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Neoplasia del retto con metastasi sincrone

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The problem

450,000 Rectal Cancer cases/year (worldwide)

15-25% synchronous metastases
Additional ~40% will develop metastases
Most commonly to the liver and lung

10–25% candidates for SURGERY
Aim: R0 resection

75–90% not resectable

Initially resectable

Borderline resectable

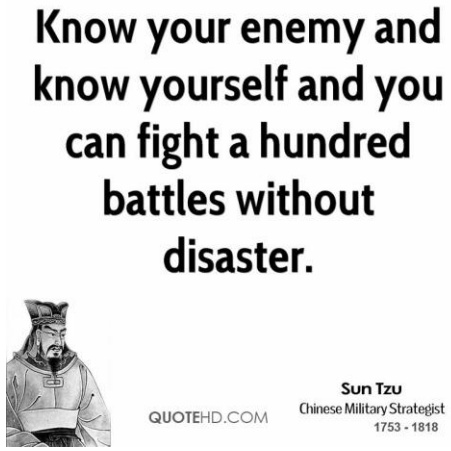
Torre LA, CA Cancer J Clin 2015; Chu, et al. Clin Colorectal Can 2006; Manfredi S, Ann Surg 2006;;
Kemeny, et al. Oncologist 2007; Leichman. Surg Oncol Clin N Am 2007;
Leonard, et al. JCO 2005; Tomlinson, et al. JCO 2007; Van Cutsem, et al. EJC 2006

Know your enemy…

- Symptoms (pain, bleeding, obstruction)

- Adequate stadiation:
  - ✓ Local staging by MRI abdomen inferior and pelvis
  - ✓ Distant staging by CT scan of thorax and abdomen
  - ✓ In case of liver mets, MRI with liver-specific contrast

    (for lesions < 10 mm MRI is more accurate than CT, 81.1 vs 74.8%; p=.05.
    Better definition of biliary tree, vascular anatomy and parenchyma)
  - ✓ PET-CT is not routinely indicated
  - ✓ Intraoperative US



Fowler KJ et al. Ann Surg Oncol 2012
Adam R et al. Oncologist 2012

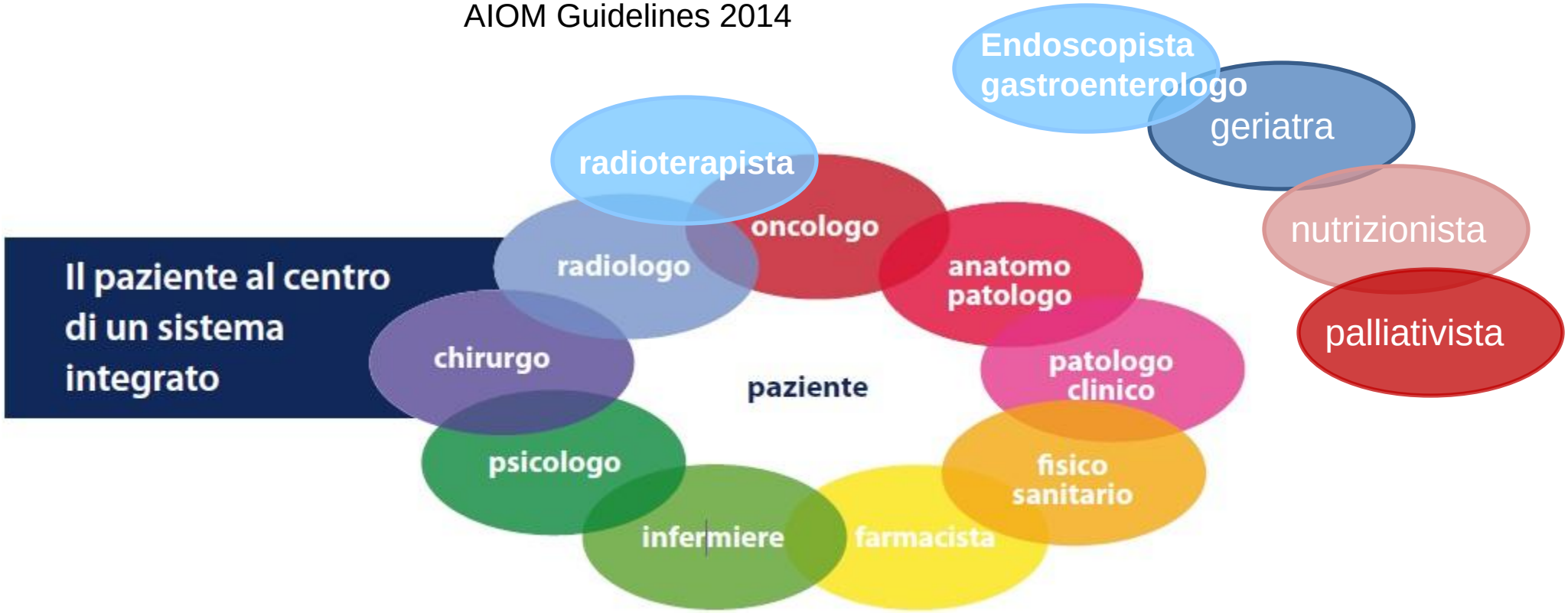
- Mutational status
  - ✓ RAS and BRAF mutation

…and discuss with your “friends”

multidisciplinary approach for selecting the best treatment strategy

The optimal treatment strategy for patients with metastatic CRC (mCRC) should be discussed in a multidisciplinary expert team.

ESMO Guidelines 2014
AIOM Guidelines 2014



The multidisciplinary approach in daily practice

- **The medical oncologist needs the surgeon…**
  - ✓ advising on potential resectability
  - ✓ advising on timing of surgery
  - ✓ improving long-term survival

- **The surgeon needs the medical oncologist…**
  - ✓ making resectable patients unresectable
  - ✓ controlling the disease before surgery
  - ✓ improving survival by therapy
  - ✓ preventing recurrence after surgery

Rectal cancer and synchronous metastases

- No randomized trials
- Only retrospective series
  - ✓ A minority of patients with rectal cancer
  - ✓ Heterogeneity of surgical approach
- Treatment options depends on site and extent of primary tumor and metastatic disease

Tanaka et al, Surgery 2004
Chua et al, Dis Colon Rectum 2004

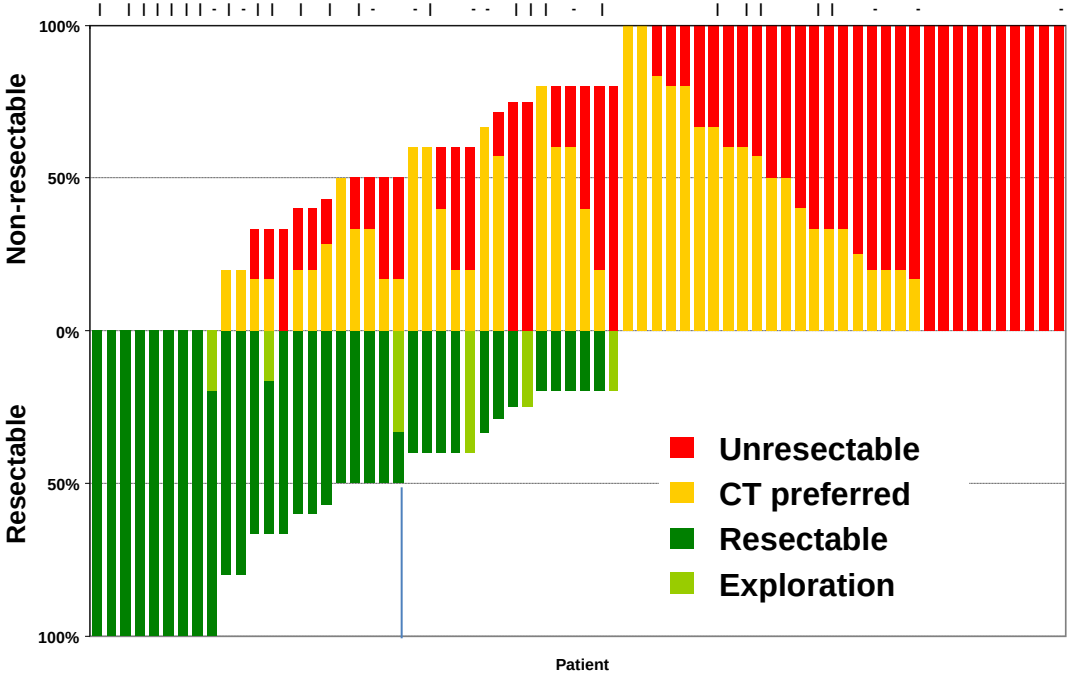
Upper third or T2N0 rectal cancer with synchronous metastases

No need for radiation

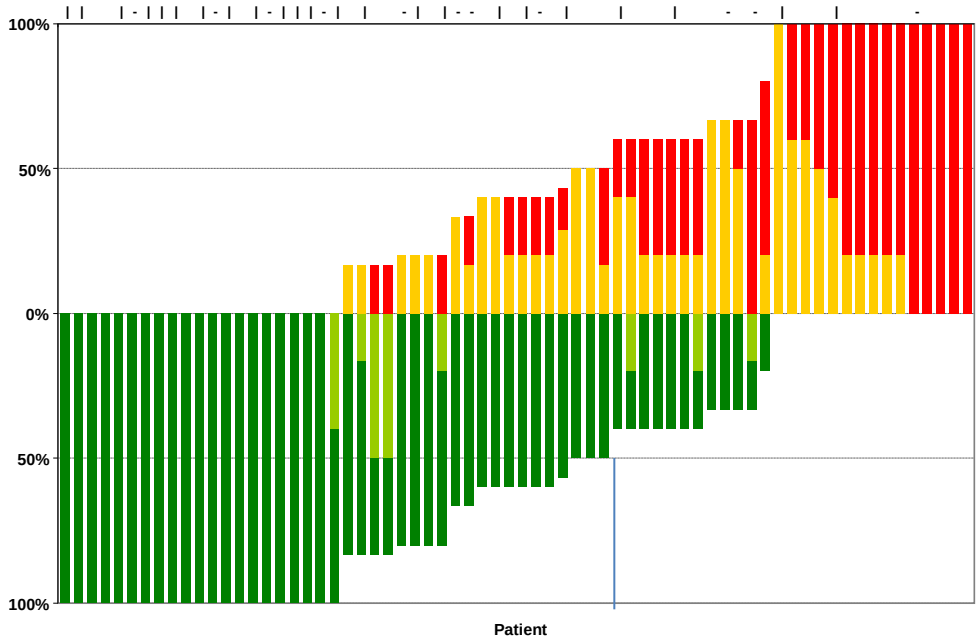
Treatment strategy similar for colon cancer

CELIM: Resectability according to blinded assessment by 7 surgeons

Before cetuximab + CT



After cetuximab + CT



Disagreement between surgeons in 30% of cases
Resectability increased 32 → 60%

Folprecht et al, Lancet Oncol 2009

Scenario 1: Resectable patient

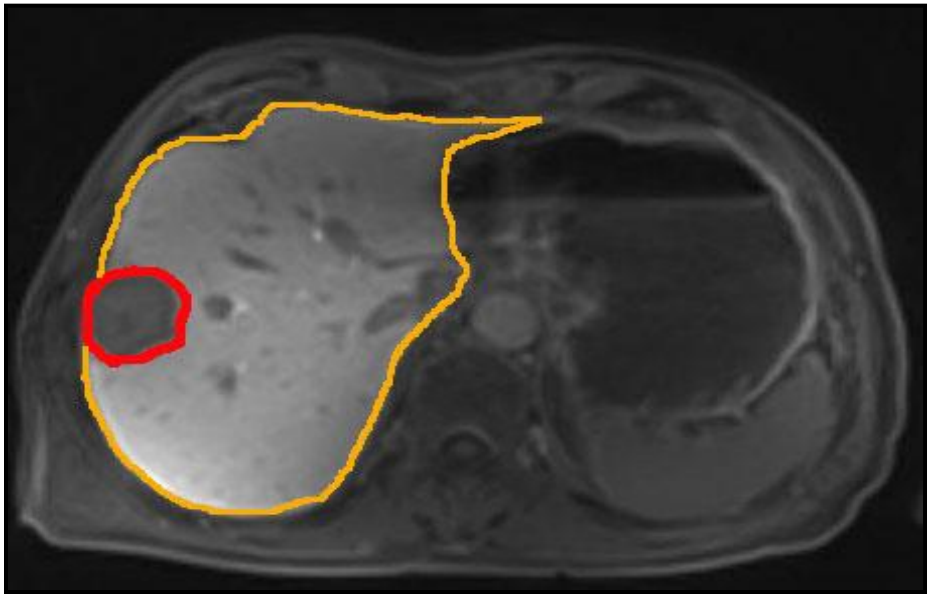
Definition

- Complete resection (± ablation) and free resection clearance
- Adequate future remnant liver parenchyma
  (25-30%, 40% after CT)
- Preservation of at least 1 of 3 hepatic veins
- Preservation of adequate biliary drainage

Ann Surg Oncol 2006;13:1261-68

Goals

- **Cure**
- **Prolonged DFS/PFS**
- Local control of rectal cancer and
  ↓ pelvic recurrence
- Avoid progression of mets
  during treatment of primary



Mid or low T3N+ or T4N0/+

Option 1: neoadjuvant CT → surgery → CT

- advantage: adequate treatment for mets
- limitation: suboptimal control of rectal cancer
- simultaneous surgery feasible for small and easily accessible mets
- for other pts, which resection first?

  Traditional or reverse approach? (CT → liver surgery → CRT → rectal surgery)
- chemo for 6 months globally

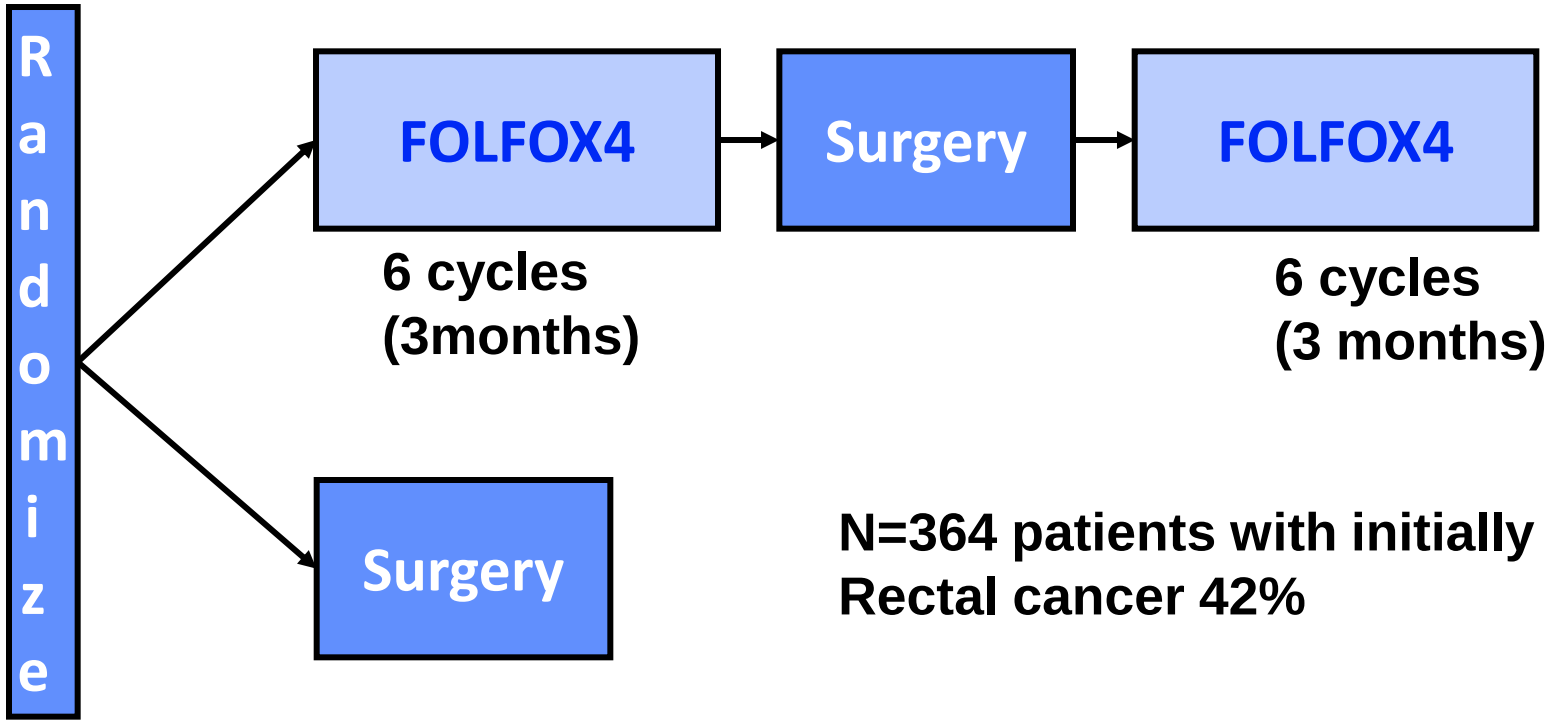
Boostrom SY et al. J Gastr Surg 2011

Mentha G et al. J Surgery 2006

Lancet 2008; 371: 1007–16

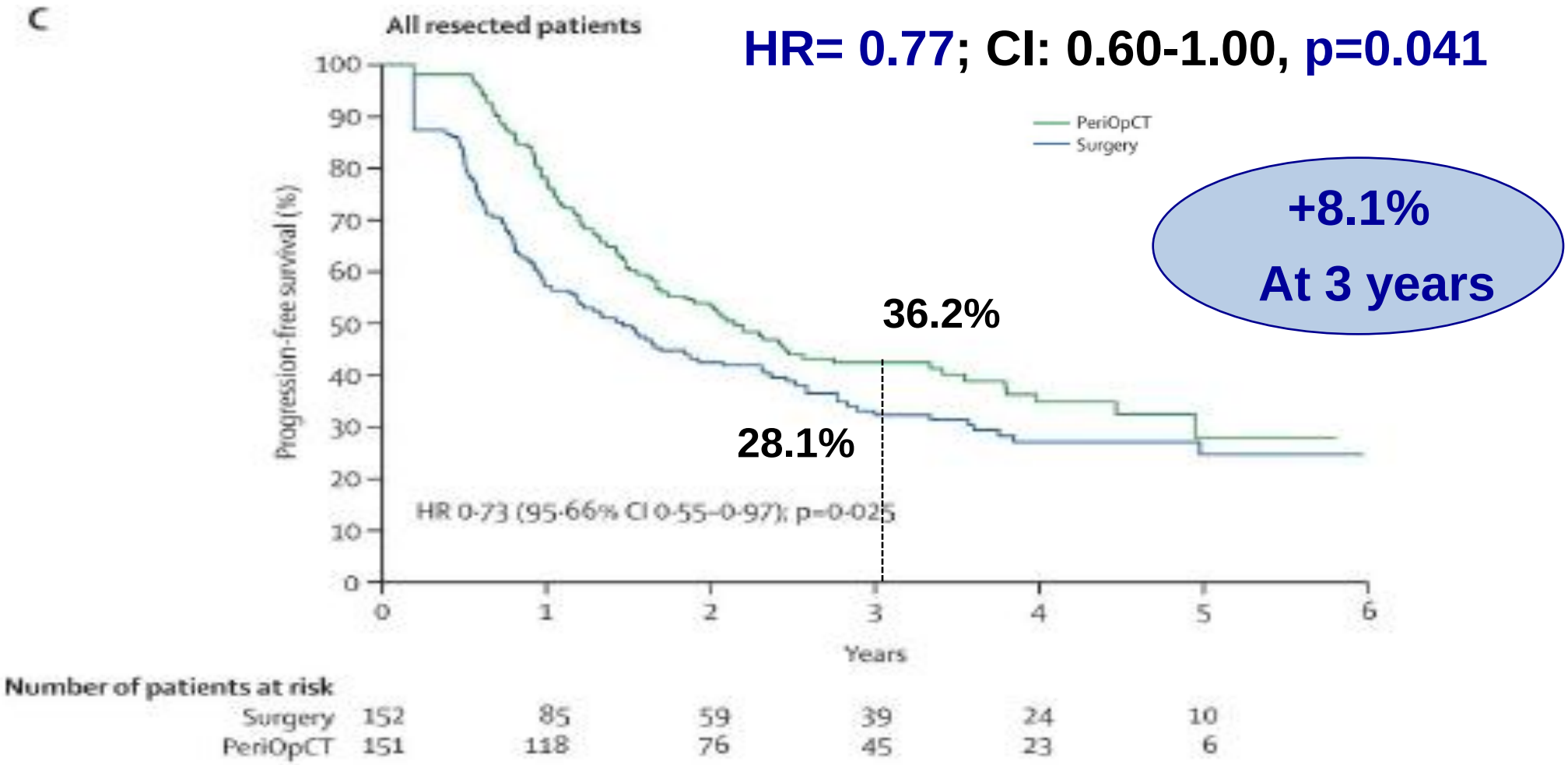
Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

Bernard Nordlinger, Halfdan Sorbye, Bengt Glimelius, Graeme J Poston, Peter M Schlag, Philippe Rougier, Wolf O Bechstein, John N Primrose, Euan T Walpole, Meg Finch-Jones, Daniel Jaeck, Darius Mirza, Rowan W Parks, Laurence Collette, Michel Praet, Ullrich Bethe, Eric Van Cutsem, Werner Scheithauer, Thomas Gruenberger for the EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK,* Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO),* Australasian Gastro-Intestinal Trials Group (AGITG),* and Fédération Francophone de Cancérologie Digestive (FFCD)**



N=364 patients with initially resectable mCRC
Rectal cancer 42%

Primary endpoint: PFS in elegible pts



Long term results (ASCO 2012): Primary end-point of PFS benefit met, not significant benefit in OS (+4.1% at 5-y; HR 0.87, CI 0.66-1.14)

At a median follow-up of 8.5 years: patients alive 39%

B Nordlinger, Lancet 2008

Mid or low T3N+ or T4N0/+

Option 2: neoadjuvant CT → short course RT → surgery

- advantage: adequate control of mets and better control of the primary tumor for T3 (may be not sufficient for T4); not delay surgery
- rectal surgery first
- (then interval CT)
- and liver surgery

Mid or low T3N+ or T4N0/+

Option 3: chemoradiation 45 to 50.4 Gy → surgery on T

- advantage: improved local control of the primary tumor
- limitation: suboptimal control of mets during CRT and delay surgery
- rectal surgery first
- (then interval CT)
- and surgery of mets

Preliminary observations shows that the risk for progression of mets during RT+CT is less than 20% and this risk may be decreased to 5% by inclusion of oxaliplatin in RCT

ManceauG et al. Surgery 2013

Mid or low T3N+ or T4N0-1

Option 4: neoadjuvant CT → CRT → surgery

- advantage: adequate control of mets and primary tumor
- limitation: suboptimal control of mets during CRT and delay surgery
- rectal surgery first
- (then interval CT)
- and liver surgery

Mid or low anyT, N0/+

Option 5: surgery → CT "adjuvant" ± RT

- advantage: immediate control of mets and primary tumor
- not treatment of micrometastases
- increased risk of R1 resection in advanced locally cancer (CRM+)
- reasonable option for limited T and "easily" resectable mets
- surgery simultaneously or staged

In the 2014 version of these guidelines, the panel removed the option of surgery as the initial treatment because they believe that the majority of patients should receive preoperative therapy. The panel acknowledges that some patients may not be candidates for chemotherapy or radiation; clinical judgment should be used in such cases.

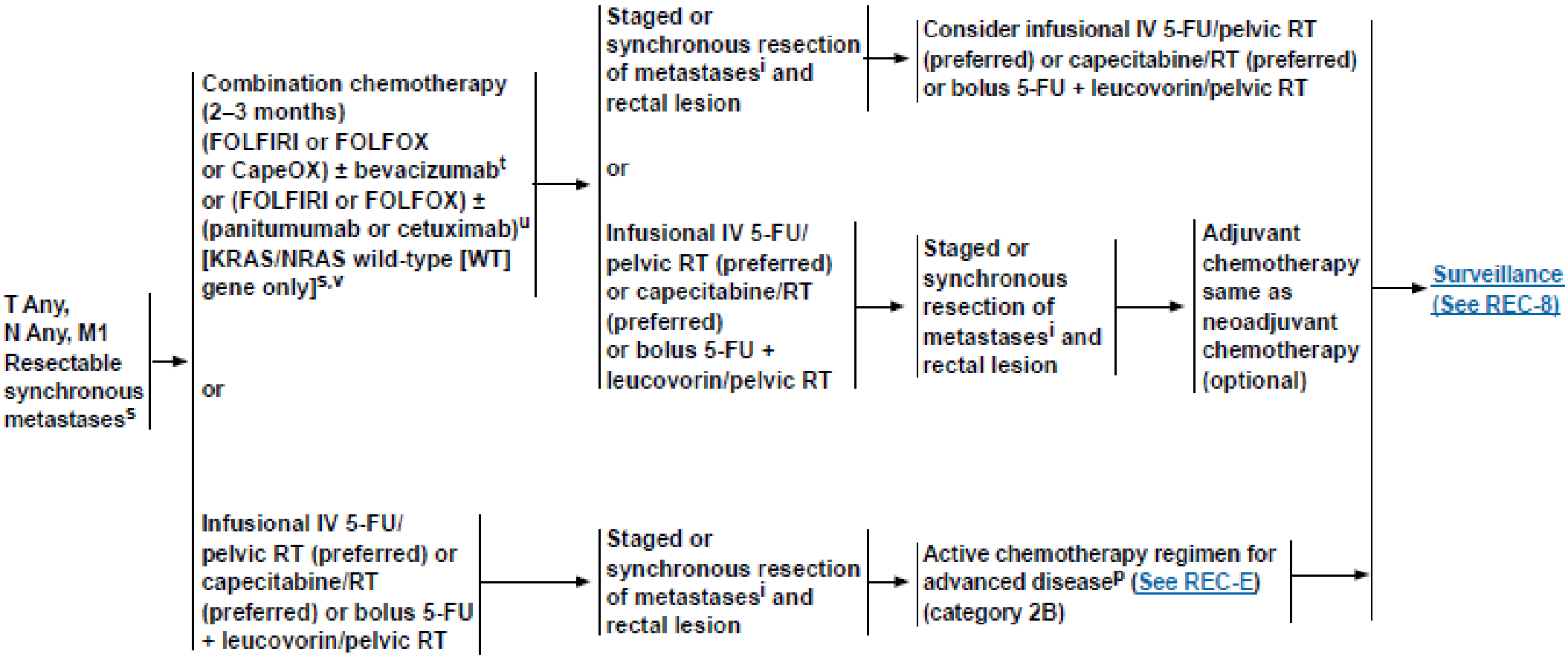
NCCN Guidelines 2015

NCCN guidelines for resectable metastatic rectal cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2015
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

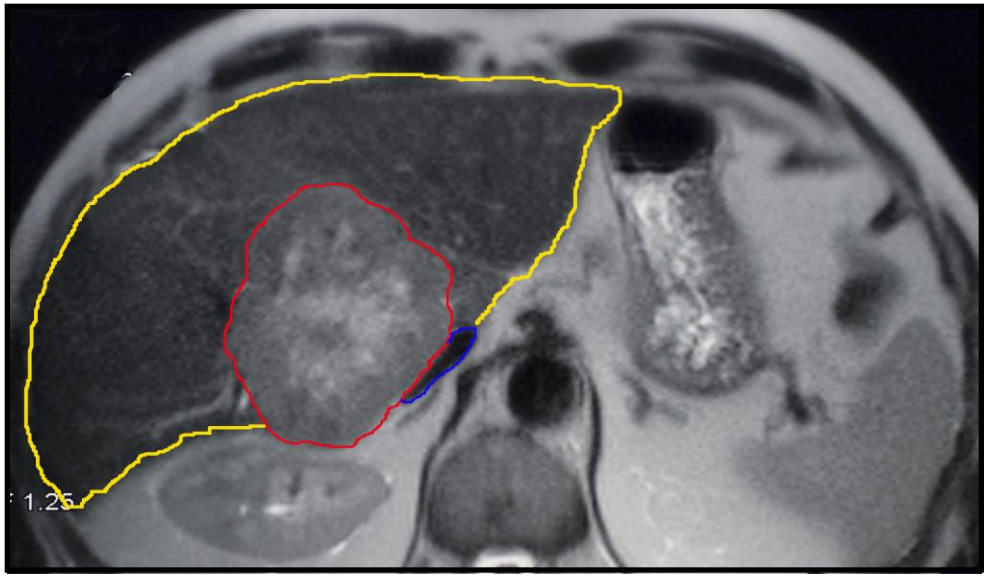


Scenario 2: 'borderline' resectable patient

Definition

- non-resectable liver metastases (PVE required)
- metastases in contact with both portal triads or all hepatic veins
- **>1 known risk factor for early recurrence e.g.**
  - synchronous disease
  - metastases >5cm
  - >1 metastases
  - LN positive primary
  - positive tumour markers

PVE = portal vein embolisation



Goals:

- Increase PFS/OS
- Improve QoL
- Avoid complications related to T
- **Cure, if mets become resectable**

“Si può fare…!”

…In many ways resectability is in the eyes of the beholder and different decisions may be made by different surgeons

John L. Marshall

Prof. Henry Bismuth

VS

Dr. Frankestein Jr

OS, PFS and RR benefit in randomized trials using biologics vs CT only in 1st-line mCRC

Biologic agent	Study	Regimen	OS	PFS	RR
Bevacizumab	Hurwitz	IFL	✓*	✓	✓
Bevacizumab	MAX	Capecitabine	X	✓*	X
Bevacizumab	Kabbinavar	5-FU	X*	✓	X
Bevacizumab	NO16966	Ox-CT	X	✓*	X
Panitumumab	PRIME	FOLFOX	X	✓*	X
ERBITUX	CRYSTAL	FOLFIRI	✓	✓*	✓
ERBITUX	OPUS	FOLFOX	X	✓	✓*
ERBITUX	COIN	Ox-CT	X*	X	✓
ERBITUX	NORDIC	Ox-CT	X*	X	X

*Primary endpoint; NR, not reported

Triplet +/- bev in first line treatment

	n	RR	PFS	OS
FOLFOXIRI/Bev	252	65%	12.1	31.0
FOLFIRI/Bev	256	53%	9.7	25.8
Falcone, ASCO 2013		p<0.01	HR 0.77 p<0.01	HR 0.83
FOLFOXIRI	122	60%	9.8	22.6
FOLFIRI	122	34%	6.9	16.7
Falcone, JCO 2007		p<0.0001	HR 0.63; p<0.01	HR 0.80;p=0.032
FOLFOXIRI/Bev	41	81%	18.8	
FOLFOX/Bev	39	62%	12.0	
Bridgewater, ECC 2013		p=0.061	p<0.01	

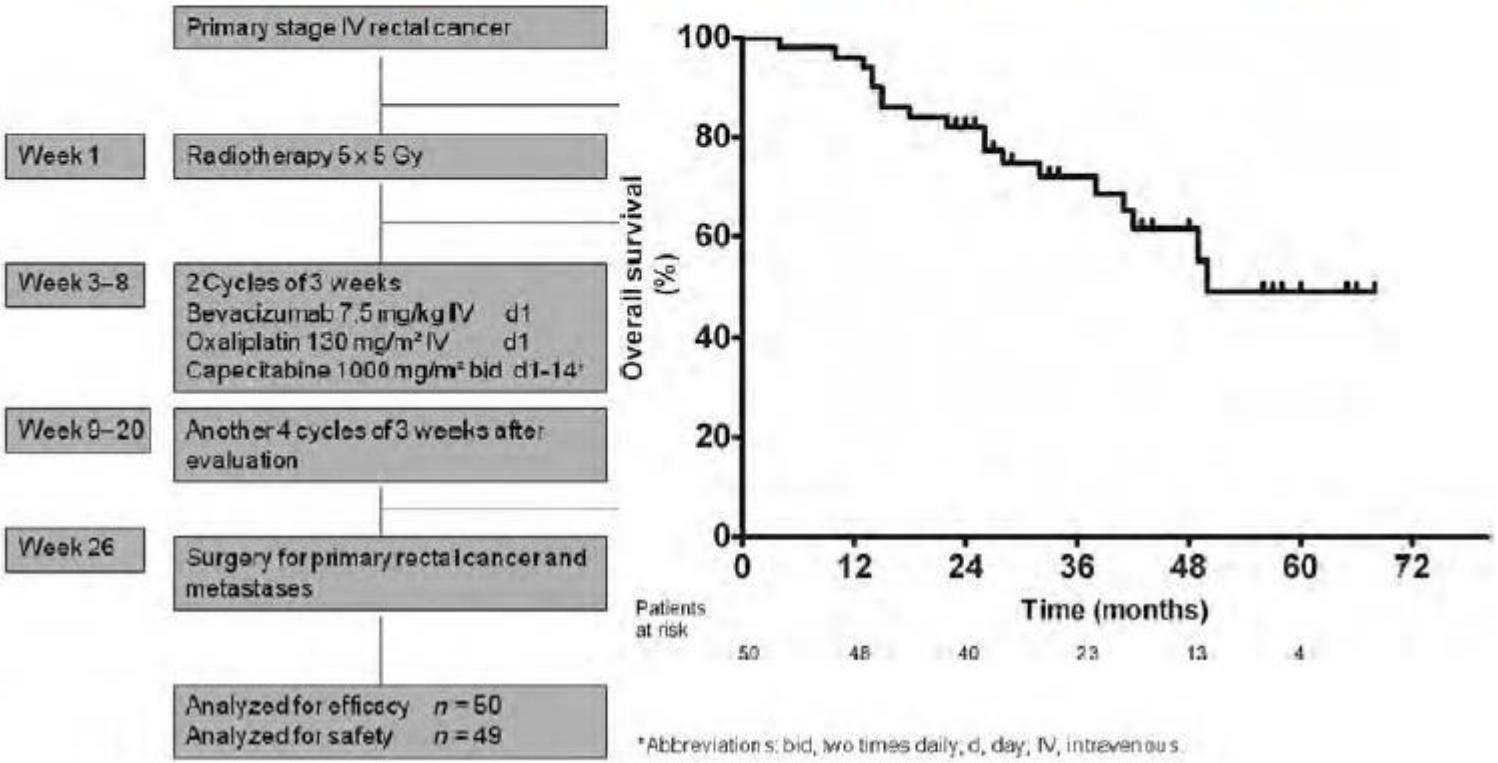
R0 resection
49% vs 23%

Consider RT on primary if the disease becomes resectable

Annals of Oncology 24: 1762–1769, 2013
doi:10.1093/annonc/mdt124
Published online 22 March 2013

Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer†

T. H. van Dijk[1]*, K. Tamas[2], J. C. Beukema[3], G. L. Beets[4], A. J. Gelderblom[5], K. P. de Jong[6], I. D. Nagtegaal[7], H. J. Rutten[8], C. J. van de Velde[9], T. Wiggers[1], G. A. Hospers[2] & K. Havenga[1]

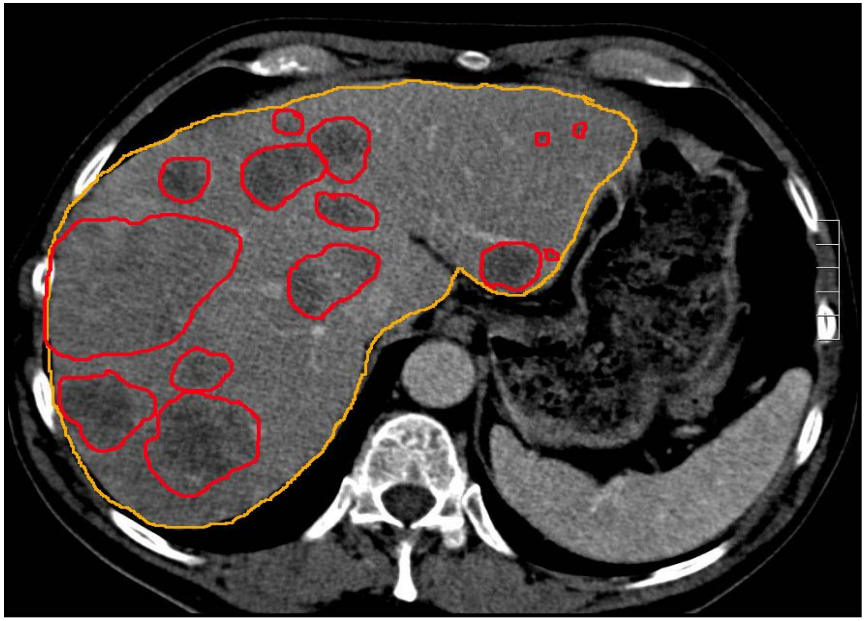


*Abbreviations: bid, two times daily; d, day; IV, intravenous.

Scenario 3: non-resectable patient

Definition

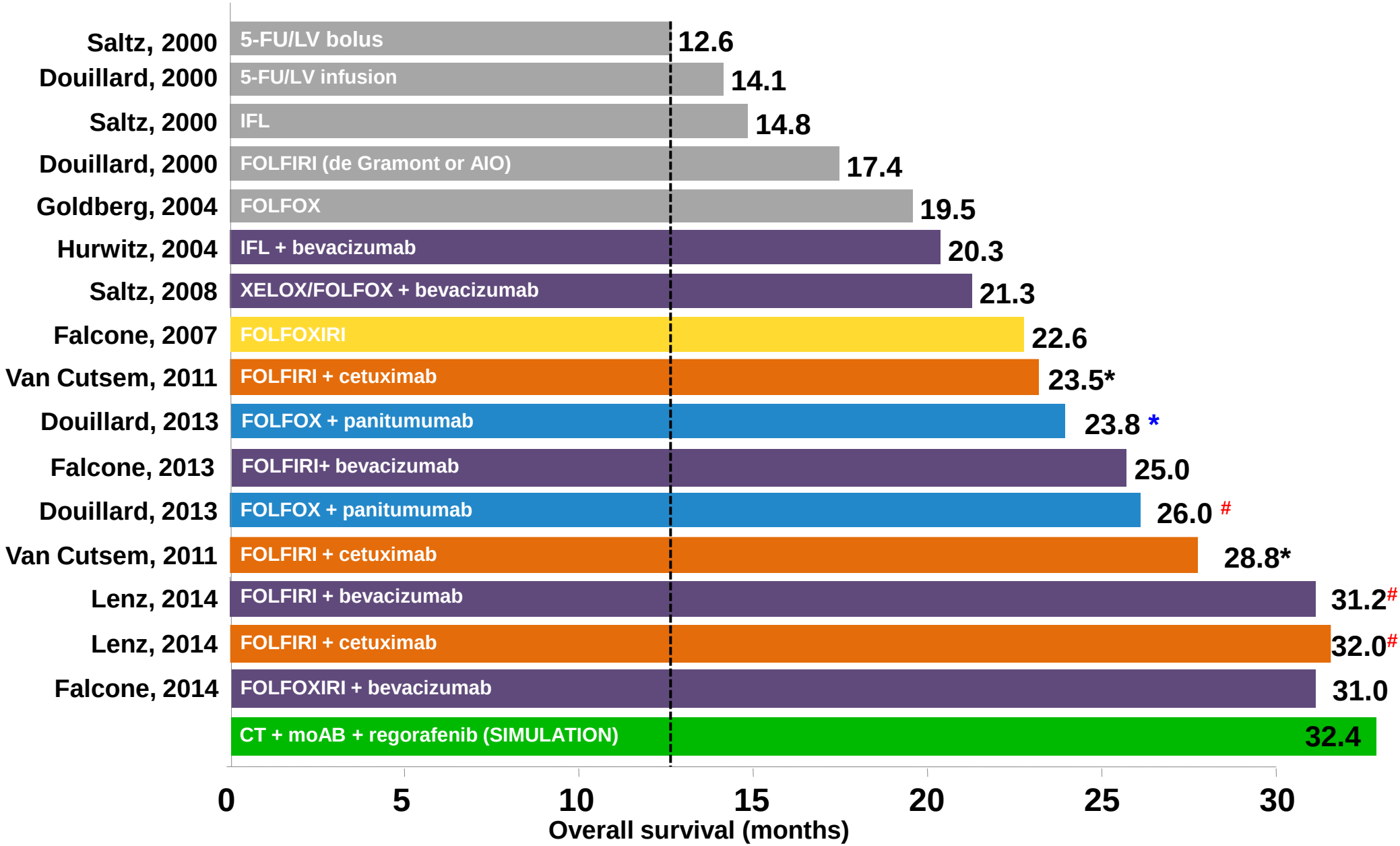
- multiple, bilobar liver or lung metastases
- extrahepatic, unresectable disease e.g.
  - bilateral lung metastases
  - multiple LN metastases
  - carcinosis



Goals:

- **Increase PFS/OS**
- **Improve QoL**
- Avoid complications related to T

Incremental improvements in OS in mCRC



Informal comparison as these are not head-to-head clinical trials;

* WT *KRAS*; # WT *RAS*, WT in *KRAS* & *NRAS* exons 2/3/4

Linee guida NCCN

National Comprehensive Cancer Network®

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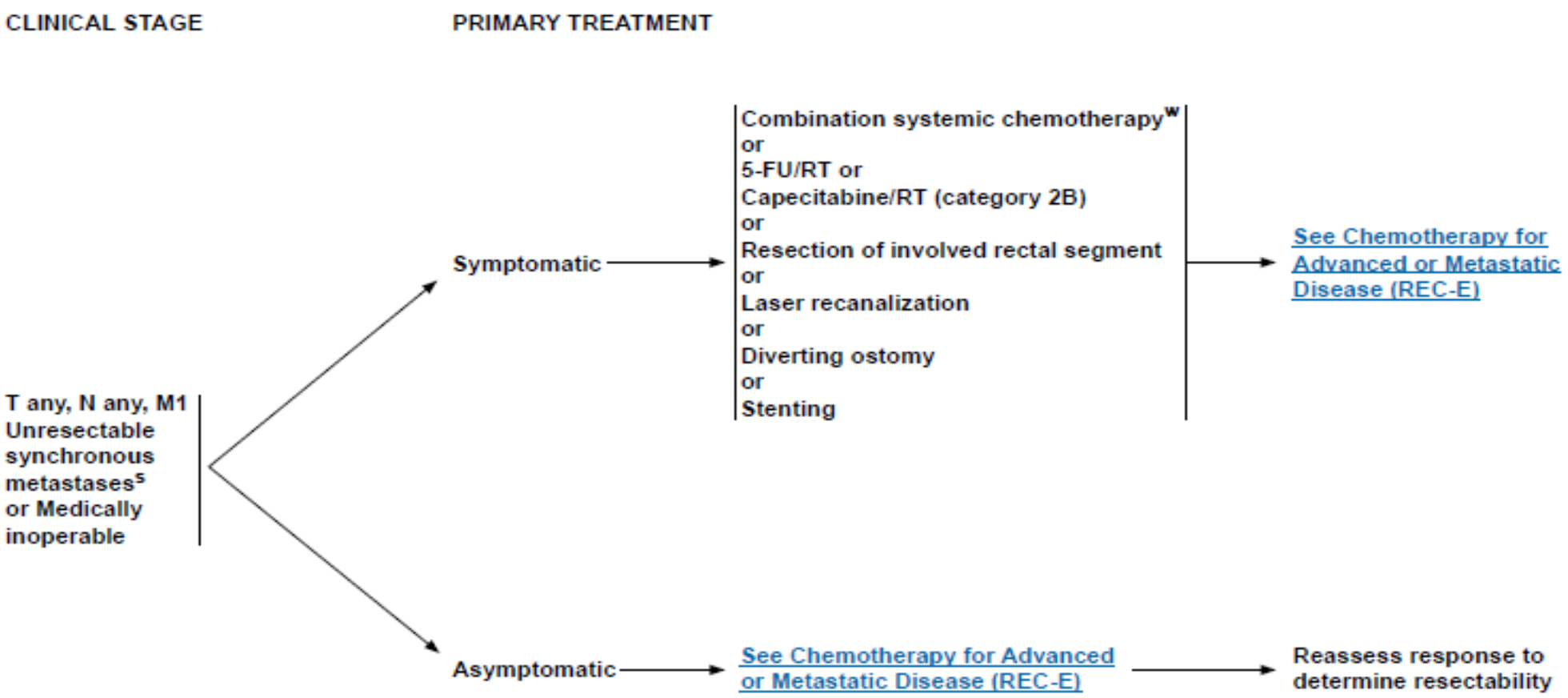
Rectal Cancer

NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion



Up-front treatment of primary rectal cancer

Fegato	Retto	
+	-	CHT → +/-chirurgia
+	+ (sintomatico)	chirurgia → CHT

	Pro	Contra
Resezione	Completa risoluzione dei sintomi Staging accurato	Morbilita alta (fino a 50%) Ritardo nella CHT
Stomia	Bassa morbilità/mortalità Rapido inizio CHT	Scarsa efficacia sui sintomi *Joffe ´81, Longo ´88, Nash ´02*
Stent	Bassissima morbilità/mortalità Rapido inizio CHT	Scarsa efficacia sui sintomi Non sempre utilizzabile

Courtesy D. Ribero

…but resection seems to be not always necessary

- Pooled analysis of individual pts' data from 4 randomized trials → primary tumour resection was independently associated to a better OS
- Phase II NSABP C-10: mFOLFOX/bev → acceptable morbidity without resection of T and no compromising of survival
- Cochrane systematic review → resection of T does not improve OS and does not reduce complications
- Retrospective studies have observed low rate of primary tumor related complications during treatment in pts with initially asymptomatic disease
- **Prospective randomised trials ongoing (Synchronous, CAIRO-4,…)**

Farn M et al. EJC 2015

McCahill LE, et al. JCO 2012

Cirocchi R, Cochrane DB Syst Rev, 2012

Poultsides et al. JCO 2009

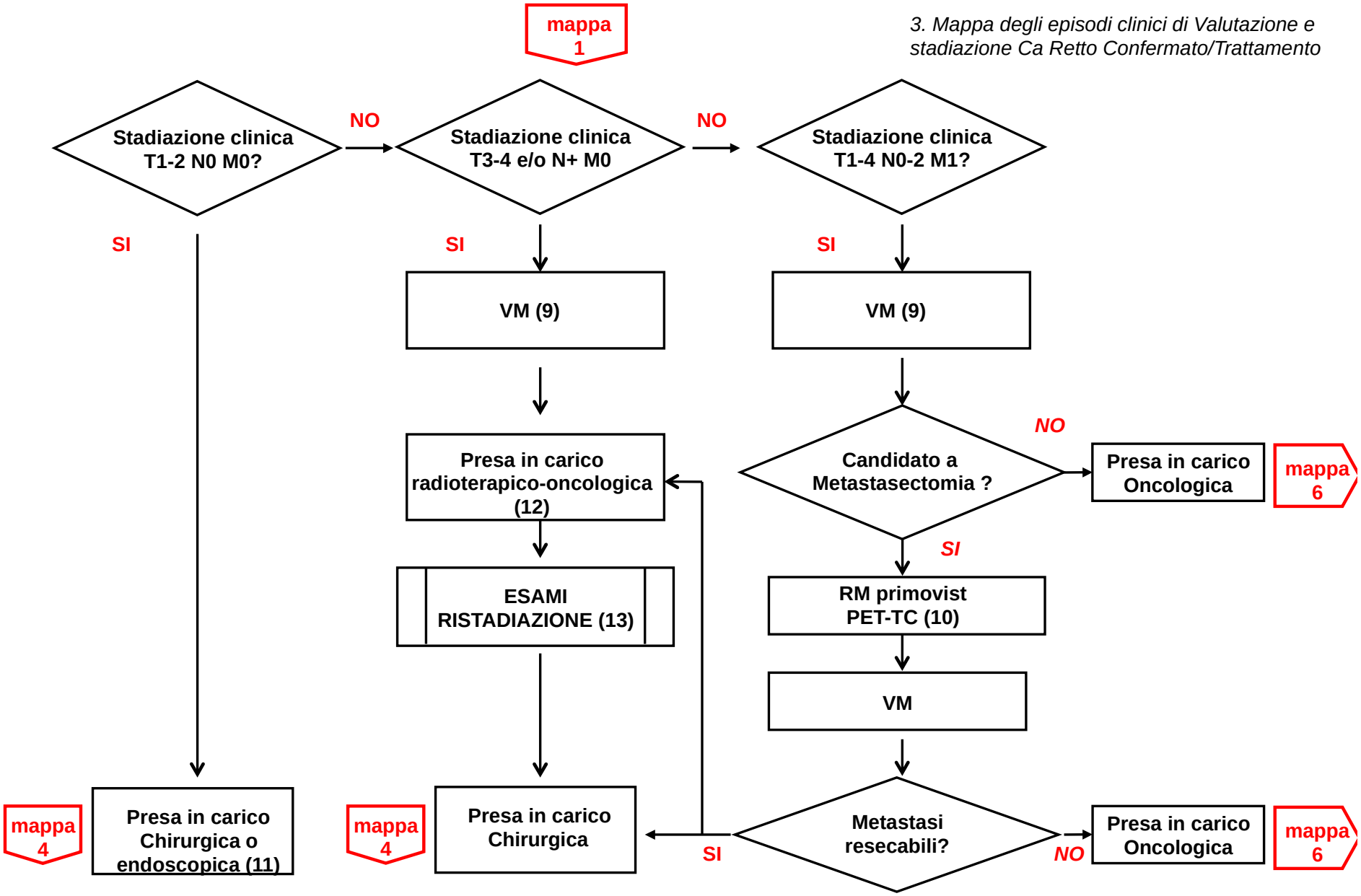
Resezione del primitivo

Gli aspetti ad oggi certi sono che:

- **va considerato il rischio di complicanze (ostruz/sanguinamento)**
- **il T in sede non rappresenta una controindicazione al trattamento oncologico (in particolare per beva)**
- **l'opportunità della resezione del primitivo va stabilita nel contesto di una discussione multidisciplinare**
- **qualora si decida per la resezione, anche in presenza di malattia a distanza non operabile, essa va effettuata secondo criteri di radicalità oncologica**

PDTA

3. Mappa degli episodi clinici di Valutazione e stadiazione Ca Retto Confermato/Trattamento



Conclusions

No universal approach to rectal cancer with synchronous resectable metastases

Discussion in multidisciplinary team the treatment strategies:

- ✓ **Preoperative systemic chemotherapy ± RT**
- ✓ **Surgical approach based on:**
  - Patient physical status (PS, comorbidities,…)
  - Resectability of primary and metastases
  - Response to chemotherapy
  - Extent of T and mets → treat the more threatening first
  - Operate site at higher risk of progression first or simultaneously
  - Consider risk of disappearance of mets

Grazie!

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