Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Comprehensive Oncology Review: Colorectal Cancer - Adjuvant

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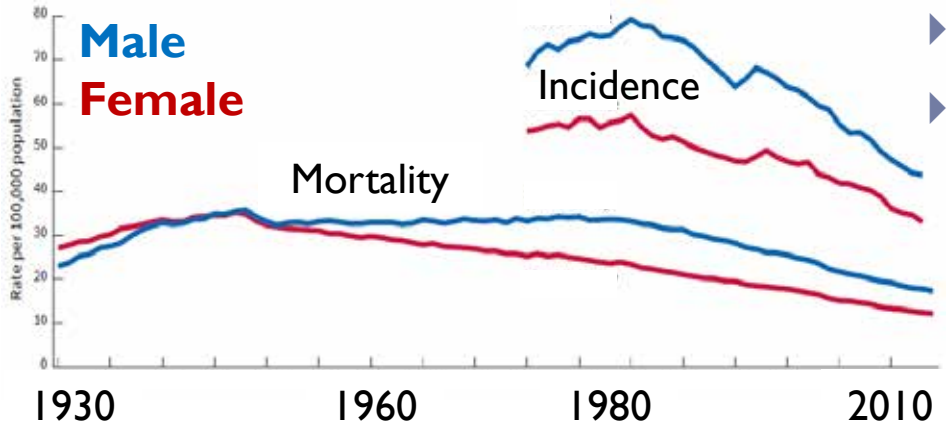
Outline

- Epidemiology and risk factors
- Evaluation and initial management
- Adjuvant chemotherapy for colon cancer
- Localized rectal cancer

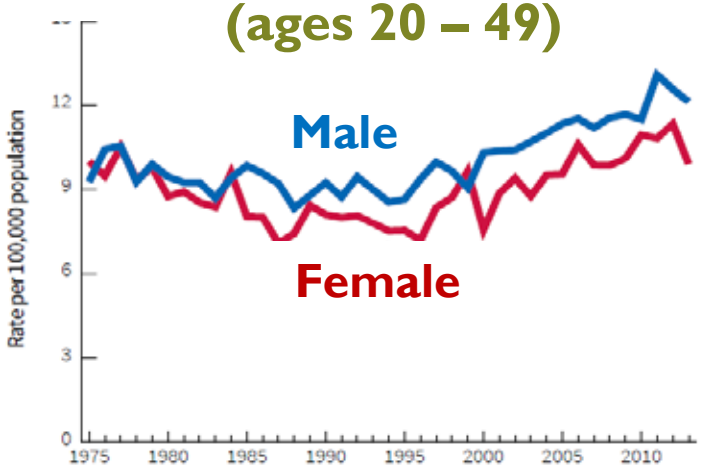
Epidemiology and Risk Factors

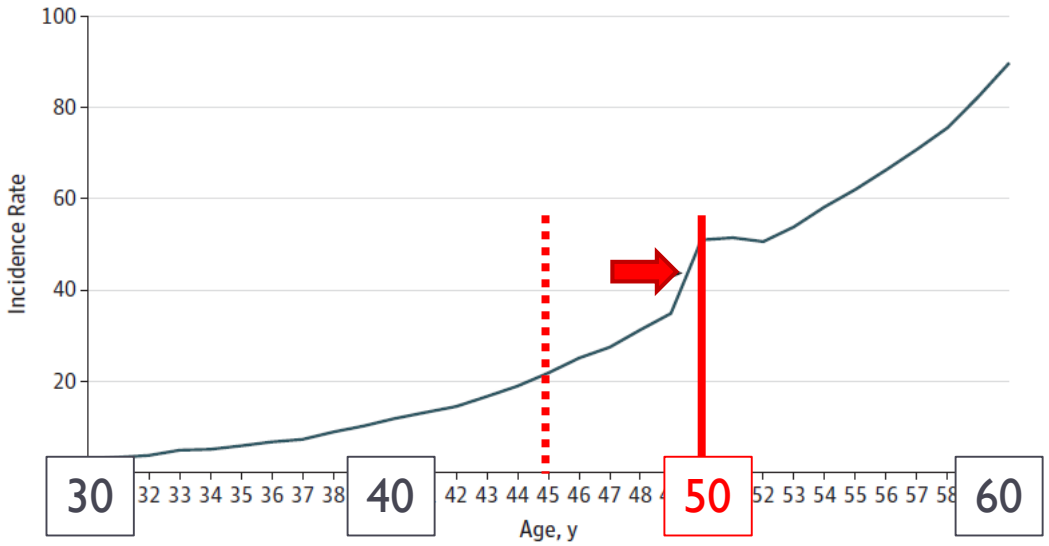
Epidemiology



- 90% are diagnosed after age 50
- But rising incidence in younger individuals
  - Diet? Environment? Microbiome? (in unscreened population)
  - Start screening earlier?
    50 (NCCN, ASCO, USPSTF) ⇨ ?45 (ACS)

Rising in the unscreened (ages 20 – 49)





- SEER: 1930 – 2016; Abualkhair *JAMA Network Open* 2020; Yarden, *AACR* 2019

Risk factors for colorectal cancer

Environmental

(*Increase*)

- Tobacco
- Alcohol
- Low fiber
- Red meat
- Antibiotics
- Sedentary lifestyle

(*Decrease*)

- Aspirin
  - *PIK3CA* mutations?
- NSAIDs
- Post-menopausal hormones
- Calcium
- Vitamin D

Genetic

- Estimated 12-35% is familial
  - Higher risk for siblings than a parent-child
- 5-10% due to highly penetrant cancer family syndromes
  - Lynch syndrome (2-5%)
  - Familial Adenomatous Polyposis (1%)

  …and others

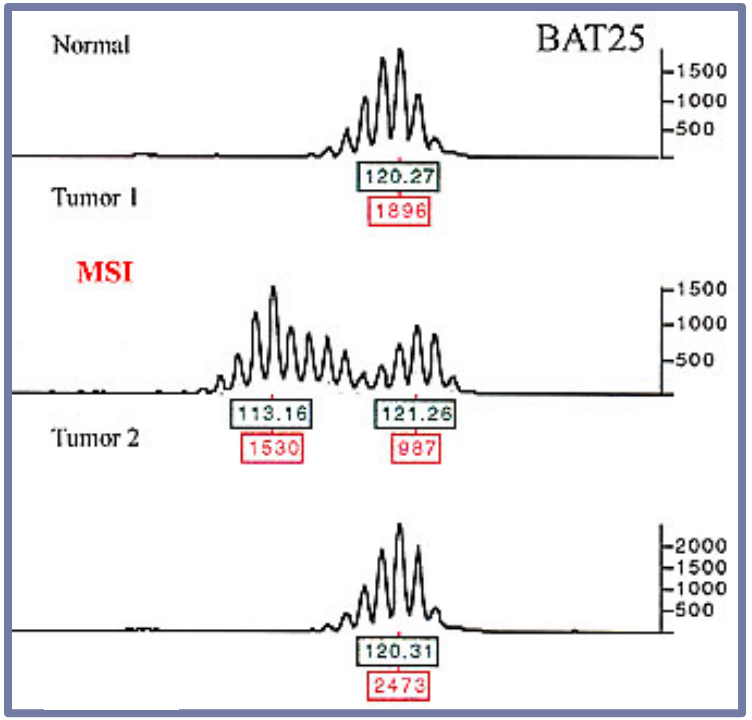
Inflammatory bowel disease

Chan, *Gastro* 2010; Jiao, *Hum Mol Genet* 2014; Hemminki, *CEBP* 2004; Chubb *JCO* 2015; Seigel *JNCI* 2017, Zhang, Gut 2019

Microsatellite instability (MSI)

- 15% of colorectal cancers are MSI-high
  - Detect with PCR, IHC, and/or next-generation sequencing
  - Prognostic and predictive biomarker
- 20% MSI-high = germline
  - Lynch syndrome (formerly: HNPCC)
- 80% MSI-high = somatic
  - Typically due to *MLH1* promoter hypermethylation
  - Often also *BRAF* mutated
- **Universal testing recommended**

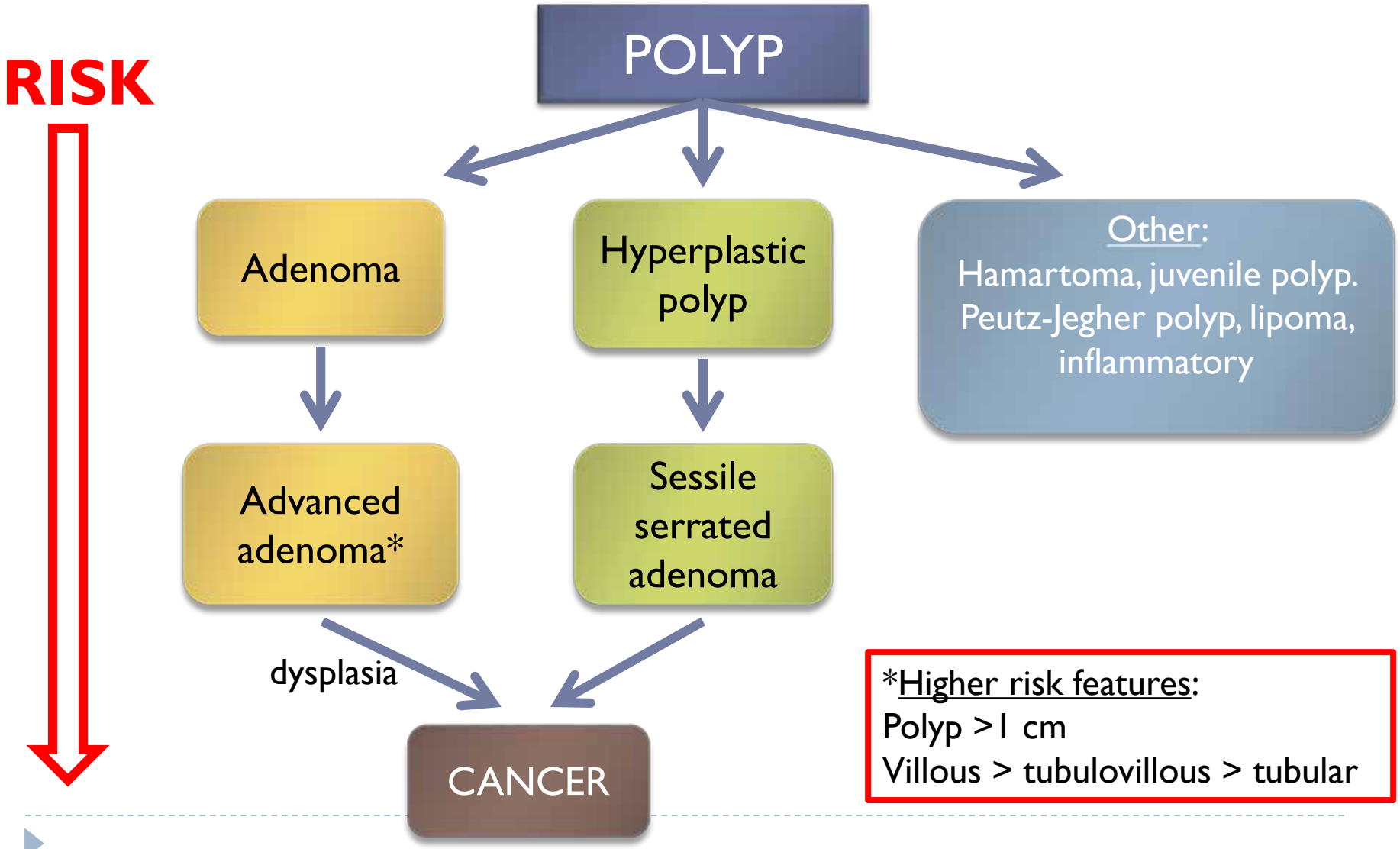
MSI-H = ≥30% loci instable



Hampel, *NEJM* 2005

www.ous-research.no/home/lothe/methods/2766

Polyps as precancerous lesions



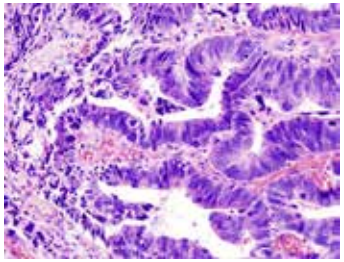
Key points

- Lynch syndrome
  - Most common hereditary CRC syndrome
  - Due to germline mismatch repair mutations → tumor MSI
  - But, not all MSI is due to Lynch (esp. *BRAF*-mutant)

- >1cm and villous adenomas have the highest likelihood of devolving into cancer

Evaluation and Initial Management

Work-up of suspected cancer



Colonoscopy to terminal ileum

Pathology (CK7- CK20+ CDX2+ villin+)

Labs (including CEA)

Tumor molecular testing (MSI, ± extended RAS/RAF)

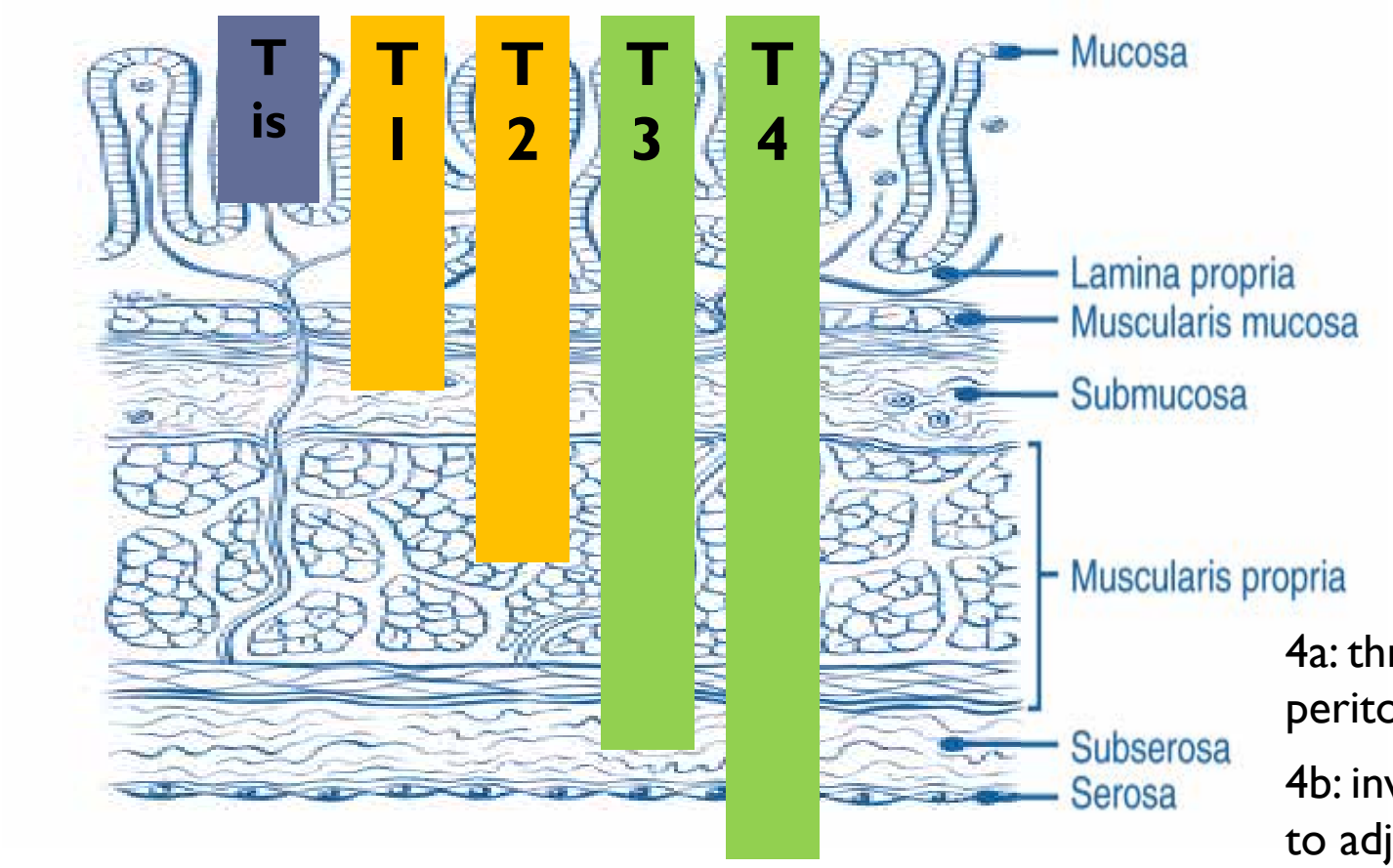
CT chest, abdomen, pelvis with contrast
(and rectal MRI for rectal primary)

PET scans are NOT routinely part of staging

- Use to evaluate equivocal CT findings, or
- if IV contrast contraindicated

Colorectal cancer staging

"TNM" score: T (tumor)



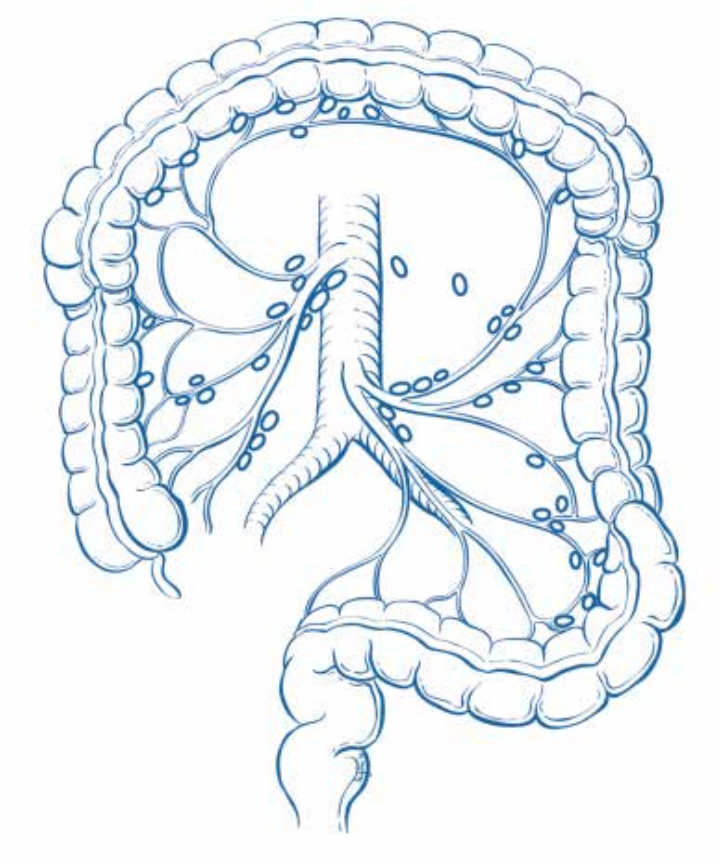
4a: through visceral peritoneum

4b: invade/adherent to adjacent organs or structures

- AJCC 7: www.cancerstaging.org

Colorectal cancer staging

"TNM" score: N (nodes)*



N0	**0**	
N1	**1-3**	N1a = 1 N1b = 2-3 N1c = deposits
N2	**≥ 4**	N2a = 4-6 N2b = 7+

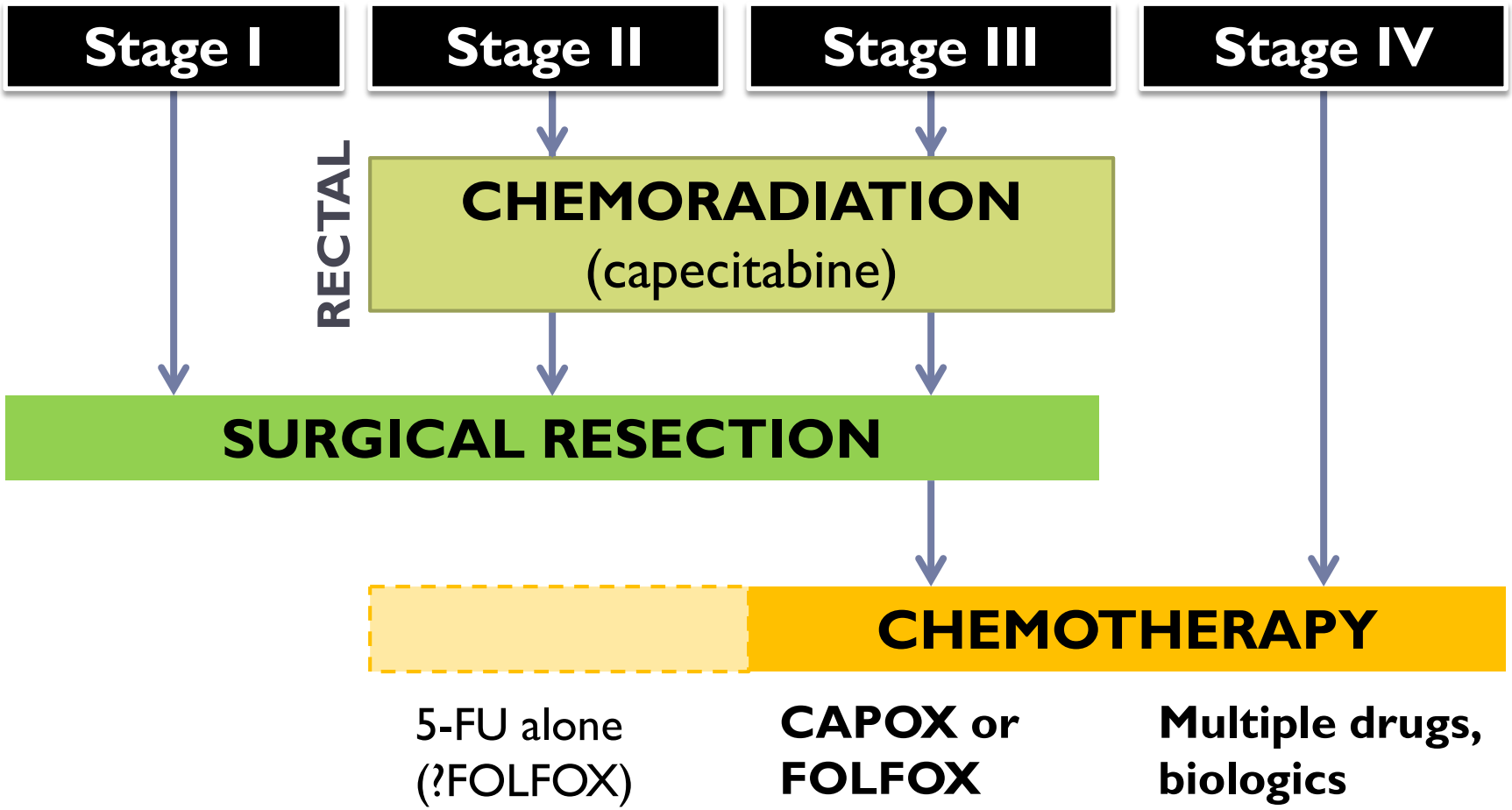
*Non-regional nodes are considered M1a

Colorectal cancer staging

TNM	AJCC Stage	Sub-stage
T1-2 N0 M0	I	
T3-4 N0 M0	II	IIA: T3 N0 IIB: T4a N0 IIC: T4b N0
T **N1-2** M0	III	IIIA: T1-2 N1, T1 N2a IIIB: T3-4a N1, T2-3 N2a, T1-2 N2b IIIC: T4a N2a, T3-4a N2b, T4b N1-2
Tx Nx **M1**	IV	IVA: Tx Nx M1a (single site/organ) IVB: Tx Nx M1b (2+ sites)

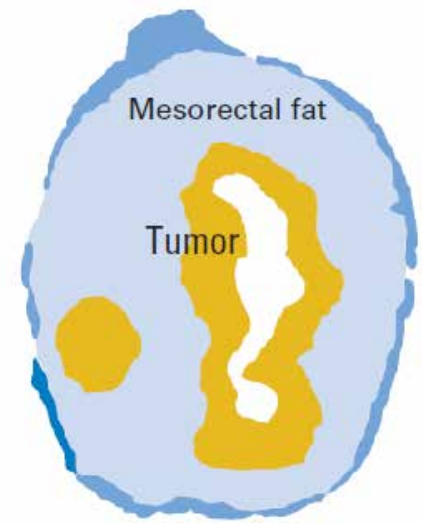
- AJCC 8th edition; SEER data 2004-2010: colon

Treatment overview



Surgery: Partial colectomy with en bloc lymph node removal

- Sufficient margins
  - >5cm proximal and distal to the tumor
- Lymph node sampling
  - En bloc resection with removal of regional LN
  - Minimum 12 removed
- Total mesorectal excision (TME) for rectal
  - Low anterior (LAR) or abdominoperineal (APR)
  - Follows anatomic guidelines
  - Improved circumferential margin clearance
  - Reduced local recurrence with complete TME



Nagtegaal, JCO 2008

Endoscopic colon polyp resection

Endoscopic polypectomy

- Complete polyp removal (not fragmented)
- Negative margins
  - Controversial, but ideally >1mm
- Favorable histologic features
  - Grade 1-2, no angiolymphatic invasion
- Pedunculated
  - Consider for sessile polyp, but higher risk of recurrence

- Otherwise full oncologic bowel surgery

Rectal Transanal Excision*

NCCN Criteria for Transanal Excision

- T1 tumors only (limited to submucosa), N0 M0
- < 30% circumference of bowel
- < 3 cm in size
- Mobile, non-fixed lesion within 8 cm of anal verge
- Favorable histologic features
  - Grade 1-2, no angiolymphatic or perineural invasion
- Clear margin (>3mm) obtainable

- Less complications
  - Sphincter, bladder, sexual dysfunction
- Higher risk of local recurrence

*Modern transanal excision microsurgery (TEM) outperforms classic transanal excision (TAE)

Monson, *Dis Colon Rectum* 2013

Key points

- PET-CT should not routinely be part of the work up of colorectal cancer
- Surgical removal of ≥12 LN is a benchmark metric
- Standard surgery includes colorectal resection with en bloc LN removal
  - Total mesorectal excision improves recurrence rates
  - Polypectomy, transanal excision are options in select cases

Adjuvant Chemotherapy for Colon Cancer

Stage **II**: Adjuvant chemotherapy

- Historically, use is controversial
  - 3% overall benefit based on Cochrane review
- May be beneficial for tumors with "high-risk" features:

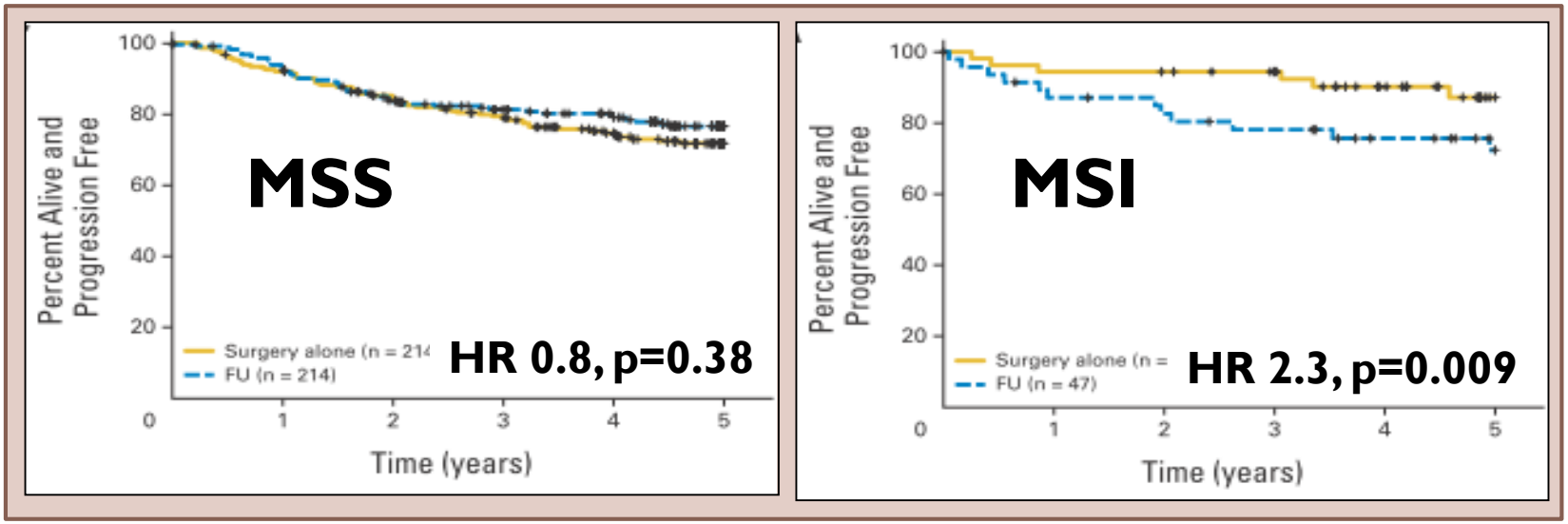
pT4	Bowel obstruction / perforation
Poorly differentiated	< 12 lymph nodes evaluated
Lymphovascular or perineural invasion	Close, indeterminate, or positive margins
Tumor budding	

- Newer data may support adjuvant therapy in high-risk MSS stage II, but observation is also acceptable
  - Regimen and duration are debatable

Meyers, ASCO 2015; Meyers, *Curr Oncol* 2016; Seymour, ASCO 2019; Iveson, ASCO 2019

Stage II guided by molecular sub-types

- ~~Use of multigene assays? (Oncotype DX)~~
  - Validation study did not show predictive benefit
- Microsatellite instability is a useful biomarker
  - Retrospective data of adjuvant **5-FU** vs. **observation**



- Adjuvant chemotherapy is currently NOT recommended in stage II colon cancer that is MSI-H (and this outweighs "high-risk" features)

QUASAR: Gray, *JCO* 2011; Sargent, *JCO* 2010; Yothers, *JCO* 2011

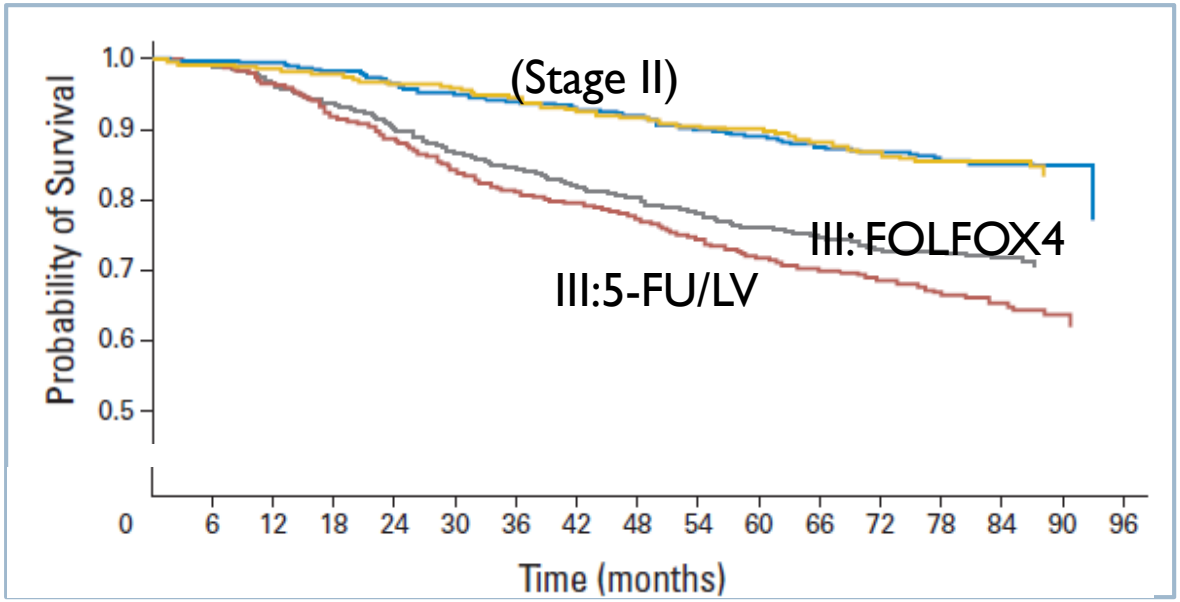
Stage **III**: Adjuvant chemotherapy

Recommendation

- FOLFOX x 3-6 months
  - CAPOX (capecitabine + oxaliplatin) generally considered equivalent
  - ?Benefit for oxaliplatin if ≥70yo (up to 85 included in IDEA)

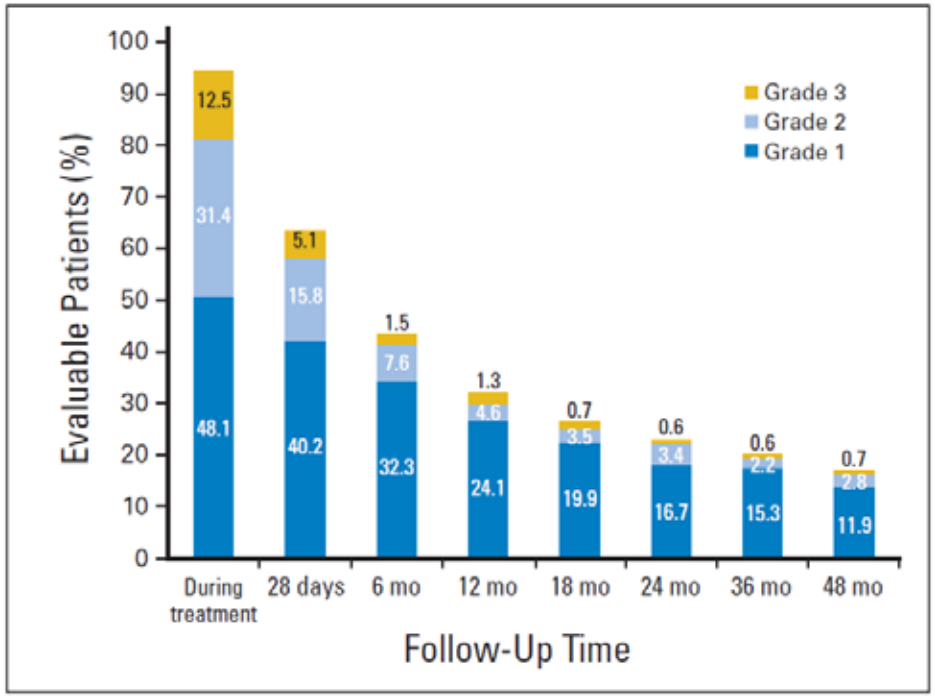
Benefit (vs. 5-FU)

- 3-year DFS:
  - 78 vs. 73%, p=0.002
  - HR 0.76 (24% better)
- 6-year OS:
  - 73 vs. 68%, p=0.02



MOSAIC: Andre, *JCO* 2004, 2009; Tournigand, *JCO* 2012

Oxaliplatin neuropathy



>90% get neuropathy from oxaliplatin
15% is "permanent," but usually mild

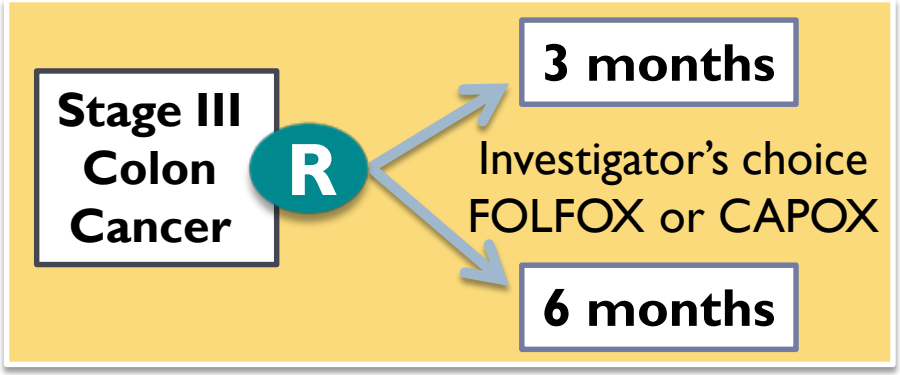
Longer duration of oxaliplatin is associated with greater neuropathy

Neuropathy	3 months		6 months	
	FOLFOX	CAPOX	FOLFOX	CAPOX
Grade 2	9%	14%	26%	29%
Grade 3-4	1%	2%	9%	8%

- MOSAIC: Andre, *JCO* 2009; IDEA: Iveson, *ASCO* 2019

Is 3 months sufficient?

- IDEA consortium
  - 6 trials, 12,800 participants
    - 60% FOLFOX
    - 66% T3, 21% T4; 28% N2



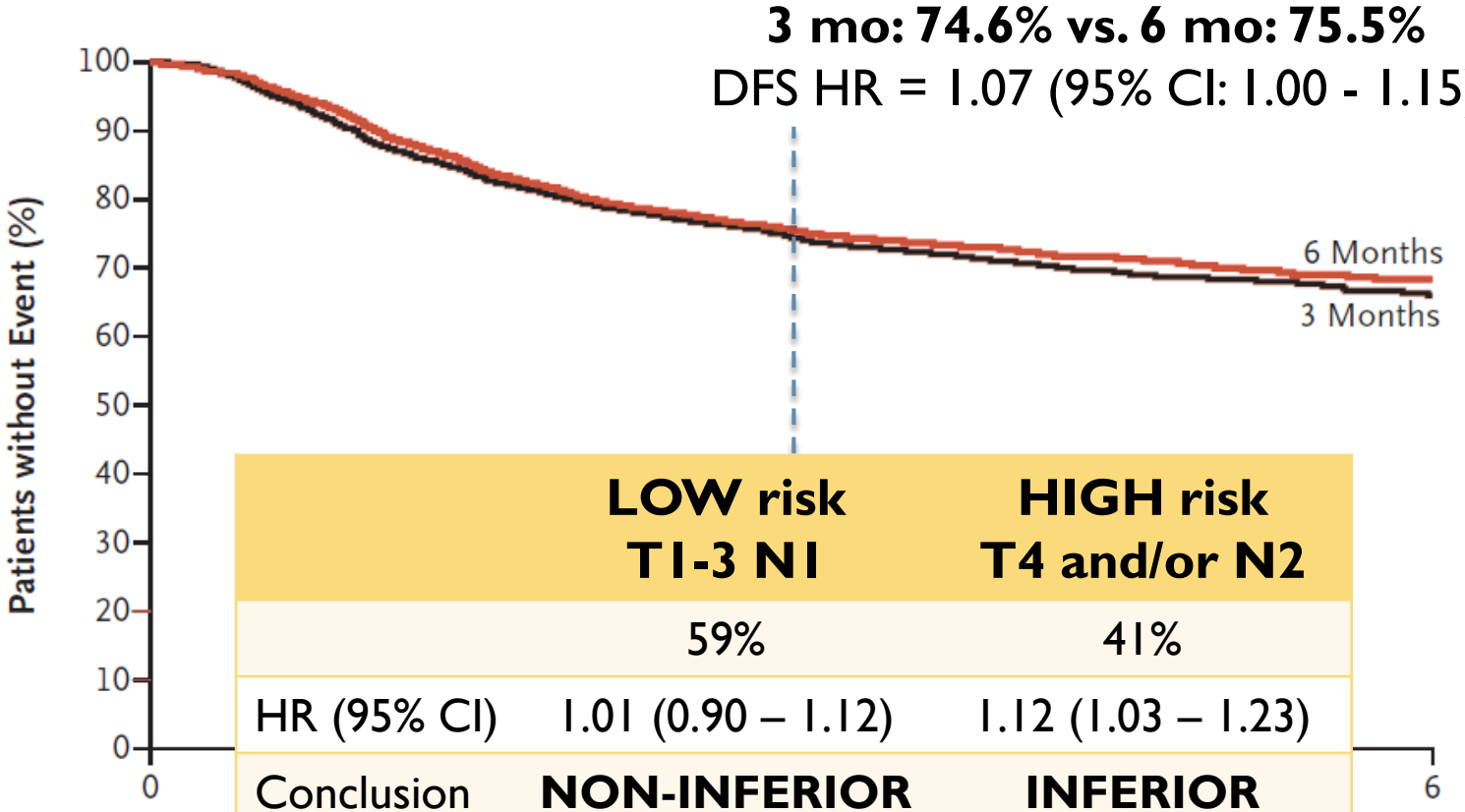
  - C80702 (n=2440) was the trial conducted in North America
    - And all participants were required to receive FOLFOX

  - Designed as a non-inferiority trial with DFS HR 1.12
    - 12% "harm" arbitrarily decided to be acceptable to change to 3 mo.

Sobrero, *JCO* 2018; Andre, *JCO* 2018; Grothey, *NEJM* 2018

Primary outcome: disease-free survival

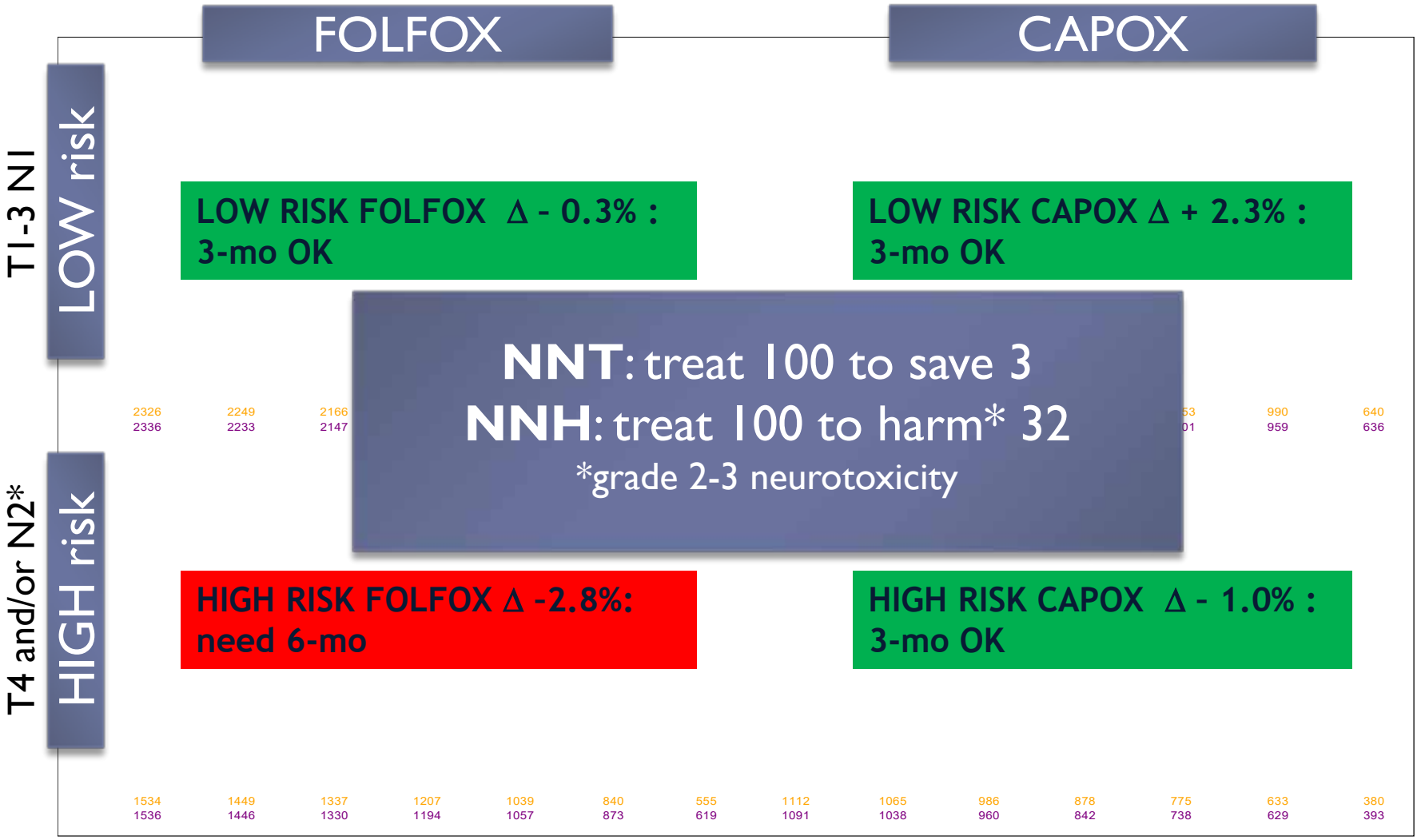
- NOT non-inferior



	LOW risk T1-3 N1	HIGH risk T4 and/or N2
	59%	41%
HR (95% CI)	1.01 (0.90 – 1.12)	1.12 (1.03 – 1.23)
Conclusion	**NON-INFERIOR** 3 mo likely ok	**INFERIOR** 6 mo needed

Grothey, *NEJM* 2018

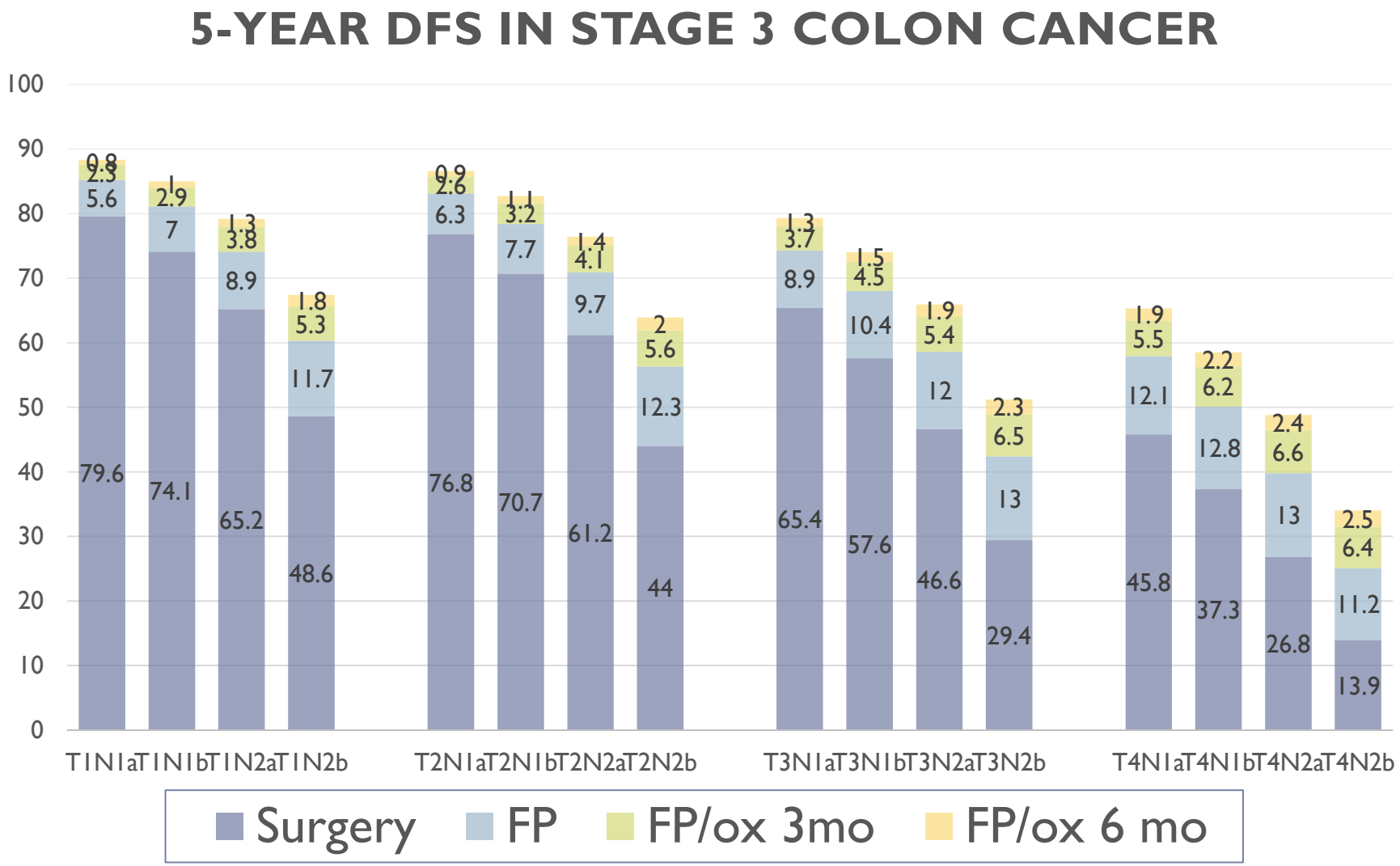
OS outcomes by risk and by regimen



Sobrero, *ASCO* 2020; Yamanaka, *ASCO* 2020

*T4 risk > N2

Incremental benefits in adjuvant therapy



Adapted from: Sobrero, *ASCO* 2020

The future of adjuvant therapy

- NO benefit to irinotecan
  - Benefit in CIMP+ MMR-intact?
- NO benefit to cetuximab
  - Benefit in T4 N2?
- NO benefit to bevacizumab

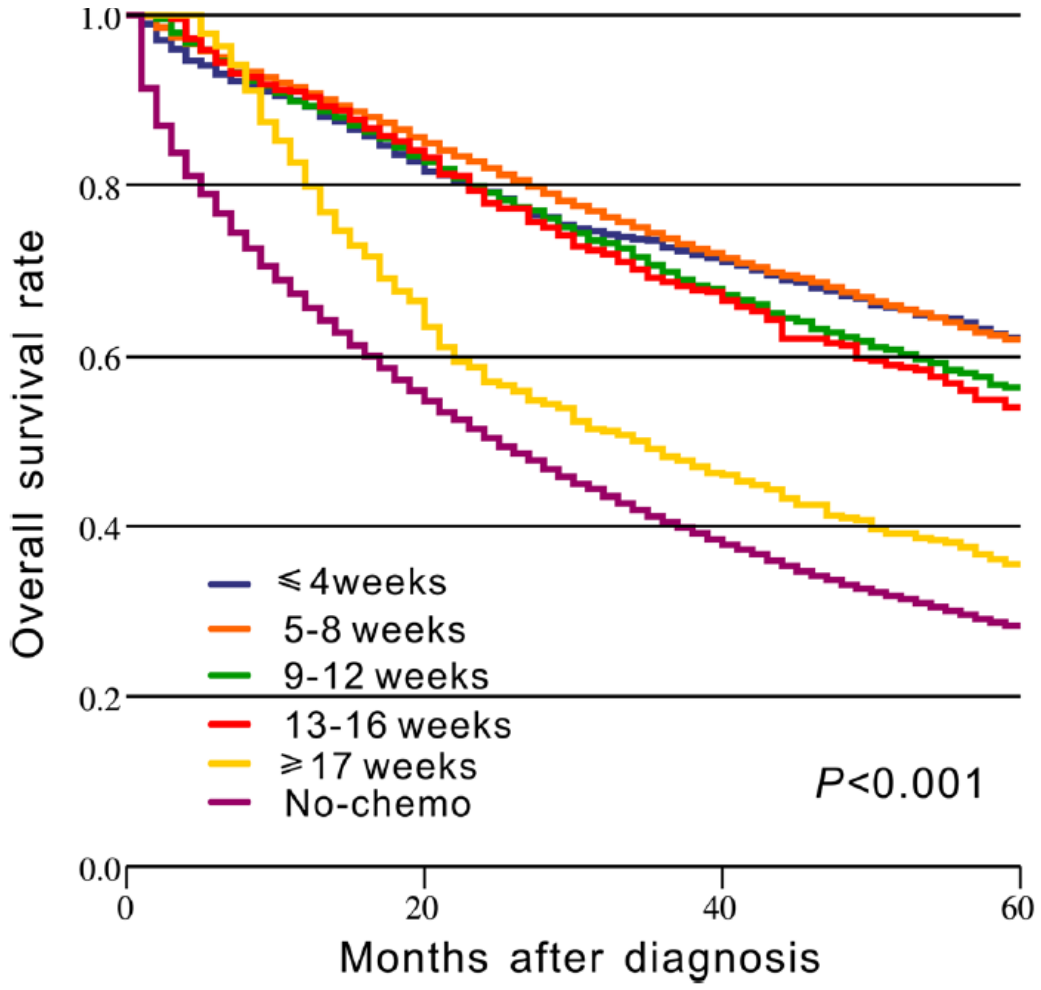
Biomarkers are needed to better tailor therapy

- Expect future (exploratory) subgroup analyses within the IDEA 3 vs. 6 mo trials
  - MSI (dMMR)?
  - Elderly (≥70yo)?
  - Right vs. left?

And what about 3 mo FOLFOX or CAPOX and then just 5-FU/capecitabine alone through 6 mo?

CALGB 89803; N0147, PETACC-8; NSABP C-08, AVANT

Time to adjuvant chemotherapy vs. survival



- Meta-analysis of >18,000 patients
- Most benefit from adjuvant <8 weeks post-op
  - But still some benefit up to +16 weeks
- Prior analysis suggested 14% mortality increase for each 4-week delay after 8 weeks

Gao, *BMC Cancer* 2018; Biagi, *JAMA* 2011

Key points

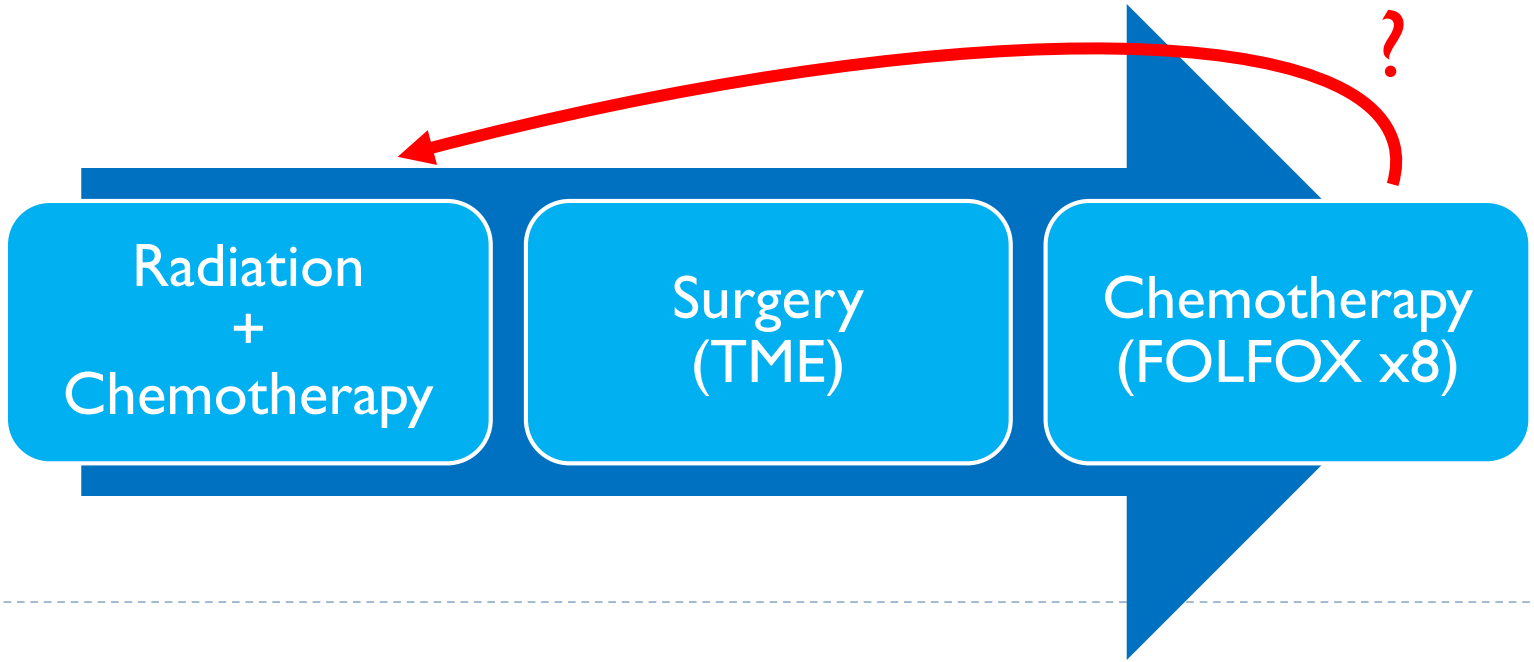
- Overall, no benefit for adjuvant chemotherapy in stage II
  - Consider for select "high-risk" MSS patients
  - Avoid adjuvant chemotherapy in MSI-high stage II
- 3 months of adjuvant chemotherapy is becoming the new standard for stage III
  - 6 months is still recommended for high-risk (T4 or N2) patients who receive FOLFOX
    - And potentially for all high-risk patients?
  - CAPOX may be more effective (though not studied in the US population)
- No indication for irinotecan, cetuximab, or bevacizumab

Localized Rectal Cancer

Rectal cancer: General principles

- Definition: primary lesion within 12 cm of anal verge by rigid proctoscopy
  - Consider treating cancers entirely above the anterior peritoneal reflection "as colon" (i.e. upfront surgery)

- Higher rates of local recurrence compared to colon



Neoadjuvant radiation therapy

- German CAO/ARO/AIO-94 trial:
  - 5-FU/RT → TME vs. TME → 5-FU/RT
  - All T3-4 or N+ (n=823)

	Pre-op radiation	Post-op radiation	
Pelvic Relapse (10-yr)	7%	10%	p=0.048
5-year DFS	68%	65%	NS
5-year OS	76%	74%	NS
Sphincter preservation	39%	13%	p=0.006
Toxicity	27%	40%	p=0.001

- Neoadjuvant therapy may allow sphincter-preserving surgery and reduces risk of local recurrence

Sauer, *NEJM* 2004; Sauer, *JCO* 2012

Neoadjuvant chemotherapy with radiation

NSABP R-04: stage II-III rectal (n=1608)

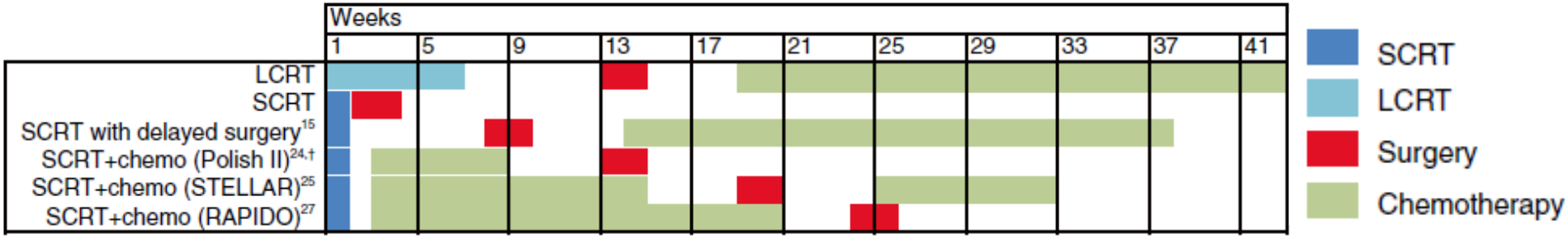
5-FU	Capecitabine	5-FU + oxaliplatin	Cape + oxaliplatin

- Conclusions:
  - No benefit to addition of oxaliplatin
  - Capecitabine appears as good as 5-FU
  - No difference in surgical outcomes
- 5-year OS about 80%
  - Oxaliplatin trended to better DFS, but similar OS
- Today: Recommend capecitabine alone

NSABP R-04: O'Connell, *JCO* 2014; Allegra, *JNCI* 2015

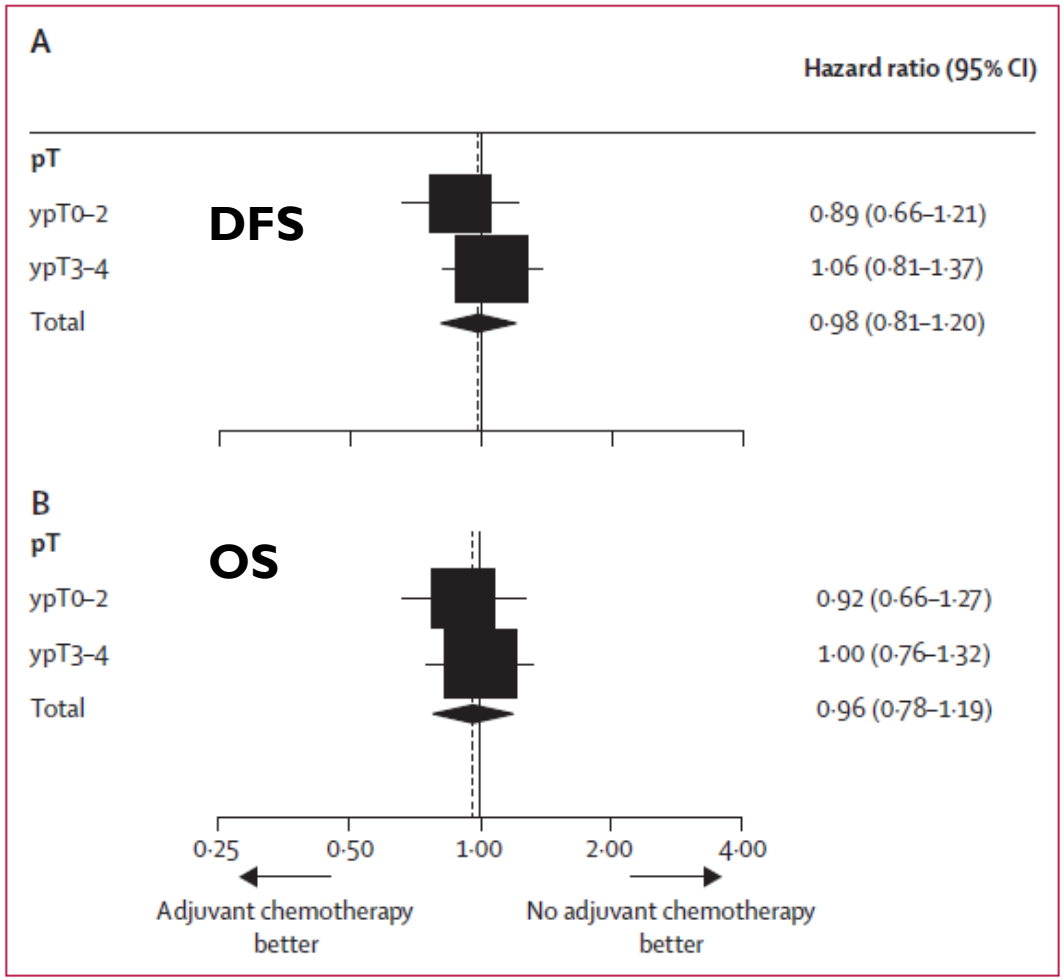
Short-course radiation

- Hypofractionated 25Gy (5Gy x 5 days), NO chemo
  - (Standard/long-course: 28 fractions over 5.5 weeks, 50.4 Gy)
  - Surgery 1 or 4+ weeks later
- If plan for surgery soon after, best when primary tumor down-staging is not required, limited/no nodal disease
  - Lower pCR rate (unless wait a similar interval as long-course)
  - Sequencing with surgery, systemic chemotherapy needs to be further elucidated



Mullen, *Curr Colorectal Cancer Rep* 2017; Bahadoer, *ASCO* 2020

Rectal: Adjuvant chemotherapy



- cT3-4 (n=1101)
  - Neoadjuvant 5-FU/RT → Surgery
  - RCT to adjuvant 5-FU vs. surveillance
- Trend to benefit only in ypT0-2

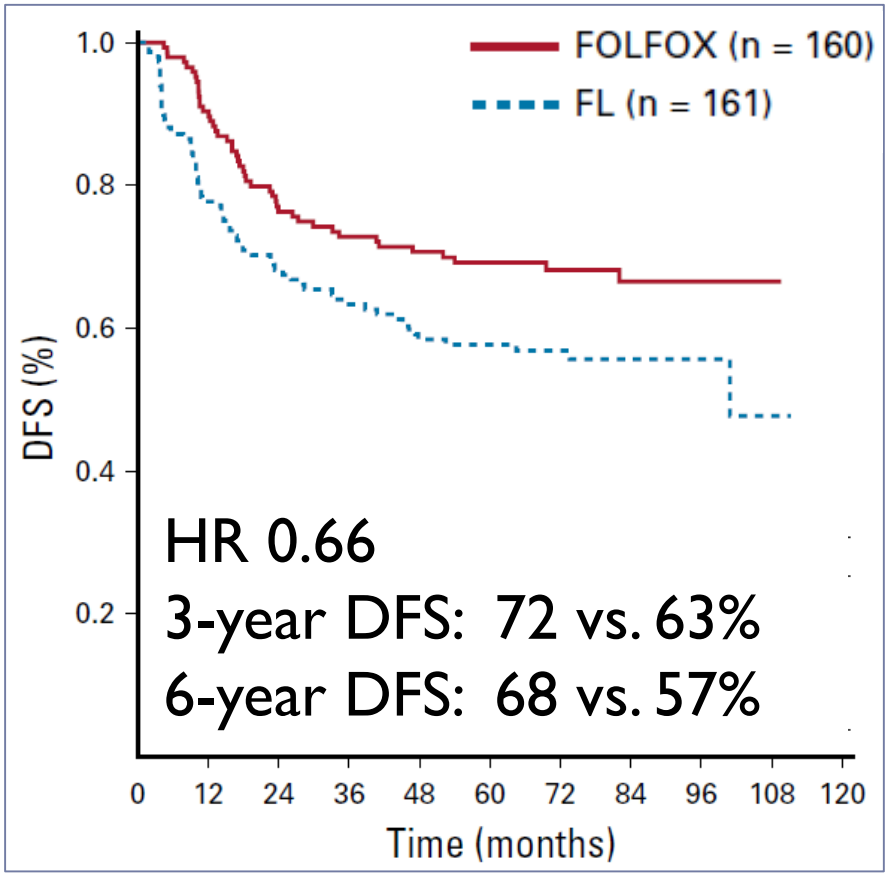
- EORTC 22921: Bosset, *Lancet Onc* 2014

Adjuvant FOLFOX

- ADORE: 5-FU/RT → TME → **ypT3-4** N0 or Tx **ypN1-2**

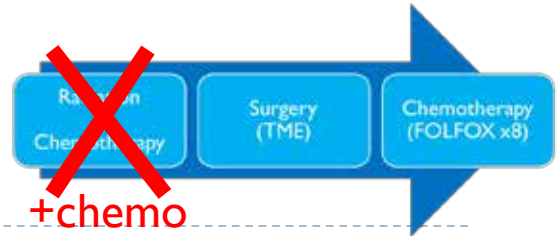
- FOLFOX improved DFS
  - ypN+ > ypN0
  - Not significantly better for very good tx response

- Today, FOLFOX is recommended for all stage 2-3 rectal cancer
  - ?benefit of oxali in ≥70yo



Hong, *Lancet Onc* 2014, *JCO* 2019; Rodel, *JCO* 2005

Omit radiation?

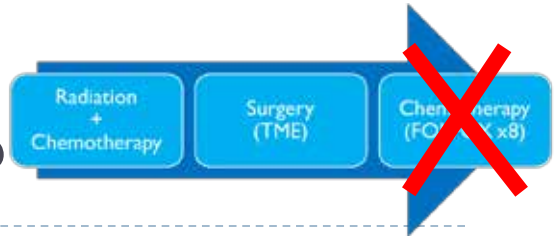


- Most patients dying from rectal cancer have distant metastases, not local recurrence
- Some patients may never start adjuvant chemotherapy because of surgical complications, or it is quite delayed
  - So are we doing patients a disservice by placing high-dose chemotherapy at the end of therapy?

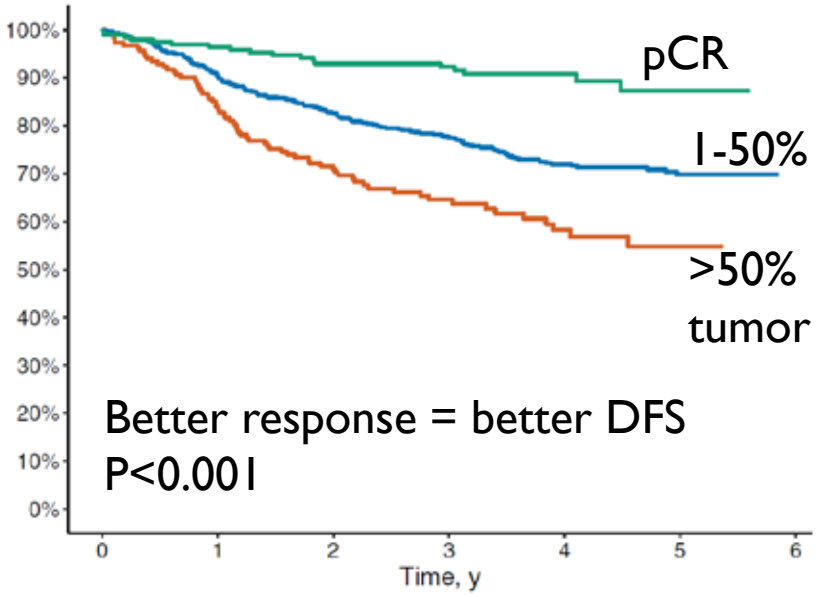
- PROSPECT trial:
  - Phase 3 trial of peri-operative FOLFOX + selective RT for poor responders or positive margins
  - Completed accrual and awaiting results (2022?)

Bosset, *NEJM* 2006; Fernandez-Martos, *JCO* 2010; Rodel, *Lancet Onc* 2012

Skip adjuvant chemotherapy?

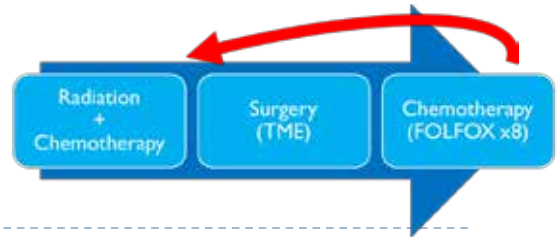


- May be delayed/omitted in patients with surgical morbidity
- Helpful if poor risk disease
- pathologic Complete Response
  - Associated with better outcomes
  - Unclear if this should affect adjuvant therapy
- Ok to use 5-FU/capecitabine alone? Observe?

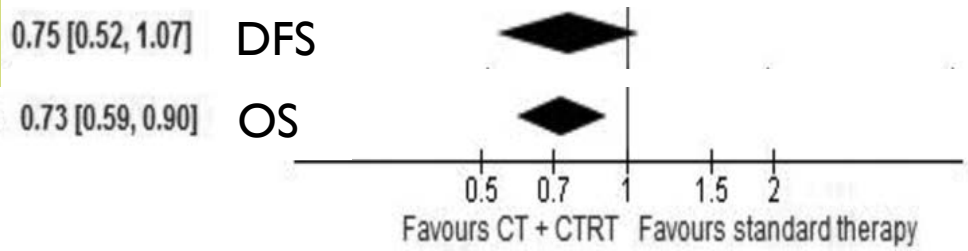


Fokas, *JNCI* 2017; Rodel, *JCO* 2005; Loree, *Clin Colorectal Cancer* 2016

Total neoadjuvant therapy



- Concept of sequencing both chemoRT and systemic chemotherapy PRIOR to surgery
  - Removes the need for adjuvant therapy
  - Could be done with short- or long-course RT



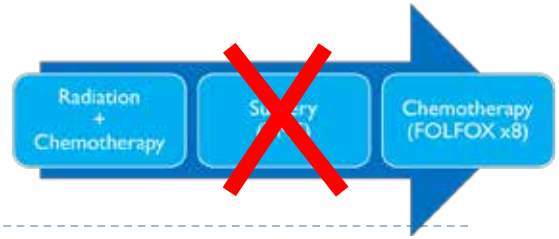
Highly consider TNT if:

- Unresectable or may convert from APR to LAR
- T4 and/or N2
- Involved circumferential margin

- Need more prospective, randomized data
- Newer studies suggest higher pCR rate (25-45% vs. 15-20%)
  - Especially if chemoRT done first?
  - Possible role for FOLFIRINOX in the neoadjuvant setting?

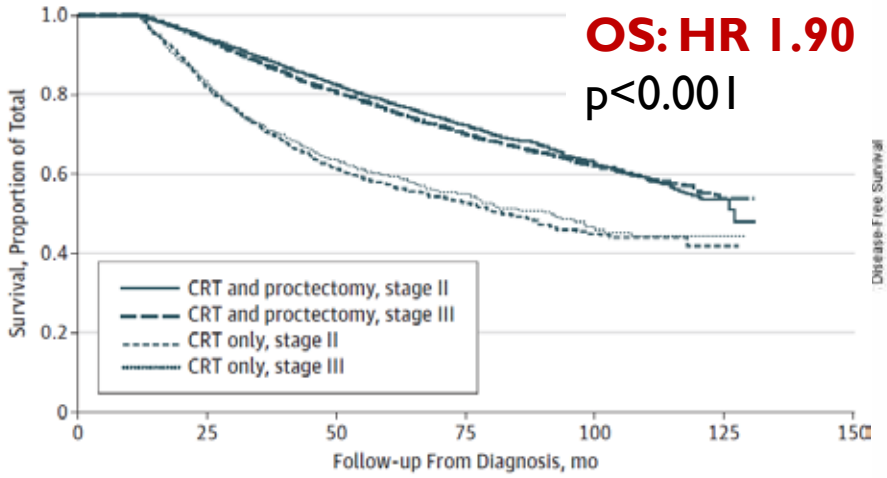
Petrelli, *Ann Surg* 2020; Garcia-Aguilar, *ASCO* 2020; Conroy, *ASCO* 2020

Nonoperative management?

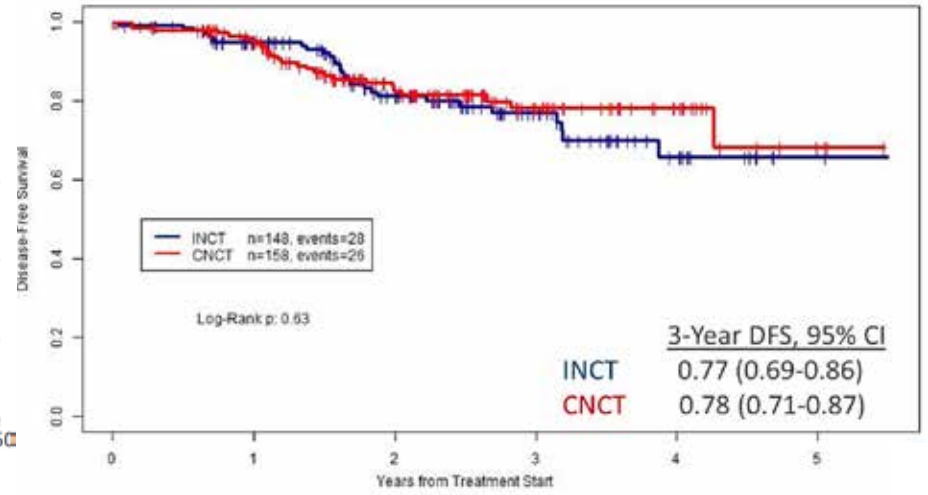


- "Watch and wait" approach
  - Avoid surgical morbidity in poor candidates
  - Avoid permanent ostomy in those that decline
- Higher rates of local and possibly distant failure
- Need a complete clinical response (by CT, MRI, flex sig)

NCDB 2004-2008



OPRA trial: 2013-2020



Ellis, *JAMA Onc* 2017; Garcia-Aguilar, *ASCO* 2020

Key points

- Preoperative chemoradiation therapy is standard-of-care for T3-4 or node-positive rectal cancers
  - Reduces local recurrence
  - Improves likelihood of sphincter-sparing surgery
  - Does not improve survival (vs. adjuvant RT)
- Do NOT use oxaliplatin with preoperative chemoradiation
- 5-FU/oxaliplatin is recommended for all stage 2-3 patients
  - Neoadjuvant systemic chemotherapy (TNT) is a growing trend