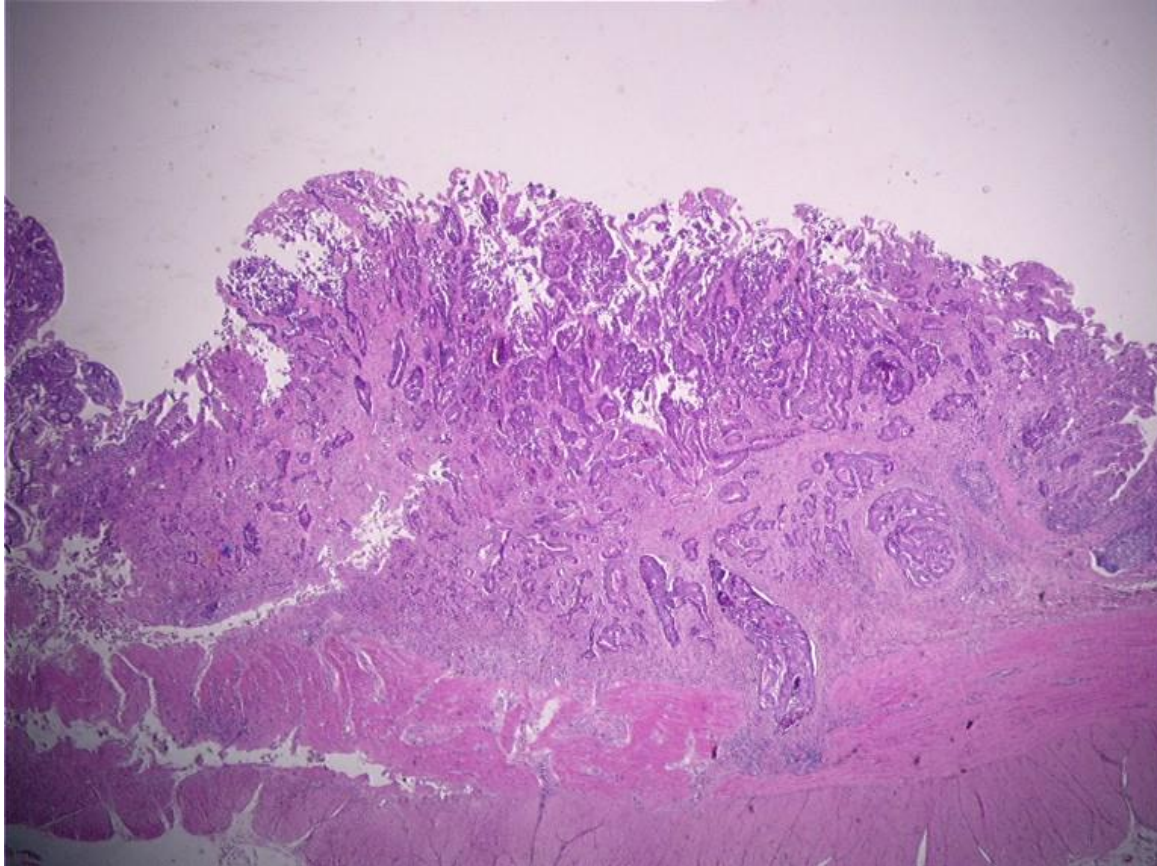# How to improve the diagnosis of stage III colorectal cancer

Han van Krieken,
Nijmegen, the Netherlands
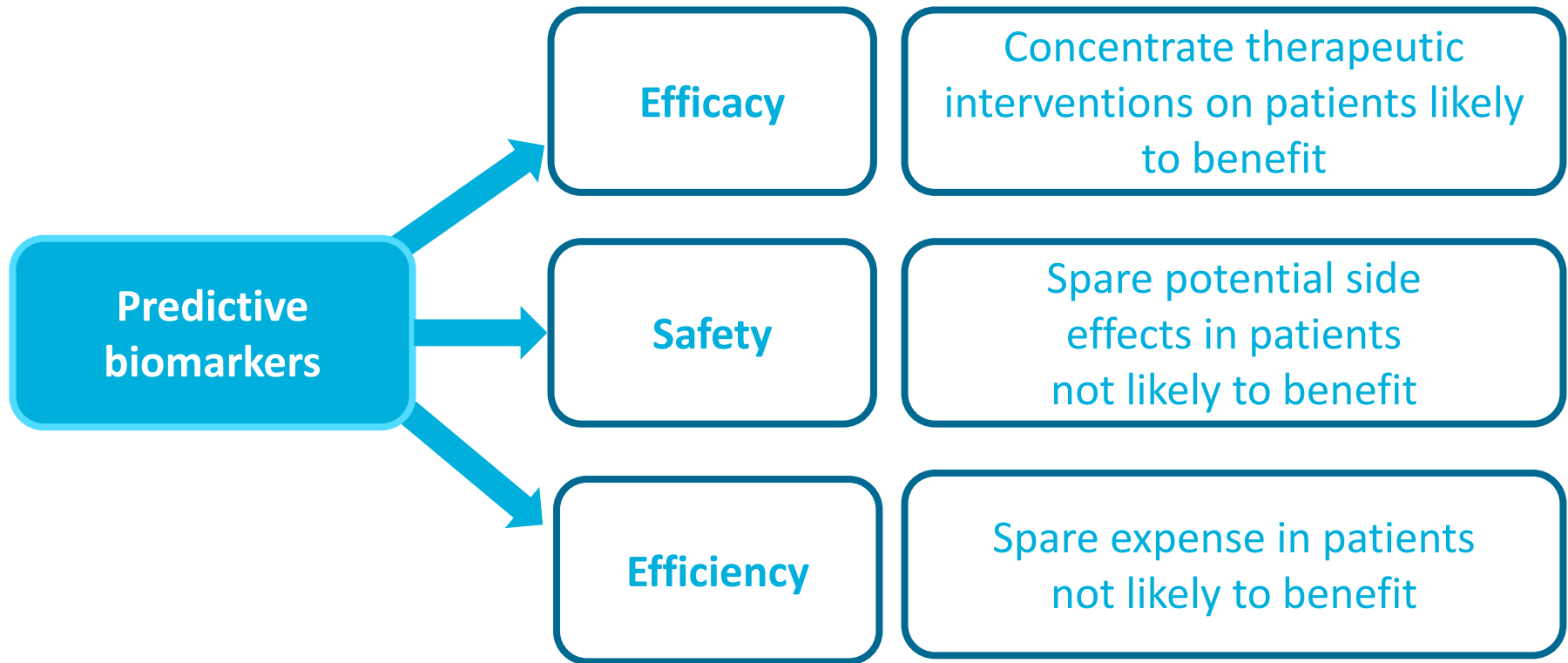
Radboudumc
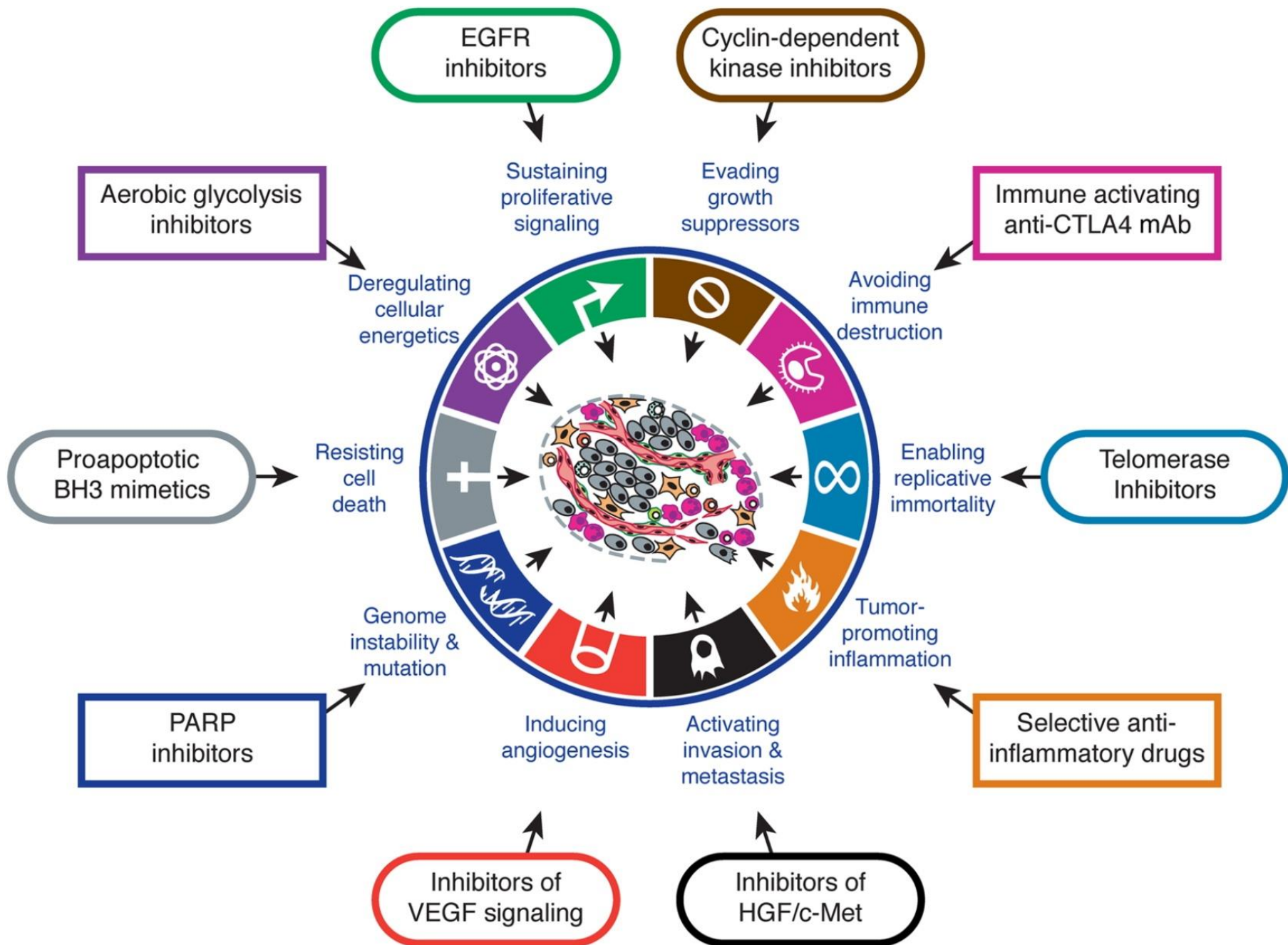
Why improving stage III (and II)?

- Staging is based on extend to disease

- This results in mixed populations

- Over- and undertreatment in stage II and III

Prognosis

- Histological type *(versus molecular subtype)*

- Differentiation/grade

- Extend (TNM)

- Additional features
    - Angioinvasion
    - Protein expression
    - Inflammatory respons
    - Stroma

Prediction

Predictive biomarkers

Efficacy → Concentrate therapeutic interventions on patients likely to benefit

Safety → Spare potential side effects in patients not likely to benefit

Efficiency → Spare expense in patients not likely to benefit

EGFR inhibitors → Sustaining proliferative signaling

Cyclin-dependent kinase inhibitors → Evading growth suppressors

Aerobic glycolysis inhibitors → Deregulating cellular energetics

Immune activating anti-CTLA4 mAb → Avoiding immune destruction

Proapoptotic BH3 mimetics → Resisting cell death

Telomerase Inhibitors → Enabling replicative immortality

PARP inhibitors → Genome instability & mutation

Selective anti-inflammatory drugs → Tumor-promoting inflammation

Inhibitors of VEGF signaling → Inducing angiogenesis

Inhibitors of HGF/c-Met → Activating invasion & metastasis

First priority: optimizing TNM

- Improve TNM itself: TNM 8 in December 2016

- Proper use and interpretation
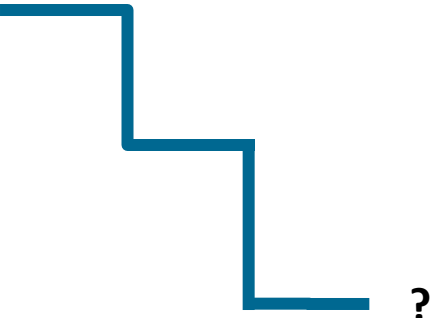
5th edition TNM
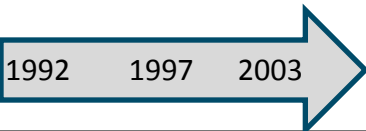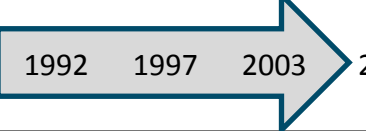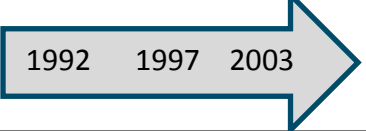
- A tumour nodule greater than 3mm in diameter in perirectal or pericolic adipose tissue without histological evidence of residual lymph node is classified as a regional lymph node metastasis.
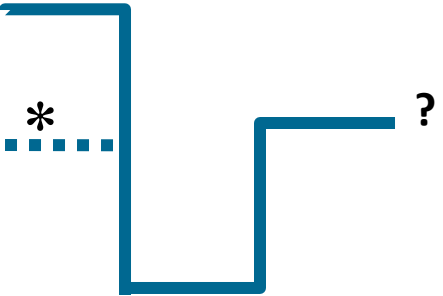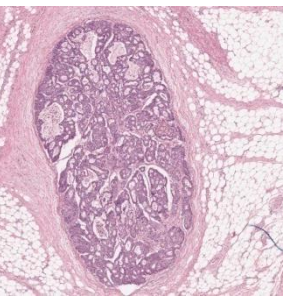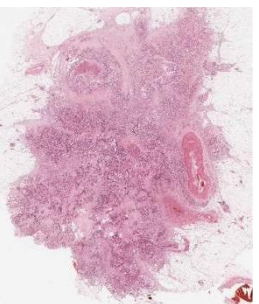
- However, a tumour nodule up to 3mm in diameter is classified in the T category as discontinuous extension, i.e. T3

Radboud umc

6th edition TNM

- "A tumour nodule in the pericolic/perirectal adipose tissue without histologic evidence of residual lymph node is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node.

- If the nodule has an irregular contour, it should be classified in the pT category, and also coded as V1 (microscopic venous invasion) or V2, if it was grossly evident, because there is a strong likelihood that it represents venous invasion"

- An objective assessment (size) has been replaced by a subjective one (form and contour)

Radboud**umc**

TNM staging: (courtesy Iris Nagtegaal)

	TNM4 TNM5 TNM6 TNM7	TNM4 TNM5 TNM6 TNM7	TNM4 TNM5 TNM6 TNM7
TNM stage	1992 1997 2003 2009	1992 1997 2003 2009	1992 1997 2003 2009
I			
II			* ?
III		?	
	Lymph node metastasis	Smooth tumour deposit (2 mm)	Irregular tumour deposit (5 mm)

TNM system 5 versus 6

- TNM revisions - no guidelines for changes and not informed by clinical trials/population data
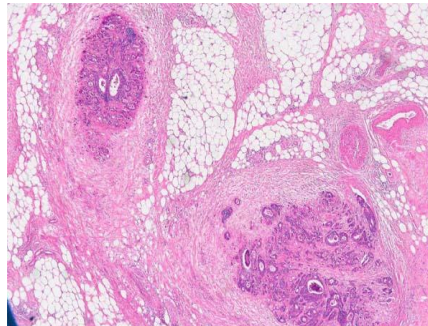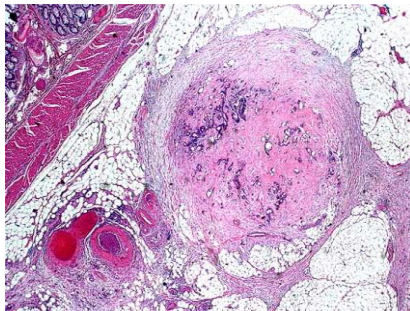
  - Significant number cases changed stage13/80 changed stage 7/80 N0/N1 (5 up 2 down)
  - Howarth SM *et al. Gut* 2004; 53:A21

- TNM6 not adopted in UK, Belgium, Scandinavia, the Netherlands

Radboud umc

Quality of data: review of 300 cases of rectal cancer

Total error (n = 300)

10%
66%
24%

Circumferential margin error (n = 60)

27%
48%
25%

37%
38%
25%

T stage errors (n = 14)

□ 1: data manager

■ 2: review pathologist

□ 3: quality manager

Radboudumc
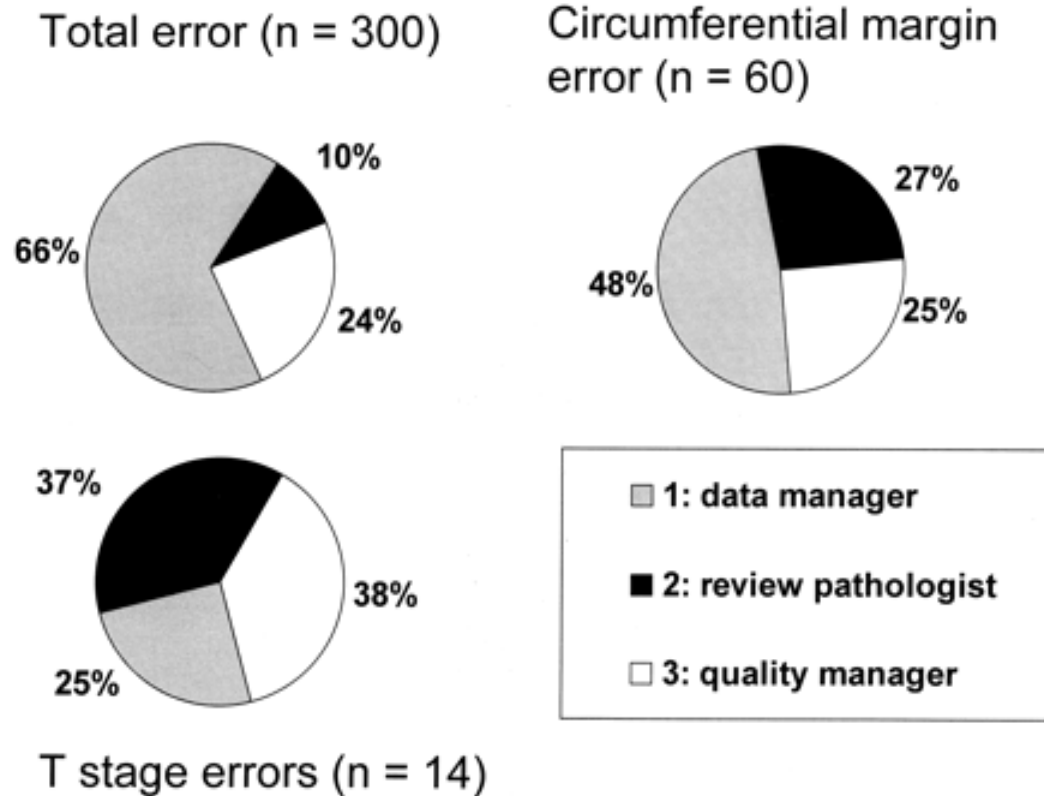
Improvement of lymph node sampling
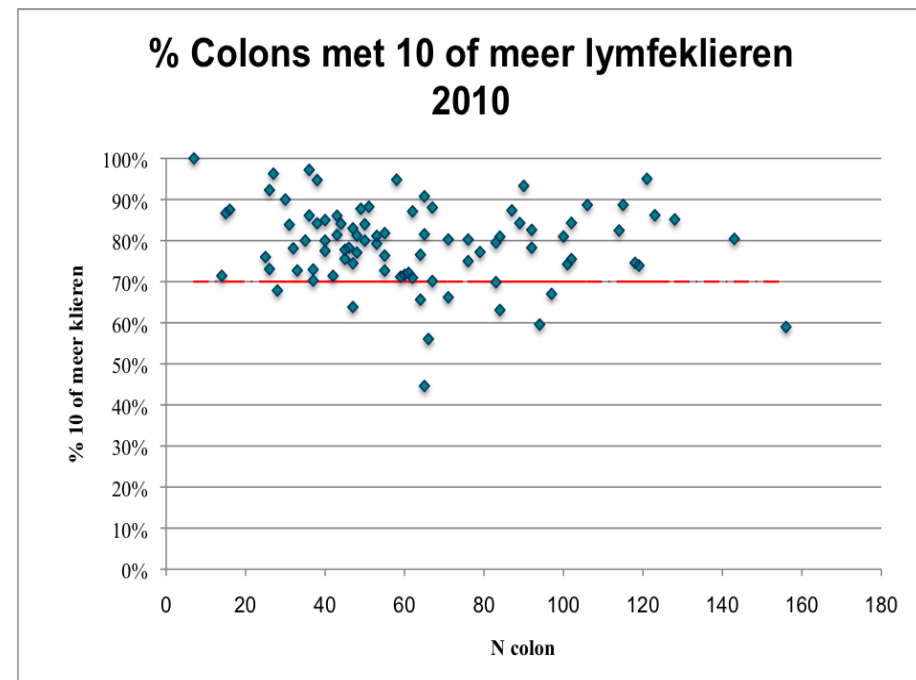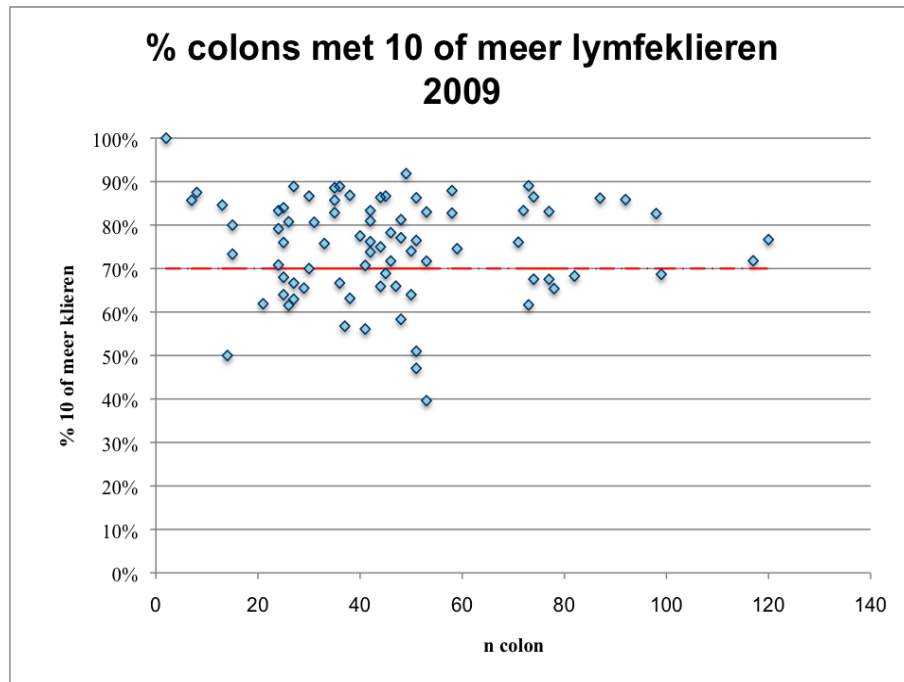
% colons met 10 of meer lymfeklieren 2009

% Colons met 10 of meer lymfeklieren 2010

palga

T05-00125			
Rapport	PatientNummer	PatientNaam	Verkrijgingswijze
1	Man		colon
Rapport fase	Geslacht	GeboorteDatum	Aardmateriaal

Inzage rapport

Scherm 1

Perforatie
- ○ Aanwezig ● Niet aanwezig ○ Dubieus ○ Onbekend

Klinisch obstructie/ileus
- ● Nee ○ Ja ○ Onbekend

Klinisch metastase(n)
- ☐ Niet aangetroffen ☐ Peritoneum (bevestigd) ☐ Long (onbevestigd)
- ☐ Lever (bevestigd) ☐ Peritoneum (onbevestigd) ☐ Onbekend
- ☐ Lever (onbevestigd) ☑ Long (bevestigd) ☐ Elders

Lengte colon (xxx,x cm)

Tumor aanwezig
- ● Ja
- ○ Nee, status na poliepectomie
- ○ Nee, status na TEM (Transanale Endoscopische Microchirugie)
- ○ Nee, complete regressie na neoadjuvante therapie

Type tumor (WHO)(Dominante tumor)
- ● Adenocarcinoom ○ Adenosquameus carcinoom ○ Carcinoid
- ○ Mucineus adenocarcinoom ○ Medullair carcinoom ○ Hooggradig neuroendocrien carcinoom
- ○ Zegelringcelcarcinoom ○ Ongedifferentieerd carcinoom ○ Kleincellig carcinoom

Differentiatie
- ● Goed / matig ○ Weinig / niet

Lymfocytaire infiltratie
- ○ Ja ○ Nee

Ok   Annuleren   Variabelenscherm

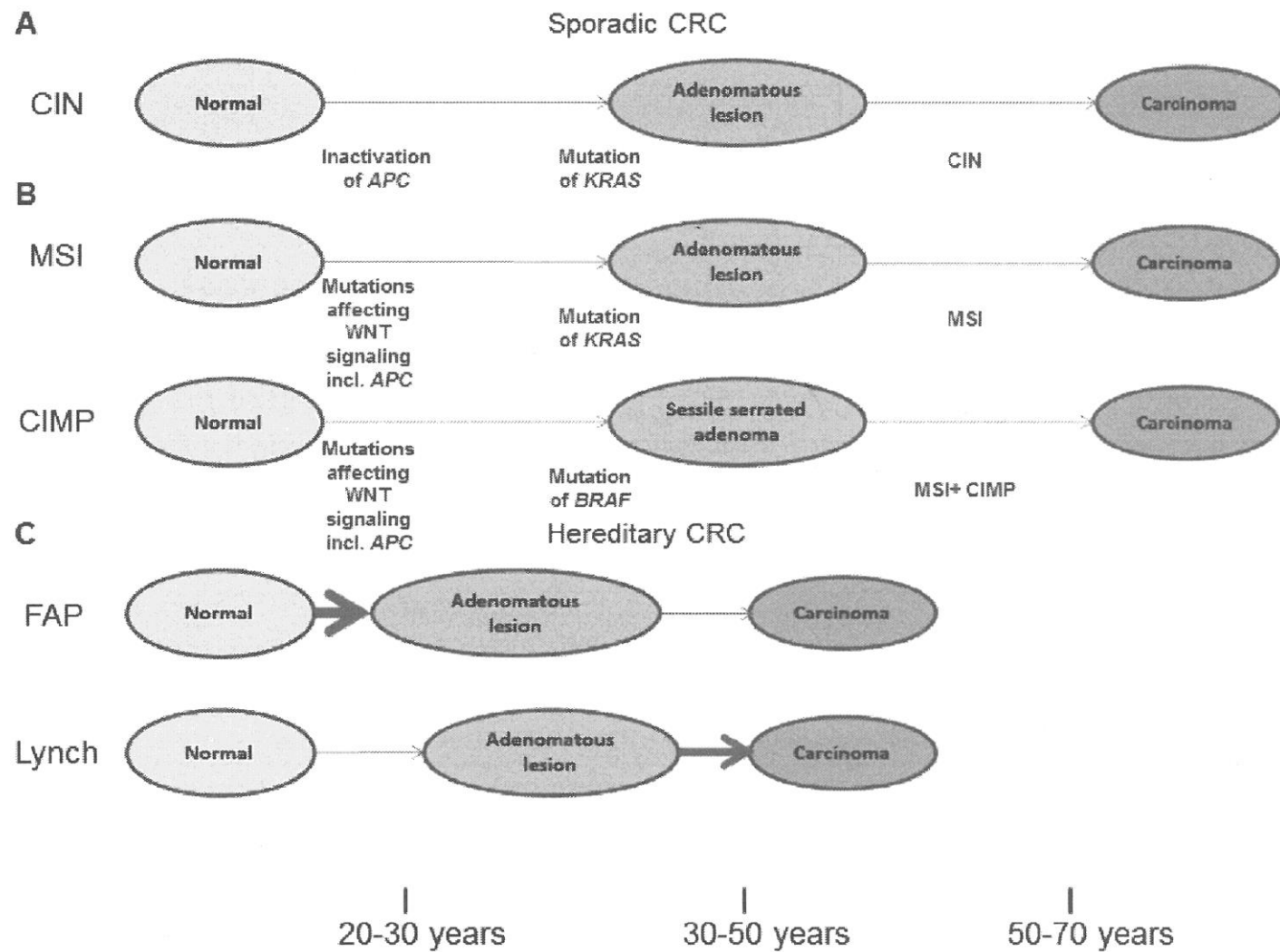# Discrepancy of c and p T-stage rectal cancer

- Without neoadjuvant therapy

ct	pt						
	X	IS	1	2	3	4A	4B
	N	N	N	N	N	N	N
X	66	179	420	143	126	15	7
IS	608	909	33	12	1	-	-
0	2	1	3	1	1	-	1
1	34	-	314	57	17	-	-
2	14	-	143	351	233	4	4
3	5	-	31	162	377	26	3
4	-	-	-	-	-	-	1
4A	1	-	-	1	9	5	1
4B	-	-	-	2	16	3	24

With neoadjuvant therapy

ct	pt							
	X	IS	0	1	2	3	4A	4B
	N	N	N	N	N	N	N	N
X	2	2	23	35	121	131	4	3
IS	2	15	-	1	1	1	-	-
0	-	-	-	1	5	3	-	-
1	1	-	14	27	39	10	-	-
2	16	-	132	142	605	425	5	2
3	37	-	547	215	1150	2182	63	26
4A	2	-	12	6	26	75	9	6
4B	1	-	56	15	76	229	7	122

Maybe more important than optimizing TNM…..

- Classification of cancer into disease entities

- Prognostic categorization

- Liquid biopsy

- Predicitve markers: only when therapy is indicated

A Sporadic CRC

CIN: Normal → Adenomatous lesion → Carcinoma
- Inactivation of *APC*
- Mutation of *KRAS*
- CIN

B

MSI: Normal → Adenomatous lesion → Carcinoma
- Mutations affecting WNT signaling incl. *APC*
- Mutation of *KRAS*
- MSI

CIMP: Normal → Sessile serrated adenoma → Carcinoma
- Mutations affecting WNT signaling incl. *APC*
- Mutation of *BRAF*
- MSI+ CIMP

C Hereditary CRC

FAP: Normal → Adenomatous lesion → Carcinoma

Lynch: Normal → Adenomatous lesion → Carcinoma

20-30 years   30-50 years   50-70 years

Maybe more important than optimizing TNM.....

- Classification of cancer into disease entities

- Prognostic categorization
    - Morphology
    - Protein expression
    - Gene signatures

- Liquid biopsy

- Predicitve markers: only when therapy is indicated