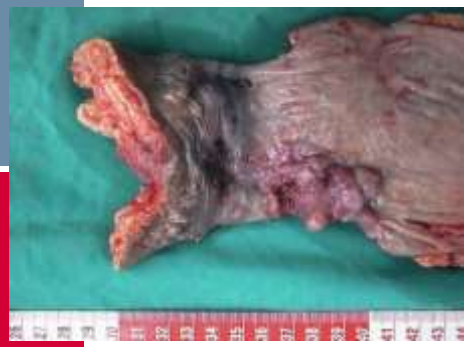
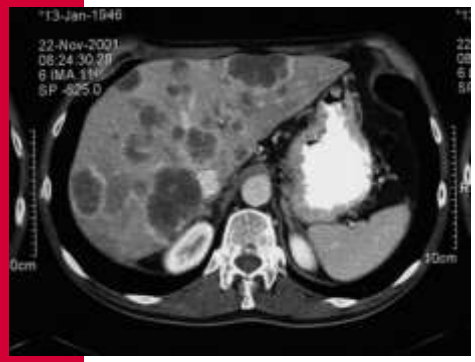
Marc Peeters MD, PhD
Department of Oncology
Antwerp University Hospital



Treatment of Colorectal cancer



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- The management of CRC – overview

1. Colorectal Cancer: do we have a health problem?
2. Colorectal Cancer: one drug and a single physician
3. Colorectal Cancer: multidisciplinary with multiple drugs

→ General Improvement of Outcome!

→ One drug for one patient?

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• CRC is a problem – epidemiology

CANCER	Incidence, n=	Mortality, n=	Male/Female
▪ All	59996	26647	1.3
	- Mean age at diagnosis: 67 (M) and 65 years (F)		
▪ Colorectal	8175	2930	1.5
	- Mean age at diagnosis: 70 (M) and 72 years (F) - Ranking for frequency: 3rd (M, 13.8%); 2nd (F, 13.4%) - Ranking for mortality: 2nd (M, 10.3%); 3rd (F, 11.9%)		

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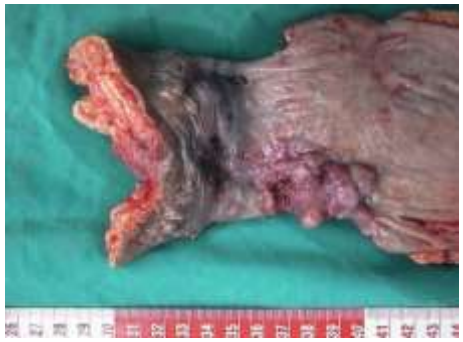
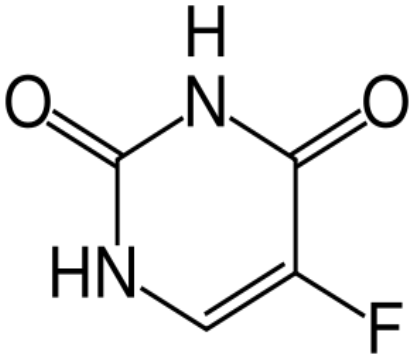
Cancer Incidence in Belgium 2008. Belgian Cancer Registry, 2011

- CRC: one drug and a single physician



Surgeon



5-Fluorouracil

Prognosis

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• Introduction – the current management of CRC

- Diagnosis and Staging

- Multidisciplinary Team Decision

- Therapeutic plan

  - local treatment
  - oncological surgery
  - radiotherapy
  - organ directed treatment
  - systemic treatment

→ Multidisciplinary

→ Personalised

- Adequate Follow up

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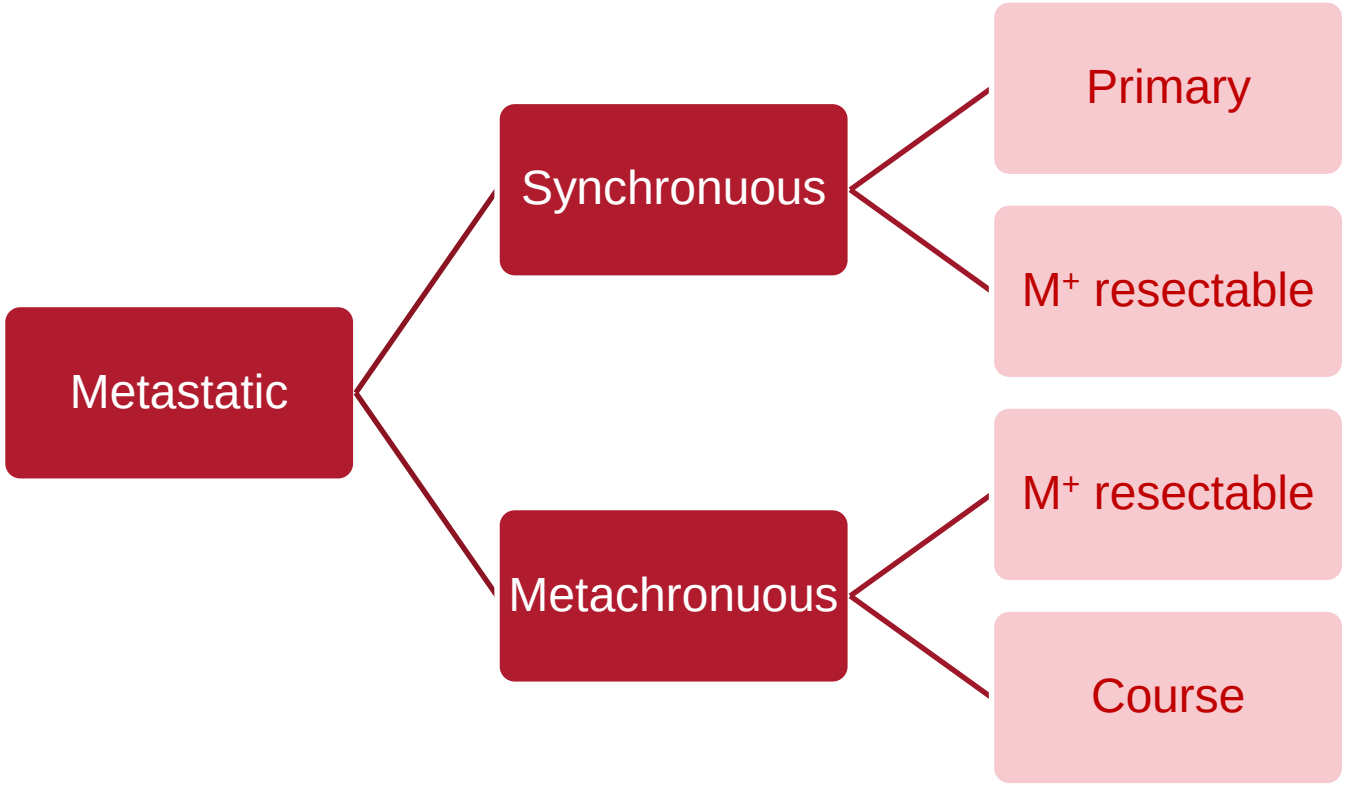
mColorectal Cancer (mCRC) – clinical presentation



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Recommendations

- Liver metastases should be resected if imaging techniques indicate that surgery is an option (strong recommendation).
- Radiofrequency ablation (RFA) should be considered in addition to surgery in patients with liver metastases in order to achieve complete response and sufficient residual liver function (strong recommendation).
- Simultaneous resection of the primary colon tumour and liver metastases can be considered if the patient is sufficiently fit and a simultaneous operation is judged technically feasible (weak recommendation).

Recommendations

- Resection of lung metastases should be considered if complete resection can be achieved (strong recommendation).
- The use of stereotactic body radiation therapy can be considered for unresectable or inoperable limited CRC lung metastases (weak recommendation).

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Peeters M et al. KCE reports 2014;218

Recommendations

- Cytoreductive surgery and HIPEC should be offered to highly selected, fit patients with metastases limited to the abdominal cavity, provided that the number of metastatic sites is limited and the metastases can be removed radically by surgery (strong recommendation).
- HIPEC should only be used with special arrangements for consent and either appropriate clinical governance, including audit or it should be used in the framework of clinical research, since it carries significant risks of morbidity and mortality which needs to be balanced against the perceived benefit (i.e. improvement in survival for patients with colorectal cancer).

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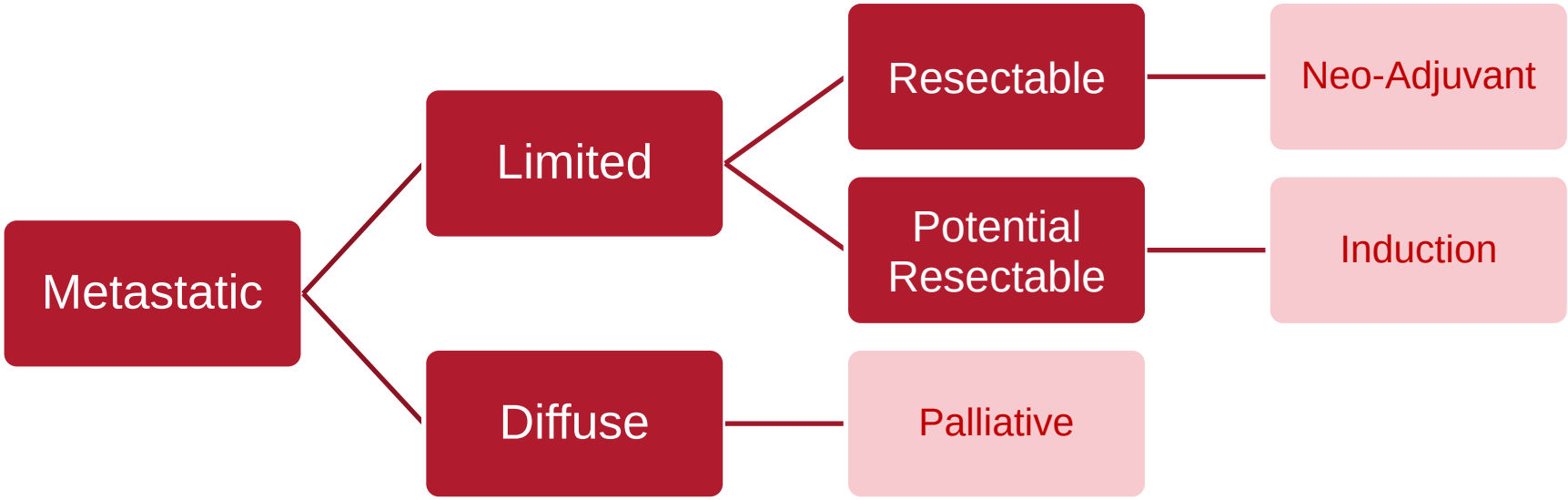
Peeters M et al. KCE reports 2014;218

mColorectal Cancer (mCRC) – clinical presentation



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Recommendations

- Systemic peri-operative or adjuvant chemotherapy can be considered in patients with resectable colorectal liver metastasis (weak recommendation).
- (Neo)adjuvant hepatic arterial infusion chemotherapy is not recommended in patients with resectable colorectal liver metastasis (strong recommendation).

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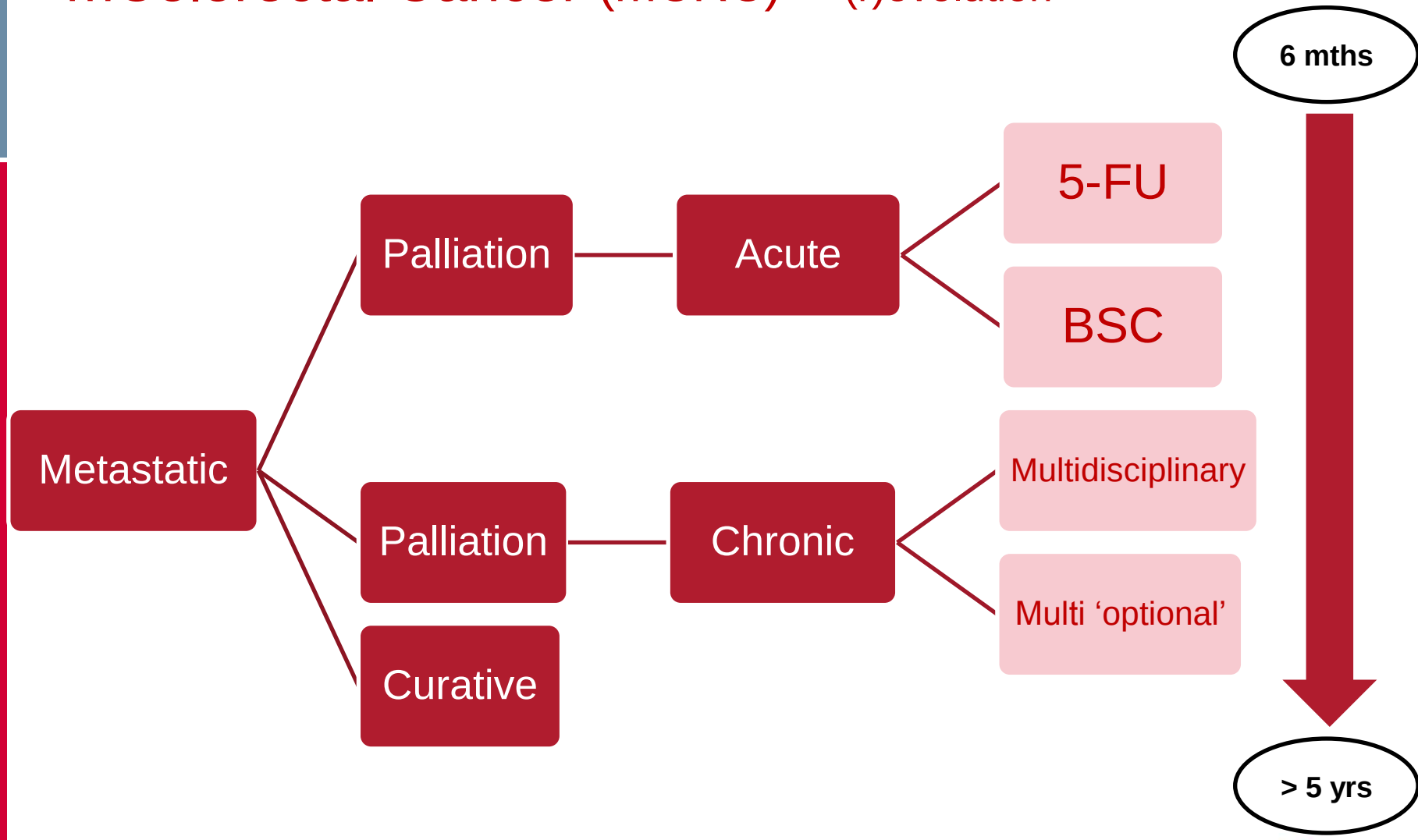
Peeters M et al. KCE reports 2014;218

▪ mColorectal Cancer (mCRC) – (r)evolution



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▪ mColorectal Cancer (mCRC) – (r)evolution

SURGERY	ORGAN DIRECTED	SYSTEMIC
▪ primary tumor	▪ RFA, RadioFrequencyAblation	▪ chemotherapy
▪ metastasis	▪ chemoembolisation ▪ drug eluting beads	▪ 'target' therapy
	▪ radioembolisation	
	▪ (tomo) radiation	

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mColorectal Cancer (mCRC) – registered/future drugs

Oral/IV Fluoropyrimidines

Raltitrexed

Irinotecan

Oxaliplatin

Bevacizumab

Aflibercept

Regorafenib

Cetuximab

Panitumumab

Angiogenesis

Growth

TAS102

Erlotinib/Cmab

…

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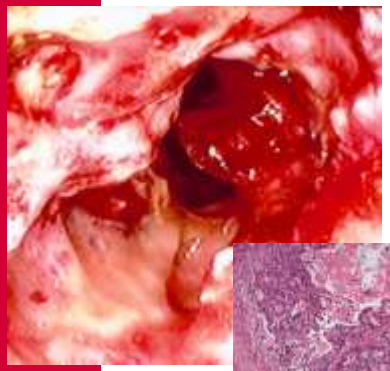
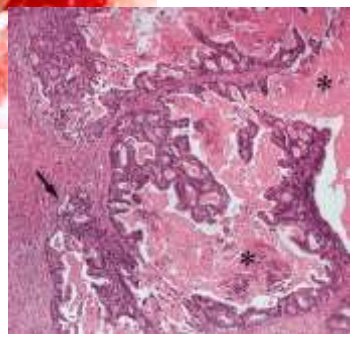
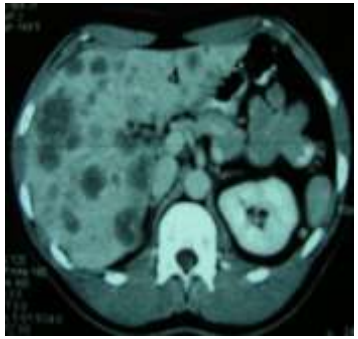
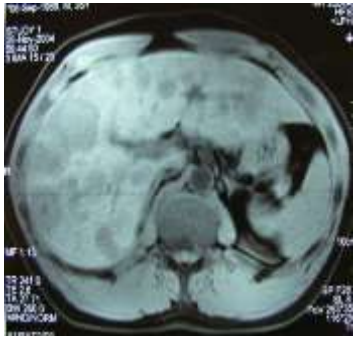
Hemoglobin (g/dl)	Alk. Phosph. (U/l)	AST (U/l)	ALT (U/l)	LDH (U/l)	CEA (µg/l)
12.4 (12.0-15.0)	173 (53-141)	34 (< 31)	43 (< 34)	1367 (84-246)	14507 (< 3.0)



- colonoscopy: stenotic tumor at 25 cm (sigmoid)
- biopsy: moderately differentiated (G_2) adenocarcinoma







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Recommendations

- Combination chemotherapy containing oral or intravenous fluoropyramidines and oxaliplatin or irinotecan is considered the first choice regimen for first–line treatment of metastatic colorectal cancer (strong recommendation).
- If combination chemotherapy contains fluoropyrimidines and irinotecan, fluoropyrimidines should be administered intravenously (weak recommendation).

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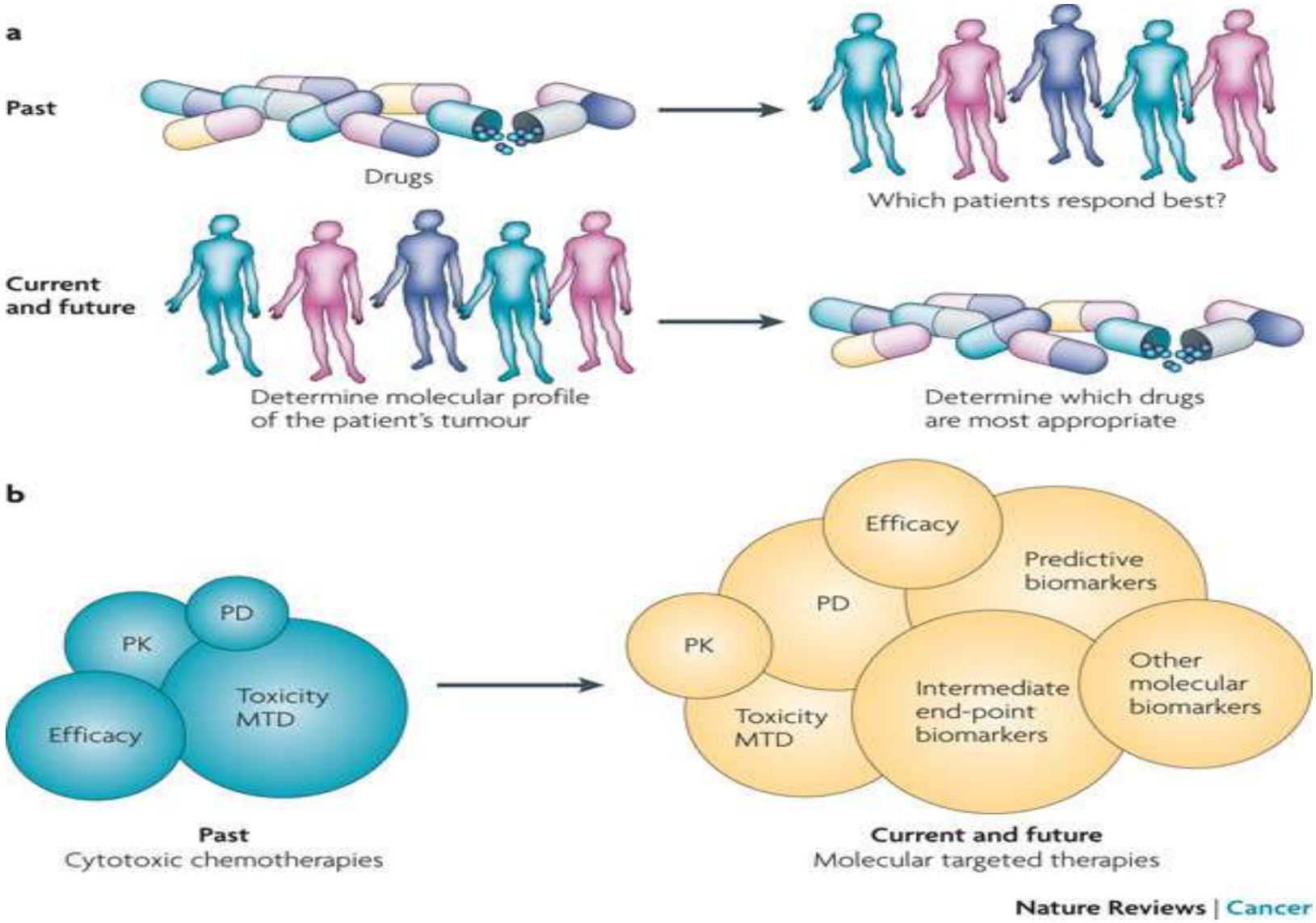
Peeters M et al. KCE reports 2014;218



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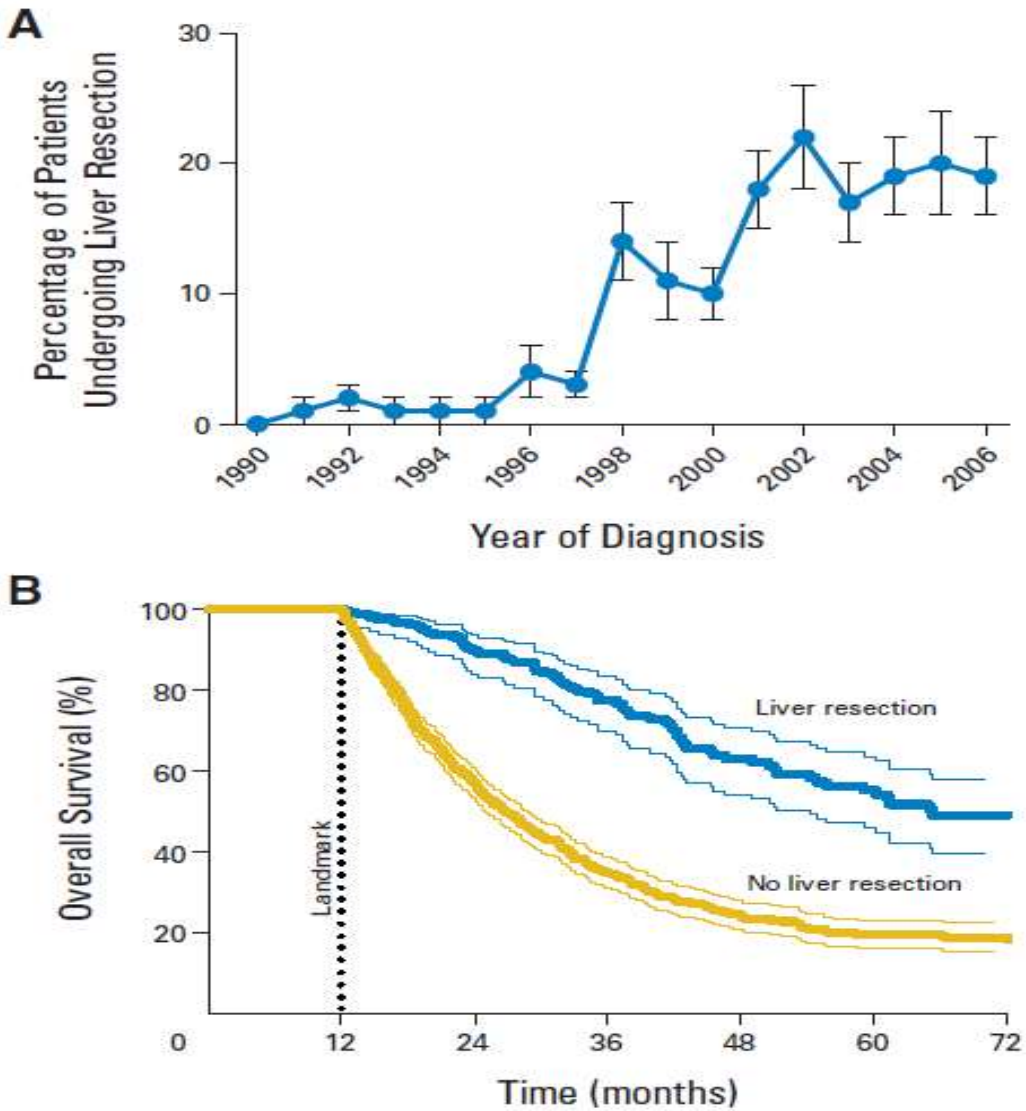
• Introduction – impact on survival (multidisciplinary approach)



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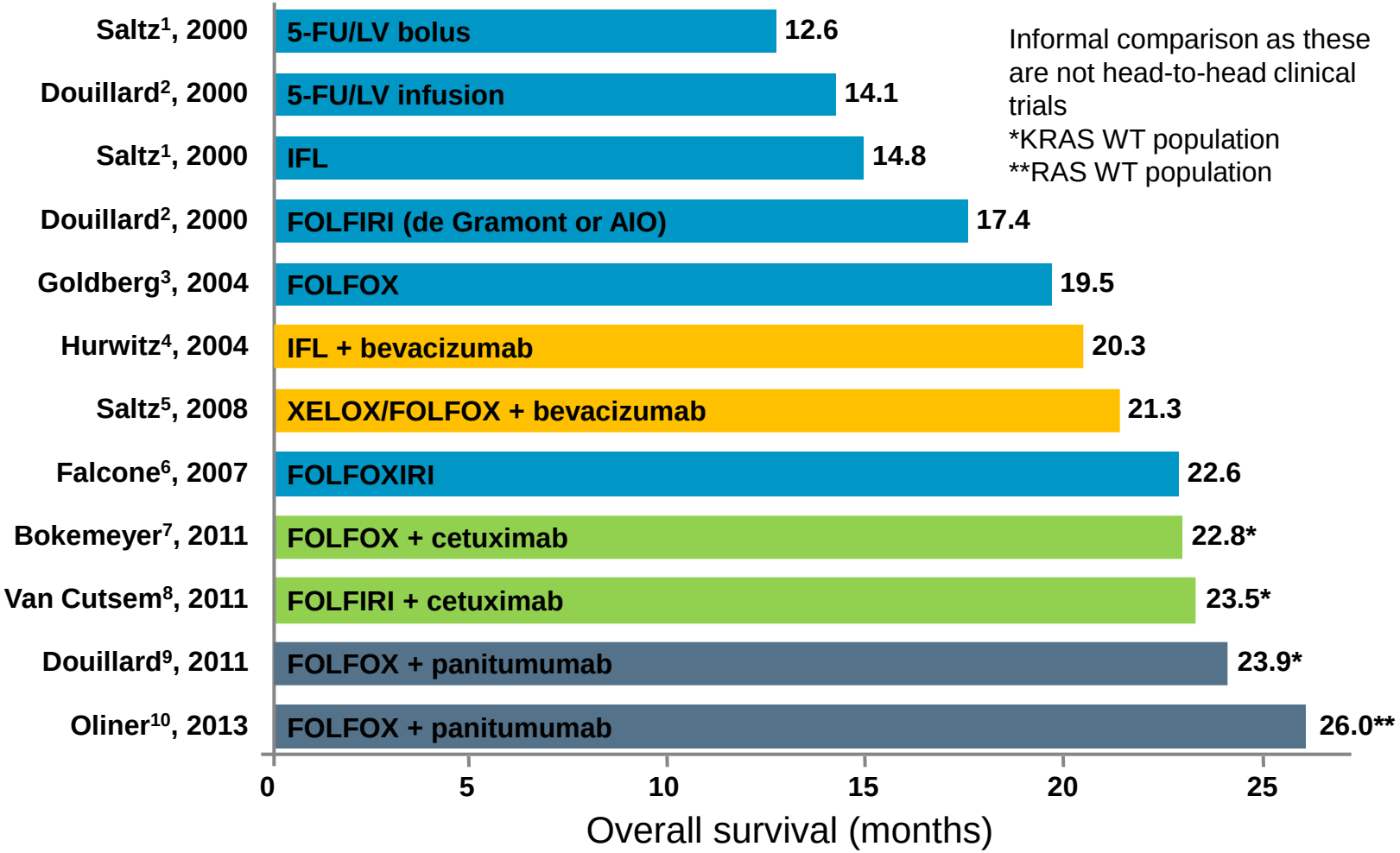
Kopetz S et al. J Clin Oncol 2009;27:3677-3683



Informal comparison as these are not head-to-head clinical trials
*KRAS WT population
**RAS WT population

1. N Engl J Med 2000; 343:905-14; 2. Lancet 2000; 355:1041-7; 3. J Clin Oncol 2004; 22:23-30; 4. N Engl J Med 2004; 350:2335-42; 5. J Clin Oncol 2008; 26:2013-9; 6. J Clin Oncol 2007; 25:1670-6; 7. Ann Oncol 2011; 22:1535-46; 8. J Clin Oncol 2011; 29:2011-9; 9. J Clin Oncol 2011; 29(Suppl):3510 (oral); 10. . J Oliner K, et al. Clin Oncol 31, 2013 (suppl; abstr 3511) (poster)

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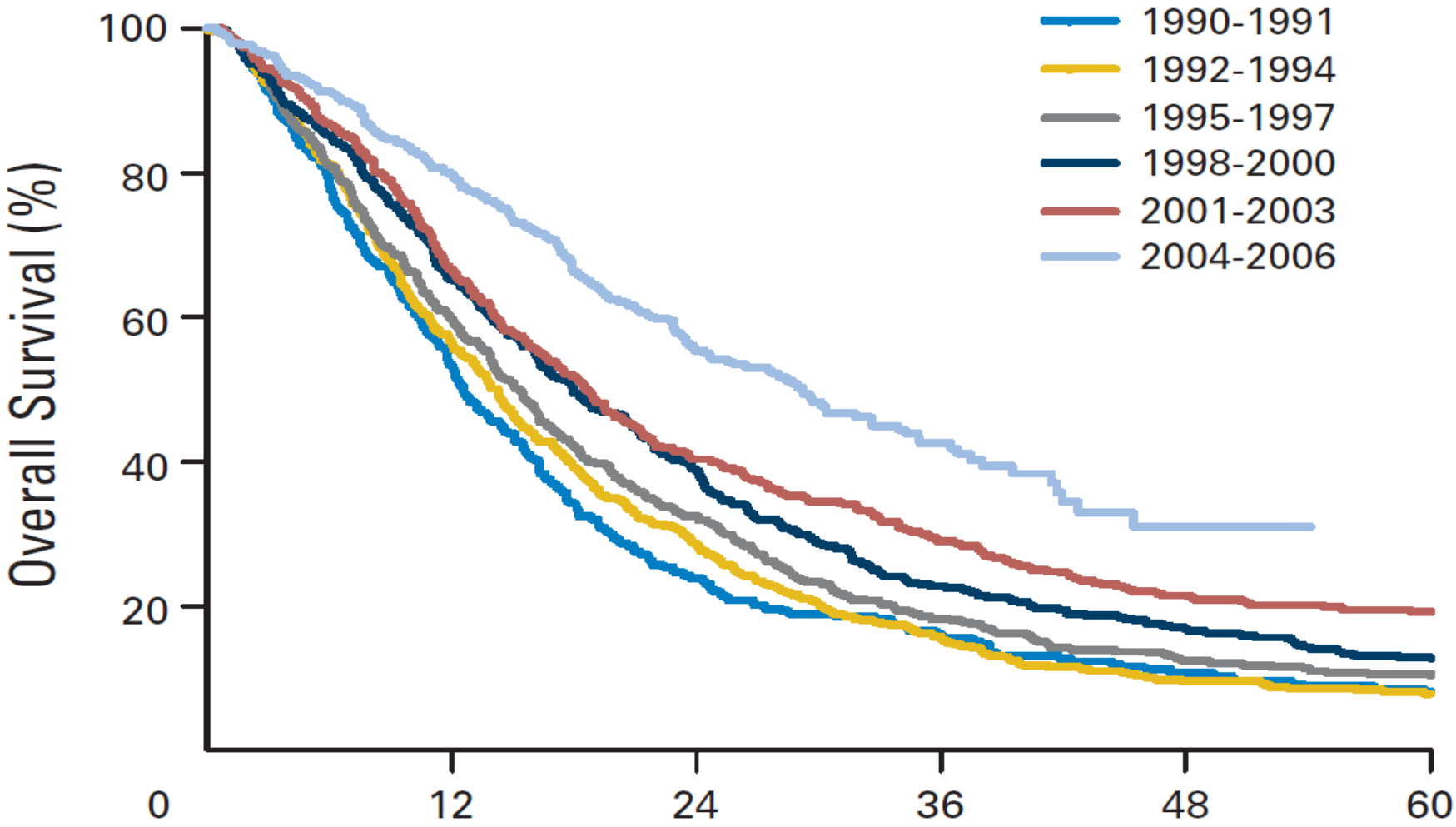
- Introduction – impact on survival



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Kopetz S et al. J Clin Oncol 2009;27:3677-3683

• metastatic colorectal cancer

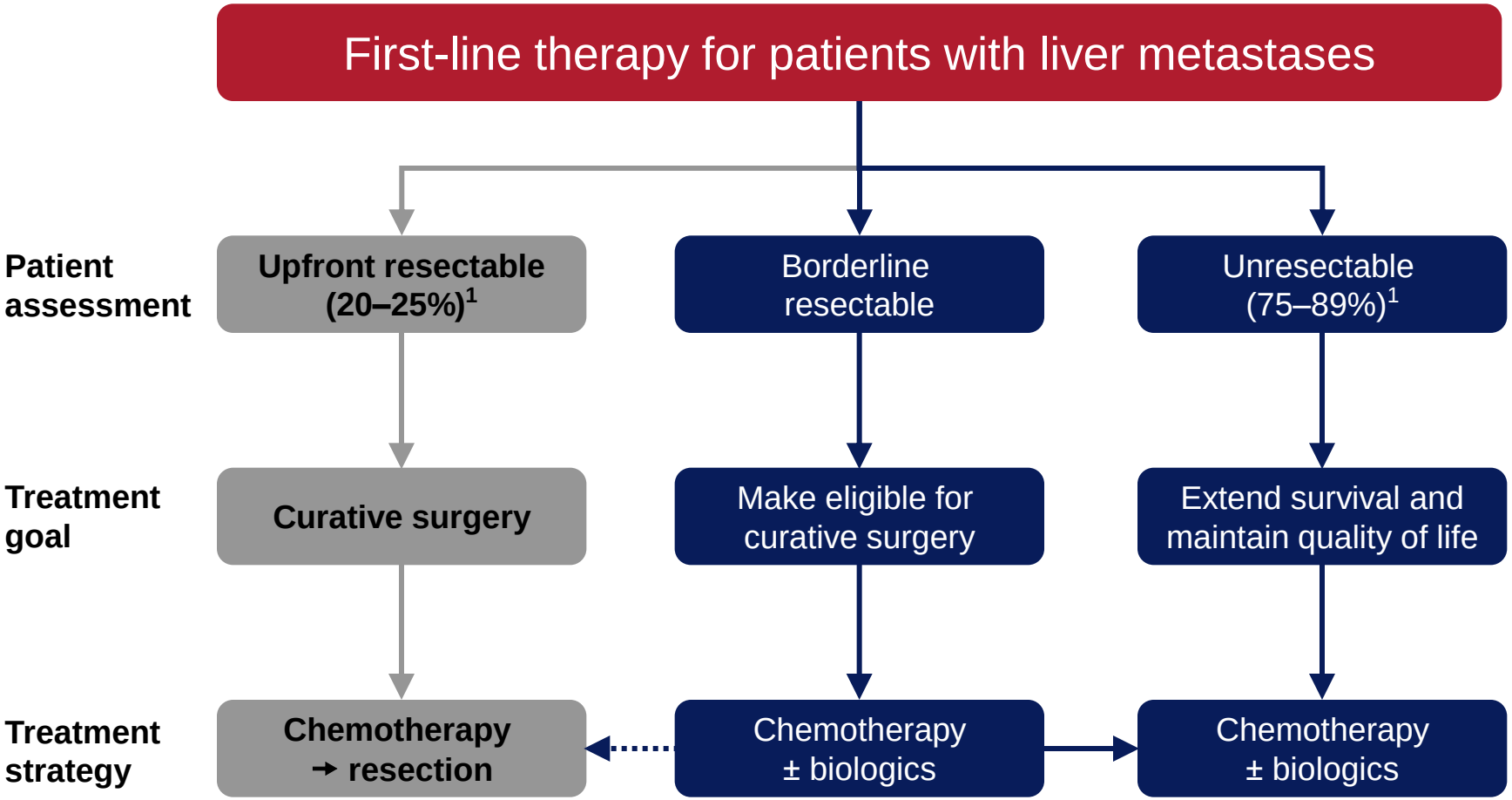

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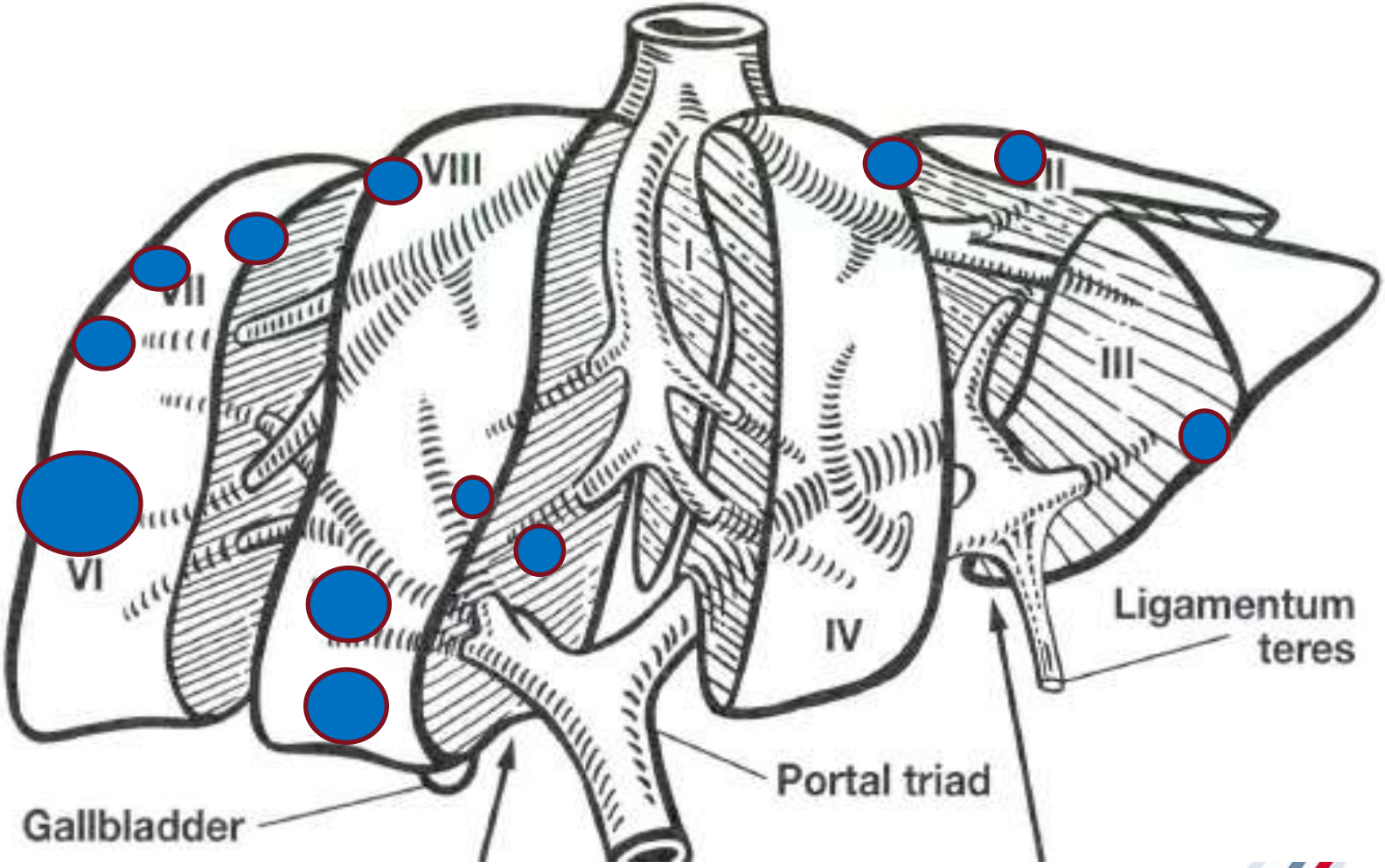
Figure modified from Nordlinger B et al. Ann Oncol. 2009; 20: 985-992; 1. Saif MW. et al. World J Gastroenterol. 2009; 15: 3855-3864

- metastatic colorectal cancer



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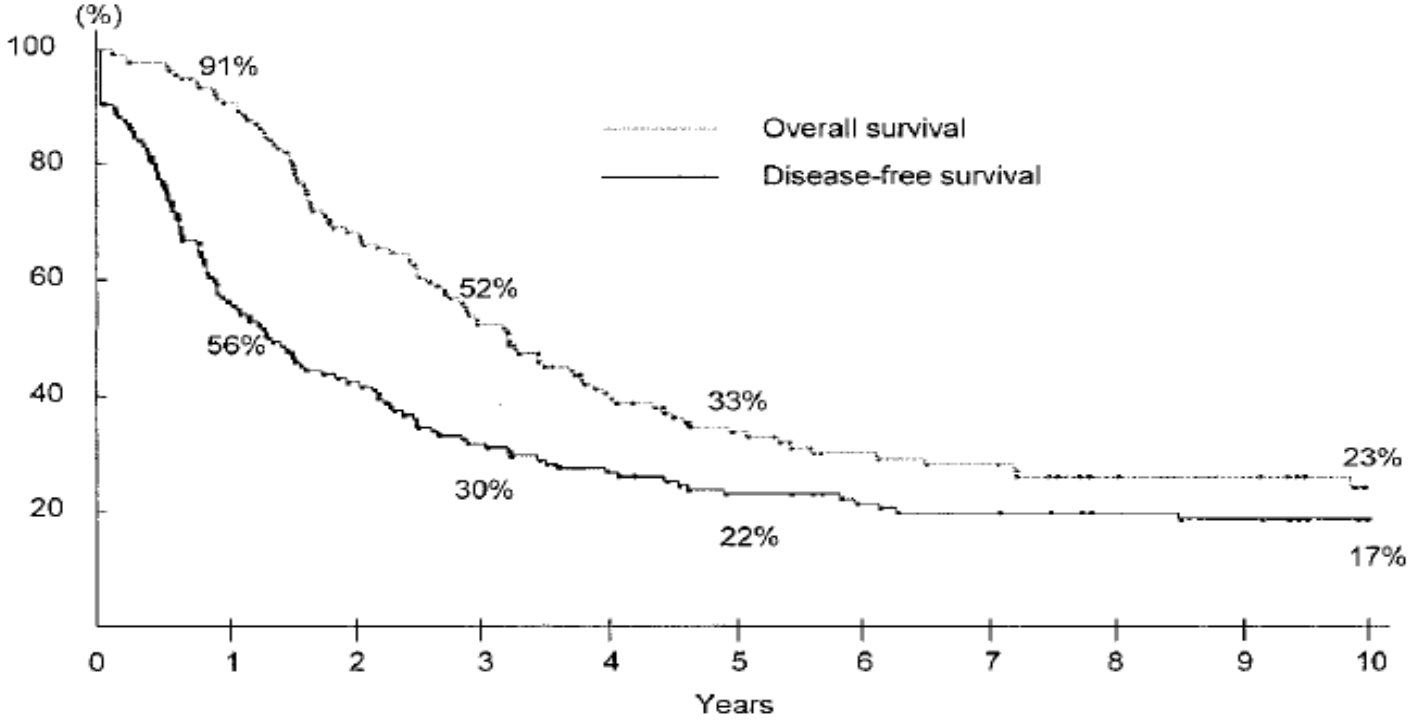
• metastatic colorectal cancer – resection



No Pts at risk	0 Yr	1 Yr	3 Yrs	5 Yrs	8 Yrs	10 Yrs
Overall	138	124	69	37	18	12
Disease-free	138	77	42	28	17	12

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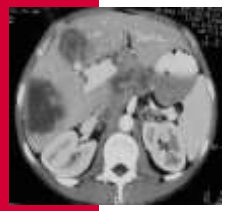
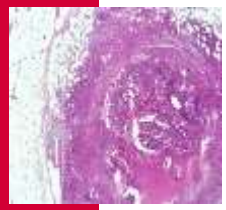
Adam R et al. Ann Surg. 2004 ; 240(4): 644-57

• metastatic colorectal cancer – induction therapy





a) Potential Benefits

- To test chemoresponsiveness (potential prognostic indicator)
- The potential elimination of micrometastatic disease
- The possibility of tumor downsizing

b) Potential Disadvantages

- The possibility of hepatic damage
- The caveat of complete radiological/metabolic response

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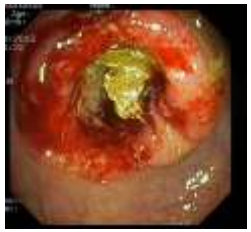
• metastatic colorectal cancer – induction therapy



- Retrospective study
- Responsiveness of the tumour

OUTCOME

	5-year survival	
	Surgery	Pre-operative CT
• All patients	35%	43%
– responders		85%
– non-responders		35%

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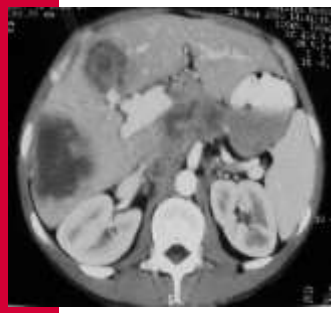
Allan PJ et al. J Gastrointest Surg 2003;7:109-115

- metastatic colorectal cancer – induction therapy



- Regimen with objective response (OR) > 50%
- Monitoring of patients during neoadjuvant therapy
- Impact of toxicity on surgery

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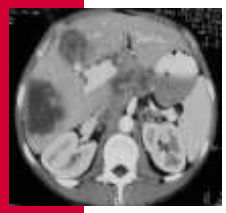
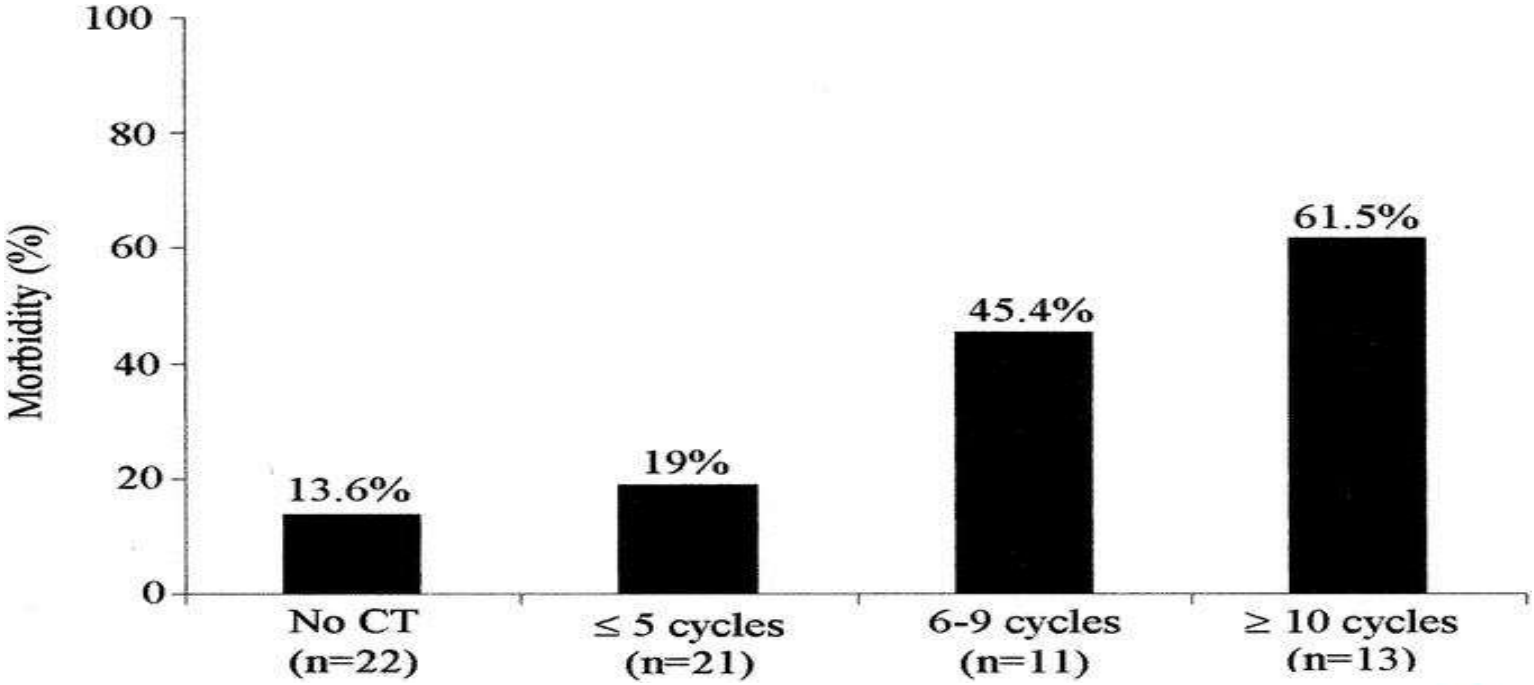
- metastatic colorectal cancer – induction therapy



Chemotherapy → Surgery → Chemotherapy

TOXICITY



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Karoui M et al. Ann Surg 2006;243:1-7

• metastatic colorectal cancer – induction therapy

1. Induction therapy
   - Regimen : maximum response potential
   - Duration : 3 to 4 months before surgery
   - Evaluation : CT (PET/CT?) every 6 to 8 weeks
2. Bevazicumab added to chemotherapy regimen
   - Be carefull with prior radiotherapy or stenting
   - Bevacizumab-free window of 6 weeks before surgery
3. Cetuximab added to chemotherapy regimen
   - No specific influence on timing or sequence of surgery

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▪ mColorectal Cancer (mCRC) – ‘current’ possibilities

	First	Second	Third	…
• **RAS mutant**	CT Beva + CT	CT Beva + CT Afli + CT	CT Regoraf.	Regoraf
	Study Protocols			
• **RAS wild**	CT Beva + CT Cetu + CT Pmab + CT	CT Beva + CT Cetu + CT Pmab ± CT Afli + CT	CT Cetu + CT Pmab Regoraf	Regoraf
	Study Protocols			

CT=chemotherapy; Beva=bevacizumab; Cetu=cetuximab; Pmab=panitumumab; Afli=aflibercept; Regoraf=regorafenib

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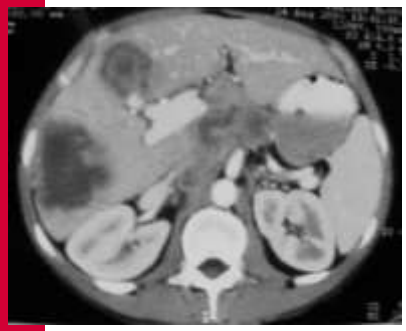
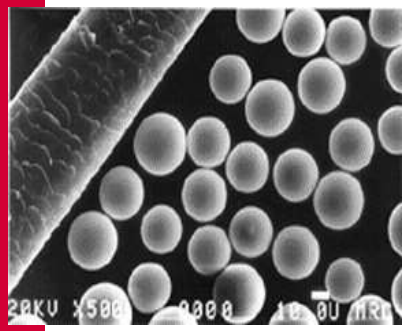
- metastatic colorectal cancer – palliative treatment





- Chemoembolisation (1964); floxuridine, oxaliplatin
- Local Ablative Therapies; RadioFrequency, Cryo, Laser,…
- Drug-eluting Beads; irinotecan, doxorubicin
- Radioembolisation; Yttrium-90 microspheres (SIR-Spheres, TheraSpheres)

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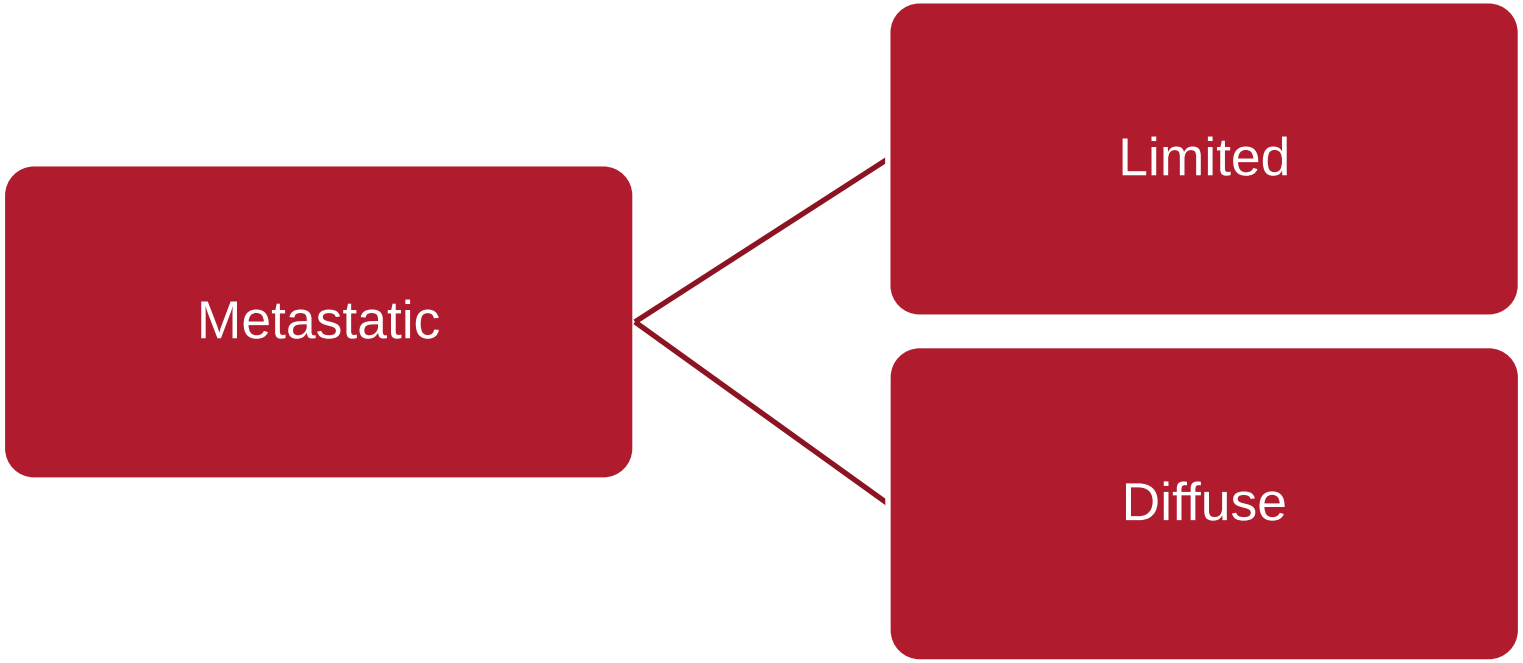

‘OLD’

Line of Treatment

S

PD

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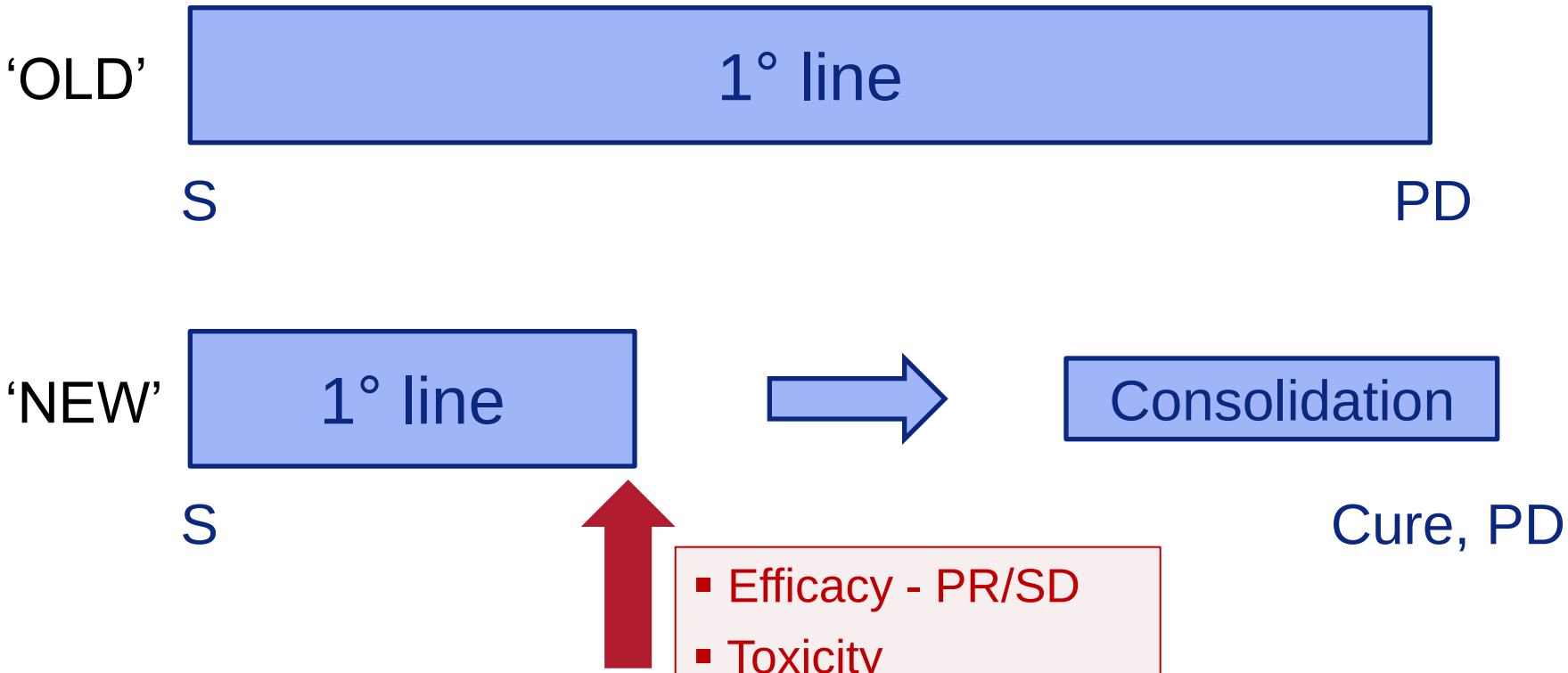
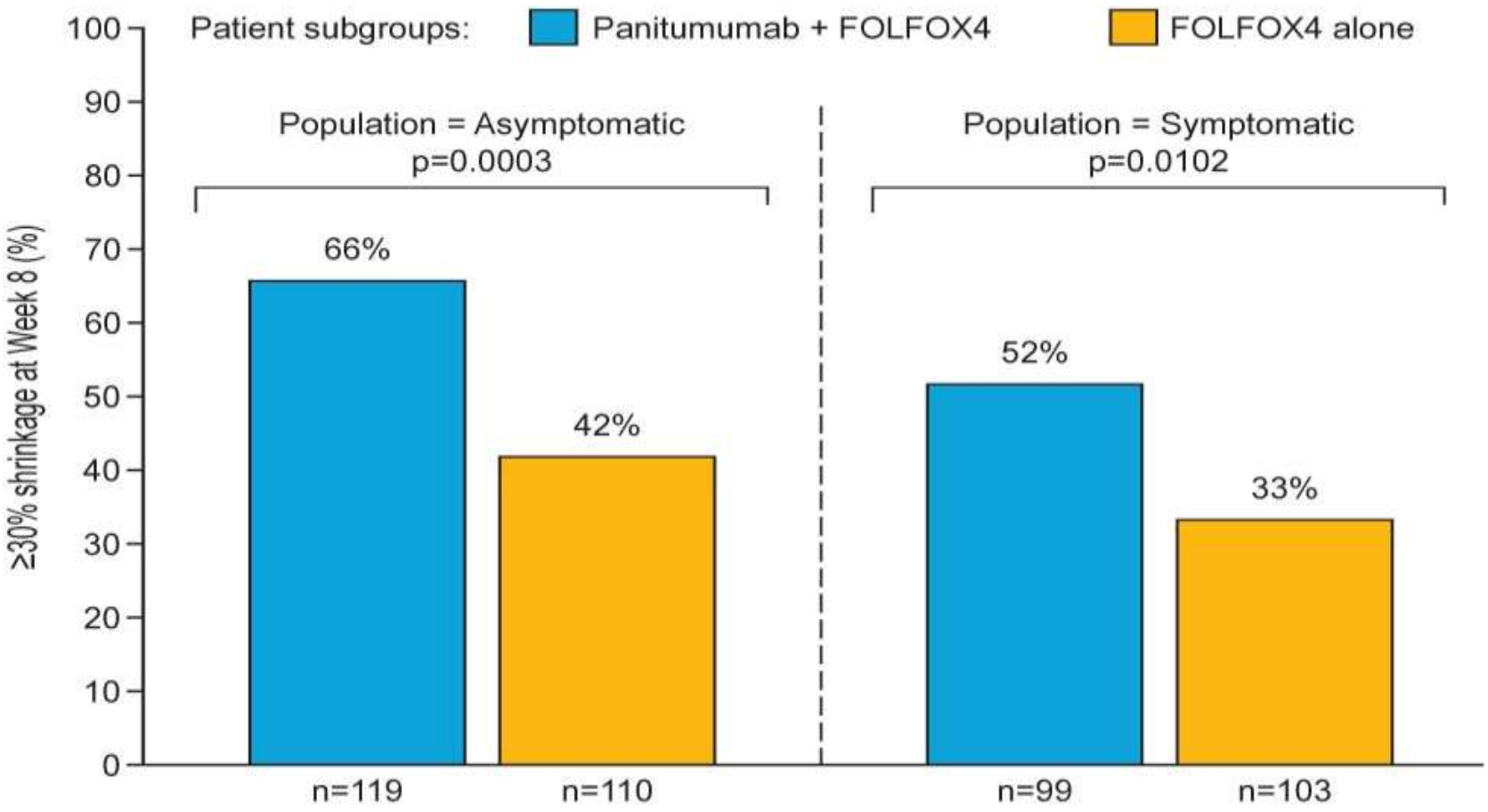
Consolidation/Maintenance treatment



- Efficacy - PR/SD
- Toxicity
- 'Holiday'
- R_0 resection

S = start; PR = partial response; SD = stable disease; PD = progressive disease

Consolidation/Maintenance treatment – efficacy



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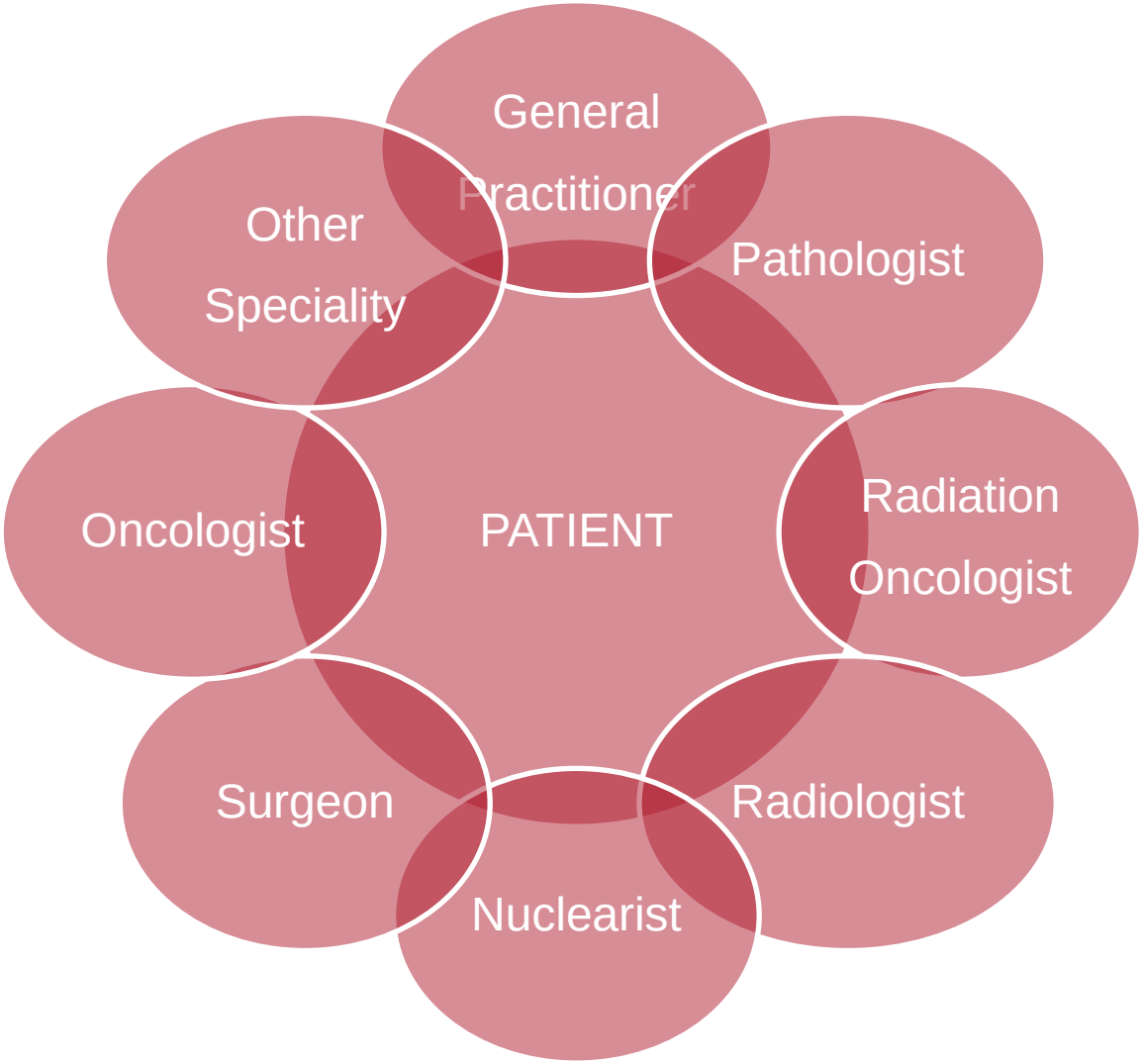
Douillard JY et al. WCGI 2013



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‘The optimal **treatment** in the **correct** patient at the **perfect** moment in an **experienced** center’

→ mCRC is a chronic disease

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I wish to thank

The Multidisciplinary Oncology Team at Antwerp University Hospital

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