Neoadjuvant behandling koloncancer stadium I-III?

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Region Syd

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PGGI-kurs 241007

REGIONALT CANCERCENTRUM SYD

Behandling

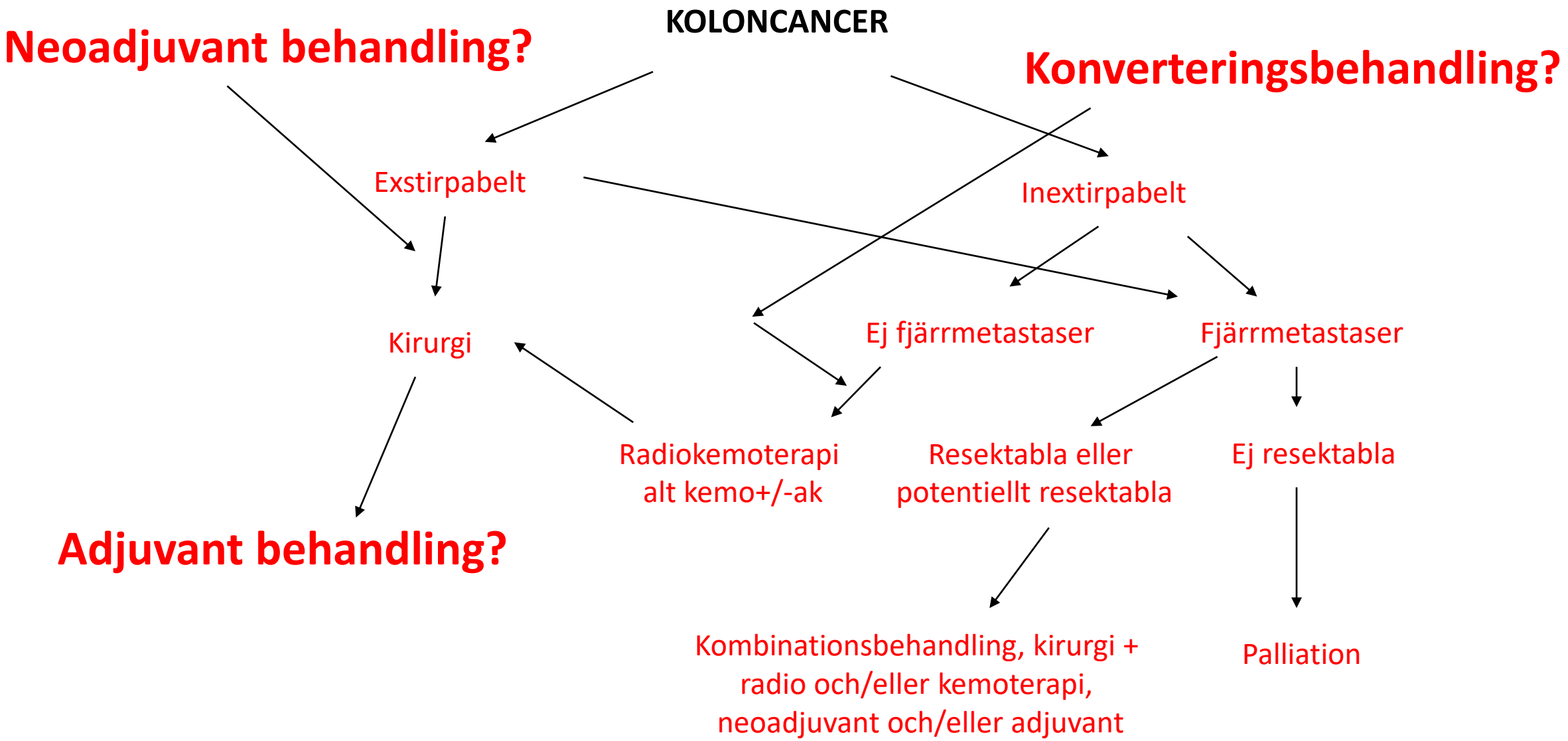
- Historiskt sett KIRURGI
- Fortfarande i princip alltid nödvändigt för bot

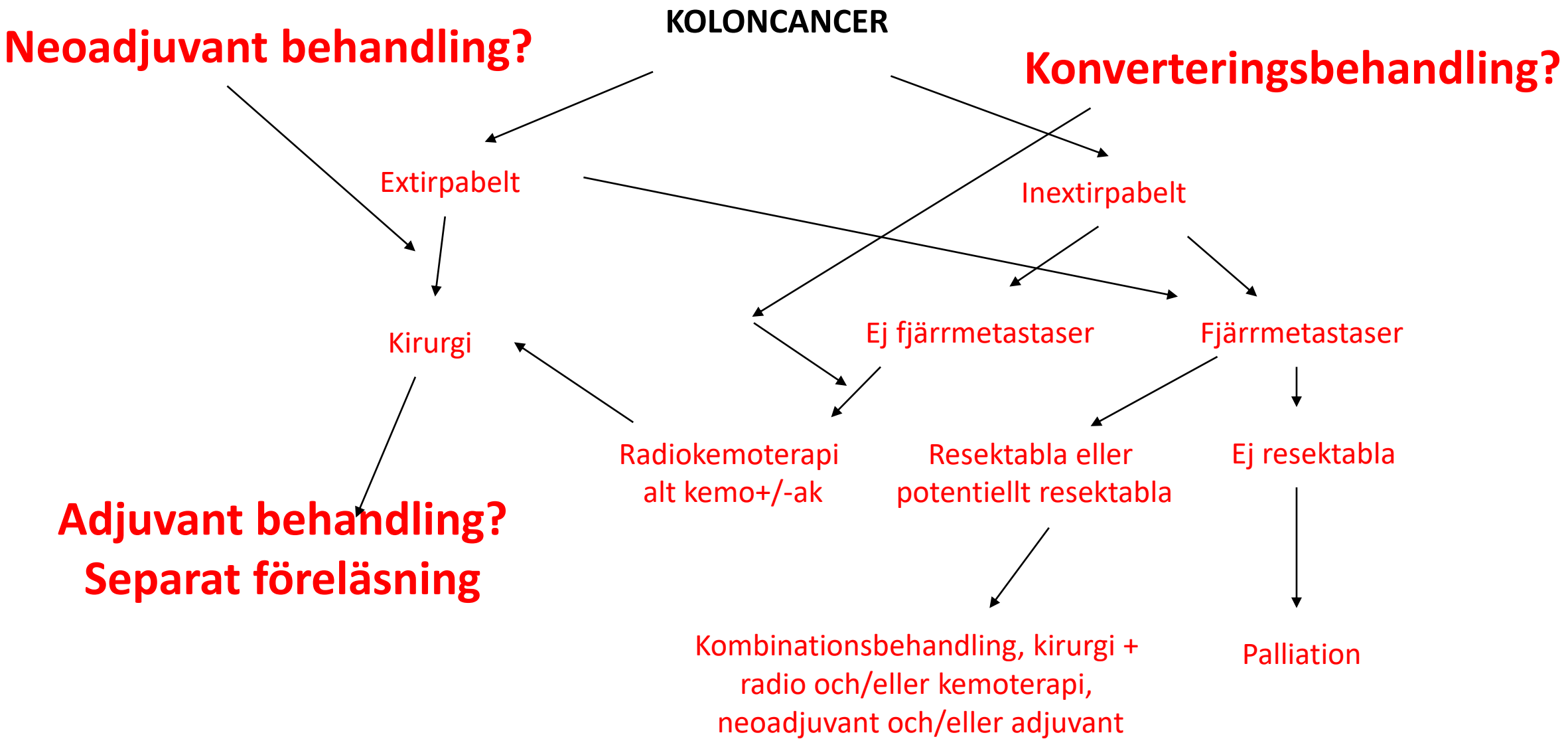
Neo- och Adjuvant behandling

- Systemisk behandling före/efter kirurgi
- Slå ut mikrometastaser
- Minska risk för återfall
- Öka chans till bot

Konverterings eller downsizing behandling

- Systemisk eller lokaliserad behandling före kirurgi
- Minska tumörvolym för att möjliggöra resektabilitet
- Förutsättning för chans till bot


KOLONCANCER
Neoadjuvant behandling?
Konverteringsbehandling?
Exstirpabelt
Inextirpabelt
Kirurgi
Ej fjärrmetastaser
Fjärrmetastaser
Radiokemoterapi
alt kemo+/-ak
Resektabla eller
potentiellt resektabla
Ej resektabla
Adjuvant behandling?
Kombinationsbehandling, kirurgi +
radio och/eller kemoterapi,
neoadjuvant och/eller adjuvant
Palliation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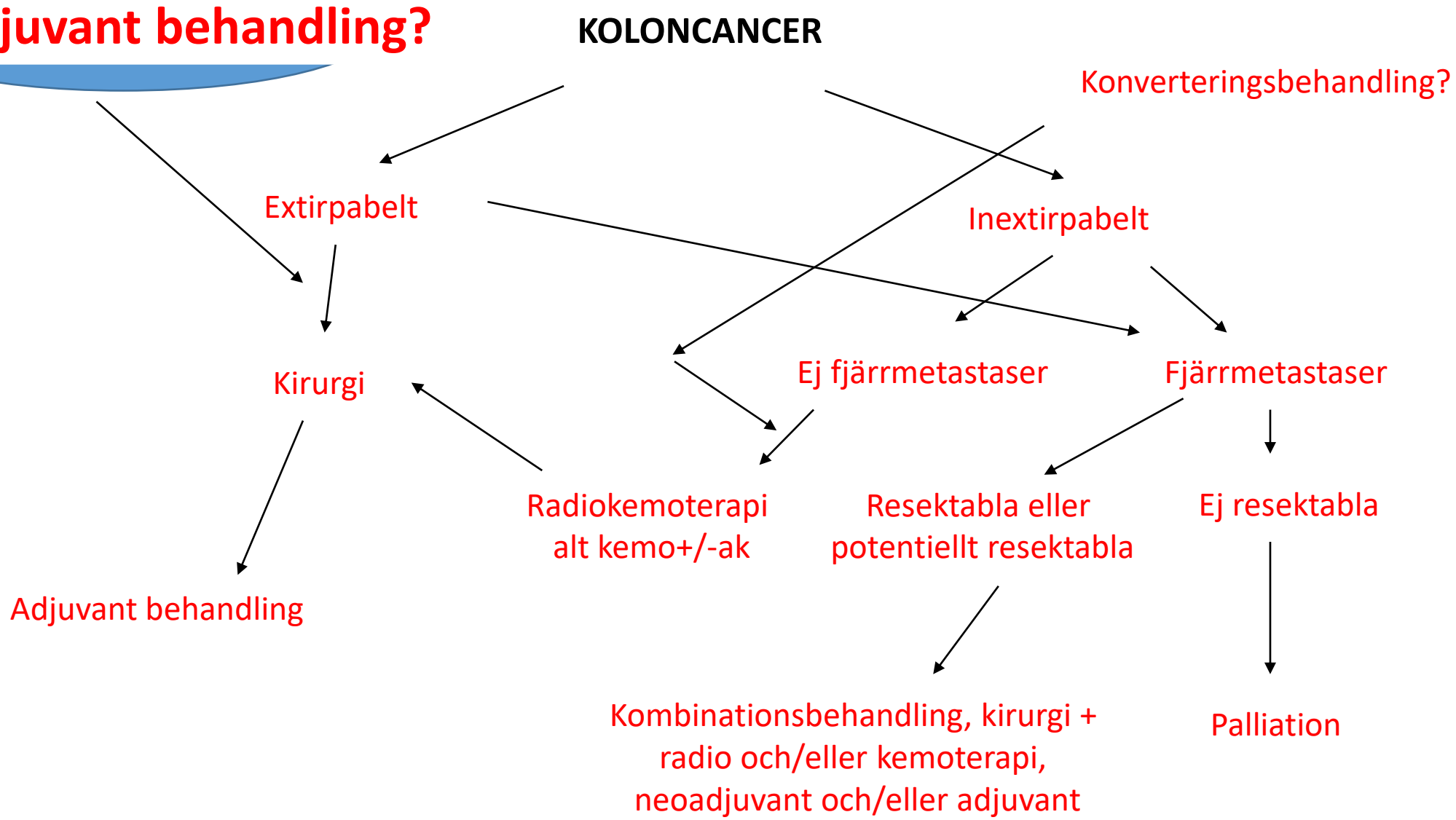
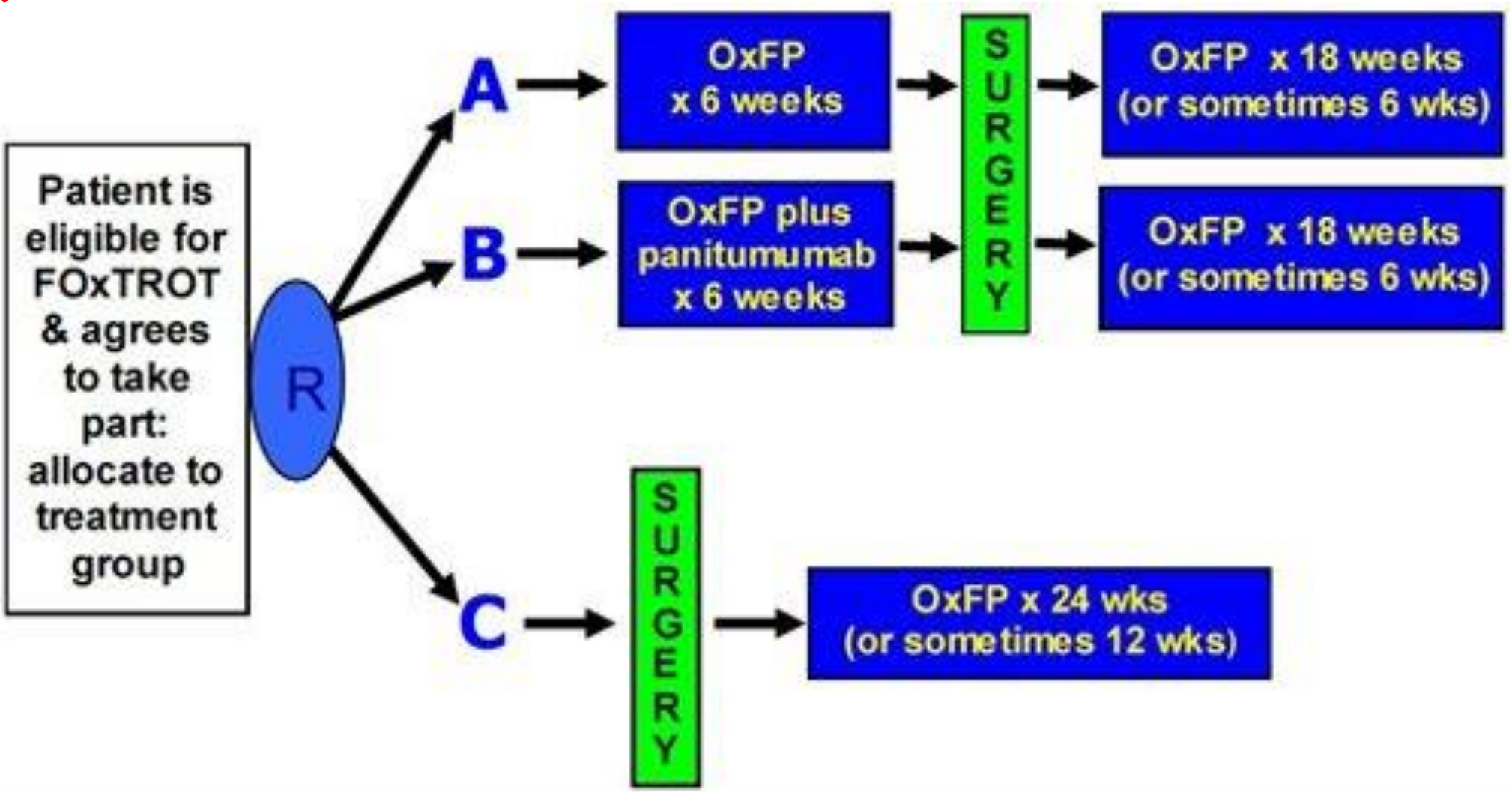
Neoadjuvant behandling?



Neoadjuvant terapi

- FOxTROT

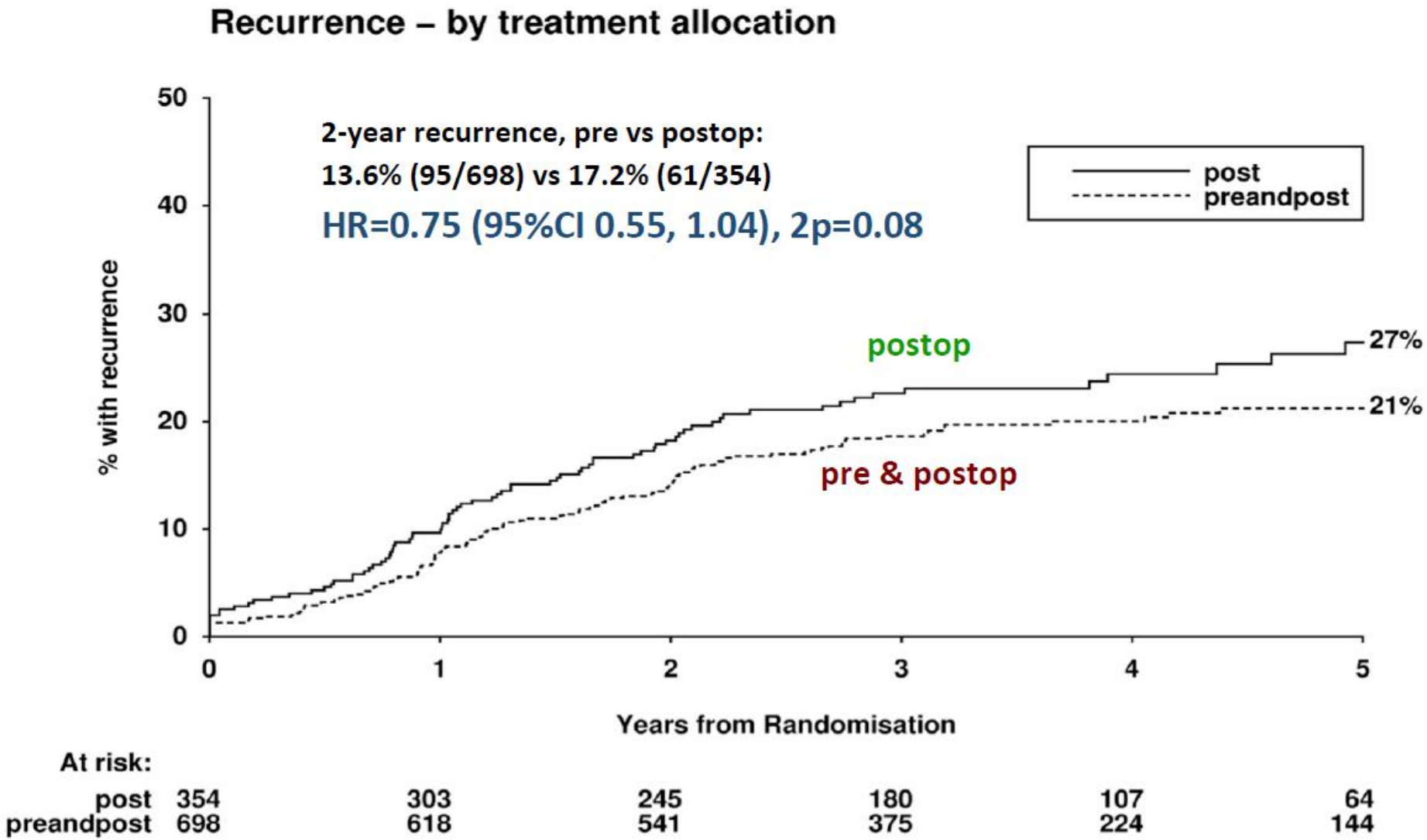
FOXTROT


Patient is eligible for FOxTROT & agrees to take part: allocate to treatment group
R
A
B
C
OxFP x 6 weeks
OxFP plus panitumumab x 6 weeks
SURGERY
OxFP x 18 weeks (or sometimes 6 wks)
OxFP x 18 weeks (or sometimes 6 wks)
SURGERY
OxFP x 24 wks (or sometimes 12 wks)

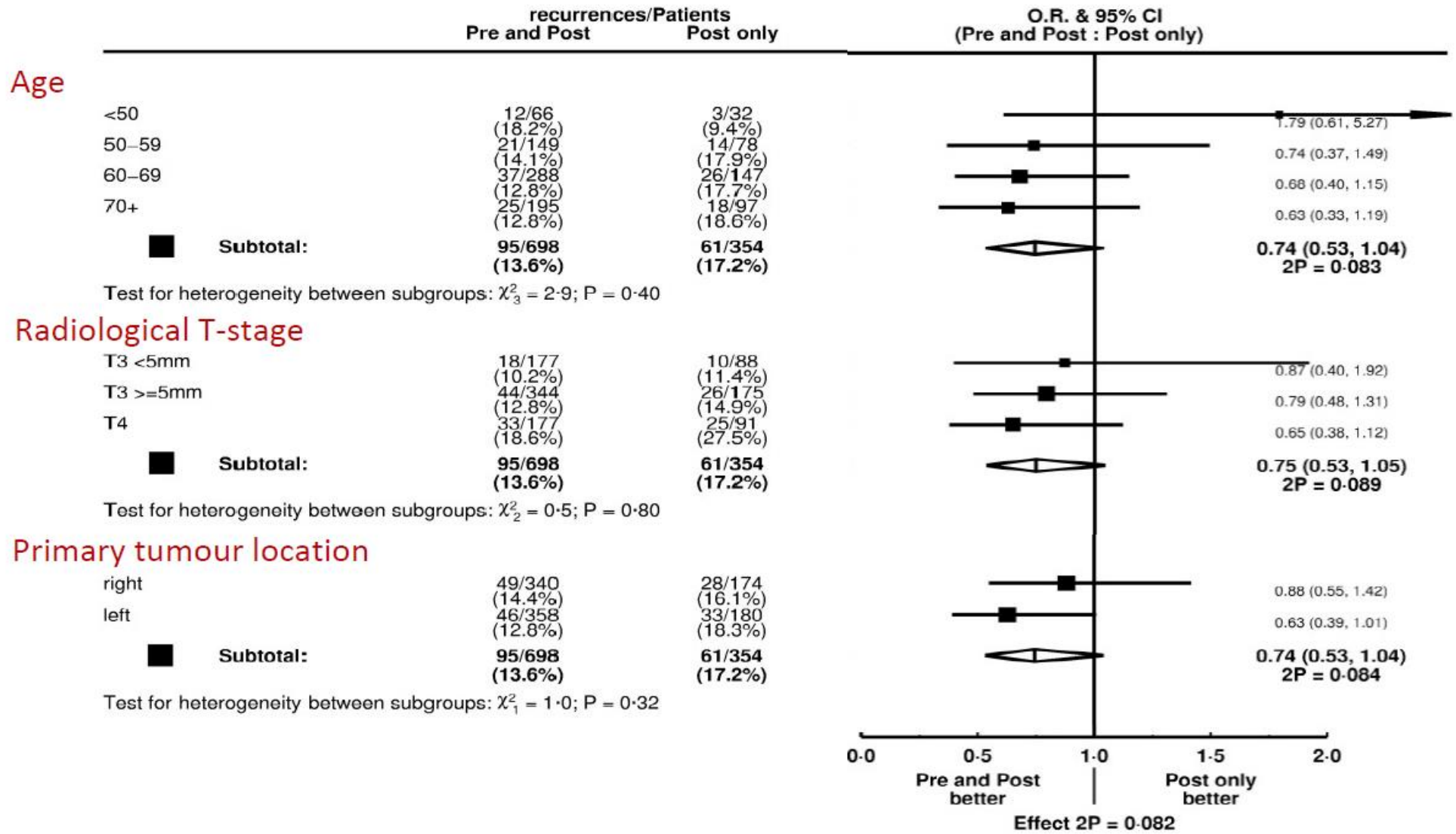
Perioperative Complications

Underwent surgery	Pre&post n=684	Post n=351	
Procedure involved a stoma	**11.7%**	**9.0%**	p=0.18
Wound infection	**8.5%**	**8.9%**	p=0.85
Bronchopneumonia	**1.8%**	**3.1%**	p=0.16
PE ± DVT	**1.6%**	**0.6%**	p=0.18
Anastomotic leak or intra-abdo abscess	**4.7%**	**7.4%**	p=0.07
complication requiring further surgery	**4.3%**	**7.1%**	p=0.05
complication prolonging hospital stay	**11.6%**	**14.3%**	p=0.21
Death within 30 days	**0.6%**	**0.6%**	p=0.98

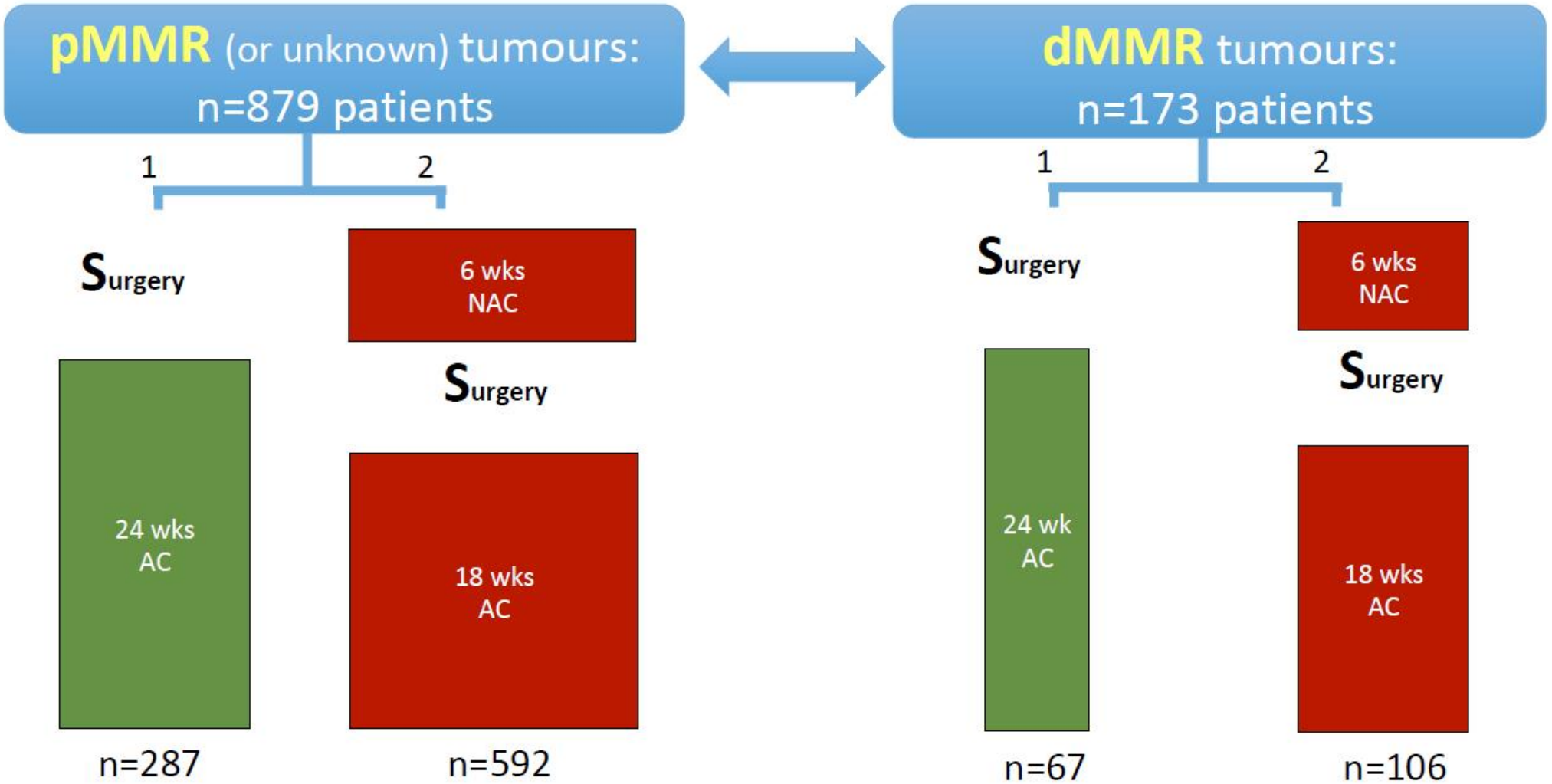
Primary outcome: 2-year efficacy



Primary outcome by baseline factors:



Key subgroup analysis: MMR



Subgroup analysis conclusion:

- dMMR tumours: no regression in most (but some pCRs); no benefit seen at 2 years.
- pMMR tumours: borderline significant impact on 2-year endoint.

FOxTROT – main conclusions

FOxTROT did not reach target significance for its primary endpoint

But: moving 6 weeks of chemotherapy ahead of surgery,
without major addition to the cost or patient burden...

- was safe, with less major postoperative morbidity
- significantly downstaged tumours and reduced incomplete resections
- trended towards reduced 2-year relapse (HR=0.75; p=0.08) and long-term cancer-specific survival (HR=0.71; p=0.07)

...can be considered a new therapeutic option
for locally advanced operable colon cancer

FOxTROT – additional findings

- No benefit seen in dMMR cancers
- Inevitably some low-risk patients will receive 6 weeks chemo
  - 24% of our control arm patients had “low-risk” disease
- No benefit from adding panitumumab in unselected KRAS-wt
  - full analysis of enriched biomarker population ongoing - results soon
- Opportunity to assess tumour biology and adapt postop therapy

OPTICAL

- Redovisades vid ASCO 2022, kinesisk studie, inkluderat 744 patienter
- Jämför neoadjuvant kemoterapi, FOLFOX/CAPOX i 3 månader, med standardbehandlingen operation direkt, denna gång på T3-4 tumörer.
- Igen sågs en tydlig effekt avseende downsizing histopatolgiskt, däremot ingen ökad sjukdomsfri överlevnad

NeoCol

- Redovisades ASCO 2023, dansk studie, inkluderat 250 patienter
- Jämfört standardbehandling, dvs operation, mot 3 cykler Capox eller fyra cykler Folfox, vid T3-4, N0-2 tumörer
- Adjuvant behandling gavs utifrån PAD kriterier och lokala guidelines.
- Studien visade varken OS eller DFS vinst
- Däremot gavs totalt mindre kemoterapi i studiearmen och analogt sågs downsizing av tumörerna.

Hur göra med dMMR

- Vanligare i tidigare stadier
- Cirka 20% av stadium II
- Cirka 15% av stadium III
- Cirka 5% av stadium IV

- Vanligare ju mer proximal tumör
- Koppling till Lynch syndrom (cirka 1/3 av alla med dMMR/MSI-H har Lynch)

PARIS 2022 ESMO congress

Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: the NICHE-2 study

M. Chalabi[1], Y. Verschoor, J. Van den Berg, K. Sikorska, G. Beets, A. Van Lent, C. Grootscholten, A. Aalbers, N. Buller, H. Marsman, E. Hendriks, P. Burger, T. Aukema, S. Oosterling, R. Beets-Tan, T.N. Schumacher, M.E. Van Leerdam, E.E. Voest, J.B. Haanen

[1]Dept. of Gastrointestinal Oncology, Netherlands Cancer Institute
Amsterdam, the Netherlands

September 11th 2022

Mismatch Repair Deficient Colon Cancer

Approximately 10-15% of colon cancers are mismatch repair deficient (dMMR)

1/3 of dMMR colorectal cancers are associated with Lynch Syndrome

Recurrence rates of 20-40% for **stage III dMMR** tumors **despite** standard-of-care chemotherapy

- High-risk disease (T4 or N2) is highly associated with poor survival

Eikenboom et. al, Clin Gastroenterol Hepatol 2022; Cohen et al, JCO 2021; Andre et. al JCO 2015; Sinicrope et. al, JCO 2013

Neoadjuvant treatment of dMMR colon cancers

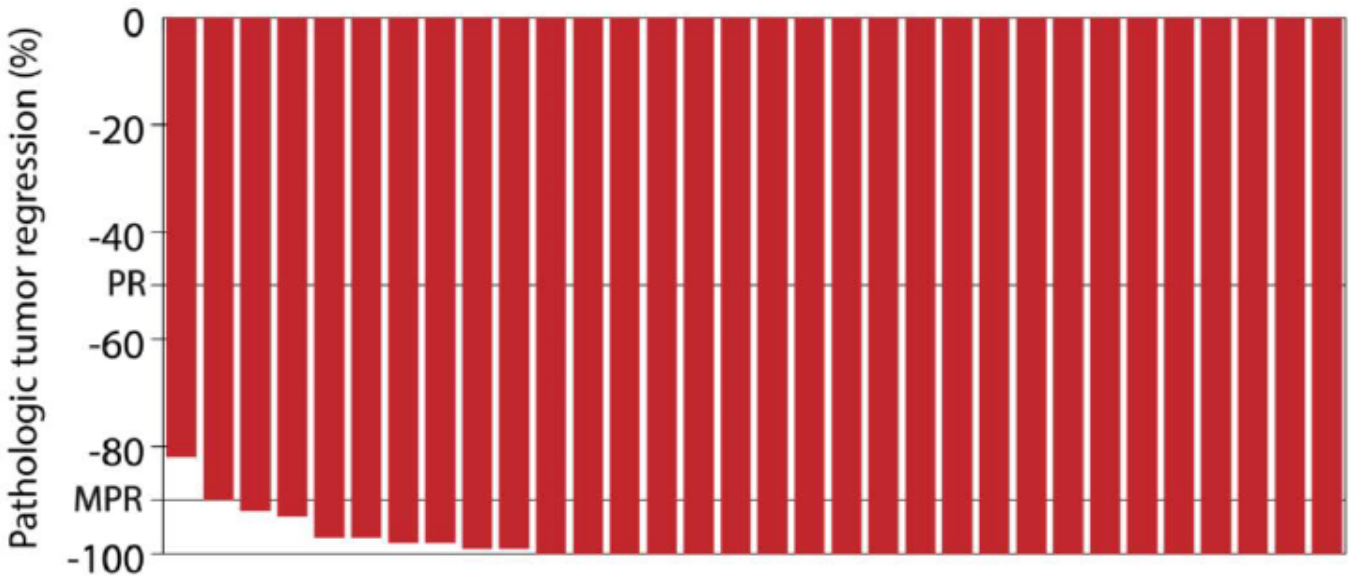
Previous data from NICHE-1 (*n*=32) show that immune checkpoint blockade is highly effective in non-metastatic dMMR colon cancers

- 100% pathologic responses and 60% pathologic complete responses

ARTICLES
https://doi.org/10.1038/s41591-020-0805-8
nature medicine
Check for updates

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

Myriam Chalabi[1,2,3], Lorenzo F. Fanchi[2,4,17], Krijn K. Dijkstra[2,4,17], José G. Van den Berg[5,17], Arend G. Aalbers[6], Karolina Sikorska[7], Marta Lopez-Yurda[7,8], Cecile Grootscholten[1], Geerard L. Beets[6,9], Petur Snaebjornsson[5], Monique Maas[10], Marjolijn Mertz[11], Vivien Veninga[2,4], Gergana Bounova[4,12], Annegien Broeks[13], Regina G. Beets-Tan[9,10], Thomas R. de Wijkerslooth[1], Anja U. van Lent[14], Hendrik A. Marsman[15], Elvira Nuijten[7], Niels F. Kok[6], Maria Kuiper[1], Wieke H. Verbeek[1], Marleen Kok[3,16], Monique E. Van Leerdam[1], Ton N. Schumacher[2,4], Emile E. Voest[1,2,4,17] and John B. Haanen[2,3,17]



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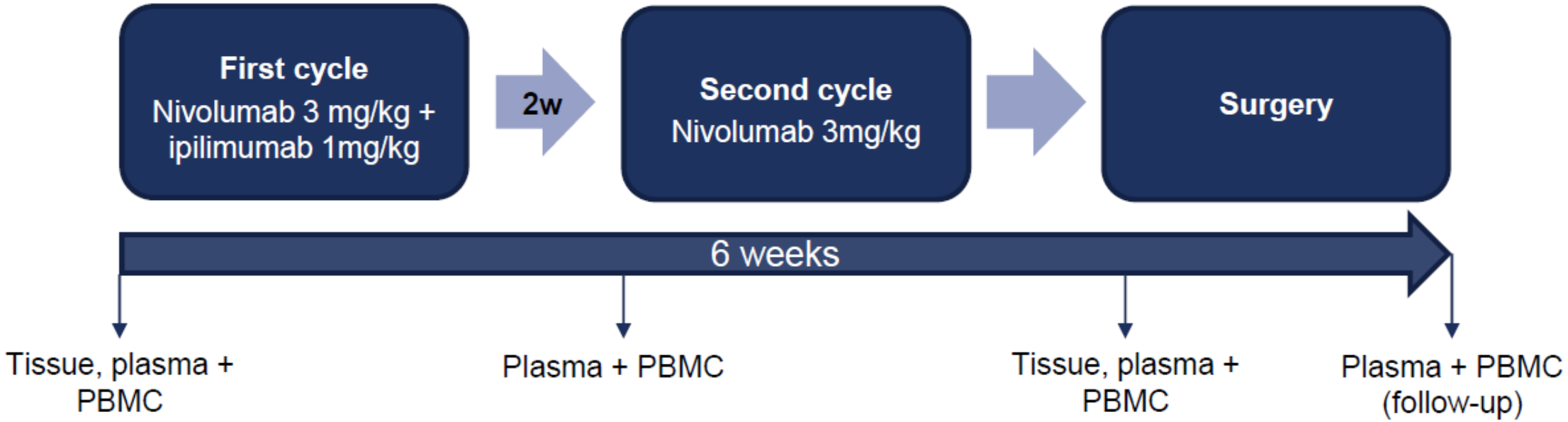
Myriam Chalabi, MD PhD

Chalabi et. al, Nat Med 2020; Verschoor et. al, ASCO 2022

NICHE-2 study design

- Investigator-initiated, non-randomized multicenter* study



*6 participating hospitals in the Netherlands
PBMC = peripheral blood mononuclear cells

Study Objectives

Primary Objectives

- Safety and feasibility
- 3-year disease-free survival (DFS)

Secondary Objectives

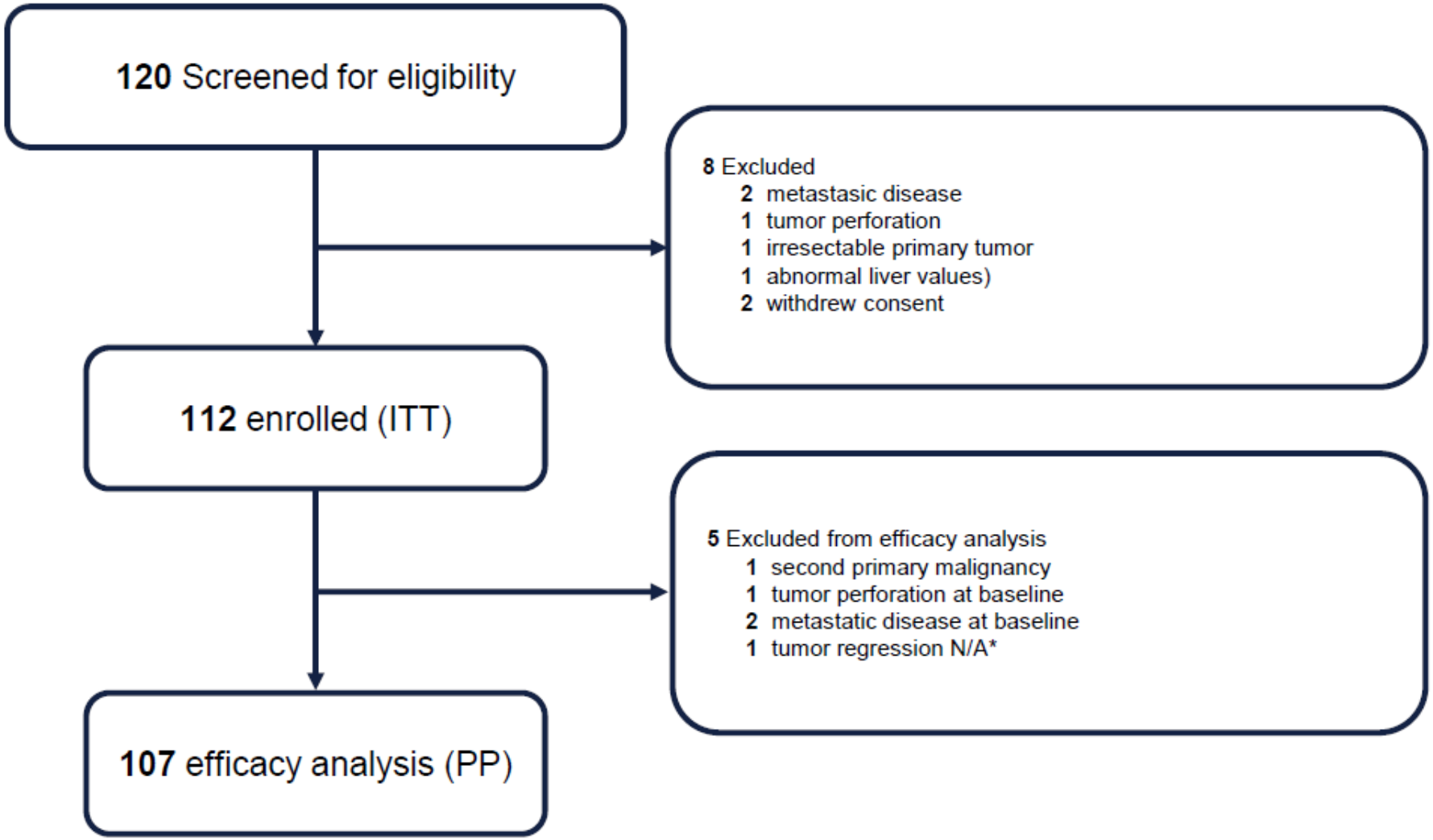
- Major and complete pathologic response rate in post-treatment surgical specimen
- Circulating tumor DNA dynamics
- Translational research (DNA, RNA sequencing, single-cell sequencing, multiplex imaging)

Main Inclusion Criteria

- Non-metastatic, previously untreated dMMR colon adenocarcinoma
- cT3 and/or N+ disease based on radiologic staging*
- No clinical signs of obstruction
- No clinical symptoms or radiologic suspicion of perforation
- No active autoimmune disease or other medical conditions requiring systemic steroid or immunosuppressive medications

*Protocol revision October 2020 added a primary endpoint of 3-year DFS and a new cohort of 70 patients with at least T3 and/or N+ tumors
Current data combine *n*=30 from original cohort with new dMMR cohort

Patient enrollment



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Database cut-off date: 23 August 2022. Patients were included from July 2017 until June 2022. All patients are included in safety analysis (intention to treat (ITT) population).

*Surgical delay of 6 months, hampering assessment of tumor regression.

Results - Surgery

- All patients underwent surgery, with 100% R0 resections
- Median time from first dose (nivolumab + ipilimumab) to surgery = 5.4 weeks
- No new safety signals

98% of patients underwent timely surgery, meeting the safety primary endpoint

Surgery-Related Adverse Events (*n*=112)	*n* (%)
Any	24 (21)
Grade ≥ 3	15 (13)
Anastomotic leakage or wound infections	6 (5)

Pathologic Response Definitions

Pathologic response: 50% or less residual viable tumor (RVT)

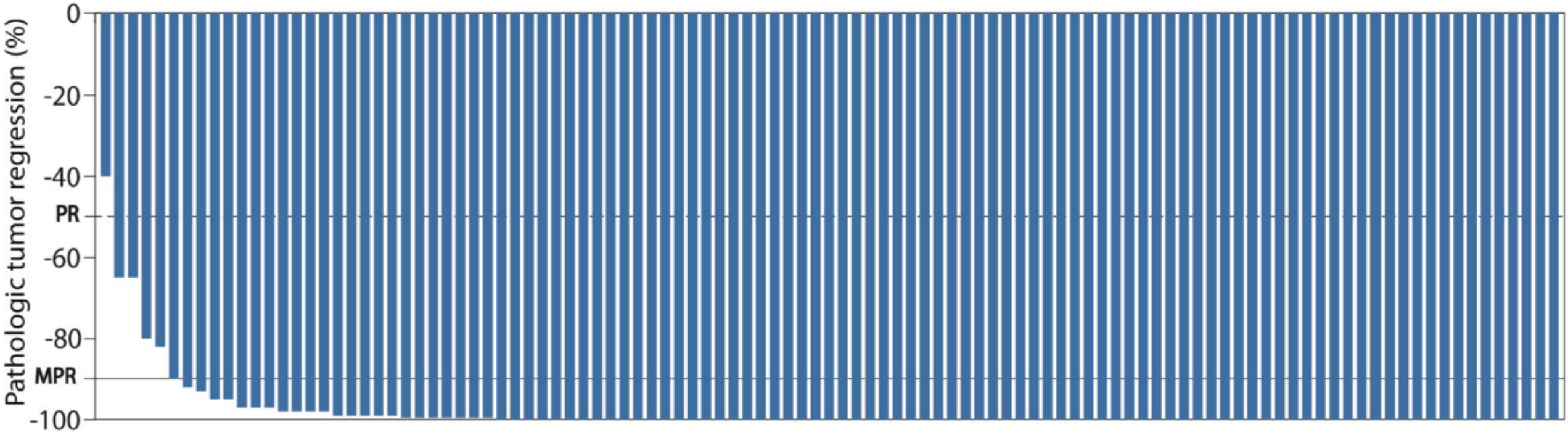
Major pathologic response (MPR): 10% or less RVT

- Including tumors with pCR in the primary tumor, yet residual viable tumor in the lymph nodes

Pathologic complete response (pCR): 0% RVT in both the primary tumor bed **and** lymph nodes

Myriam Chalabi, MD PhD

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



Myriam Chalabi, MD PhD

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

Pathologic response (RVT)		Patients *n*= 107
Yes	**(≤ 50%)**	**106 (99%)**
Major	(≤10%)	**102 (95%)**
Complete	(0%)	**72 (67%)**
Partial	(10% - 50%)	4 (4%)
No	**(≥50%)**	**1 (1%)**

RVT = residual viable tumor

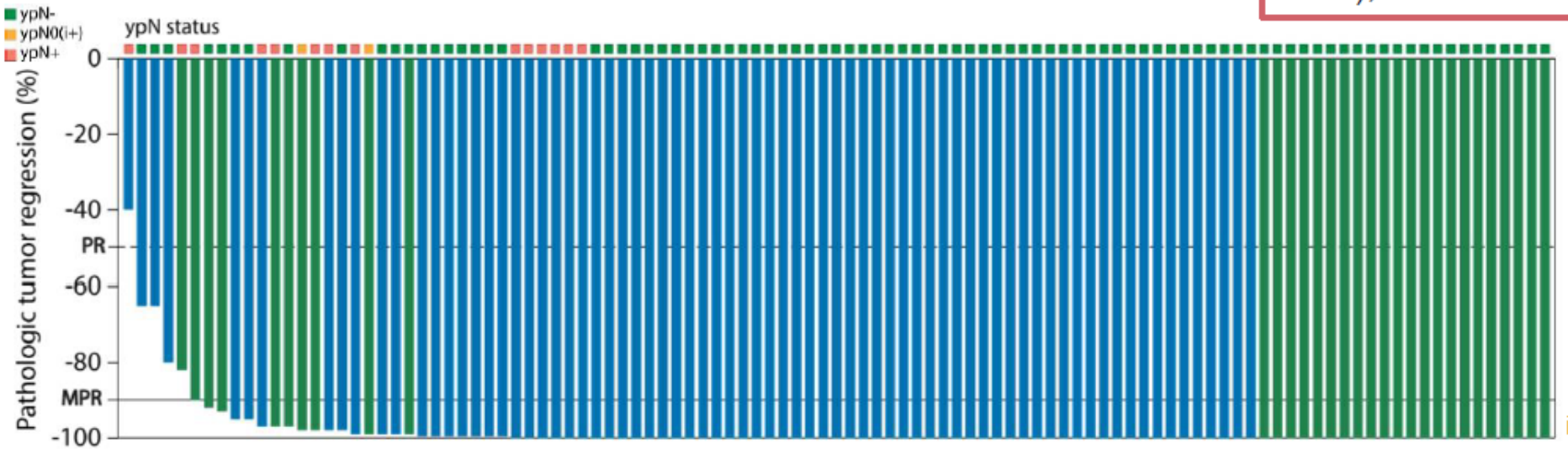
Adjuvant chemotherapy (CTx)

14 patients with ypN+ disease
- 3 patients received adjuvant CTx*
- 5 patients >70 years
- 6 patients refused

* 1 non-responder, 1 partial responder and 1 MPR

Disease recurrence

With a median follow-up of 13.1 months (1.4 - 57.4), there have been no disease recurrences



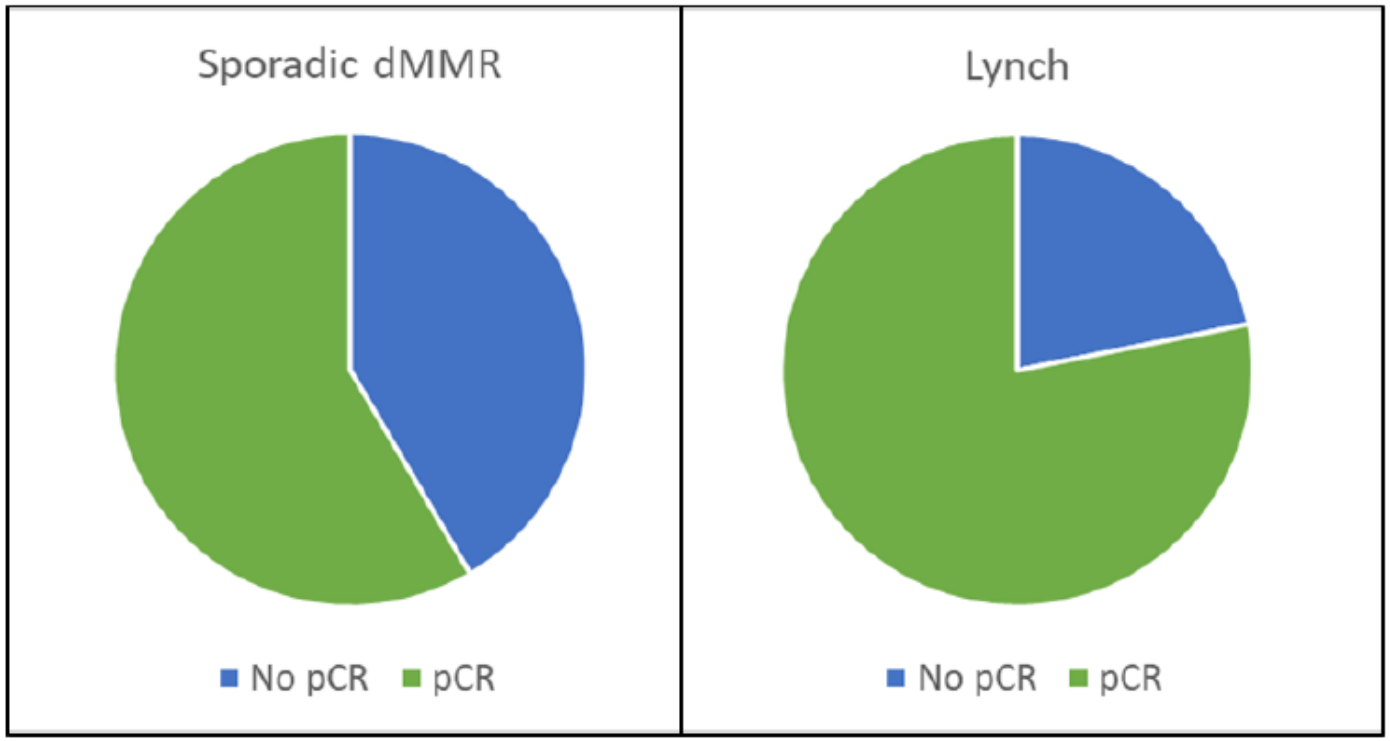
Green bars = NICHE-1 cohort
Blue bars = NICHE-2 cohort

ypN- = tumor-free lymph nodes; ypN+ = lymph nodes with tumor, including micrometastases; ypN(i+) = lymph nodes with isolated tumor cells

pCR rate according in Lynch *vs* sporadic tumors

	No pCR	pCR	
Sporadic tumor *n* = 65	27 (42%)	38 (58%)	**p = 0.056**
Lynch Syndrome *n* = 32	7 (22%)	25 (78%)	

N totals 97 patients in the per protocol population for whom Lynch status was available at data cut-off



Conclusions

- With only 4 weeks of treatment, unprecedented major pathologic responses in 95% of patients with dMMR colon cancer, including 67% pathologic complete responses
- Treatment is well-tolerated with only 4% grade 3-4 immune-related adverse events
- No disease recurrences to date: 3-year disease-free survival data expected in 2023

Future Directions

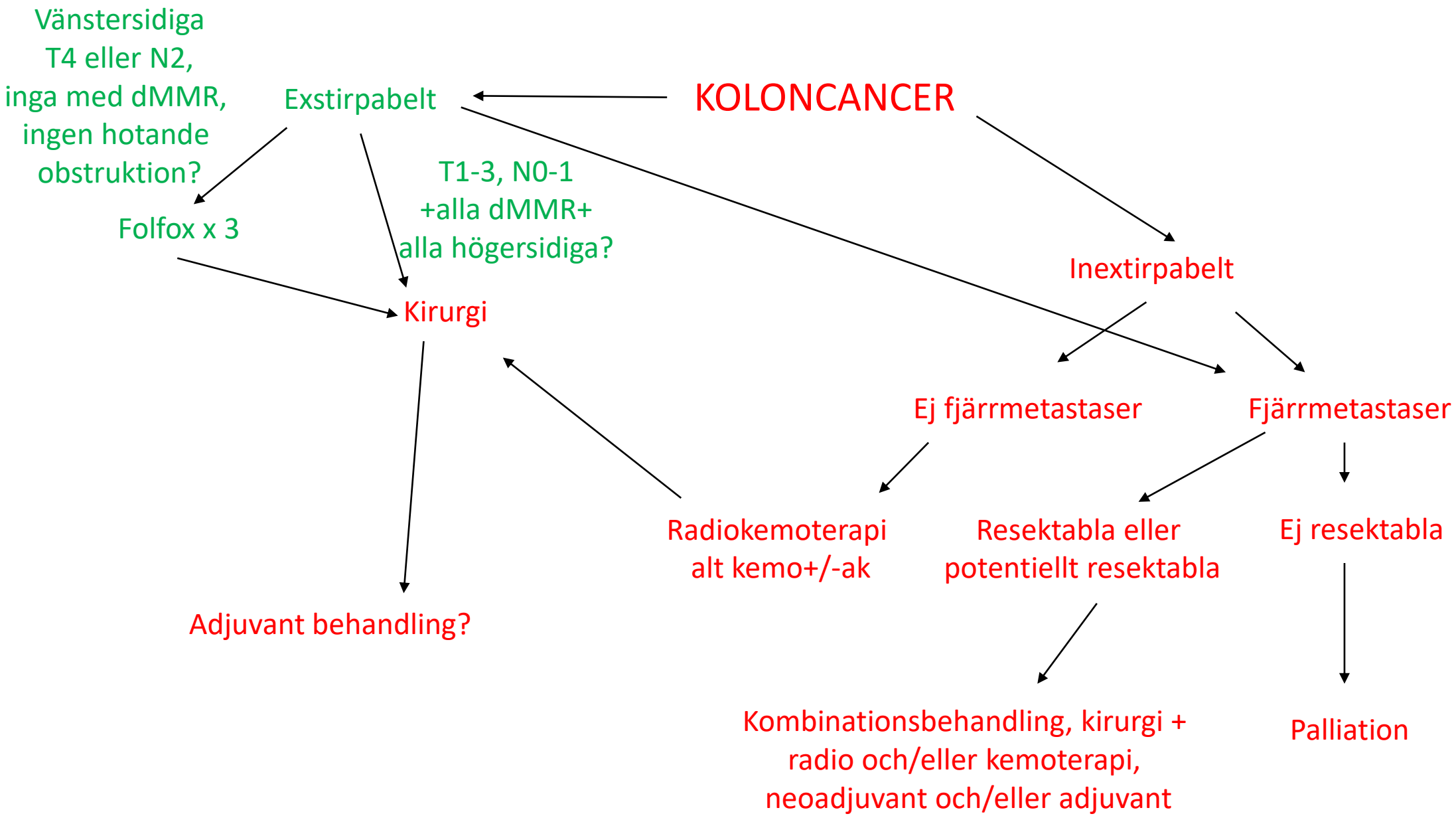
- Organ-sparing approaches in dMMR colon cancers to be considered in future studies
- Circulating tumor DNA dynamics and novel imaging techniques must be explored and may aid in organ preservation
- **Neoadjuvant immunotherapy has the potential to become standard of care for patients with dMMR colon cancer**

AZUR 2

- A Phase 3, Open-Label, Randomized Study of Perioperative Dostarlimab Monotherapy Versus Standard of Care in Participants With Untreated T4N0 or Stage III dMMR/MSI-H Resectable Colon Cancer

- Planeras randomisering, 2:1, av 711 patienter

- Flera centra i Sverige är med


Vänstersidiga
T4 eller N2,
inga med dMMR,
ingen hotande
obstruktion?
Exstirpabelt
KOLONCANCER
T1-3, N0-1
+alla dMMR+
alla högersidiga?
Folfox x 3
Inextirpabelt
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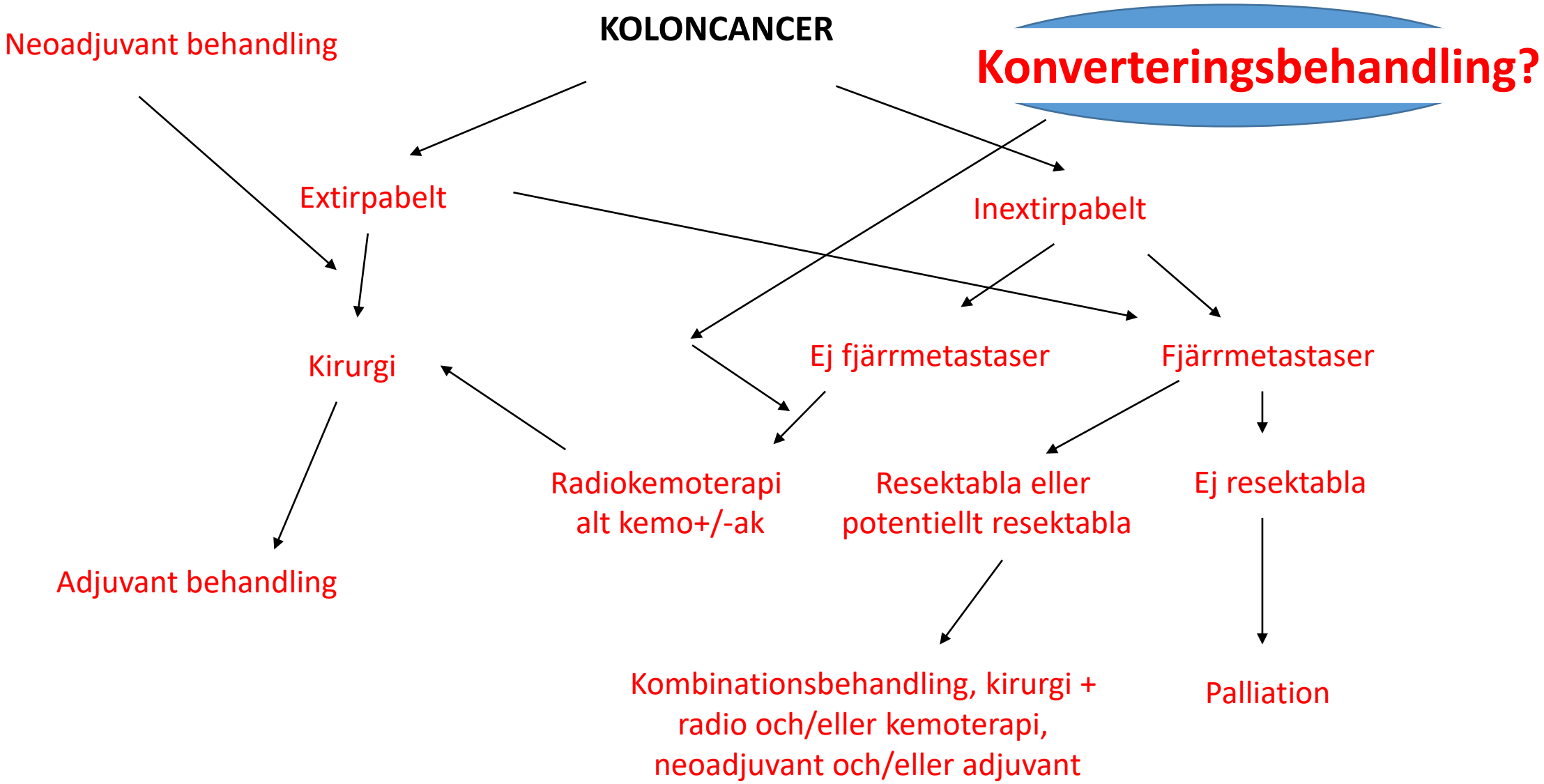
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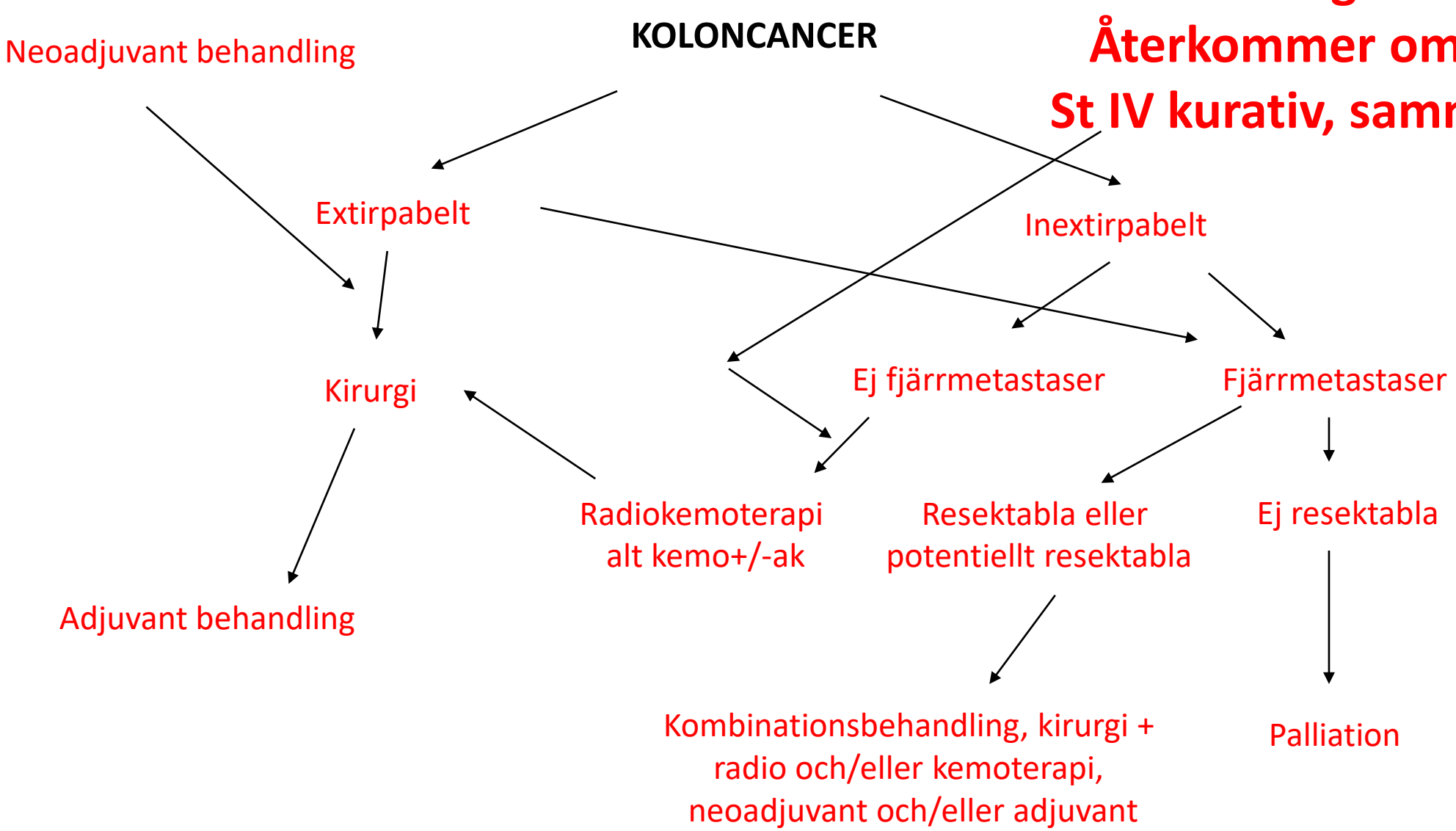
Konverteringsbehandling?
Återkommer om det vid
St IV kurativ, samma princip



Preparatval utifrån situation

- Adjuvant och neoadjuvant behandling
  - Vi är ute efter mikroskopisk spridning, inte eg krympning
    - 5-FU analog (tex Fluorouracil eller Capecitabin) ingår alltid
    - Oxaliplain enda tillägg som bevisat förbättrar

- Konverteringsbehandling
  - Vi är i första hand ute efter krympning
    - Dubbel- eller trippelbehandling med 5-FU analog kombinerat med oxaliplatin och/eller irinotekan
    - EGFRi om RAS/RAF wt
    - Strålbehandling kan i vissa fall ingå

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Sammanfattning

- Viktigt att skilja på pMMR/MSS vs dMMR/MSI-H

- Vid pMMR, operabelt
  - Vänstersidiga, WHO PS 0-1, ingen obstruktivitet, T4 eller N2, överväg neoadjuvant kemo (FOLFOX/CapOx i 6 veckor)
  - Övriga op direkt

- Vid dMMR, operabelt
  - Op direkt
  - OBS AZUR2

- Vid pMMR, konvertering
  - Maximal krympande behandling, dubbel/trippel kemo, ev med ak tillägg (RAS/RAF status)

- Vid dMMR, konvertering
  - Svårt, logiskt med immunterapi

Tack för er uppmärksamhet