

Onkologisk behandling av cancer coli og cancer recti

Marianne G. Guren

Overlege, professor II

Avd. for kreftbehandling

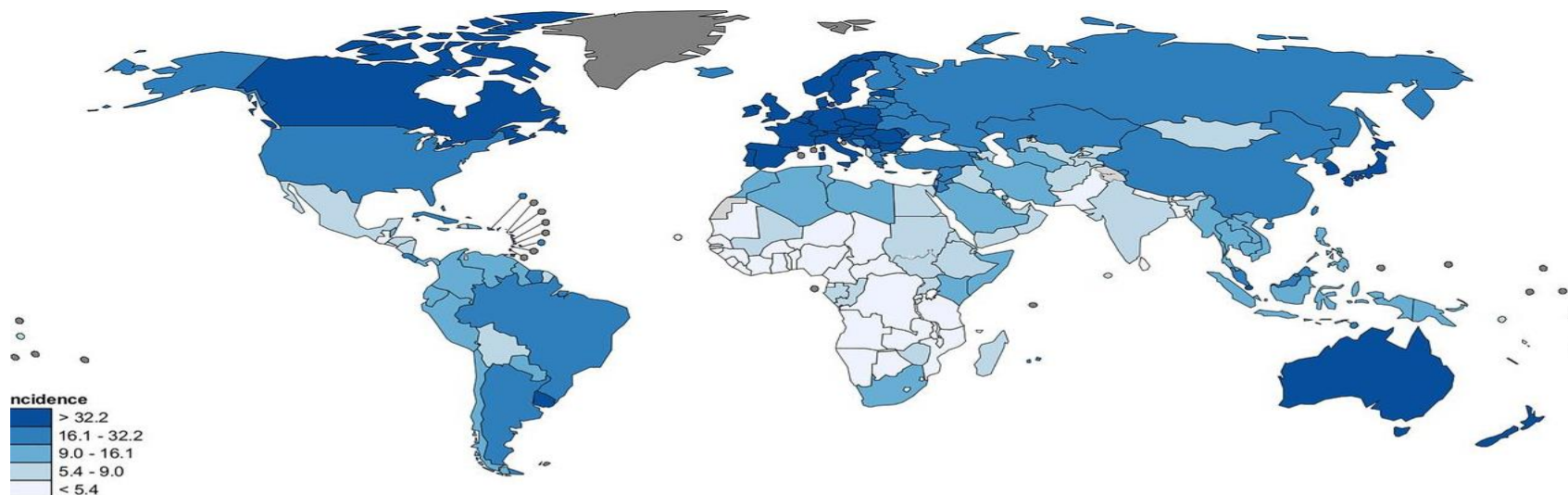
Oslo Universitetssykehus, Universitetet i Oslo

Oversikt

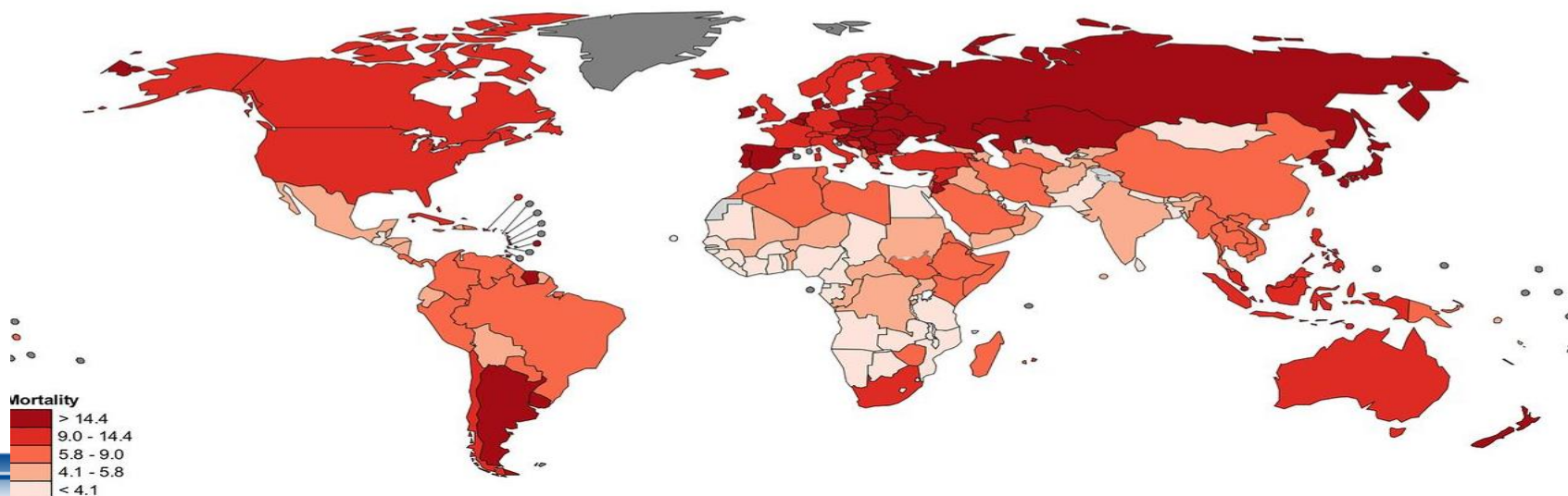
- Kort om epidemiologi
- Lokalisert tykktarmskreft
- Lokalisert endetarmskreft
- Tykk- og endetarmskreft med spredning

Tykk- og endetarmskreft har høy forekomst og dødelighet

Worldwide colorectal cancer incidence and mortality rates in males 2012 (GLOBOCAN).



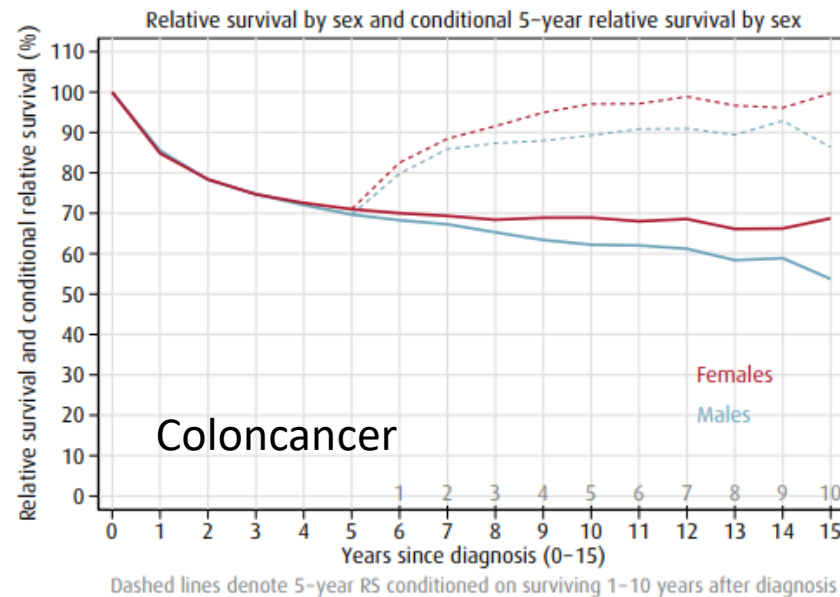
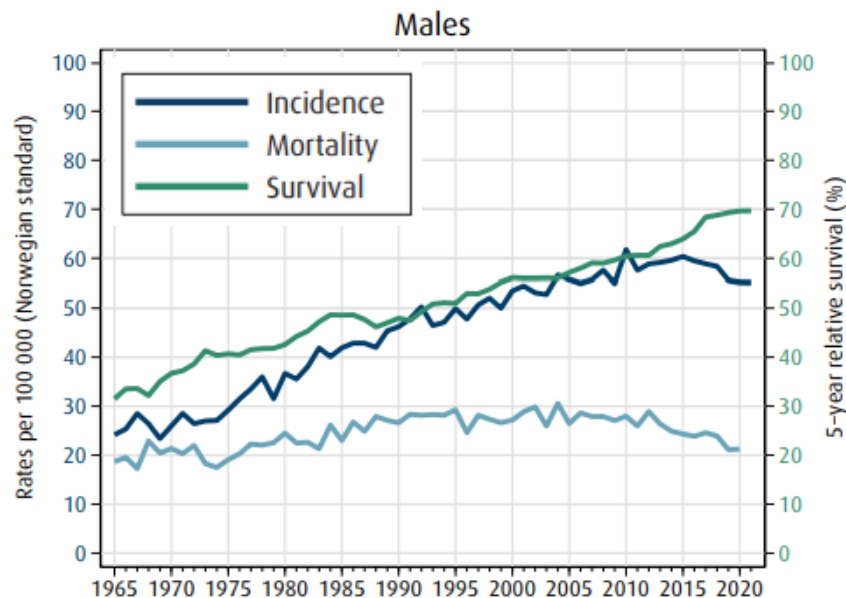
Norge har høy forekomst
Økende forekomst eldre og yngre
Relativt god overlevelse



Arnold M et al, Gut 2017;
Araghi M, Lancet Gastro Hep 2019;
Benitez Majano S, Lancet Oncol 2019

Tykk- og endetarmskreft i Norge i 2021

- Forekomst tykktarmskreft 3200 per år; endetarmskreft 1350 per år
- Relativ 5-års overlevelse økt fra ca. 46% i 1985 til ca. 70% i 2020
- Prevalens 22 000 personer har / har hatt tarmkreft og er i live



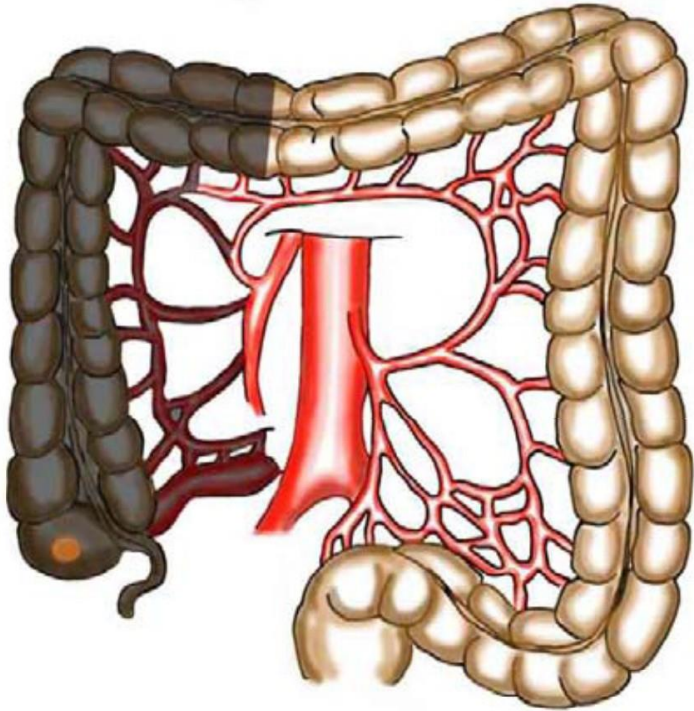
Cancer in Norway 2021

Tarmscreeningprogrammet

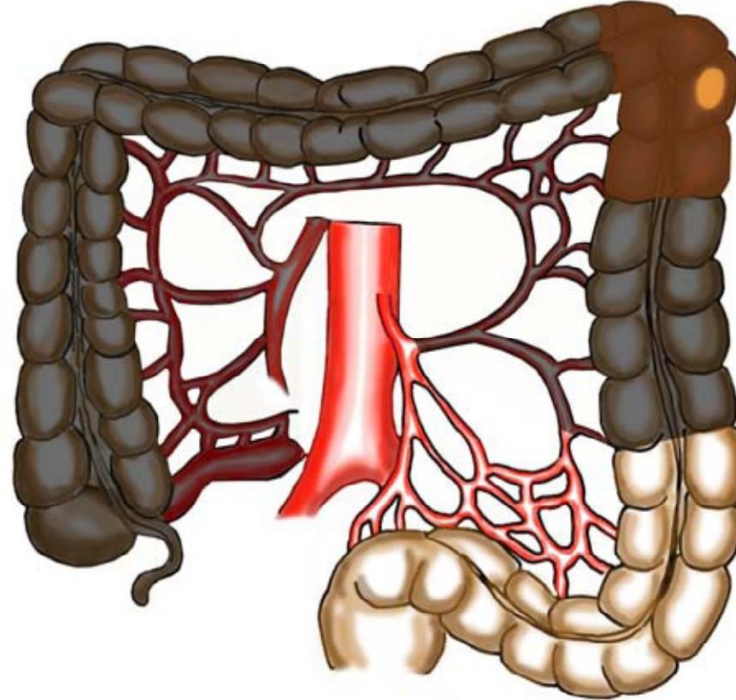
- menn og kvinner inviteres første gang ved 55 års alder
- **Imunkjemisk test for blod i avføringen**
 - Kvantiterer humant hemoglobin i prøven
 - Terskelverdi 15 µg hemoglobin/g avføring
 - analyseres ved ett laboratorium
 - Kapasitet 600 prøver /time



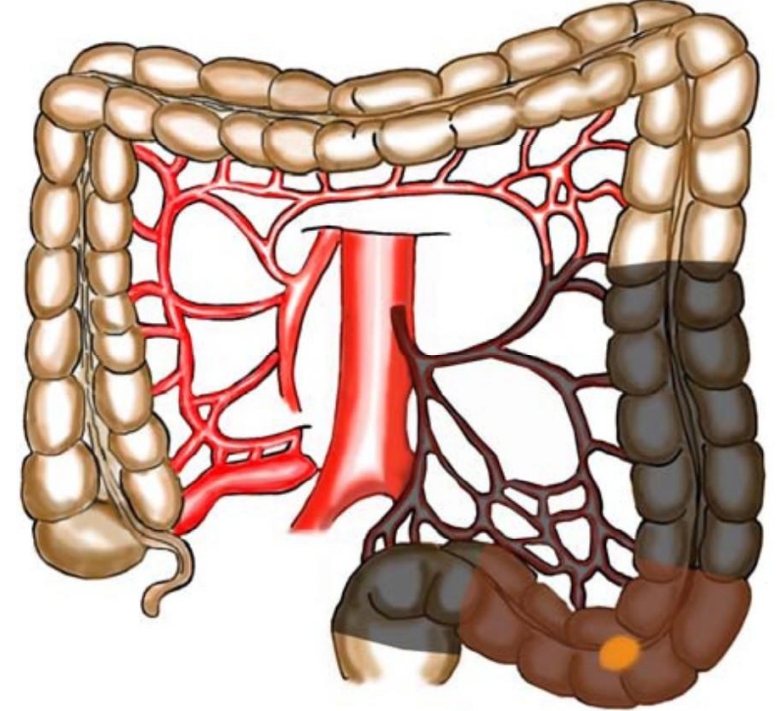
Tykkarmskreft kirurgi tumor og lymfeknuter



Høyresidig hemicolectomi



Subtotal colectomi

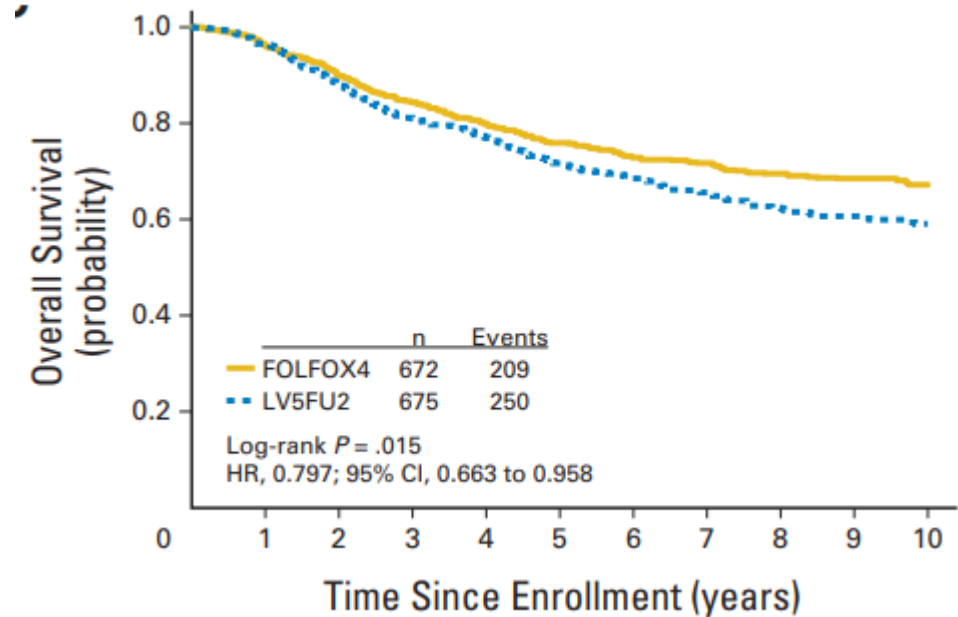


Venstresidig hemicolectomi

Handlingsprogram tykk- og endetarmskreft

Adjuvant kjemoterapi

- Stadium III
- Høy-risiko stadium II
 - Perforasjon, pT4, få lymfeknuter
- FOLFOX eller CAPOX (5-FU og oxaliplatin)
- Individuell vurdering
 - > 70 år monoterapi 5-FU eller FOLFOX/CAPOX?
 - > 75 år monoterapi 5-FU?
- Test DPYD før behandling med 5-FU



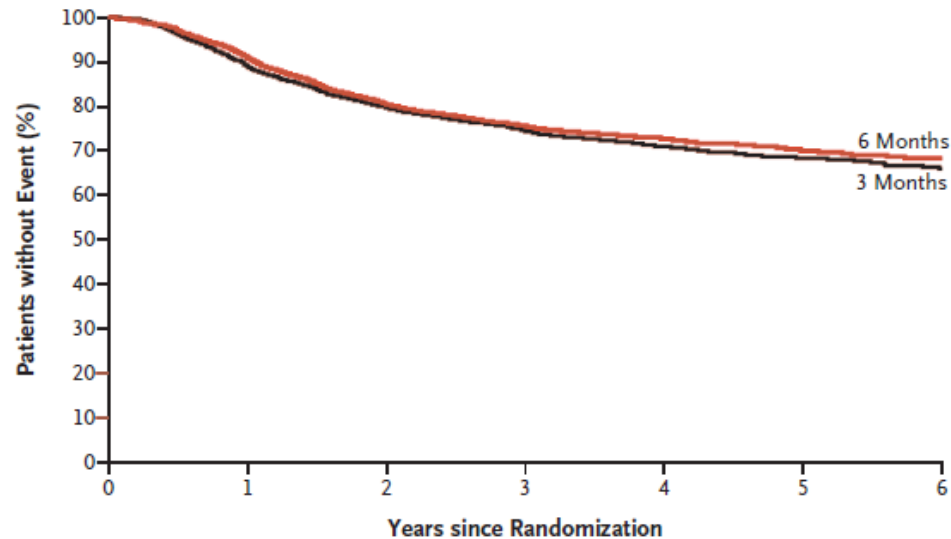
MOSAIC, colon cancer stadium III, FOLFOX bedre overlevelse enn 5-FU

Andre T, JCO 2015

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

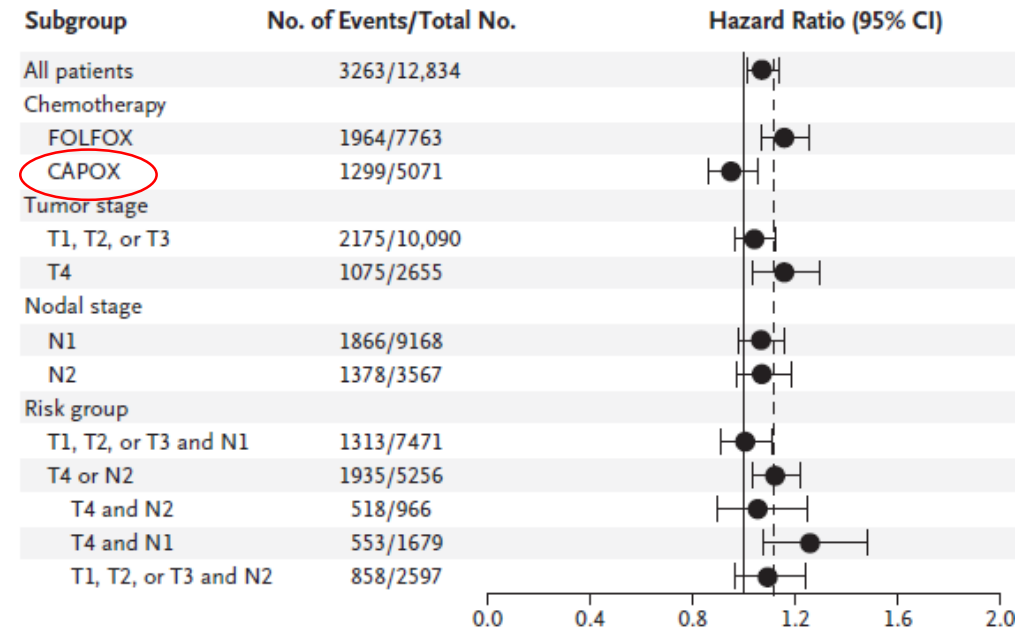
A. Grothey, A.F. Sobrero, A.F. Shields, T. Yoshino, J. Paul, J. Taieb, J. Souglakos, Q. Shi, R. Kerr, R. Labianca, J.A. Meyerhardt, D. Vernerey, T. Yamanaka, I. Boukovinas, J.P. Meyers, L.A. Renfro, D. Niedzwiecki, T. Watanabe,* V. Torri, M. Saunders, D.J. Sargent,* T. Andre, and T. Iveson

Disease-free Survival in Overall Population



No. at Risk							
6 Months	6410	5530	4477	3065	1679	873	334
3 Months	6424	5446	4464	3000	1609	826	321

Varighet 3 vs. 6 mnd



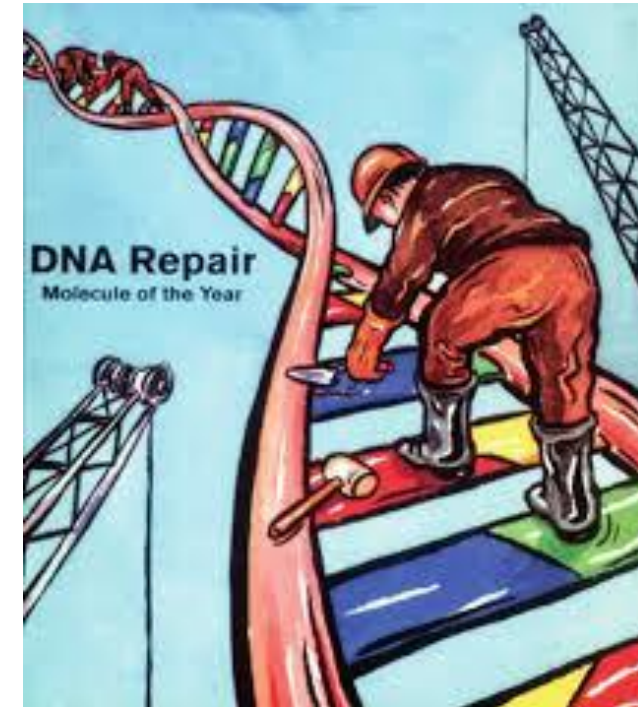
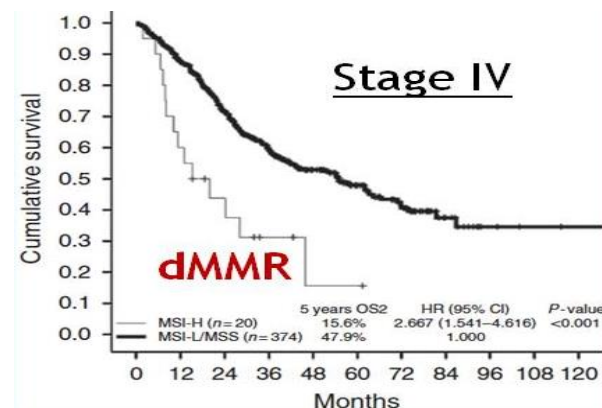
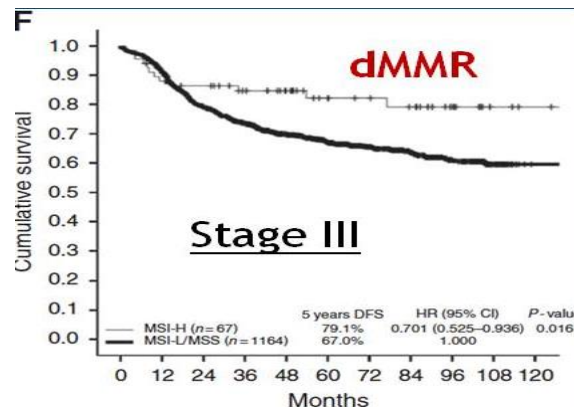
- Mindre neurotoksisitet ved 3 mnd kjemoterapi
- CAPOX 3 mnd for de fleste pasienter
- Ved høyrisiko (T4, N2) eller FOLFOX 6 mnd
- 5-FU/capecitabine monoterapi 6 mnd

Grothey A et al, NEJM 2018; Andre T, Lancet Oncol 2020

Deficient mismatch repair (dMMR) Microsatellitt instabilitet (MSI)

Ved svikt i mismatch repair systemet (dMMR) oppstår stort antall mutasjoner definert som microsatellitt instabilitet (MSI)

- IHC (MLH1, MSH2, MSH6, PMS2)
- PCR (MSI)
- NGS (MSI)



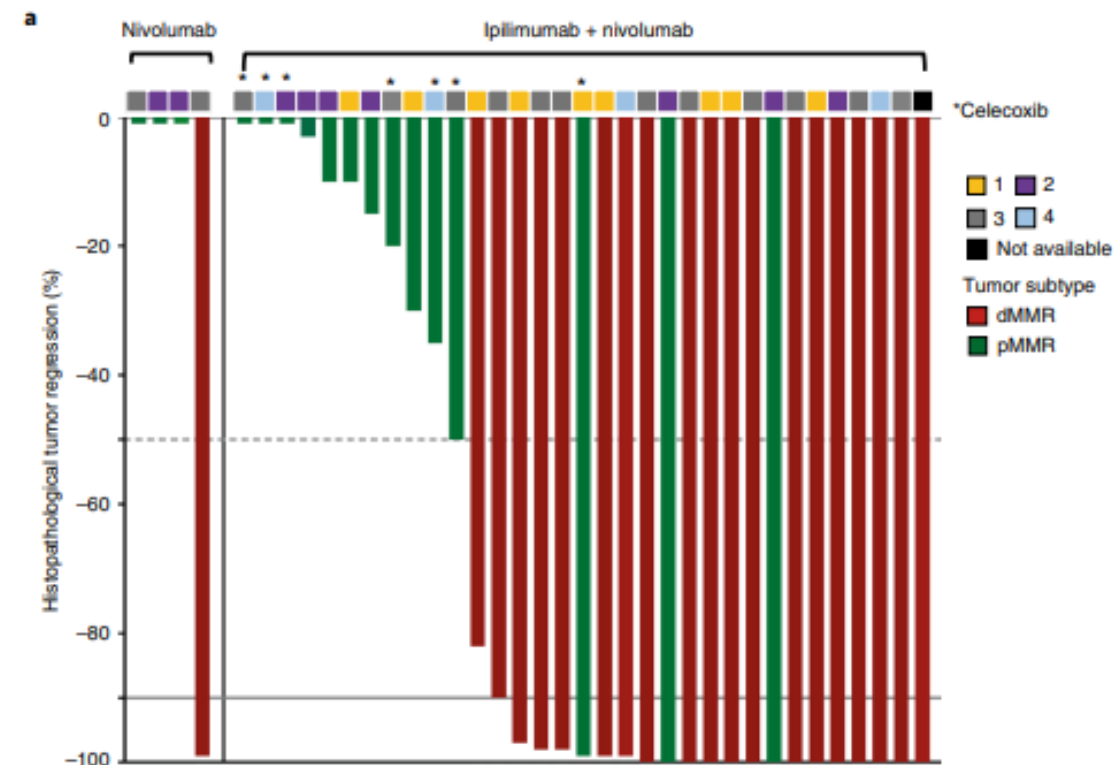
Luchini C, Ann Onc 2019
Kim CG, BJC 2016

NICHE studien, dMMR/MSI

- 41 pasienter coloncancer (20 med dMMR)
- Ipilimumab dag 1 + nivolumab dag 1 og 15
- Kirurgi etter 6 uker
- dMMR: 19 patologisk respons, hvorav 12 pCR

Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers

Myriam Chalabi^{1,2,3,5}, Lorenzo F. Fanchi^{2,4,7}, Krijn K. Dijkstra^{2,4,7}, José G. Van den Berg^{5,7}, Arend G. Aalbers⁵, Karolina Sikorska⁷, Marta Lopez-Yurda^{7,8}, Cecile Grootsholten¹, Geerard L. Beets^{6,9}, Petur Snaebjornsson¹⁰, Monique Maas¹⁰, Marjolijn Mertz¹¹, Vivien Veninga^{2,4}, Gergana Bounova^{4,12}, Annegien Broeks¹³, Regina G. Beets-Tan¹⁴, Thomas R. de Wijkerslooth¹, Anja U. van Lent¹⁴, Hendrik A. Marsman¹⁵, Elvira Nuijten¹, Niels F. Kok¹, Maria Kuiper¹, Wieke H. Verbeek¹, Marleen Kok^{1,16}, Monique E. Van Leerdam¹, Ton N. Schumacher^{2,4}, Emile E. Voest^{1,2,4,7,8,17} and John B. Haanen^{2,3,17}



Chalabi M, Nature Med 2020

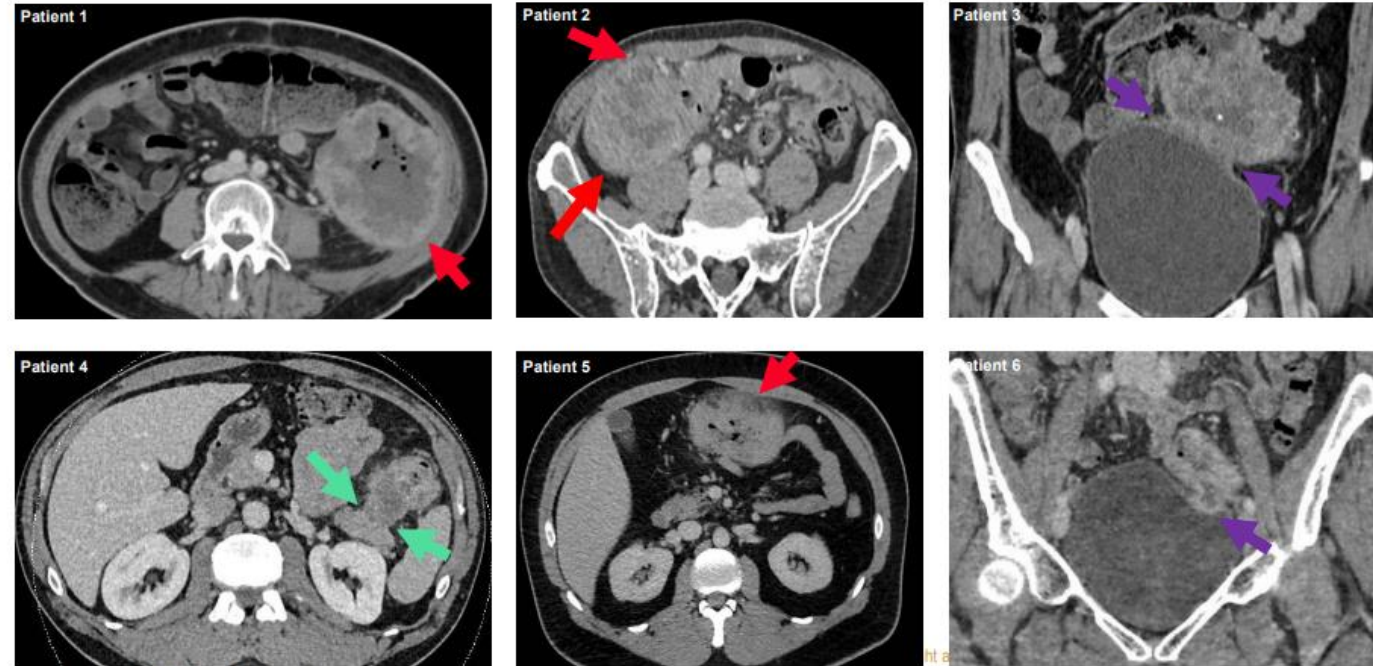
NICHE 2

Colon cancer (n=112)

- cT3 og/eller N+
- dMMR

Ipilimumab dag 1 +
nivolumab dag 1 og 15
Kirurgi etter 4 uker

63% clinical T4a or T4b tumors

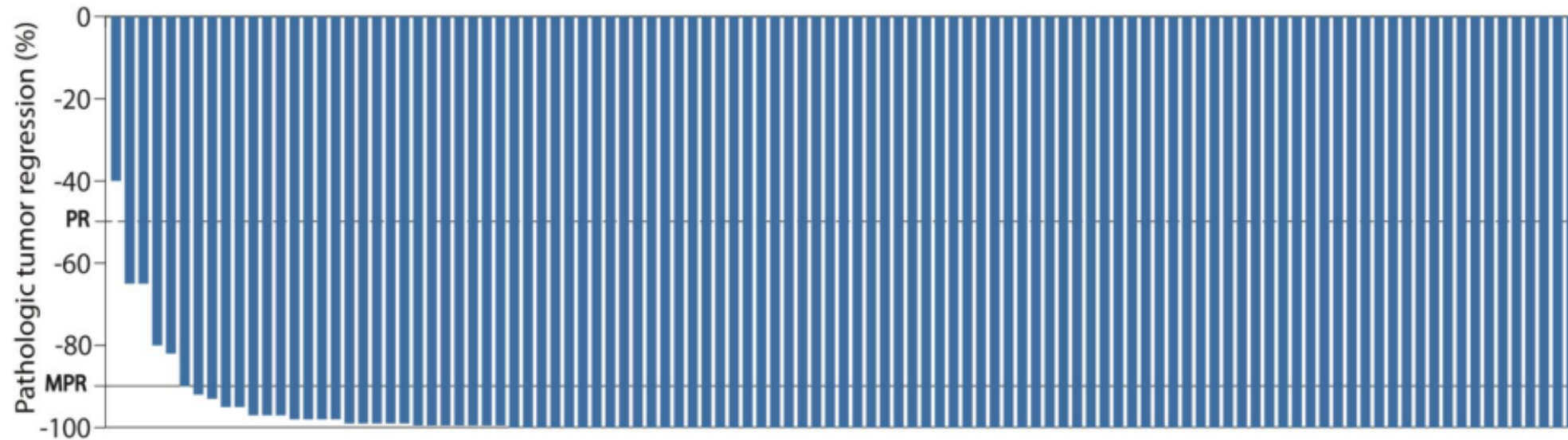


Images are from six distinct patients within the study

Chalabi M, ESMO 2022

NICHE 2

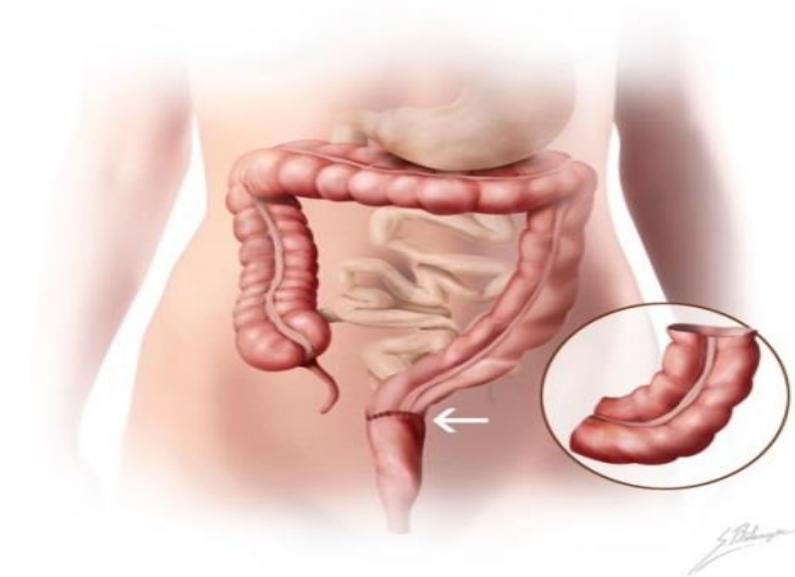
Major pathologic response in 95% of patients; 67% pCR



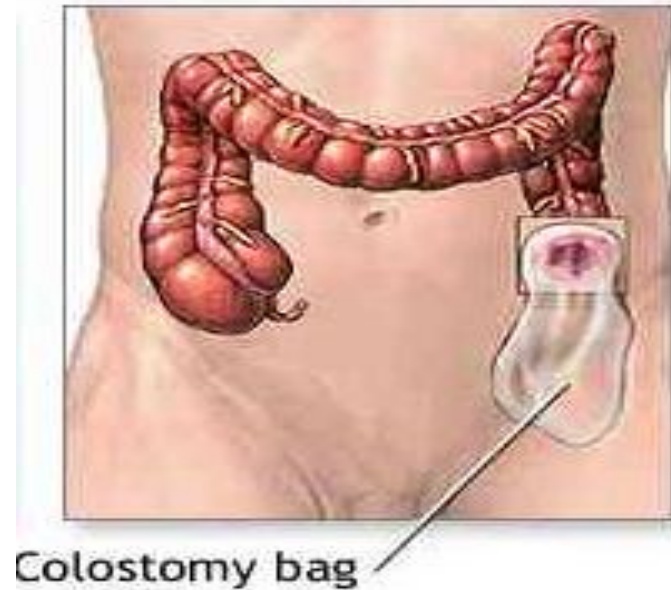
Chalabi M, ESMO 2022

Kirurgi av endetarmskreft

Lav fremre reseksjon (LAR)



Rektumamputasjon (APR)

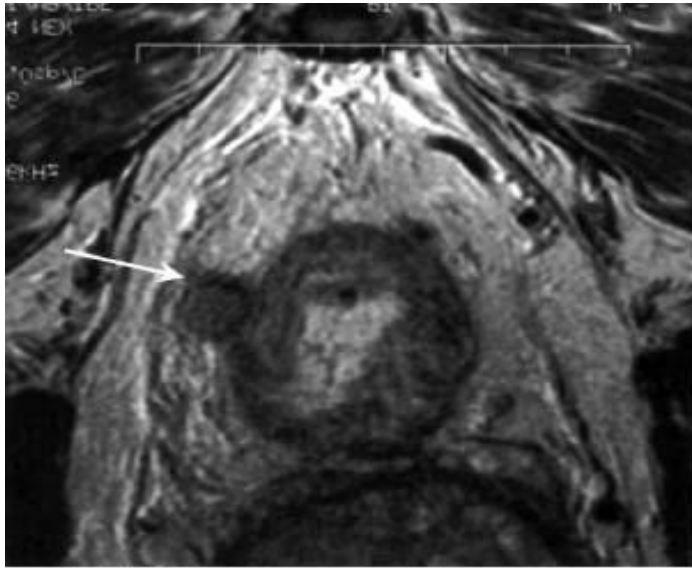


Strålebehandling endetarmskreft

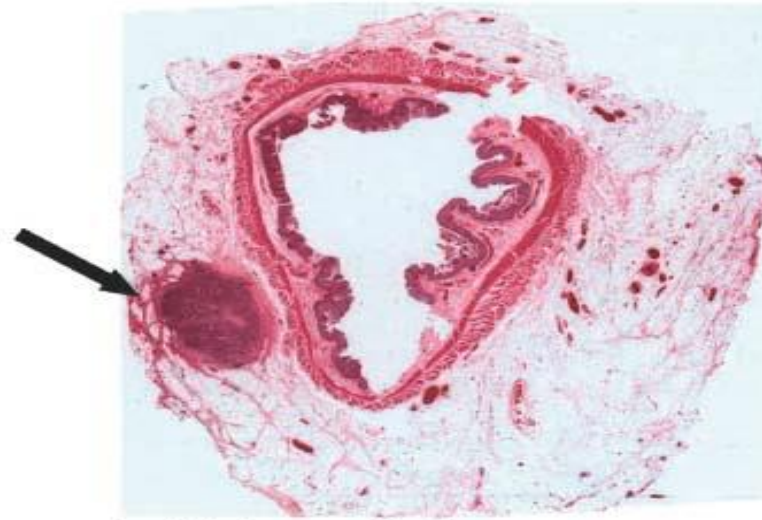
- Kjemoradioterapi
 - 2 Gy x 25
 - Kapecitabin eller 5-FU
- Kort strålebehandling
 - 5 Gy x 5
- Strålebehandling og kjemoterapi
 - RAPIDO regimet
 - Total neoadjuvant treatment (TNT)



MDT møte indikasjon for strålebehandling



a Axial MRI



b Whole-mount histology

Involvert MRF på MR og CRM på histologi.

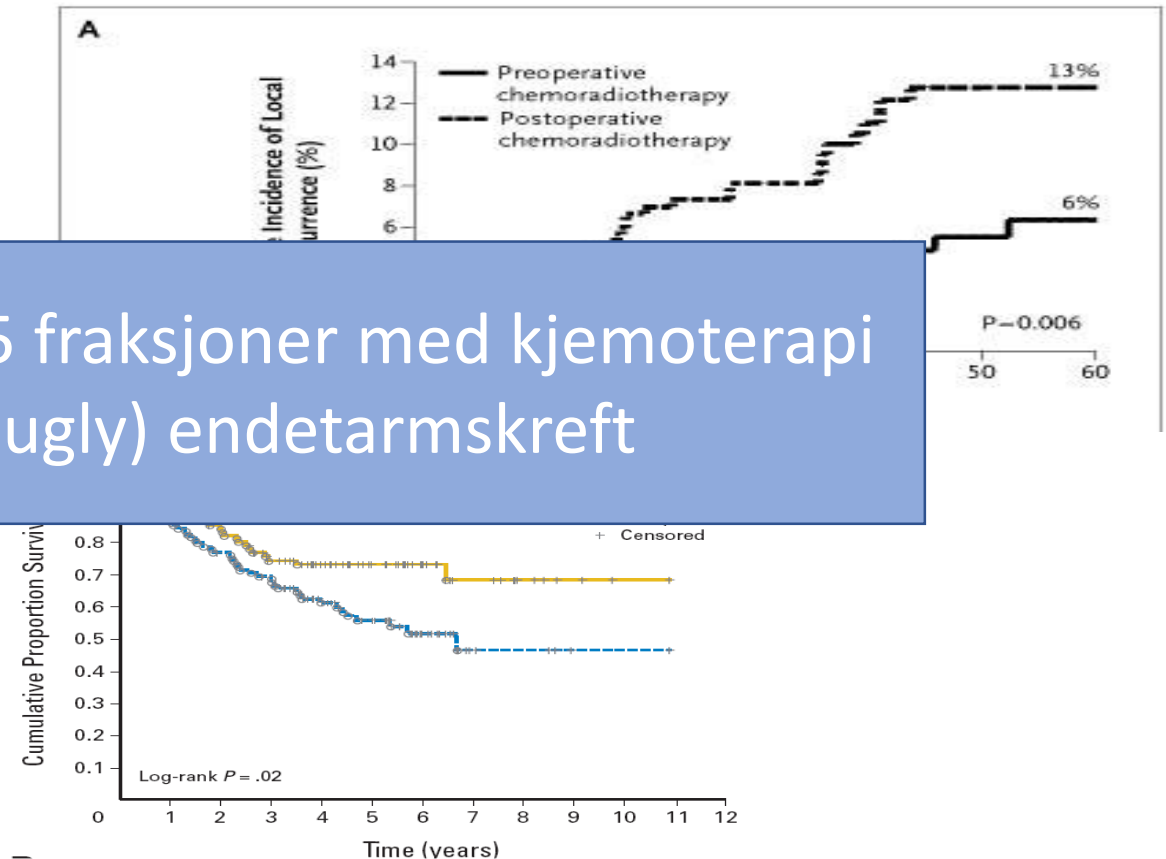
Brown, Br J Surg 2003.

Kjemoradioterapi lokalt avansert endetarmskreft

- Preoperativ kjemoradioterapi (CRT) bedre enn postoperativ

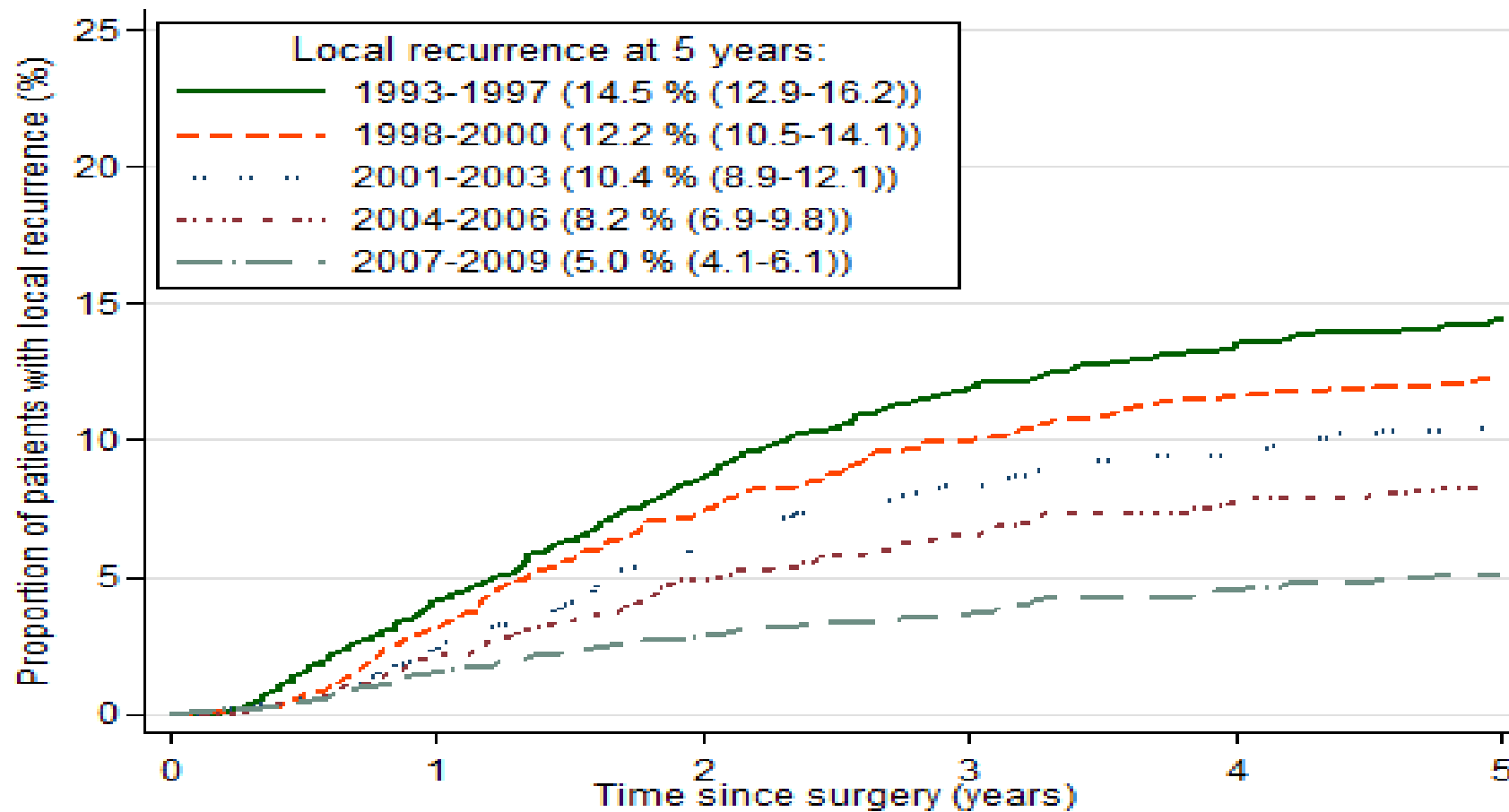
Preoperativ CRT 50 Gy på 25 fraksjoner med kjemoterapi ved lokalt avansert (ugly) endetarmskreft

- CRT strålebehandling alene
 - Bedre lokal kontroll



Sauer, NEJM 2004; Brændengen M, JCO 2008

Reduksjon lokale residiv til ca. 5%



Før 1993
28 %

Redusert
14.5 %

5 %

Guren MG, Acta Onc 2015

Strålebehandling for resektabel endetarmskreft

Preoperativ strålebehandling 5 Gy x 5 og kirurgi er bedre enn kirurgi alene

The Stockholm I Trial of Preoperative Short Term Radiotherapy in Operable Rectal Carcinoma

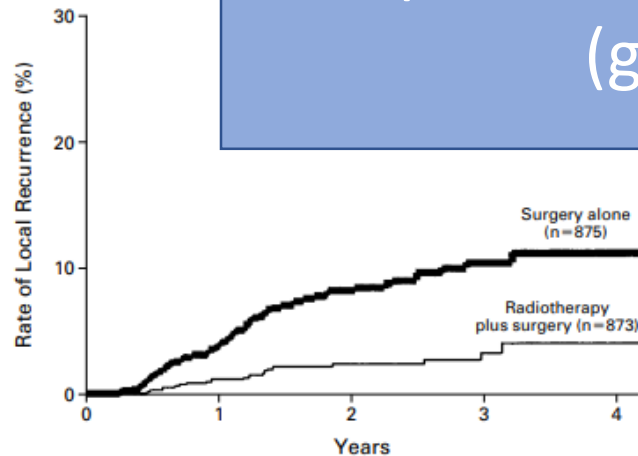
A Pros

The New England Journal of Medicine

Björn Ce

RAPY IN RESECTABLE

Preoperativ RT 25 Gy på 5 fraksjoner ved lokalt resektabel (good) endetarmskreft – i noen land



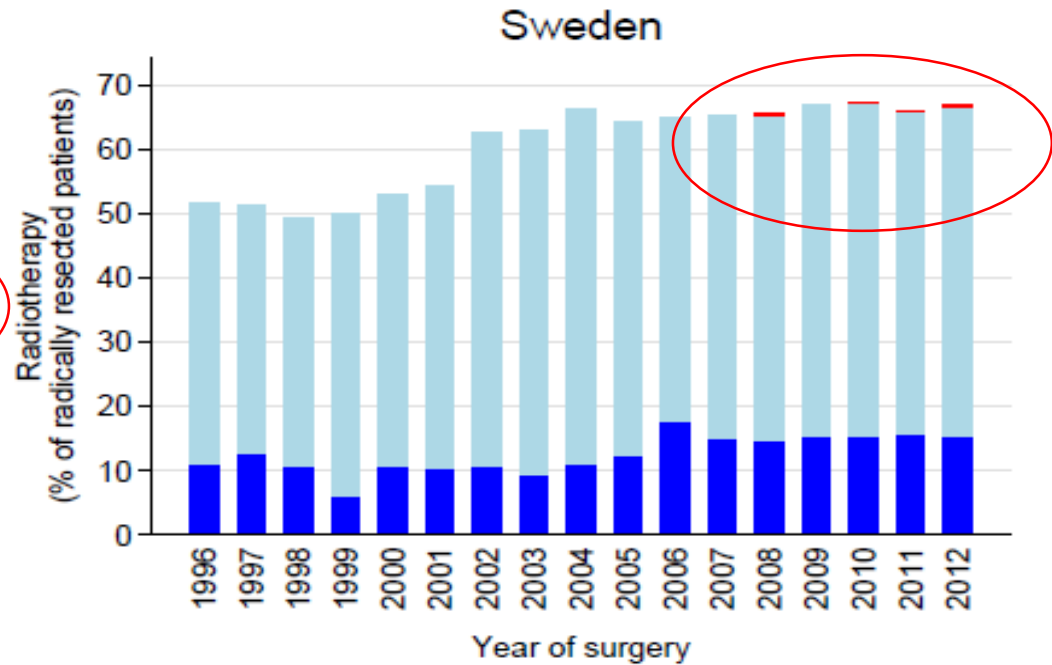
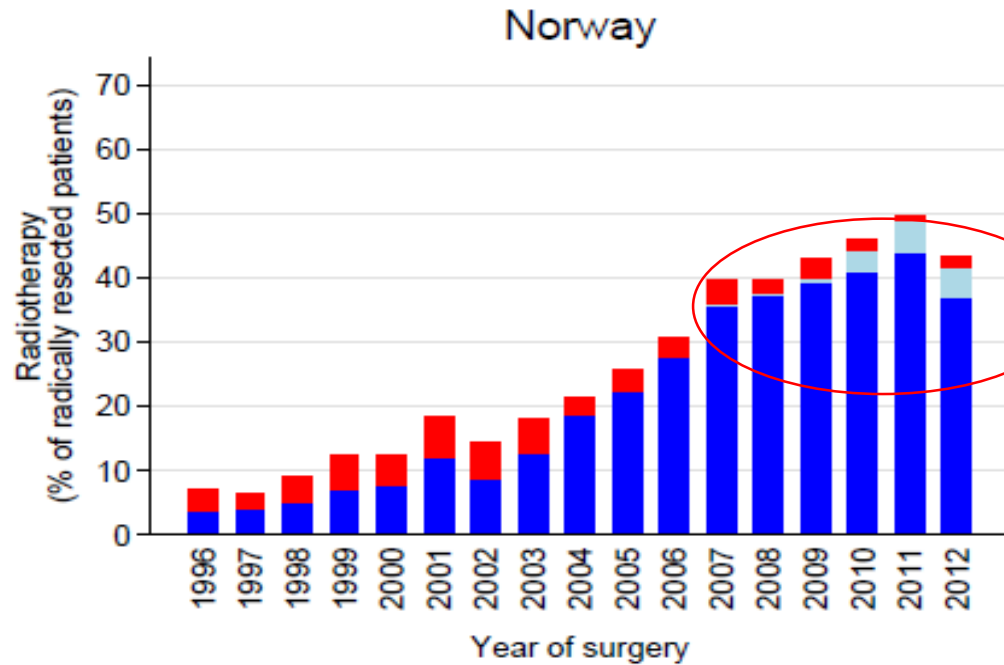
Anna Martling, M.D.¹
Torbjörn Holm, Ph.D.¹
Hemming Johansson, B.A.²
Lars Erik Rutqvist, Ph.D.³
Björn Cedermark, Ph.D.¹
for the Stockholm Colorectal Cancer Study Group

The New England Journal of Medicine

PREOPERATIVE RADIOTHERAPY COMBINED WITH TOTAL MESORECTAL EXCISION FOR RESECTABLE RECTAL CANCER

ELLEN KAPITEIJN, M.D., CORRIE A.M. MARIJNEN, M.D., IRIS D. NAGTEGAAL, M.D., HEIN PUTTER, Ph.D.,
WILLEM H. STEUP, M.D., Ph.D., THEO WIGGERS, M.D., Ph.D., HARM J.T. RUTTEN, M.D., Ph.D.,
LARS PAHLMAN, M.D., Ph.D., BENGT GLIMELIUS, M.D., Ph.D., J. HAN J.M. VAN KRIEKEN, M.D., Ph.D.,
JAN W.H. LEER, M.D., Ph.D., AND CORNELIS J.H. VAN DE VELDE, M.D., Ph.D.,
FOR THE DUTCH COLORECTAL CANCER GROUP*

Strålebehandling radikalt opererte pasienter Norge-Sverige

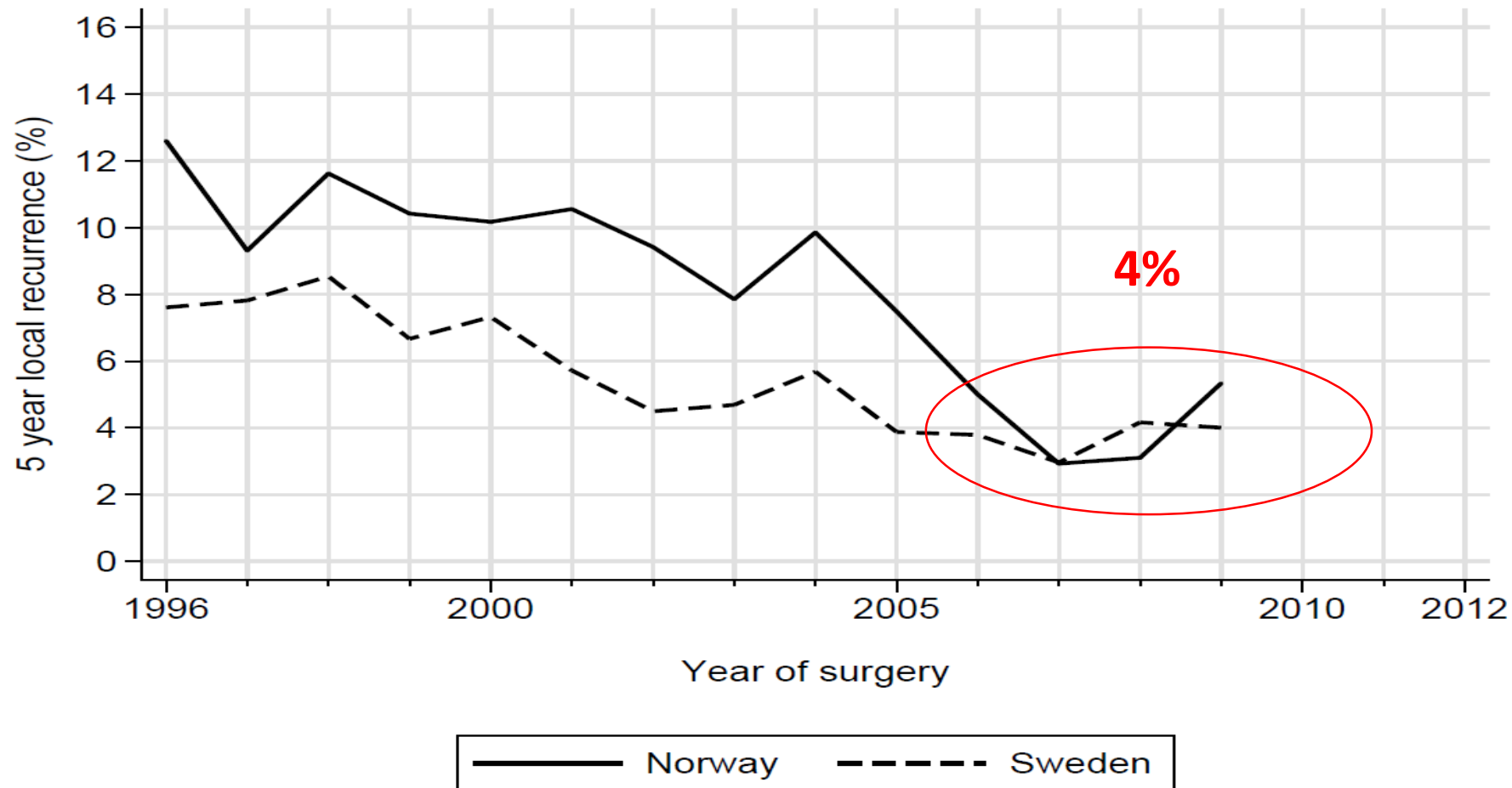


Long-course preoperative (C)RT
Postoperative CRT

Short-course preoperative RT

Glimelius B, Radiother Oncol 2016

5-års lokalt residiv 4-5% i begge land fra 2006



Ingen forskjell i andel med metastaser eller overlevelse mellom land

Glimelius B, Radiother Oncol 2016

Stockholm III studien

Resektabel rektumcancer

- 5 Gy x 5, operasjon 1 uke
- 5 Gy x 5, operasjon 4-8 uker
- 2 Gy x 25, operasjon 4-8 uker

Inger
10%

Strålebehandling 5 Gy x 5 ved lav risiko
- og til eldre, og ved metastaser

5 Gy x 5 og operasjon etter 4-8 uker god
behandling for resektabel rektumcancer

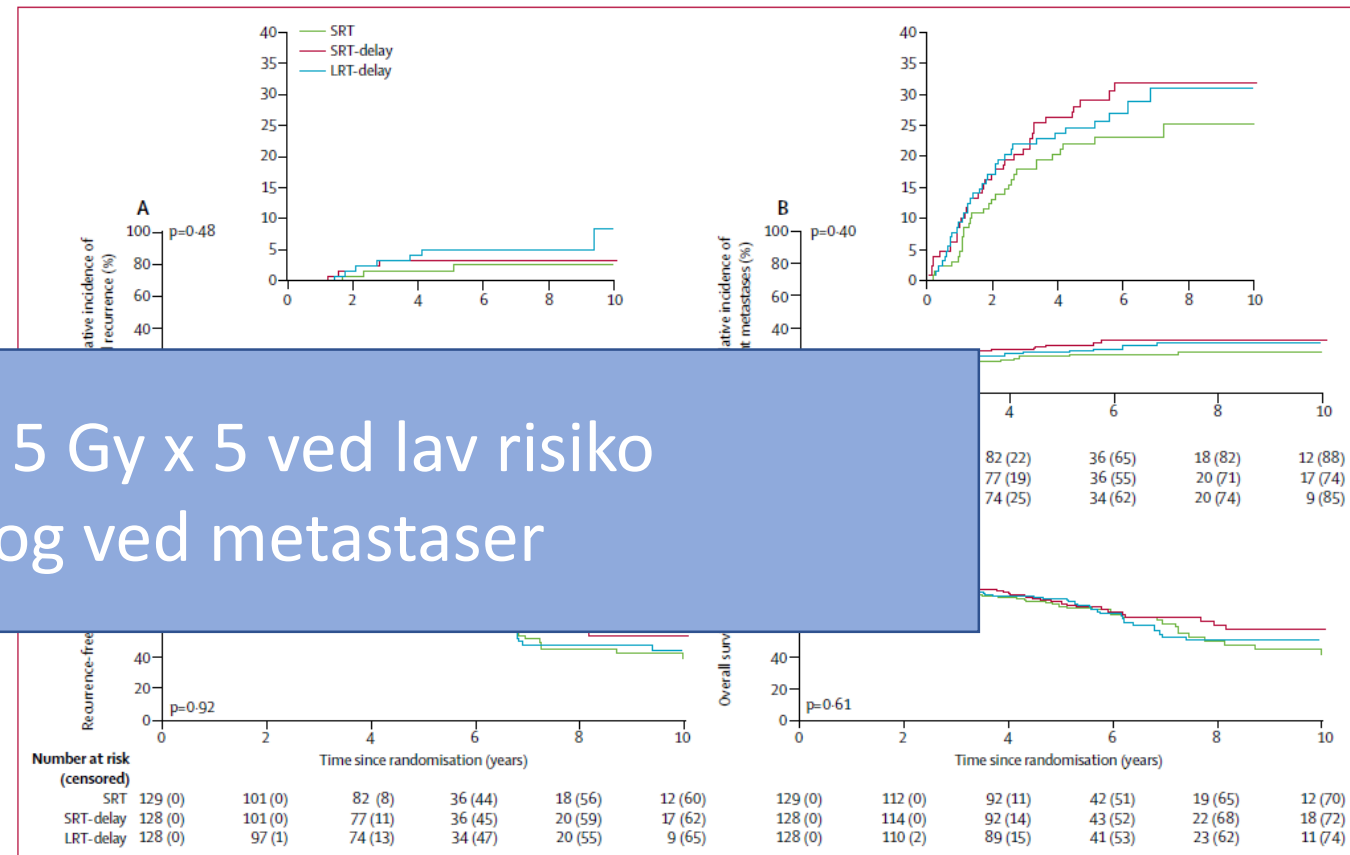
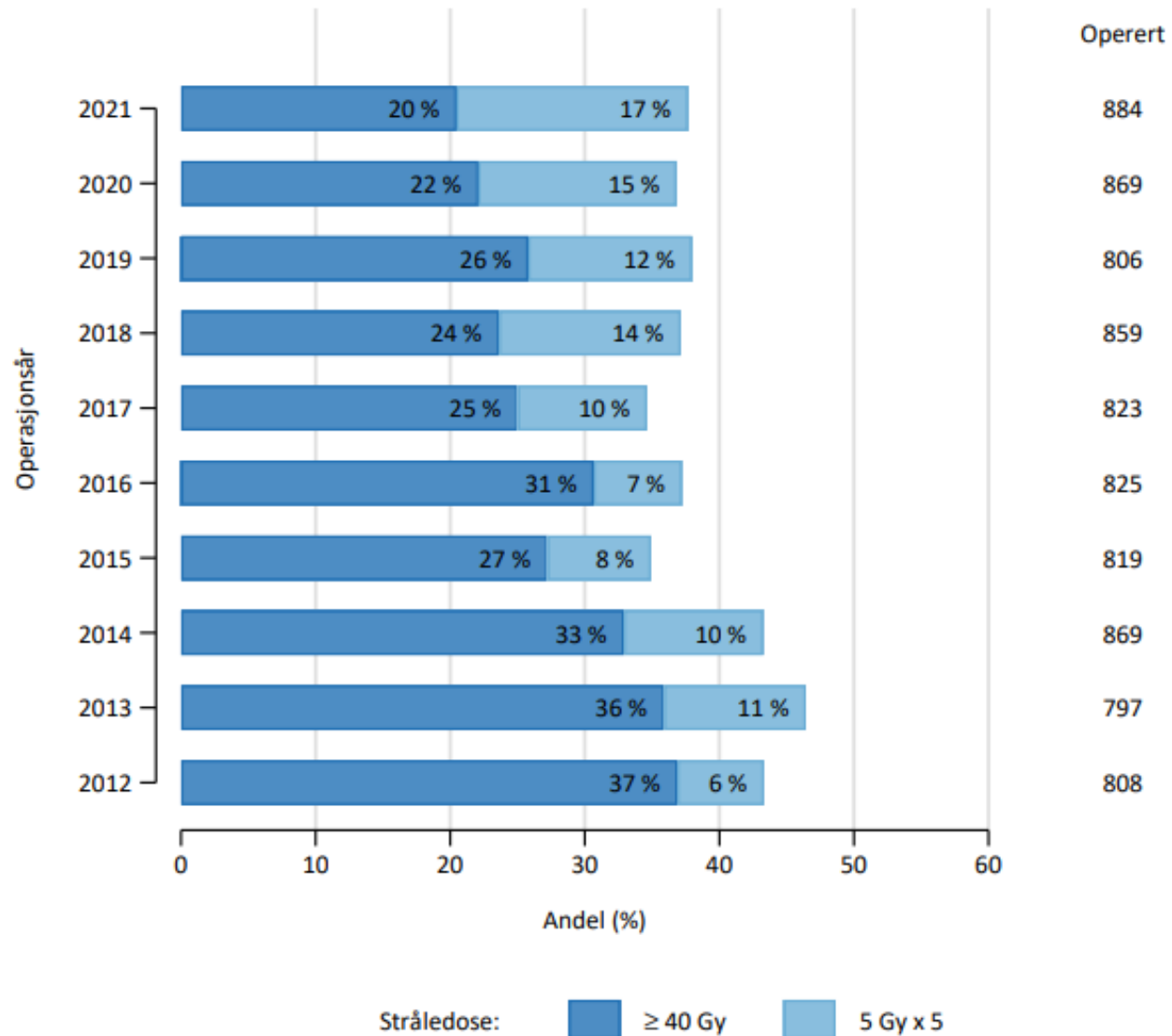


Figure 2: Local recurrence (A), distant metastases (B), recurrence-free survival (C), and overall survival (D) in the three-arm randomisation with a minimum of 2 years of follow-up. SRT=short-course radiotherapy (5 x 5 Gy with surgery within 1 week). SRT-delay=short-course radiotherapy (5 x 5 Gy with surgery after 4-8 weeks). LRT-delay=long-course radiotherapy (25 x 2 Gy with surgery after 4-8 weeks)

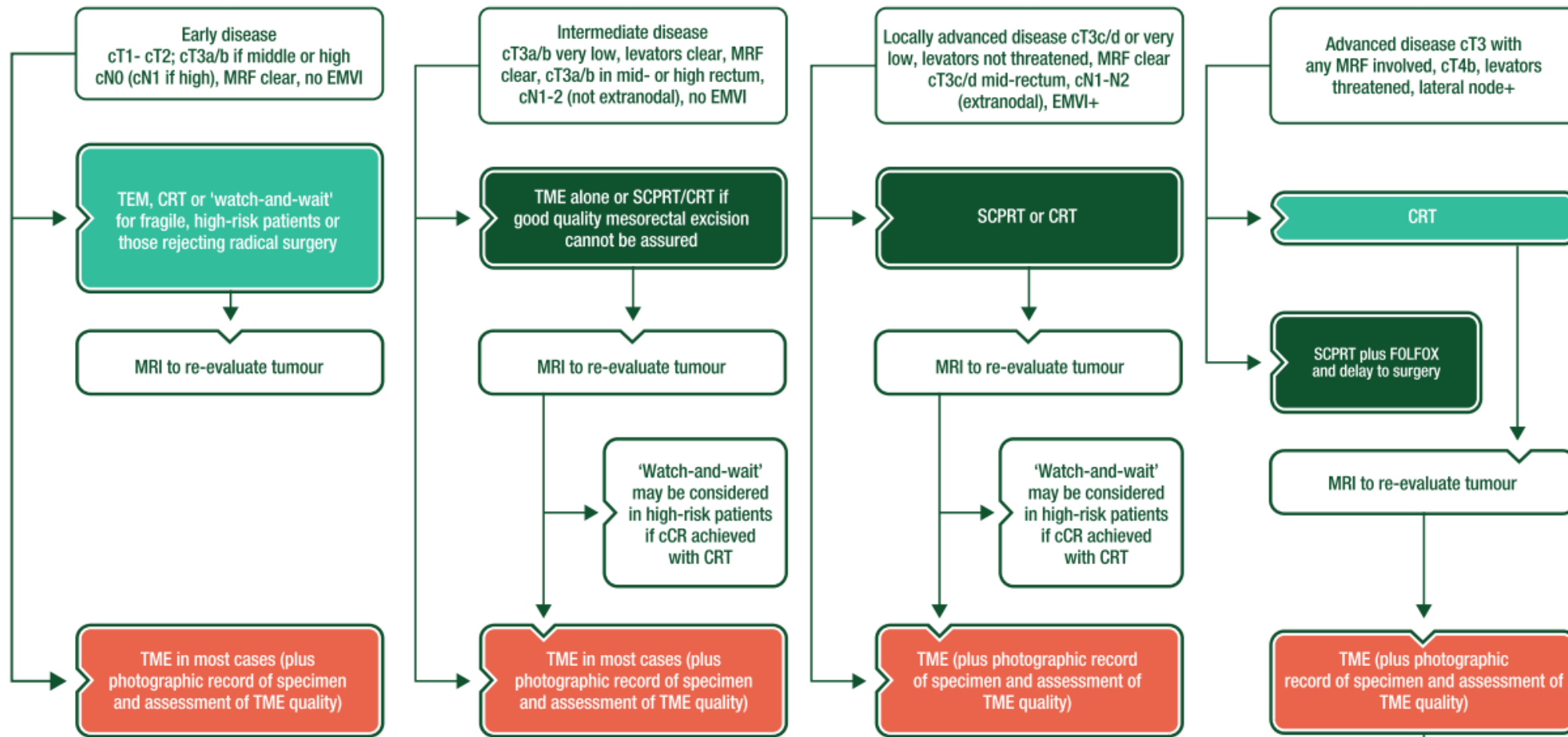
Erlandsson J, Lancet Onc 2017; Erlandsson J, Rad Onc 2019

Preoperativ strålebehandling endetarmskreft



Colorectalancerregisteret

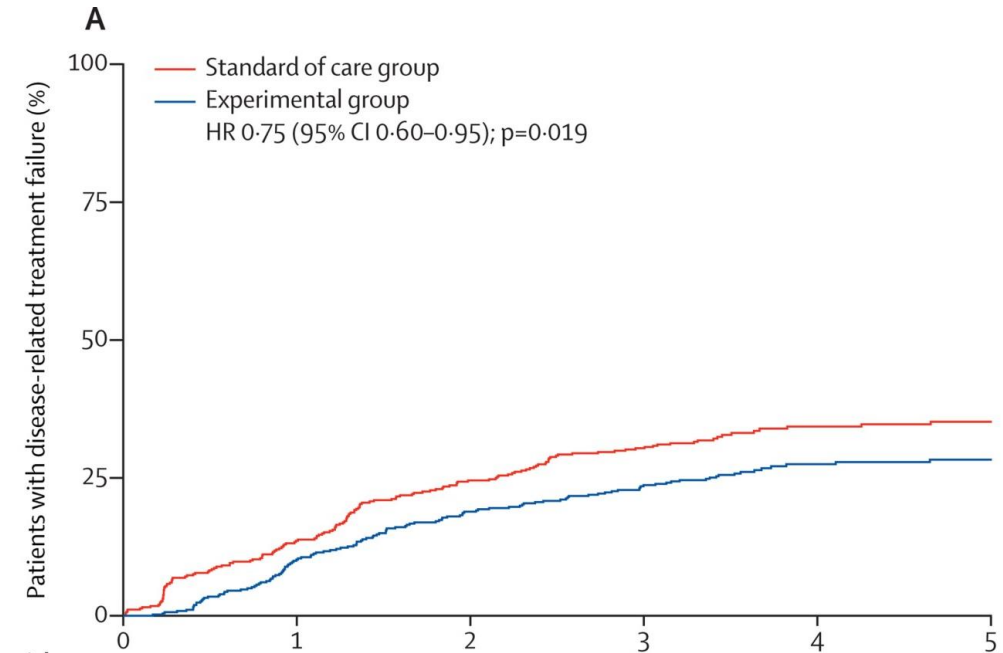
ESMO retningslinjer



Glynne-Jones R, Annals Oncol 2017

Strålebehandling og kjemoterapi for operasjon

ved høy-risk rektumcancer (T4, N2, LN, EMVI+)

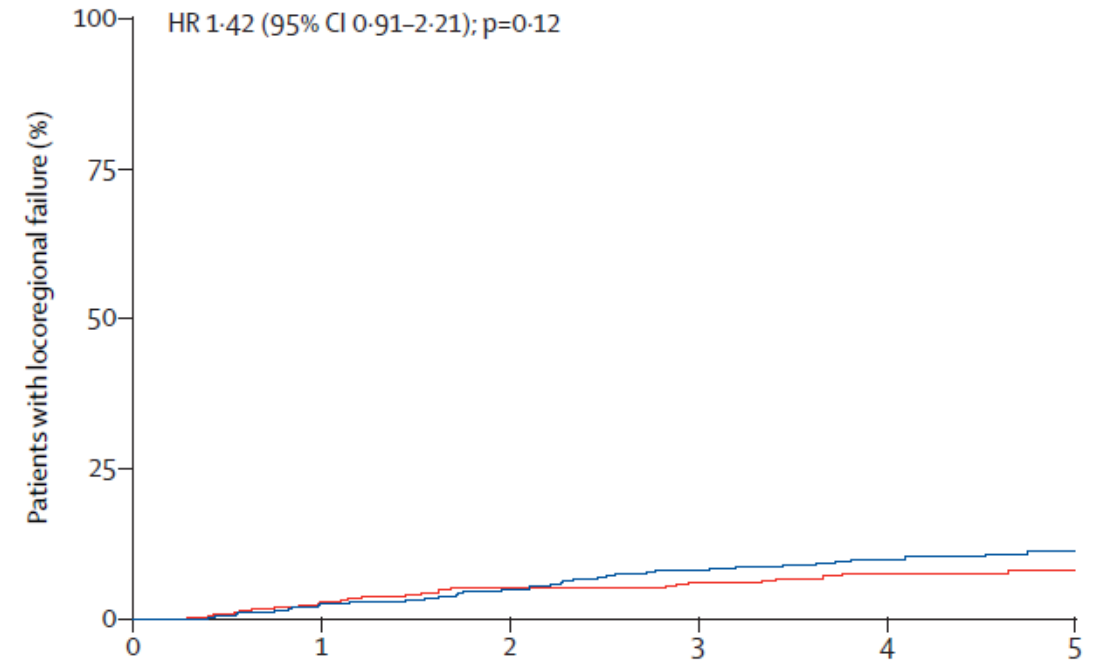
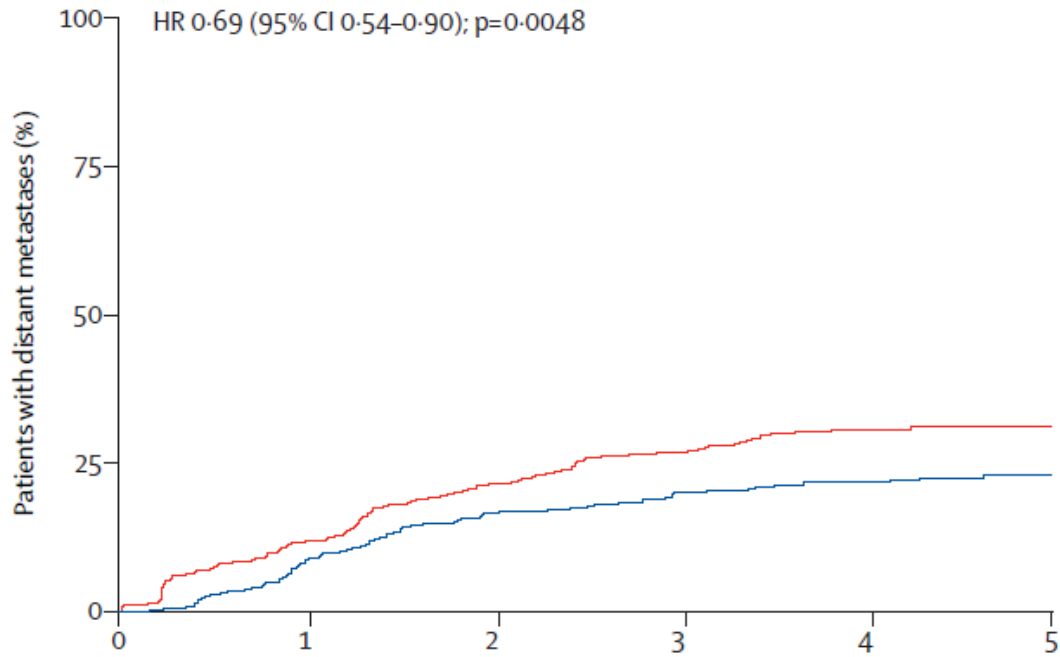


- Bedre disease-related treatment failure 23.7% vs 30.4%

Bahadoer RR, Lancet Oncol 2021

Fjernmetastaser 20,0% vs 26,8%

Lokoregional failure 8,3% vs 6,0% (ns)



Bahadoer RR, Lancet Oncol 2021

Andre studier

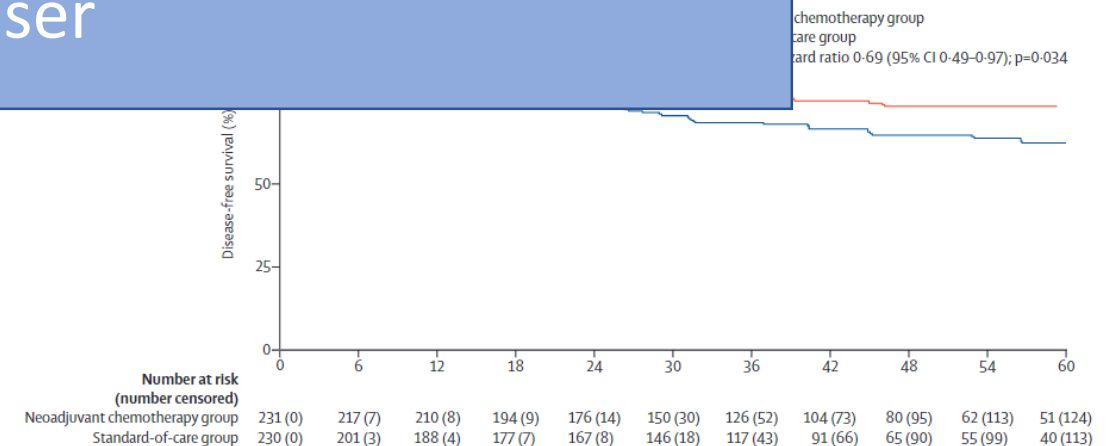
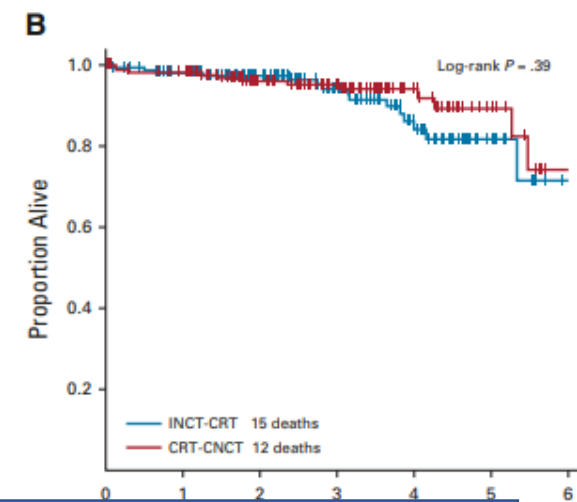
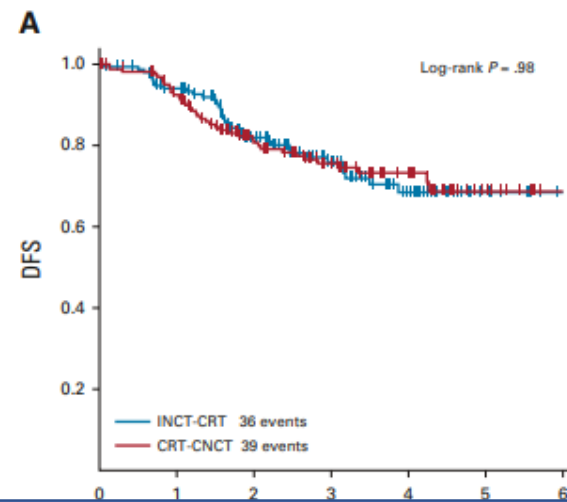
- CAO/ARO/AIO-12, OPRA

- CRT FOLFOX x 8

• Strålebehandling og kjemoterapi ved høy risiko for residiv og metastaser

- PR

- cT3-4 M0, ECOG 0-1
- FOLFIRINOX x 6, CRT 50 Gy, kirurgi, FOLFOX 3 mnd vs CRT 50 Gy, kirurgi, adjuvant FOLFOX 6 mnd
- 3-y DFS 76% vs 69%

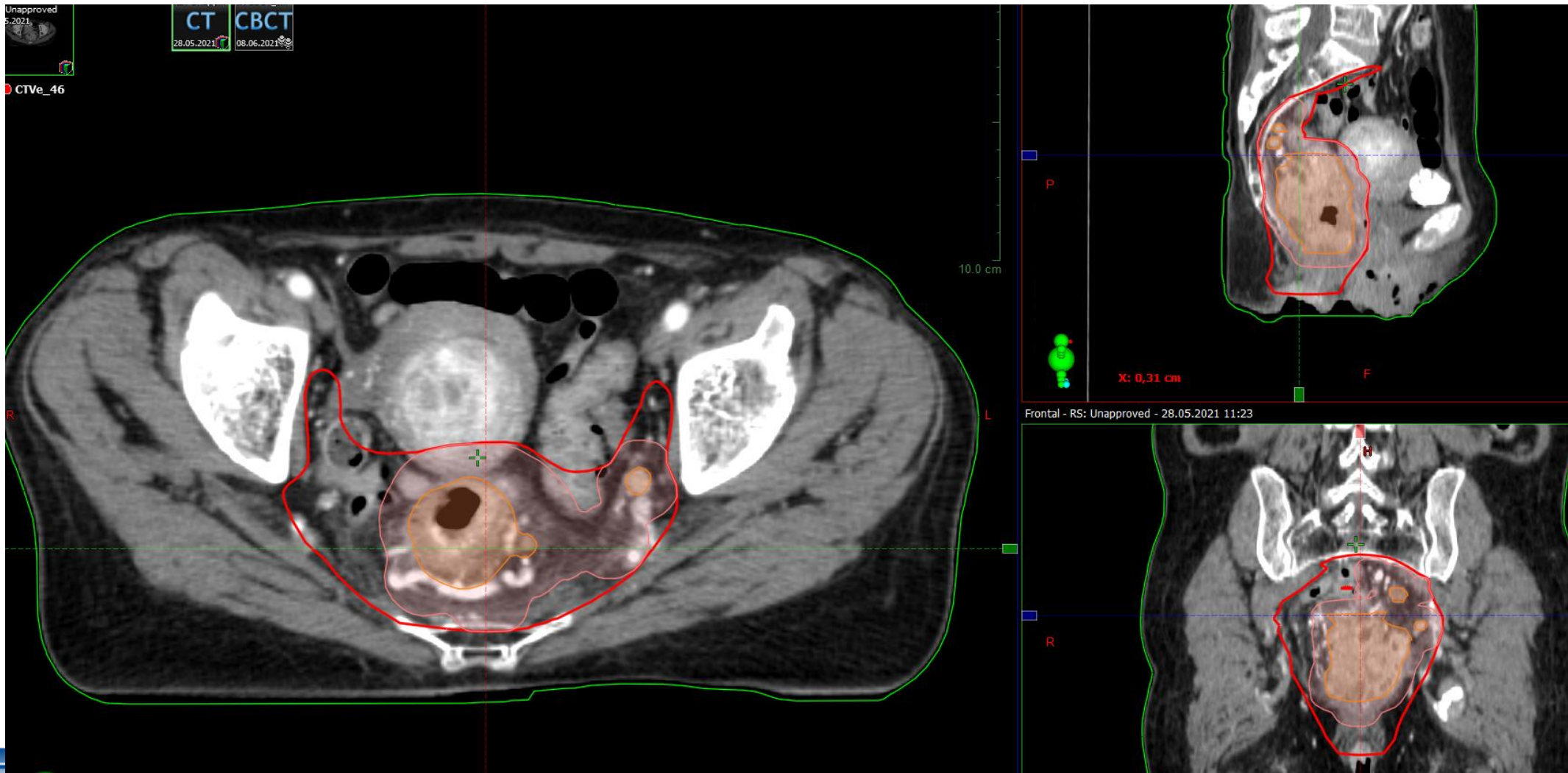


Garcia-Aguilar J, JCO, 2022 og Conroy T, Lancet Oncol 2021

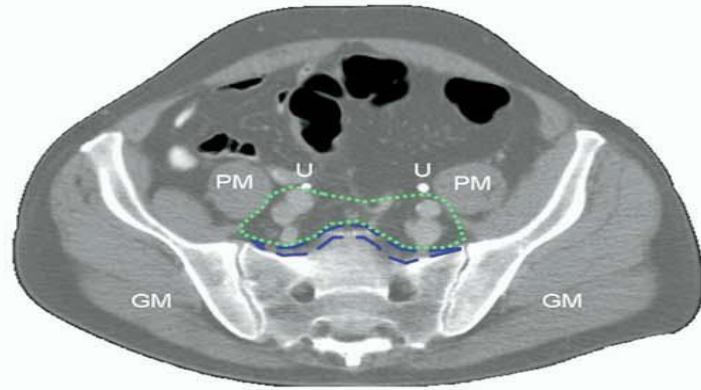
Anbefalinger

- Preoperativ 5 Gy x 5
 - ved ≤ 2 mm til MRF uten andre risikofaktorer
 - eller eldre/komorbide
- Preoperativ 5 Gy x 5 og 4-6 CAPOX (FOLFOX) – RAPIDO regime
 - ved høy-risiko rektumcancer T4a (omslagsfold), MRF ≤ 1 mm, N1c, N2, EMVI+
 - ECOG 0-1 uten kontraindikasjoner
 - Pasienter som ikke tåler dette kan vurderes for CRT 2 Gy x 25 eller RT 5 Gy x 5
- Preoperativ 2 Gy x 25 med capecitabine
 - ved T4b, usikker resektabilitet
 - tillegg kjemoterapi (TNT) dersom toleranse

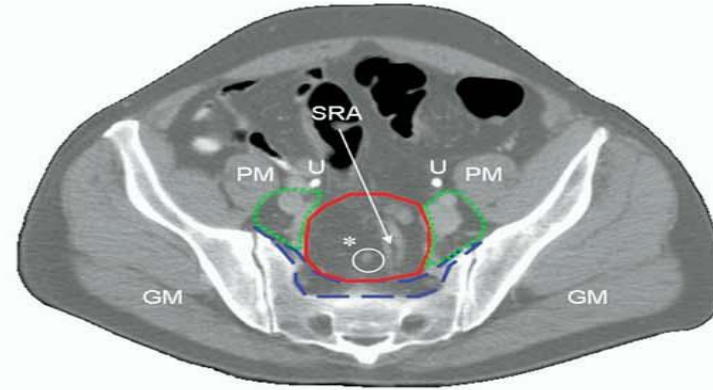
Inntegning målvolum



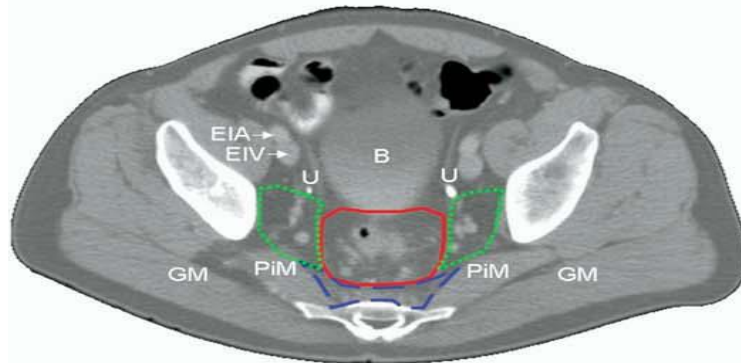
Områder som strålebehandles



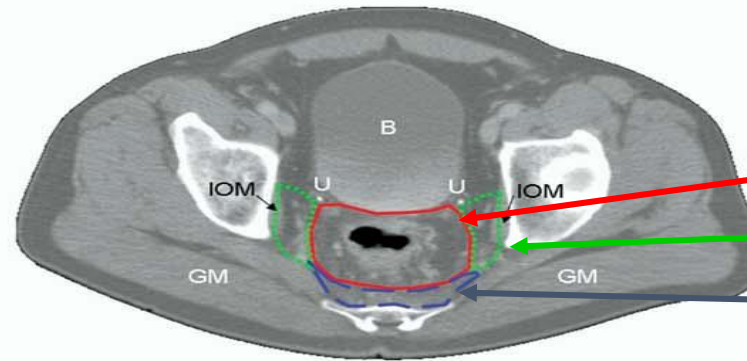
(a)



(b)



(c)

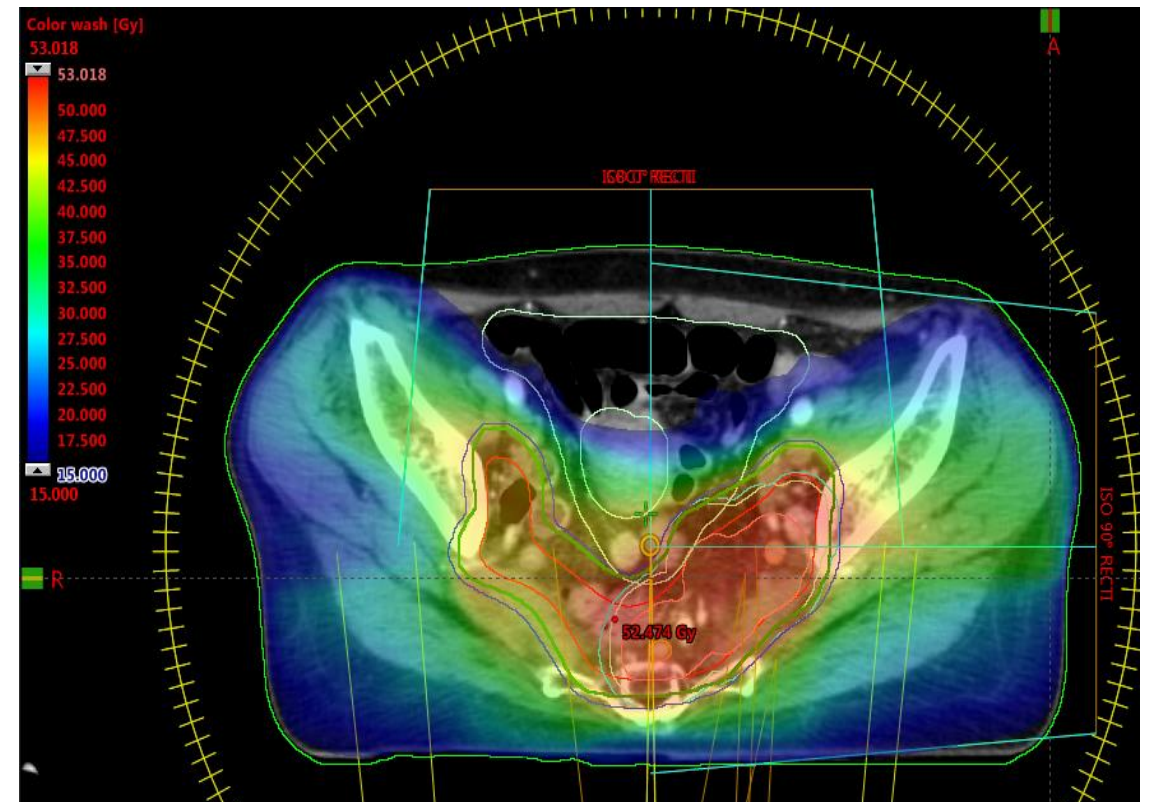
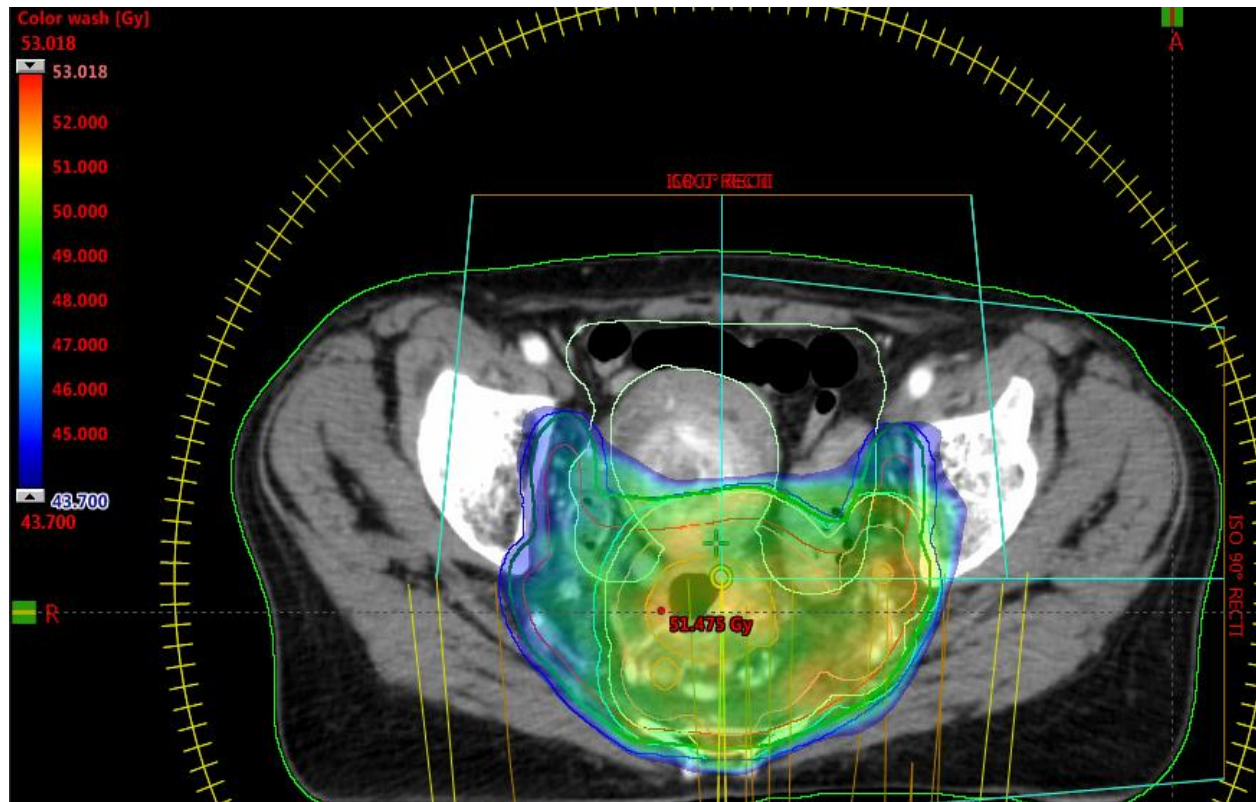


(d)

Subsites:
Mesorektum
Lateralt
Bakre

Roels S, IJROBP 2006

Ønsket dose til svulst og risiko-område - og lavest mulig uønsket dose til normalvev



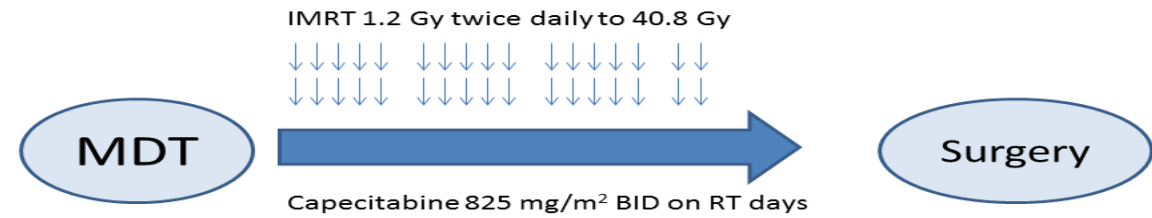
Balanse mellom effekt og seneffekter

- Endetarmsfunksjon
 - Low anterior resection syndrome (LARS)
 - Inkontinens, hyppig avføring, urgency, tømming
- Påvirkning av livskvalitet
- Menopause, infertilitet, hormoner
- Seksuell funksjon
- Mikrofrakturer i bekkenet



Bruheim K, Acta Onc 2010; Lange MM, Nat Rev Urol 2011; Emmertsen KJ, Br J surg 2013; Buchli C, Ann Surg 2018

Rebestråling ved residiv

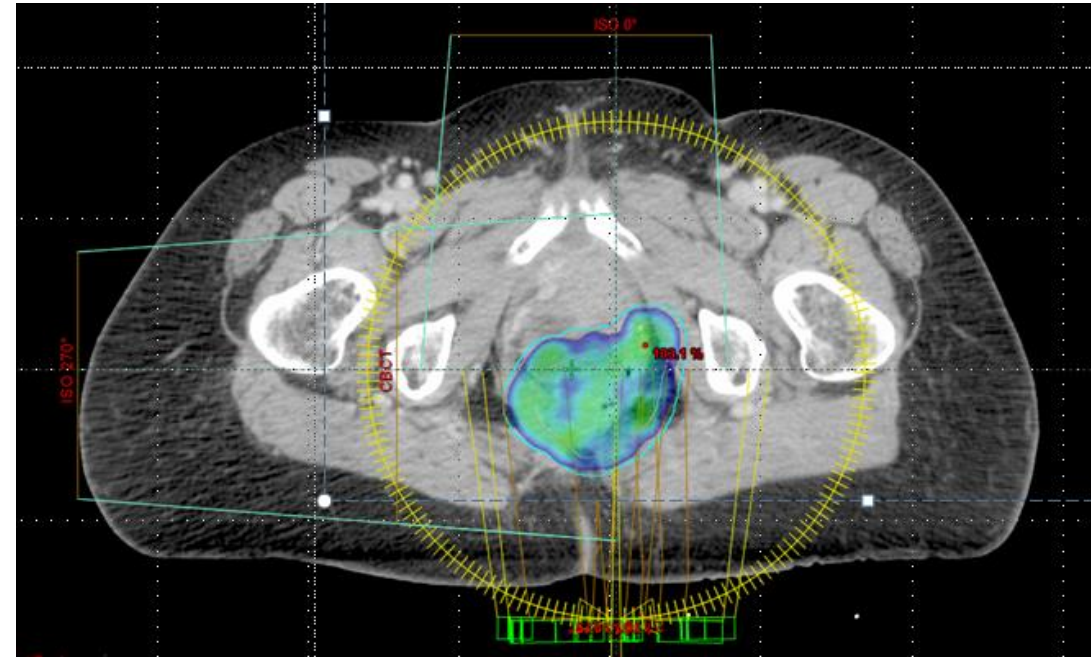


Begrenset volum GTV + margin til PTV

Kurativ hyperfraksjonert strålebehandling
1,2-1,5 Gy 2 ganger daglig til 40,8-45 Gy
med capecitabine før operasjon

Palliativt 2 Gy x 15

PelvEx II studien undersøker effekt av
neoadjuvant kjemoterapi før RT og kirurgi



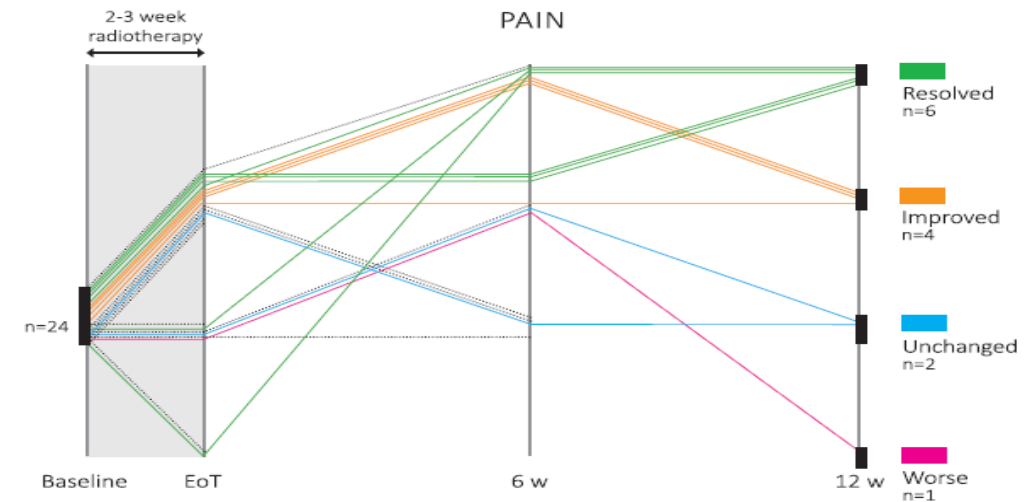
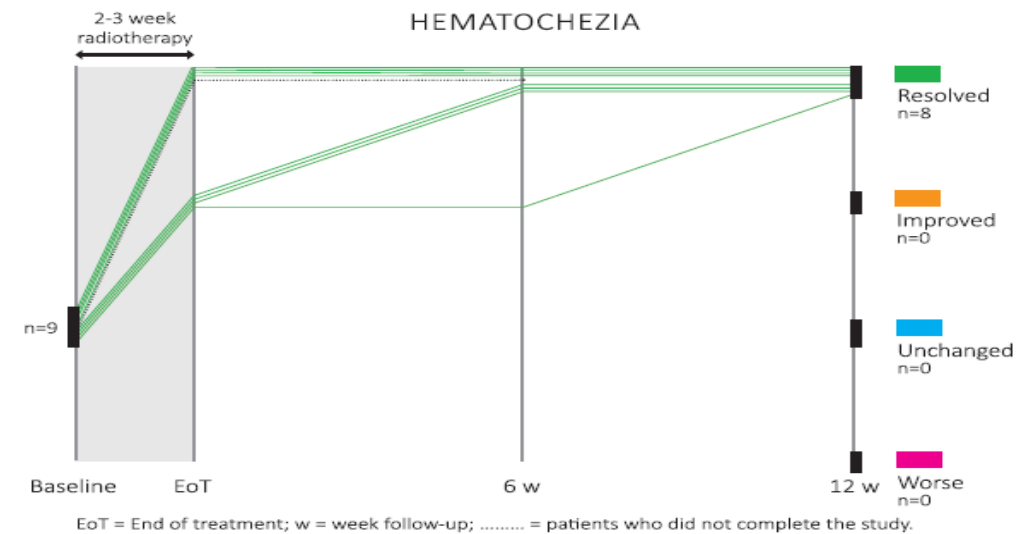
Guren MG, Rad & Onc 2014

Palliativ strålebehandling

Symptomlindring hos 70-80%

PallRad1 studien – symptomlindring rektumtumor

- 3 Gy x 10-12, GTV med 1,5 cm margin til PTV
 - God symptomlindring
 - Ofte brukes 5 Gy x 5 ved palliasjon



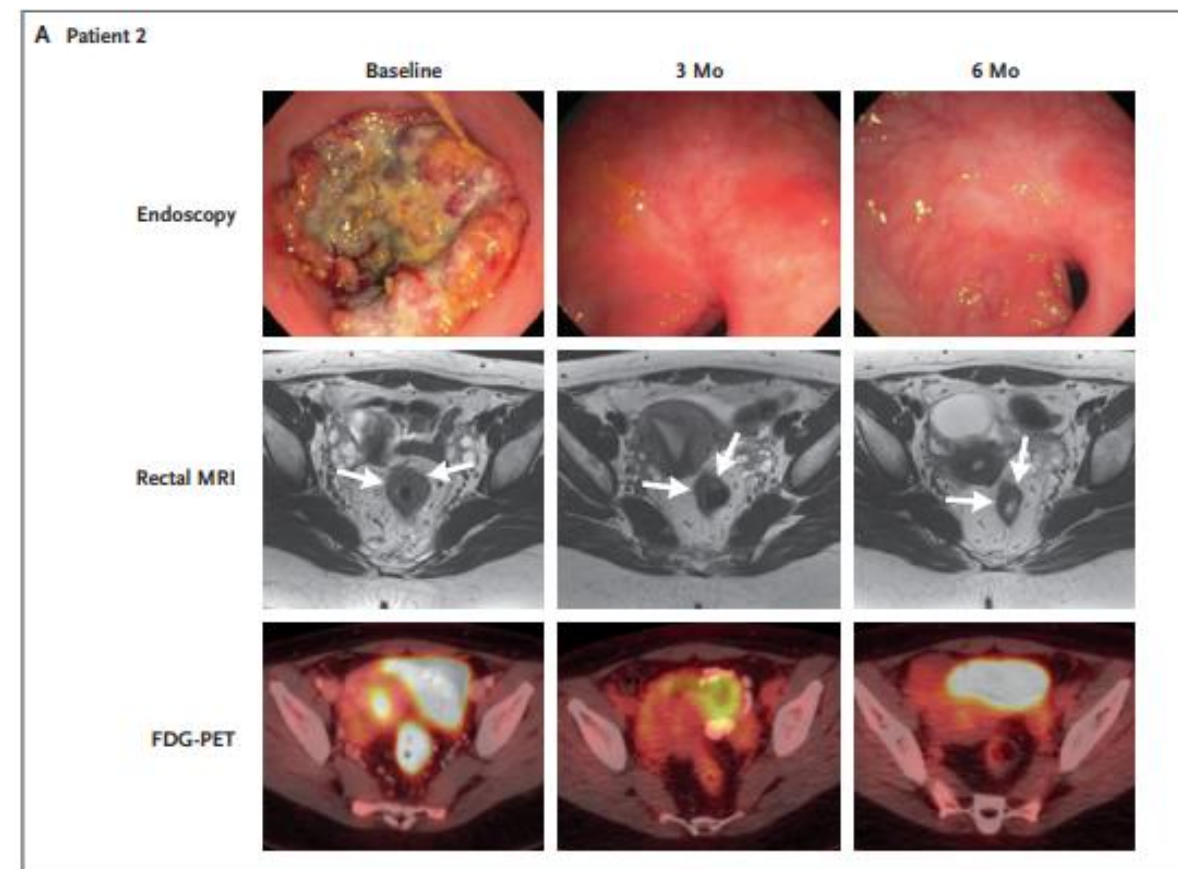
Cameron MG, Acta Onc 2014 og 2016

PD-1 Blockade in Mismatch Repair–Deficient, Locally
Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

Rektumcancer dMMR/MSI

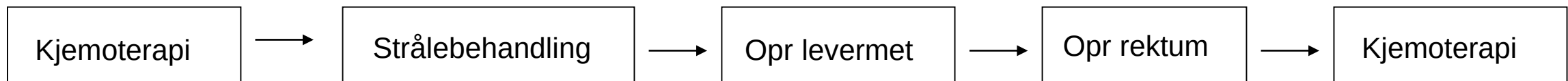
- Rektumcancer stadium II-III, dMMR (n=12)
- Dostarimab (anti PD-1) i 6 mnd, deretter planlagt CRT og kirurgi
- Alle 12/12 (100%) klinisk komplett respons
- Ingen har fått CRT eller kirurgi
- Foreløpig ingen progresjon eller residiv
- Avventer langtidsresultater



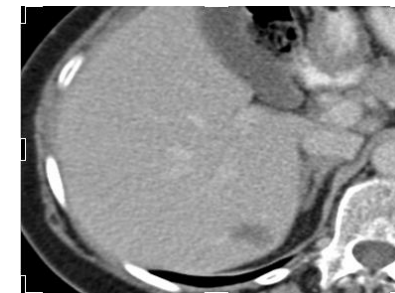
Cercek A, NEJM 2022

Rektumcancer med resektable levermetastaser

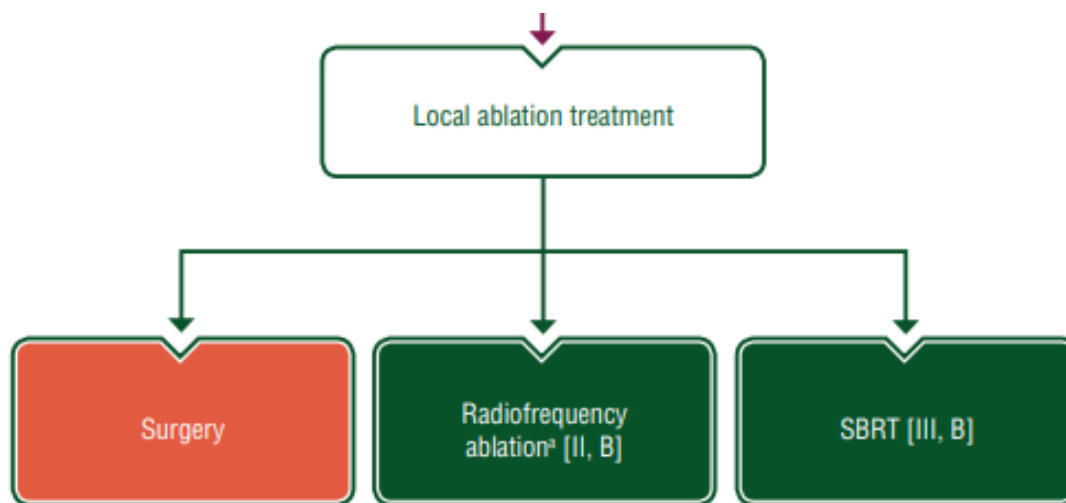
- God behandling av både primærtumor og metastaser
- Kirurgi av primærtumor og metastaser
 - Hvilken rekkefølge?
- Strålebehandling før kirurgi av rektumtumor?
 - 5 Gy x 5
 - 2 Gy x 25 med capecitabine
- Kjemoterapi før/etter kirurgi levermetastaser?
 - FOLFOX/CAPOX (totalt 6 mnd, ofte 2-3 mnd før operasjon og resten etter opr)
- Eksempel på forløp



Resektable metastaser



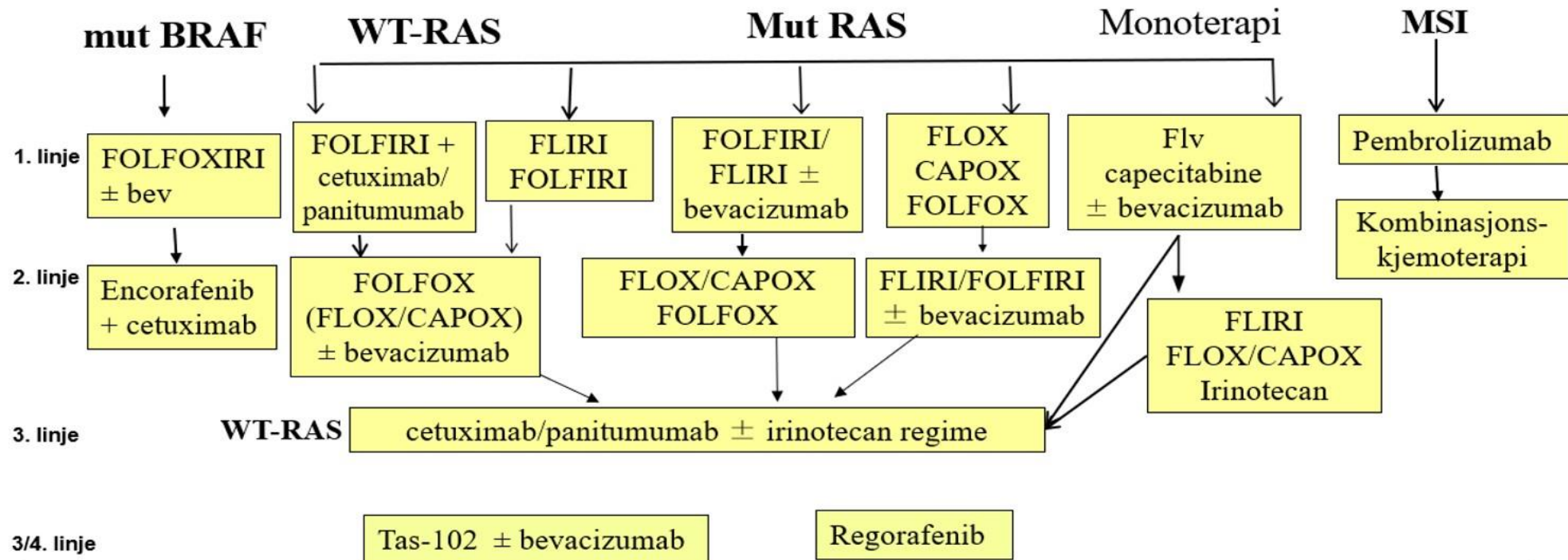
- Levermetastaser, lungemetastaser, peritoneale metastaser
- Kjemoterapi kan bidra til at metastaser blir resektable
- Radikal behandling av både primærtumor og metastaser



Cervantes A, Annals Oncol 2023

Medikamentell behandling ved metastatisk colorektalcancer

Palliativ intensjon



Medikamentell kreftbehandling

5-FU

- FLV, capecitabine

Oxaliplatin kombinasjon

- FOLFOX / FLOX
 - Oxaliplatin og 5-FU hver 2. uke
- CAPOX
 - Oxaliplatin og capecitabine hver 3. uke

Irinotecan kombinasjon

- FOLFIRI / FLIRI
 - Irinotecan og 5-FU hver 2. uke

- EGFR-hemmer
 - Cetuximab, panitumumab
- VEGF-hemmer
 - Bevacizumab
- Andre
 - Regorafenib
 - TAS-102

FOLFIRI eller FOLFOX best 1. linje behandling?

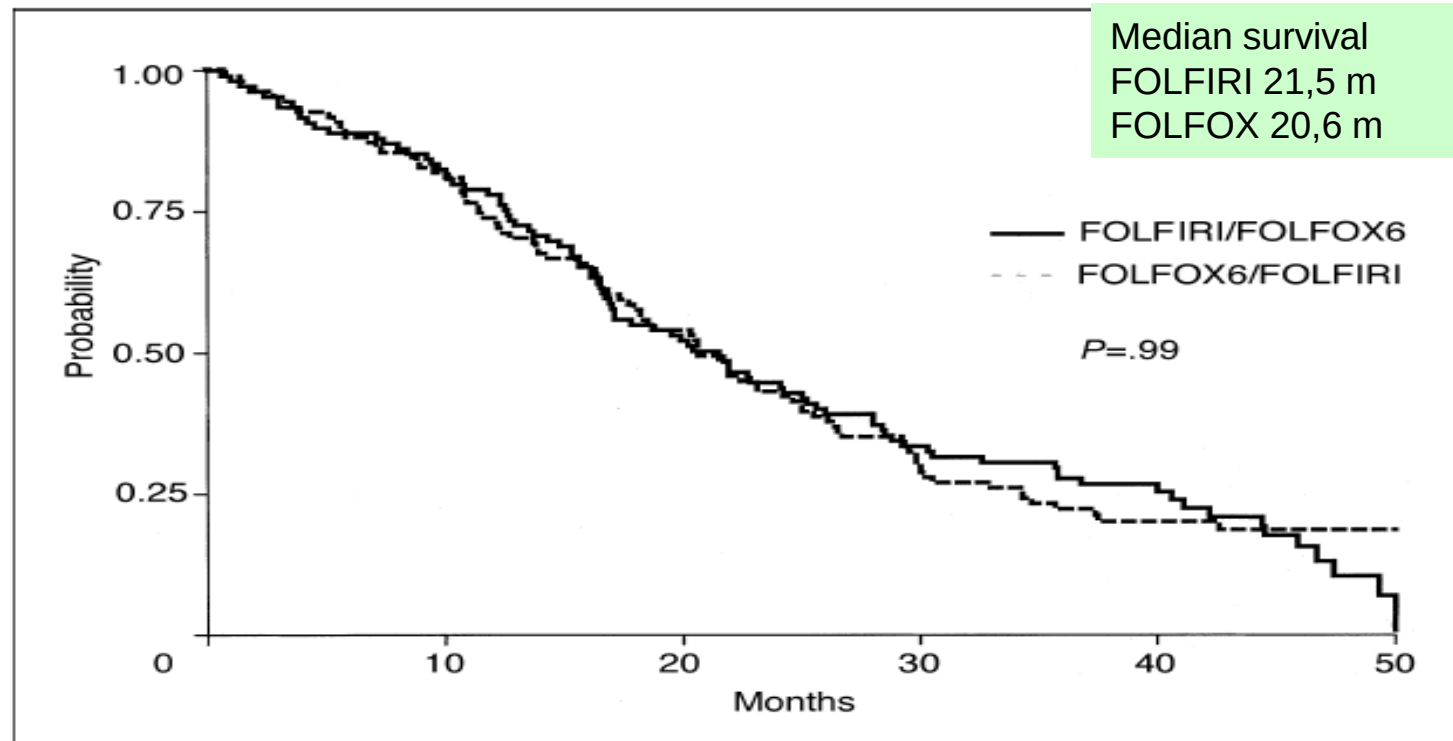
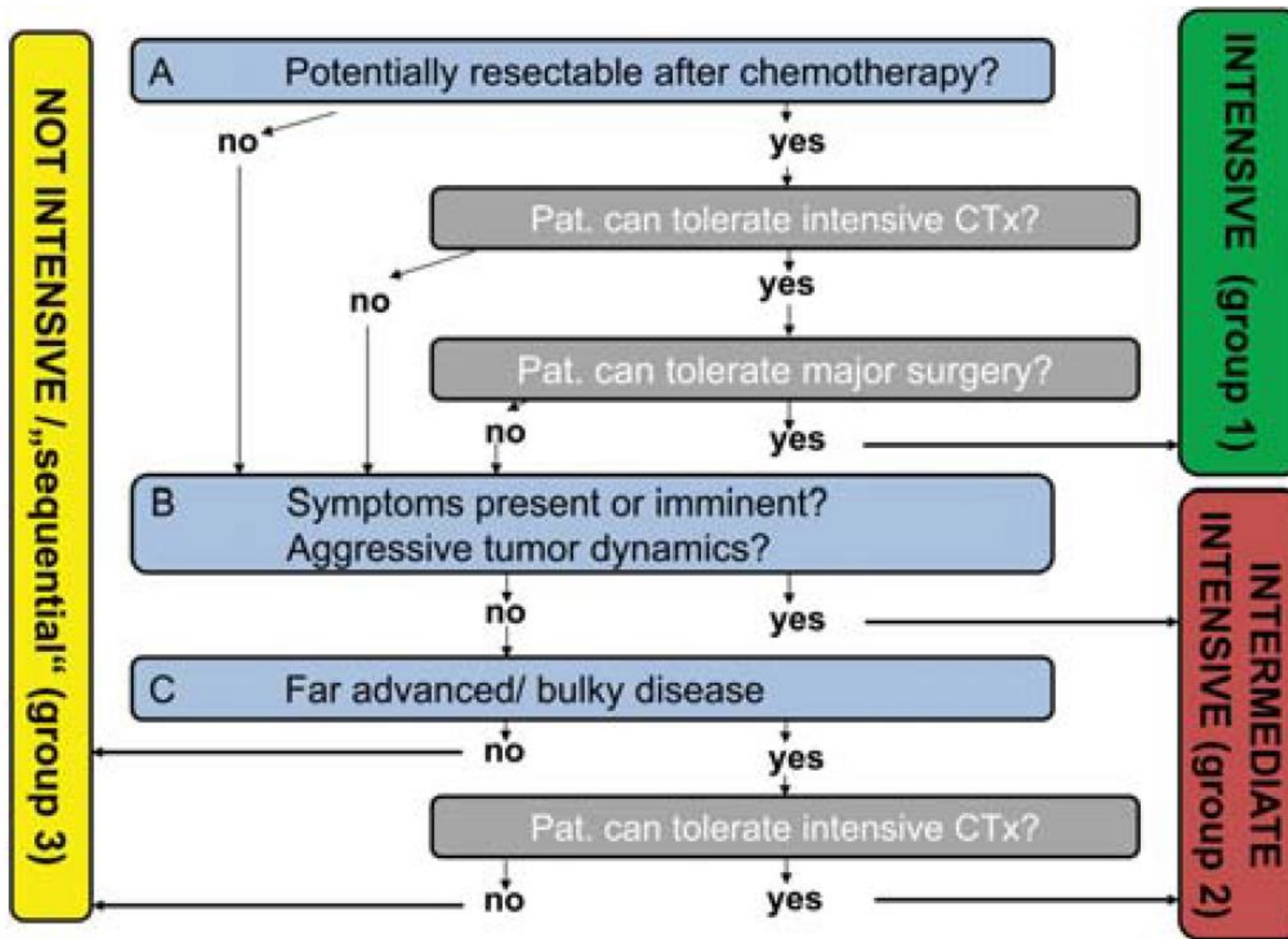


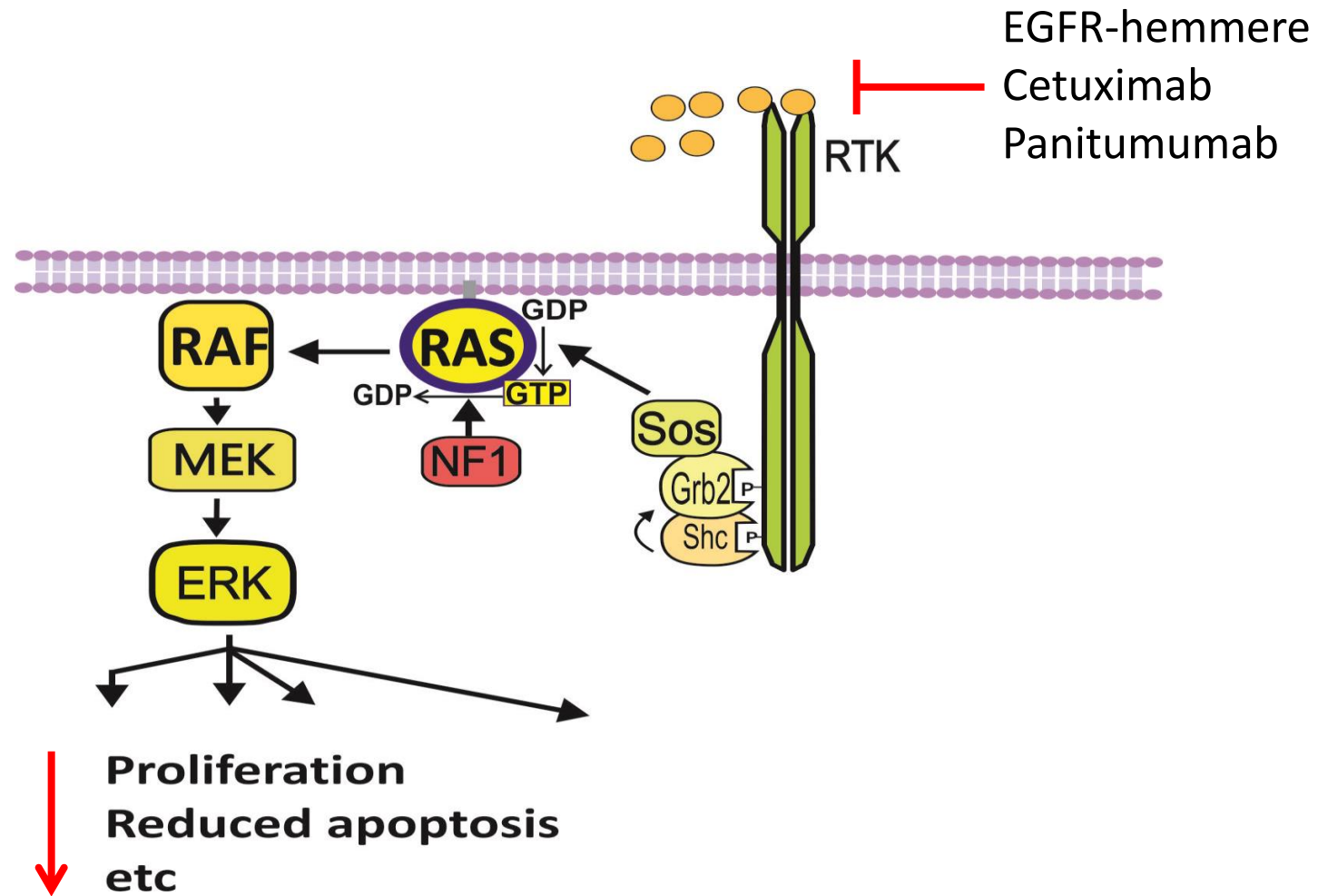
Fig 4. Overall survival curves. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

Tournigand et al. JCO 2004



Schmoll HJ, Ann Onc 2012

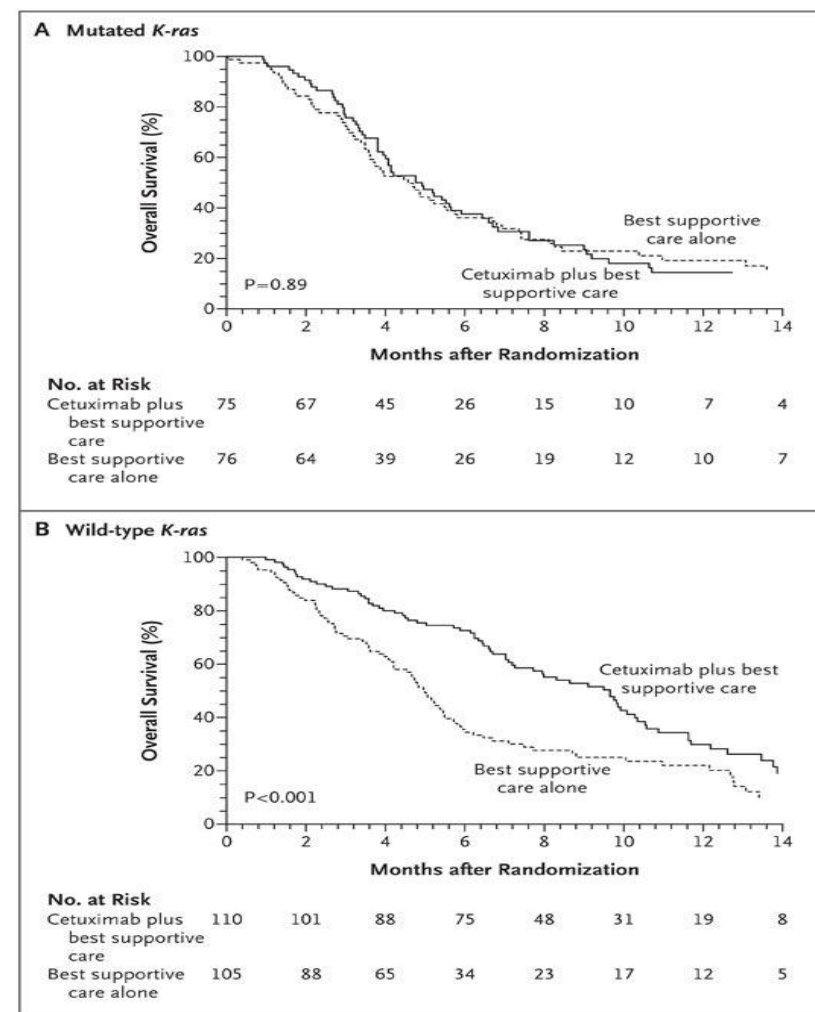
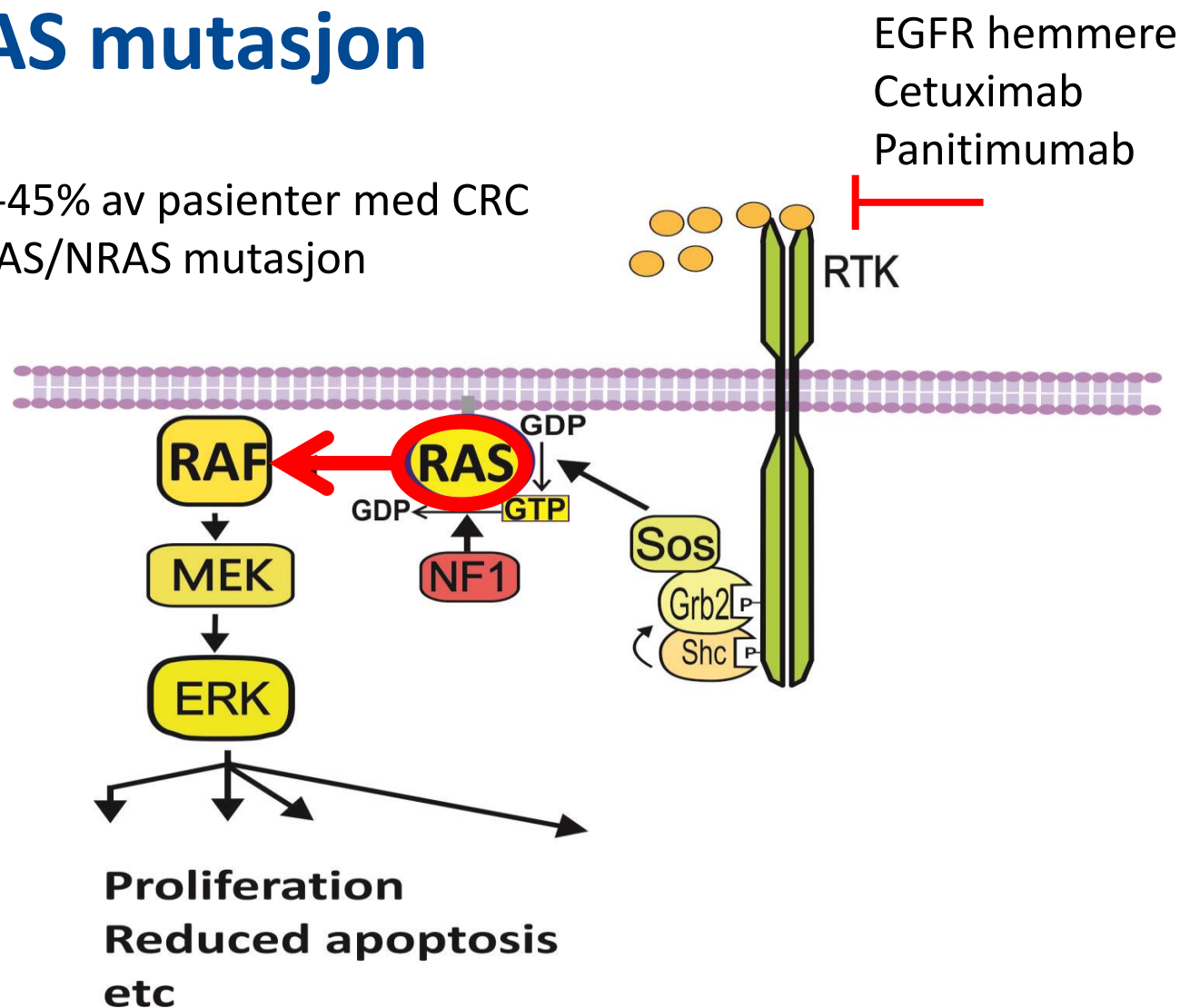
RAS villtype (ikke mutert)



Figur fra T Christoffersen

RAS mutasjon

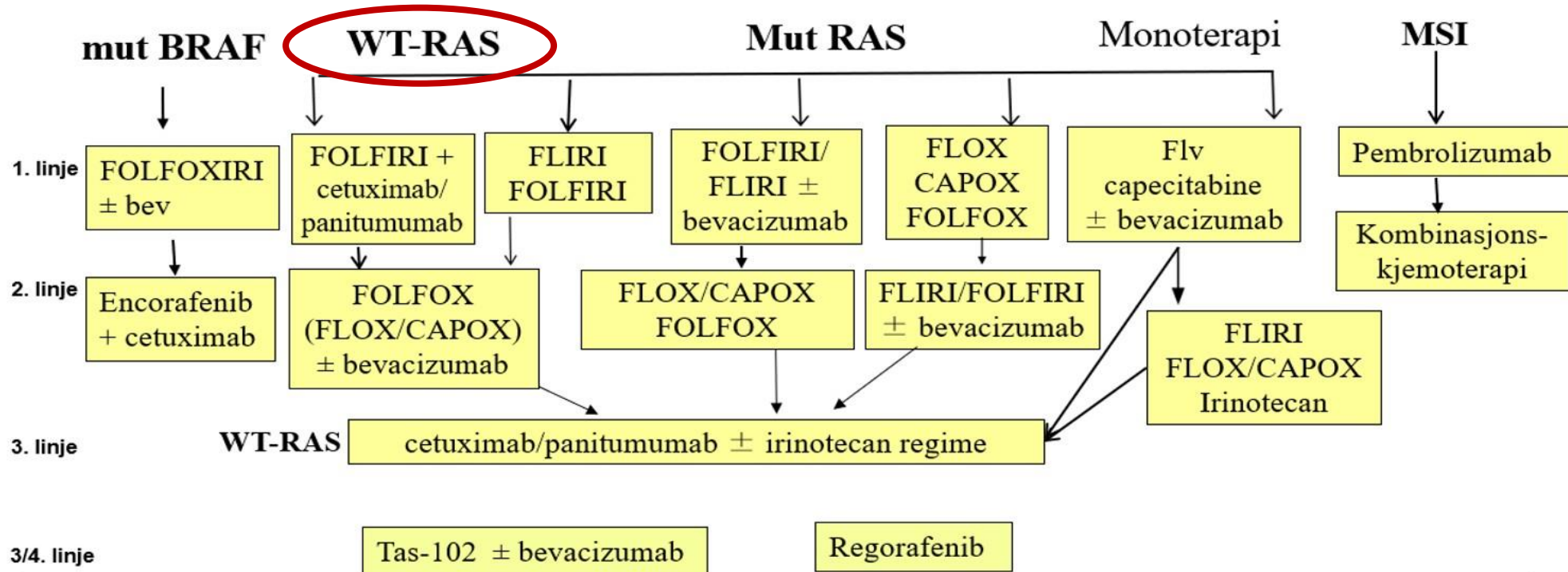
40-45% av pasienter med CRC
KRAS/NRAS mutasjon



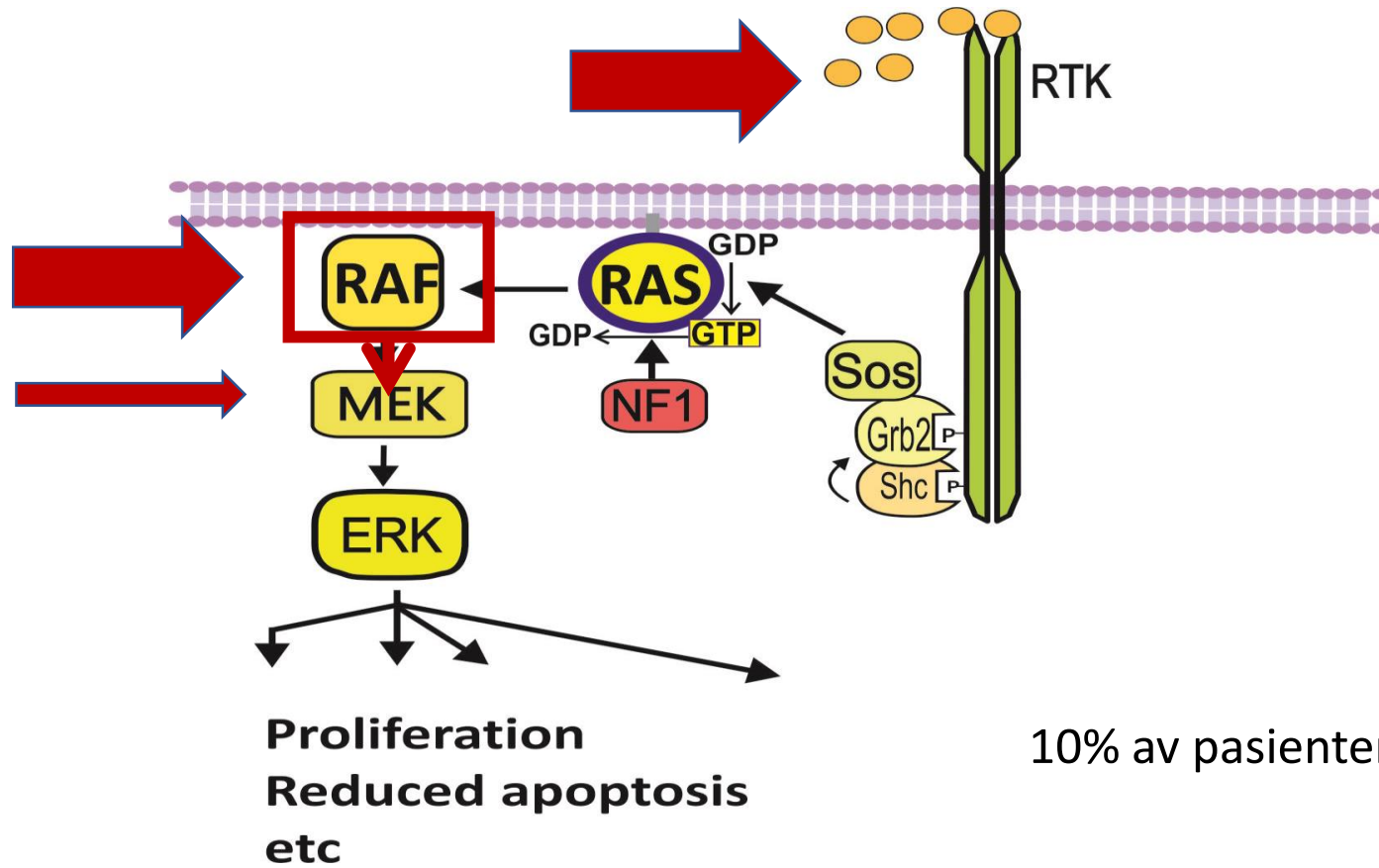
Figur fra T Christoffersen; Karapetis CS et al, N Engl J Med 2008

Medikamentell behandling ved metastatisk colorektalcancer

Palliativ intensjon



BRAF mutasjon

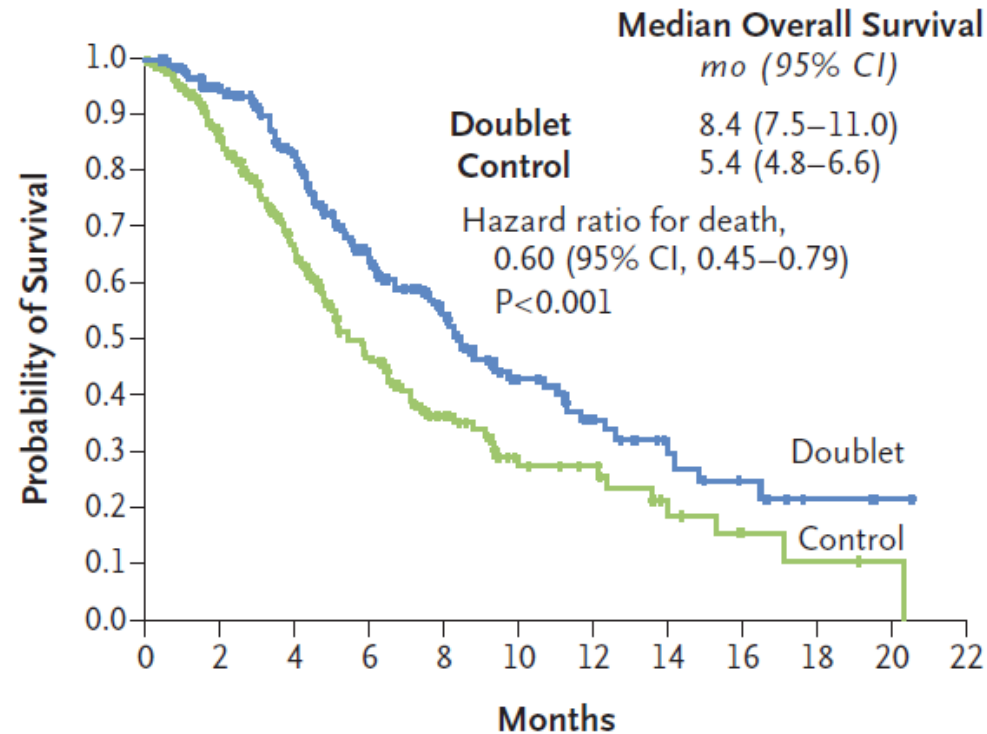


10% av pasienter med metastatisk CRC

Figur fra T Christoffersen

Encorafenib og cetuximab BRAF mut CRC

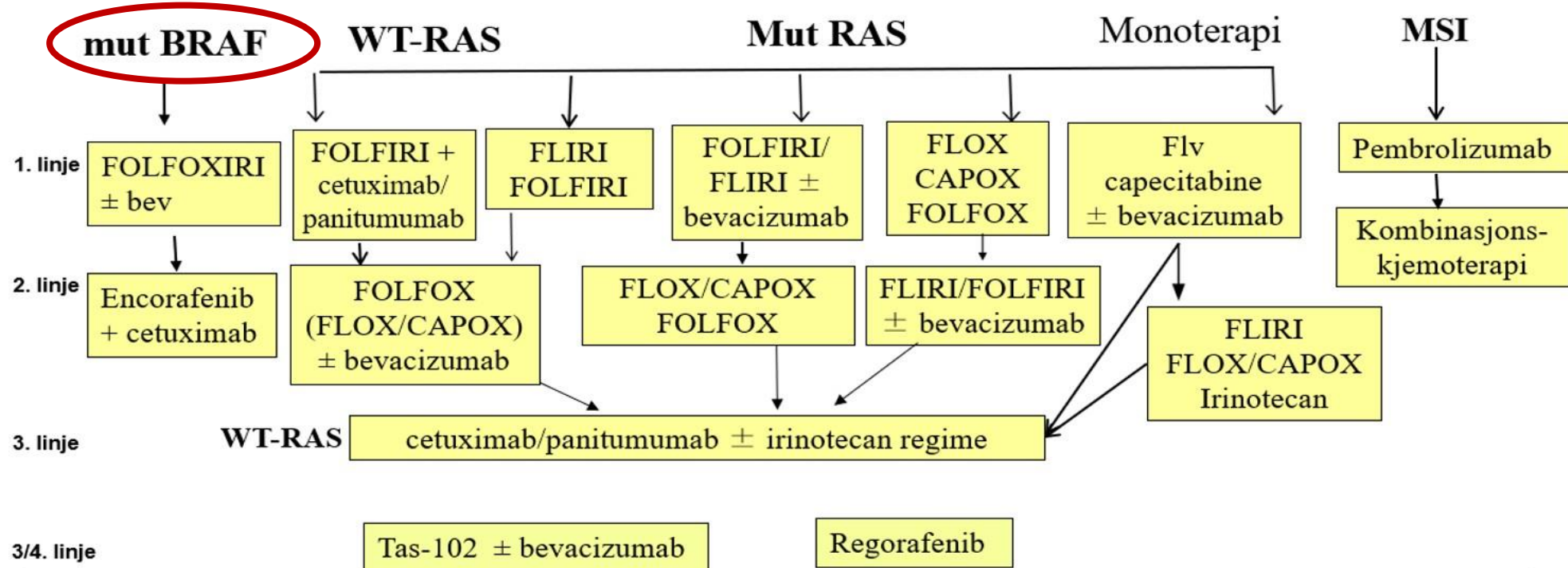
B Overall Survival, Doublet Regimen vs. Control



Kopetz S, NEJM 2019

Medikamentell behandling ved metastatisk colorektalcancer

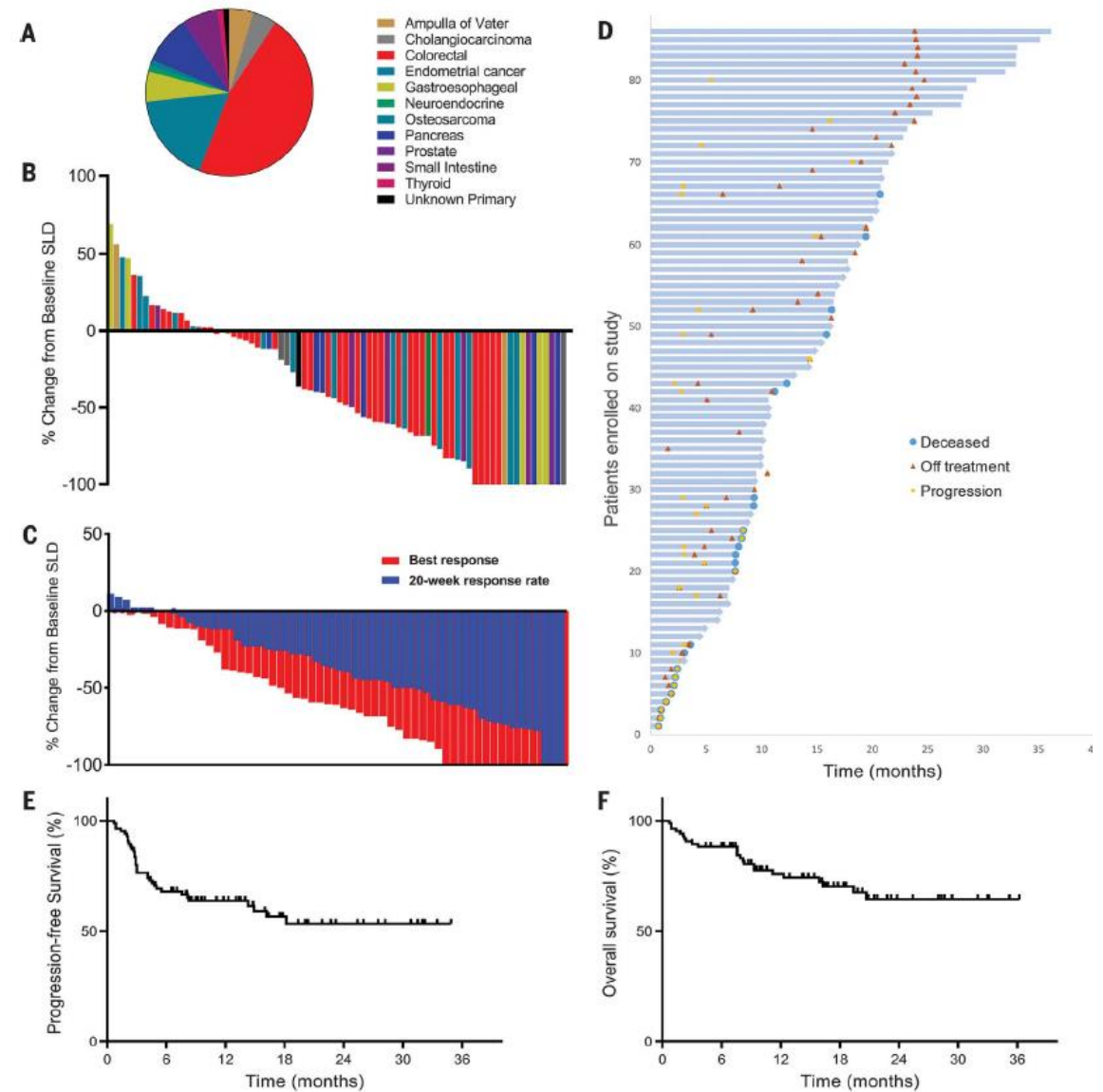
Palliativ intensjon



Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Dung T. Le,^{1,2,3} Jennifer N. Durham,^{1,2,3*} Kellie N. Smith,^{1,3*} Hao Wang,^{3*}

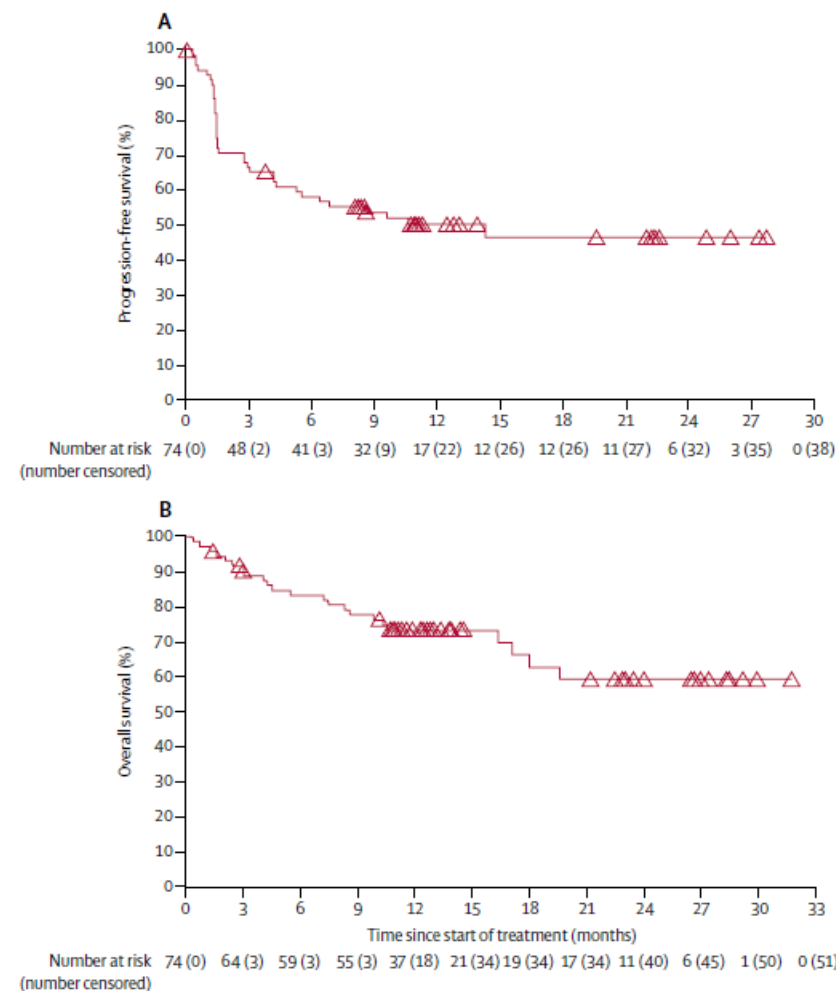
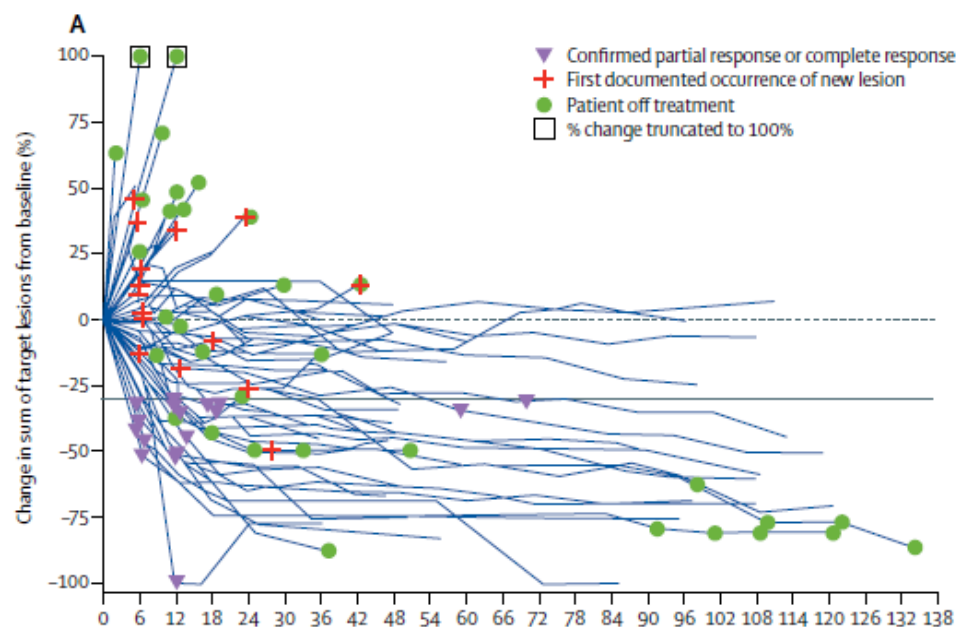
Type of response	Patients (n = 86)
Complete response	18 (21%)
Partial response	28 (33%)
Stable disease	20 (23%)
Progressive disease	12 (14%)
Not evaluable	8 (9%)
Objective response rate	53%
95% CI	42 to 64%
Disease control rate	77%
95% CI	66 to 85%
Median progression-free survival time	NR
95% CI	14.8 months to NR
2-year progression-free survival rate	53%
95% CI	42 to 68%
Median overall survival time	NR
95% CI	NR to NR
2-year overall survival rate	64%
95% CI	53 to 78%



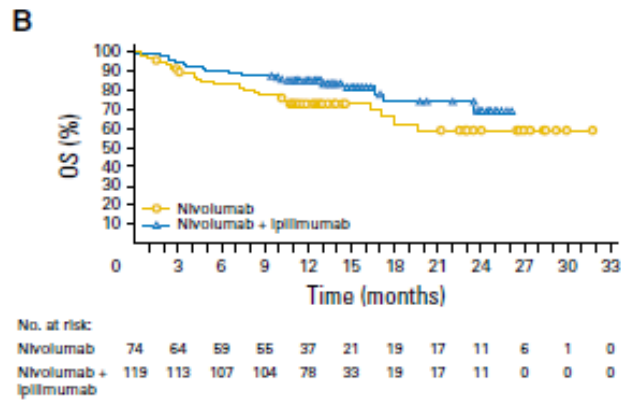
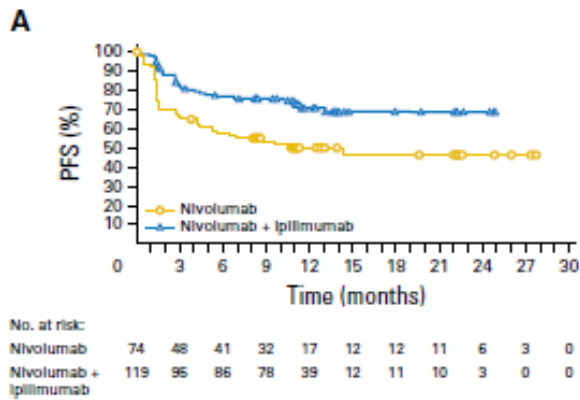
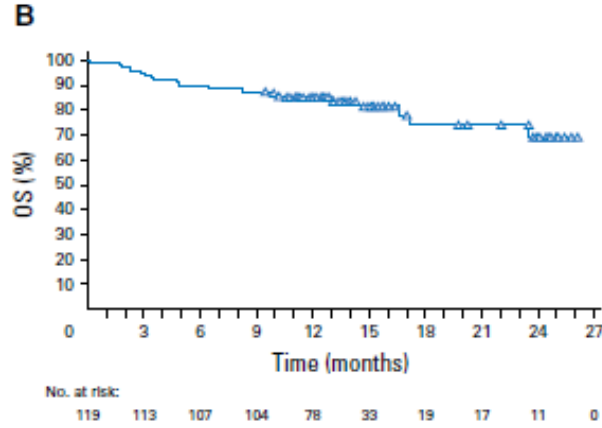
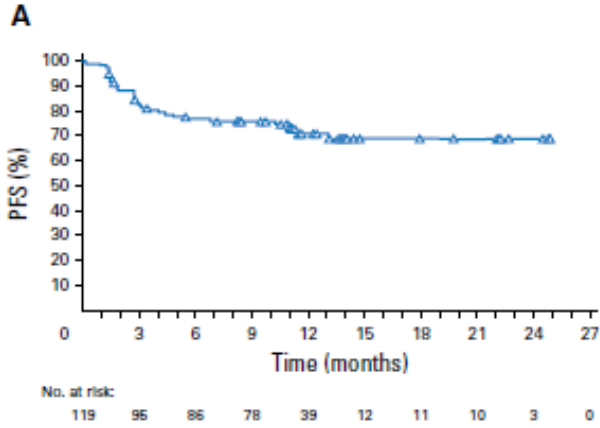
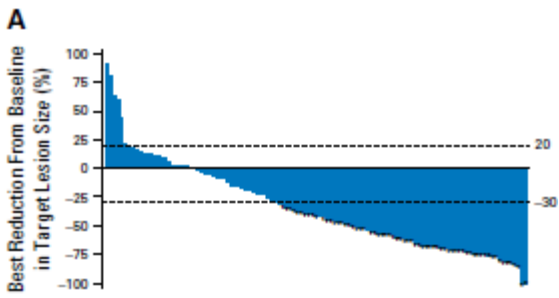
Le DT, Science, 2017

Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study

Michael J Overman, Ray McDermott, Joseph L Leach, Sara Lonardi, Heinz-Josef Lenz, Michael A Morse, Jayesh Desai, Andrew Hill, Michael Axelson, Rebecca A Moss, Monica V Goldberg, Z Alexander Cao, Jean-Marie Ledeine, Gregory A Maglinte, Scott Kopetz*, Thierry André*



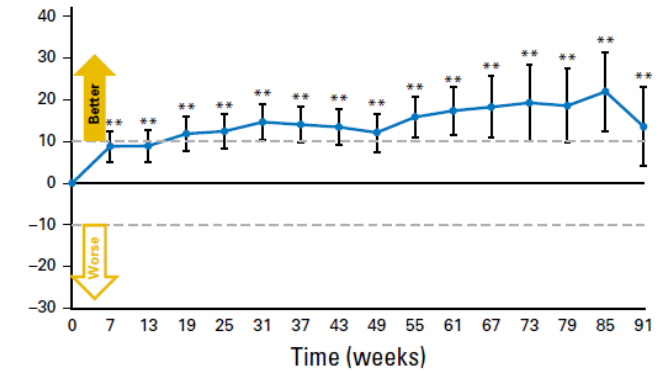
Overman MJ, Lancet Oncol 2017



Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlish, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

QOL



Overman MJ, JCO 2018

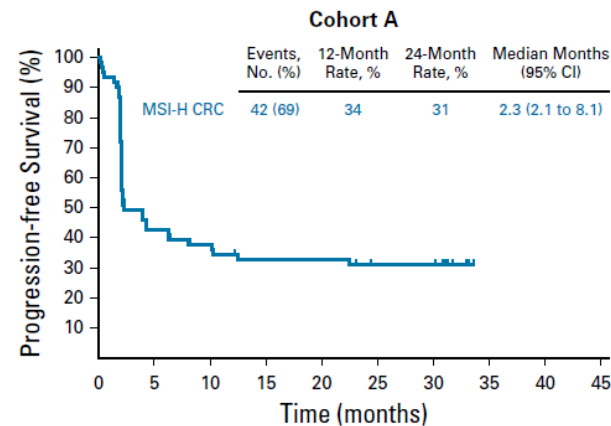
Phase II Open-Label Study of Pembrolizumab Treatment-Refractory, Microsatellite Instability–High/Mismatch Repair–Deficient Metastatic Colorectal Cancer: KEYNOTE-164

Dung T. Le, MD¹; Tae Won Kim, MD²; Eric Van Cutsem, MD, PhD³; Ravit Geva, MD⁴; Dirk Jäger, MD⁵; Hiroki Hara, MD⁶; Matthew Burge, MBChB, FRACP⁷; Bert O'Neill, MD⁸; Petr Kavan, MD, PhD⁹; Takayuki Yoshino, MD¹⁰; Rosine Guimbaud, MD, PhD¹¹; Hiroya Taniguchi, MD, PhD¹²; Elena Elez, MD, PhD¹³; Salah-Eddin Al-Batran, MD¹⁴; Patrick M. Boland, MD¹⁵; Todd Crocenzi, MD¹⁶; Chloe E. Atreya, MD, PhD¹⁷; Yi Cui, PhD¹⁸; Tong Dai, MD, PhD¹⁹; Patricia Marinello, PharmD¹⁹; Luis A. Diaz Jr, MD²⁰; and Thierry André, MD²¹



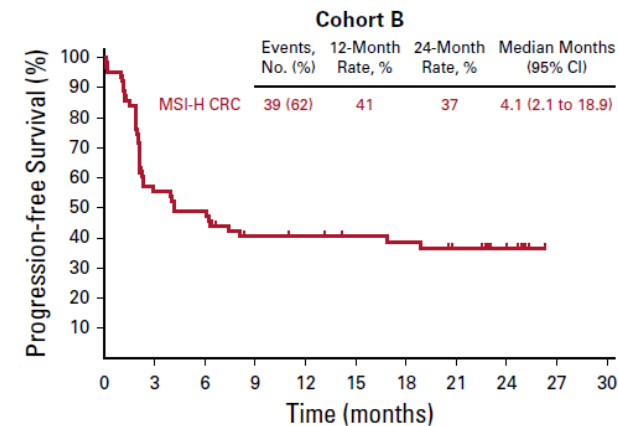
A: ≥ 2 linjer, B: ≥ 1 linje

A



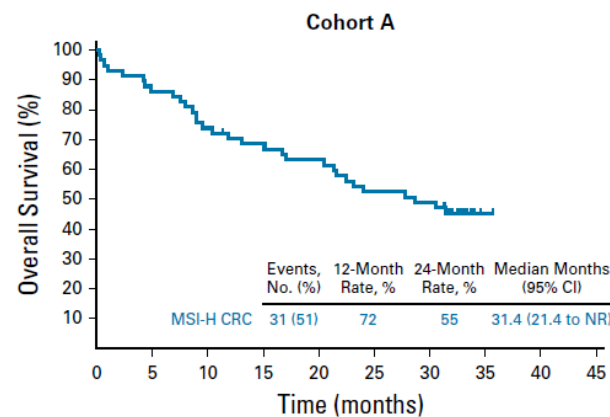
No. at risk:
MSI-H CRC 61 26 23 19 19 15 15 0 0 0

B



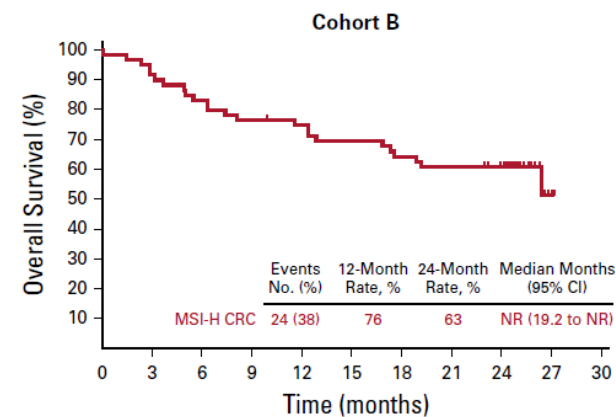
No. at risk:
MSI-H CRC 63 34 30 23 22 20 19 16 7 0 0

A



No. at risk:
MSI-H CRC 61 53 46 42 39 33 31 1 0 0

B



No. at risk:
MSI-H CRC 63 58 53 49 47 44 41 39 36 1 0

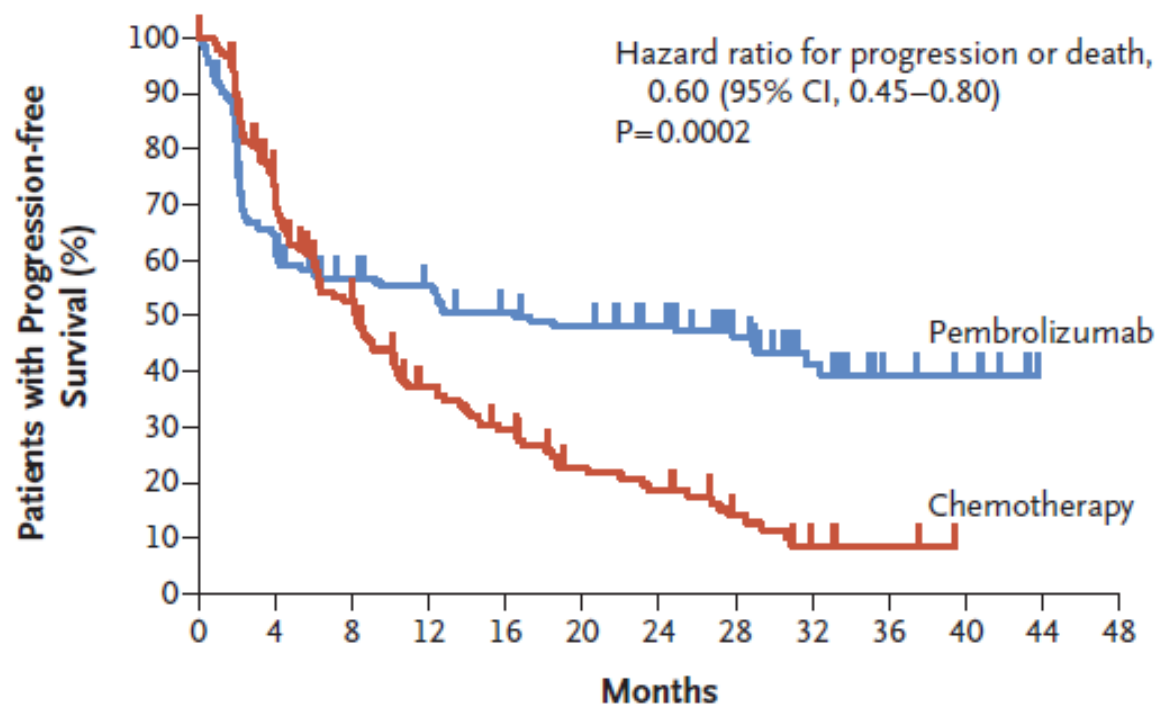
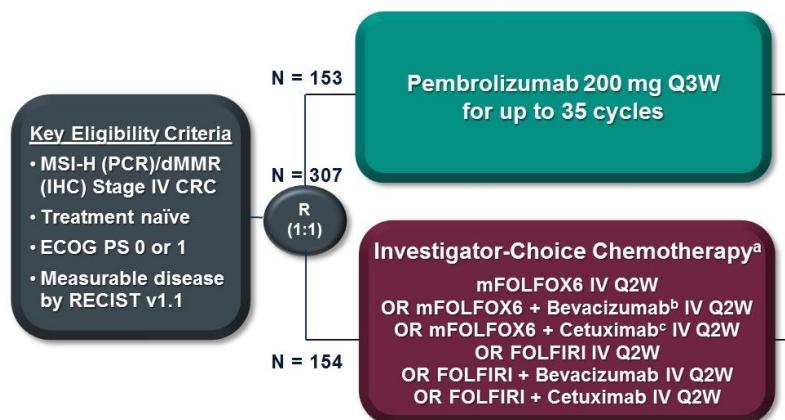
Let DT, JCO 2019



Keynote-177

Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer

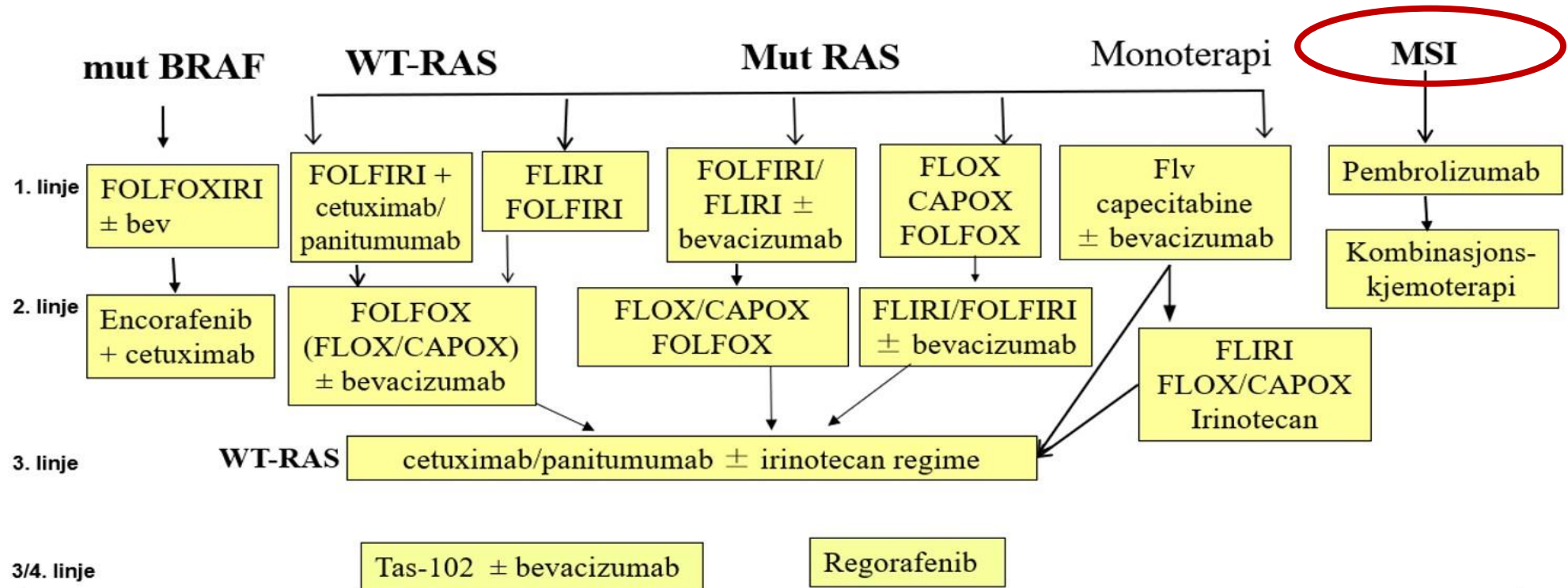
T. André, K.-K. Shiu, T.W. Kim, B.V. Jensen, L.H. Jensen, C. Punt, D. Smith, R. Garcia-Carbonero, M. Benavides, P. Gibbs, C. de la Fouchardiere, F. Rivera, E. Elez, J. Bendell, D.T. Le, T. Yoshino, E. Van Cutsem, P. Yang, M.Z.H. Farooqui, P. Marinello, and L.A. Diaz, Jr., for the KEYNOTE-177 Investigators*



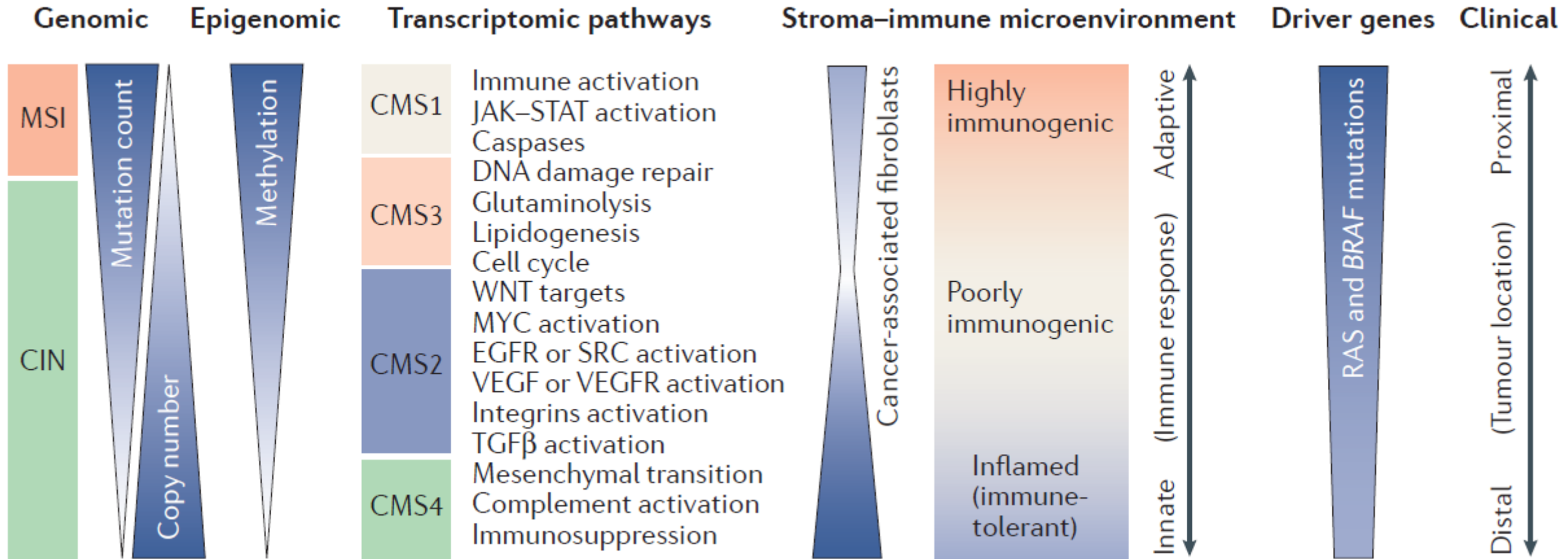
André T, NEJM 2020

Medikamentell behandling ved metastatisk colorektalcancer

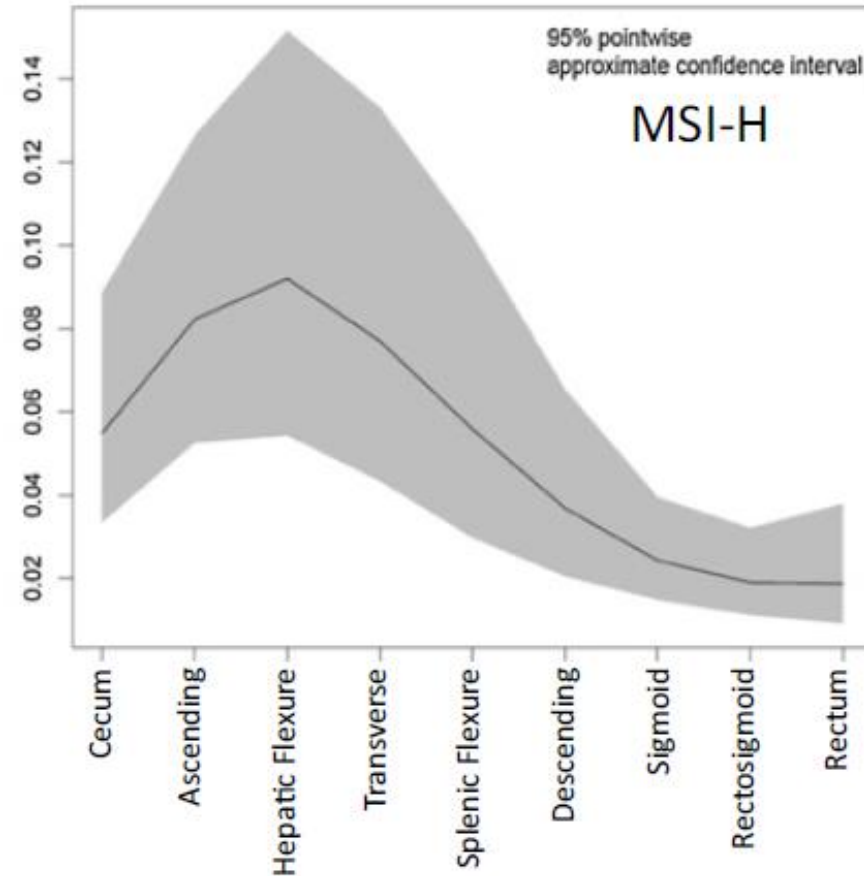
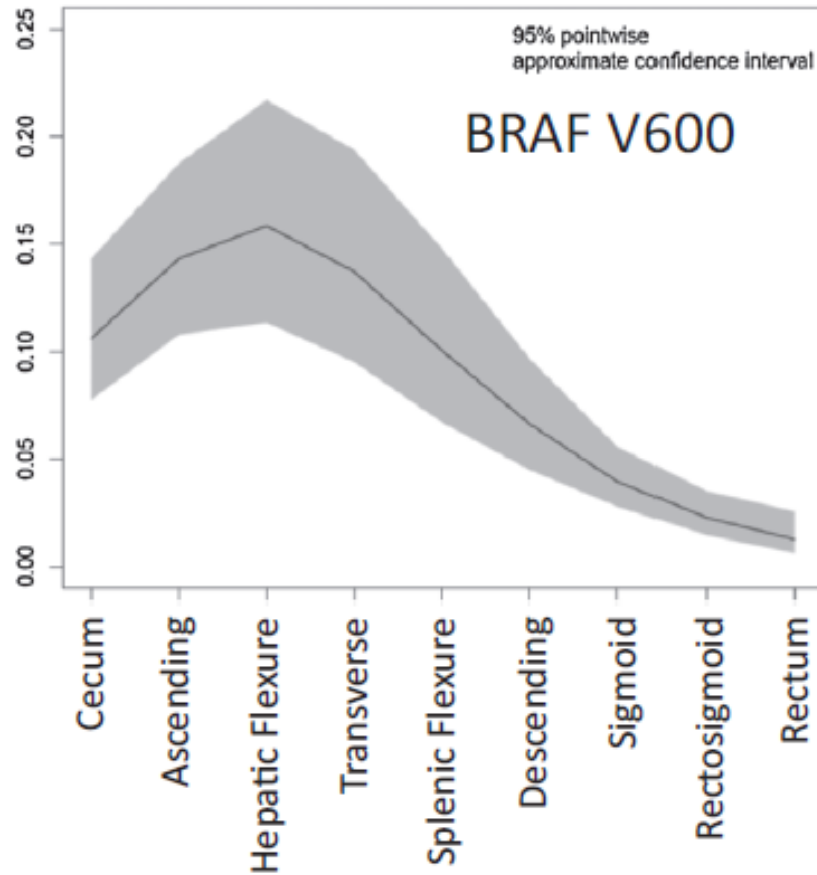
Palliativ intensjon



Biologi og «sidedness»



BRAF mut og MSI ved høyresidig coloncancer



Loree JM, Clin Cancer Res 2017

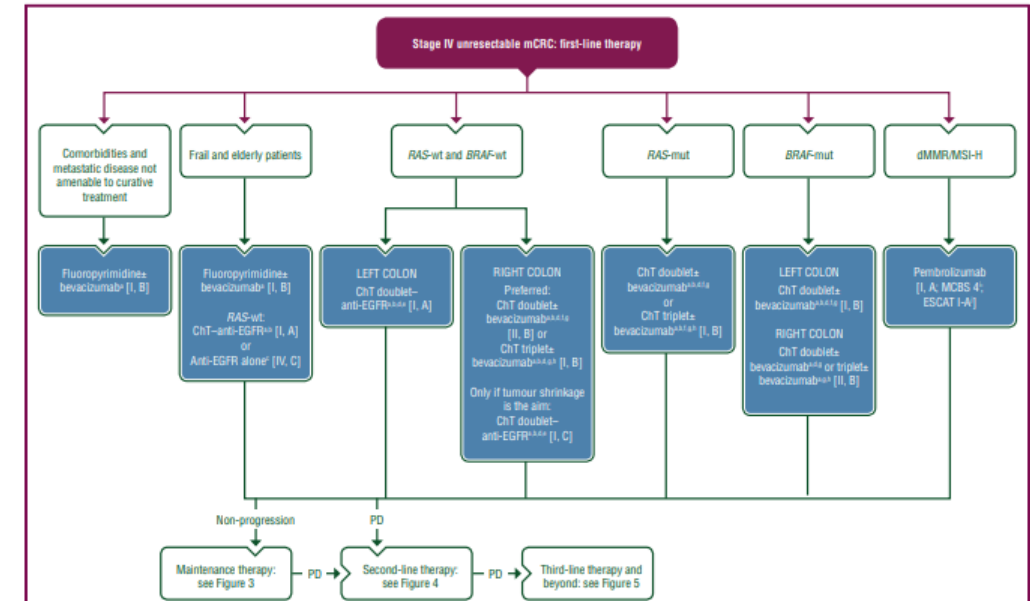
Nye ESMO

SPECIAL ARTICLE

Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up ☆

A. Cervantes^{1,2}, R. Adam³, S. Roselló^{1,2}, D. Arnold⁴, N. Normanno⁵, J. Taïeb^{6,7}, J. Seligmann⁸, T. De Baere^{9,10,11}, P. Osterlund^{12,13}, T. Yoshino¹⁴ & E. Martinelli¹⁵, on behalf of the ESMO Guidelines Committee

- Høyre- vs. venstresidig cancer
 - Venstresidig RAS/BRAF villtype og EGFR-hemmer i 1. linje
- HER-2 pos
 - Anti-HER2 medikamenter i 3. linje (ikke godkjent i Norge, men studie)



Cervantes A, Annals Oncol 2023

Takk for oppmerksomheten!



 Helsedirektoratet

Kreft i tykktarm og endetarm – handlingsprogram

Nasjonal faglig retningslinje

Først publisert: 20. juni 2017
Sist faglig oppdatert: 20. mai 2022

