

# Latest Advances in Colorectal Cancer



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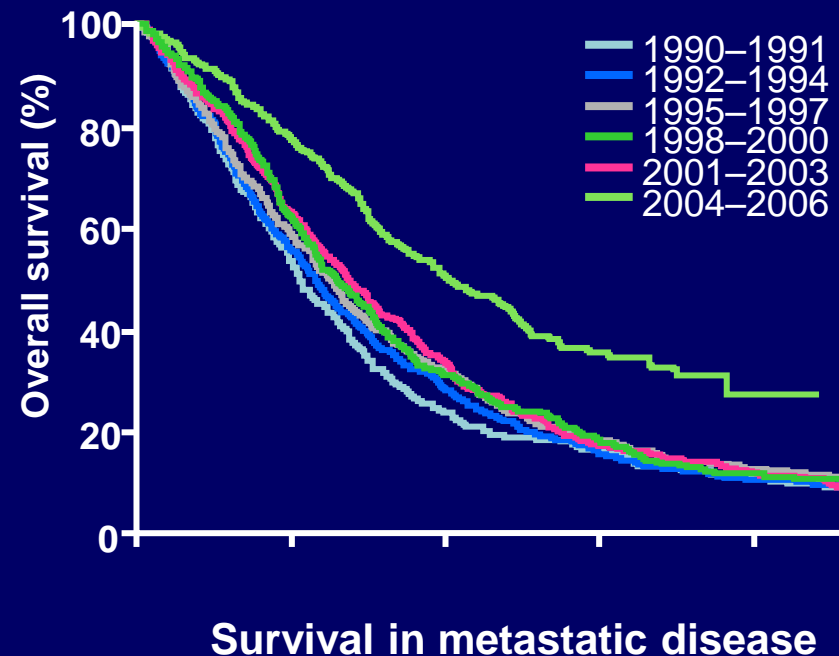
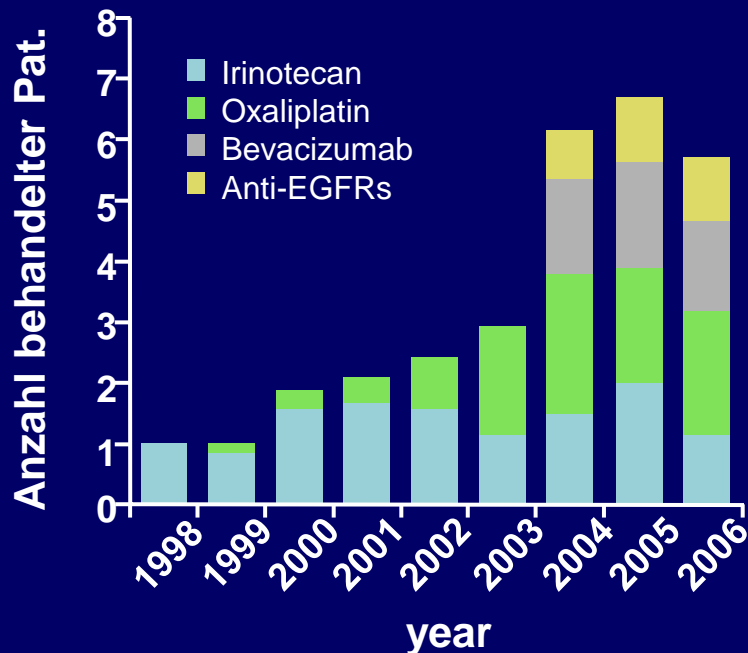
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# Disclosure of potential conflicts of interests:

- 1. Consultant activities:
  - Amgen, Bayer, Celgene, Merck, Roche
- 2. Honoraries as invited speaker:
  - Amgen, Bayer, Celgene, Ebewe, Fresenius, Pfizer, Merck, Roche, Sanofi-Aventis
- 5. Any other financial relationships:
  - none

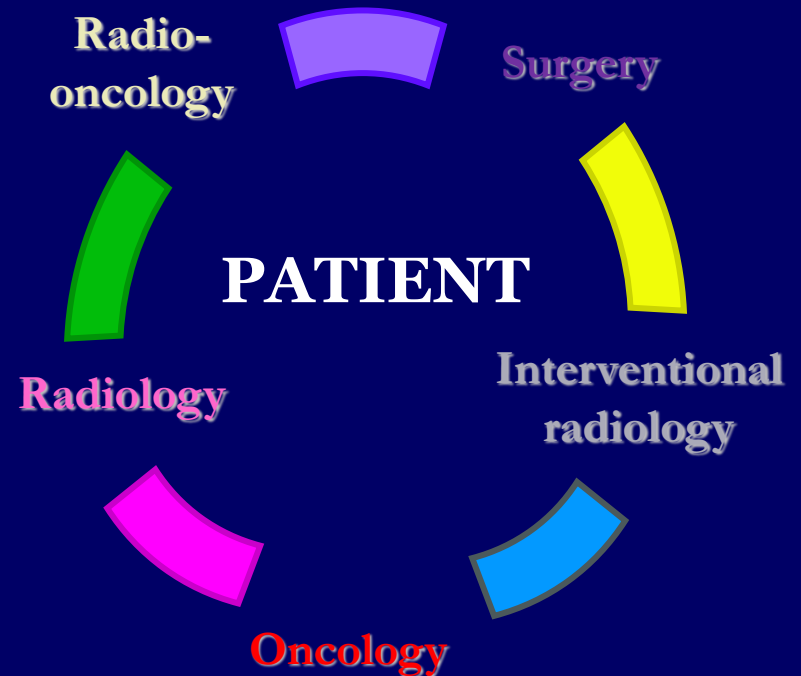
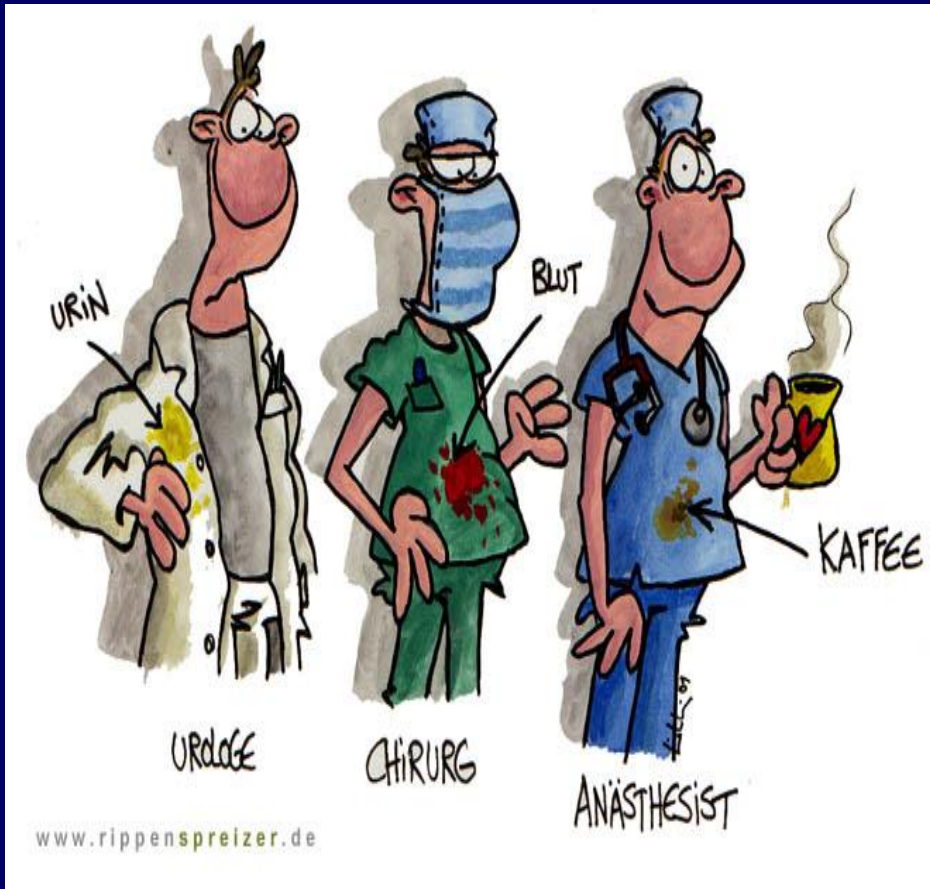
# The most important advances in colorectal cancer treatment:

## (1) Availability & use of novel agents



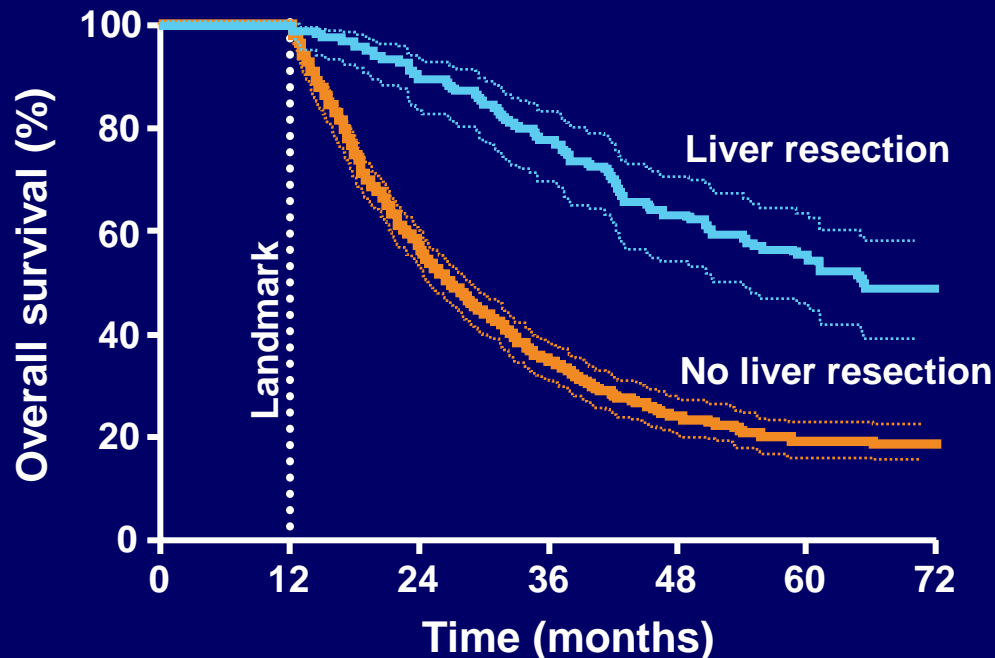
# The most important advances in colorectal cancer treatment:

## (2) Adoption of the interdisciplinary patient management



# The most important advances in colorectal cancer treatment:

## (3) Optimal timing of treatment, secondary liver resection



Patient status	Median survival	5-year survival
Resected	65.3 mos	55%
Non-resected	26.7 mos	19.5%

# The most important advances in colorectal cancer treatment:

## (4) Identification of prognostic & therapeutic relevant biomarkers in the tumour tissue



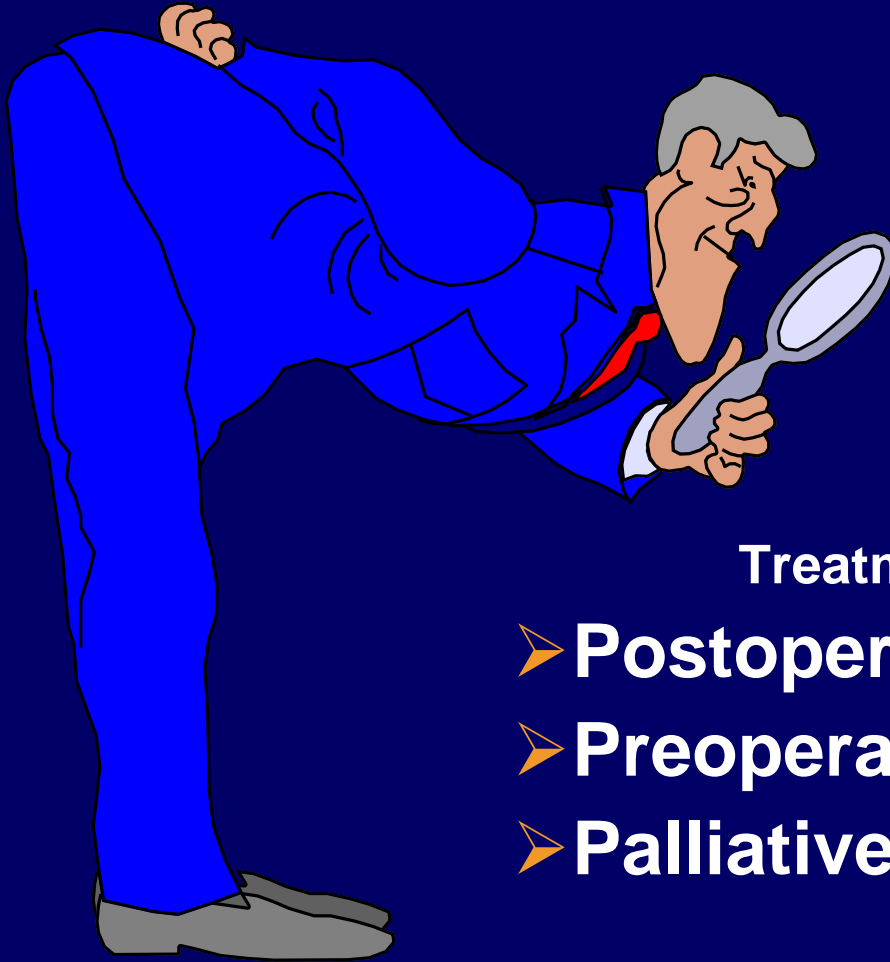
- ☀ **KRAS mutational status in metastatic colorectal cancer:**

- ☀ Which targeted therapy ?

- ☀ **Microsatellite instability:**

- ☀ Postoperative chemotherapy necessary ?

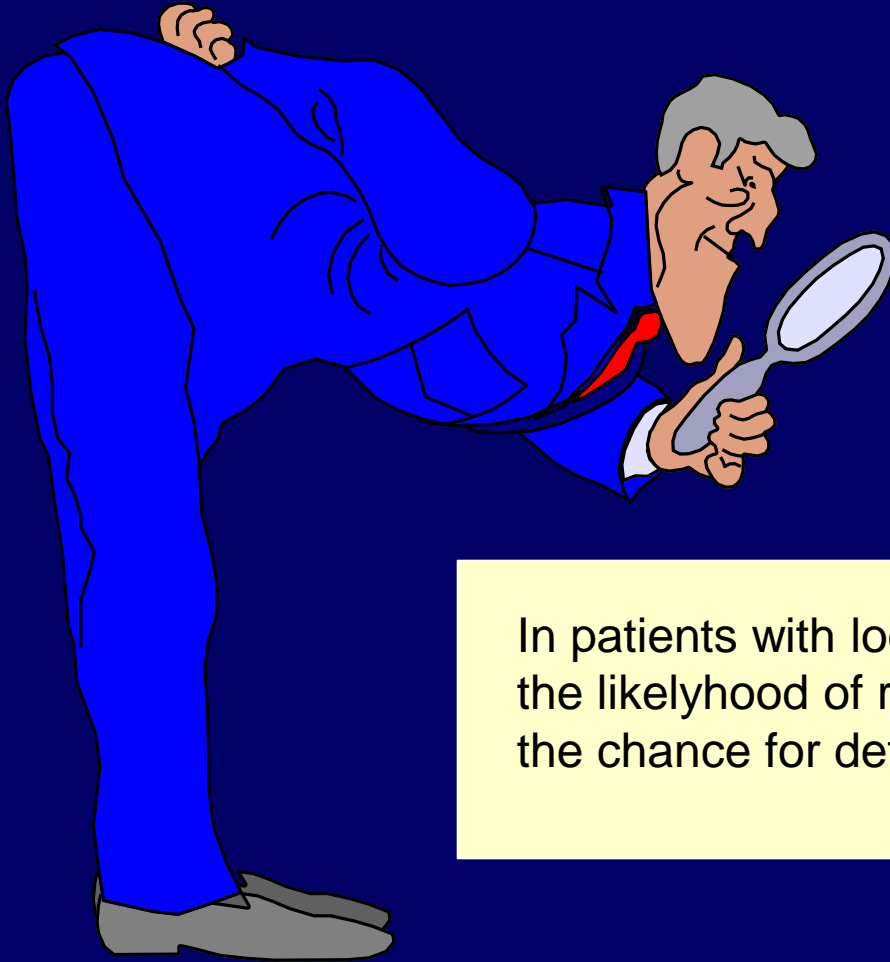
# Indications for chemotherapy in colorectal cancer:



## Treatment settings

- Postoperative (adjuvant)
- Preoperativ (neoadjuvant)
- Palliative (metastatic disease)

# Postoperative adjuvant chemotherapy

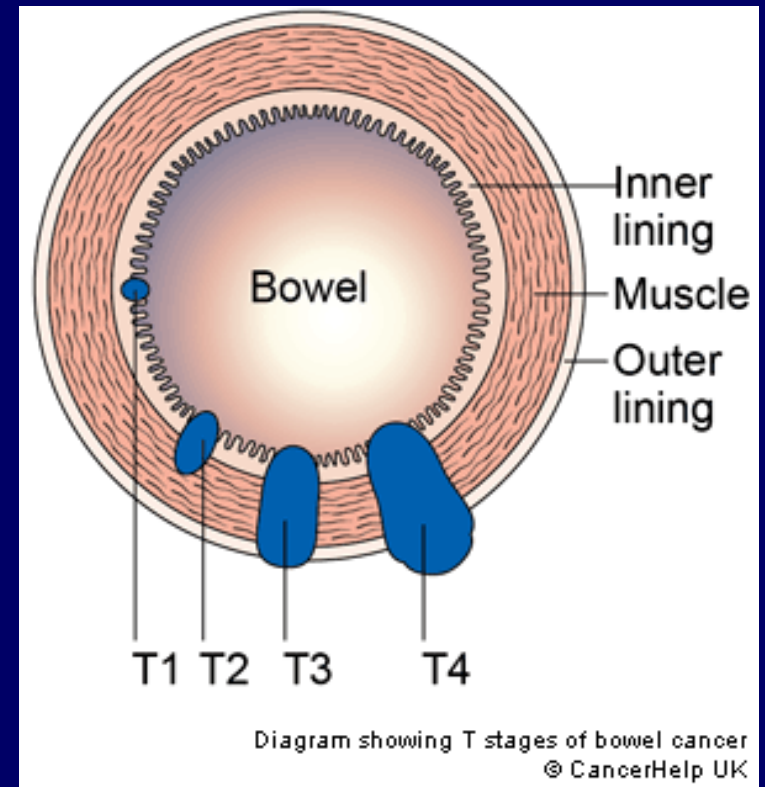


In patients with locally advanced, resected tumours the likelihood of recurrence can be reduced, i.e., the chance for definitive cure can be improved.

# Postoperative adjuvant chemotherapy ?

Decision depends on **(1) tumour stage**

- ☀ Stage I  
T1 N0 M0  
T2 N0 M0
- ☀ Stage II  
T3 N0 M0  
T4 N0 M0
- ☀ Stage III  
T1-4 N 1-3 M0 (lymphe nodes involved)



# Postoperative adjuvant chemotherapy ?

depends on **(2) histopathological risk factors**

- ✱ Obstruction or perforation at the time of initial surgery
- ✱ Depth of tumour infiltration of the bowel wall (T1-3 vs T4)
- ✱ Number of involved or analysed lymph nodes ( $\pm 12$  !)
- ✱ Histologic differentiation (grading 1,2 vs. 3)
- ✱ Infiltration of lymph- or blood vessels

# Postoperative adjuvant chemotherapy ?

depends on (3) individual patient characteristics



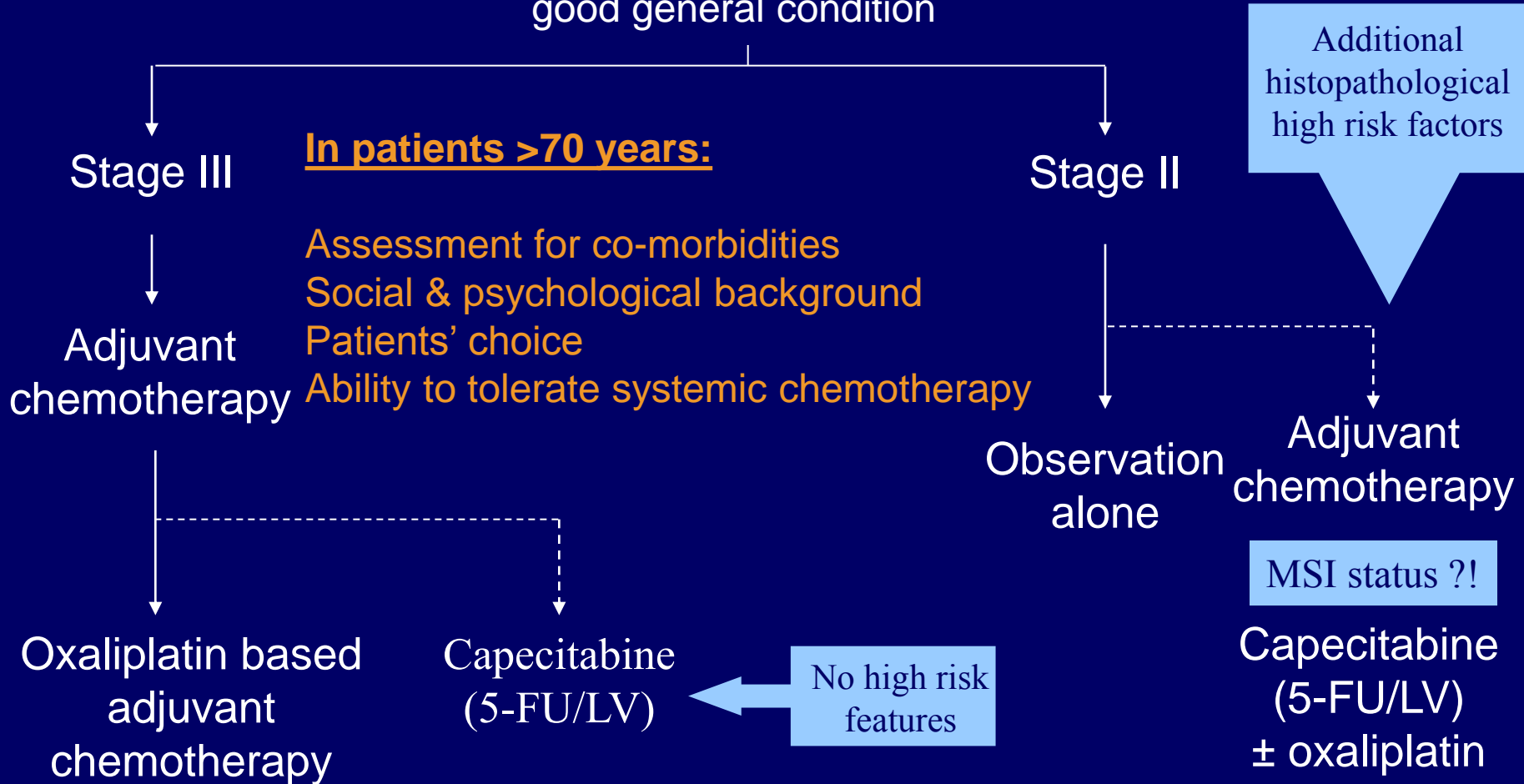
- Biological age
- Comorbidities
- Risk of toxicities
- Social & psychological background
- Patient's choice

# Recent advances in postop. adjuvant chemo:

	Study	Therapy	3-years tumour-recurrence free
No therapy	Moertel	Observation	52%
	IMPACT	Observation	44%
Monotherapy	IMPACT	5FU/LV	62%
	Punt	5FU/LV	65%
	Fields	5FU/LV	67%
	André	5FU/LV	61%
	MOSAIC	5FU/LV	65%
	X-ACT	Capecitabine	64%
	MOSAIC	FOLFOX4	72%
Combi-therapy	NSABP C-07	FLOX	72%
	XELOXA	XELOX	71%

# ESMO 2012 adjuvant treatment recommendations in colon cancer

Patients having undergone colon cancer surgery in good general condition



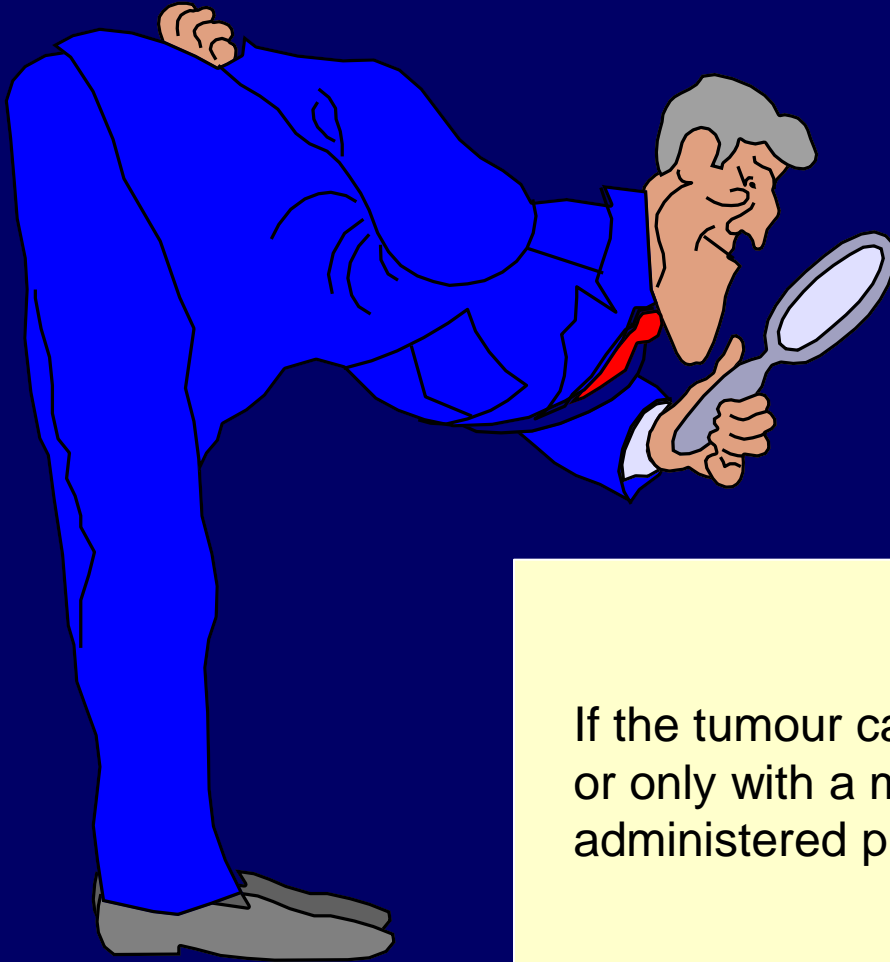
No routine role for any adjuvant biological agents

# Adjuvant chemotherapy & “optimale timing”

A meta-analysis of the impact of time to adjuvant chemotherapy (TTAC) on survival (14.357 patients from 9 clinical studies)

12% increase in the risk of death for each 4 weeks of chemo delay !  
Still some benefit after a 3 months delay.....

# Neoadjuvant chemotherapy



If the tumour can not be operated with curative intent, or only with a major surgical effort, chemotherapy is administered preoperatively.

# Neoadjuvant chemotherapy - Rationale

- Minimise the extent of surgery
- Reduce the risk of operative complications
- Destruction of frequently coexistent micrometastases
- Identify the chemosensitivity of the tumour
- Identify aggressive, chemotherapy-resistant disease
- Avoid unnecessary surgical interventions
- Increase the likelihood of curative surgery
- Improve recurrence-free & overall survival

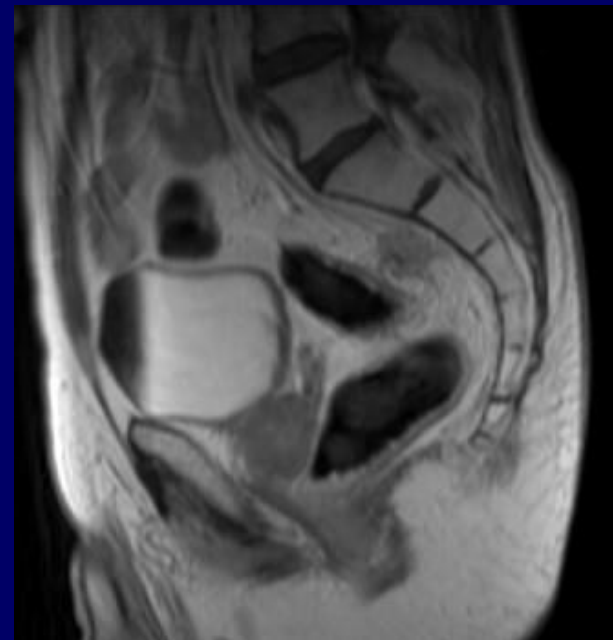
# Neoadjuvant chemotherapy in colorectal cancer liver metastases



Treatment	>50% ▼ size	Potential cure
FOLFOX	50%	33%
FOLFIRI	48%	33%
FOLFOXIRI	64%	41%
FOLFOXIRI	71%	38%

# Neoadjuvant chemotherapy in locally advanced rectal cancer

Before combined radiochemotherapy



After completion of treatment,  
before surgery

# Indications for chemotherapy in colorectal cancer:



## Treatment Settings

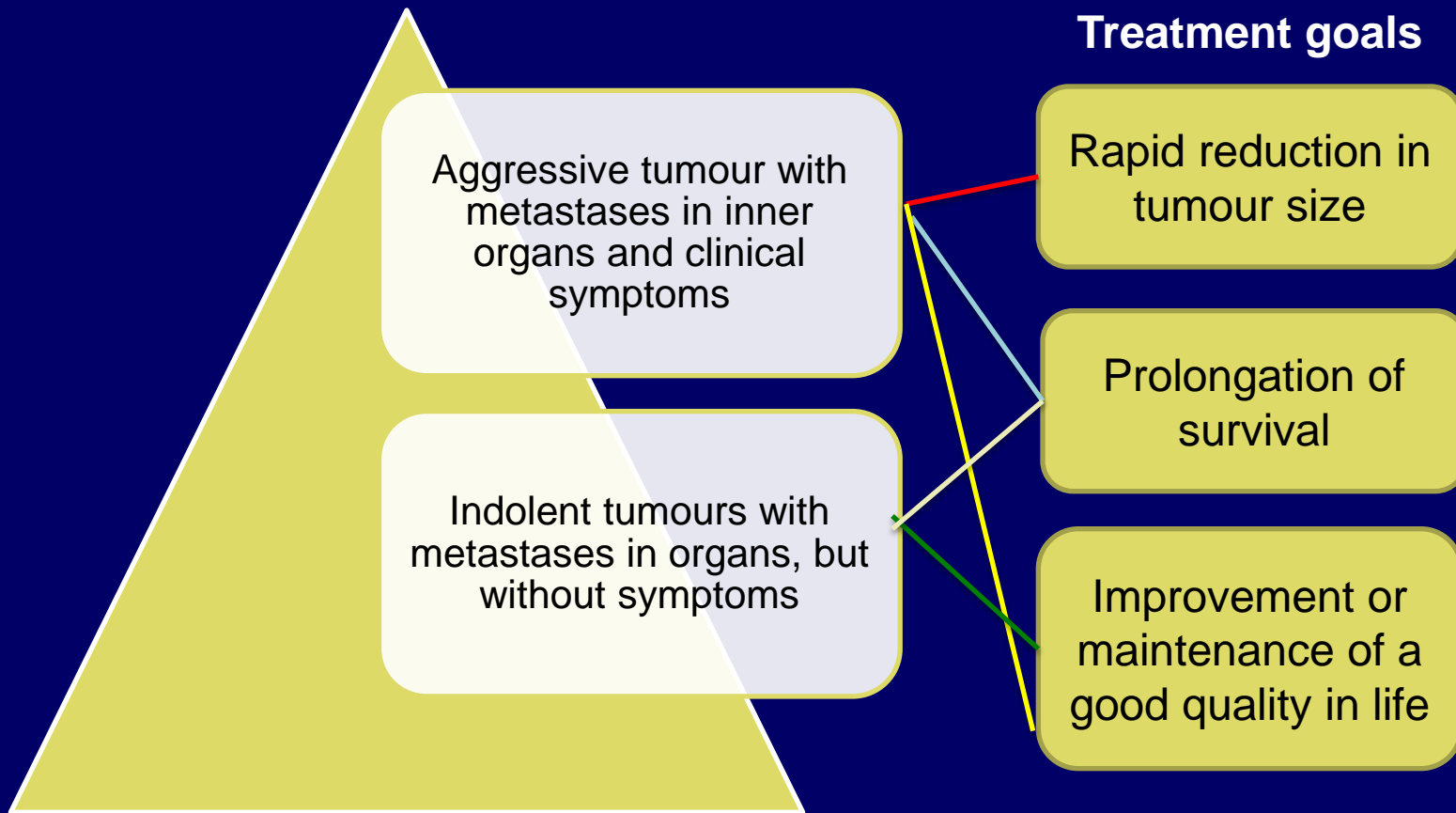
- Adjuvant
- Neoadjuvant
- Palliative

# Palliative chemotherapy

## Treatment goals in patients with metastases

- Cure
- Prolongation of survival
- Release of tumour-related symptoms
- Improve the quality of life

# Palliative treatment szenario must be defined



- 1) Therapy must be effective, tolerable, convenient, and should be conducted for an optimal duration.
- 2) Biological age, physical condition, comorbidities, toxicity profile & acceptance must be taken into consideration.

# Anticancer drugs used in colorectal cancer

## Conventional chemotherapeutic agents

- Oxaliplatin
- Irinotecan
- 5-Fluorouracil
- Capecitabine
- Uracil/Tegafur

## Tumour-targeted agents (“biologicals”)

- Bevacizumab
  - Aflibercept
  - Cetuximab
  - Panitumumab
  - Regorafenib
- } antiangiogenetic drugs
- } anti-EGFRs

# Antiangiogenic drugs (e.g., Bevacizumab) mechanism of action

## EARLY EFFECTS

## CONTINUED EFFECTS



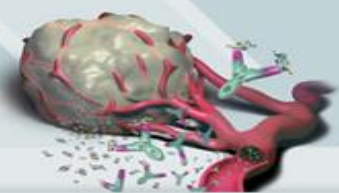
### 1 Regression

Decreases  
tumour size



### 2 Normalisation

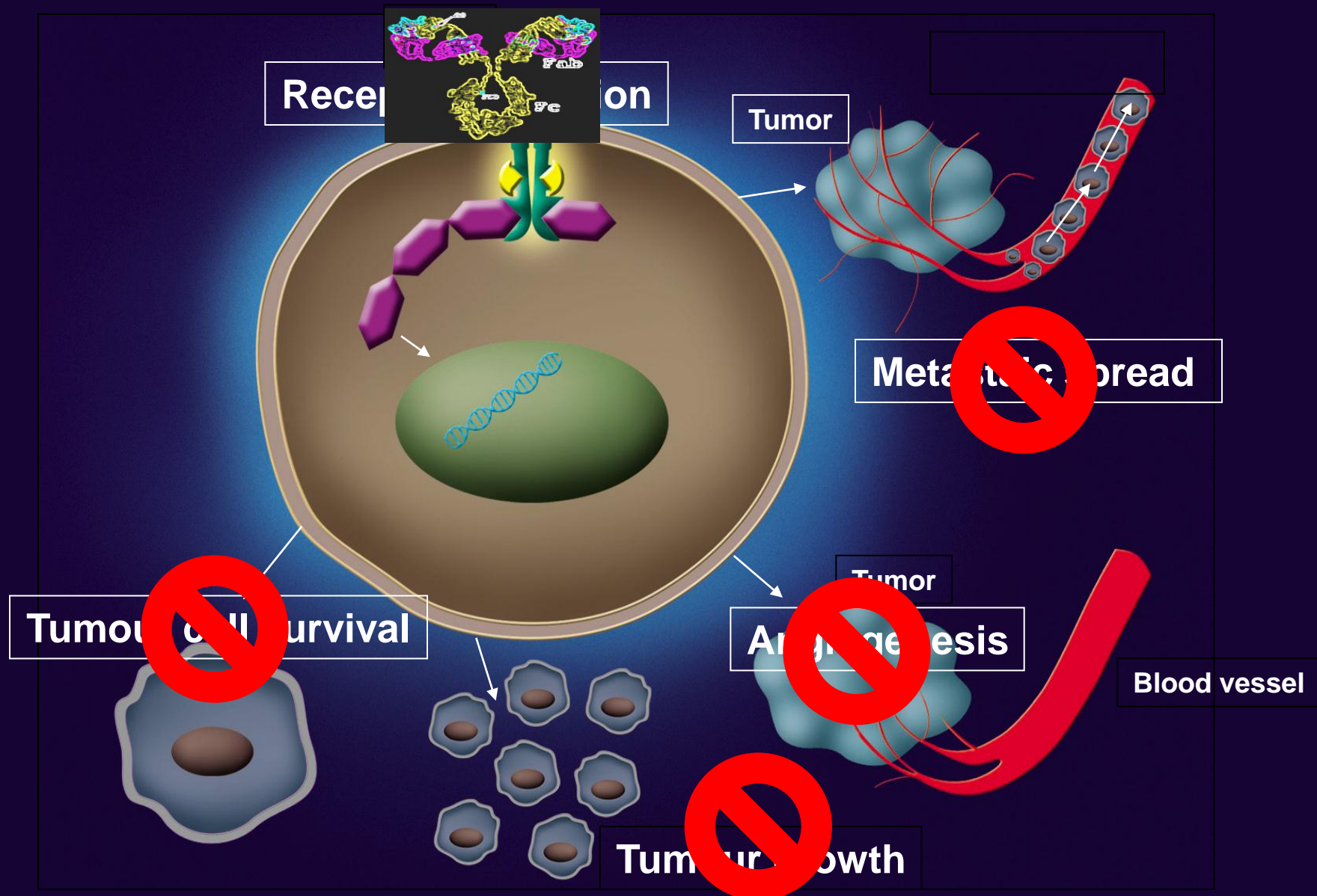
Improves  
delivery of  
chemotherapy



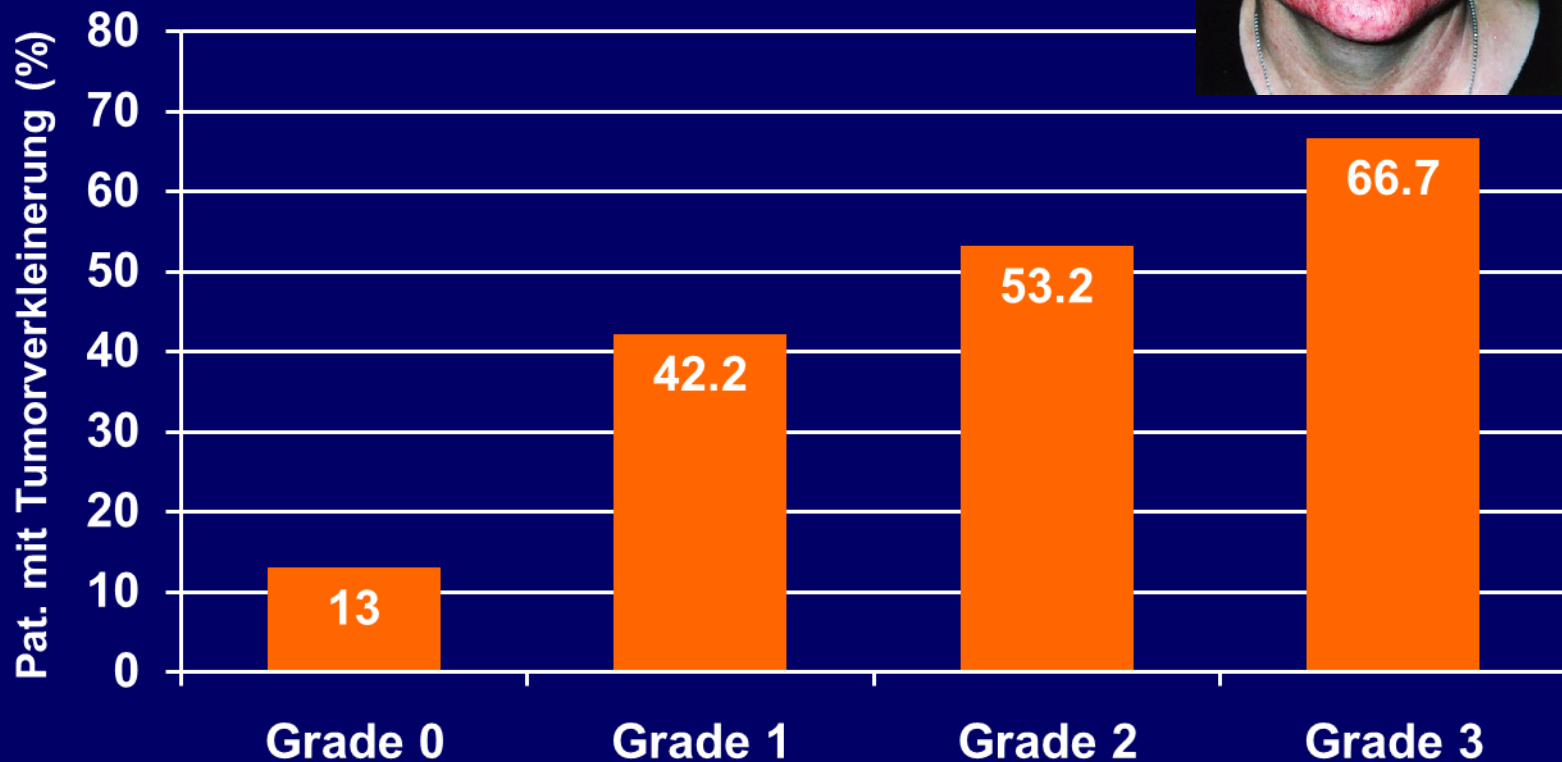
### 3 Inhibition

Suppresses new vessel  
growth

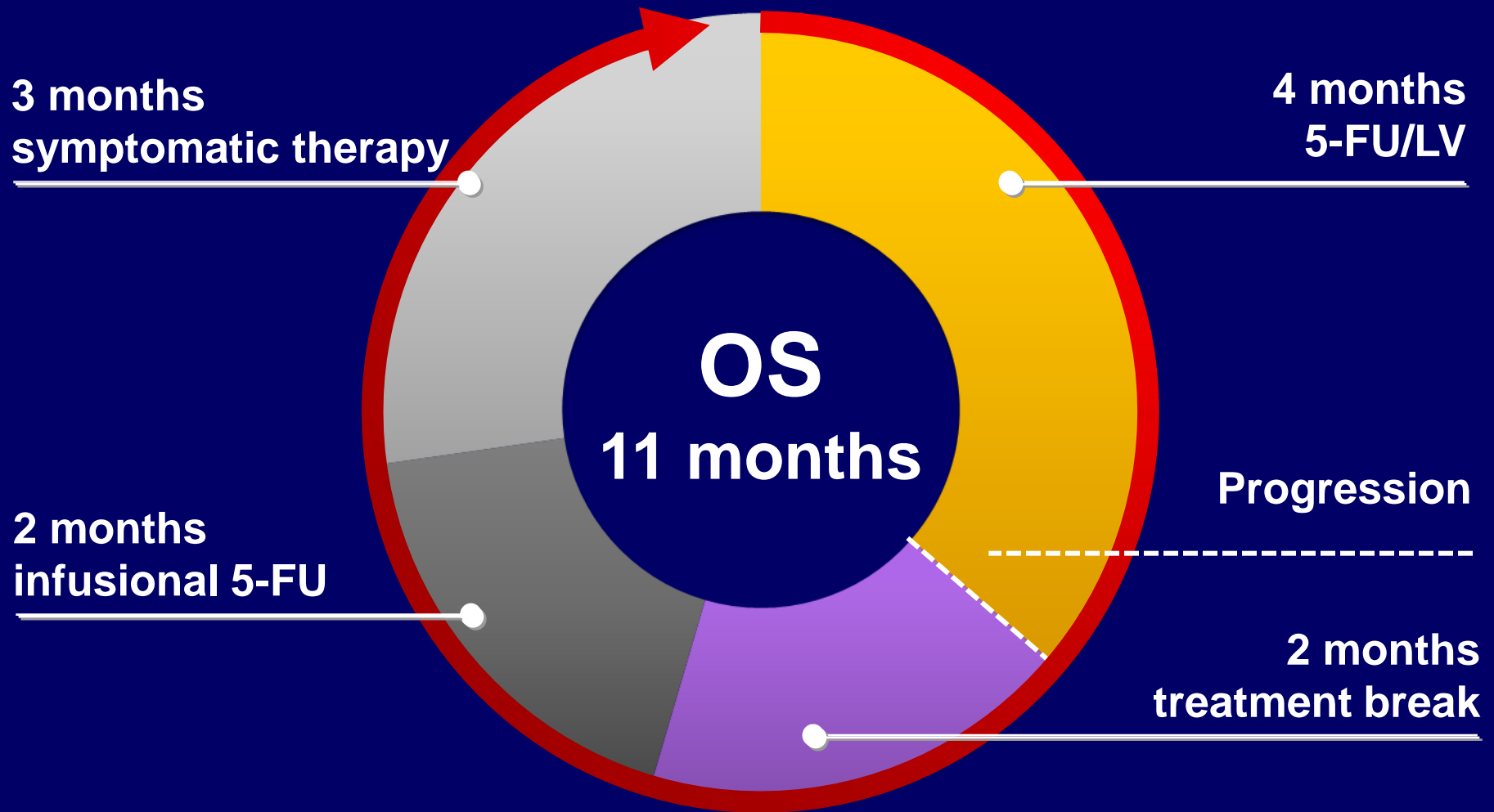
# Anti-epidermal growth factor (EGFR) drugs: mechanism of action



# Anti-EGFR drugs: correlation between skin reaction and tumour shrinkage



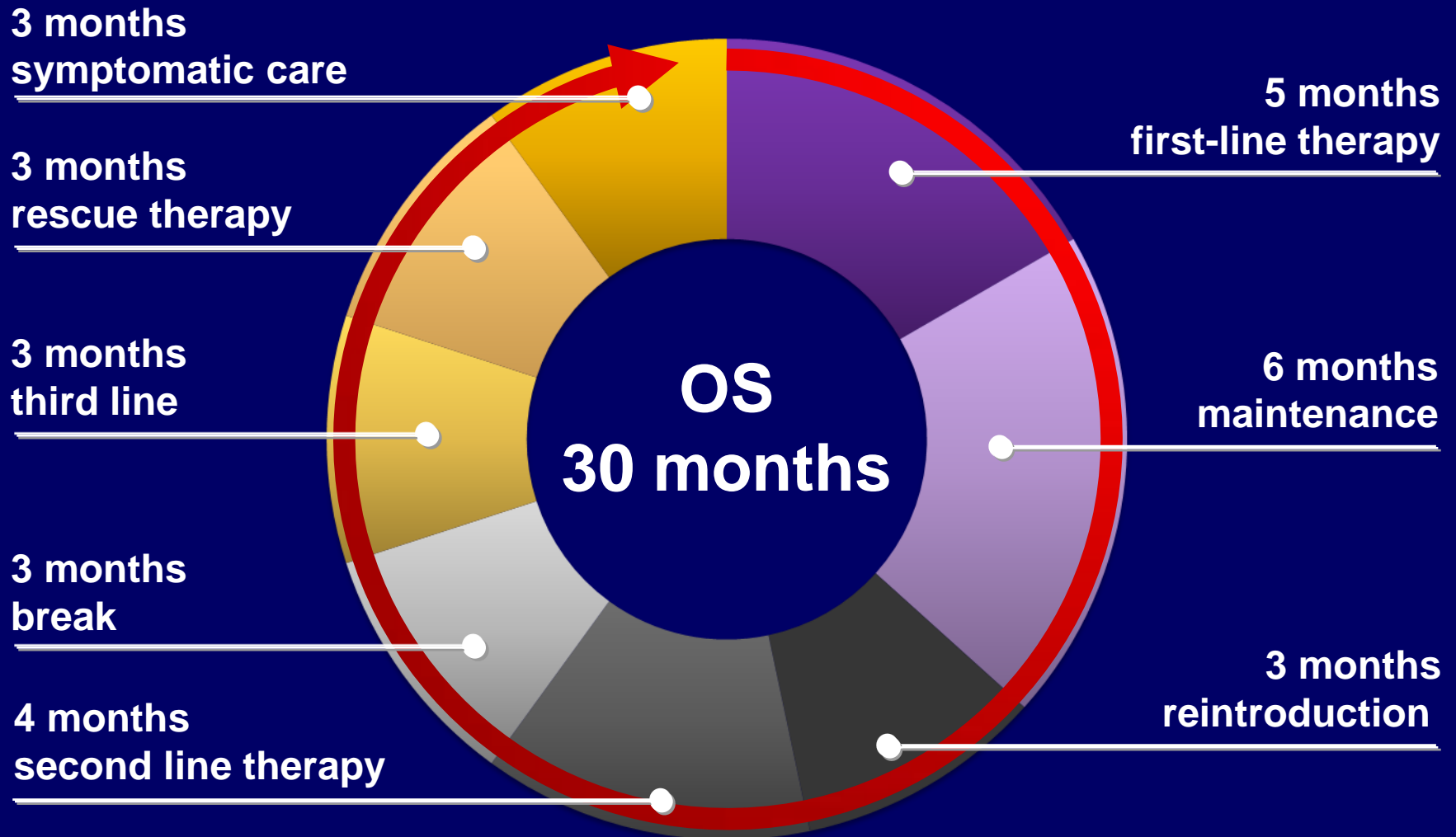
# 1991: A classical case of mCRC



# **The new principles of mCRC management**

- **Biologicals have definitively enriched our therapeutic armamentarium**
- **Exposure to multiple chemotherapy agents is associated with prolonged survival**
- **No need to continue chemo until progression: breaks / holidays or mild maintenance treatment  $\pm$  reintroduction**

# 2012: A classical case of mCRC



# Advances in Colorectal Cancer: Conclusions

- Primary prevention
- Screening
- Better preoperative diagnostic means
- Better surgical techniques
- Superior oncological therapeutical armamentarium
- Adoption of the interdisciplinary patient management
- Increasing knowledge about the optimal timing of available anticancer treatment strategies



Herzlichen Dank