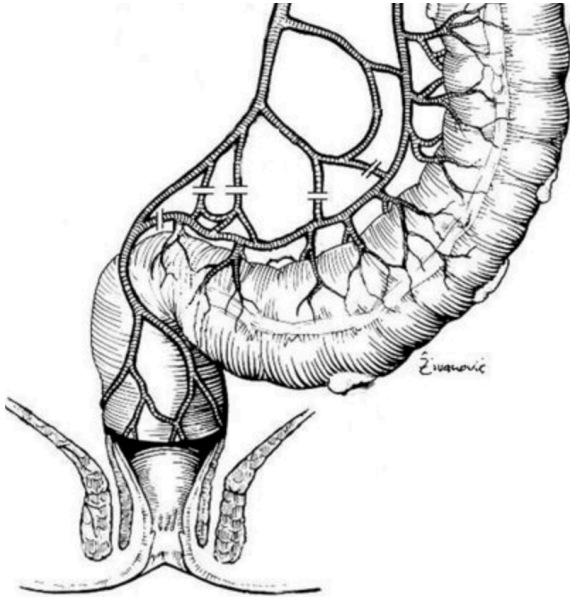
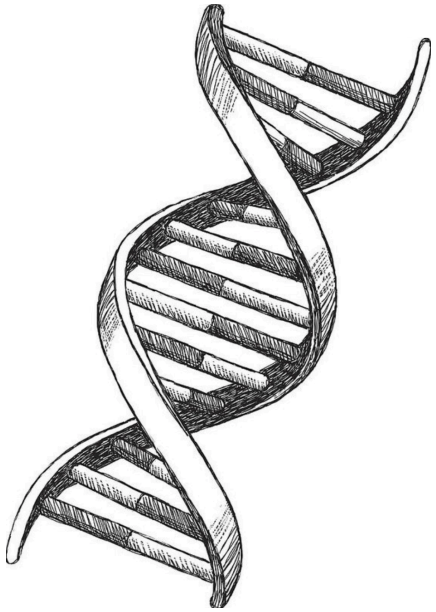




Rectal cancer

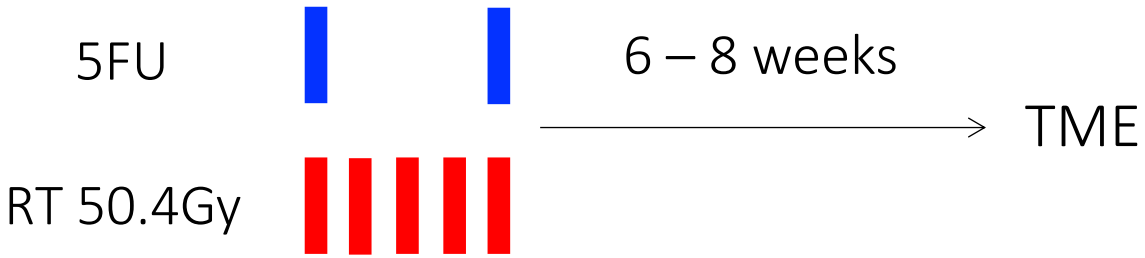
What is the standard neoadjuvant approach:

Total Neoadjuvant Therapy or RT with fluoropyrimidines?

Alexandre A. A. Jácome, MD, PhD

Postdoctoral Fellow in Gastrointestinal Oncology at MD Anderson Cancer Center

Rectal cancer: What is the standard neoadjuvant approach?



Sauer R. N Engl J Med 2004

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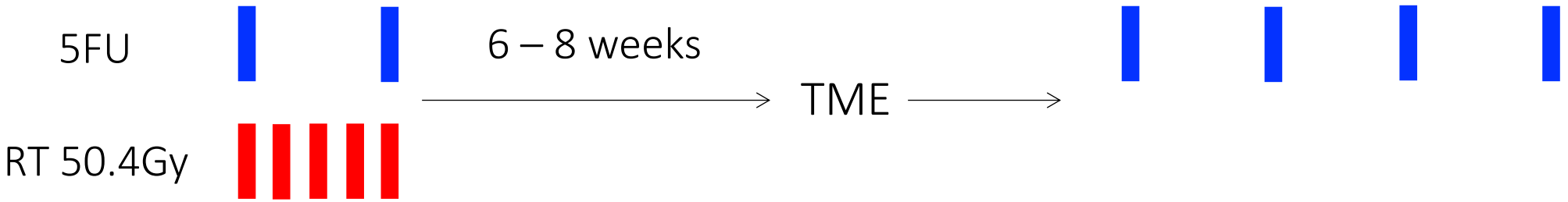

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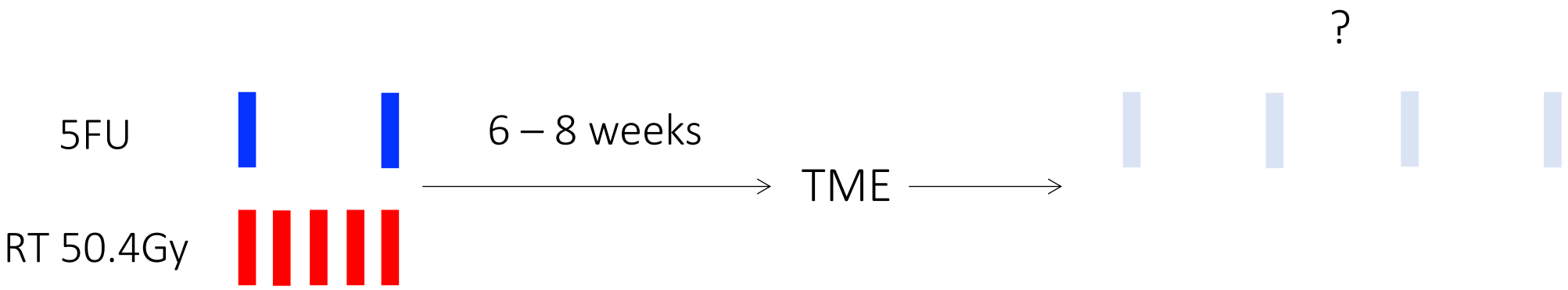

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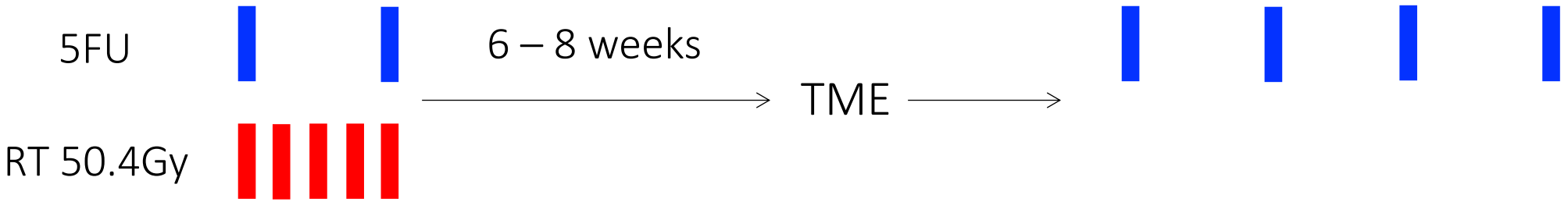

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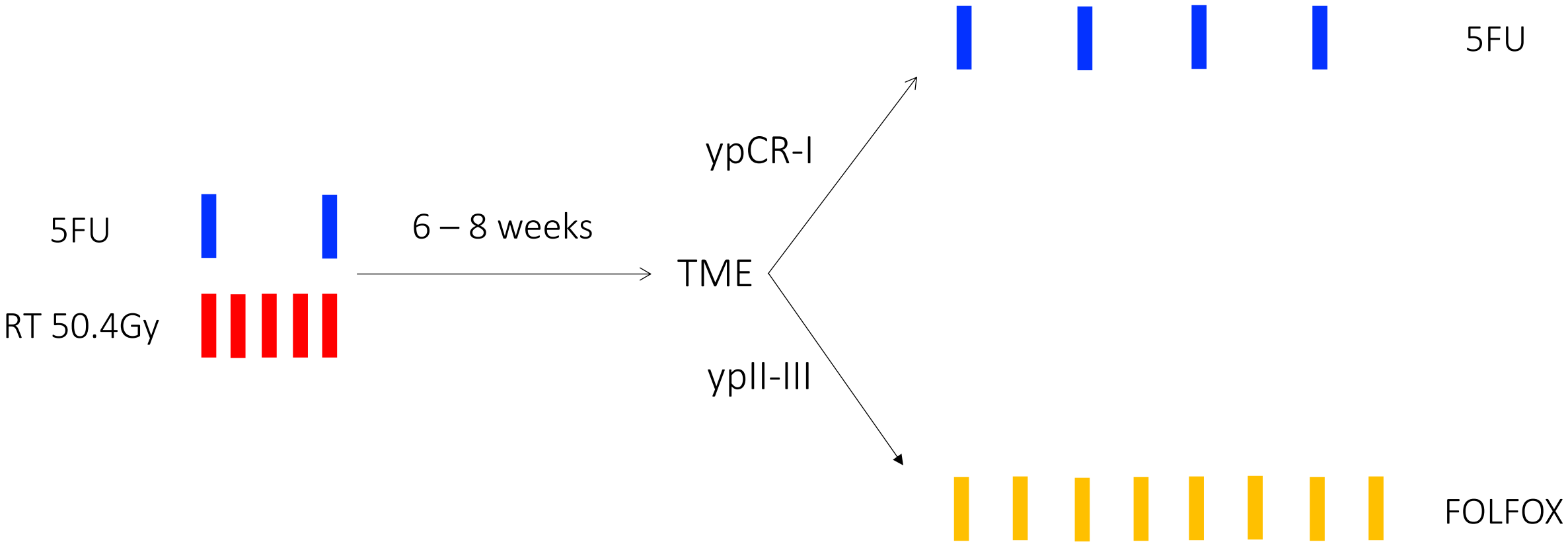
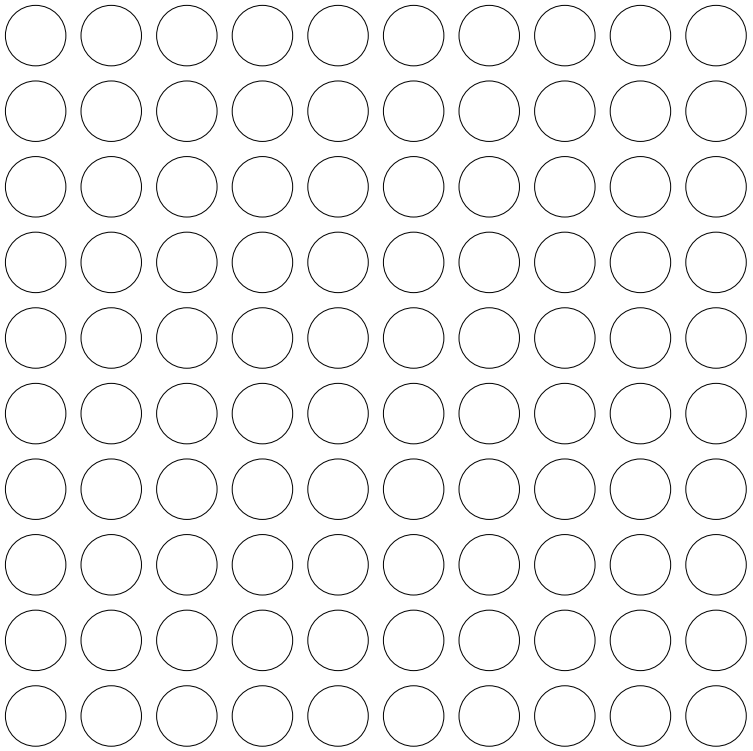


Sauer R. N Engl J Med 2004, Hong YS. Lancet Oncol 2014

Precision Medicine



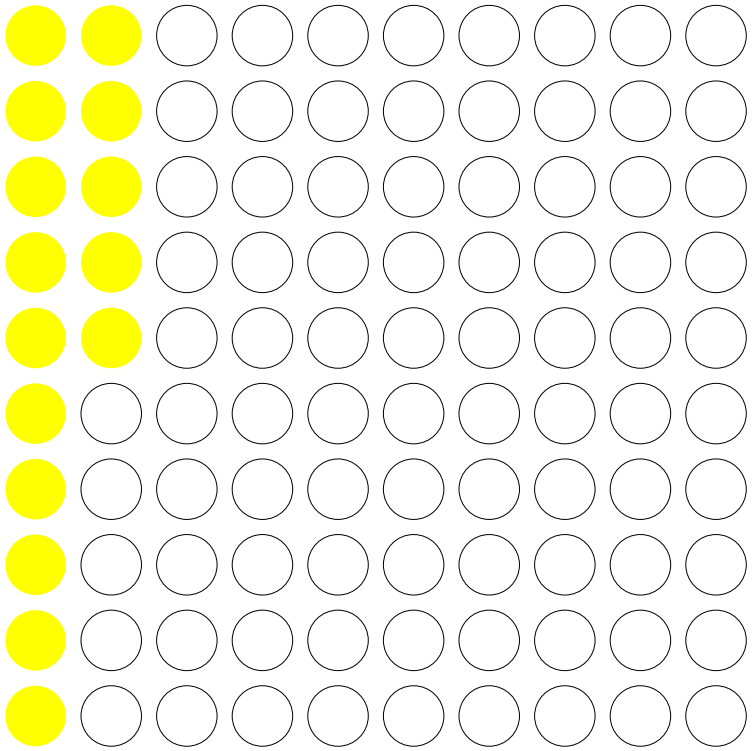
100 patients

cT3-4 N+

Neoadjuvant CRT + TME + adjuvant oxaliplatin

Sauer R. N Engl J Med 2004, Hong YS J Clin Oncol 2018

Precision Medicine



Cured by CRT

100 patients

cT3-4 N+

Neoadjuvant CRT + TME + adjuvant oxaliplatin

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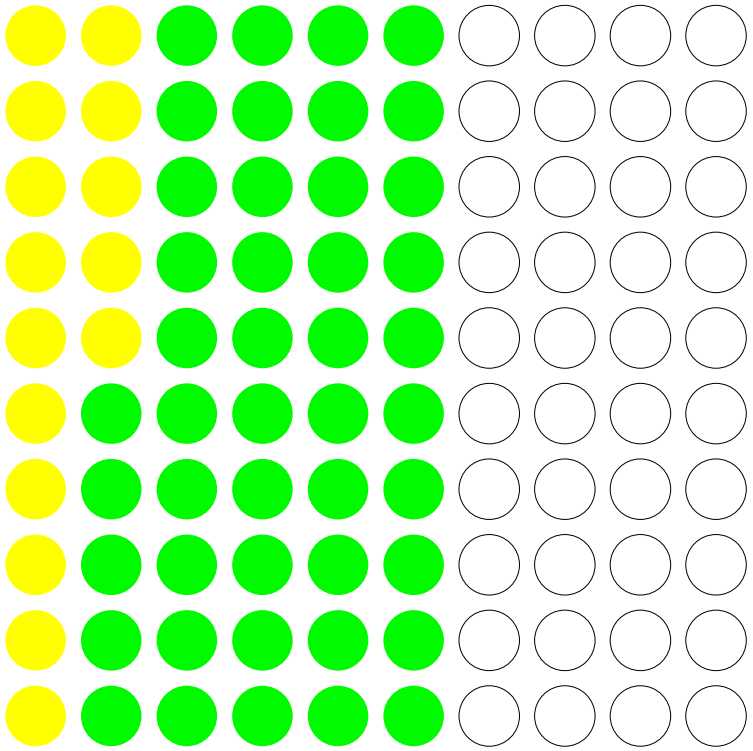

Cured by CRT

Cured by TME

100 patients

cT3-4 N+

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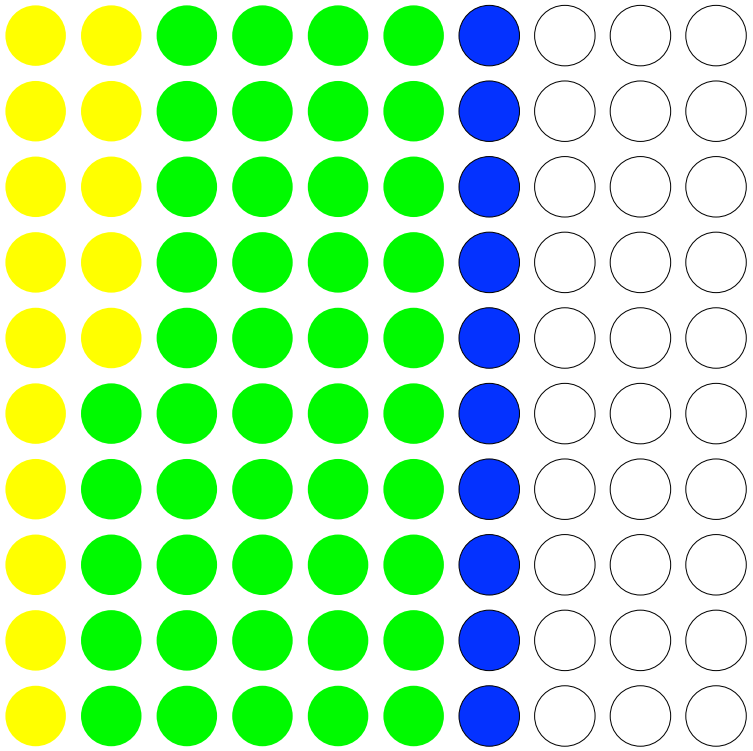

Cured by CRT

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Sauer R. N Engl J Med 2004, Hong YS J Clin Oncol 2018

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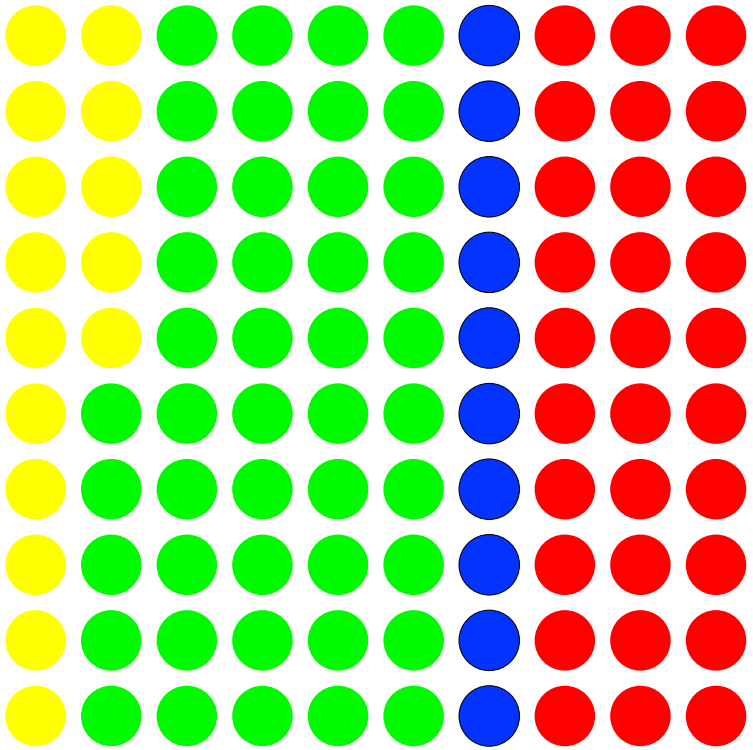
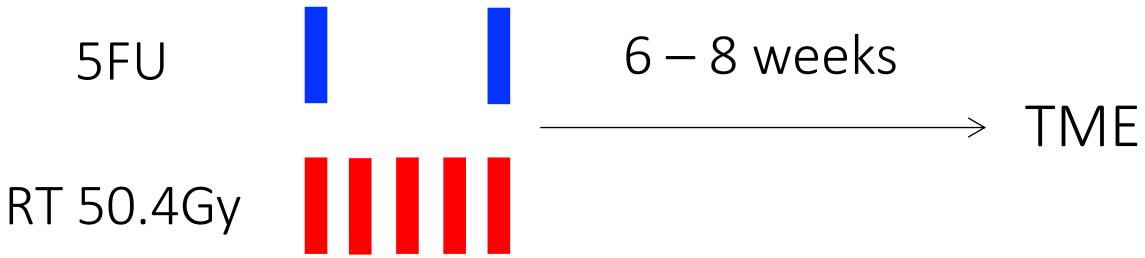


100 patients
cT3-4 N+
Neoadjuvant CRT + TME + adjuvant oxaliplatin

Cured by CRT
Cured by TME
Cured by adj. oxaliplatin
Recurrence

Sauer R. N Engl J Med 2004, Hong YS J Clin Oncol 2018

Rectal cancer: What is the standard neoadjuvant approach?



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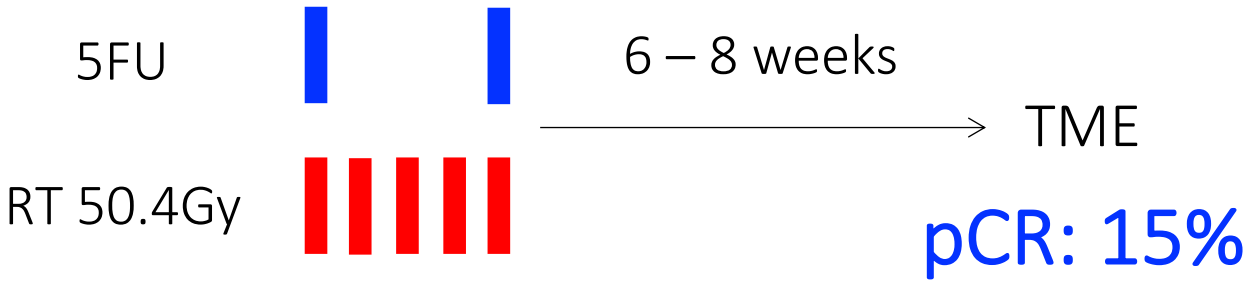
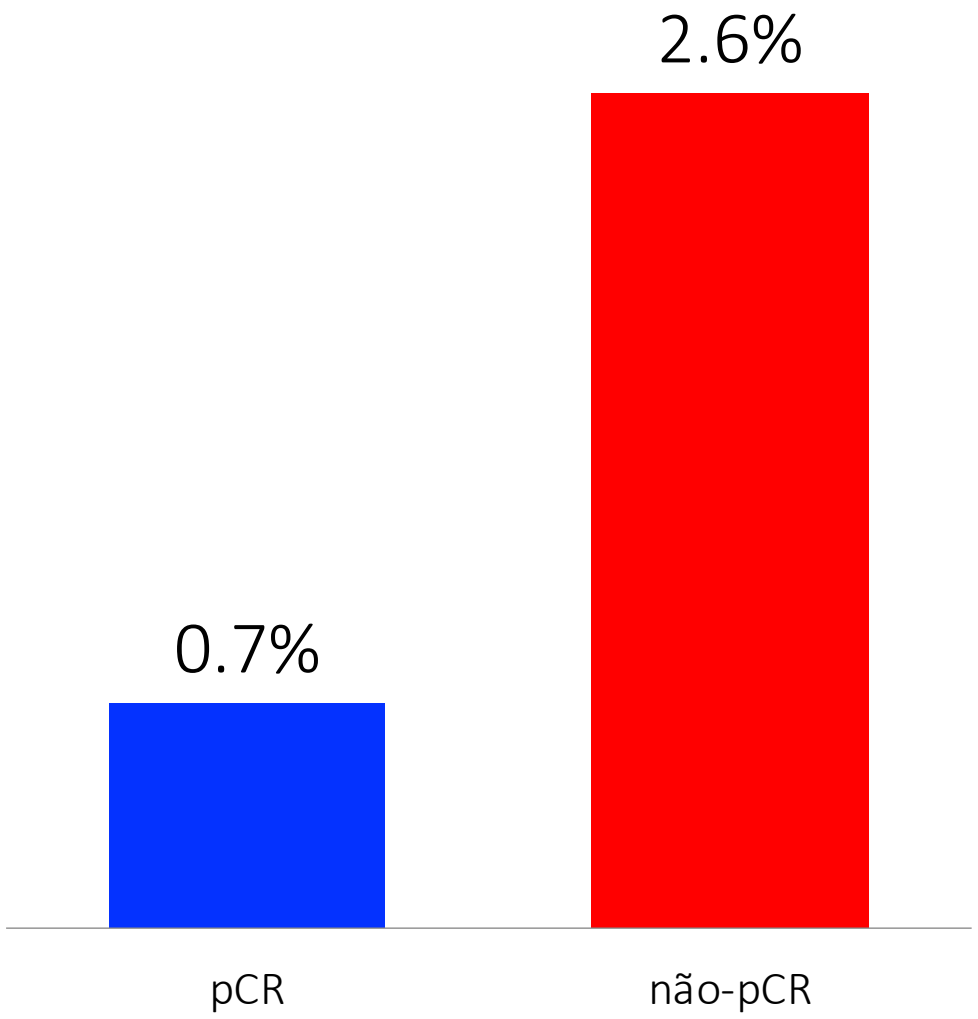


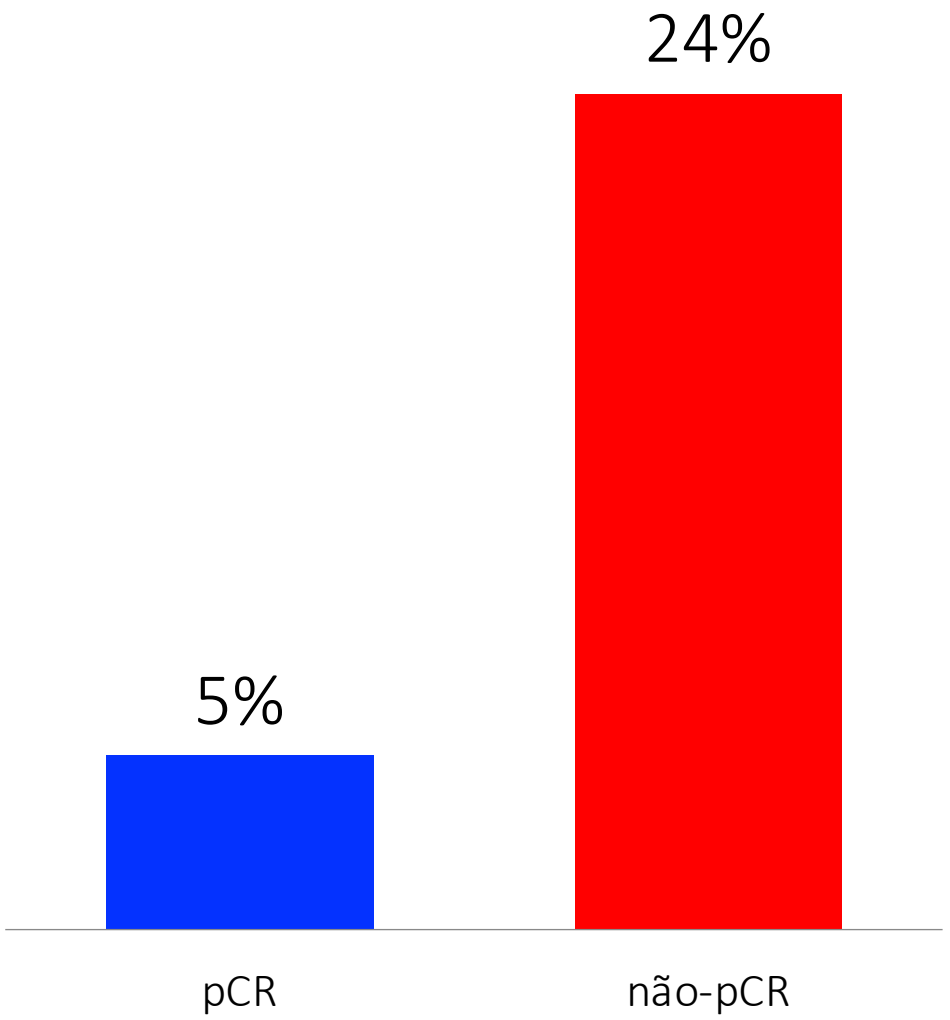
Sauer R. N Engl J Med 2004

Local recurrence



Zorcolo L. Ann Surg Oncol 2012, Martin ST. Br J Surgery 2012

Distant recurrence



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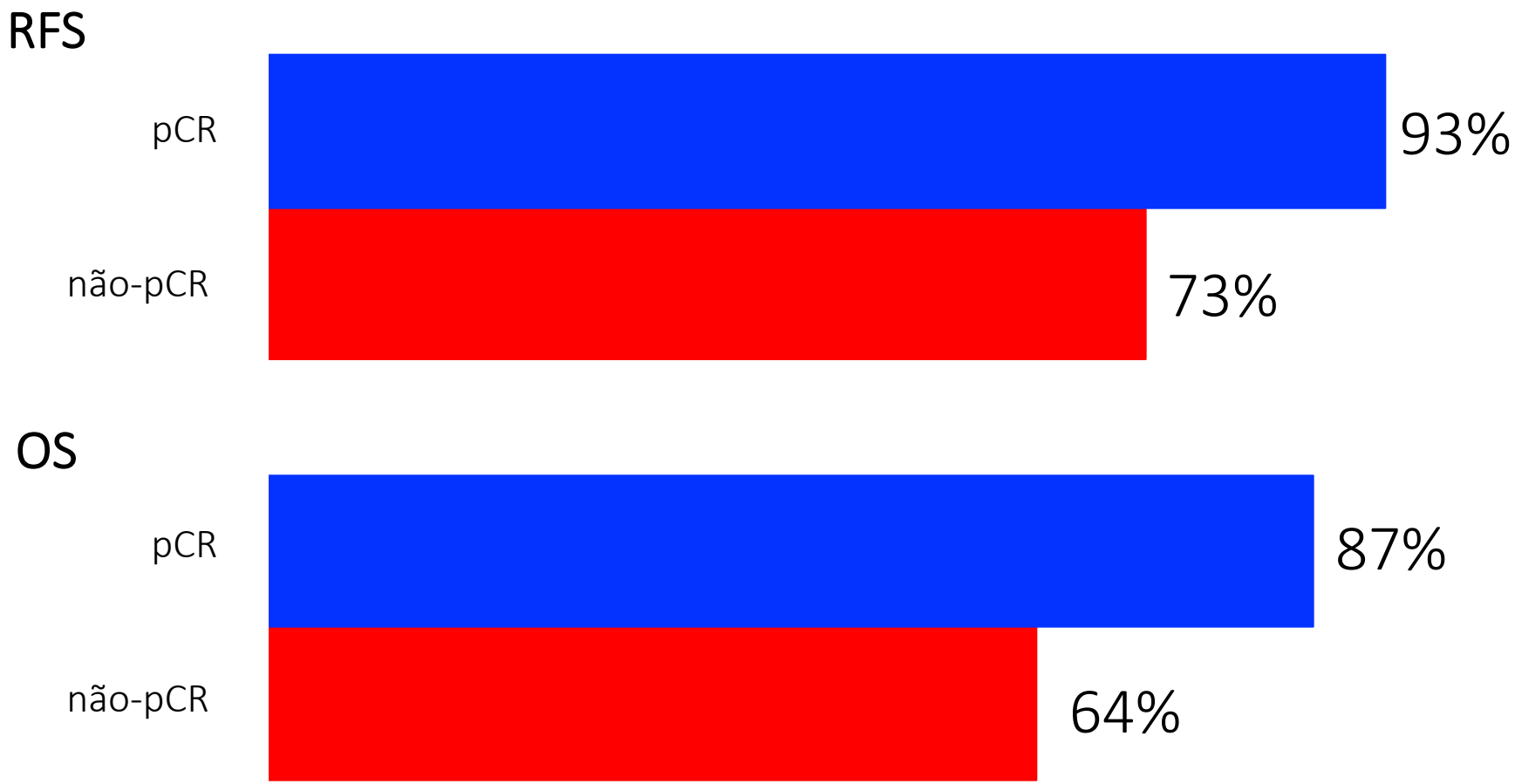
5-year recurrence-free and overall survival



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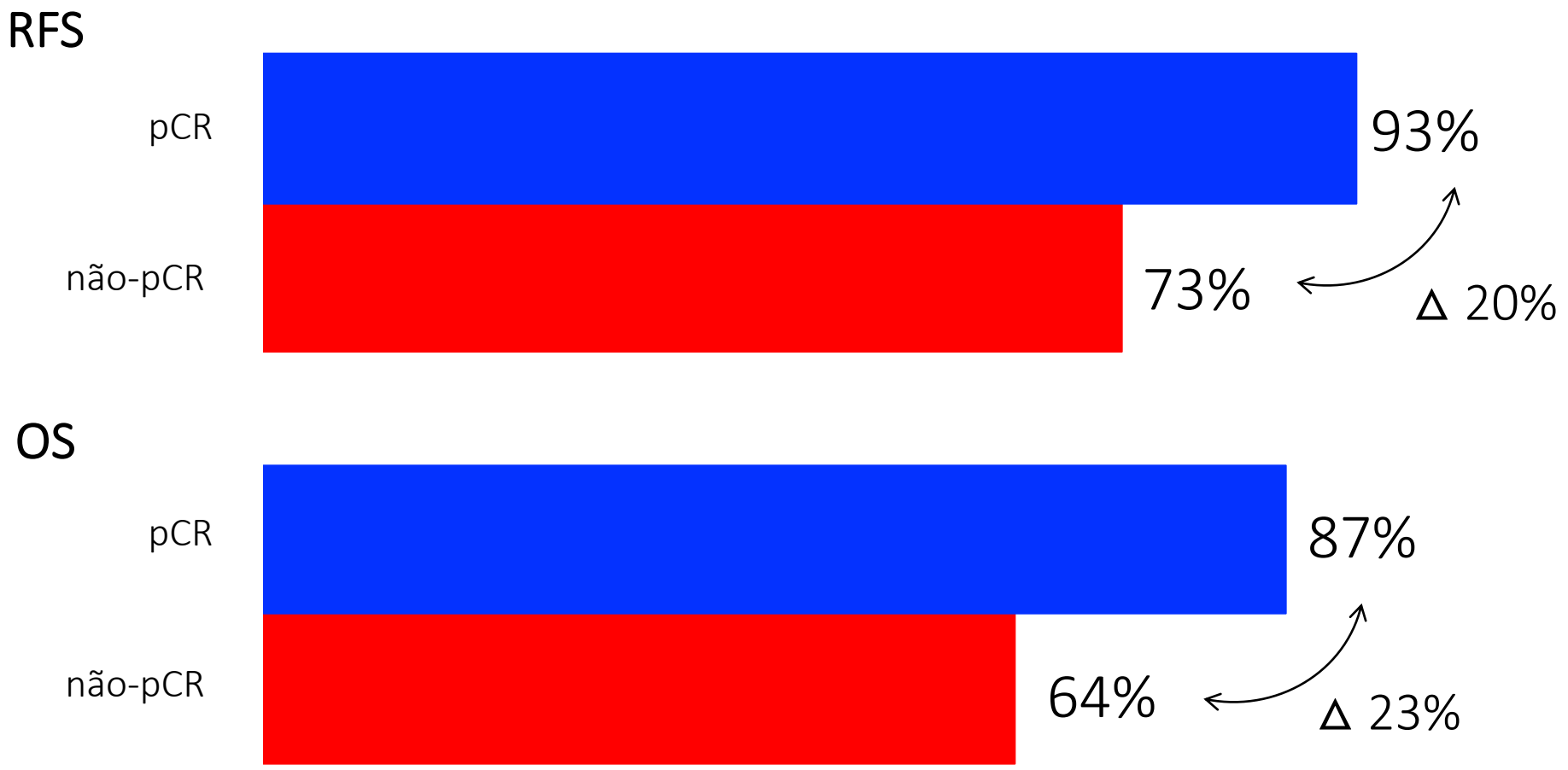

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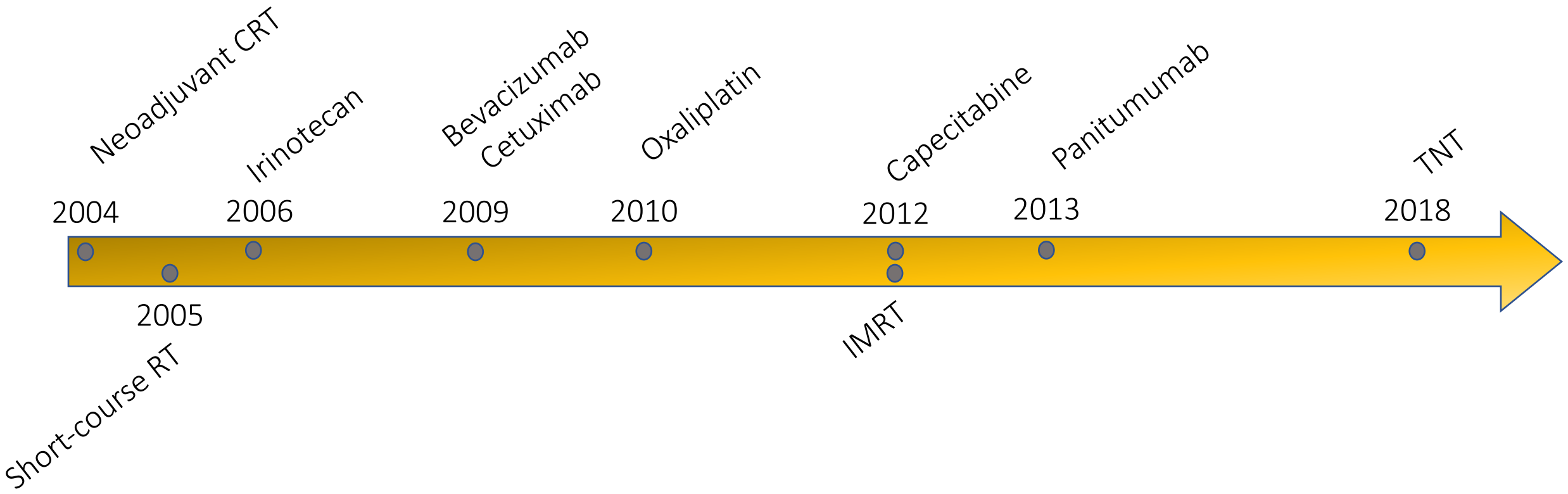

Sauer R N Engl J Med 2004, Peeters KC J Clin Oncol 2005, Navarro M Int J Radiat Oncol Biol Phys 2006, Horisberger K Int J Radiat Oncol Biol Phys 2009, Willett CG J Clin Oncol 2009, Gérard JP J Clin Oncol 2010, Jabbour SK Int J Surg Oncol 2012, Hofheinz RD Lancet Oncol 2012, Helbling D Ann Oncol 2013, Cercek A JAMA Oncol 2018

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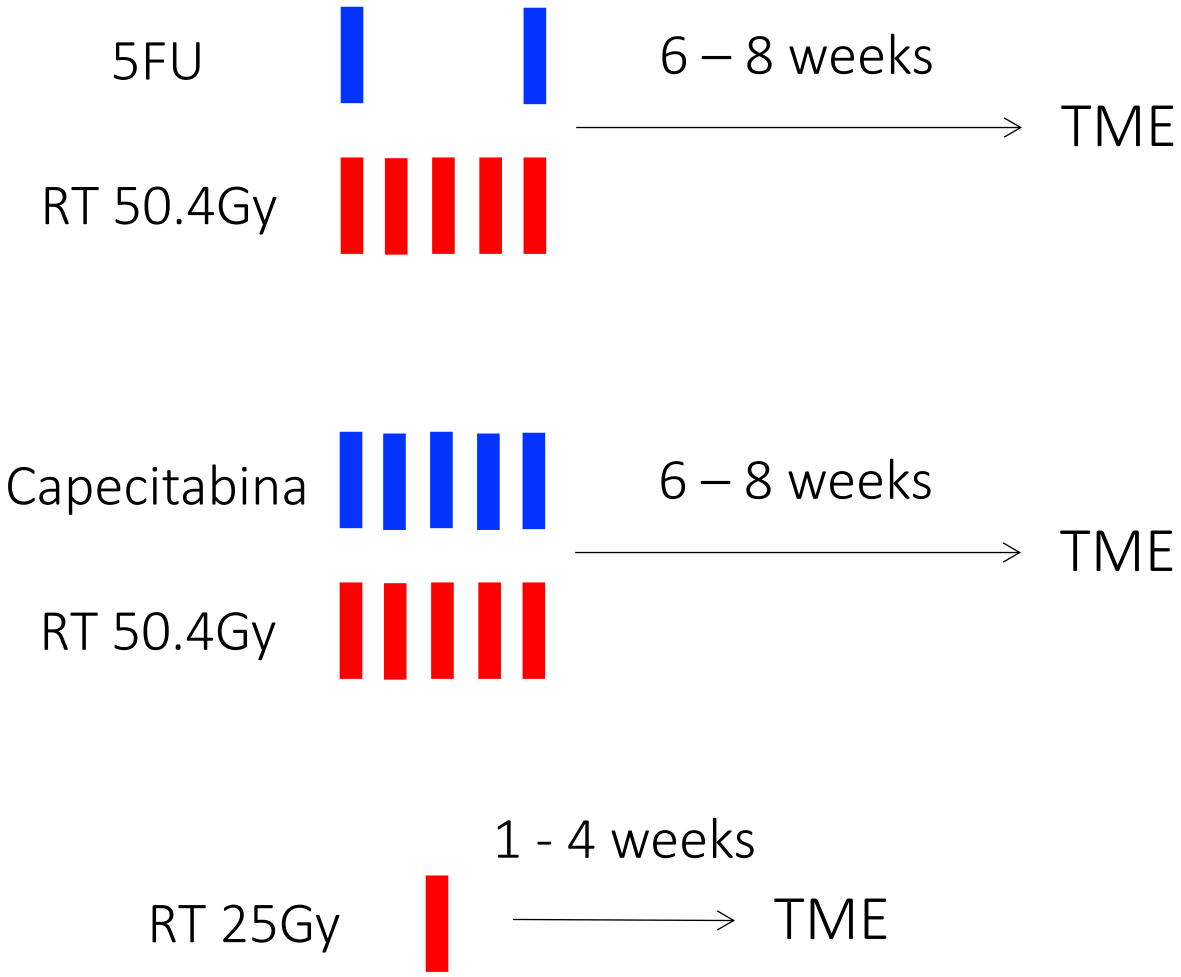

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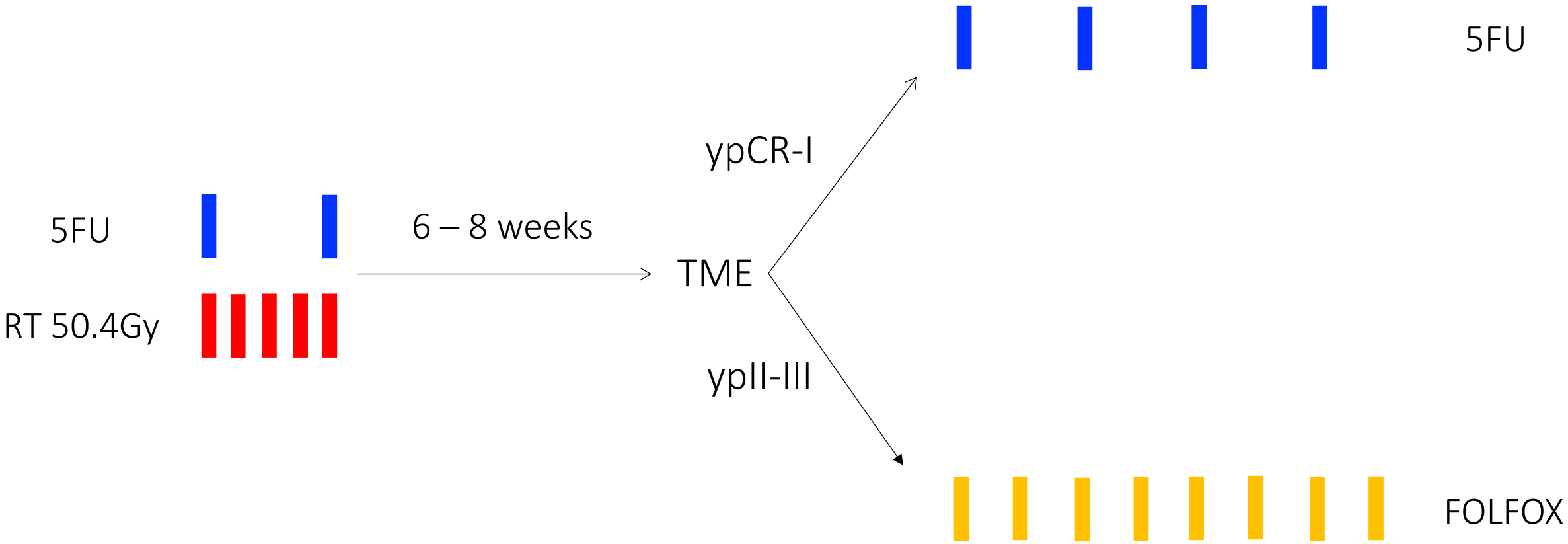

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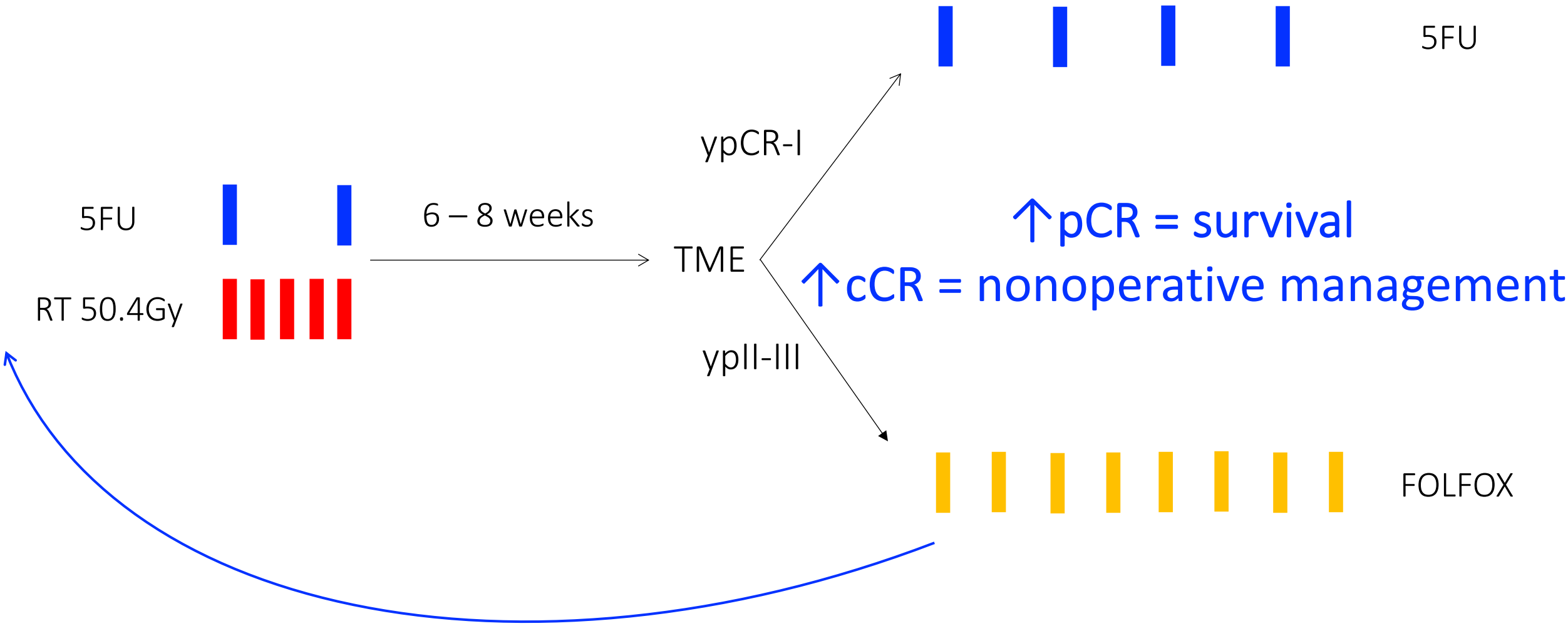

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Clinical evidence

Author	Year	N	Population	Phase	Regimen	Modality	pCR
Chau et al.	2006	77	MRI high-risk	II	XELOX	Induction	24%
Fernandez-Martos et al.	2010	108	T3-4 N+	II Random	XELOX QTRT	Induction	14% 14%
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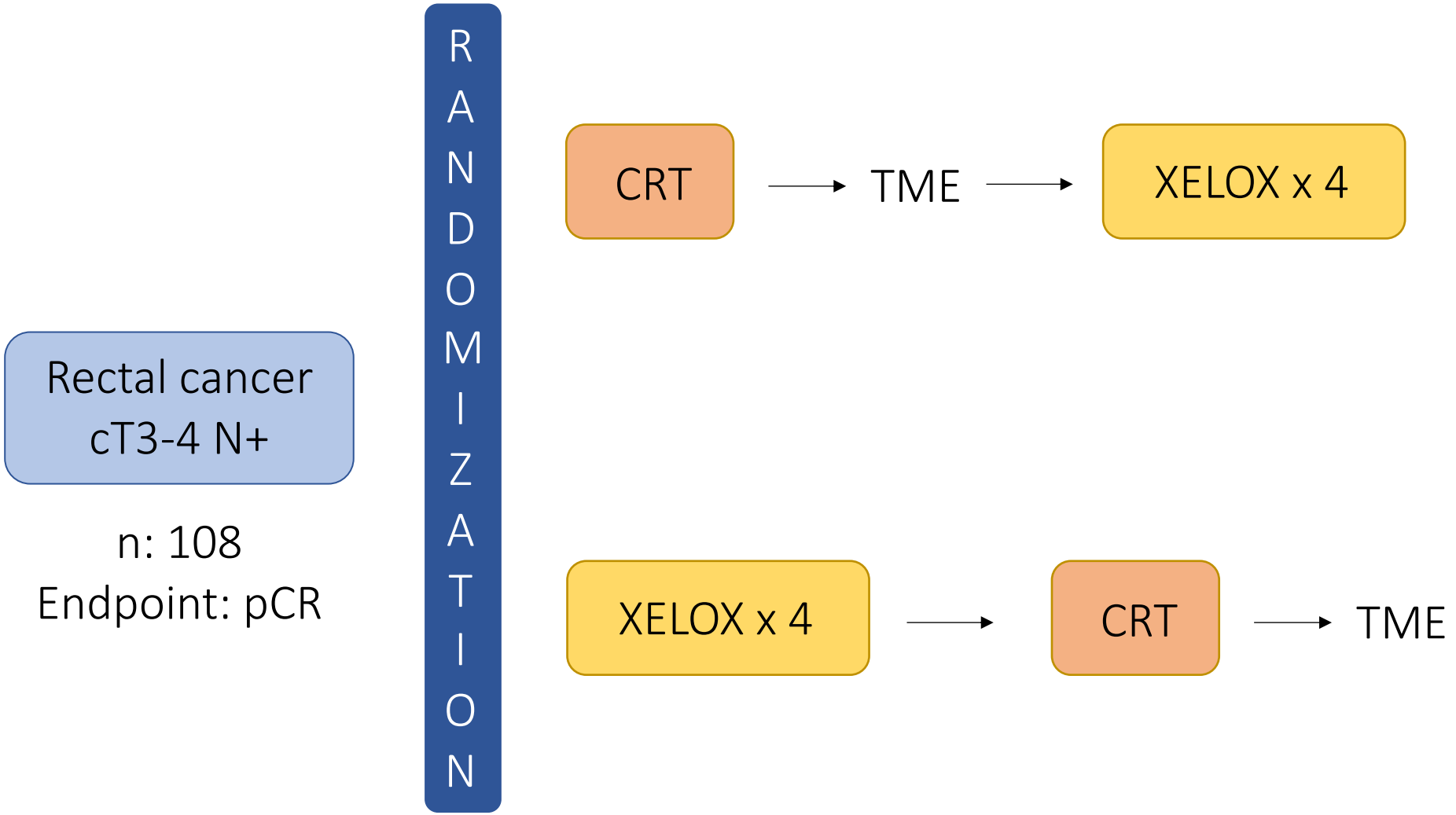
Randomized phase II clinical trials



Fernandez-Martos C. J Clin Oncol 2010

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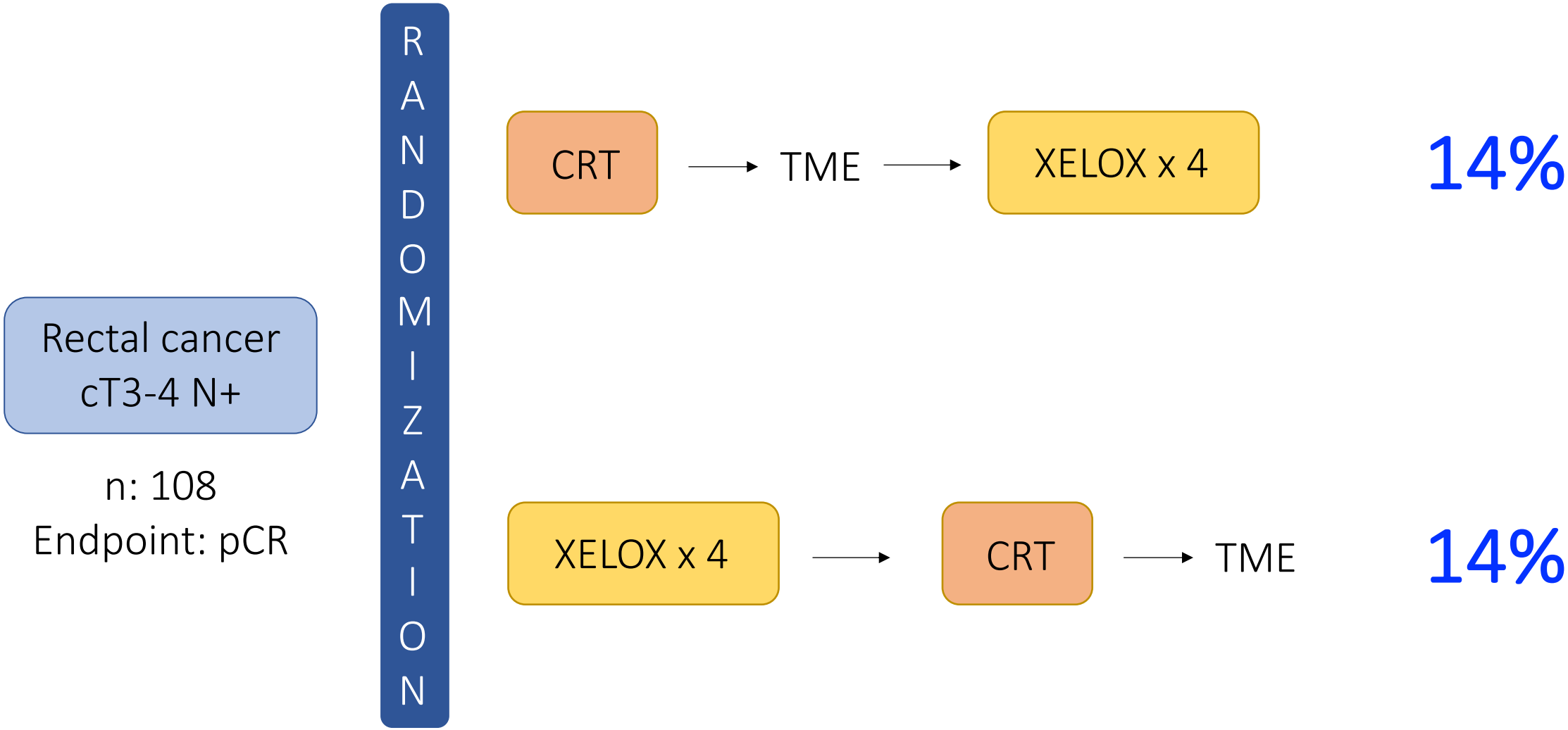


Fernandez-Martos C. J Clin Oncol 2010

Randomized phase II clinical trials

Rectal cancer
cT3-4 N+

n: 108
Endpoint: pCR

RANDOMIZATION

CRT → TME → XELOX x 4

↑ toxicity

14%

≅ downstaging and R0 resection

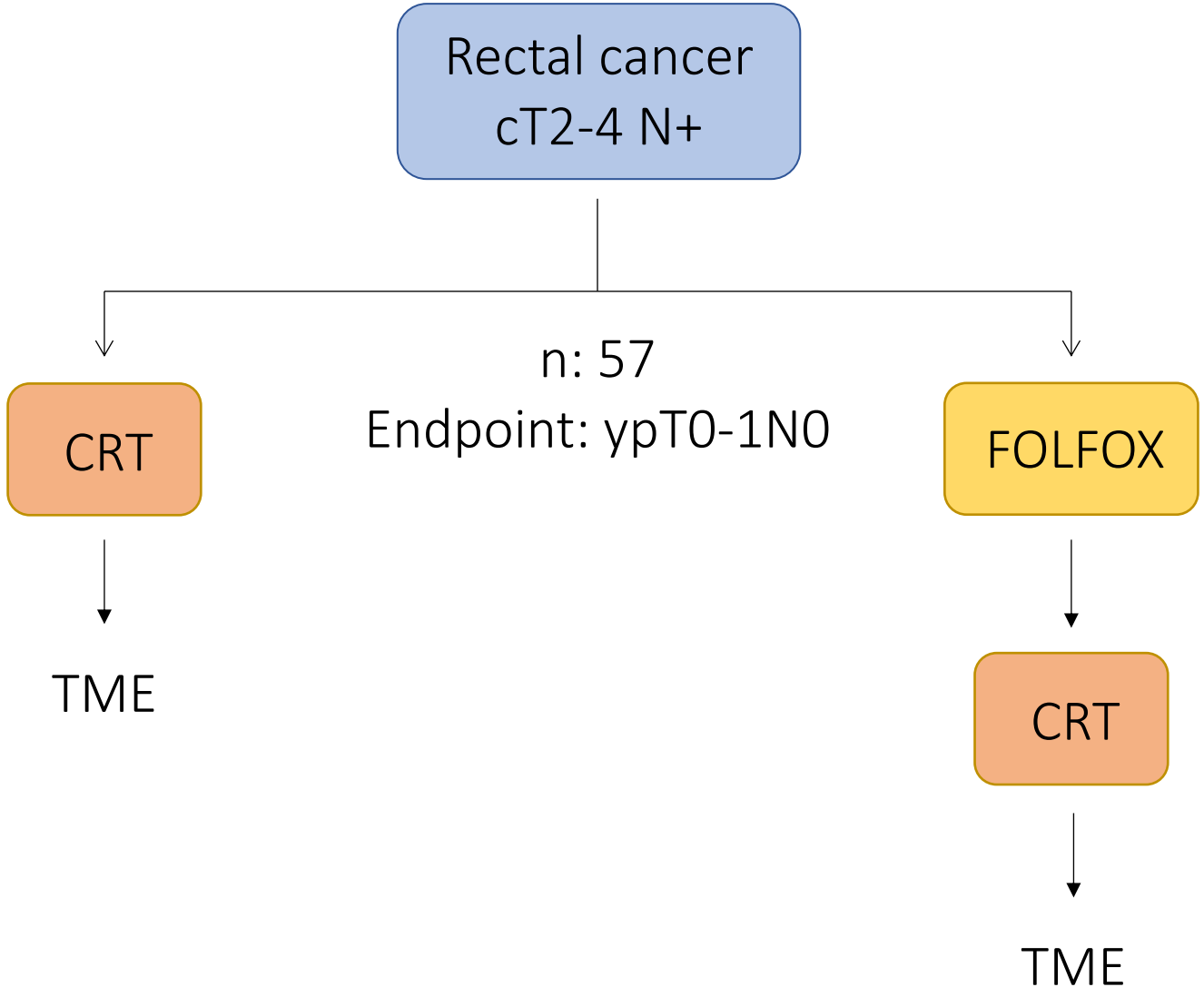
XELOX x 4 → CRT → TME

↑% capecitabine and oxaliplatin doses

14%

Fernandez-Martos C. J Clin Oncol 2010

Randomized phase II clinical trials



Maréchal R. Ann Oncol 2011

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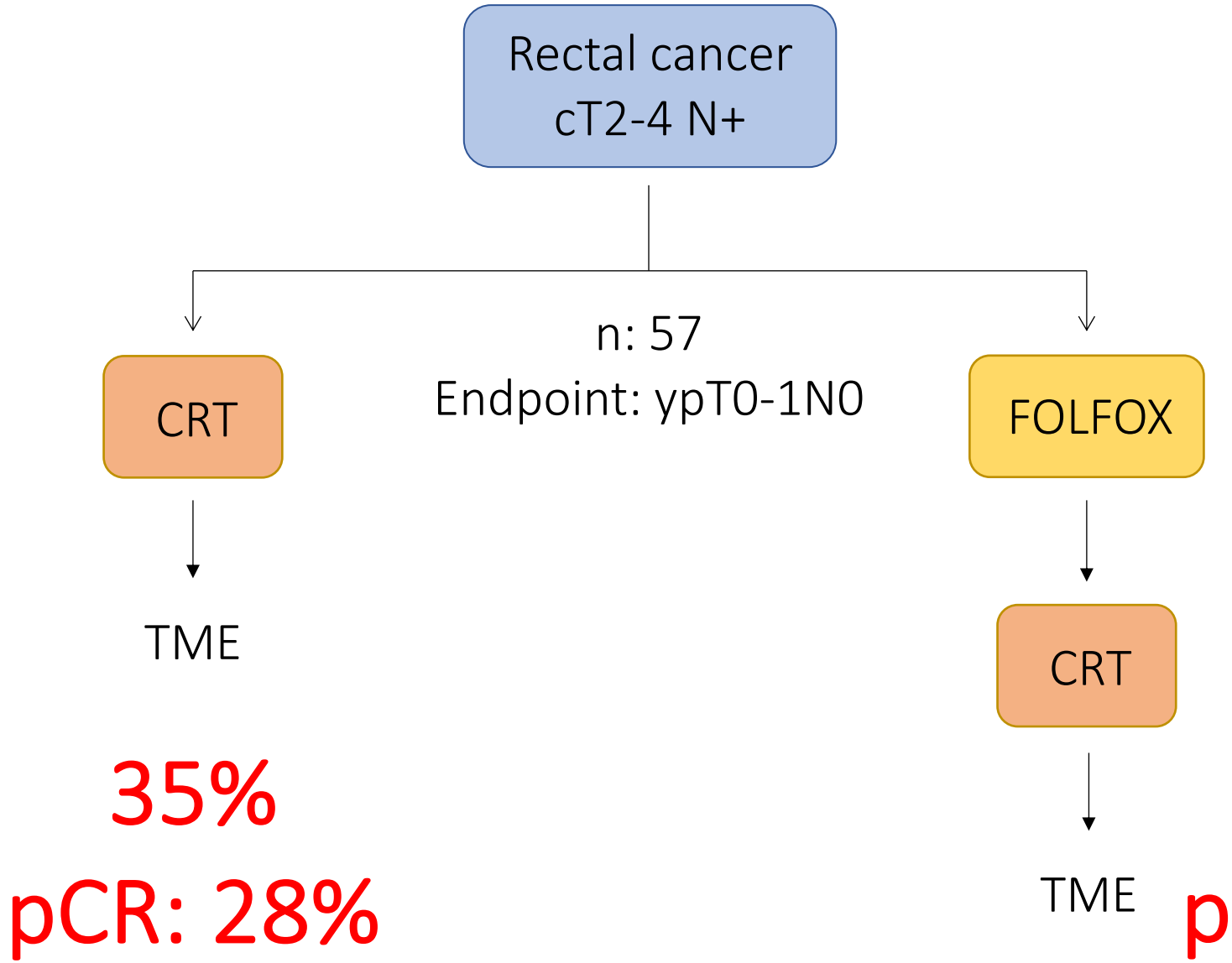

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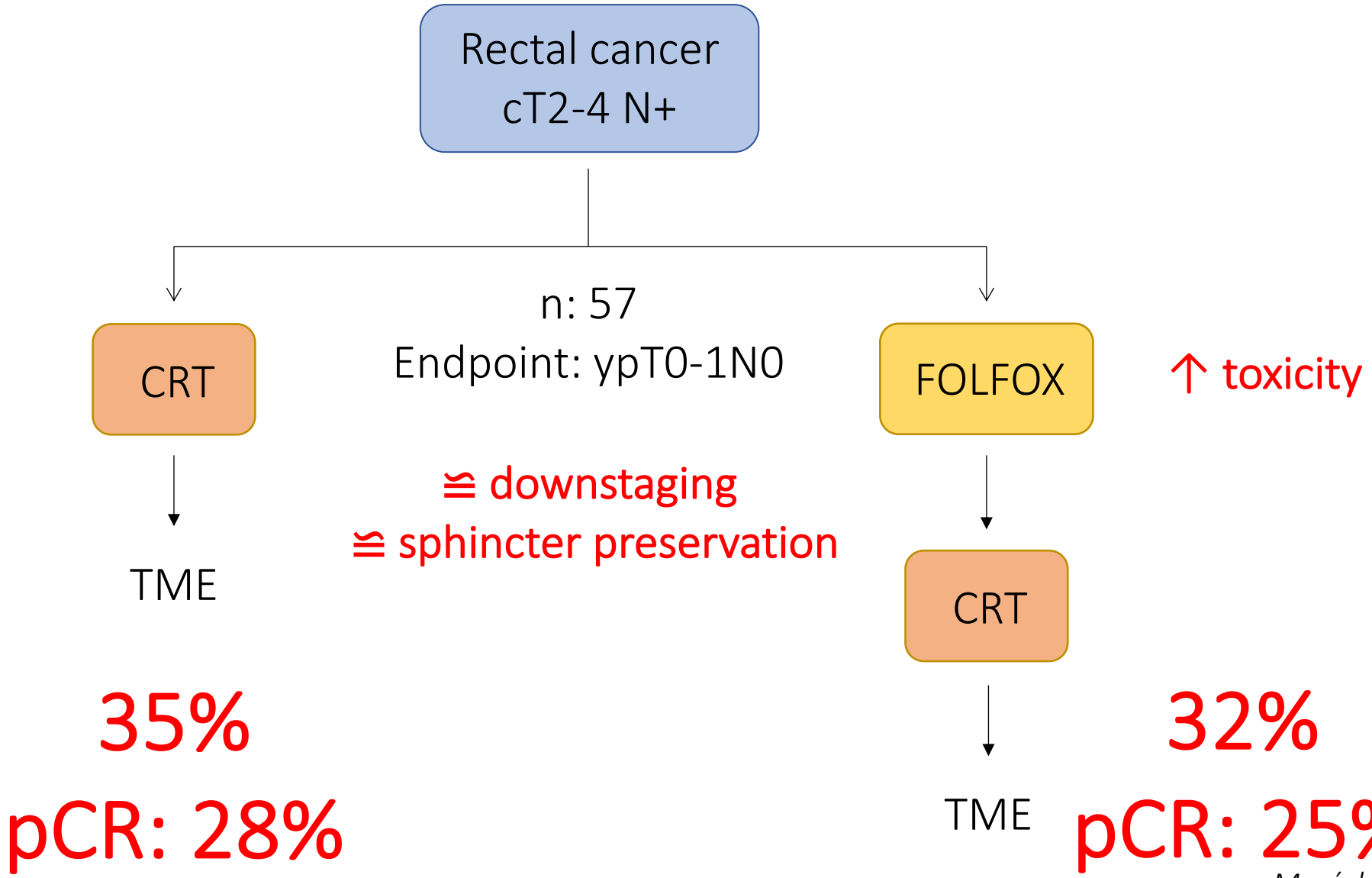

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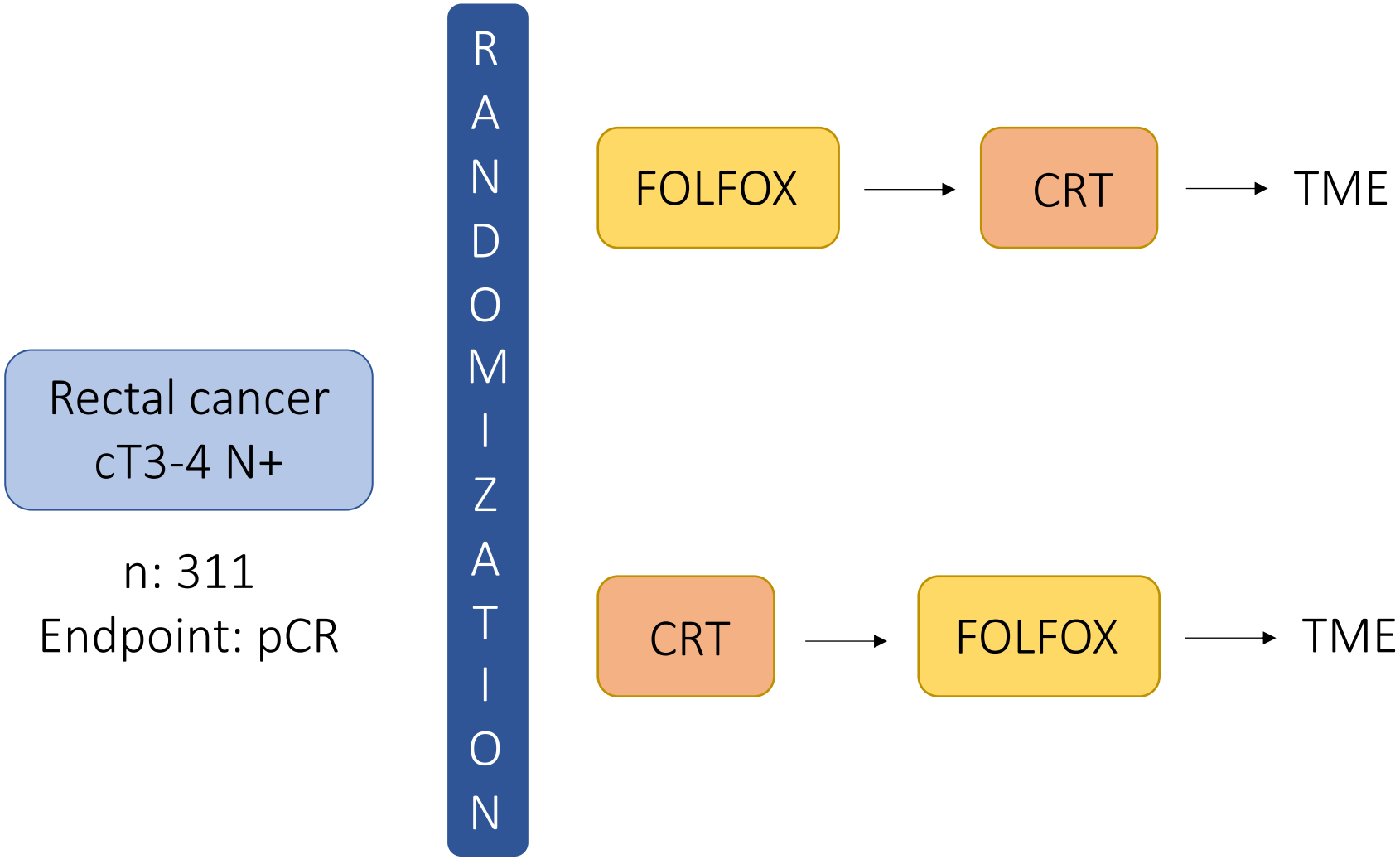
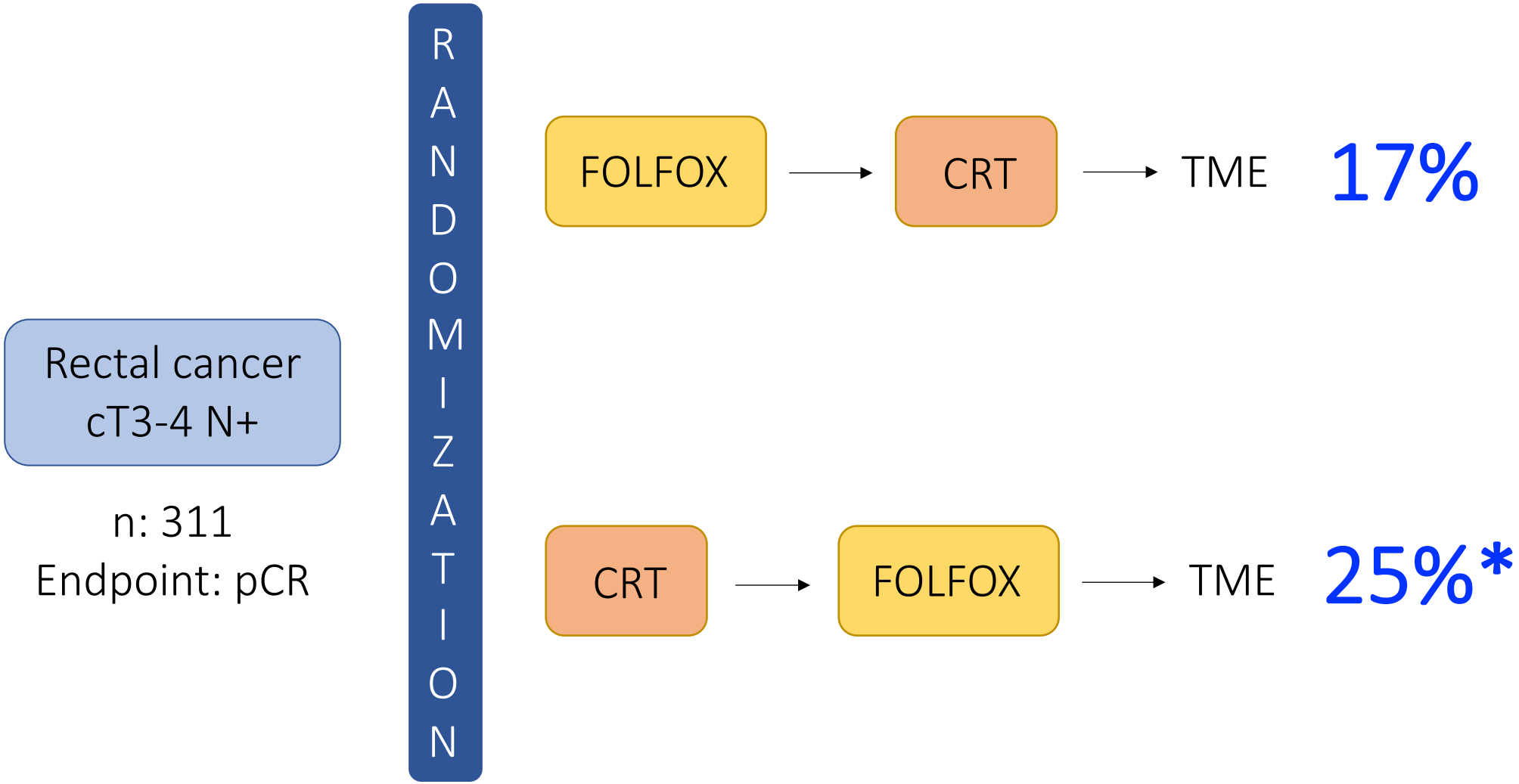


Fokas E. J Clin Oncol 2019

Randomized phase II clinical trials



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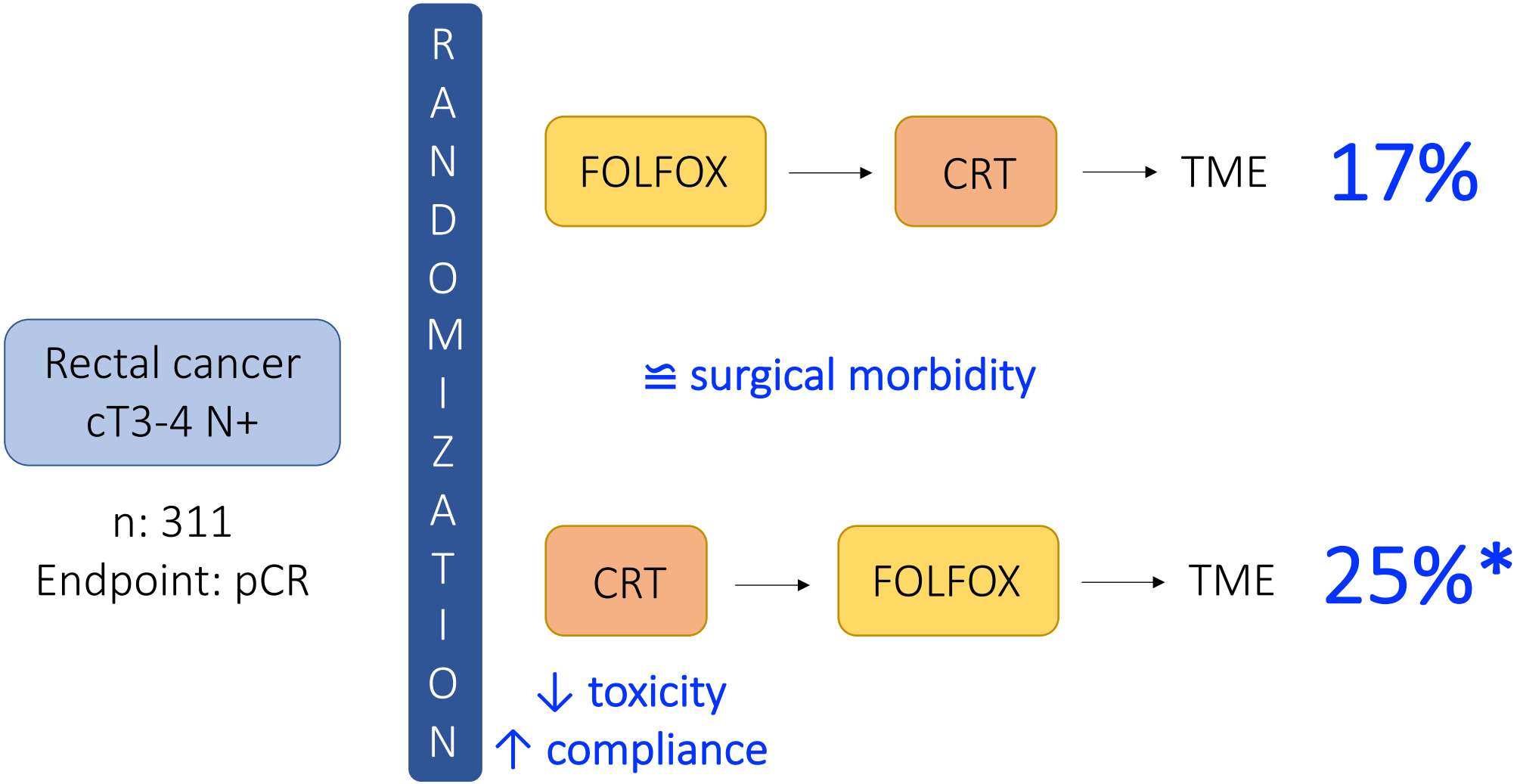
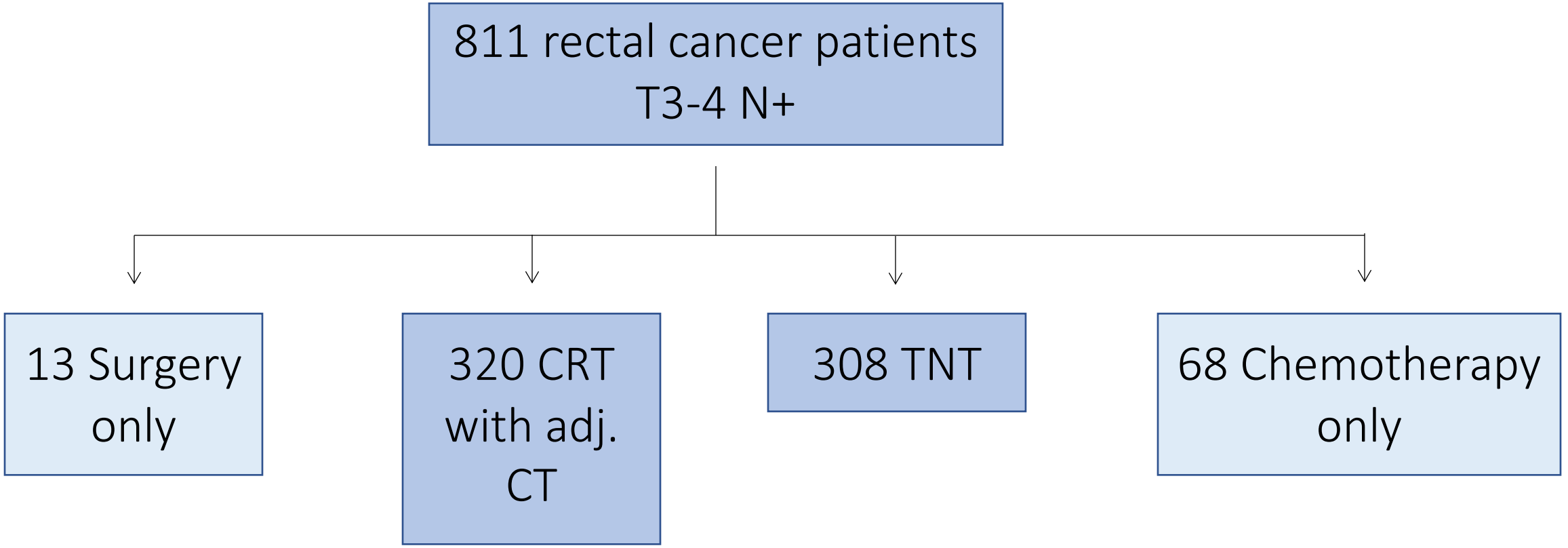


Fokas E. J Clin Oncol 2019

Comparative retrospective study



Cercek A. JAMA Oncol 2018

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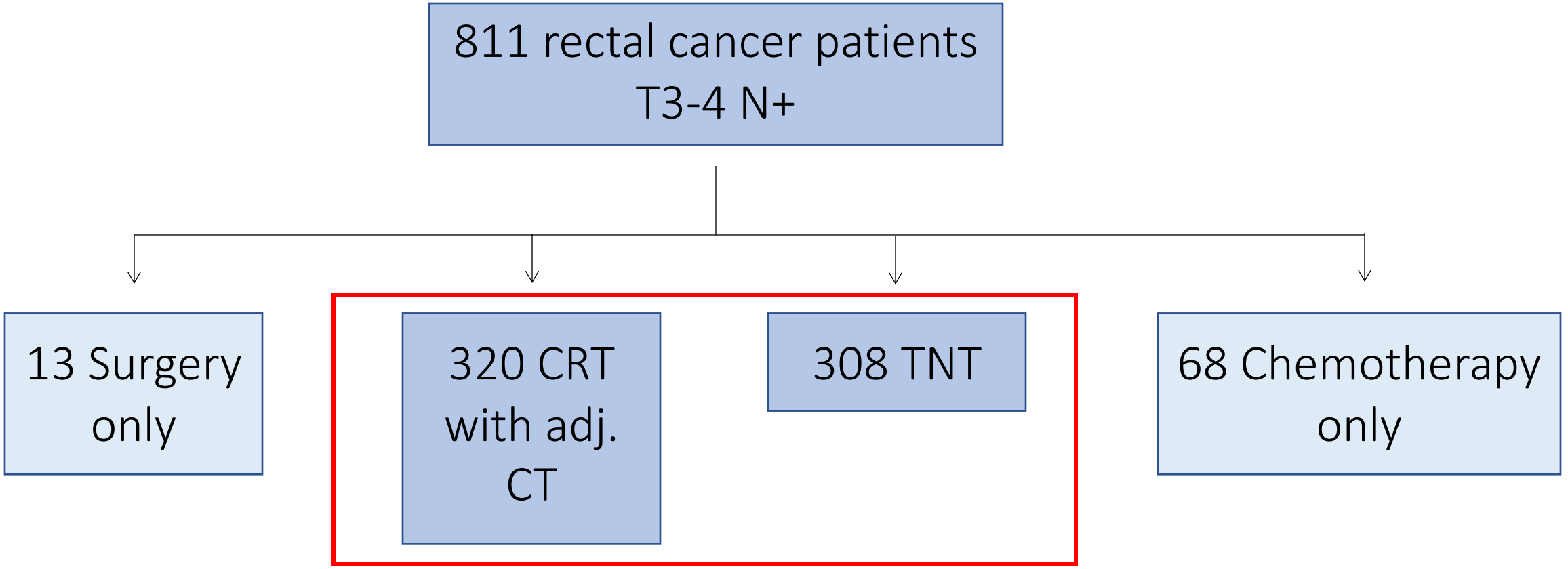

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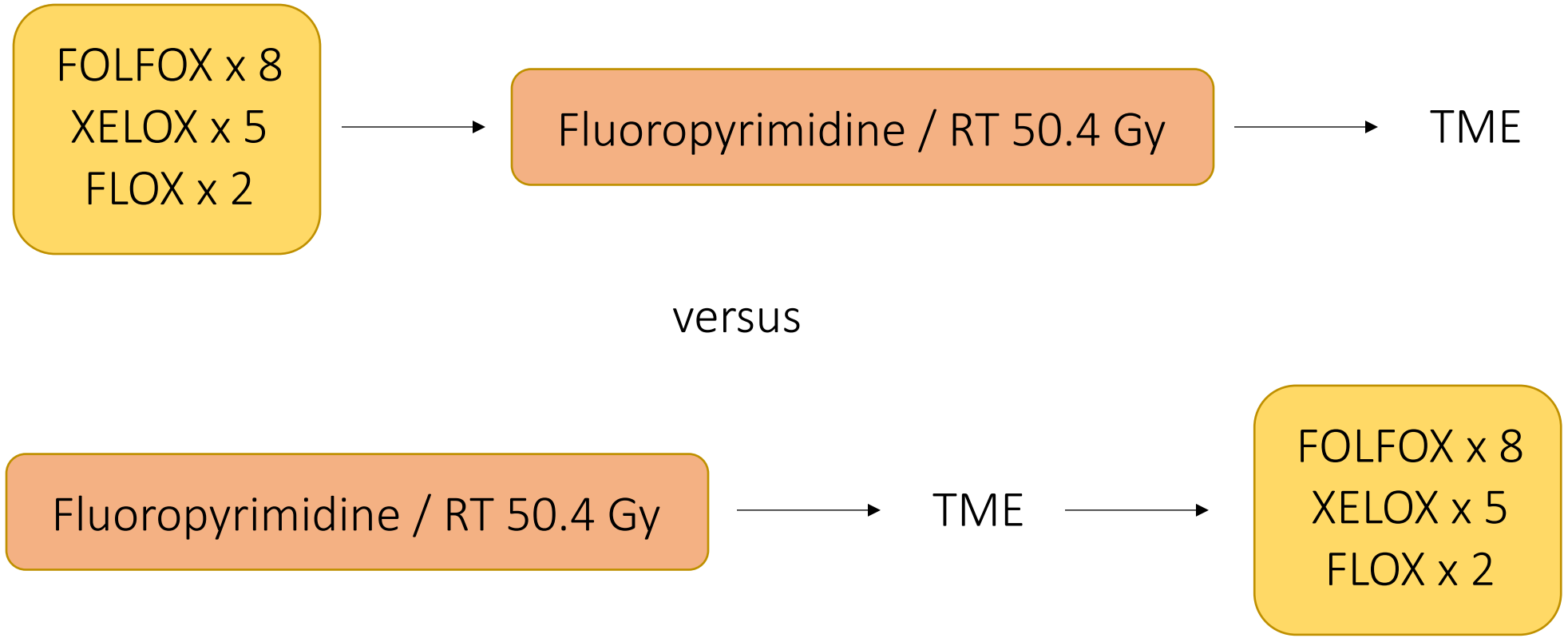

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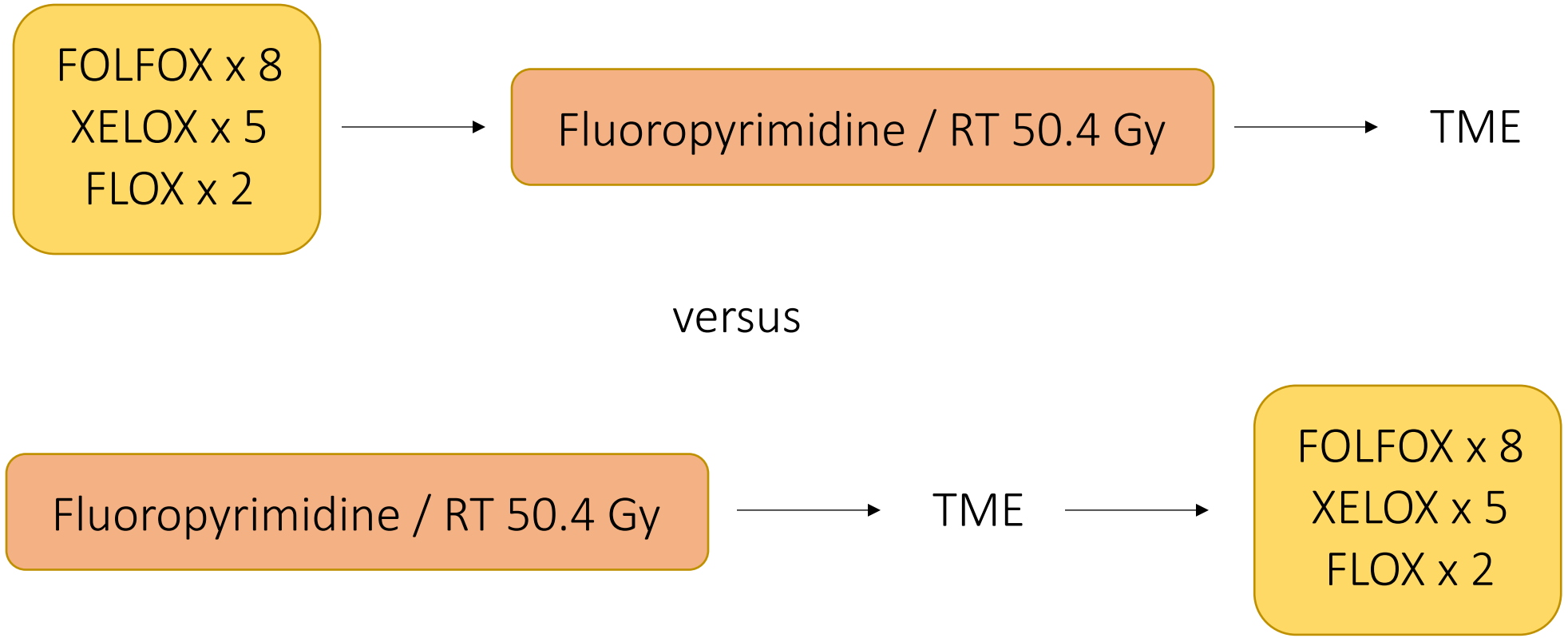
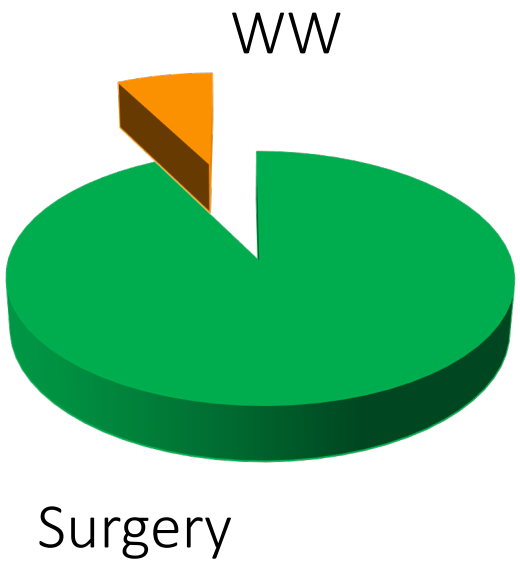


Endpoint: Complete response (ypCR + complete response ⩾ 12 months if watch-and-wait)

Cercek A. JAMA Oncol 2018

Comparative retrospective study

CRT

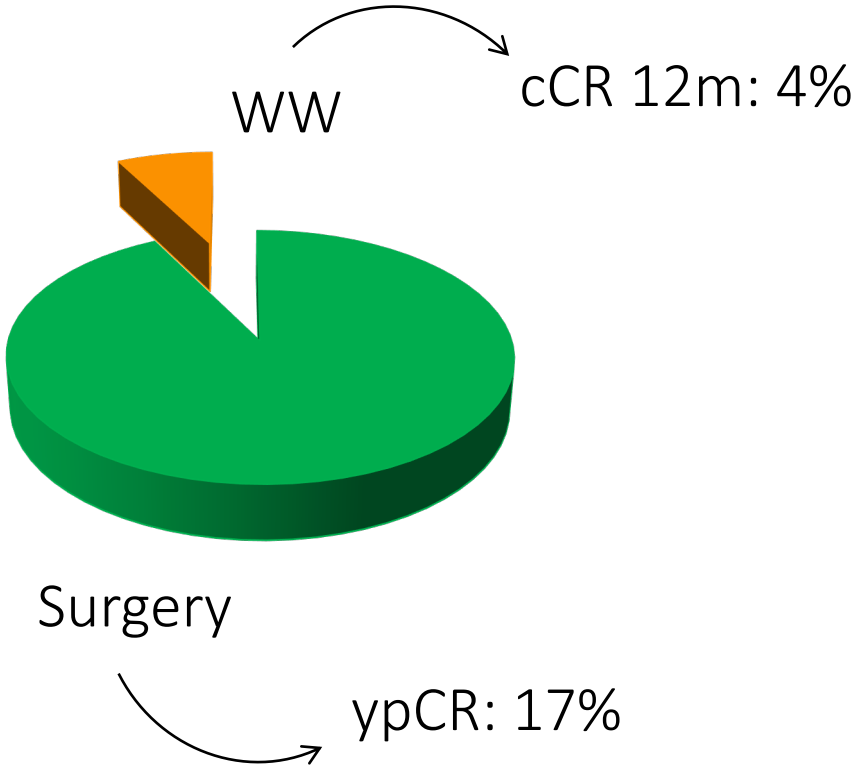


TNT

Cercek A. JAMA Oncol 2018

Comparative retrospective study

CRT

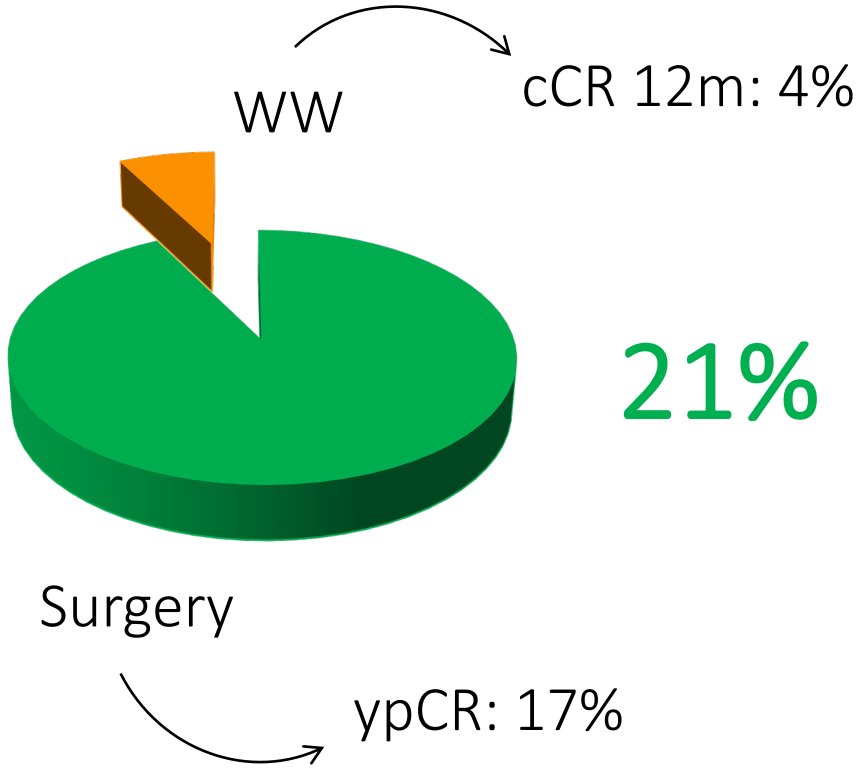


TNT

Cercek A. JAMA Oncol 2018

Comparative retrospective study

CRT



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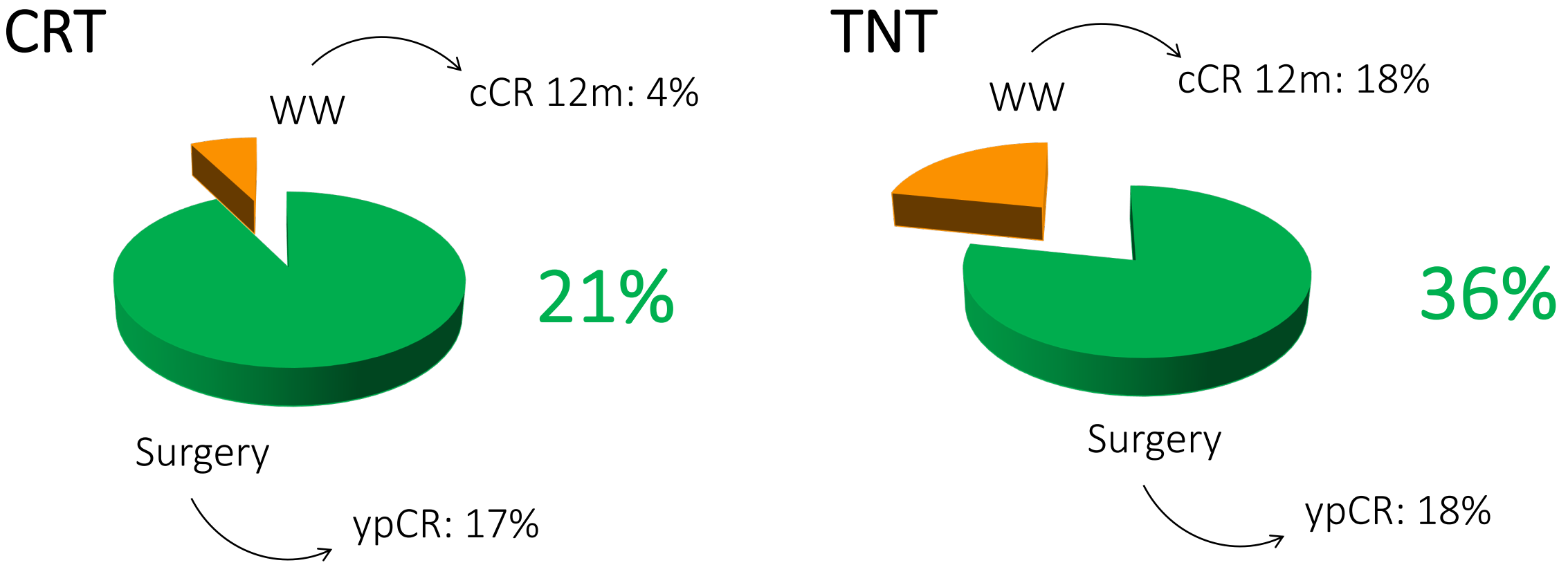

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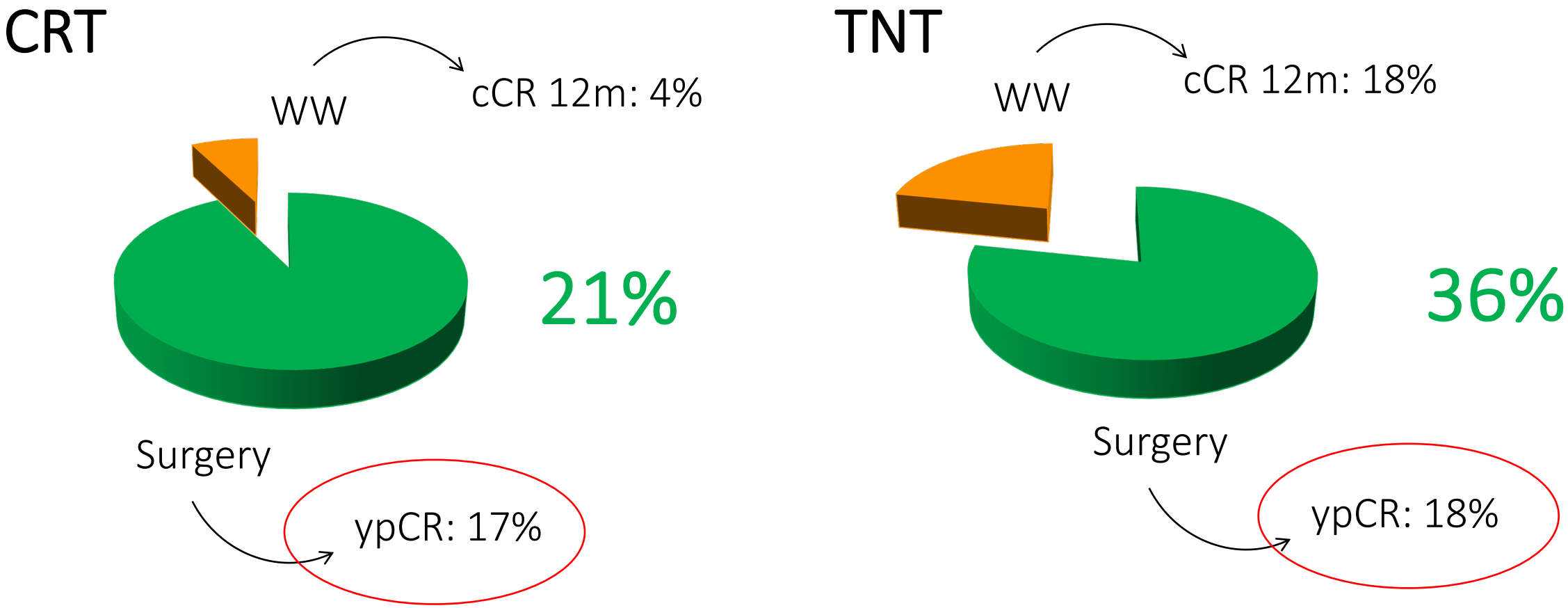

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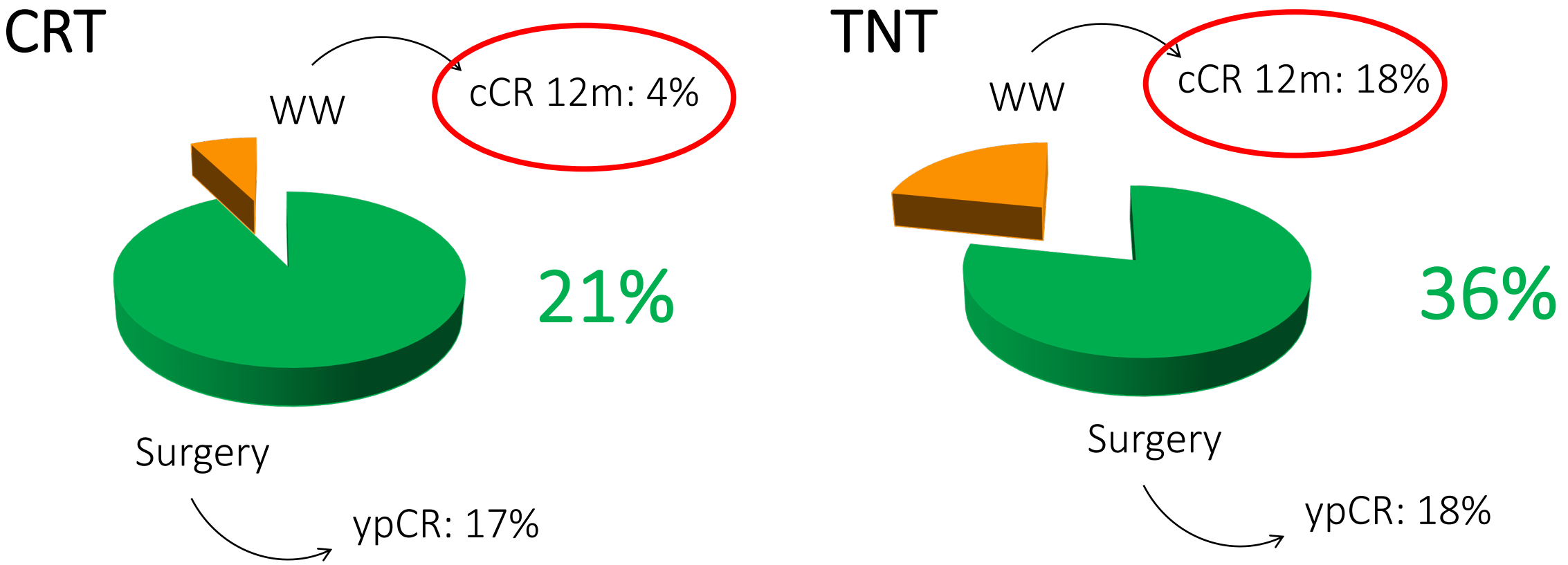


Cercek A. JAMA Oncol 2018

Comparative retrospective study

Variable	CRT	TNT	*p*
< 55 years	40%	52%	< 0.01
cN+	71%	86%	< 0.01
Δt < 8 weeks	52%	35%	< 0.01

TNT group: younger patients, higher tumor burden, late surgery

Cercek A. JAMA Oncol 2018

Comparative retrospective study

Variable	CRT	TNT	*p*
< 55 years	40%	52%	< 0.01
cN+	71%	86%	< 0.01
Δt < 8 weeks	52%	35%	< 0.01

Multivariate analysis for association with CR:

TNT: OR: 2.06 (95% CI 1.44 - 2.96)

Cercek A. JAMA Oncol 2018

Meta-analyses

Petrelli F et al. 2019

- ✓ 28 studies
  - ✓ 10 comparative
- ✓ N: 2688 TNT versus 891 QTRT
- ✓ pCR: 22.4%
- ✓ OR: 1.40, 95% CI 1.08-1.81

Zaborowski A et al. 2019

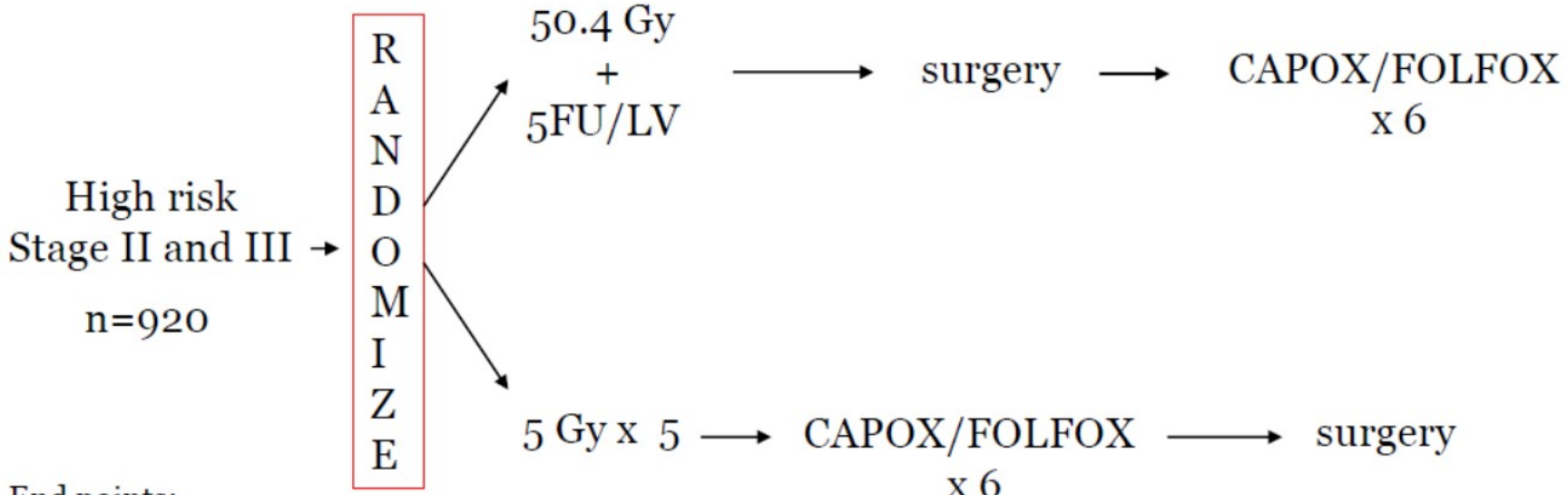
- ✓ 10 prospective studies
- ✓ N: 648 TNT
- ✓ pCR: 21.8%
- ✓ 5-year DFS: 65%
- ✓ 5-year OS: 75%

Petrelli F et al. Ann Surg 2019, Zaborowski A et al. Br J Surg 2019

Perspectives

Testing Short Course XRT:
RAPIDO - Ongoing Randomized Phase II

NCT01558921



End points:

1. Time to treatment failure
2. Survival
3. pCR
4. Negative margin rate
5. Complications
6. QoL

Nilsson P., et al. *BMC Cancer* 2013;13:279

NRG ONCOLOGY

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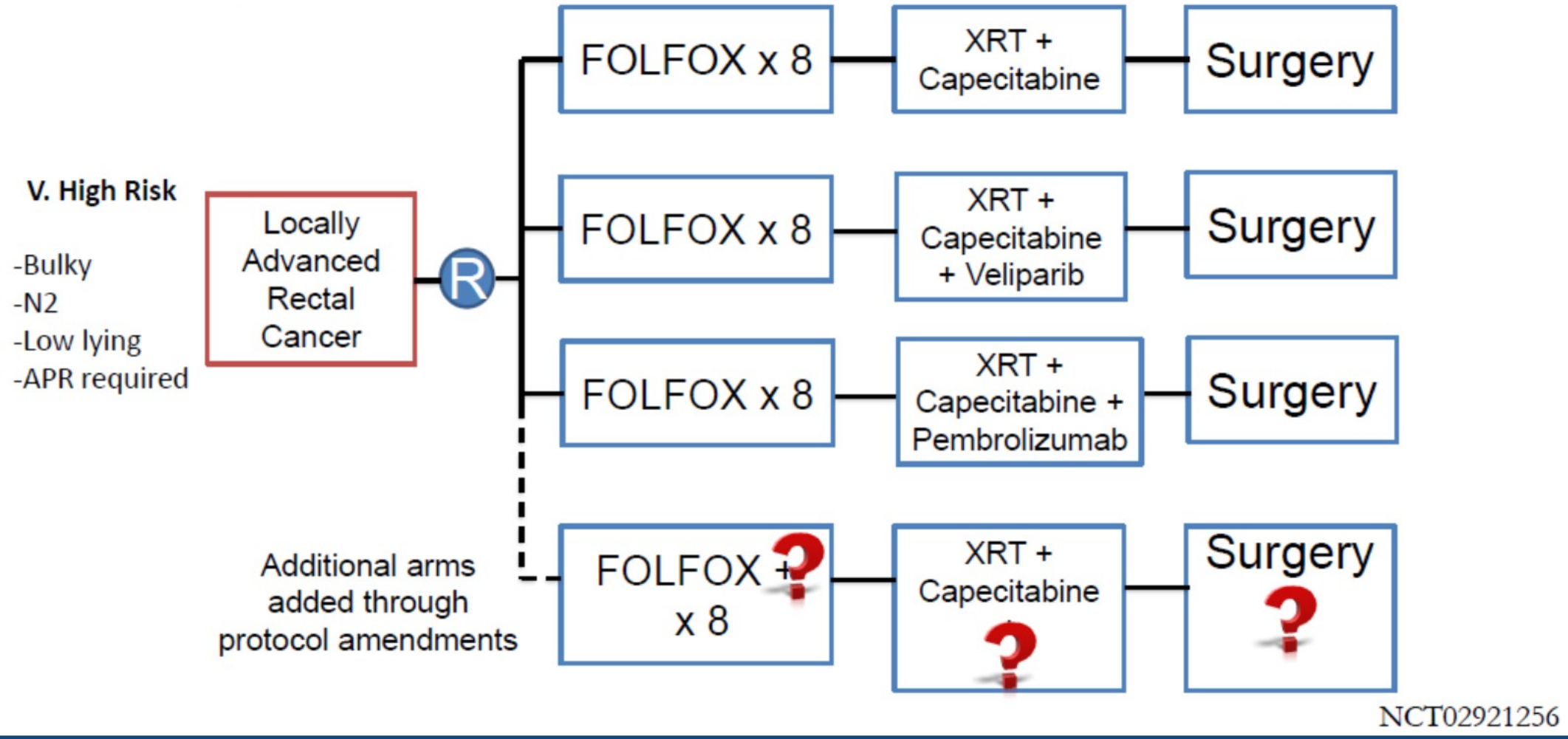
NRG-GI002 (TNT) Schema

Non-comparative experimental arms

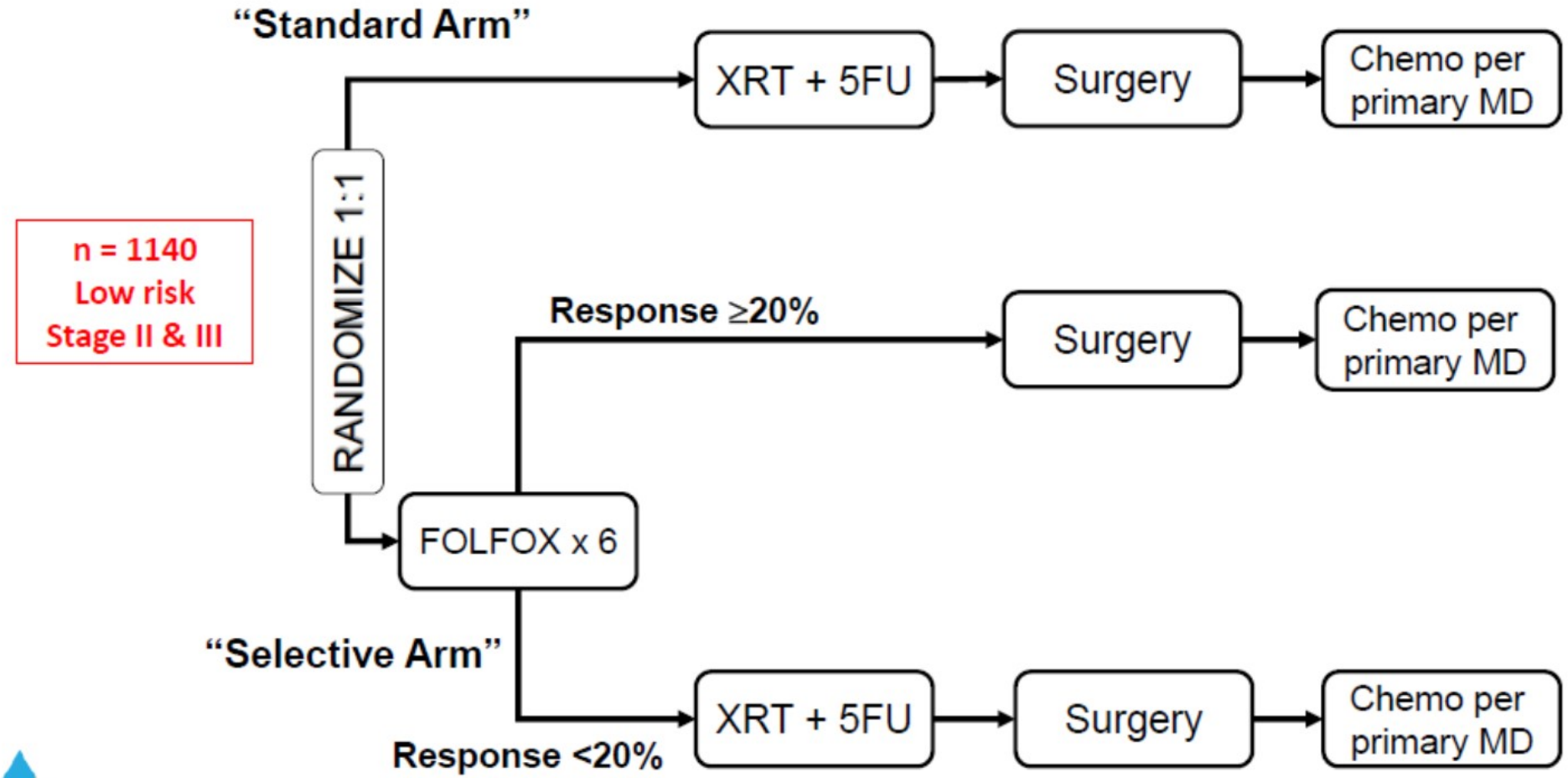


NCT02921256

PROSPECT

A phase II/III study

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

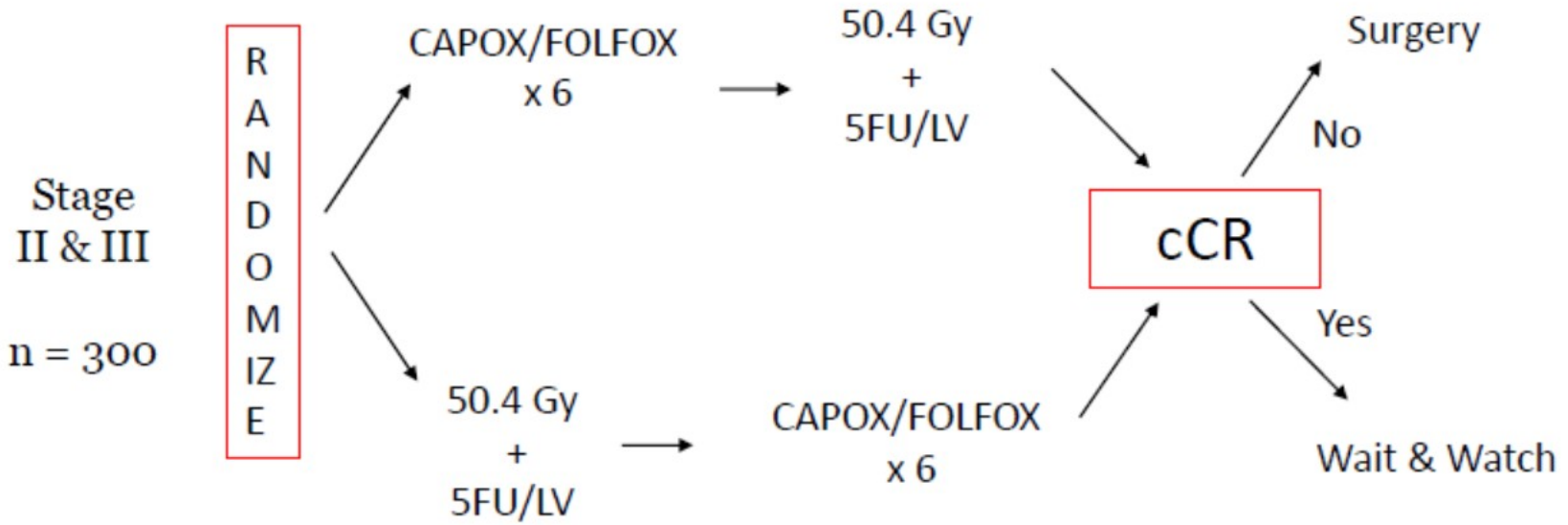


Alliance for Clinical Trials in Oncology

NCT01515787

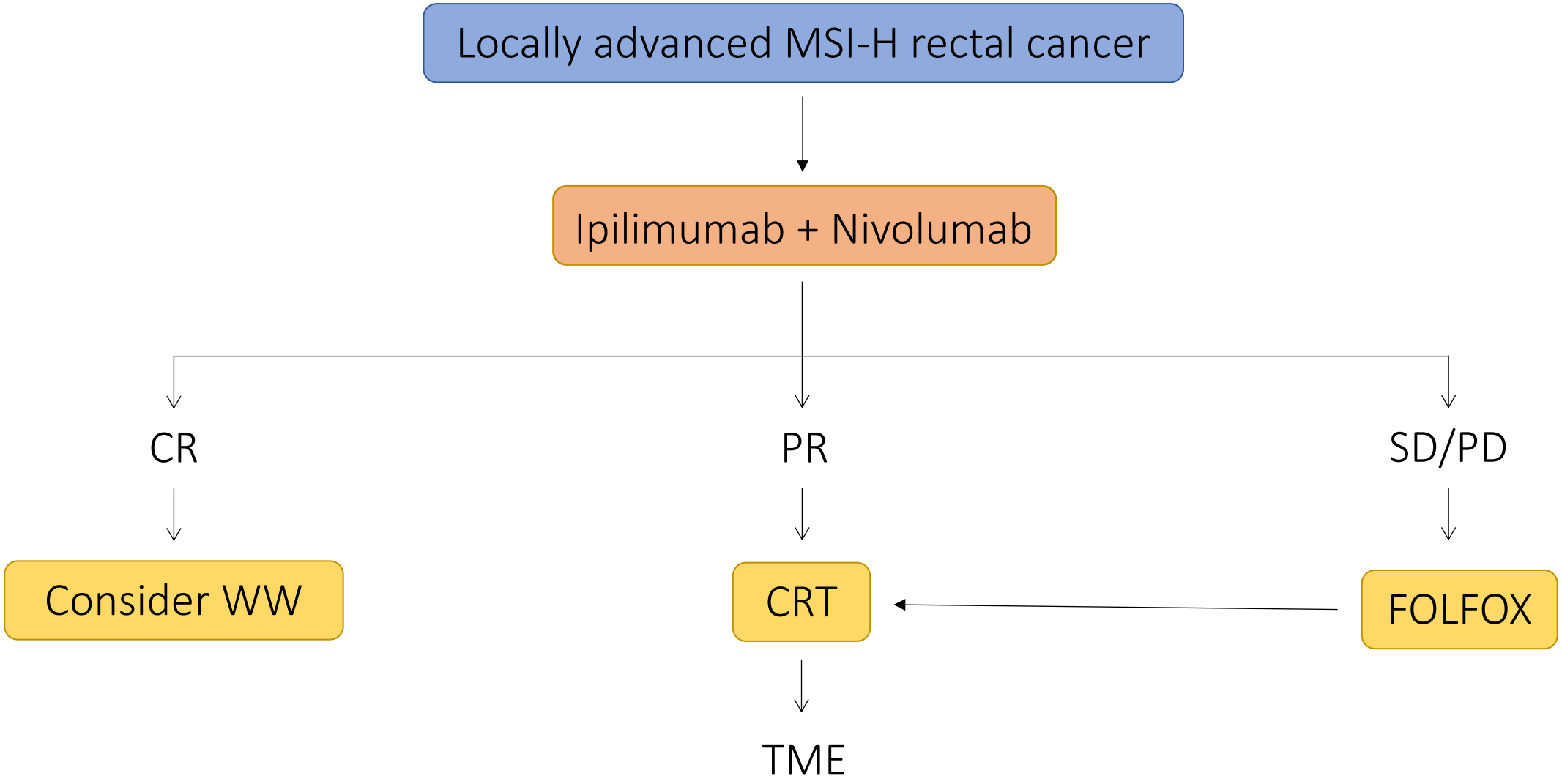
Selective Non-Operative Mgmt (OPRA Trial)

NCT02008656

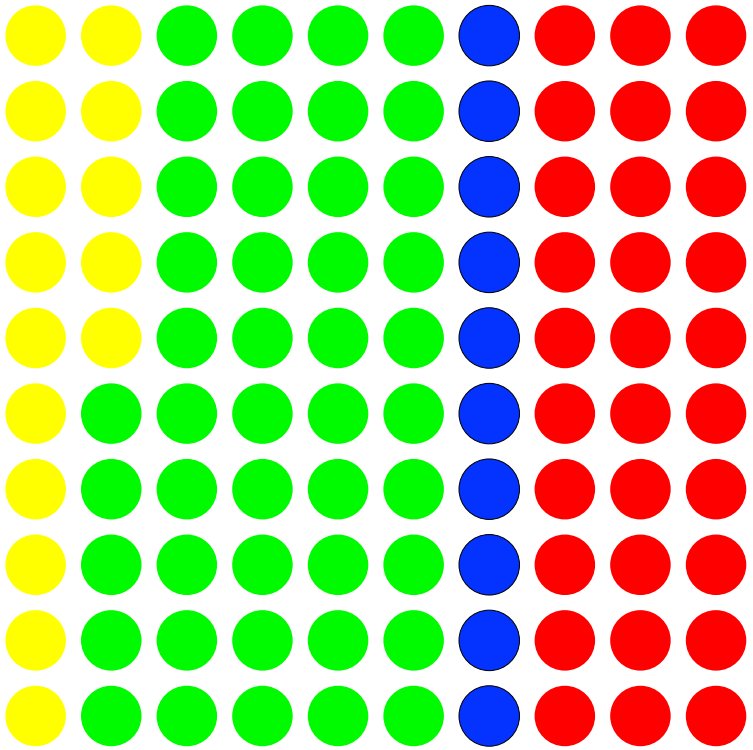


Smith JJ, et al. *BMC Cancer* 2015;15:767

Perspectives



Precision Medicine

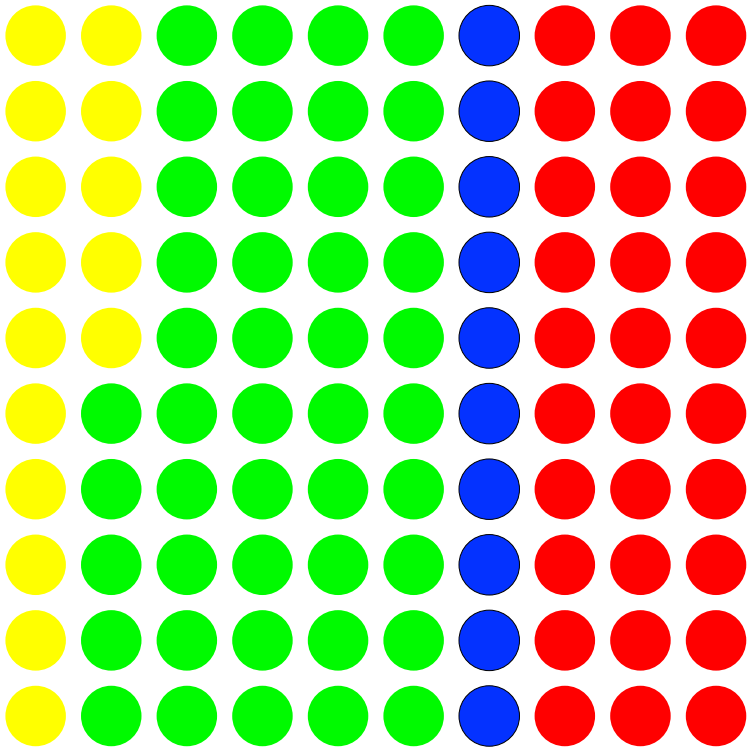


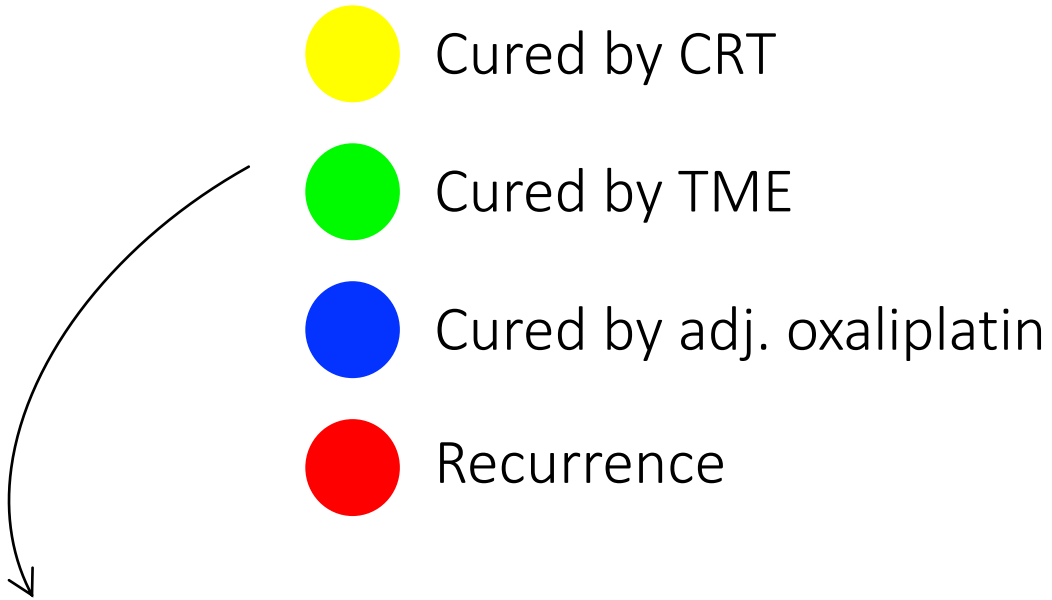
100 patients
cT3-4 N+
Neoadjuvant CRT + TME + adjuvant oxaliplatin

Cured by CRT
Cured by TME
Cured by adj. oxaliplatin
Recurrence

Sauer R. N Engl J Med 2004, Hong YS J Clin Oncol 2018

Precision Medicine





Who are these patients?
How to identify them?

100 patients
cT3-4 N+
Neoadjuvant CRT + TME + adjuvant oxaliplatin

Sauer R. N Engl J Med 2004, Hong YS J Clin Oncol 2018

Perspectivas

JAMA Oncology

Prognostic Potential of Circulating Tumor DNA Measurement in Postoperative Surveillance of Nonmetastatic Colorectal Cancer

Yuxuan Wang, MD, PhD; Lu Li, PhD; Joshua D. Cohen, MPhil; et al.

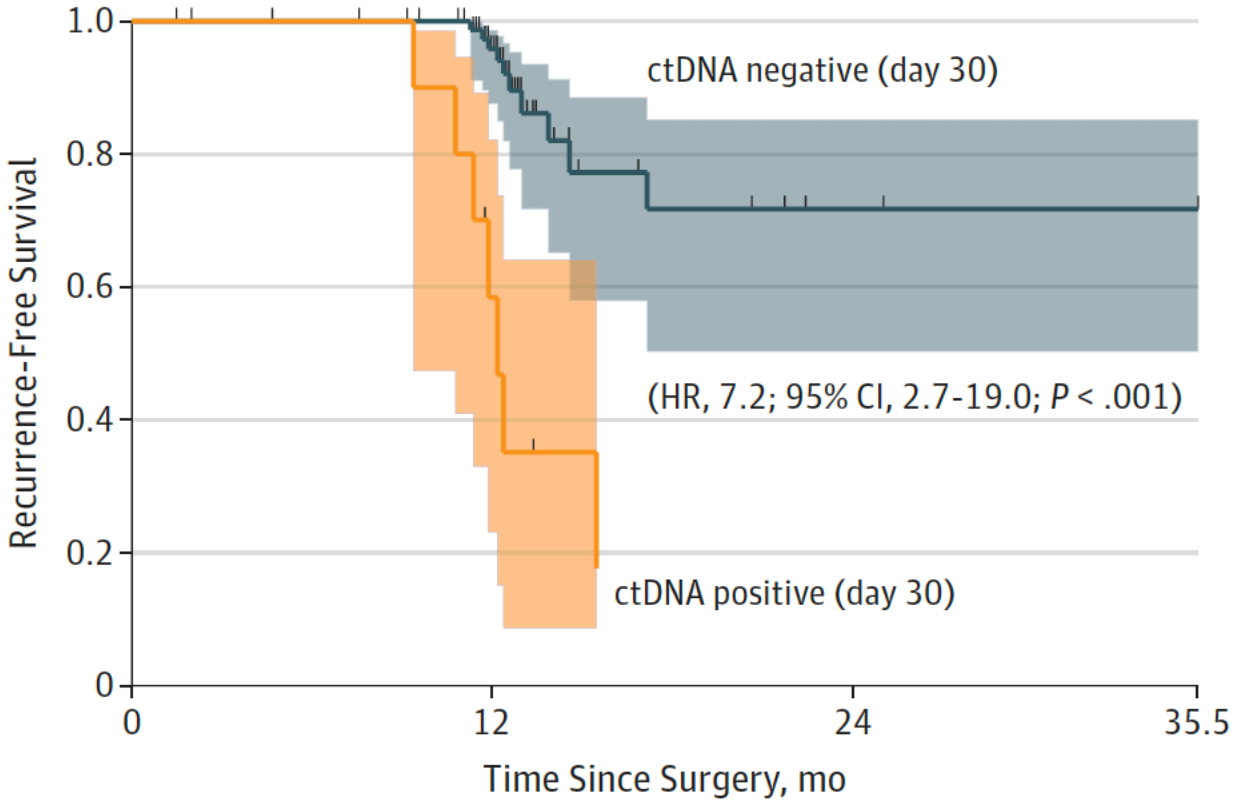
Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer

Thomas Reinert, PhD; Tenna Vesterman Henriksen, MSc; Emil Christensen, PhD; et al.

Wang Y et al. JAMA Oncol 2019, Reinert T et al. JAMA Oncol 2019

Perspectives

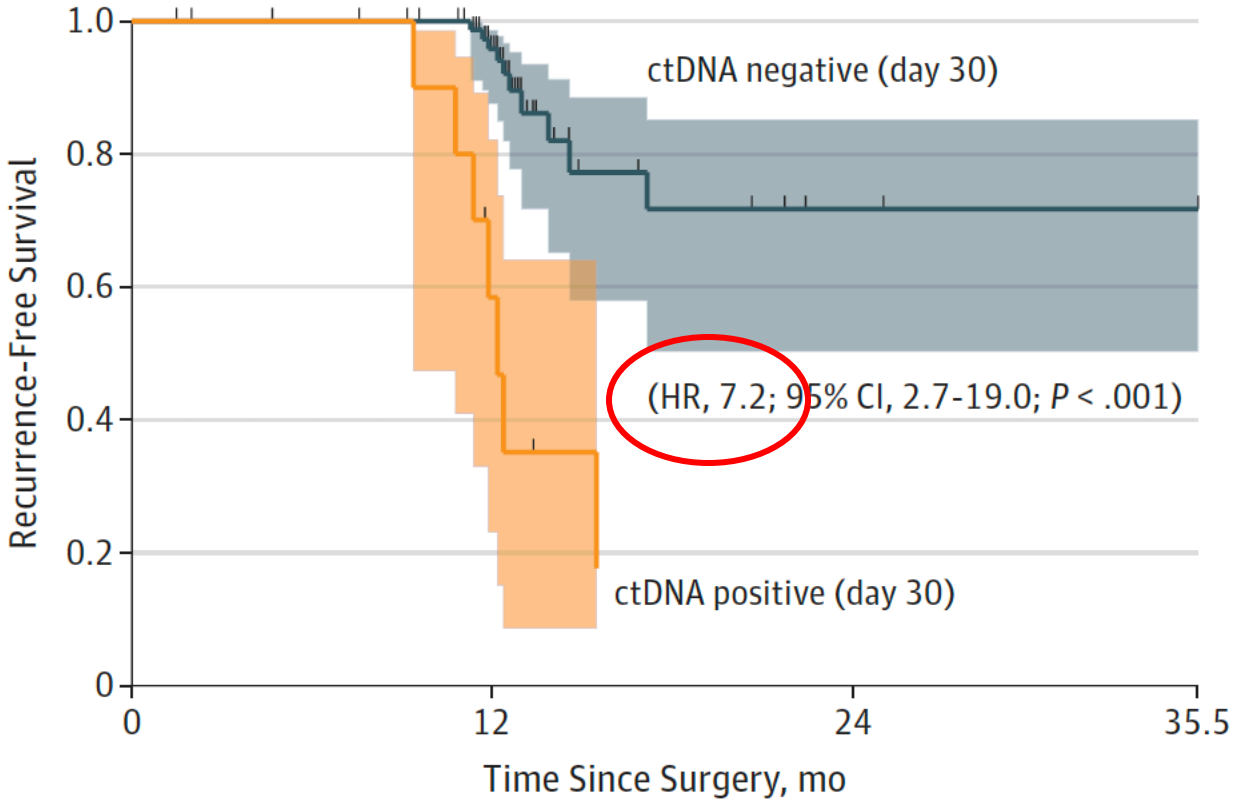
Recurrence-free survival and ctDNA status at 30th postoperative day



Extraído de Reinert T et al. JAMA Oncol 2019

Perspectives

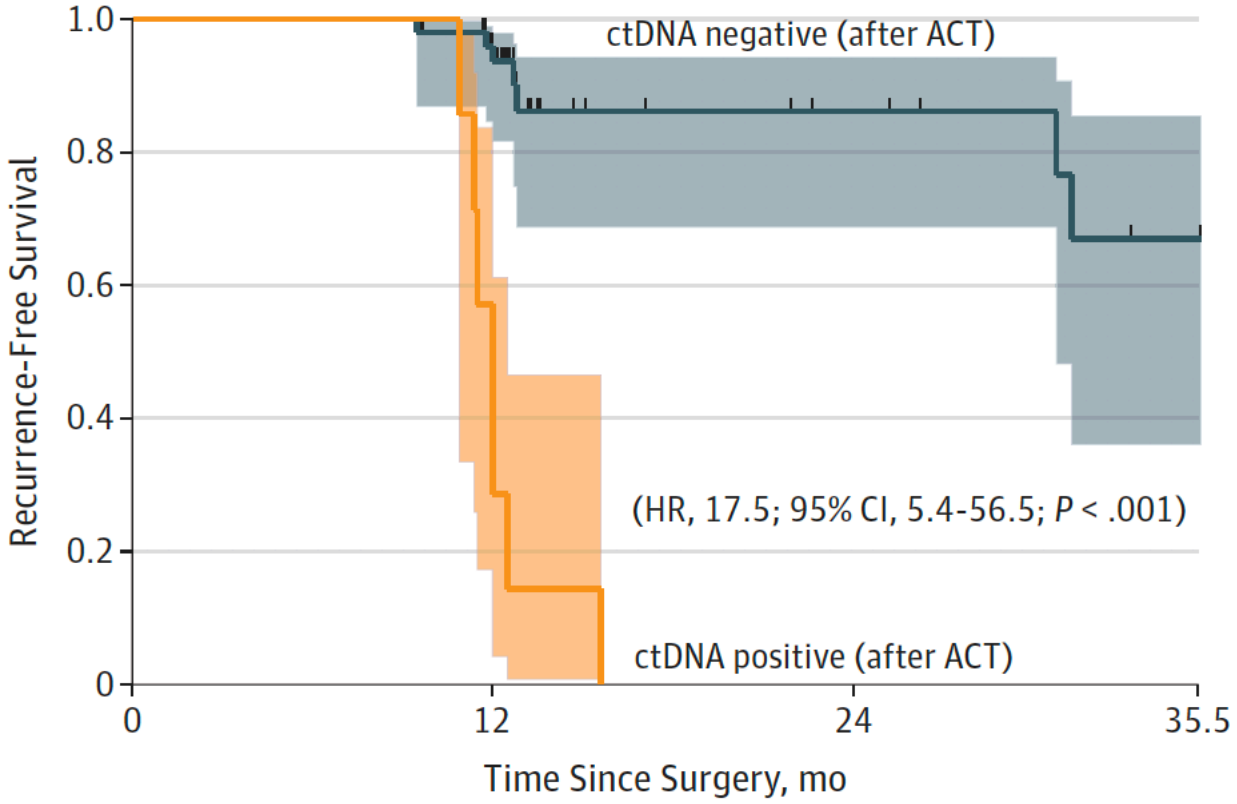
Recurrence-free survival and ctDNA status at 30th postoperative day



Extraído de Reinert T et al. JAMA Oncol 2019

Perspectives

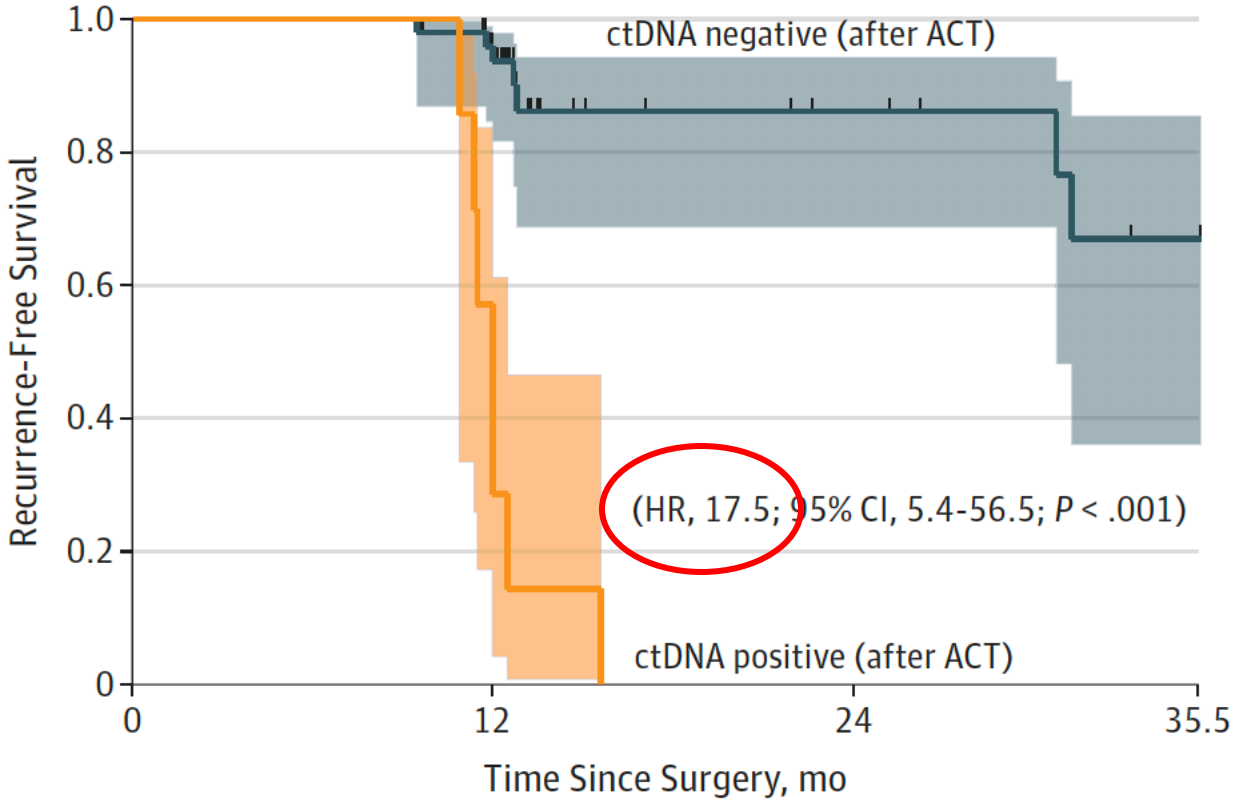
Recurrence-free survival and ctDNA status after adjuvant chemotherapy



Extraído de Reinert T et al. JAMA Oncol 2019

Perspectives

Recurrence-free survival and ctDNA status after adjuvant chemotherapy



Extraído de Reinert T et al. JAMA Oncol 2019

Take-home message

- Neoadjuvant chemoradiotherapy remains as the standard neoadjuvant approach of locally advanced rectal cancer
- Phase III studies addressing the relative benefit of TNT are eagerly awaited.
- Escalation of therapy for all patients will certainly not be the best choice.
- Molecular risk stratification might be incorporated in the therapeutic management.
- The improvement of molecular techniques will help to identify the patients eligible for escalation (TNT) or de-escalation of treatment (watch-and-wait).