Adjuvant Management of Rectal Cancer

Bruce Minsky

Disclosures

1) Leader Project 1: 2U19CA021239-35 NCI. Improving the Clinical Effectiveness and Understanding of the Biophysical Basis of Protons

2) Co-investigator: U10 CA180858-0-NCI National Clinical Trials Network

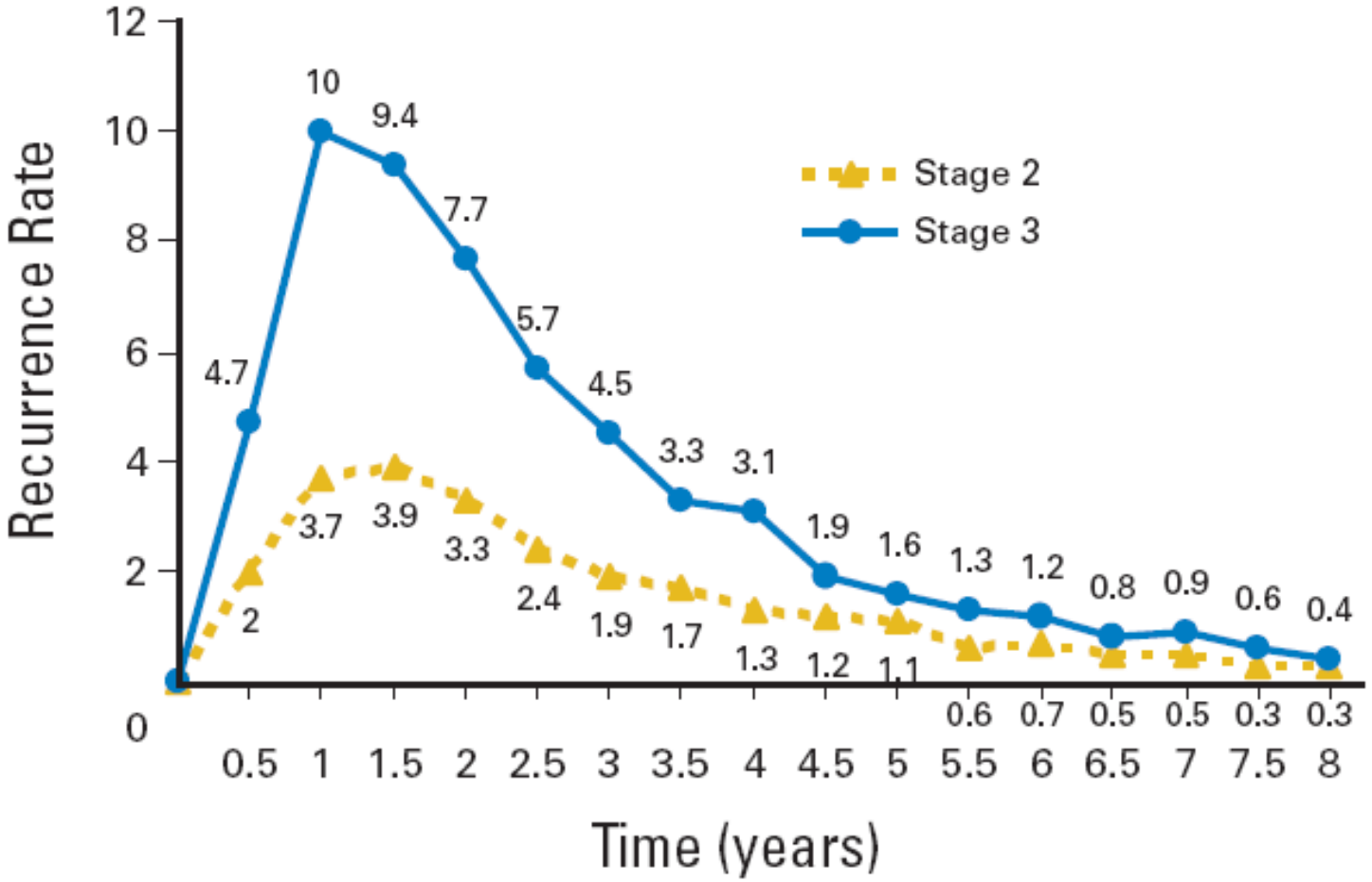
3) Co-Chair: NCI GI Steering Committee

4) Member, Clinical Steering Committee – Atlantic Consortium – MR Linac

Controversies

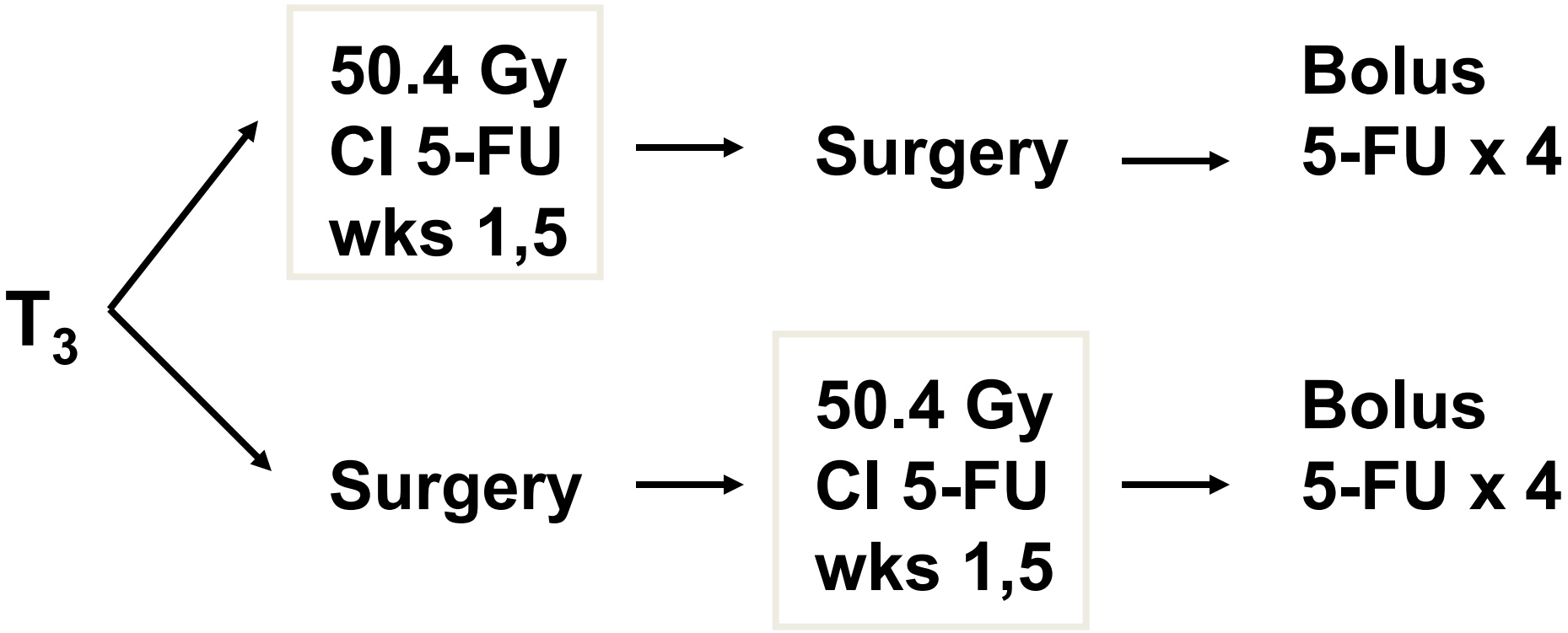
1) Short course vs. long course chemoRT
2) Is response prognostic?
3) Non-operative approach (watch and wait)
4) Role of postop adjuvant chemotherapy
5) ChemoRT beyond 5-FU
6) Selective pelvic RT
7) IMRT

Colon: Time to Recurrence

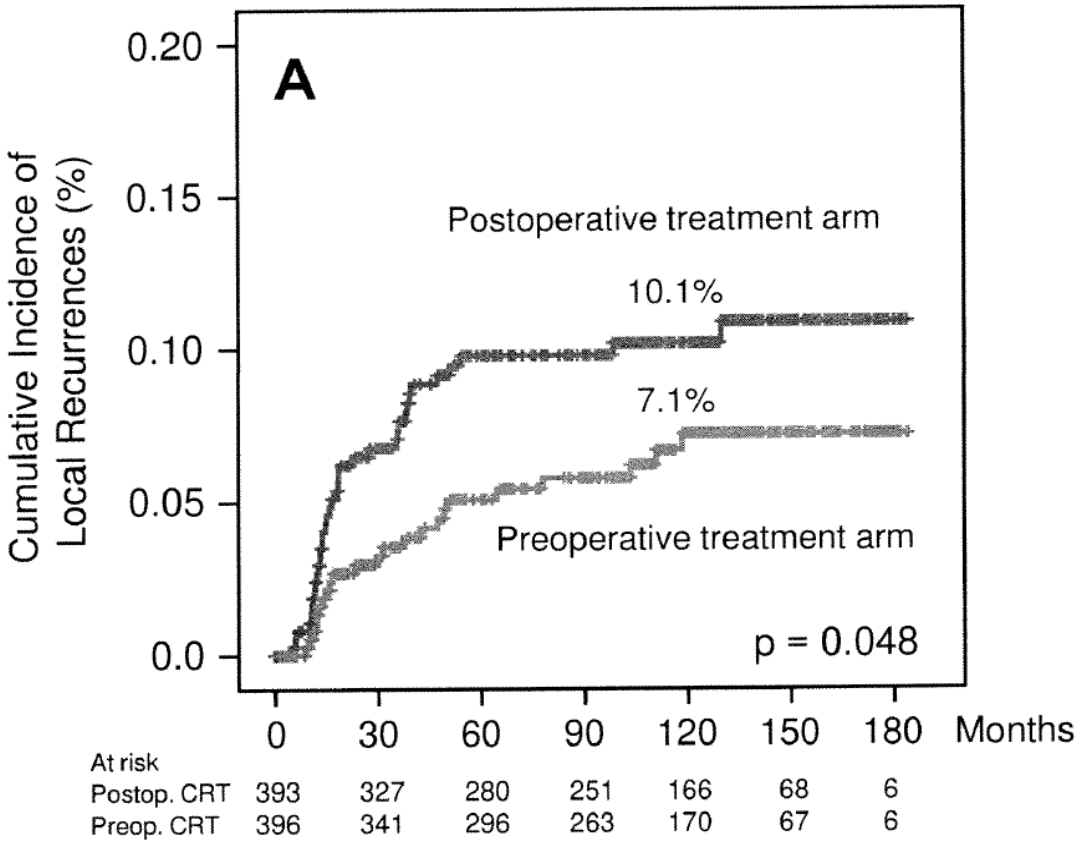


Sargent et al JCO 2007

CAO/ARO/AIO 94



CAO/ARO/AIO-94



Roedel et al JCO 2012

POF With MDACC Preop CMT

- 735 Pts, T3+ and/or N+
- Preop CMT, 1993-2008

Overall recurrence: 21%

- 85% single site
- 15% multiple

Site(s) of recurrence

- 10% lung (11% low, 10% middle, 8% upper)
- 6% liver
- 5% local

Ikoma et al, JCO 2017

Recommendations for CMT

Ideal regimen (pre or postop):

- **CI 5-FU**
- **Capecitabine (X-ACT, NSABP R-04)**

? Avoid Postop RT:

- **If TME with $\geq$ 12 LNs sampled then CT but no RT for T_3N_0**

Randomized Preop RT

- PMH
- MRC
- VA I
- VA II
- Stockholm I
- Stockholm II

- Norway
- MRC
- EORTC
- CVKO 95-04
- Swedish Rectal**

Meta-analysis

- JAMA 2000**
- Lancet 2001

CKVO 95-04 TME ± RT Trial

** = postop 50 Gy x 25 if margins +*

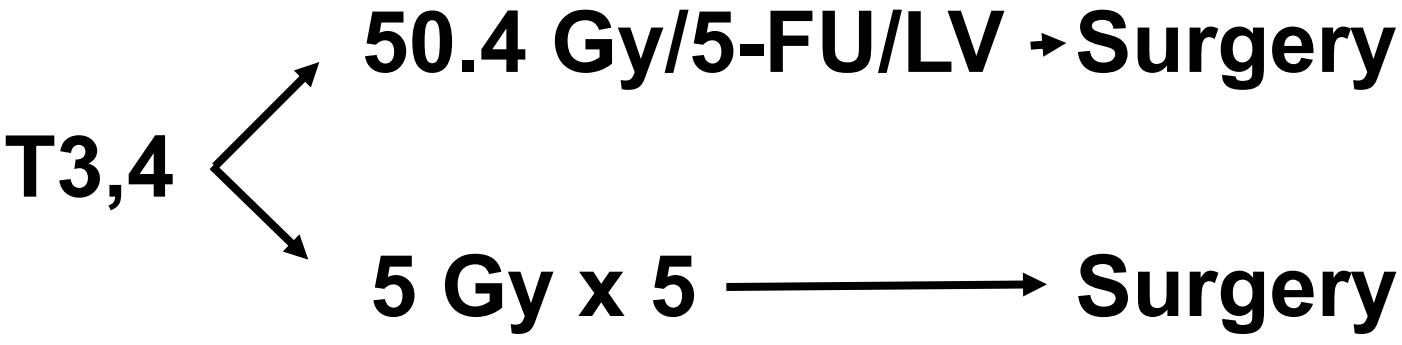
CKVO 95-04 TME ± RT Trial

Ann Surg 2007

	% 5-Yr Local Failure
TME	**11**
TME+RT	**6****

21% LF with TME alone for Stage III

Polish Preop Phase III Trial



- 316 pts
- no involvement of the sphincter
- TME only for distal tumors
- no QA

Bujko et al Br J Surg 2006

Polish I Phase III Trial

Results (%)	5 Gy x 5	50.4 Gy/CMT
pCR	1	16 *
% SP Preserv	61	58
% CRM+	13	4 *
% Compliance	98	69
% LF	9	14
% 4-Yr Surv	67	66

* = statistically significant

Polish II Phase III Trial

- 515 eligible pts, Median f/u 35 M
- Primary endpoint: R0 resection

Fixed cT3/4

5 Gy x 5 → 1 Wk → FOLFOX4 x 3 → S

50.4 Gy + b5-FU/LV wks 1&5 ⟶ S
+ b oxali weekly

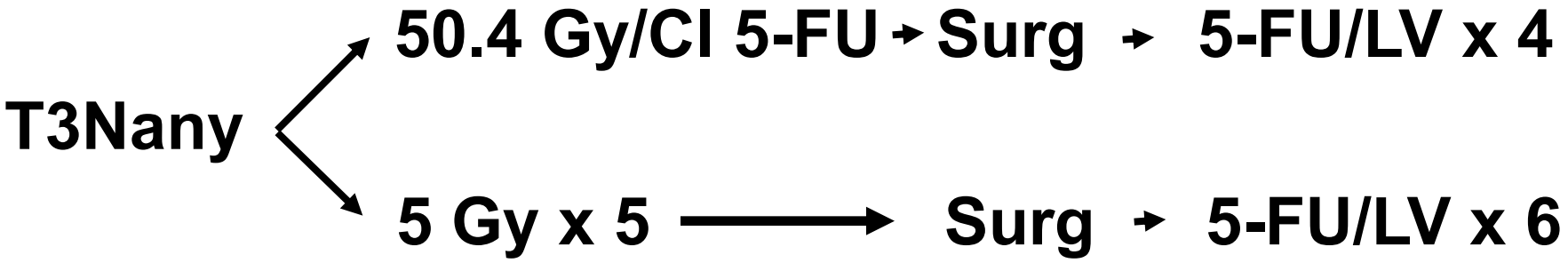
Bujko et al Ann Oncol 2016

Polish II Phase III Trial

	5 Gy x 5	ChemoRT
#	261	254
Gr 3+ toxicity	23%	21%
R0 resection	77%	71%
pCR	16%	12%
3-Yr LF	22%	21%
3-Yr DFS	53%	52%
3-Yr OS	73%	65% p=0.046

Bujko et al Ann Oncol 2016

Australian/NZ Preop Phase III



- 326 pts
- Median F/U: 5.9 Yr
- 56% N0 (staging not specified)
- Powered for LR of 15% (SC), 5% (LC)

Ngan JCO 2012

Australian/NZ Preop Phase III

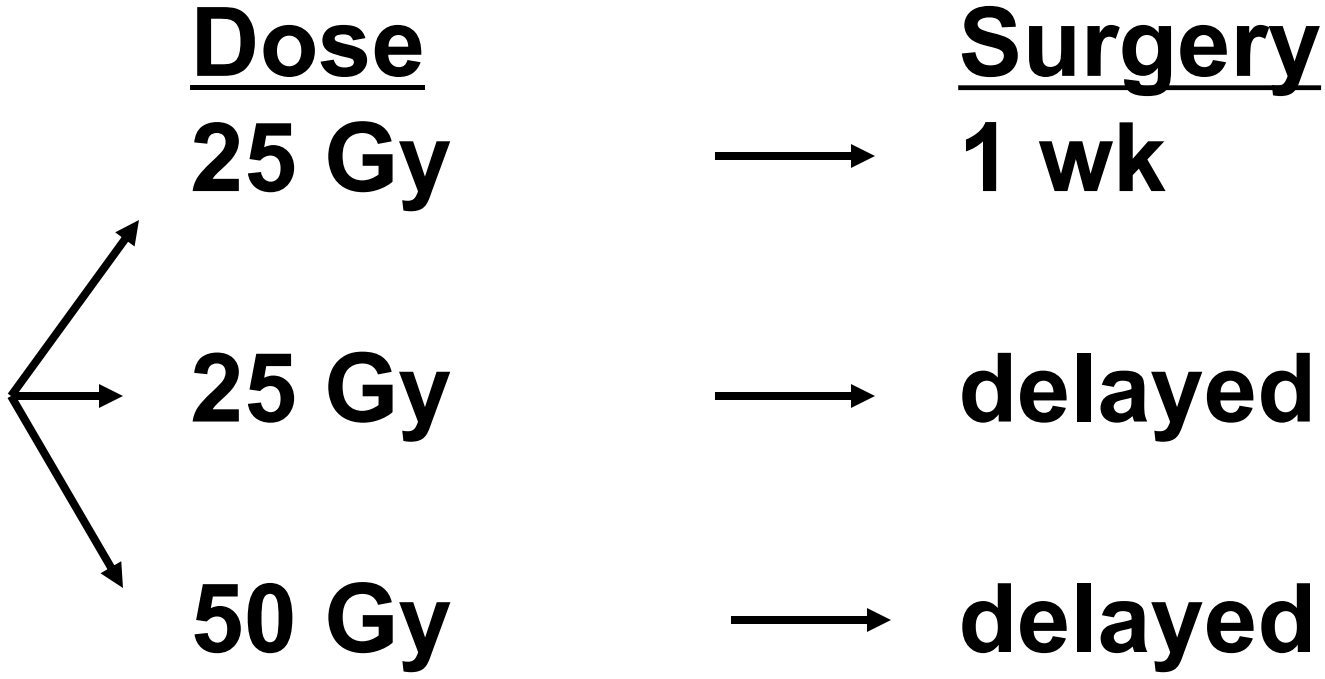
Results (%)	5 Gy x 5	50.4 Gy/CMT
5-Yr LF	7.5	5.7
5-Yr LF*	12.5	0
5-Yr Surv	74	70
Gr 3-4 Late Tox	7.7	8.9

*79 pts with distal tumors

Ngan et al JCO 2012

Stockholm III Trial

cT1-3, ≤ 15 anal verge (26-41% stage I), 5 yr med f/u



840 Pts = 385 in 3 arm and 455 in 2 arm (25 Gy only) randomization

Stockholm III Trial

Post-op (%)	25 Gy-*I*	25 Gy-*D*	50 Gy-*D*
Local Recur	2	3	5
Acute RT tox	1	7	5
Postop tox	50	38	39
(pooled)	53	41 (p=0.001)	
pCR	2	--------10------ (p=0.001)	

2019: pCR associated with ↑ OS (p=0.046) and TTP (0.027)

Erlandsson et al, Lancet Oncol 2017, Radiother Oncol 2019

Phase II: Post CMT FOLFOX

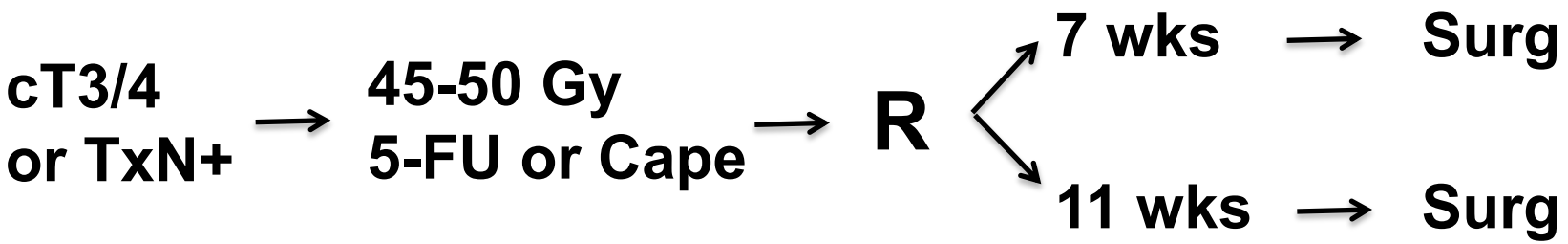
- 259 Pts, T3/4 and/or N+, 4 sequential arms
- ≤ 12 cm verge

		# Cycles mFOLFOX6	TME Week	%pCR	% Gr 3+ Surg Tox
Preop		0	12	18	15
50.4-54 Gy	→	2	18	25	6
CI 5-FU		4	22	30	4
		6	26	38	9

- no tumor progression prior to TME

Garcia-Aguilar et al, Lancet Oncol 2015

GRECCAR-6: 7 vs. 11 weeks



#	%Med Wks	%pCR	% Postop Morbidity	Comp
			p=0.04	p=0.02
126	7	15	32	19
129	11	17	45	33

Lefevre et al, JCO 2016

5 Gy x 5 + Induction CT

- 50 pts resectable/abatable M1 (84% liver, 10% lung, 6% both)

- 5 G x 5 → 2 wks → CAPOX/Bev x 6 → 6-8 wks → Surg+ RFA

Total

- 72% R0 resection (all sites)
- 3.8 Yr median survival

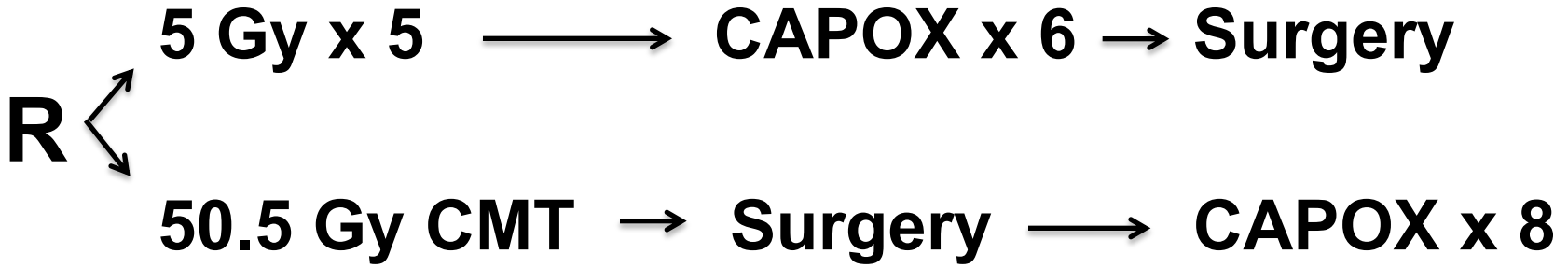
Pelvis

36 Pts had radical surgery

- 26% pCR
- 6% LR
- Exp arm of RAPIDO phase III

Van Dijk et al. Ann Oncol 2013
Bisschop et al. Ann Surg Oncol 2017

RAPIDO Phase III Trial



- Primary endpoint: 3-Yr DFS

Management of CRM+ s/p Preop Treatment

- 409 Pts – preop 45-50 Gy +/- CT
- 48 microscopic CRM+
- 23 M median f/u
- Excluded 2 pts who received postop EBRT

#	IORT	% 5-Yr LR
31	yes	16
		p=0.004
17	no	66

Alberda et al, IJROBP 2014

Watch and Wait PRISMA Review

- 920 Pts, 15 trials, 2004-2016

- 575 underwent w&w after cCR
  345 surgery

#	Rx	(M) F/U	%LF	%Salvg	%DFS	%OS
575	w&w	40	21	93	83	92
345	surg	40	8	-	88	92

Chang et al, Ann Surg Oncol 2017

Watch and Wait:
IWWD International Database

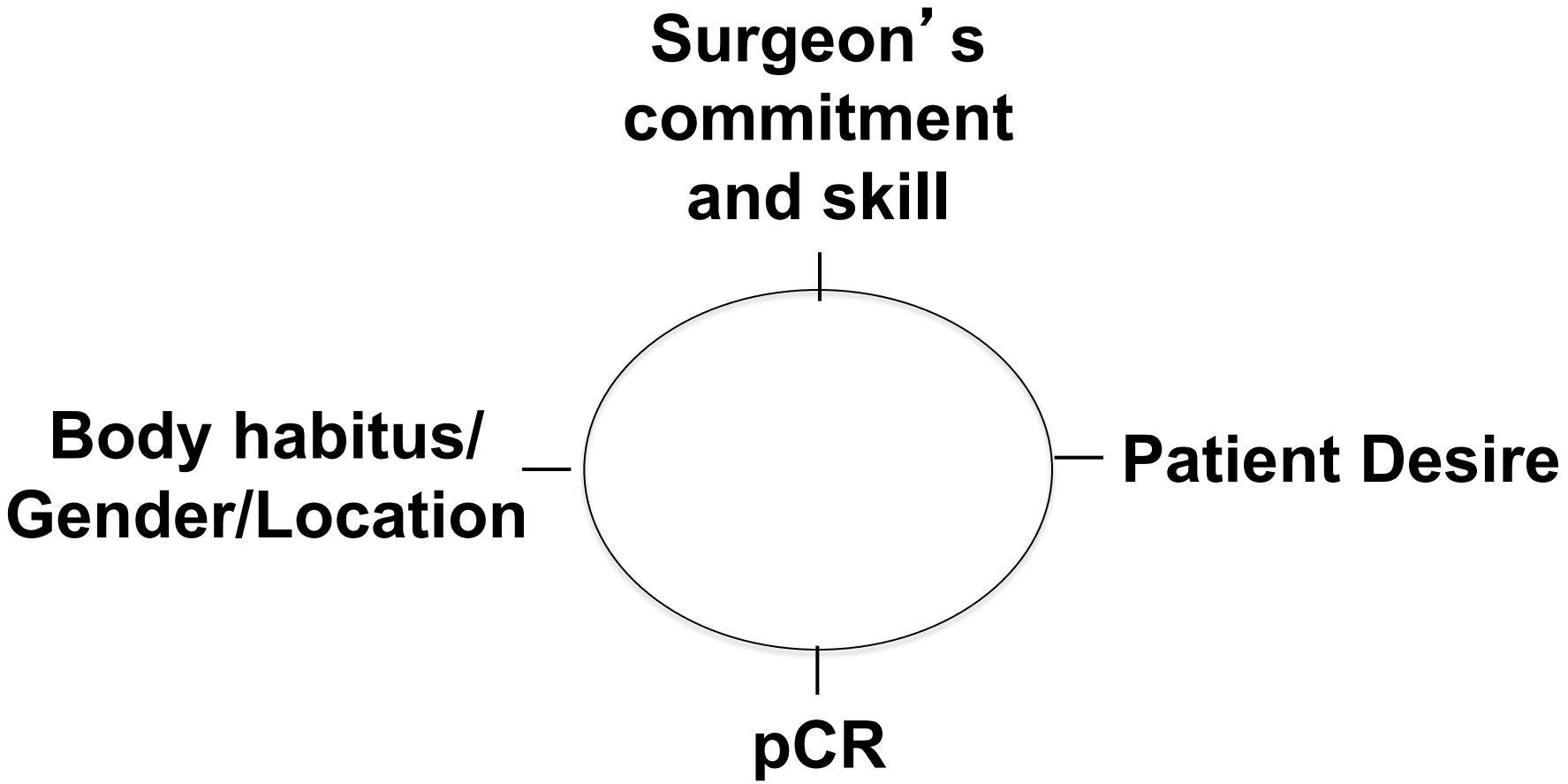
- 1009 Pts - 880 with a cCR
- 2015-2017

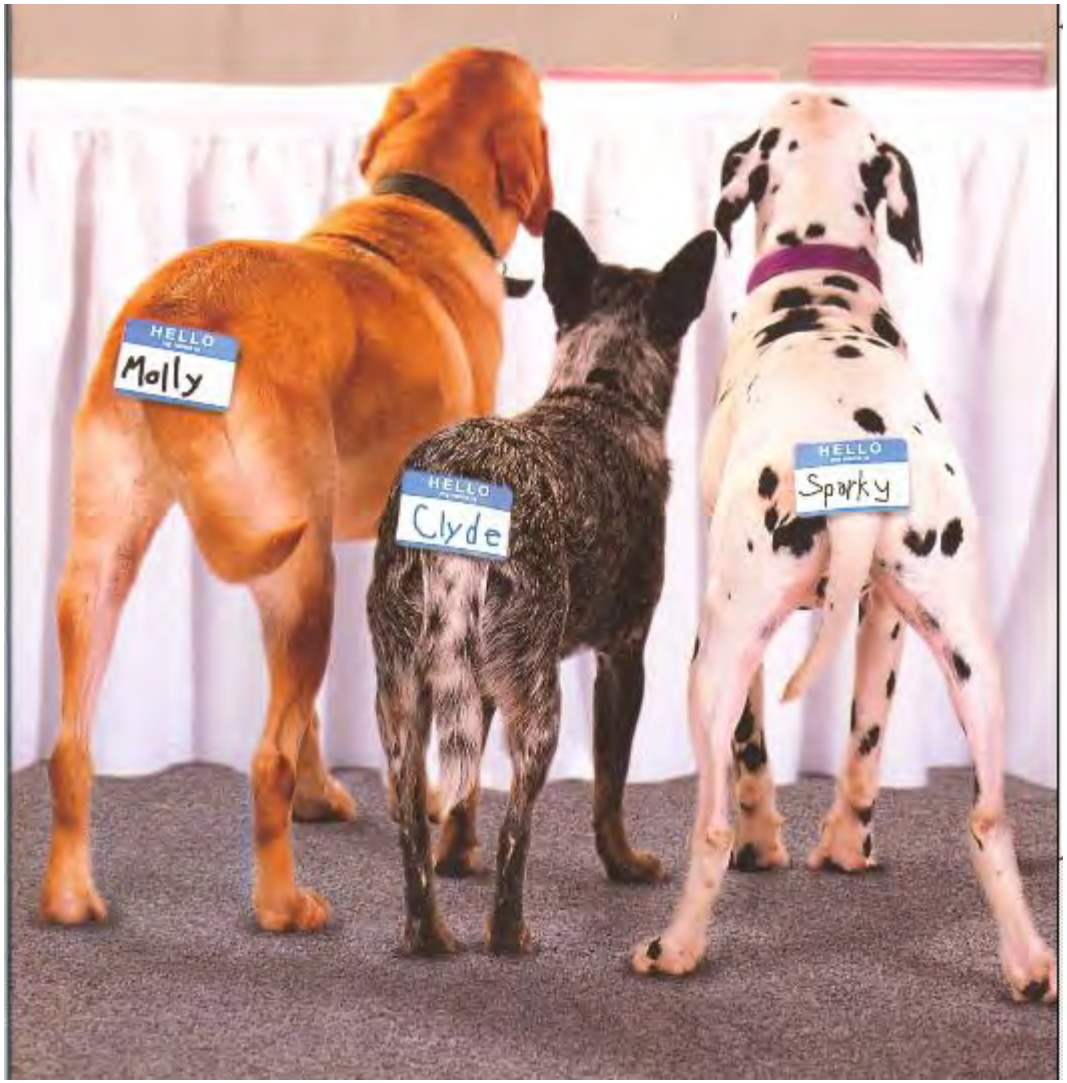
- 2-yr cummulative regrowth
  - 25% overall
  - 88% in the first 2 years
  - 97% in the bowel wall

85% 5-Yr surv

van der Valk et al Lancet 2018

Sphincter Preservation




HELLO
Molly
HELLO
Clyde
HELLO
Sparky

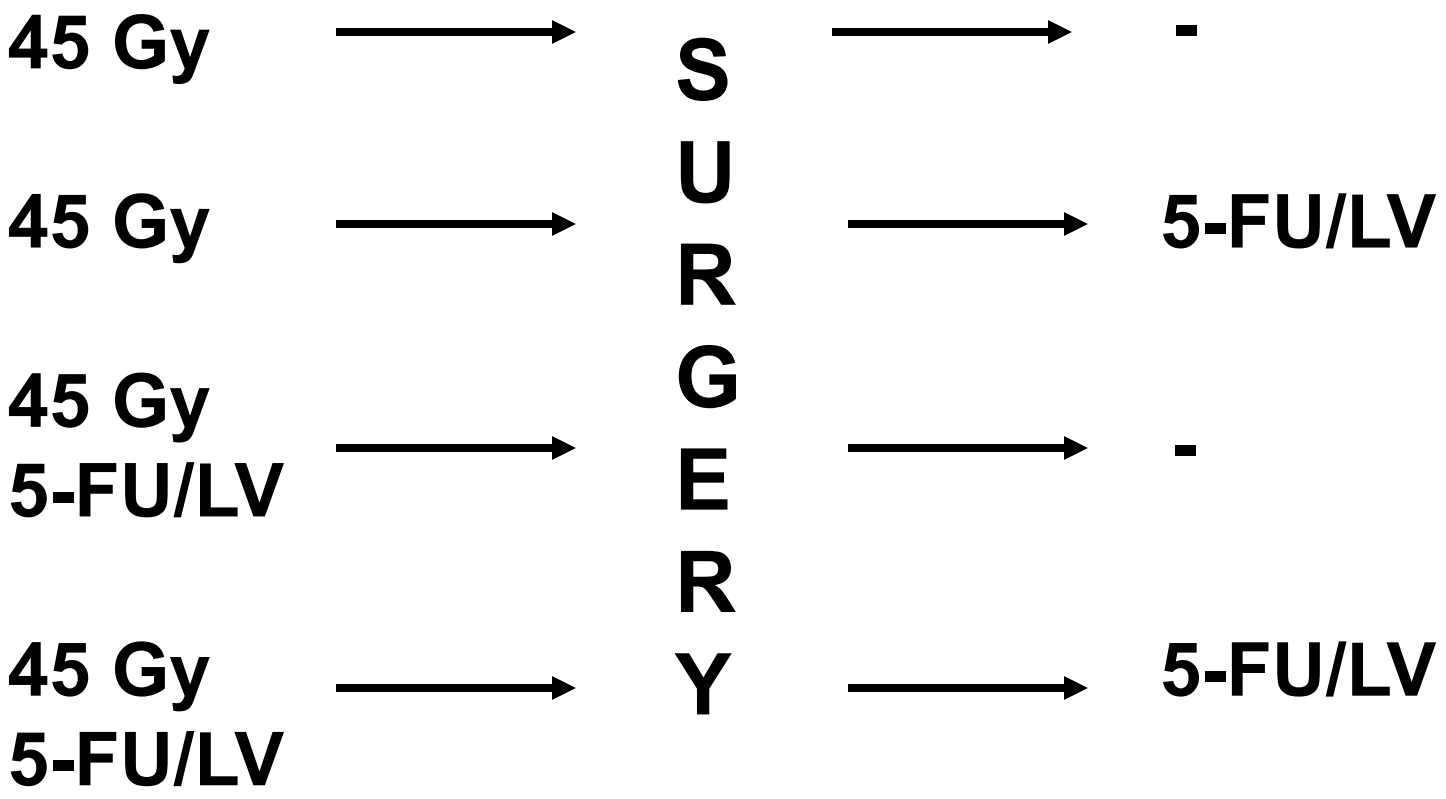
CAO/ARO/AIO 94

Median F/U 11 Years – Intent to Treat

Outcome	% 10 Yr Actuarial		
	Preop	Postop	
Local recur	7	10	0.009
Distant failure	28	28	ns
Survival	60	60	ns

Sauer et al JCO 2012

EORTC 22921



PROCTOR-SCRIPT

Preop 5 Gy x 5 or 45 Gy/cape → R ⇄ Observe / 5FU/LV or Cape

- **470 of 840 pts enrolled, median f/u 5-yr**

Rx	%LF	% DF	%5-Yr Surv
Observ	8	39	80
CT	8	35	79

Breugom et al Ann Oncol 2015

Chronicle Trial

≥ 45 Gy
FU based → Surg ⇄ Xelox x 6 / Observation

Post-op	#	% Comp 6 Cy	% 3-Yr Surv
Xelox	54	48	89
Observ	59	-	88

Glynne-Jones et al Ann Oncol 2014

Selected New Agents in Colorectal Cancer

Cytotoxics

- CPT-11
- Oxaliplatin
- Capecitabine
- UFT
- Tomudex
- S-1

Targeted

- EGFR
  - MAb: Cetuximab, Panitumumab
  - TK: Gefitinib, Erlotinib
- VEGF
  - MAb: Bevacizumab
  - TK: Vatalanib

Randomized Phase II Preop CMT: CAPOX ± Cetuximab

- EXPERT-C, 149 pts, 90 KRAS WT
- MRI: 98% T3, 56% CRM+, 72% extramural inv

CAPOX x 4 ± Cetuximab → 50.4+ Cape → TME → CAPOX x 4 ± Cetuximab

s/p CMT:	% ORR		% pCR*		% 3-Yr Surv	
	C+	C-	C+	C-	C+	C-
KRAS wt	93	75	11	9	92	65
	p=0.028		p=NS		p=0.02	

* = endpoint

Sclafani et al JNCI 2014

Preop CMT + Bevacizumab

Series	#	Preop	%pCR	%Grade 3+ Toxicity
Brown	26	FOLFOX Bev/50.4	20	76
Austria	8	Cape/Bev	25	50

· Both trials stopped early due to toxicity

Dipetrillo et al, IJROBP 2012
Resch et al. Radiother Oncol 2012

Role of Oxali

Trial	% Comp		%pCR		%LF		% DFS	
	Ox+	Ox-	Ox+	Ox-	Ox+	Ox-	Ox+	Ox-
ACCORD			19	14	4	6	83	88
STAR-01			16	16				
NSABP			21	19	nd	nd	nd	nd
PETACC-6	54[1]	67					74[3]	75
AIO	77[2]	78	17	13*			69[4]	64*

1 = completed, 2 = started, 3 = 3-yr DFS, 4 = 5-yr

ACCORD 12/0405 PRODIGE 02

- 598 Pts, all TME
- cT3 and/or N+

(%)

	Gr 3+ toxicity	SSS	pCR	CRM+	3-Year LF	Surv
45 Gy CAPE	11	75	14	11	6	88
	(<0.001)					
50 Gy CAPOX	25	78	19	6	4	83

5-Yr F/U: no diff in DFS, S, LC, toxicity

Gerard et al: JCO 2012
Azria et al. Ann Oncol 2017

CAO/ARO/AIO-04 Preop

- 1265 Pts, median f/u: 50 M
- cT3/4 and/or N+, ≤ 12 cm AV
- 77-78% started postop CT
- endpoint - DFS

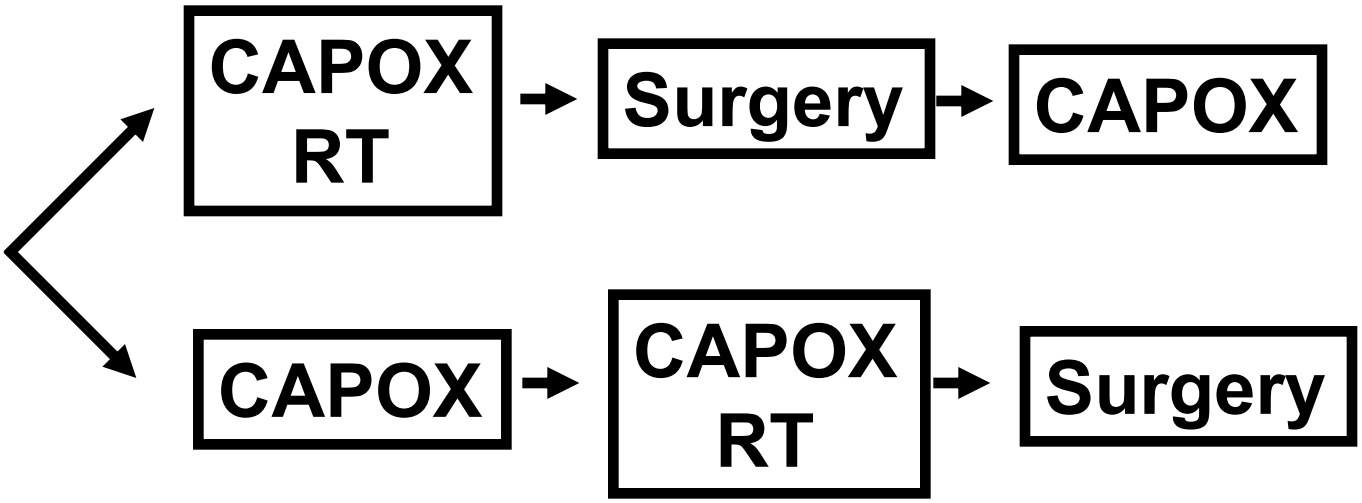
	%Gr3+	%pCR	%3yrDFS
50.4 Gy*			
5-FU (1 g/m2 w 1,5)	20	13	71
		(p = 0.031)	(p=0.03)
50.4 Gy			
5-FUOX (50 mg/m2/w)	24	17	76

** Best arm of CAO/ARO/AIO-94:*

Rodel et al Lancet Oncol 2015

GCR-3 Randomized Phase II

- 108 pts



Fernandez-Martos et al. JCO 2010

GCR-3 Randomized Phase II

	Induction	Standard	p
% pCR	14	13	-
% Gr 3-4 toxicity	17	51	0.00004
% received all 4 cycles	93	51	0.0001

Fernandez-Martos et al. JCO 2010

GCR-3 Randomized Phase II

	Induction	Standard
% LF	2	5
% DF	21	23

Fernandez-Martos et al. ASCO GI 2014

Phase II Randomized Trial: Post CMT Chemotherapy

- 144 pts stage II/III rectal cancer
- Cl5-FU + 50.4 Gy

Rx				%pCR	%Postop Comp
CMT →	Surg (6 wks) (6 wks)			18	40
				(p=NS)	
CMT →	mFOLFOX6 if cResponse	→	Surg (11 wks)	25	40

Garcia-Aguilar et al, Ann Surg 2011

TNT - MSKCC

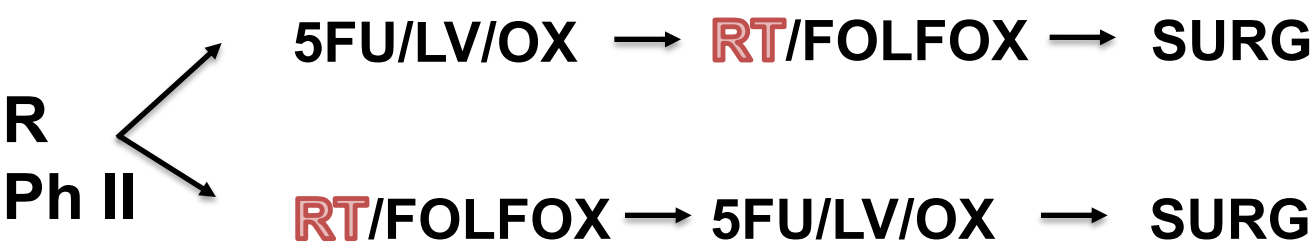
2009-2015
Retrospective cohort analysis

	TNT	Std ChemoRT
#	308	320
TotalCR*	36%	21%
pCR	18%	17%
cCR (1Yr)	22%	6%

TNT inc cCR @ 1 yr but pCR was the same

Cercek et al JAMA Oncol 2018

CAO/ARO/AIO-12



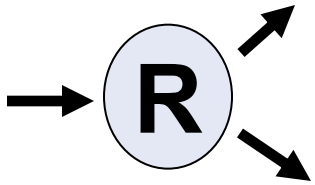
	Induction	ChemoRT
#	156	150
Gr 3+ tox	37%	27%
Compliance	78%	91%
pCR	17%	25%

Fokas et al, JCO 2019

NRG TNT (Total Neoadjuvant Therapy) RPhase II

- *T3-4; any N*
- *<5cm verge*

FOLFOX X 8



Capecitabine (825 mg BID) 50.4 Gy RT

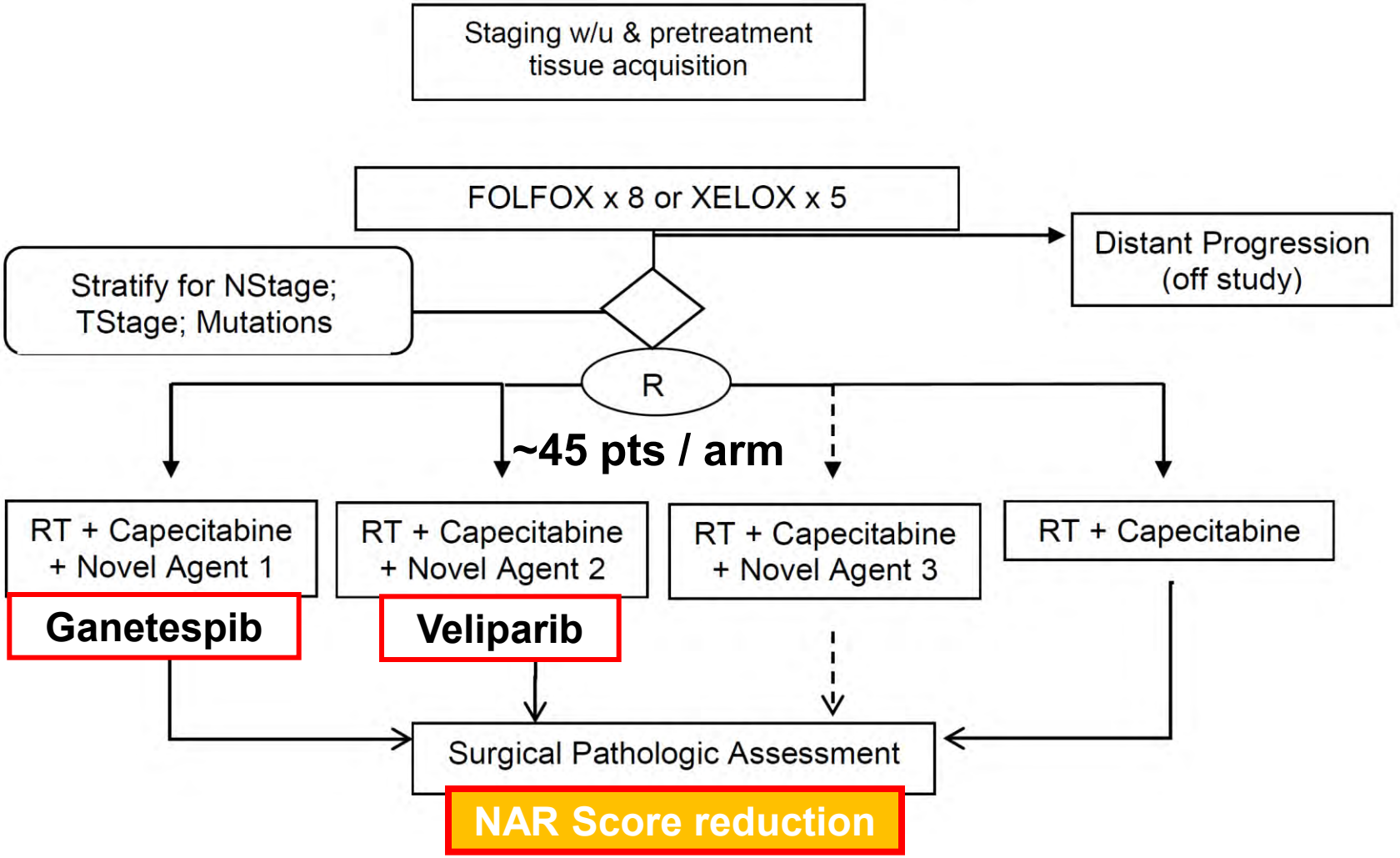
Cape/RT + rolling biologics (i.e. perifosine)*

N=170
Endpoint: NAR
Secondary: pCR 22 to 35%

****Awaiting pilot data for biologics***

TNT Master Modular Protocol

DISTAL (T3-4; any N; ≤ 5 cm from anal verge) or **BULKY** (T4 or close pelvic margin)
or **HIGH RISK FOR METS** (N2)
Randomized Phase II Platform with PARALLEL (non-comparative) ARMS



Preop CMT – Selective RT

· 32 Pts, LAR eligible, uT2N1, uT3N0-1

FOXFOX/BEV x 4 → FOLFOX x 2 → Surgery

· If preop POD ⟶ salvage preop RT
· If pT4, N2, or margin+ → post RT

· R0: 30/30
· pCR: 25%
· No preop RT, 2 postop RT
· 4 years: 0 LF, 84% DFS

**** Alliance N1048 – 1000 pt trial***

Schrag et al JCO 2014

Radiation Dose Escalation

Phase III randomized
248 pts, cT3-4
50.4 pelvic RT + UFT/LV
HDR: 5 Gy x 2 @ 1 cm

	cPR	R0 (T3)		TRG+2		Surg Comp
HDR +	22	99	*	44	*	19
None	20	90		29		19

* p = ss

Jakobsen et al Proc ASCO 2011

Preop CMT – Selective RT

- 46 pts, Multicenter phase II
- MRI: T3 or ≥ 2mm from mesorectal fascia *(59% LN+)*
- Mid rectal (> 5 cm from AV)
- 4 cycles Induction CAPOX-Bev

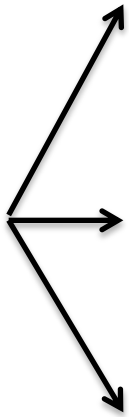
- None required preop CMT
- 15% pCR, all R0
- 7% LR median f/u 41 M

Pre-RX EMVI	3-Yr DFS %	3-Yr LR %
Yes	44	44
	(p=0.0001)	(p=0.0019)
No	96	4

Fernandez-Martos et al, Ann Oncol 2017

Preop CMT - Selective RT
FOWARC Trial

495 pts, stage II-III

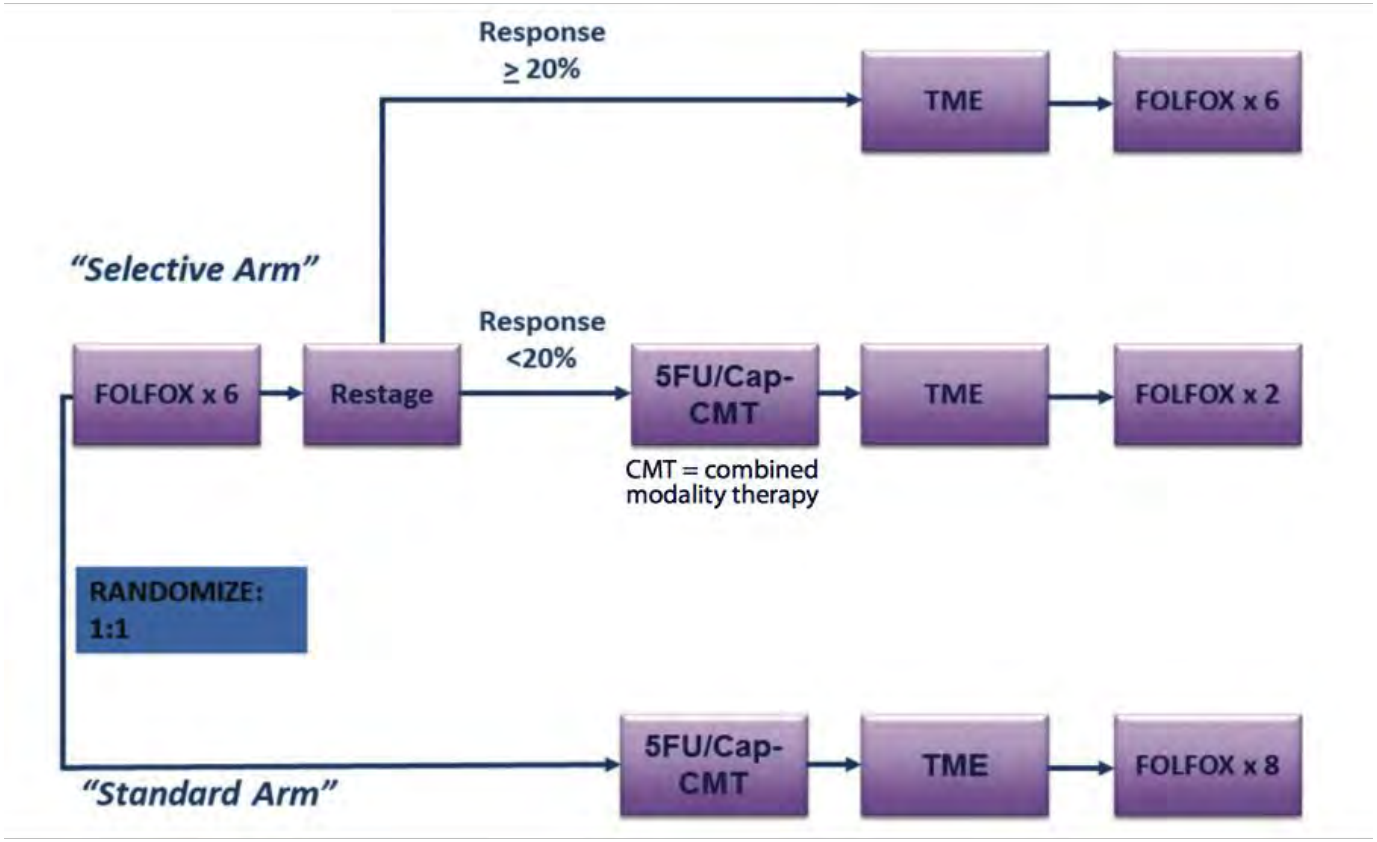


		% pCR	Gr 3+ Tox %
deGramont x 5 46-50.4 Gy	TME	14	68
mFOLFOX6 x 5 46-50.4 Gy	TME	28	55
mFOLFOX6 x4-6	TME	7	73

Deng et al, JCO 2016

PROSPECT Trial

Eligibility: cT2N1, T3N0, T3N1, non-APR
Primary endpoints: R0, 2-Yr DFS, time to LR




Butt-scented!
My favorite!
Big Sniff
Candles
smith

Conclusions

1) Short course vs. long course chemoRT
   - waiting for RAPIDO
2) TNT – reasonable but German trial negative
3) Non-operative approach
   - still watching and waiting
4) Role of postop adjuvant chemotherapy
   - data do not support but still prescribe
5) ChemoRT beyond 5-FU – none yet
6) Selective pelvic RT – PROSPECT