Adjuvant Chemotherapy for Rectal Cancer: Are we making progress?

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Objectives

- Review milestones of rectal cancer therapy
- Review multimodality therapy for locally advanced and low rectal cancer
- Discuss optimal pre-operative and post-operative chemotherapy

Question #1: Chemoradiation for rectal cancer is most effective and least toxic when given:

- 4-6 weeks prior to TME surgery
- 4-6 weeks after TME surgery
- Either pre or post-operatively, as long as sufficient time between surgery and chemoradiation

Question #2: Postoperative chemotherapy is recommended to reduce the risk of distant recurrence for patients with:

- Stage ≥ I (any invasive cancer)
- Stage ≥ II (tumor invasion through the muscularis propria, node negative)
- Stage III only (node positive)

Question #3: Pre-operative downstaging chemoradiation has been shown to increase sphincter sparing surgery.

- True
- False

Rectal Cancer: Definitions

- Adenocarcinoma
- Defined by distance from Tumor located <16 cm from anal verge
  - 0-5 low
  - >5-10 mid
  - >10-15 high
- Staging: the SAME as colon cancer:
  - Stage I: T1/T2,N0
  - Stage II: T3/T4, N0
  - Stage III: T any, N positive
  - Stage IV: metastatic

Staging

- CT abdomen/pelvis
- CXR or CT chest
- CEA!
- Imaging of primary tumor: Endorectal US or pelvic MRI
  - T stage: Invasion through muscularis propria?
  - N stage: Nodes approaching the mesorectum?

Surgical Therapy of Rectal Cancer: DIFFERENT than colon cancer

- Total Mesorectal Excision (TME) –
  - "Sharp dissection along mesorectal plain to achieve *en bloc* resection of tumor"
  - Superior surgical technique results in significant reduction in loco-regional recurrence
- TME is done as part of:
  - Anterior Resection – sphincter sparing, or
  - Anterior-Perineal Resection (APR) – non sphincter sparing

Purpose of Adjuvant Therapy

- Reduce loco-regional recurrence
- Reduce distant metastasis

Adjuvant Therapy for Rectal Cancer: Milestones

- 1990: New Standard: Combined Postoperative chemotherapy and radiation therapy is recommended in stage II and III rectal cancer and results in improved local control and survival. (NIH Consensus Statement)
- 1994: Infusional 5-FU with radiation is superior to bolus 5FU with radiation in terms of Disease Free and Overall Survival (US)
- 1997: Pre-op short course radiation reduces Local Recurrence (HR=0.4) improves Overall Survival (Swedish)

United Nations Milestones

- 2001: Pre-op short course XRT with Total Mesorectal Excision reduces Local Recurrence (HR=0.3) but not Overall Survival (Dutch)
- 2004: PRE-OP infusional 5-FU-radiation is more effective in terms of Local recurrence (HR=0.46) and less toxic (HR=0.6) than the same therapy given POST-OPERATIVELY (German)
- 2006: 5-FU based chemotherapy added Pre- or Post-Operatively to Radiation and Surgery improves local recurrence but not survival (EORTC)

Outcomes of Rectal and Colon Cancer in BC: 1990 -2002

- Population based study of patients referred to BCCA, GI-ASCO 2008

- HYPOTHESES:
- #1: On a population basis, due to advances in local and systemic therapy, outcomes have improved for both rectal and colon cancer

- #2: Due to advances in therapy specific to rectal cancer, rectal cancer outcomes have improved to a greater degree than colon cancer outcomes

Methods

- **Patients with resected, pathological stage II or III colorectal cancer referred to BCCA in 1990, 1995/96, and 2001/02 were included**

- ***1990:*** **guidelines recommending adjuvant chemotherapy for colon and rectal cancer first released**

- ***1995/96*****: time period prior to widespread adoption of TME**

- ***2001/2002*****: increased adoption of TME, preoperative radiation therapy, and adjuvant 5-FU based chemotherapy. Prior to introduction of oxaliplatin based therapy**

Methods

- Data was collected through the BCCA colorectal cancer outcomes database
- The higher of clinical or pathological stage was used if long course preoperative chemo/radiation was given
- Kaplan Meier method was used for survival analysis

Results

- 1851 patients were included in the analysis
- The median follow up time was:

  15.7 years [1990]

  10.8 years [1995/96]

  5.3 years [2001/02]

Table 1: Patient Characteristics

	1990		1995/96		2001/02	
	RECTAL	COLON	RECTAL	COLON	RECTAL	COLON
N	96	140	223	340	374	678
Median Age	65y	67	65	67	64	69
Sex	67%	49	58	55	62	53

Table 2: Stages by cohort

	1990		1995/96		2001/02	
	RECTAL	COLON	RECTAL	COLON	RECTAL	COLON
Stage II (%)	30	39	37	44	41	41
Stage III (%)	70	61	63	56	59	59

Figure 1: Adjuvant chemotherapy for rectal and colon cancer

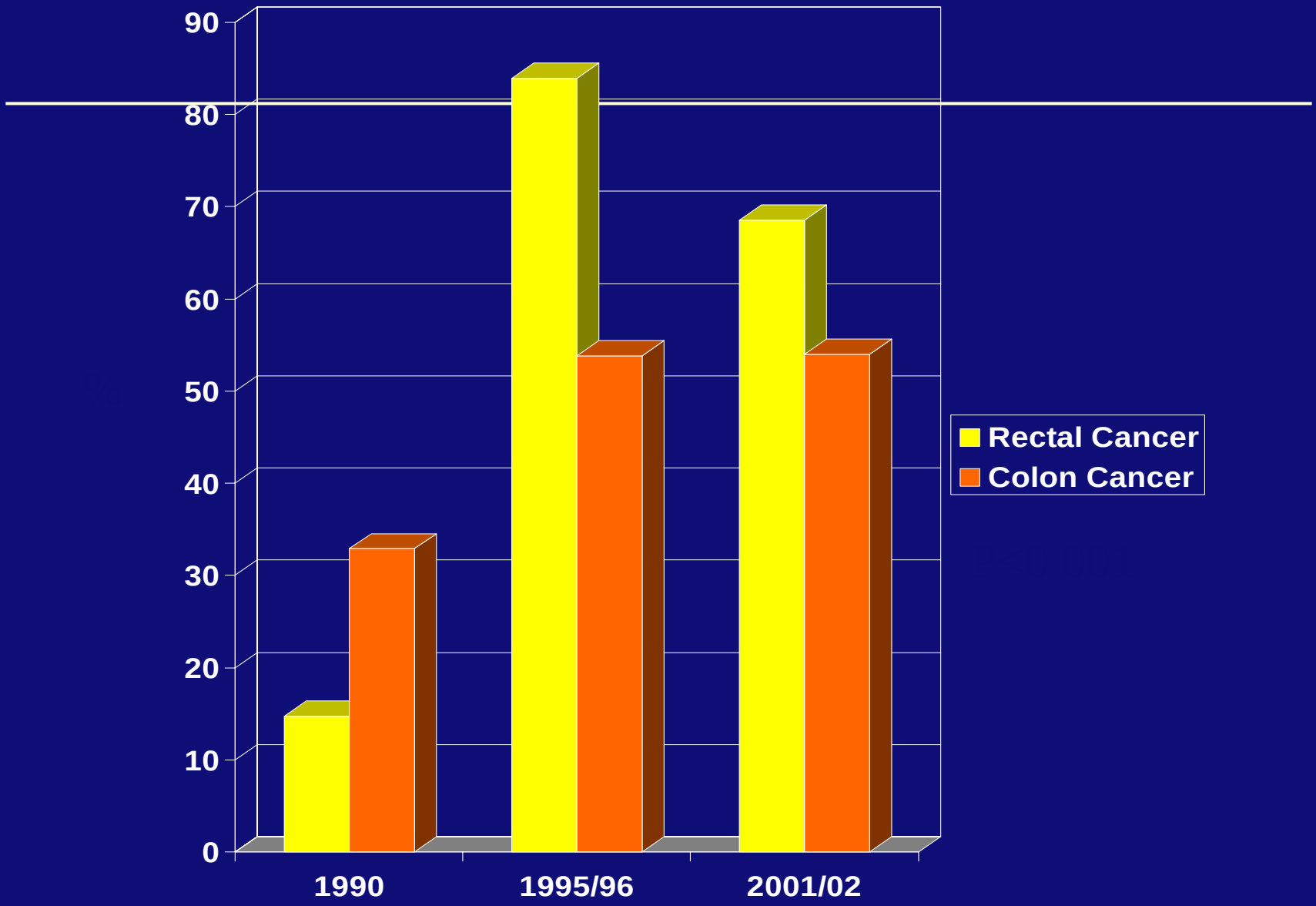


Figure 2: Radiation therapy for rectal cancer

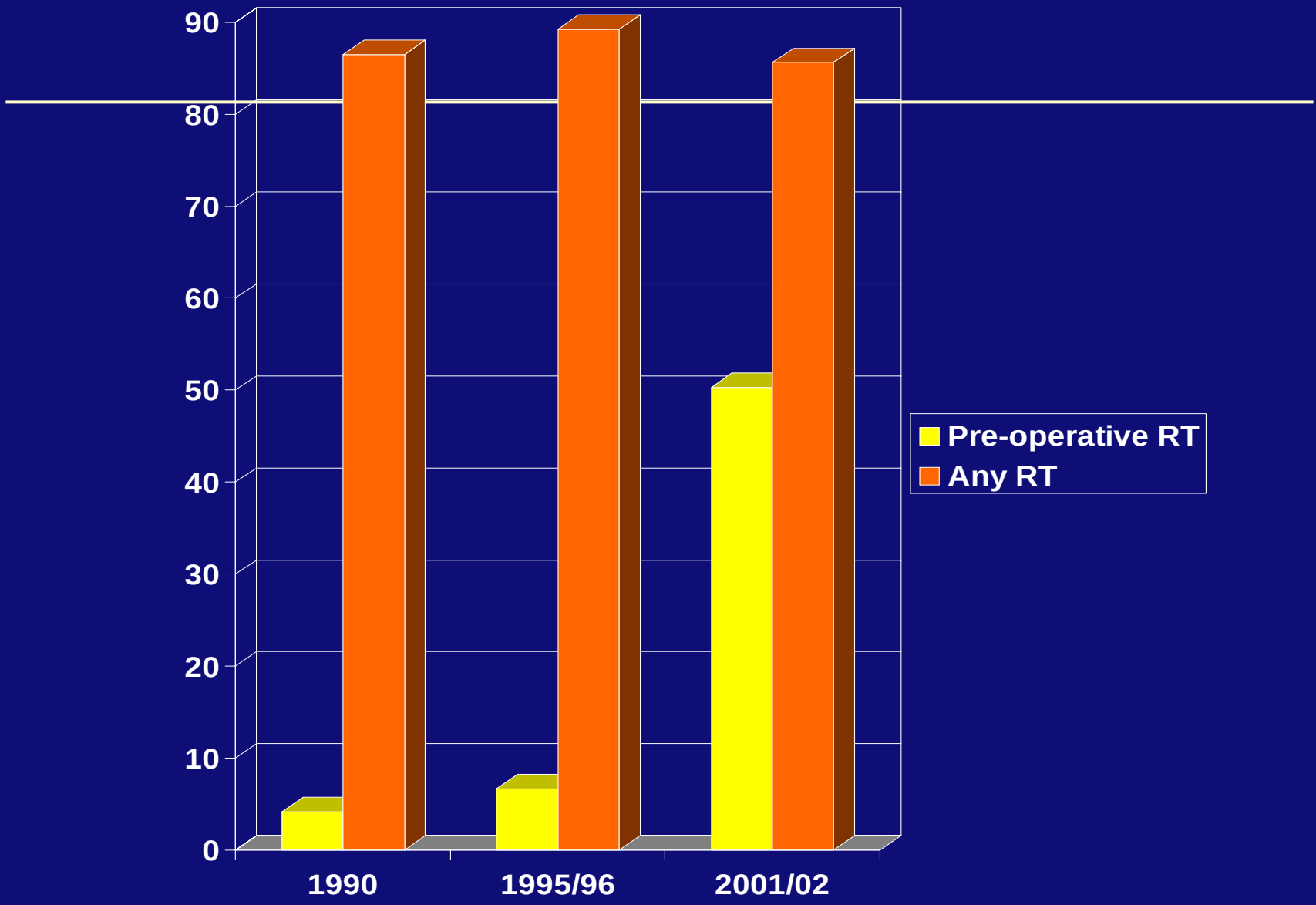


Figure 3: Rates of total mesorectal excision (TME) for rectal cancer

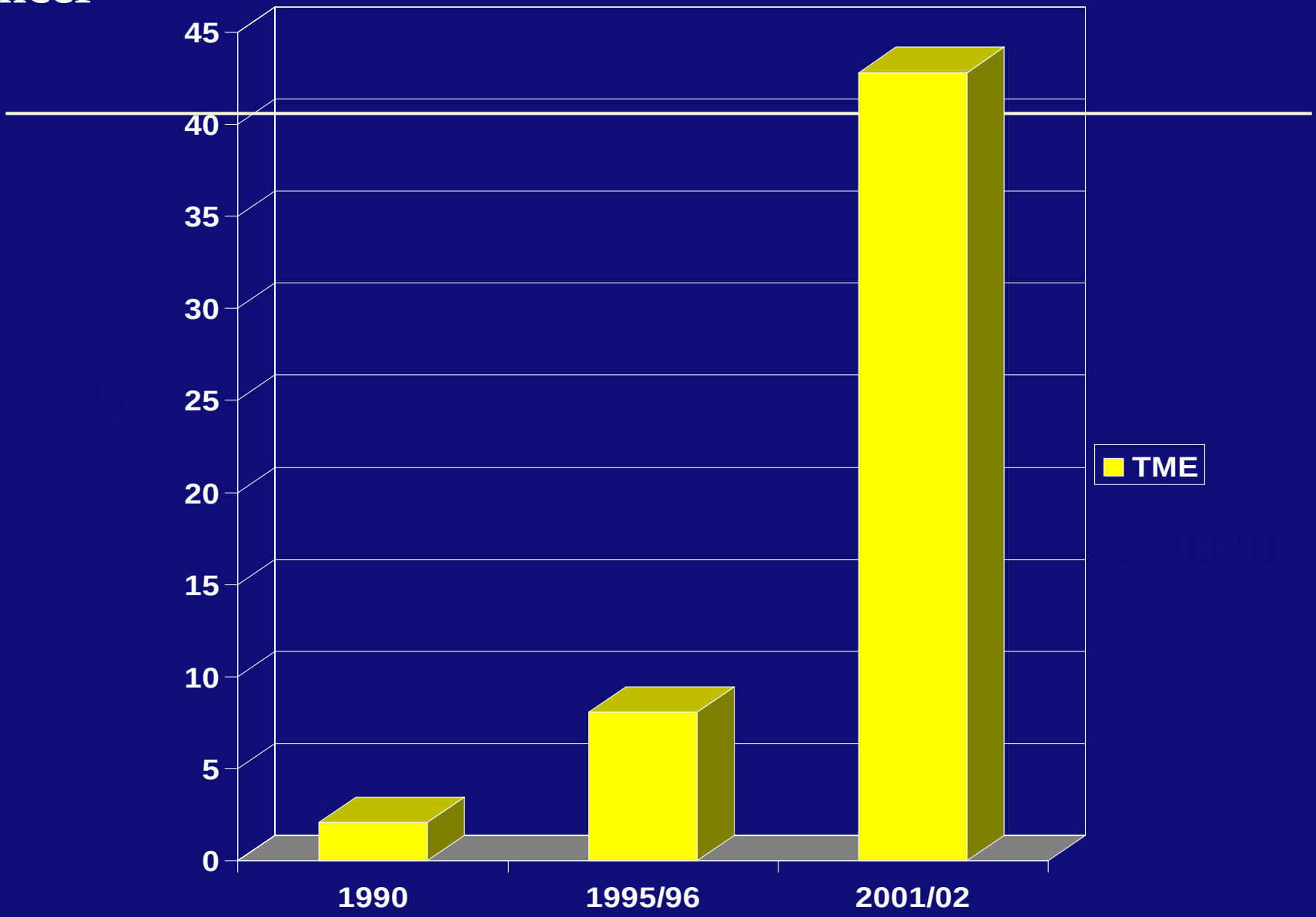
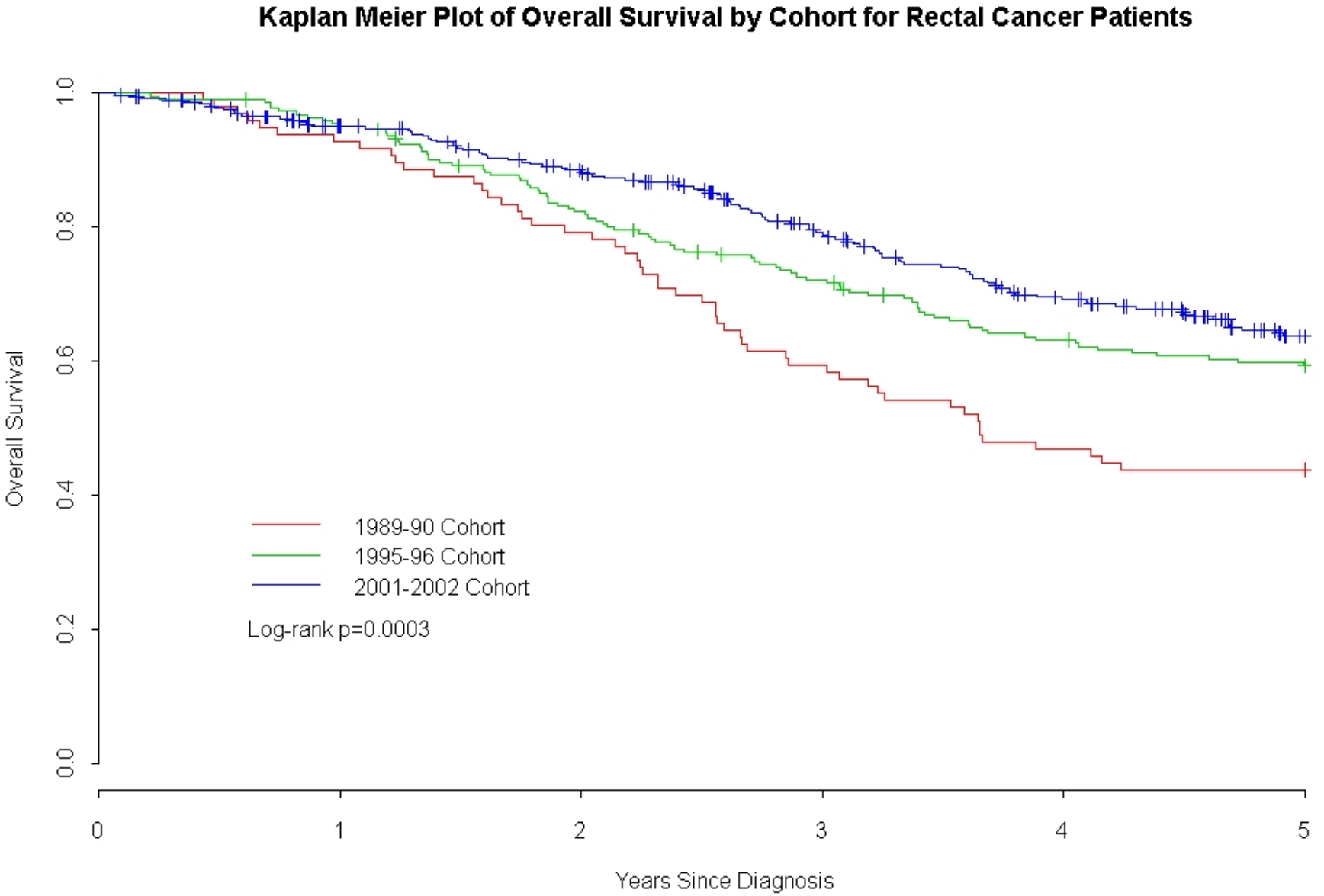
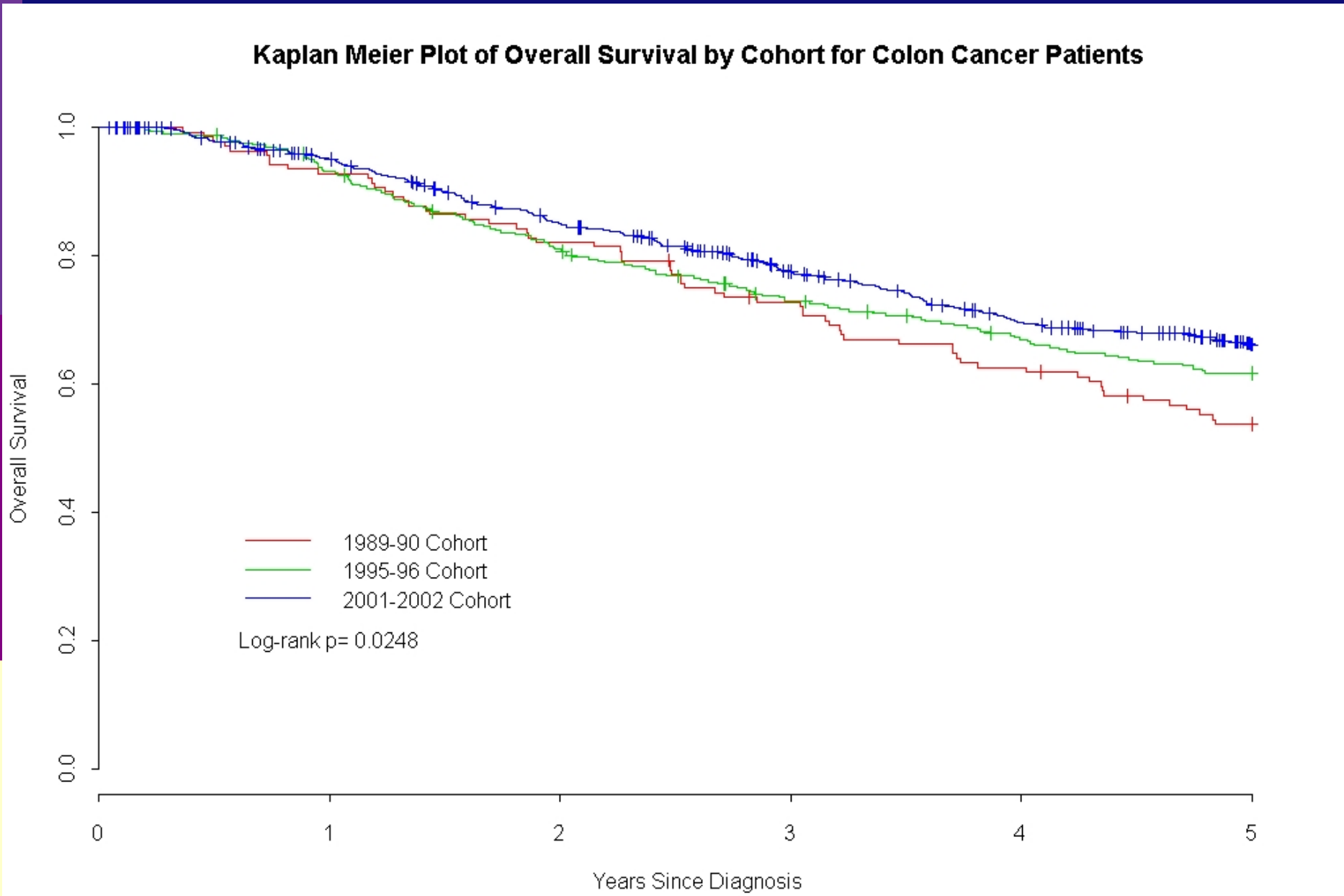


Table 3: 5 year overall survival for rectal and colon cancer

Year	N	5 Y Survival (%) Rectal Cancer	5 Y Survival (%) Colon Cancer	P-Value
1990	236	44	54	0.0969
1995-96	563	59	62	0.5607
2001-02	1052	64	66	0.4543


Kaplan Meier Plot of Overall Survival by Cohort for Rectal Cancer Patients
Overall Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
Years Since Diagnosis
1989-90 Cohort
1995-96 Cohort
2001-2002 Cohort
Log-rank p=0.0003


Kaplan Meier Plot of Overall Survival by Cohort for Colon Cancer Patients
Overall Survival
0.0
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0.8
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1
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3
4
5
Years Since Diagnosis
1989-90 Cohort
1995-96 Cohort
2001-2002 Cohort
Log-rank p= 0.0248

Conclusions

- Between 1990 and 2001/02 the use of adjuvant chemotherapy increased significantly for rectal cancer from 14.7% to 68.5% ($p<0.001$) and for colon cancer from 32.9% to 54% ($p<0.001$)
- The use of preoperative radiation therapy ($p<0.001$) and TME ($p<0.001$) in rectal cancer also significantly increased

Conclusions

- In this population based study, 5 year OS for stage II/III rectal ($p<0.001$) and colon cancer ($p=0.025$) significantly improved between 1990 and 2001/02
- Similar outcomes are now apparent for both rectal cancer and colon cancer

Conclusions

- With respect to rectal cancer, improved outcomes are likely related to increased use of TME technique, preoperative RT and adjuvant chemotherapy
- Improved outcomes for colon cancer likely reflect increased use of adjuvant chemotherapy

Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?

Chemorads for Rectal Cancer

- Pre-operative combined with radiation
  - Bolus 5-FU
  - Infusional 5-FU
  - Capecitabine
  - Multiagent chemotherapy with oxaliplatin in phase II/III trials

5-FU Based Therapy with XRT

- Standard is 5-FU based therapy
- Multiple regimens:
  - Continuous throughout Radiation
  - Continuous week 1 and 5 of radiation
  - Bolus
  - Oral in the form of Capecitabine
- Able to induce a PATHOLOGICAL COMPLETE RESPONSE (pCR) in 10-15% of cases.

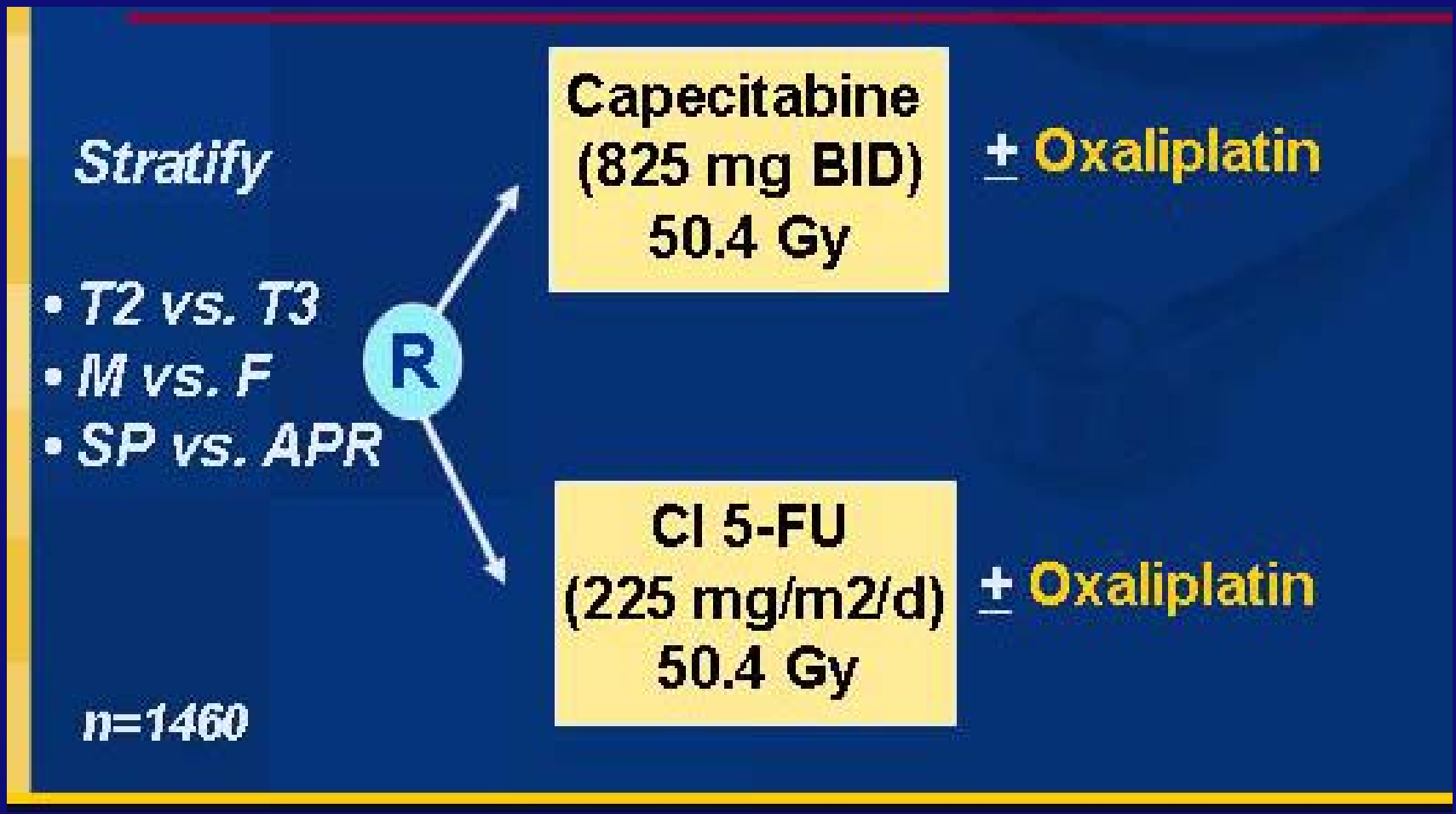
pCR with 5-FU and with Capecitabine

Reference	N	Therapy	pCR %
Sauer 2004	363	50.4 GY, 2 x 5d 5-FU CI	8
EORTC 22921	400	45 GY, 2 x 5d 5-FU,LV bolus	14
DePaoli 2006	53	50.4 Gy, Cap 825 m2 bid	24
Lin 2005	53	52.5 Gy, Cap 825 m2 bid	17
Shen ASCO 04	71	60 Gy, Cap 825 m2 bid	15
Kocakova ASCO 04	43	50.4 Gy, Cap 825 m2 bid	21
Dupuis ASCO 04	51	45 Gy, Cap 825 m2 bid	
Chau GI ASCO 05	68	50.4 Gy, Cap 825 m2 bid	24

Chemotherapy beyond 5-FU: can we improve pre-op therapy?

- Local recurrence <10% for stage II/III with TME and Radiation
- But there are high risk groups:
  - Locally advanced presentation (T4,N2)
  - Low rectal Tumors
- Better “downstaging” required
- Ongoing Phase II/III trials
  - 5-FU/capecitabine + oxaliplatin
  - 5-FU/cape + oxali + biologics

NSABP R-04


Stratify
• T2 vs. T3
• M vs. F
• SP vs. APR
R
Capecitabine
(825 mg BID)
50.4 Gy
± Oxaliplatin
Cl 5-FU
(225 mg/m2/d)
50.4 Gy
± Oxaliplatin
n=1460

Oxaliplatin with Radiation

- Oxaliplatin chemotherapy shown to improve survival in colon cancer
- Rationale:
  - Achieve better downstaging of locally advanced tumors
  - Better downstaging of low rectal cancers to reduce requirement for colostomy
  - Allow earlier systemic therapy to reduce risk of metastatic disease

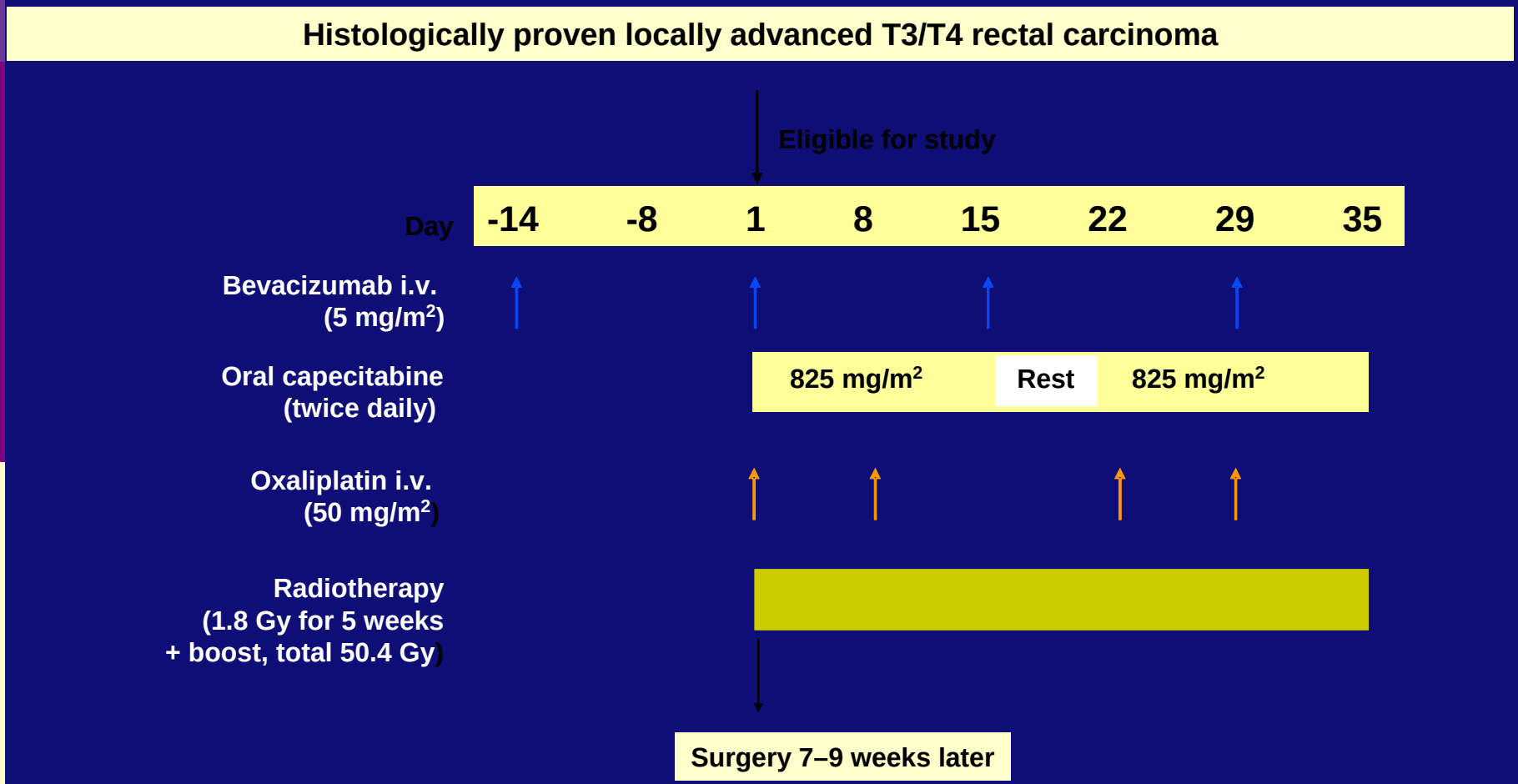
Oxaliplatin with Radiation

- Multiple phase I/II trials of 5-FU/Capecitabine plus oxaliplatin
- Therapy effectiveness determined by pathological Complete Response rate (pCR):
  - The complete absence of tumor in the resected pathological specimen
- Therapy is safe and achieves high rates of pCR of 20-25%

BCCA Study of Oxaliplatin, Capecitabine and Bevacizumab

- Aim:
  - Phase II trial is to evaluate the efficacy and safety of bevacizumab, capecitabine and oxaliplatin + XRT
  - Multicenter: Vancouver, Edmonton, Calgary, Winnipeg, Toronto
- Previous study: bevacizumab in combination with 5-FU chemoradiation followed by surgery did not result in dose-limiting toxicity in any of the evaluated patients.

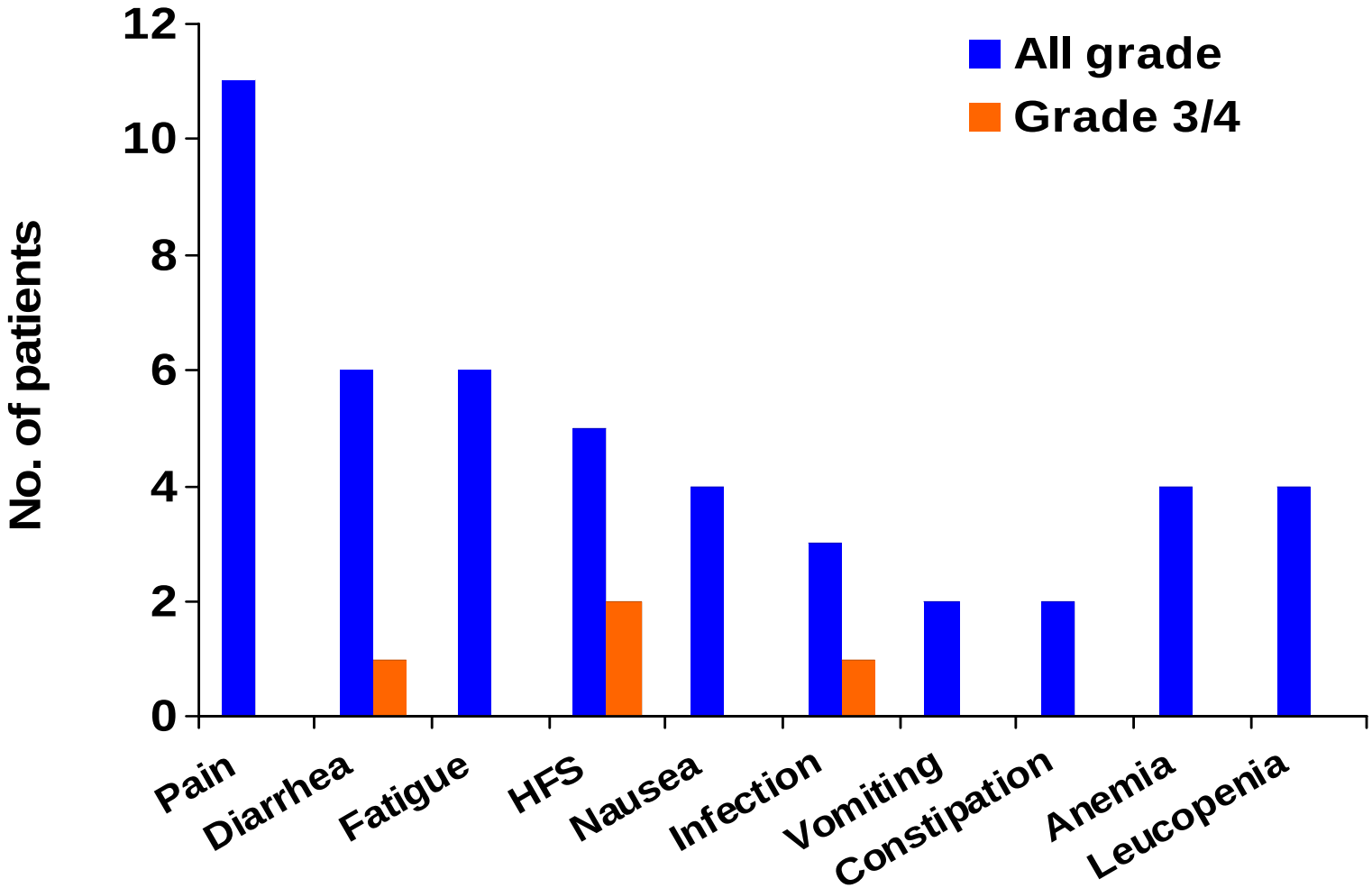
Figure 1. Treatment schedule



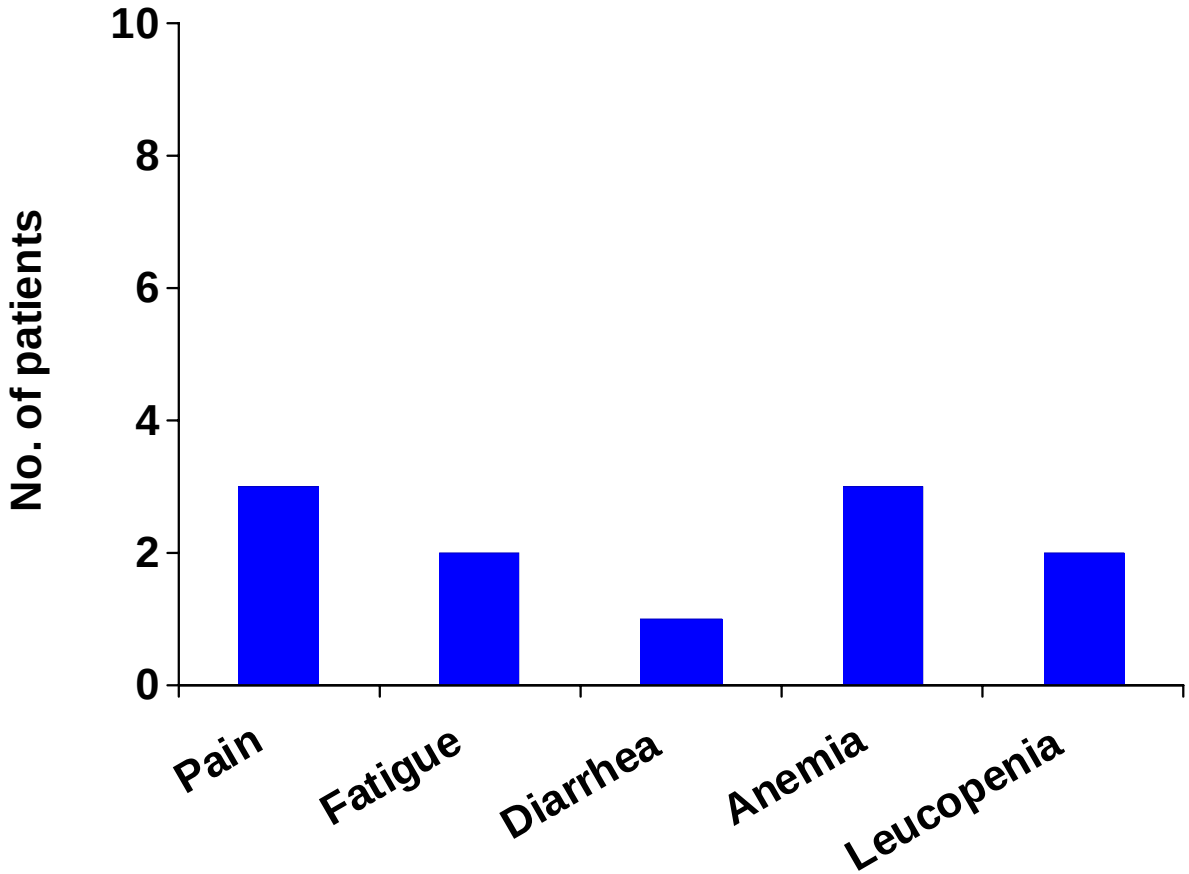
Treatment

- As of 31 December 2007, 10 evaluable patients have been enrolled.
- In total, there have been 5 cycles where dose reductions / interruptions / discontinuation (3/4/1) have occurred (4 of 8 patients); all were due to adverse events.
- All 10 of the patients that received protocol treatment have each completed a total dose of 50.4 Gy delivered to the tumor.

Pre-operative adverse events with bevacizumab, capecitabine, oxaliplatin and radiotherapy (n=10)



Post-operative adverse events with bevacizumab, capecitabine, oxaliplatin and radiotherapy (n=8)



Post-operative efficacy evaluation

- Post-operative information is available on 8 patients.
- A pCR was observed in 3 of 8 patients. Mild-Moderate regression was observed in 3 patients.
- 5 of 8 patients have had sphincter-sparing surgeries (local abdominal resection [LAR]) and 3 of 8 an abdominoperineal resection (APR).
- Complete tumor resection was possible in 7 of the 8 patients.

Conclusions: A-CORRECT study

- Interim safety analysis suggest that chemoradiation with bevacizumab, capecitabine and oxaliplatin is feasible.
- Full doses of planned radiation (50.4 Gy) were delivered to all patients.
- Accrual of a total of 55 patients

Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- What duration of therapy?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?

Post-Operative chemotherapy

- OPTIONS
  - Bolus 5-FU
  - Infusional 5-FU
  - Capecitabine
  - 5-FU and oxaliplatin *included in NCCN guidelines as adjuvant therapy for rectal cancer
  - 5-FU based, oxaliplatin and biologics in phase III trials

Evidence for Post-operative Chemo

- Distant recurrence risk significant
- Stage for stage, rectal risk at least equivalent to colon cancer
- 5-FU based chemo either pre-operatively with radiation or post-operatively reduces local recurrence (EORTC, NEJM ‘06)
- Evidence for chemo benefit difficult to estimate:
  - adjuvant chemotherapy variable in trials
  - compliance variable
  - path stage obscured by downstaging chemo-radiation therapy
  - DIFFERENT than colon cancer

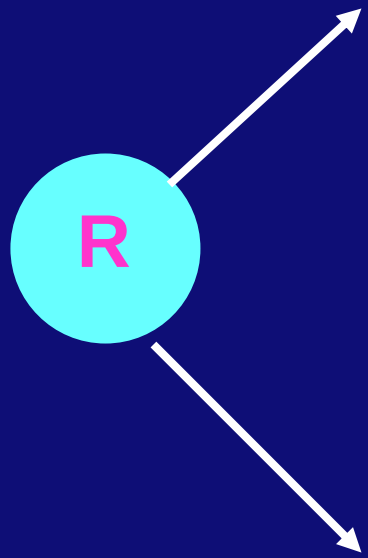
Ongoing Adjuvant Chemotherapy trials for **Rectal Cancer**

- POST-OPERATIVE THERAPY:
- E5204
  - Post-operative therapy
  - 12 cycles of FOLFOX +/- Bevacizumab
- PETTAC/EORTC:
  - Post-operative Capecitabine vs. Cap Oxaliplatin
- UK CHRONICLE STUDY:
  - Pre-Op chemo-radiation, Post-operative Observation vs. Cap Oxaliplatin

ECOG 5204 Phase III Trial
NCIC CRC.4

Stage II/II

Preop CRT
(Cape, FU)
-NSABP R04

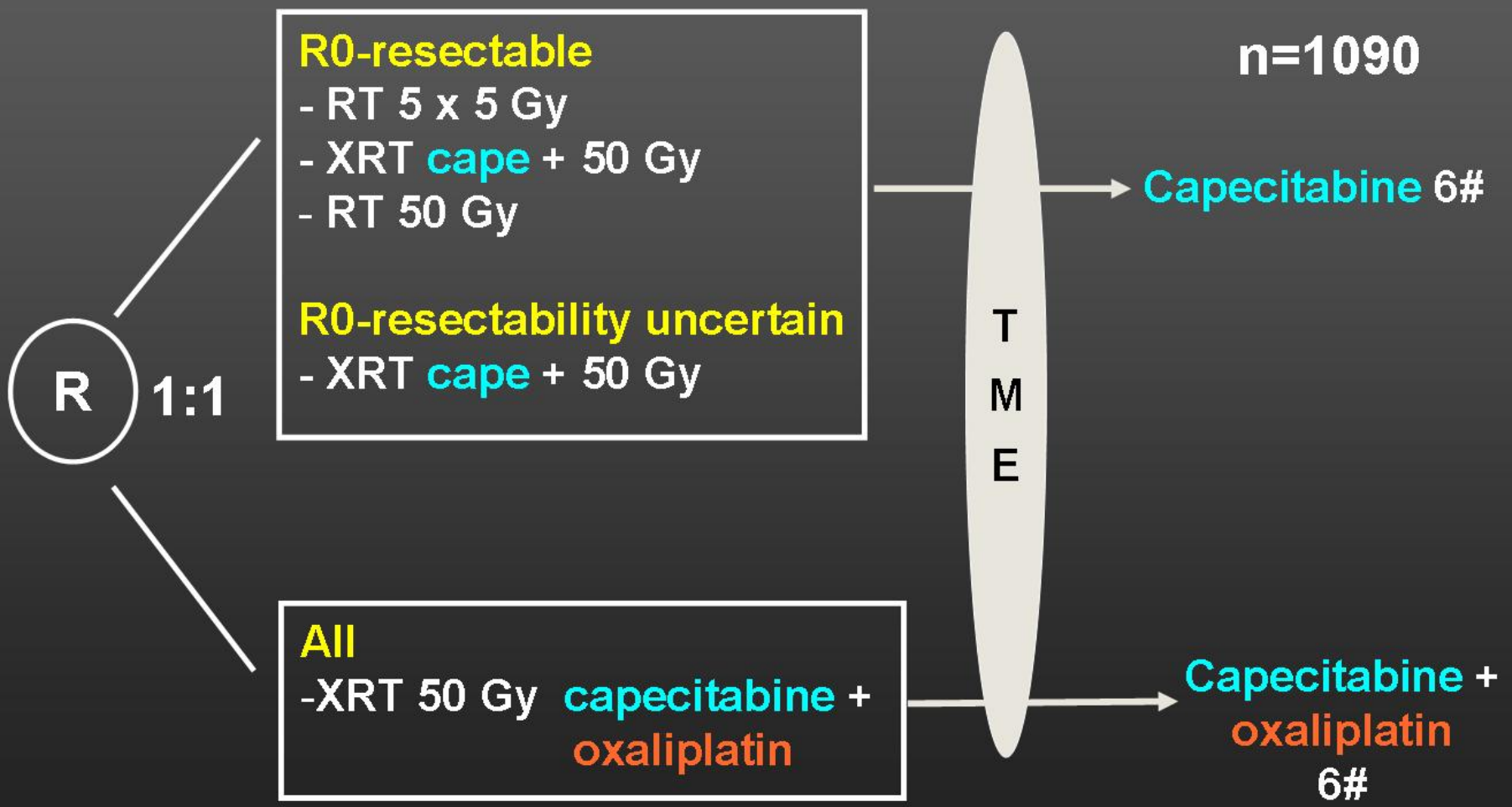


mFOLFOX6 X 12

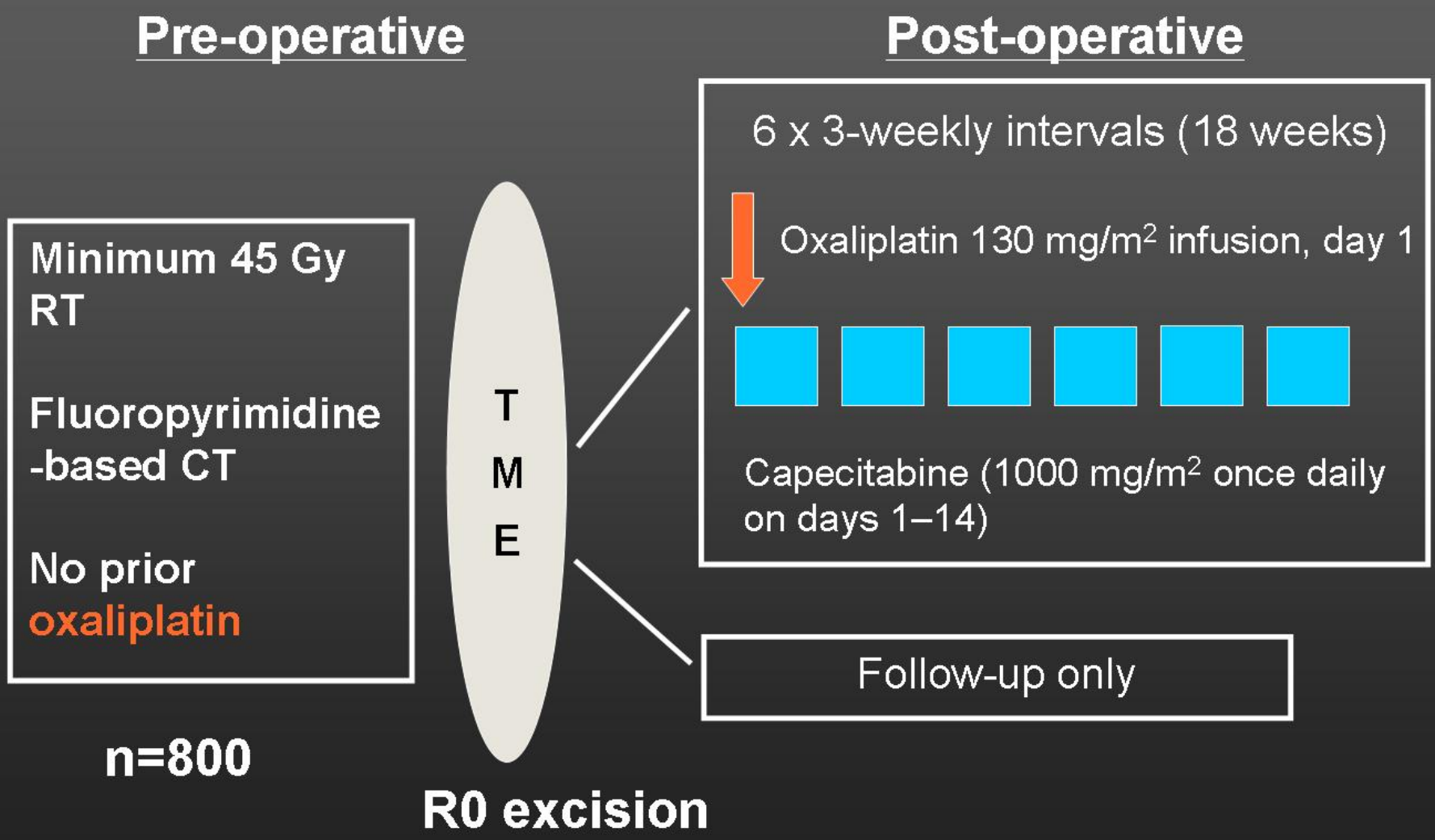
IF preop oxali:
9 cycles mFOLFOX6 +
3 cycles 5FU/LV

mFOLFOX6 + Bev
X 12

PETACC/EORTC Phase III trial



CHRONICLE Phase III study



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Clinical vs Pathologic Stage

- Pathologic stage usual standard determining adjuvant therapy in oncology
- Referred to as “Y stage” if previous tx:
  - Minimally affected by “short course” pre-operative radiation (25GY in 5)
  - Significantly affected by “long course” therapy (50.4GY in 25)
- Clinical stage in rectal less reliable
  - T stage 80-90% accurate with MRI, ERUS
  - N stage 60-80% accurate with MRI,ERUS

Pathologic CR

- 10-15% complete response with long course XRT and 5-FU/Cap
- Prognostic: 5Y DFS 86% in pts with pCR and 4 months Bolus 5-FU (German '04)
- Predictive: pT0-2 but not pT3 benefit from further adjuvant 5-FU chemotherapy (French, JCO 07)
- Thus, further chemo may be beneficial even if low Y stage

Current Questions in Rectal Cancer

- Which chemotherapy with Radiation?
- Which post-operative chemotherapy should be offered for Rectal Cancer?
- How do we interpret pathological stage to determine post-op therapy?
- What is the optimal therapy for low rectal cancer?

Low Rectal Cancer

- Low rectal tumors, any one of:
  - <5 cm
  - Palpable
  - Require abdominoperineal (APR) resection in surgeons opinion
- Higher rate of circumferential margin positivity due to resection plane of APR
- Permanent colostomy highly undesirable
- Long course CXRT recommended for downstaging

Low Rectal Tumors

- Conflicting evidence that downstaging increases rate of sphincter sparing:
  - Pre-op CXRT 39% vs. Post-op 19% (German)
  - Short XRT 62% vs Long CXRT 58% (Polish)
- Why?
  - Low rate of complete path response 10-15%
  - Reluctance among surgeons to change surgery

LOW RECTAL CANCER

- BCCA recommendation: pre-op CXRT for low tumors
- Study opportunities:
  - Phase II trials of novel agents
  - Pre-op PETCT, ERUS to asses response

BCCA Guidelines: Stage II/III rectal cancer

LOCALLY ADVANCED AND LOW TUMORS

- Locally advanced define by:
  - T4
  - Clinically fixed/tethered
  - Nodes approaching the mesorectum
- Locally advanced
  - Pre-operative chemoradiation, 45 +5.4 GY
  - Post-operative chemo according to path stage
    - Stage II or less: 4 months of capecitabine
    - Stage III: 4 months of 5 FU/oxaliplatin

BCCA Guidelines

- LOCALLY ADVANCED AND LOW TUMORS
- Pre-operative chemoradiation, 45 +5.4 GY
  - Capecitabine 825mg/m2 bid daily
  - For duration of XRT
  - AM dose 1-2 hours prior to radiation
- Post-operative chemo according to path stage
  - Stage II or less: 4 months of capecitabine
  - Stage III: 4 months of 5 FU/oxaliplatin

BCCA Guidelines

- RESECTABLE RECTAL CANCER
- Short course rads 25 GY over 5 days, surgery within 1 week
- Limited downstaging due to short interval btw radiation and surgery so path stage likely reflects “true” stage
- Post-operative chemo according to path stage
  - Stage II: 6 months of capecitabine
  - Stage III: 6 months of 5 FU/oxaliplatin

Conclusions

- Pre-operative staging and multidisciplinary care are essential in mmt of rectal cancer
- New systemic therapy options are available for patients with stage II and III rectal cancer
- Rectal cancer outcomes have significantly improved over past 20 years
- Areas for further improvement are :
  - More consistent pre-op staging
  - Locally advanced rectal cancer
  - Low rectal cancer