

II Colorectal cancer

- > 85 % of cases are sporadic colorectal cancer
- ~ 10 % of cases are hereditary colorectal cancer

Hereditary Non Polyposis Colorectal Cancer
(HNPCC)

Familial Adenomatous Polyposis (FAP)

Hereditary Non Polyposis Colorectal Cancer (HNPCC)



Microsatellite instability

Microsatellites

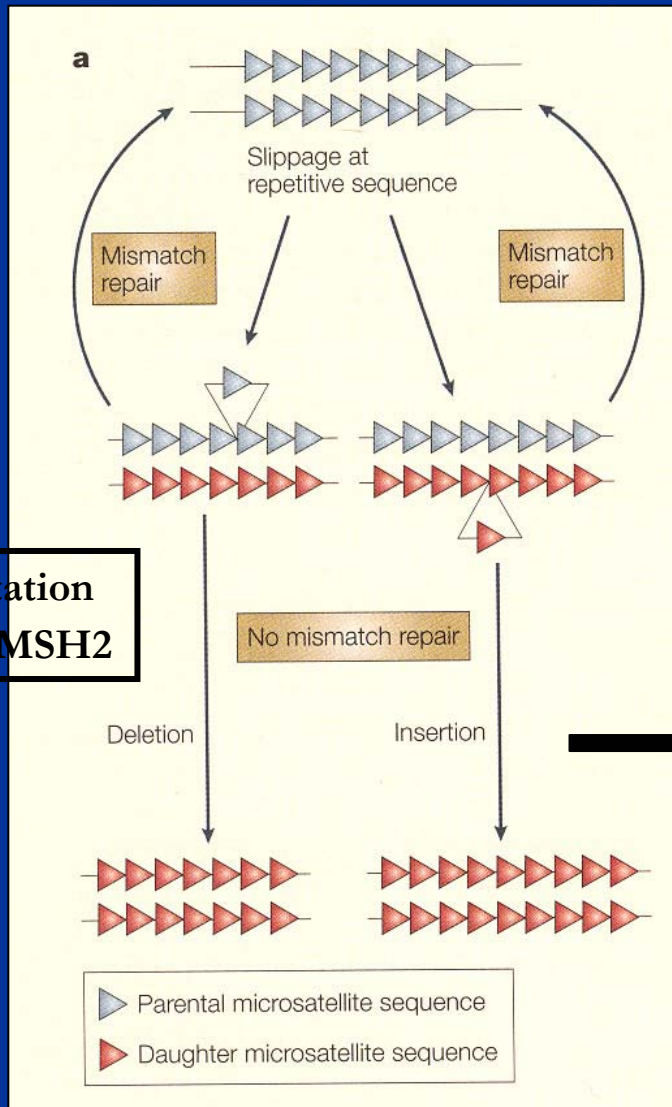
- short DNA segments widespread throughout the human genome
- tandem repetitions of a short nucleotidique sequence (1 to several bases in length)

.....CATGCATGCATGCATG_n.....

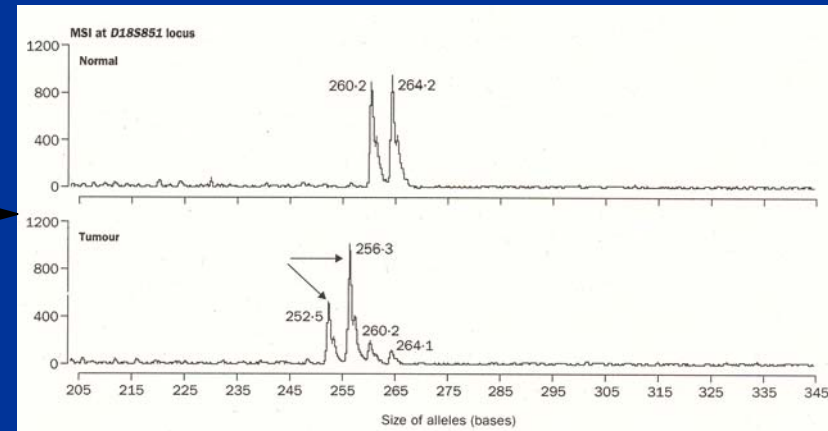
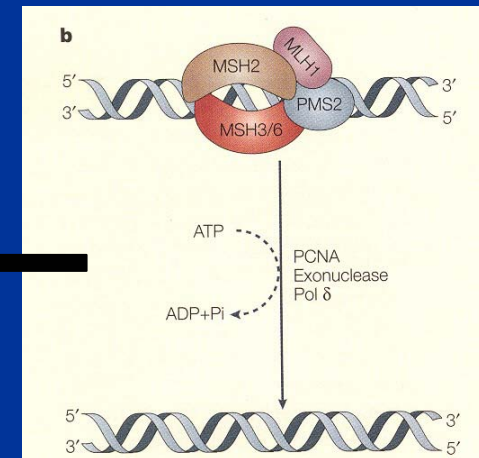
.....CACACACACA_n.....

.....AAAAAAAAAA_n.....

Microsatellites Instability



Inactive mutation
of MLH1 & MSH2



MSI

HNPCC

- Represent 2 to 6 % of all colorectal cancers
- Appears to be due to **hereditary defects in DNA mismatch repair genes** (mutations) (mainly hMSH₂ and hMLH₁)
- Cancers arising in HNPCC are thus genetically unstable
→ these tumors exhibit a “microsatellite mutation phenotype” or “**microsatellite instability**” (MSI)
- “MSI” is detectable
 - in ~ 90 % of colorectal cancers from HNPCC patients
 - in 10 to 15 % of sporadic colorectal cancers

HNPCC

Amsterdam clinical criteria for the search of “MSI”:

- at least three family members with colorectal cancer, two of whom are first-degree relatives
- no polyposis demonstrated

HNPCC

Bethesda clinical criteria for the search of “MSI” (2003)

at least one individual should be less than 50
years of age at diagnosis

synchronous ou metachronous tumours or other
types of carcinoma associated

diagnosis of colorectal cancer before 60 years of age
and morphology suggestive of associated MSI

HNPCC

Morphological features

- Polypoid
- mucinous carcinoma
- necrotic
- poorly differentiated
- lymphoid infiltration ++

HNPPC

clinical aspects : HNPPC \neq sporadic cancer

- proximal colonic segment
- increasing risk of synchronous and metachronous colonic tumours
- better prognosis

HNPCC

diagnostic tools

- IHC: MLH1 and MSH2 (not for MSH6)
- PCR: MSI (5 μ satellites)
- Sequencing: MLH1 and MSH2

IHC



MSH2

- ! false negative results !

silencing mutation

mutation PMS2, MSH6,...

- No false positive result



MLH1

MSI

National Cancer Institute recommendations (1)

- Use of five microsatellites: Bat 25
Bat 26
D2S123
D5S346
D17S250
- The test is performed on tumoral tissue (paraffin-embedded tissue)
- The tumoral profile is compared to normal tissue (blood or adjacent normal colonic mucosae)

HNPPC

National Cancer Institute recommendations (2):

- MSI + if at least 3 microsatellites are unstable
- If MSI + \longrightarrow sequencing of both hMSH₂ and hMLH₁ is required to confirm HNPPC.

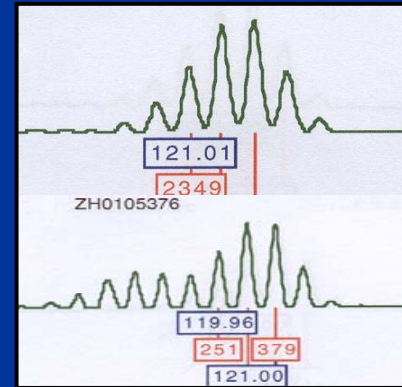
HNPPCC

MSI +

+ for Bat 25

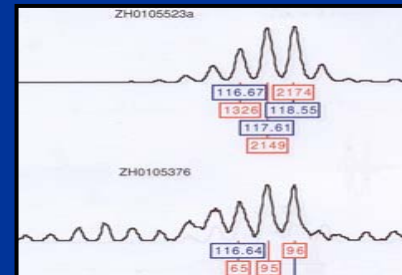
+ for Bat 26

+ for D5S346



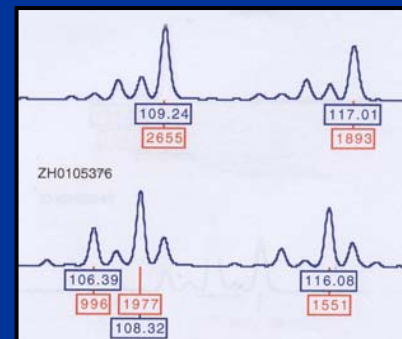
N

T+



N

T+

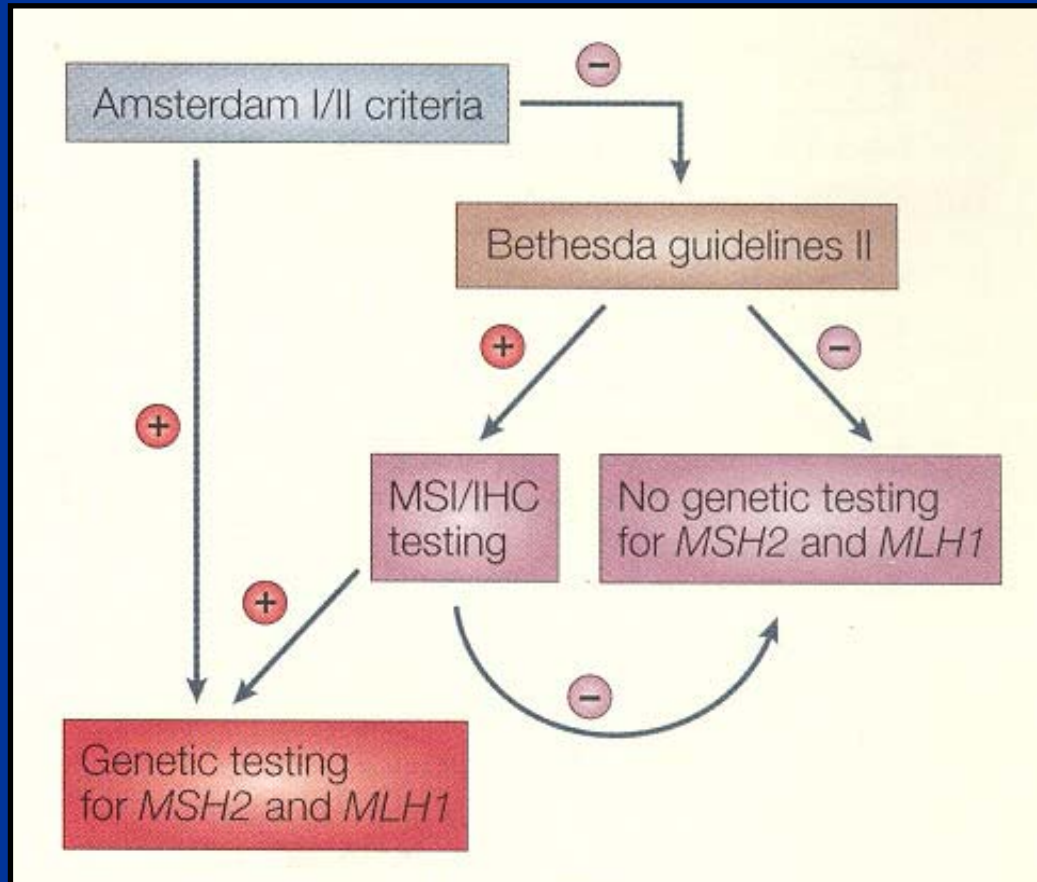


N

T+

HNPPC

strategy for genetical testing

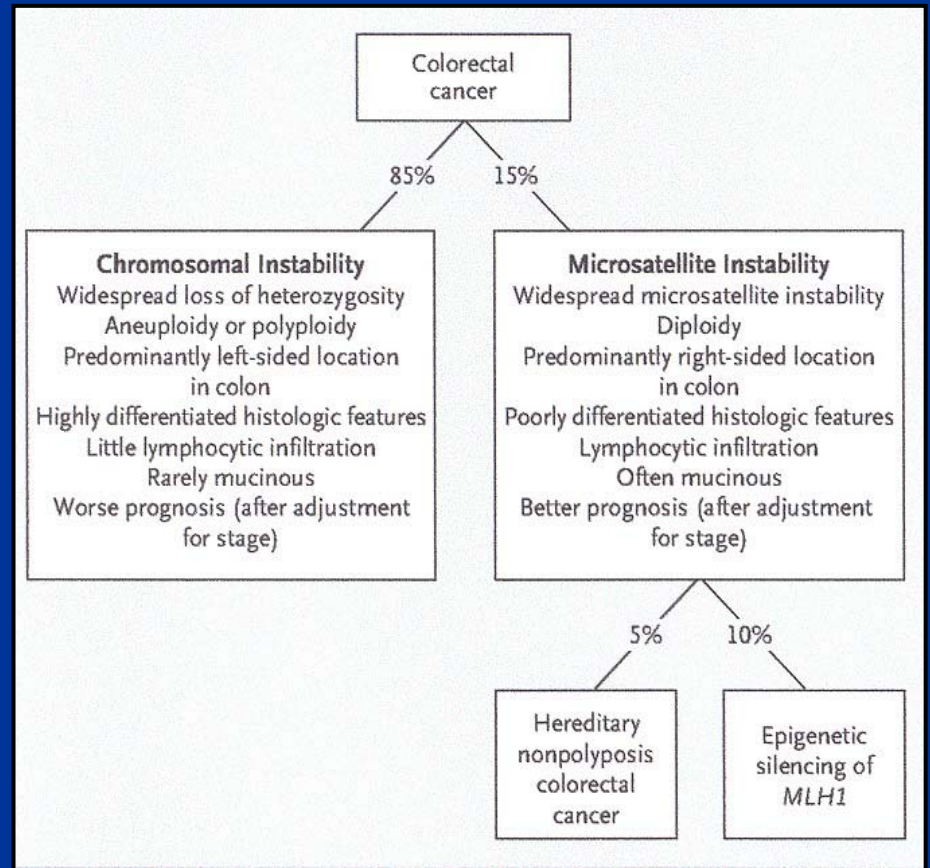


Colorectal cancer

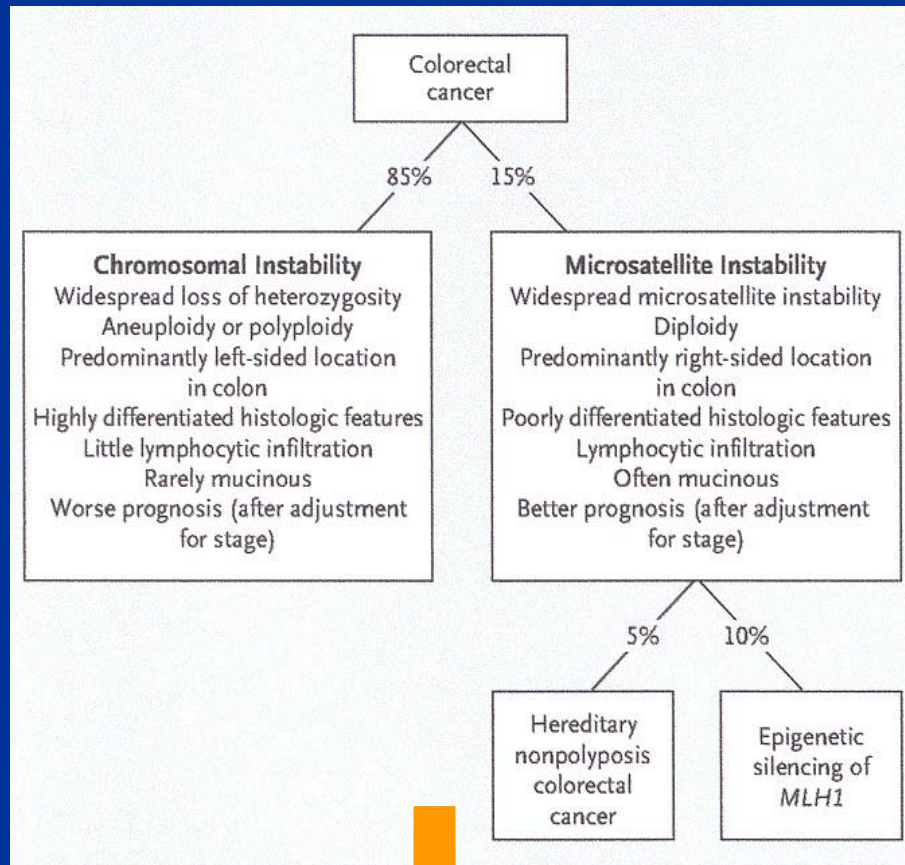
- Chromosomal instability (LOH,...)
- Microsatellites instability



- pronostic and predictive parameters



Somatic colorectal cancer (1)



MSS vs MSI colo-rectal cancer :
Different clinical and morphological aspects
→ **MSI status = predictive parameter ?**

Somatic colorectal cancer (2)

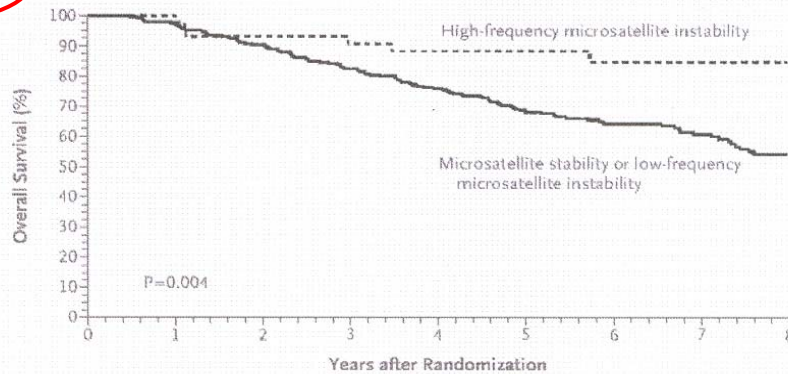
Tumor Microsatellite-Instability Status as a Predictor of Benefit from Fluorouracil-Based Adjuvant Chemotherapy for Colon Cancer

Ribic et al, NEJM 2003

- 570 patients stages II and III
- microsatellite instability analysis on paraffin embedded tissue (MSI vs MSS)
- question: adjuvant chemotherapy or not (5' FU) ?

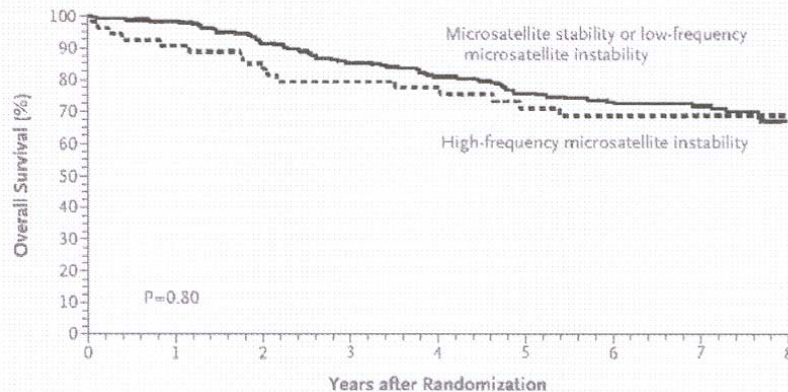
Somatic colorectal cancer (3)

A No Adjuvant Chemotherapy



OS and DFS:
MSI > MSS

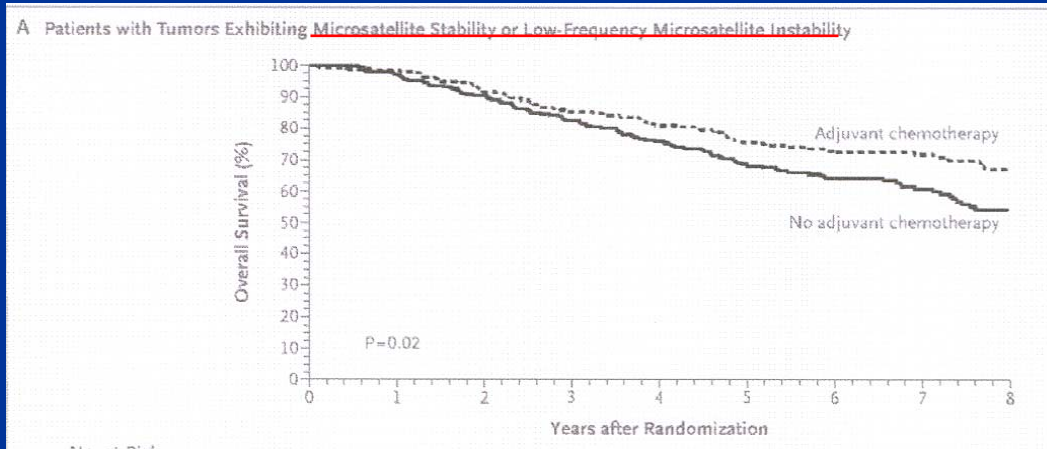
B Adjuvant Chemotherapy



OS and DFS:
no \neq MSI vs MSS

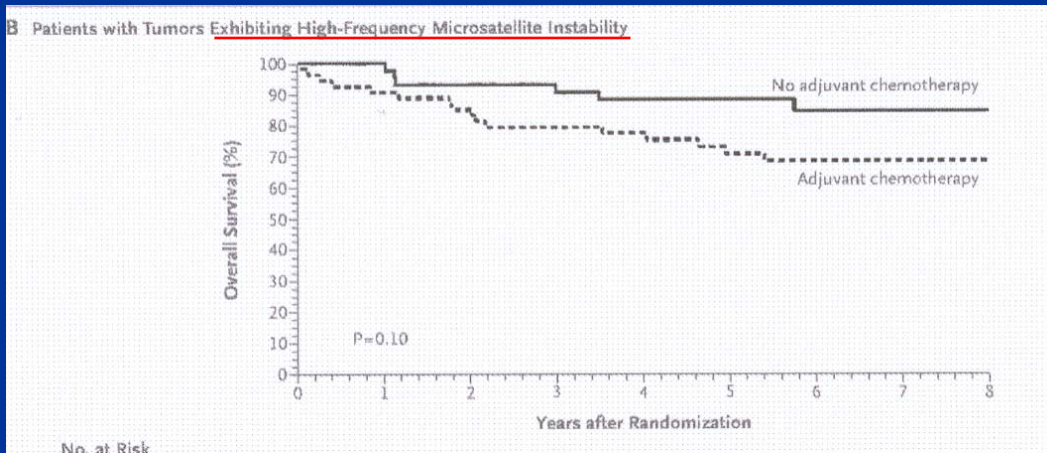
Whatever the histological grade and tumoral stage are !!

Somatic colorectal cancer (4)



MSS:

5' FU ↗ OS and EFS



MSI:

5' FU ↘ OS and EFS !!

Whatever the histological grade and tumoral stage are !!

Somatic colorectal cancer (5)

other study

Fallik et al (*Cancer Reseach*, 2003)

MSI + and *Bax* mutation → improved response to
Irinotecan



MSI analysis: are we going to perform it routinely in
the near future ?