Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

# Comprehensive Oncology Review: Colorectal Cancer - Adjuvant

Stacey Cohen, MD

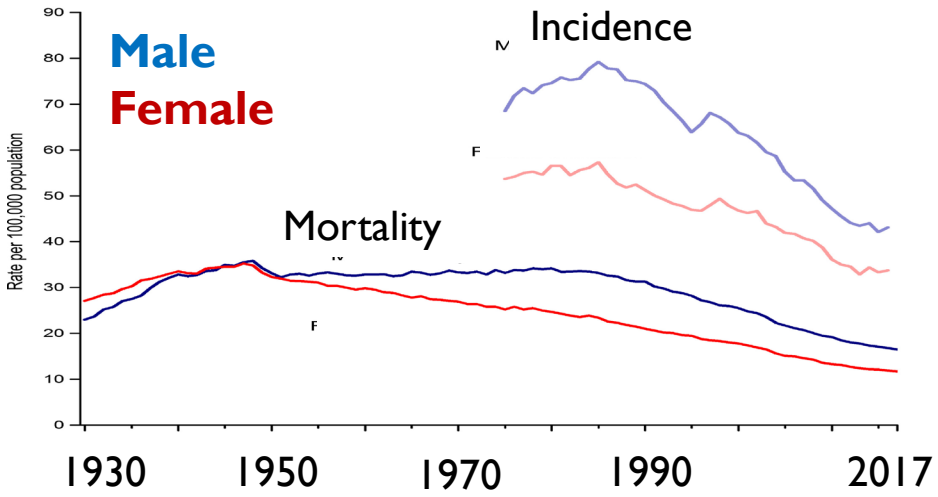
shiovitz@uw.edu

# Outline

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

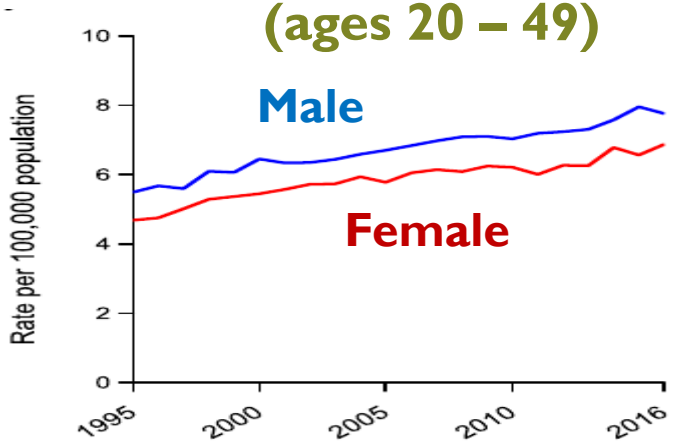
# Epidemiology and Risk Factors

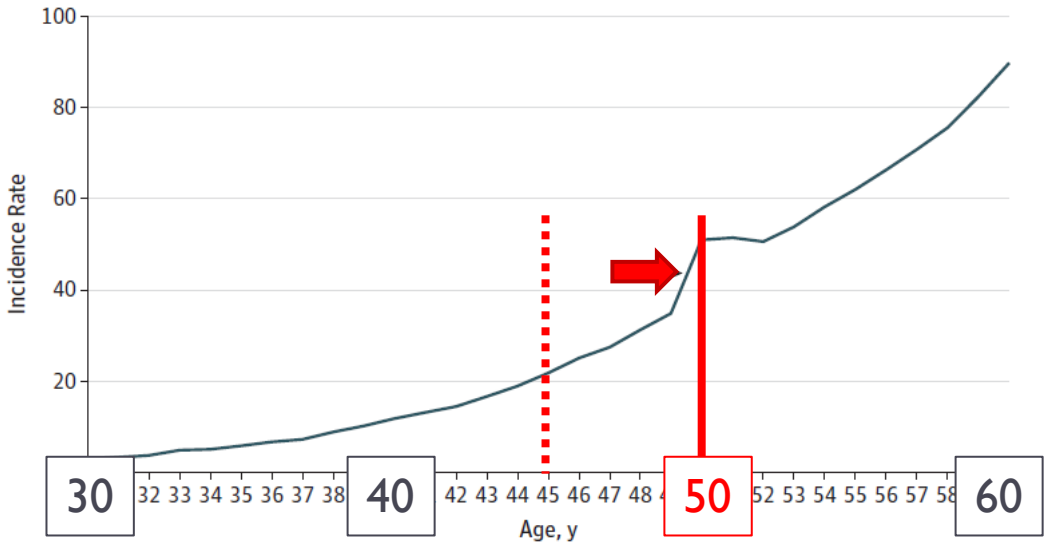
# Epidemiology




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

**Rising in the unscreened (ages 20 – 49)**




- Siegel, *CA: A Cancer J for Clin* 2020; Abualkhair, *JAMA Network Open* 2020; Yarden, *AACR* 2019; USPSTF, *JAMA* 2021

# 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

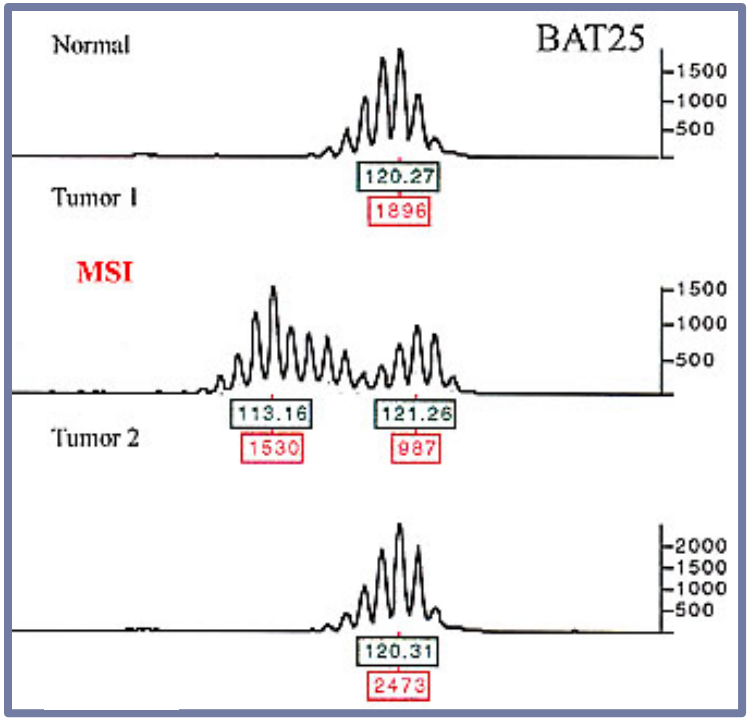
Inflammatory bowel disease

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**

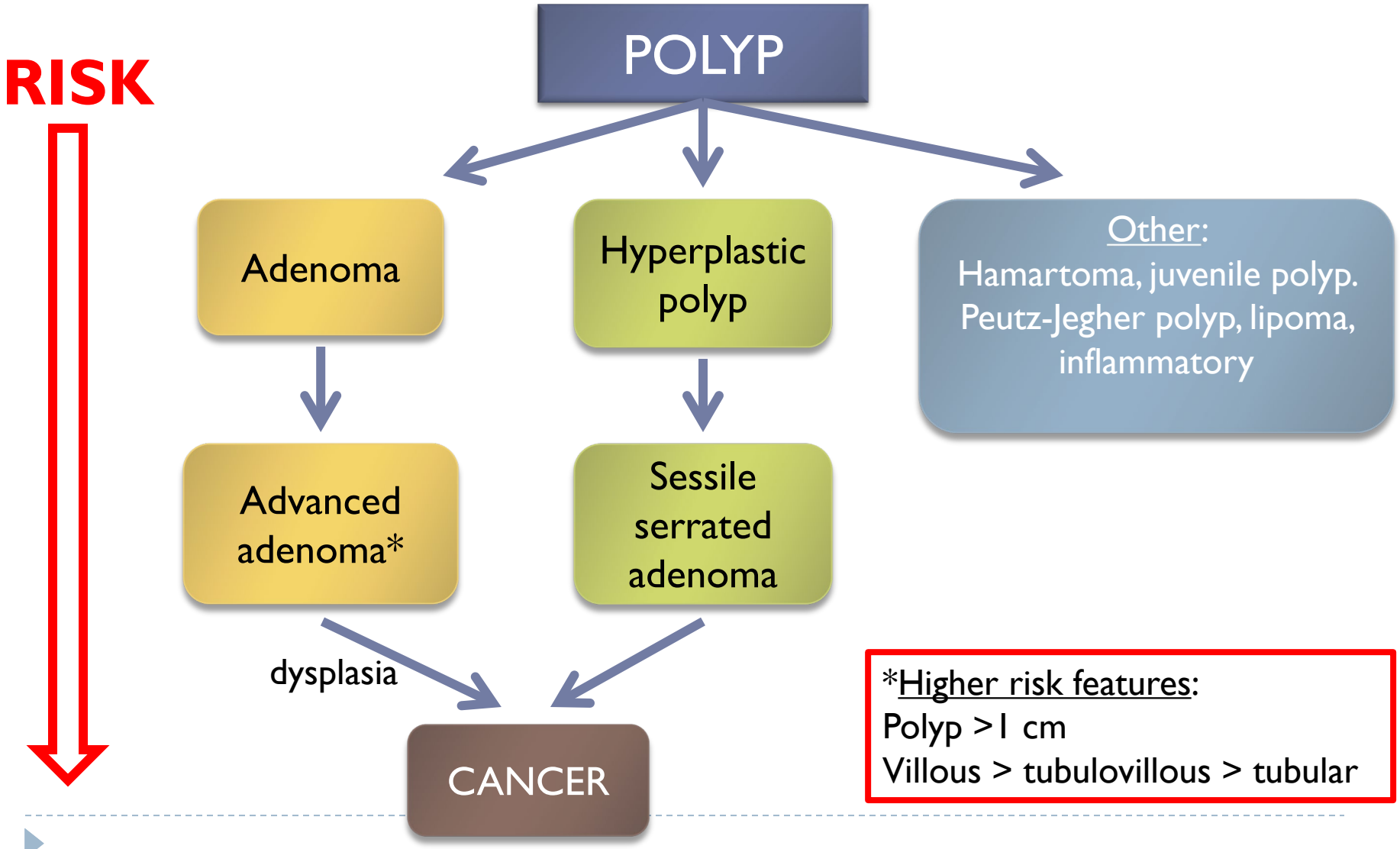
MSI-H = ≥30% loci instable




Hampel, *NEJM* 2005

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

# Polyps as precancerous lesions



# Key points

- Screening for average risk people now recommended to begin at 45yo

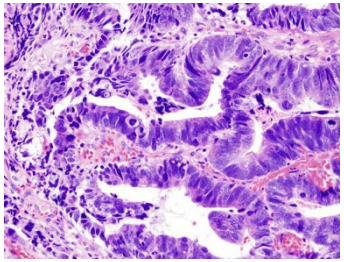
- Lynch syndrome
  - Most common hereditary CRC syndrome
  - Due to germline mismatch repair mutations → tumor MSI
  - But, not all MSI is due to Lynch (esp. *BRAF*-mutant)

- >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

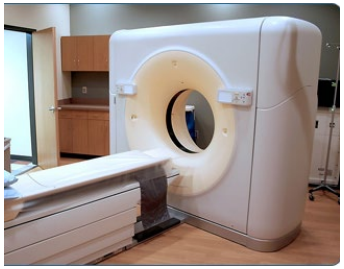


Pathology (CK7- CK20+ CDX2+ villin+)

Labs (including CEA)

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

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

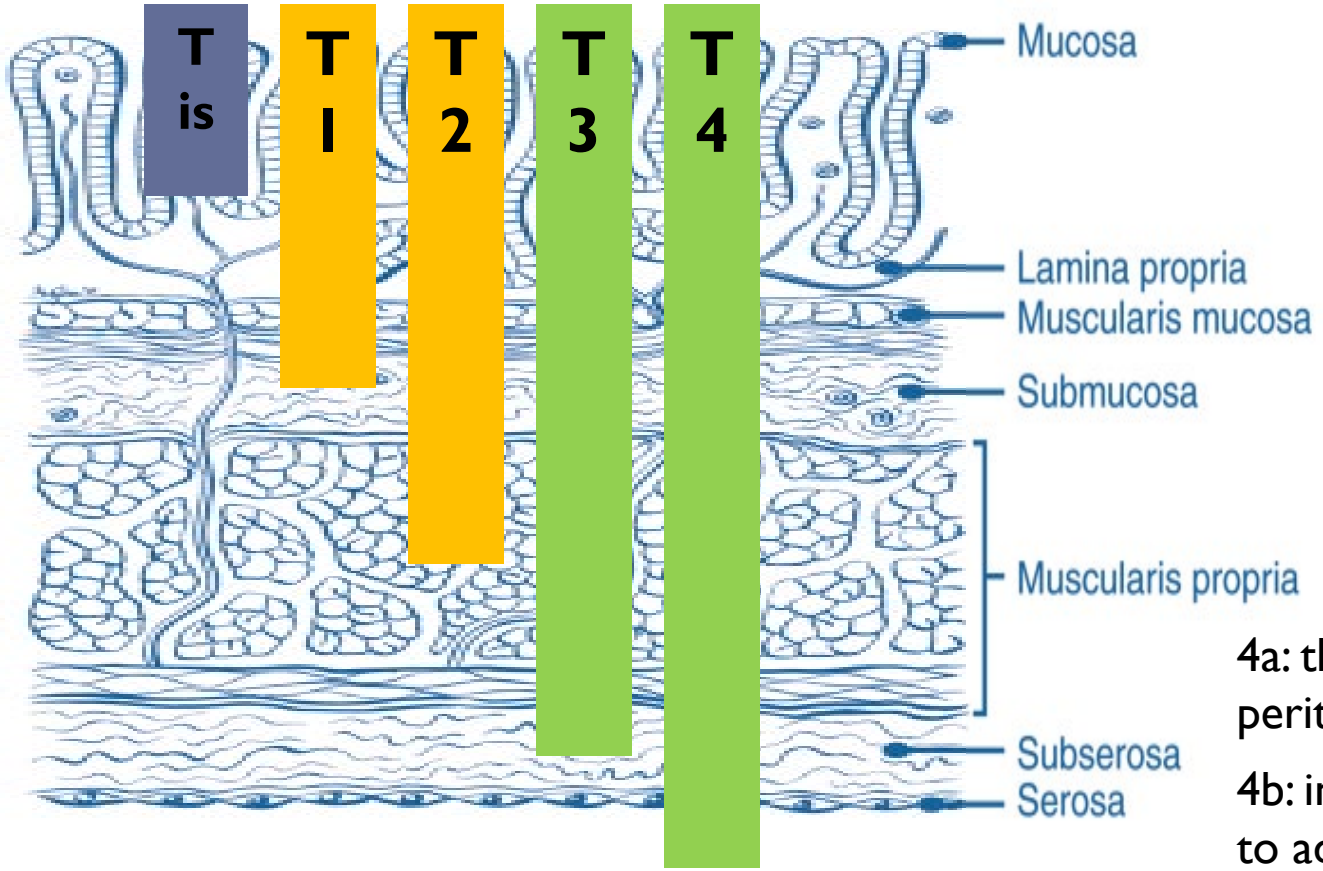


PET scans are NOT routinely part of staging

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

# Colorectal cancer staging

"TNM" score: T (tumor)



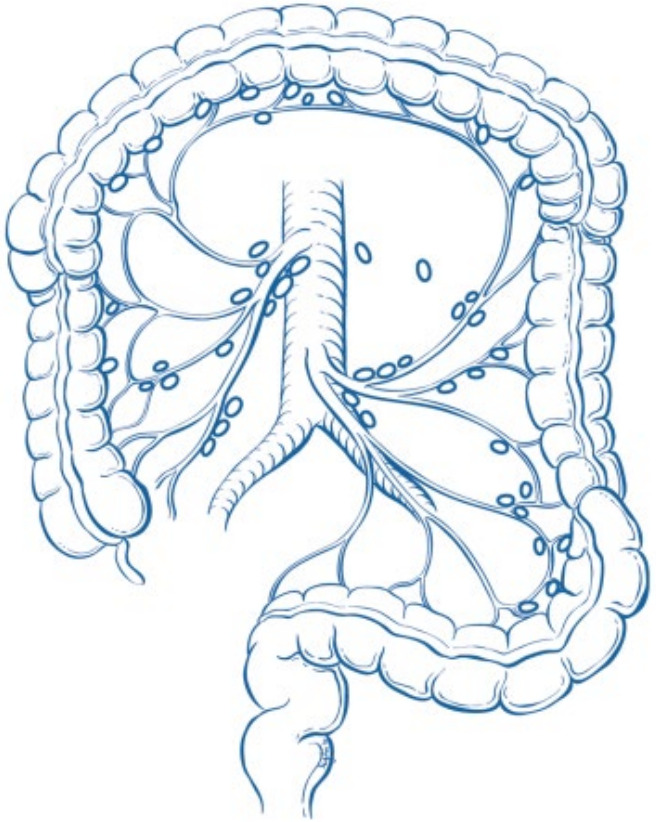

4a: through visceral peritoneum

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<br>N1b = 2-3<br>N1c = deposits |
| **N2** | **≥ 4** | N2a = 4-6<br>N2b = 7+ |

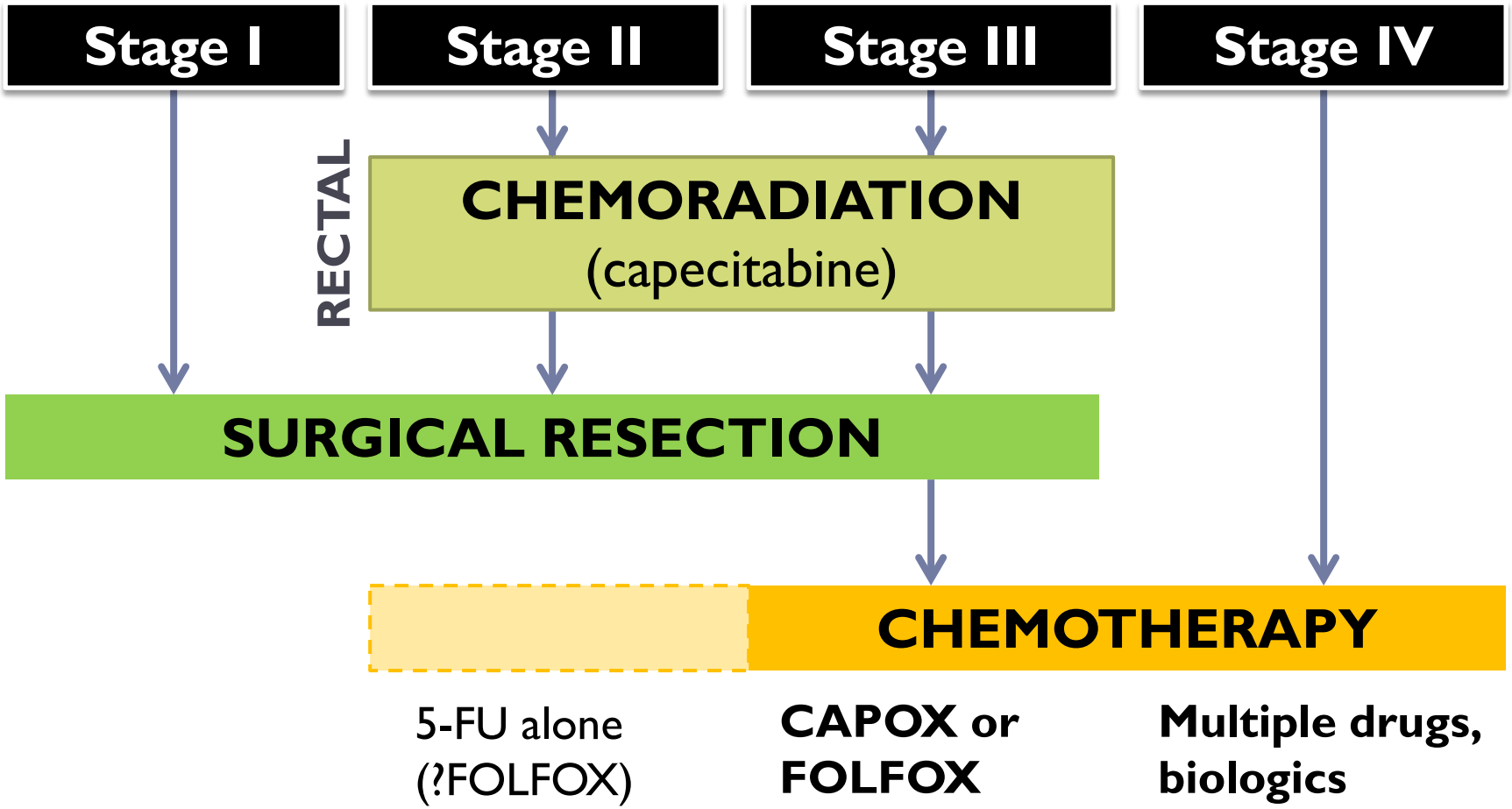
*Non-regional nodes are considered M1a

# Colorectal cancer staging

| TNM | AJCC Stage | Sub-stage |
|---|---|---|
| **T1-2** N0 M0 | I | |
| **T3-4** N0 M0 | II | IIA: T3 N0<br>IIB: T4a N0<br>IIC: T4b N0 |
| T **N1-2** M0 | III | IIIA: T1-2 N1, T1 N2a<br>IIIB: T3-4a N1, T2-3 N2a, T1-2 N2b<br>IIIC: T4a N2a, T3-4a N2b, T4b N1-2 |
| Tx Nx **M1** | IV | IVA: Tx Nx M1a (single site/organ)<br>IVB: Tx Nx M1b (2+ sites)<br>IVC: Tx Nx M1c (peritoneal ± other) |

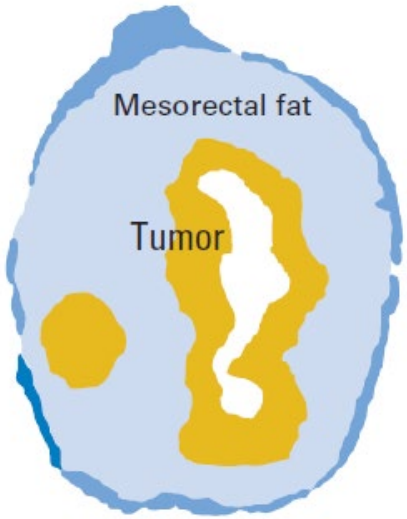
- AJCC 8th edition; SEER data 2004-2010: colon

# 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
  - 2-3% non-significant benefit
- May be beneficial for tumors with "high-risk" features:

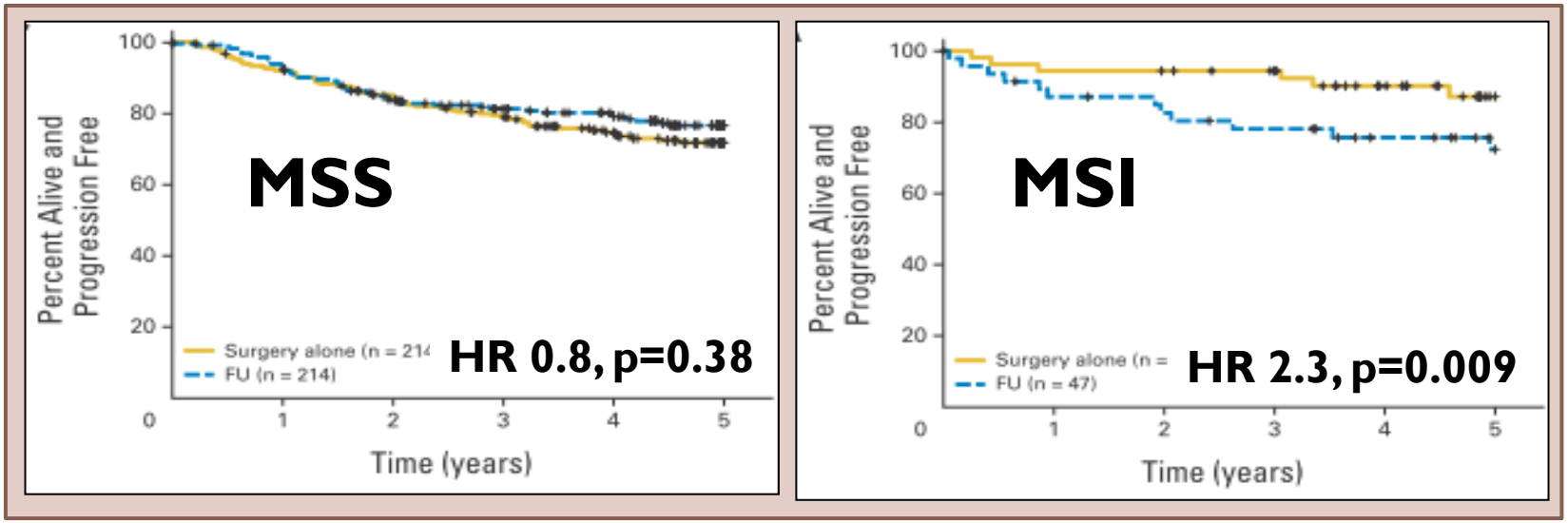
| | |
|---|---|
| pT4 | Bowel obstruction / perforation |
| Poorly differentiated | < 12 lymph nodes evaluated |
| Lymphovascular or perineural invasion | Close, indeterminate, or positive margins |
| Tumor budding | |

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

Yothers, *JCO* 2011; Meyers, *Curr Oncol* 2016; Iveson, *JCO* 2021

# Stage II guided by molecular sub-types

- 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

Sargent, *JCO* 2010; Yothers, *JCO* 2011

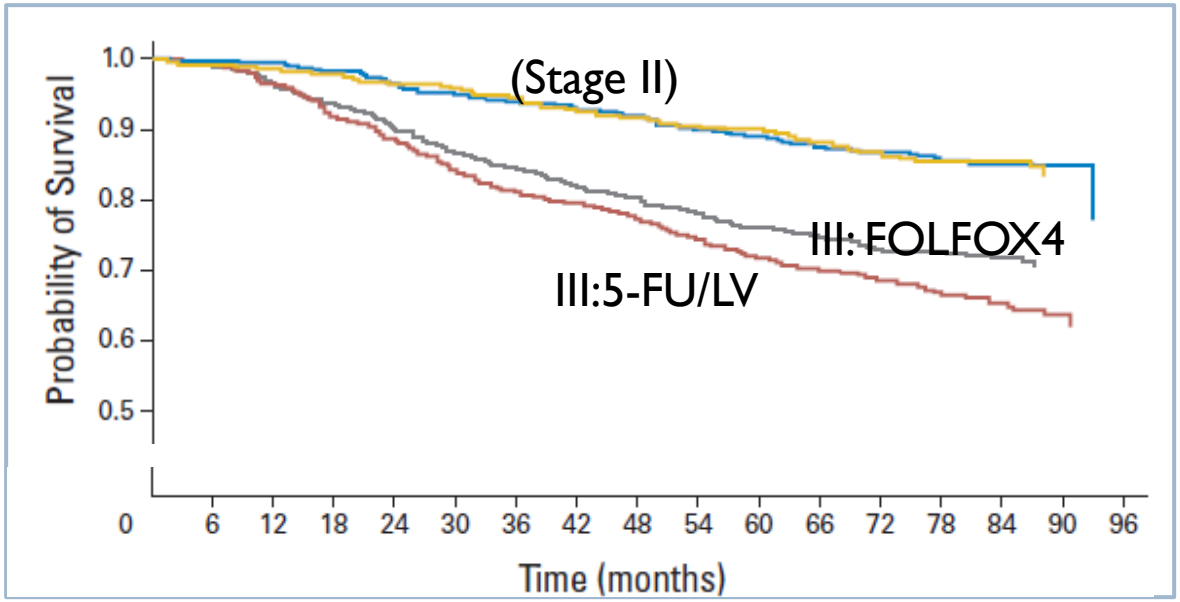
# Stage **III**: Adjuvant chemotherapy

## Recommendation

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

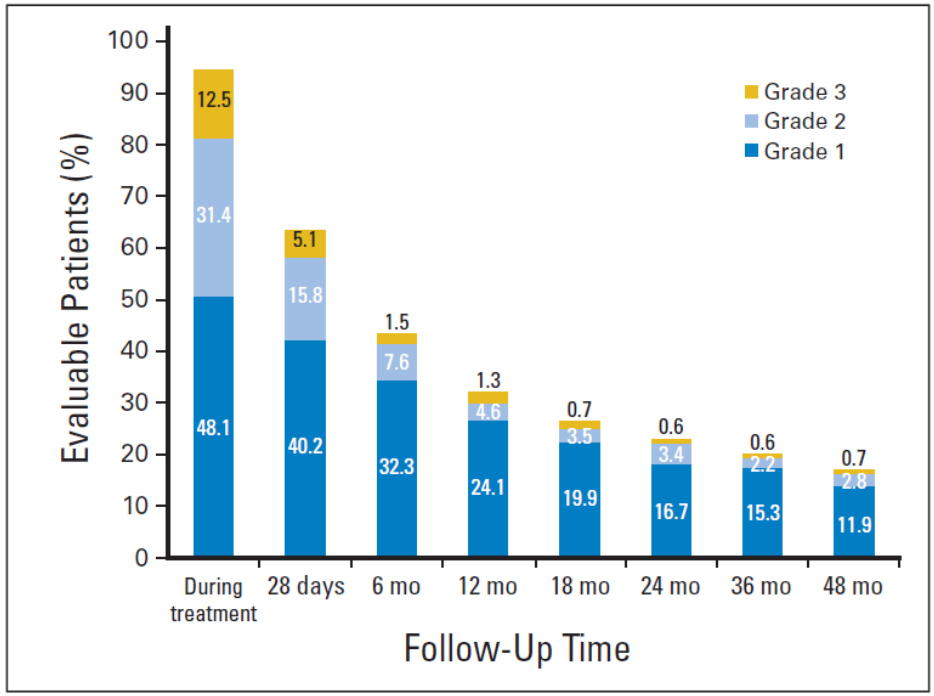
## Benefit (vs. 5-FU)

- 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

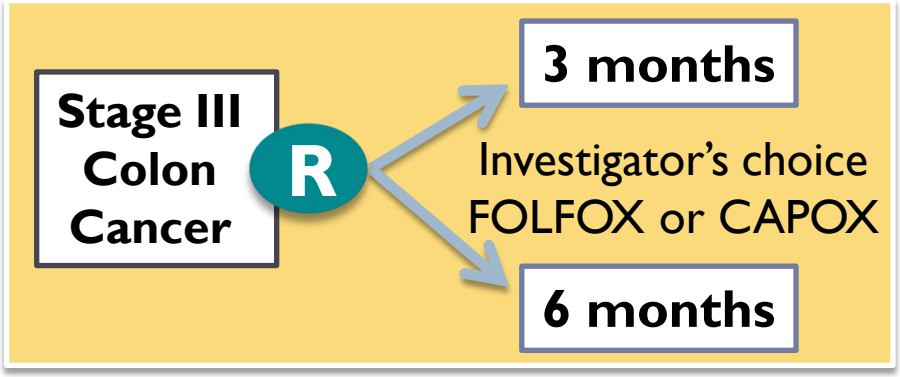
Longer duration of oxaliplatin is associated with greater neuropathy

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

- Andre, *JCO* 2009; 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 protocoled to receive FOLFOX

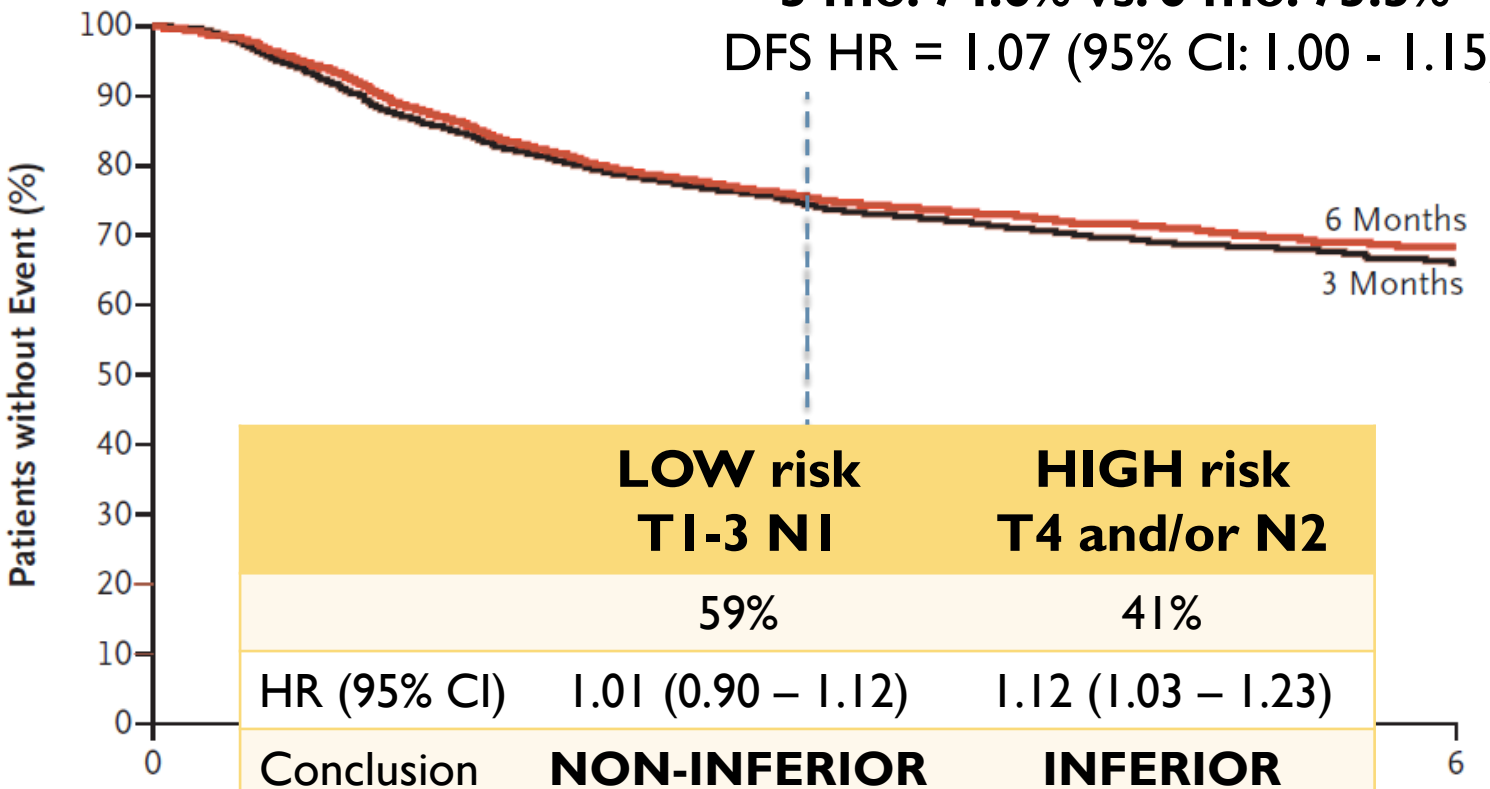
  - Designed as a non-inferiority trial with DFS HR 1.12
    - 12% "harm" arbitrarily decided to be acceptable to change to 3 mo.

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

# Primary outcome: disease-free survival

- NOT non-inferior

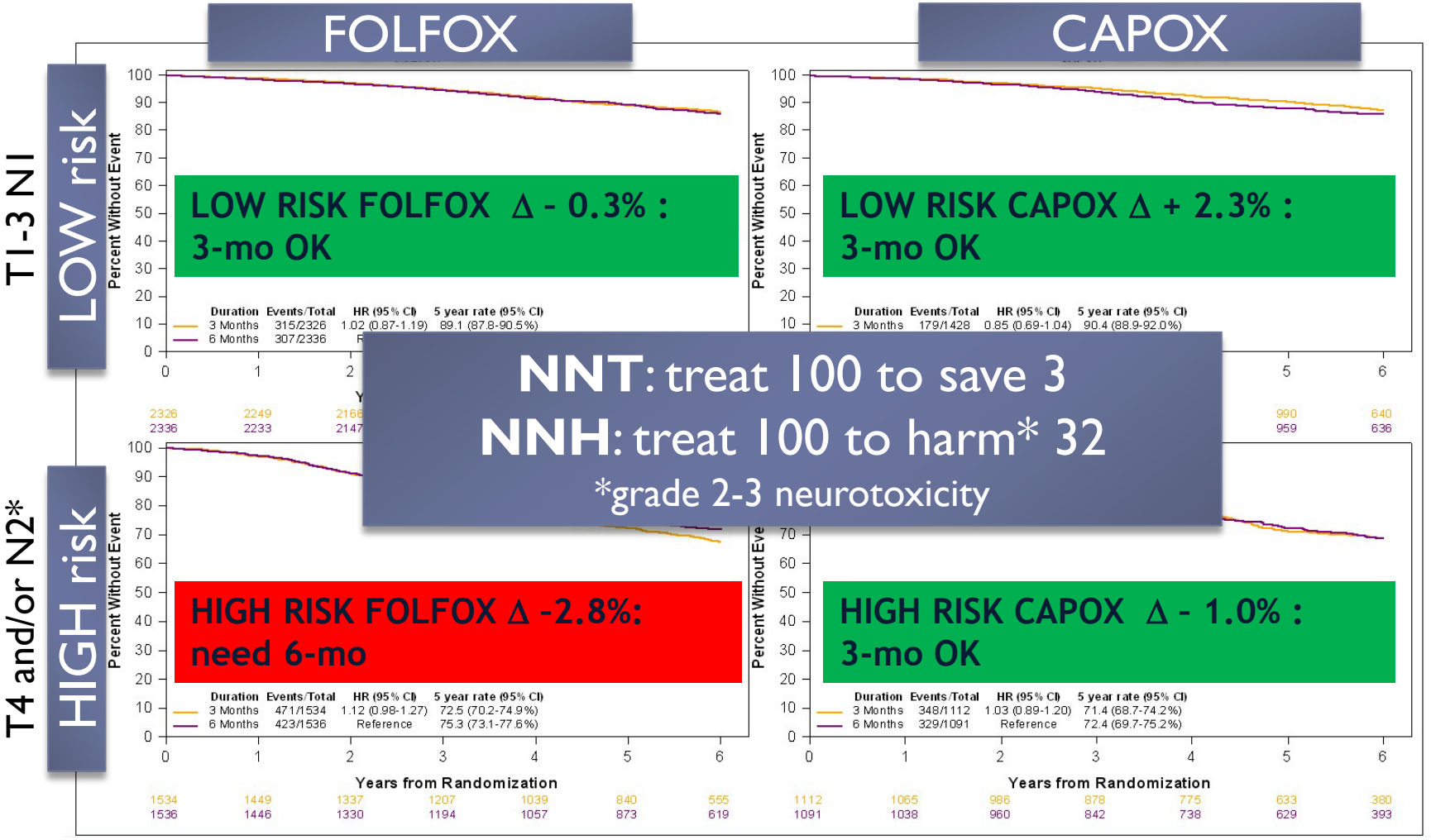
**3 mo: 74.6% vs. 6 mo: 75.5%**
DFS HR = 1.07 (95% CI: 1.00 - 1.15)




| | 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

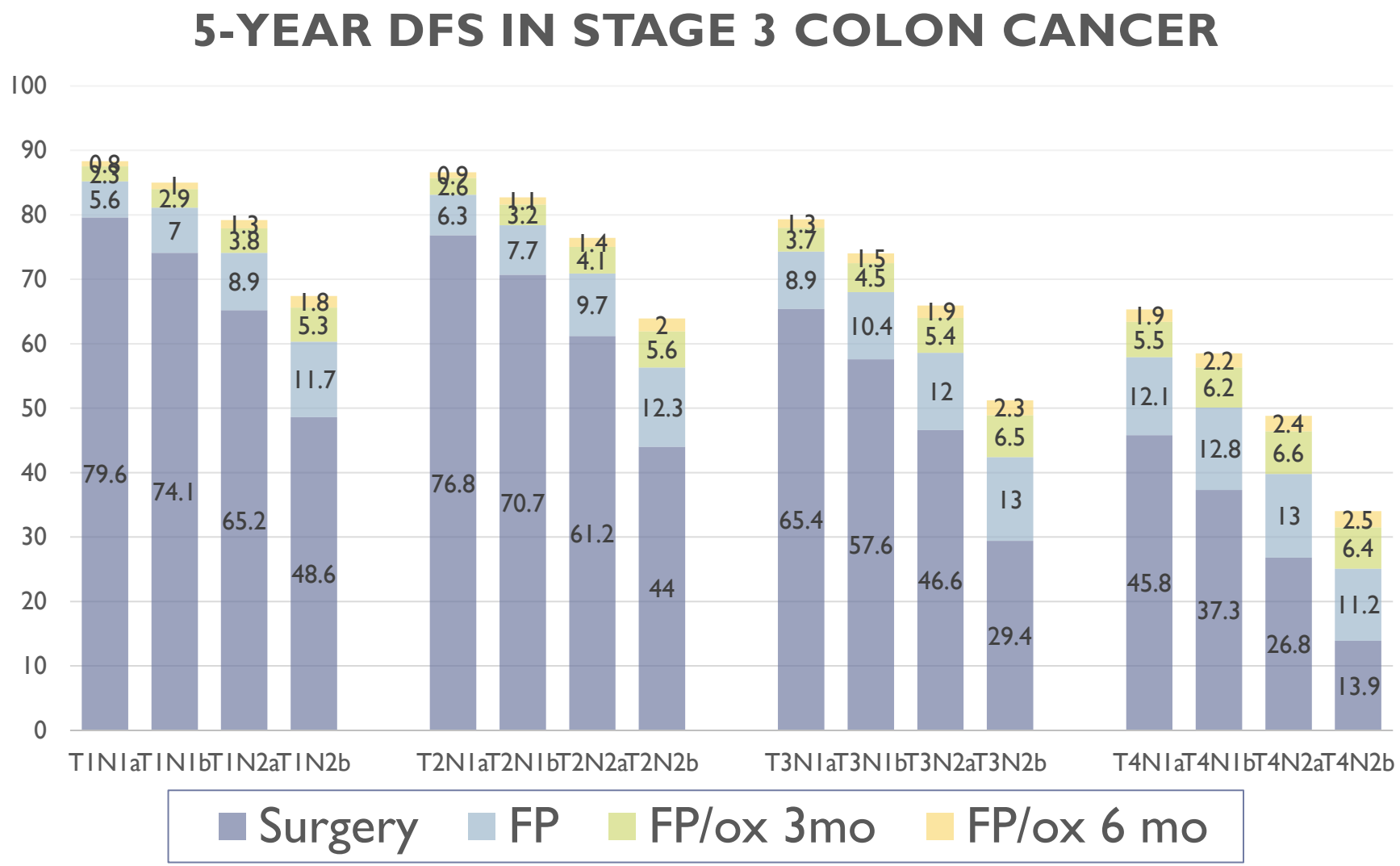
# OS outcomes by risk and by regimen




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

*T4 risk > N2

# Incremental benefits in adjuvant therapy




Adapted from: Sobrero, *Eur J Cancer* 2020

# The future of adjuvant therapy

- Younger patients have different toxicity profiles (more GI issues) and receive more chemo, but have worse outcomes

- NO benefit to irinotecan
- NO benefit to cetuximab or bevacizumab

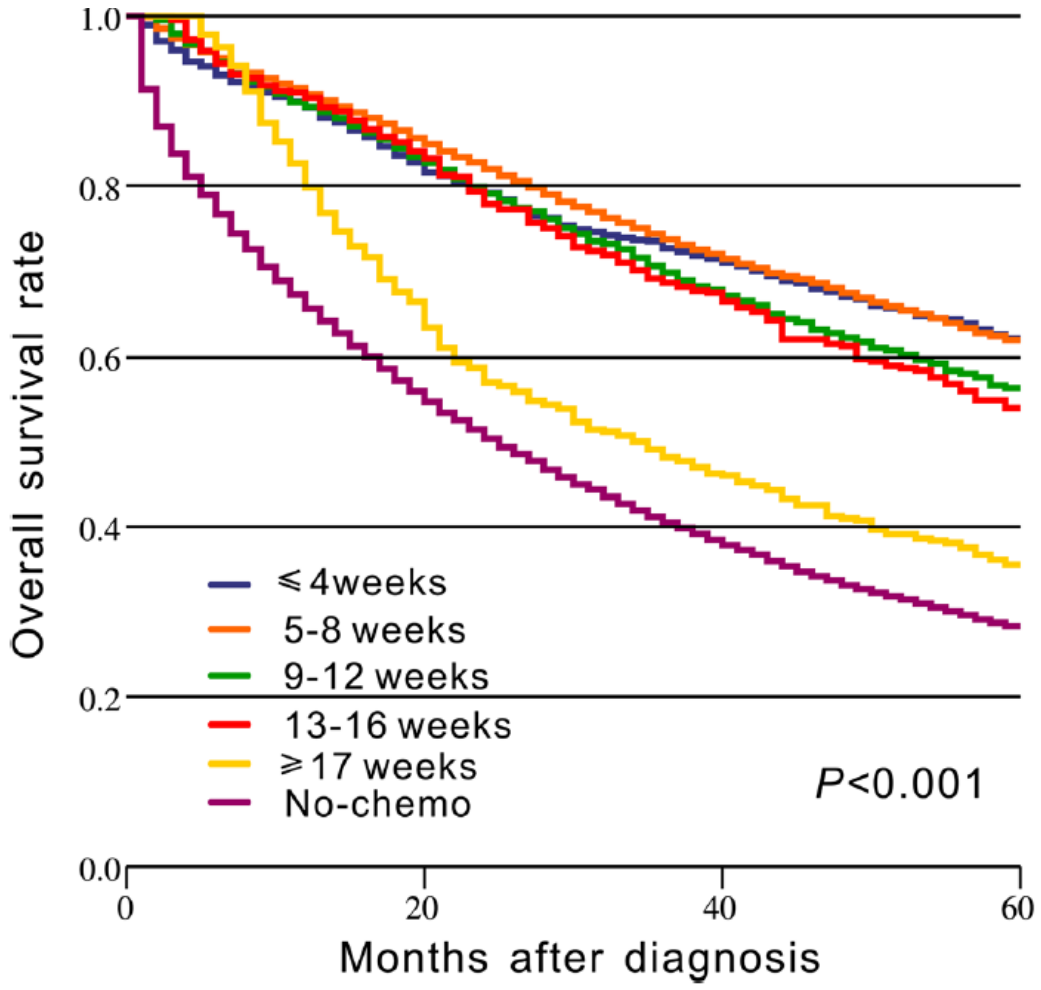
***Biomarkers are needed to better tailor therapy***

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

***3 mo FOLFOX/CAPOX then 5-FU/capecitabine alone through 6 mo?***

Fontana, *ASCO* 2021; 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

# Emerging role of ctDNA

- Low levels of cell-free DNA (cfDNA) can be detected even in healthy individuals (1-10 ng/ml)

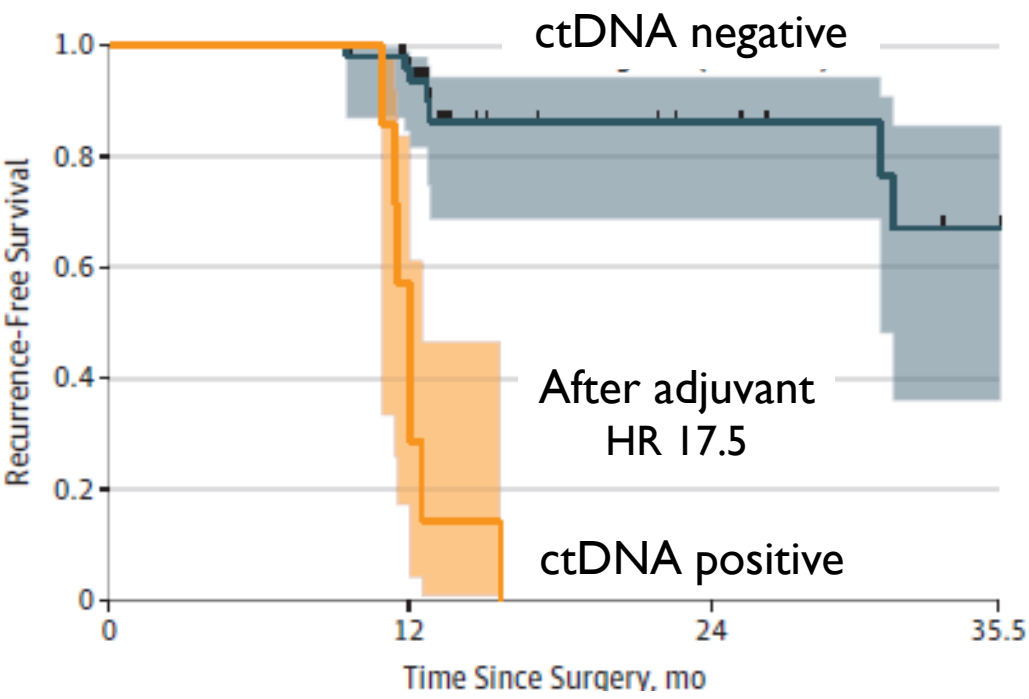
- circulating tumor DNA (ctDNA) = detecting mutations in cfDNA that are highly specific for cancer
  - Half-life: <2 hours
  - Levels are cancer burden-dependent
  - False positives: infection, inflammation, trauma, etc.

- ctDNA is a putative biomarker to demonstrate MRD
  - Minimal/molecular residual disease (MRD) = small volume disease not appreciated radiographically or with other clinical measures

Wan, *Nat Rev Cancer* 2017; Scholer, *Clin Cancer Res* 2017

# Highly associated with recurrence

- 130 stage I-III CRC
- ctDNA* positive:
  - 89% pre-surgery (stage: 40/92/90%)
  - 11% post-surgery
- 19% recurred
  - By post-op ctDNA+: 70 vs. 12%
  - ctDNA+: 70% (3/10) cleared with adjuvant chemo




58 patients received adjuvant chemo

Stratified by ctDNA status at first check after adjuvant chemo

Reinert, *JAMA Oncol* 2019

*tumor-informed panel

# Key points

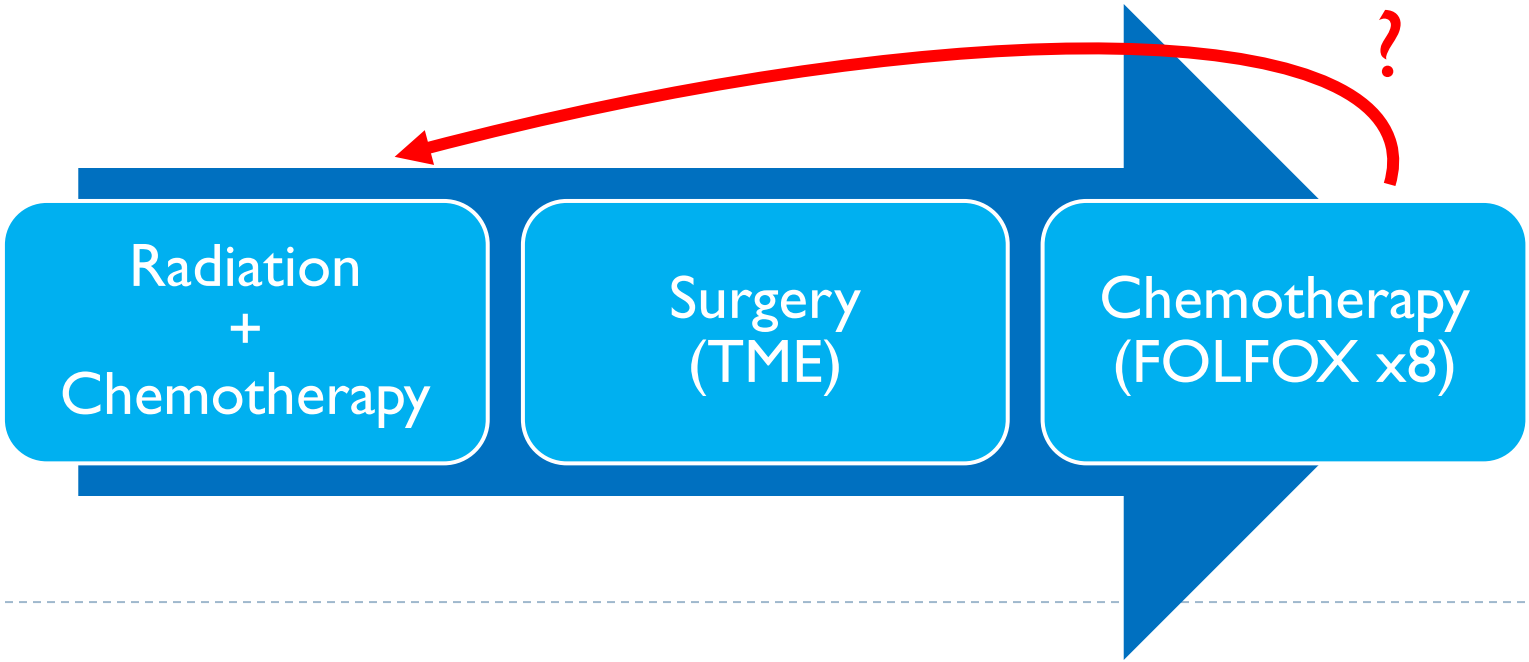
- Overall, no benefit for adjuvant chemotherapy in stage II
  - Consider for select "high-risk" MSS patients
  - Avoid adjuvant chemotherapy in MSI-high stage II
- 3 months of adjuvant chemotherapy is becoming the new standard for stage III
  - 6 months is still recommended for high-risk (T4 or N2) patients 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)

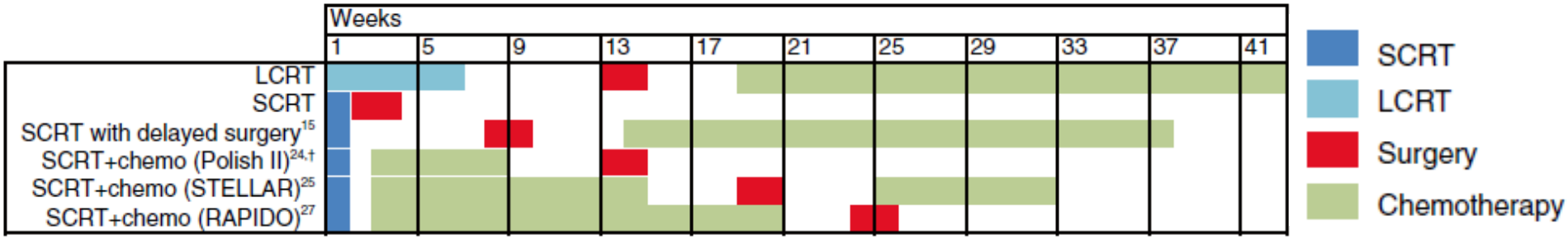
- 5-FU
- Capecitabine
- 5-FU + oxaliplatin
- Cape + oxaliplatin

- 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

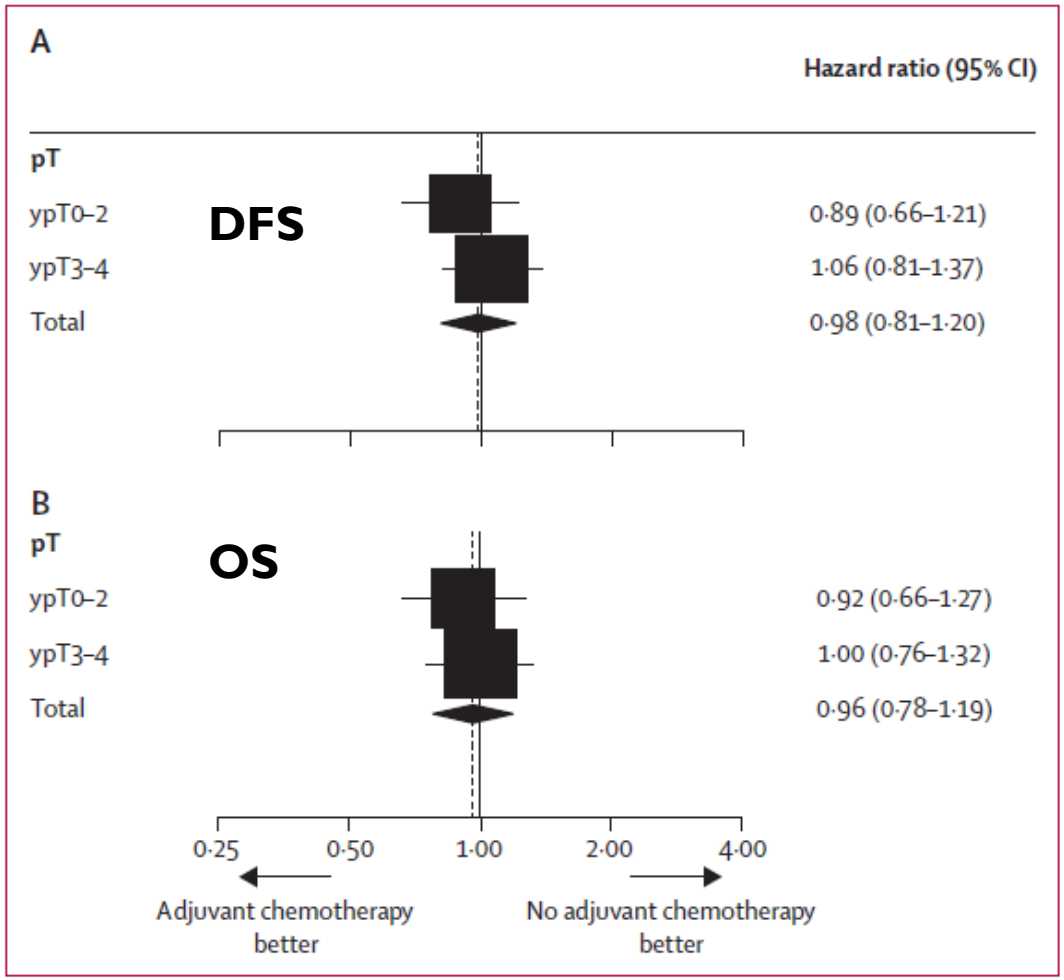
# Short-course radiation

- Hypofractionated 25Gy (5Gy x 5 days), NO chemo
  - By comparison, long-course: 28 fractions (5.5 wk), 50.4Gy
  - Surgery 4+ weeks later
- If short interval before surgery, best when primary tumor down-staging is not required, limited/no nodal disease
  - Lower pCR rate (unless wait a similar interval as long-course)
  - Not recommended for non-operative management
  - Sequencing with surgery, systemic chemotherapy needs to be further elucidated




Mullen, *Curr Colorectal Cancer Rep* 2017; Bahadoer, *Lancet Oncol* 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

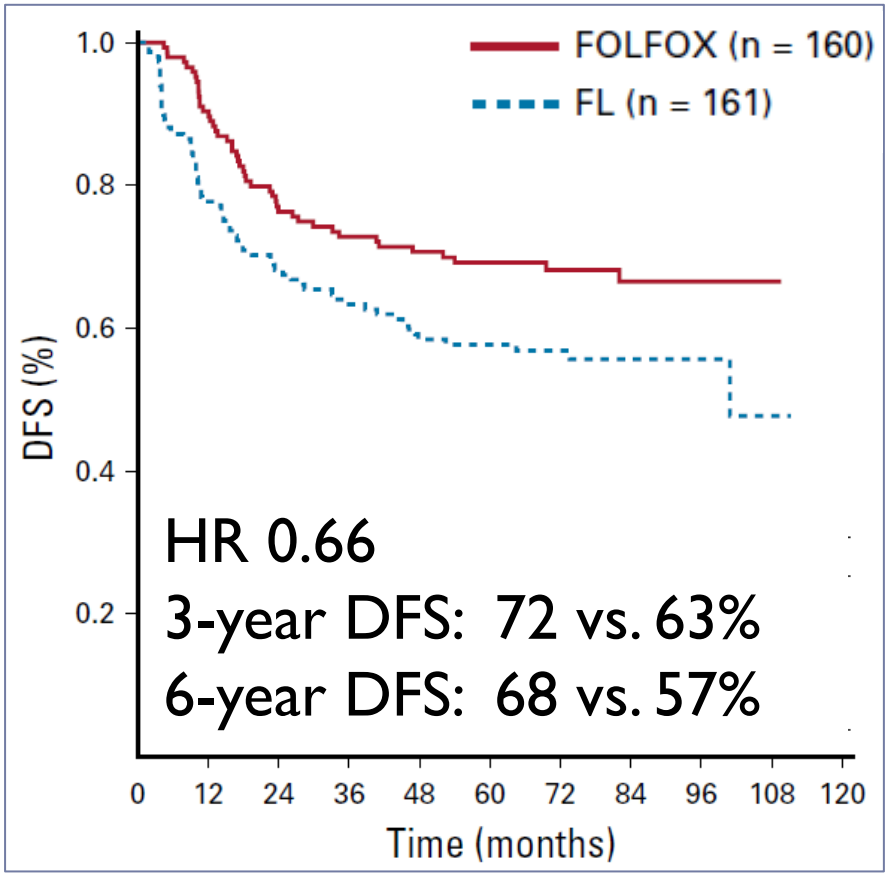
- EORTC 22921: Bosset, *Lancet Onc* 2014

# Adjuvant FOLFOX

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

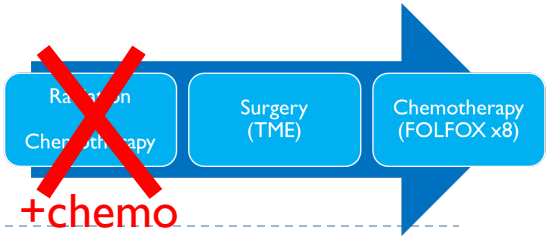
- FOLFOX improved DFS
  - ypN+ > ypN0
  - Not significantly better for very good tx response

- 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?

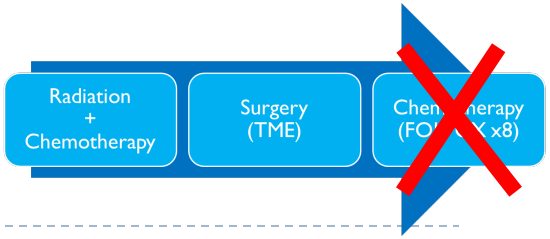



- Most patients dying from rectal cancer have distant metastases, not local recurrence
- Some patients may never start adjuvant chemotherapy because of surgical complications, or it is quite delayed
  - Are we doing patients a disservice by placing high-dose chemotherapy at the end of therapy?

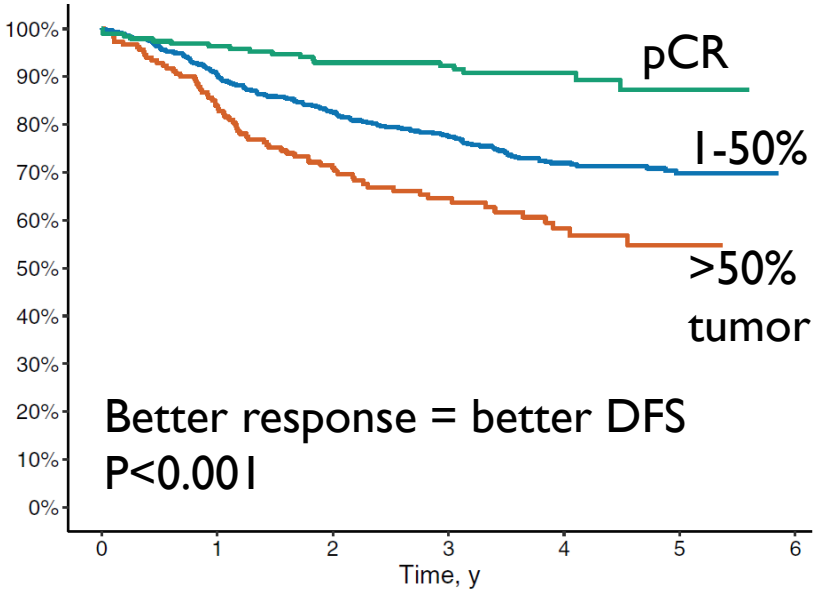
- PROSPECT trial:
  - Phase III trial of peri-operative FOLFOX + selective RT for poor responders or positive margins
  - Completed accrual and awaiting results (2022?)

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

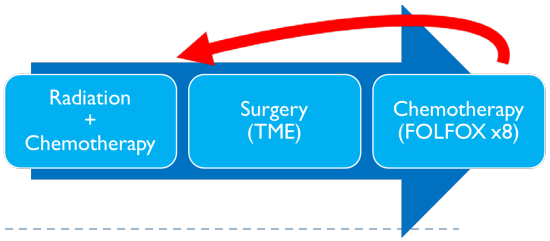
# Skip adjuvant chemotherapy?




- 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?

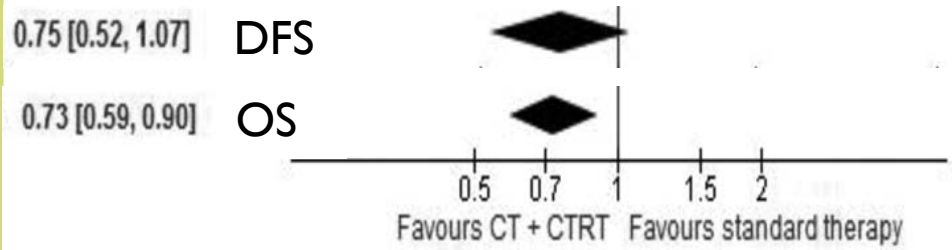



Fokas, *JNCI* 2017; Rodel, *JCO* 2005; Loree, *Clin Colorectal Cancer* 2016




# 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



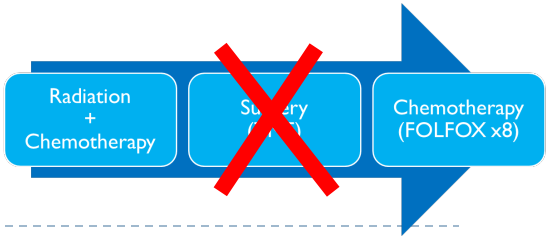

At a minimum, TNT recommended in:

- 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?

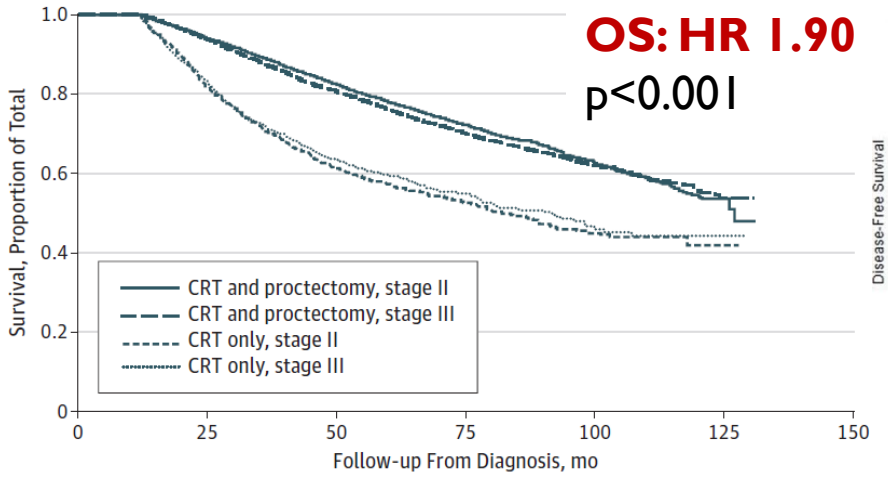
Petrelli, *Ann Surg* 2020; Garcia-Aguilar, *ASCO* 2020; Conroy, *Lancet Oncol* 2021

# Nonoperative management?

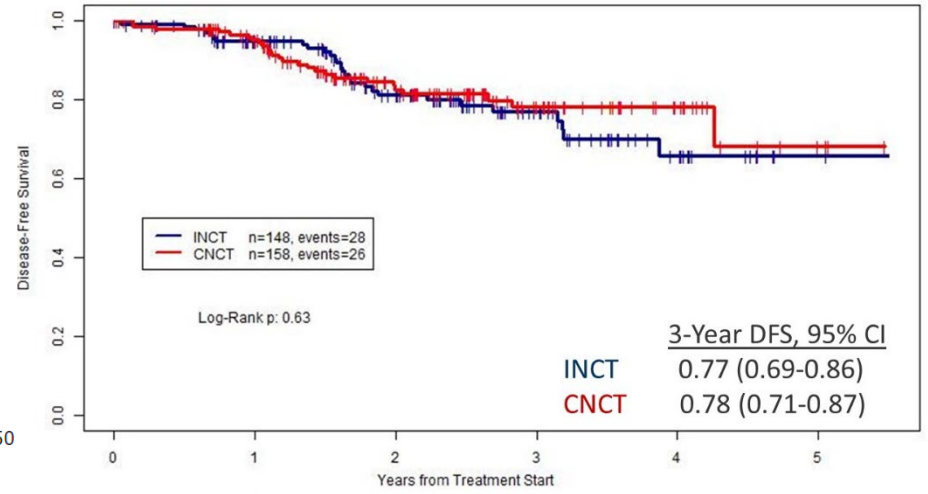



- "Watch and wait" approach
  - Avoid surgical morbidity in poor candidates
  - Avoid permanent ostomy in those that decline
- Higher rates of local and possibly distant failure
- Need a complete clinical response (by CT, MRI, flex sig)

**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 becoming standard-of-care