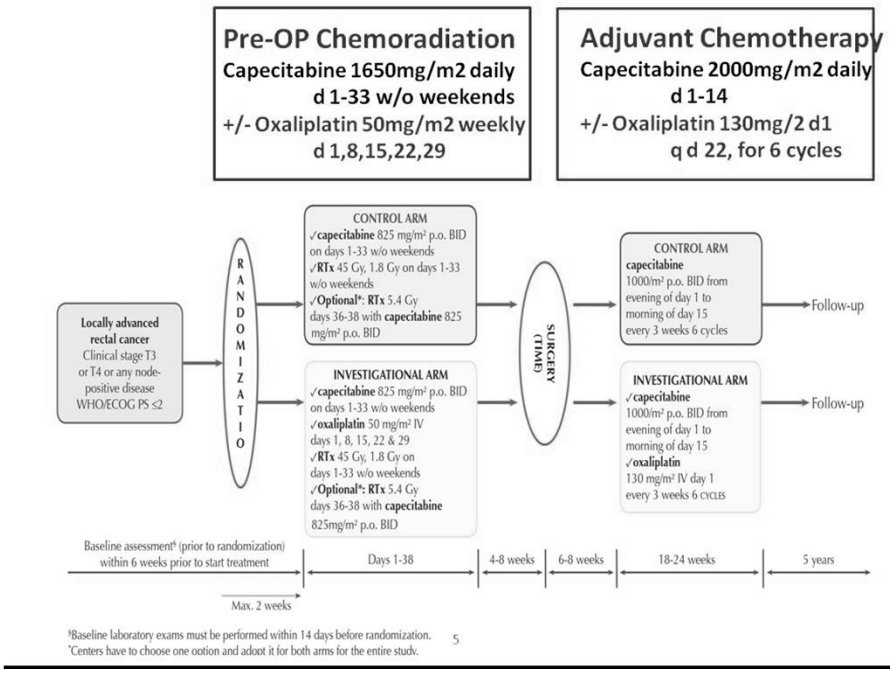
Received Pre-Op ChemoXRT



Khrizman JCO 2013

2013: adjuvant rectal ca

- Cochrane: Adjuvant 5-FU/LV ↓ recurrence (HR 0.75) and death (HR 0.83)
- No evidence for adjuvant oxaliplatin. We give it anyways: 1. ypN+ and 2. cT4/N2
- Why oxali? Evidence from colon cancer: anatomically different but biologically similar.
- 3 RCTs adding oxaliplatin post-operatively.



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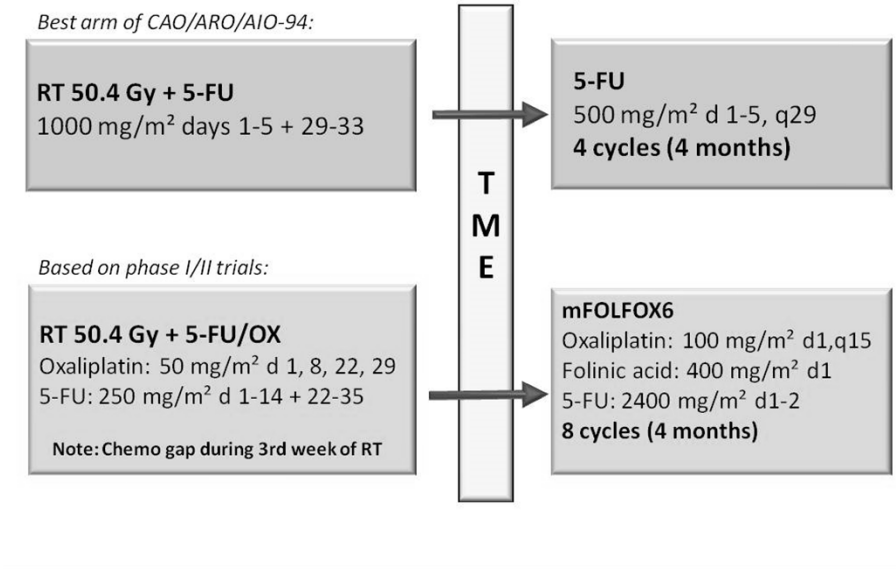
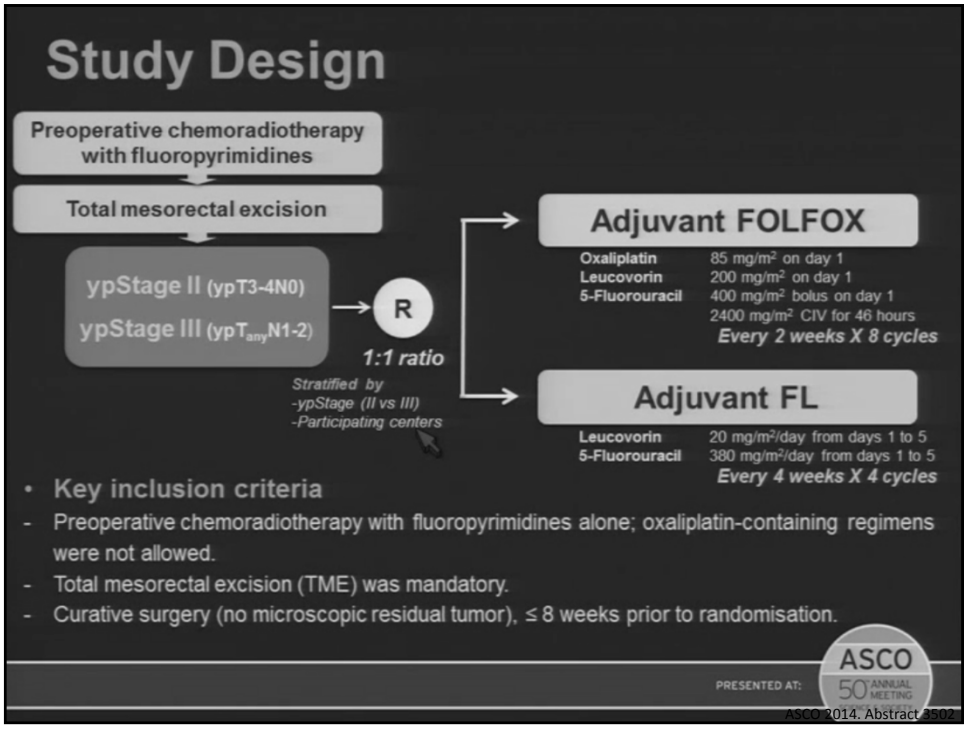
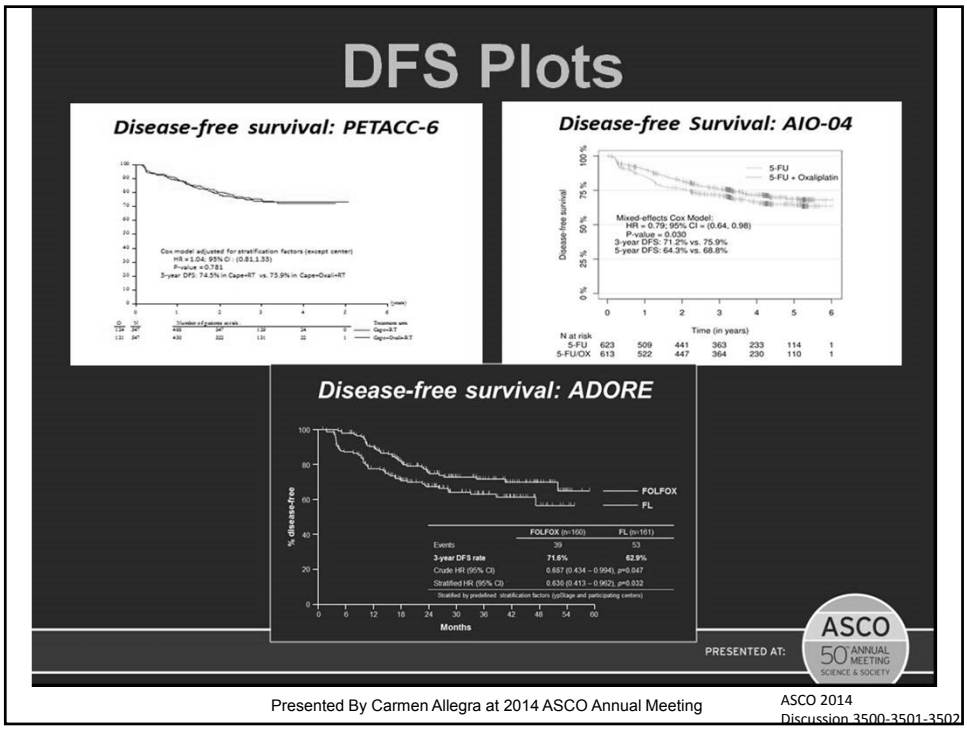


Presented By Claus Rodel at 2014 ASCO Annual Meeting



ASCO 2014. Abstract 3502



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Discussion 3500-3501-3502

DFS Summary

STUDY	REGIMEN	# pts	% LN+	3 yr DFS	HR
ADORE	"Mayo"	321	62 (yp N+)	63	
	mFOLFOX6			**72**	**0.63 p=0.03**
AIO-04	5-FU	1265	72 (clinical)	71	
	FOLFOX6			**76**	**0.79 p=0.03**
PETACC-6	Cap	1094	71 (clinical)	75	
	CAPOX			**74**	**1.04 p=0.78**
NSABP C-07	5-FU	2407	71	72	
	FLOX			76	0.80 p=0.003
MOSAIC	5-FU	2246	60	73	
	FOLFOX4			78	0.77 p=0.002

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How do We Explain the Different Outcomes?

- AIO-04 & ADORE
  - ADORE randomized AFTER surgery and excluded pCR and Stage 1
  - Arms reasonably balanced for drop-out, therapy completion & dose-intensity
- PETACC-6
  - Substantial imbalances between the arms in both drop-out & intended therapy rates & cape dose
  - 38% did not receive adjuvant CAPOX vs 23% who did not receive adjuvant single agent cape
  - Only 53% vs 68% of eligible pts received all intended adjuvant cycles in the CAPOX vs cape arms
  - 54% vs 36% received <90% of cape in the CAPOX vs cape arms

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Conclusions

- Adjuvant FOLFOX improves 3-Y DFS

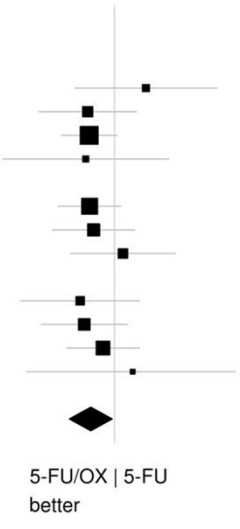
* Await Overall Survival

- 4 months appears to be enough
- Rectal Cancer ≈ Colon Adjuvant
- Stage III should be treated, Stage II?

Subgroup Analysis of DFS: Pathological factors

Intention-to-treat

Variable	5-FU Events/n	5-FU/OX Events/n	HR 95% CI
ypT-category			
ypT0-1	13/122	21/153	1.36 (0.68, 2.72)
ypT2	41/183	29/160	0.77 (0.48, 1.24)
ypT3	120/278	92/260	0.78 (0.60, 1.03)
ypT4	17/26	9/17	0.76 (0.34, 1.70)
ypN-category			
ypN0	94/423	75/416	0.78 (0.58, 1.06)
ypN1	53/131	45/133	0.82 (0.55, 1.22)
ypN2	44/60	30/42	1.09 (0.65, 1.81)
TNM stage			
Stage I	30/176	19/148	0.72 (0.40, 1.28)
Stage II	48/148	40/154	0.74 (0.49, 1.13)
Stage III	71/169	57/154	0.89 (0.63, 1.28)
ypT0ypN0	6/81	9/104	1.19 (0.43, 3.36)
Total			
all	**198/623**	**159/613**	**0.79 (0.64, 0.98)**



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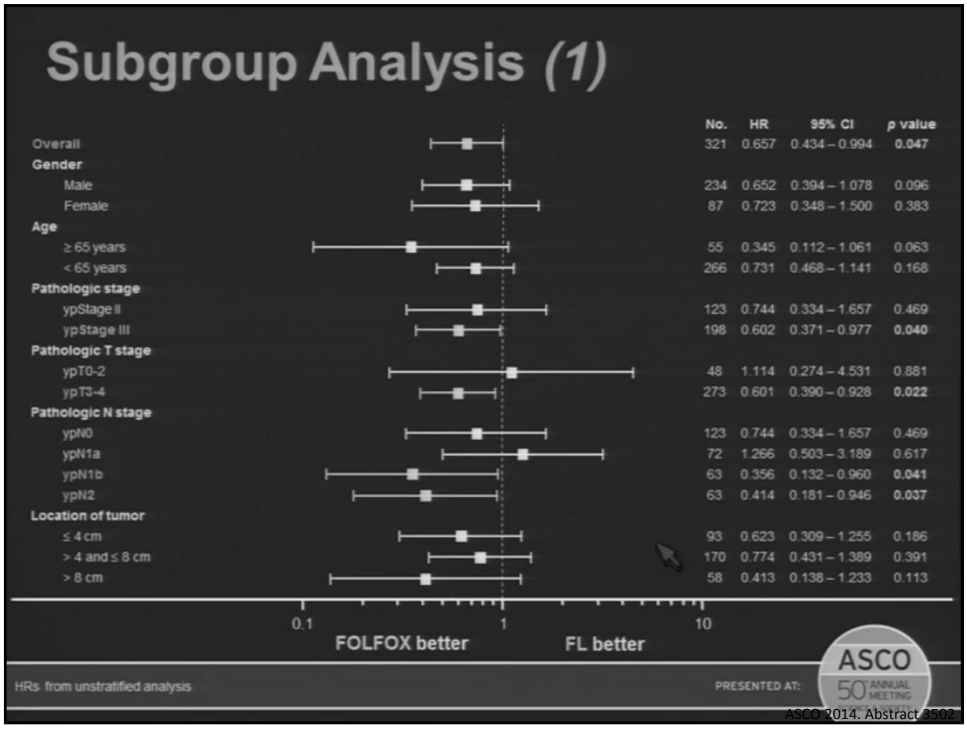

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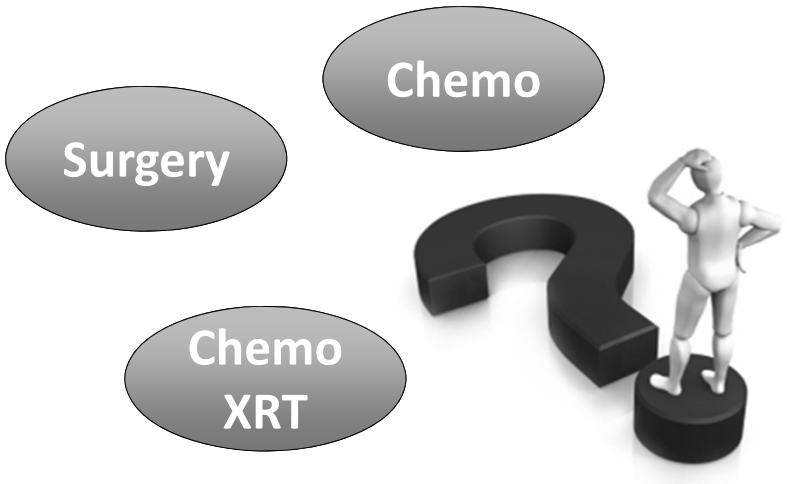
Recent Rectal Cancer Trials



Current Questions in Rectal Cancer

All 3 modalities needed for stage II/III disease?

- Surgery ✔**?**
- **–**Radiation **?**
- Chemotherapy **?**

When is the best time to introduce therapy?

- Radiation – Pre-Op ✔
- Chemotherapy – Post-Op vs. Pre-Op**?**

Are we satisfied with patient outcomes?

- Short term (LR) ✔
- Long term (OS) **X**

Selective use of XRT

- Chemo reduces LRR vs XRT alone (HR 0.5)
- CO16 - Phase III, 1350 patients with operable rectal cancer.
- Standard Arm:
  - Pre-op XRT 25Gy/5 ➔ Surgery
- Experimental Arm:
  - Surgery

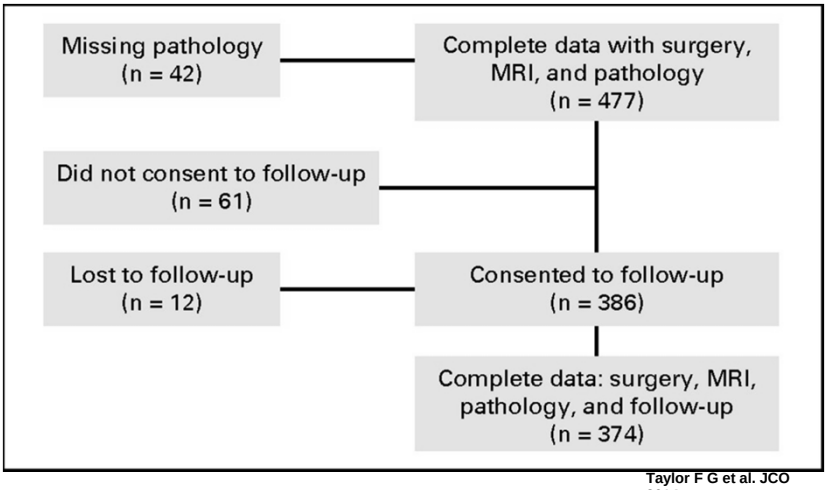
  ➔ Post-op chemoXRT 45Gy/25 ONLY if + CRM

Bossett NEJM 2006, Lancet 2009

RESULTS

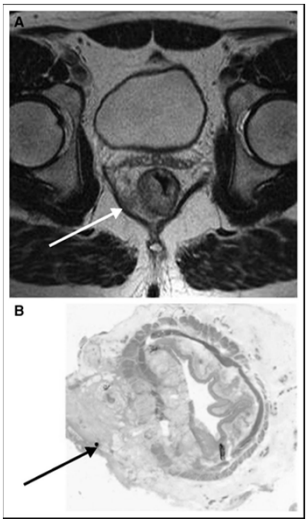
- Results – inferior LRR with selective XRT post-op chemoXRT
  - 60% decrease (HR=0.4) in LRR with routine XRT
  - 3 year LR 6.2% versus 10.6%
  - 3 year DFS 77% versus 71%
  - No difference in OS
- Issues- patient selection & post-op therapy???
  - One-third of patients had low rectal cancer
  - 22% of pts with + CRM did NOT get post-op XRT
  - Post-Op chemo: Stage II 18%, Stage III 80%

MERCURY trial:
CAN WE USE MRI TO PREDICT + path CRM



Taylor F G et al. JCO 2014

A. T2-weighted axial thin section magnetic resonance imaging scan
B. the corresponding histology section stained with hematoxylin and eosin.



Taylor F G et al. JCO 2014;32:34-43

Prognostic Value of mrCRM

Age 63 years

Pelvic XRT 42%

pathCRM + 9.6%

Sensitivity of mrCRM for pathCRM = 64%, PPV94%

Specificity mrCRM for pathCRM = 91%, NPV 53%

Pathologic Stage

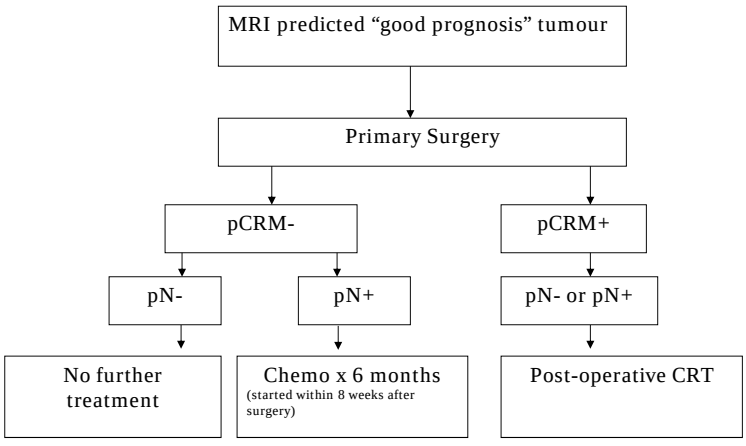
	mrCRM+	mrCRM-
Local Recurrence	20%	7%
5 year OS	30%	63%

*mrCRM strongest prognostic factor

*Canadian Quick*Silver Study

- Use MRI to exclude patients from pre-op radiation.
- Primary outcome: + pathCRM rate
- Aim to use MRI criteria to achieve a + pathCRM rate of ≤ 10%
- No primary evaluation distant outcomes

*Canadian Quick*Silver Study



*Quick*Silver MRI Criteria: risk stratification study

	Good Prognosis	Poor Prognosis
Predicted CRM	CRM > 1 mm	CRM ≤ 1 mm
T-category* and Extramural depth of invasion (EMD)	Definite T2 , T2/early T3 or definite T3 with ≤ 5 mm EMD	Definite T3 with > 5 mm EMD or T4
N-category	N0, N1, N2	N0, N1, N2
Extramural vascular invasion (EMVI)	Absent or equivocal	Present
Tumour Height	Any tumour 0-15 cm from anal verge with proximal extent at or below the sacral promontory and restorative resection is planned	

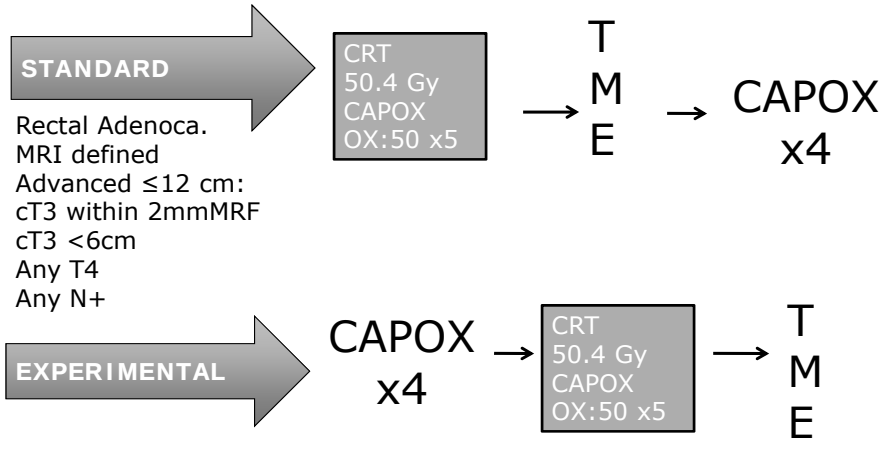
No evaluation of therapy

PRE- Operative Chemotherapy

1. NCI-CTPM: Neo-adjuvant chemotherapy is the most promising development in rectal cancer

- more effective than post-op chemo?
- can it replace radiation in some?

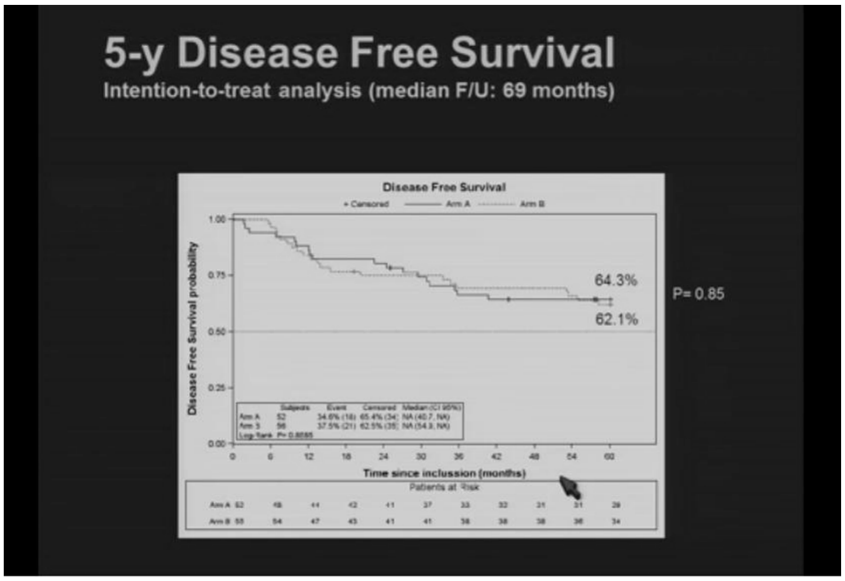
Chemotherapy: Pre vs Post-operative



C. Fernandez-Martoz JCO 2010

Pre vs Post-operative CAPOX

	post-Op	pre-Op	p-value
TIME TO ADJUVANT CHEMO	**18 weeks**	**< 1 week**	
Grade ¾ tox with CRT	29%	23%	0.4
Grade ¾ tox with chemo	54%	19%	0.0004
Chemo compliance 0 ≤2 3-4	 **25%** 14% 61%	 0 2 **98%**	 0.0001
Mean RDI oxaliplatin capecitabine XRT	 0.67 0.73 0.96	 .91 .94 .94	 <.0001 <.0001 .9



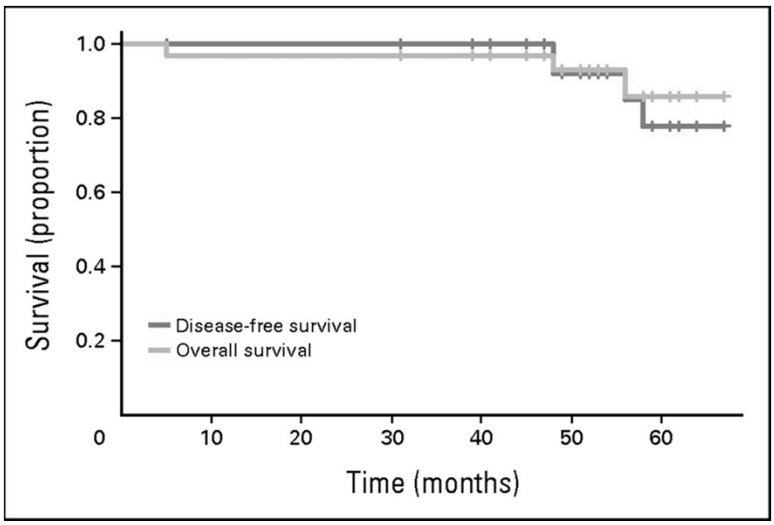
Fernandez-Martos GI ASCO 2014

Can chemo replace radiation? Neo-adjuvant FOLFOX-bev without radiation for locally advanced rectal ca

- N=32 patients with Stage II/III (no T4,low) rectal
- All patients had ERUS and MRI
- Neo-adjuvant FOLFOX-Bev x 3 mo followed by surgery: Bev stopped at 2 mo
- 30 Completed chemo, 2 early surgery
- 100% had R0 Surgery, 1 pt received post-op XRT
- 4 Year Follow-up:
  - 0% LRR
  - 84% DFS

Schrag JCO 2014

Disease-free and overall survival for the 32 study participants.



Schrag D et al. JCO 2014;32:513-518

PROSPECT

Preoperative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

- Objective:
  - To determine if selective use of chemoXRT is a reasonable alternative to routine preoperative chemoXRT for resectable rectal cancer that is amenable to sphincter sparing TME.

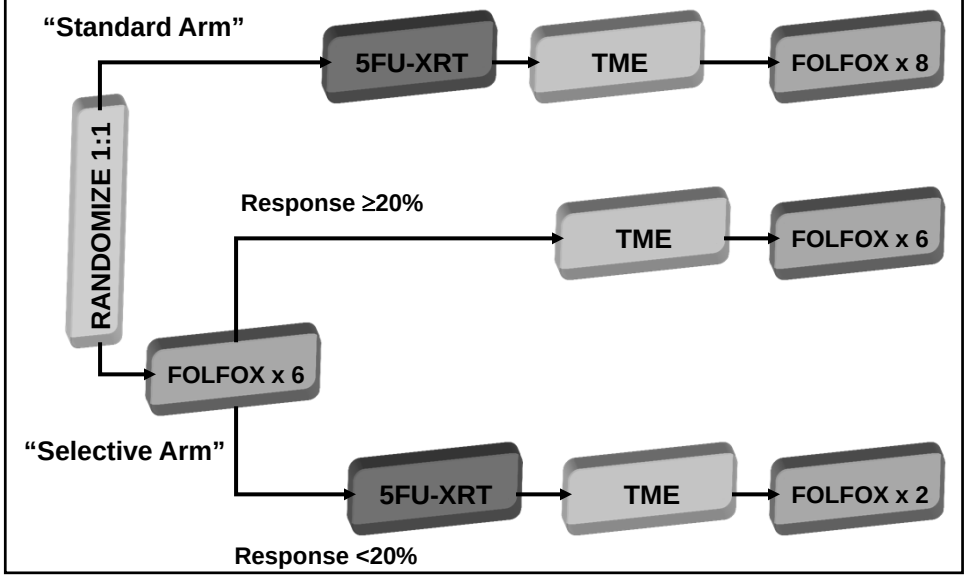
Protocol Concept Summary

- Objective:
  - To determine if selective use of chemoXRT is a reasonable alternative strategy to routine preoperative chemoXRT for resectable, non-low rectal cancer.

Background

- **Neoadjuvant radiation associated with long term toxicity and results in overtreatment of some patients.**
- **Patients with rectal cancer succumb to metastatic disease and neoadjuvant radiation delays initiation of systemic therapy.**
- **Both systemic therapy and surgical technique have substantially improved in the last decade.**

Study Schema



Study Design and Update

- A phase II/III study:
  - Randomized phase II of 366 patients with early stopping rule if failure to complete R0 resections or if high rate of Local Recurrence
  - Phase III component to include 644 additional patients with the endpoint of Disease Free Survival.
  - 198/1000 Accrued
  - Canada : 12 – WE NEED TO DO BETTER
  - Passed First Safety Analysis

Inclusion Criteria

- **Biopsy proven rectal adenocarcinoma at age 18+**
- **Tumor tissue located at 5-12 cm from the anal verge**
- **Candidate for sphincter sparing surgery according to TME experienced surgeon**
- **Baseline Clinical staging: T2N1, T3N0, T3N1**
  - **Physical exam by primary surgeon**
  - **Proctoscopy**
  - **MRI or ERUS (MRI preferred)**
    - ***MRI centrally reviewed, NOT in real time**
  - **CT scan of Chest/Abdomen/Pelvis**

Criteria

EXCLUDE:

- **Clinical T4 tumors**
- **Clinical N2 disease**
  - **Defined as 4 or more suspicious nodes >10mm in diameter**
- **EXCLUDE Low Tumors**
- **Tumor within 3mm of mesorectal fascia on MRI**

Exclusion Experiences:

- **Close CRM on MRI**
- **Clinical "N2" – 4 or more nodes >1 cm**

Staging/Restaging Evaluation

- Baseline staging is identical in both arms
- Restaging is more intensive in selective arm
  - **Evaluate whether rectal tumor is ≥ 20% smaller**
- Re-evaluation in selective arm:
  - **Proctoscopy**
  - **Physical exam by primary surgeon**
  - **Contrast enhanced CT of Chest/Abdomen/Pelvis**
  - **MRI of Pelvis or ERUS (same test as done at baseline**

  If response of primary tumor is:
  - **<20%, then 5FUCMT**
  - **≥20%, then straight to TME**

Criteria for Delivery of XRT in Selective Arm

- Preoperative ChemoXRT is administered if:
  - **Evidence of clinical progression during pre-op FOLFOX**
  - **Restaging reveals rectal tumor response is <20%**
  - **Unable to tolerate FOLFOXx6 at or above dose level-2**
  - **Patient withdraws consent**
  - **Central imaging review reveals pt was ineligible at baseline**
- Postoperative ChemoXRT is recommended if:
  - **TME pathology is T4**
  - **TME pathology is N2**
  - **TME pathology has any positive margin (R1 or R2 resection)**
  - **Surgeon's self assessment is that TME was incomplete**
  - **Surgical/Path QA report indicates incomplete TME**

Treatment Requirements

- Radiation
  - **IMRT is allowed**
  - **Short course radiotherapy is not allowed**
- Sensitizing Chemotherapy with Radiation
  - **May give capecitabine or infusional 5FU**

Post-Operative Chemotherapy

- Suggested, not mandated
- May include chemo without Oxaliplatin
  - Intervention Arm "selective use":
    - **If no ChemoXRT, then FOLFOX for 6 more cycles**
    - **If pre-op ChemoXRT, then FOLFOX for 2 more cycles**
  - Standard Arm "control group":
    - **8 cycles of post-op FOLFOX**

Surgeon Credentialing in TME

OPTION 1: Credentialing before participants register requires:

- 3 op/path reports in last 3 years
- Photos from 1 TME specimen

OPTION 2: Credentialing after 1st participant registers:

- An uncredentialed surgeon may register 1 participant and then:
- Submit credentialing materials within 8 weeks
  OR
- Submit index participant's TME photos/reports for review

•Surgeons credentialed for ACOSOG Z6051 will be considered credentialed for this trial. Email including approximate date must be sent to Regulatory@calgb.org

evolution of rectal cancer

- Therapy for stage II/III rectal cancer needs to improve:
  - Consider BOTH local AND distant control
- Better staging → more tailored therapy
- Systemic therapy likely has a greater role:
  - Post-op, Pre-op instead of radiation?
- PROSPECT will help decide whether radiation can be avoided for some patients.