

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

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

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# Outline



- ◆ Radiotherapy in rectal cancer
  - ✓ Long-course and short-course
  - ✓ Locally advanced and metastatic rectal cancer
  
- ◆ Methods
- ◆ Results and Discussion
- ◆ Conclusion

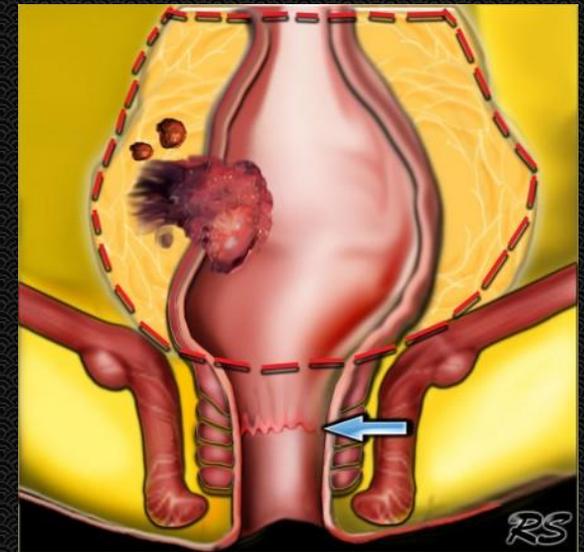
# Rectal cancer

- ◆ High local recurrent risk
- ◆ Fixed location



# Rectal cancer

- ◆ High local recurrent risk
- ◆ Fixed location
- ◆ Total mesorectal excision (TME)
- ◆ Radiotherapy



# Radiotherapy (RT)

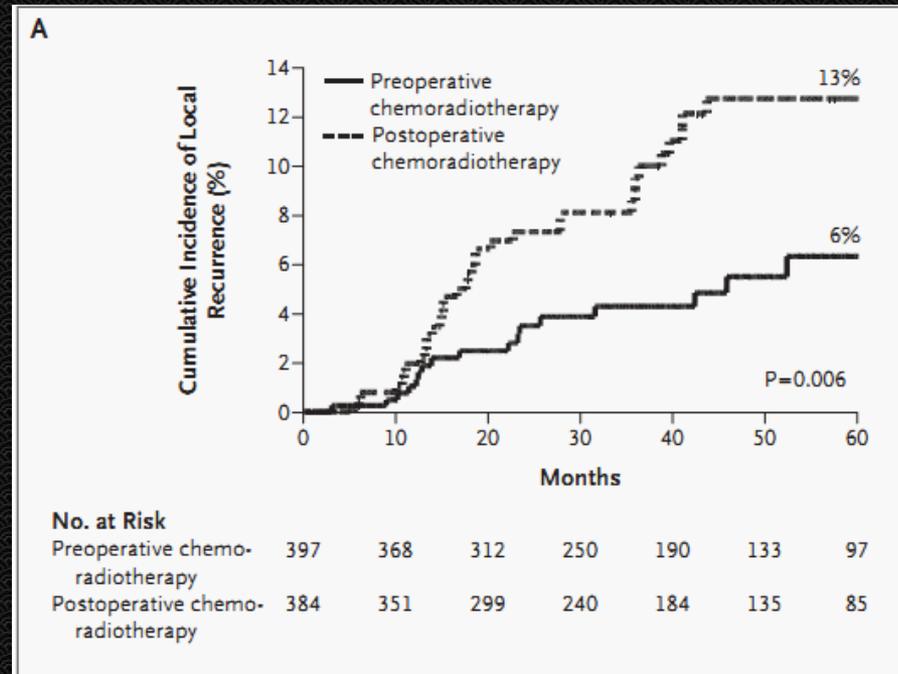


- ◆ Short-course RT (SCRT): 25Gy, 5Gy for 5 days
- ◆ Concurrent chemoradiotherapy (CCRT):  
45-50Gy / 25-28 fractions + C/T
- ◆ Decrease in local recurrence

# Stage II and III Rectal Cancer

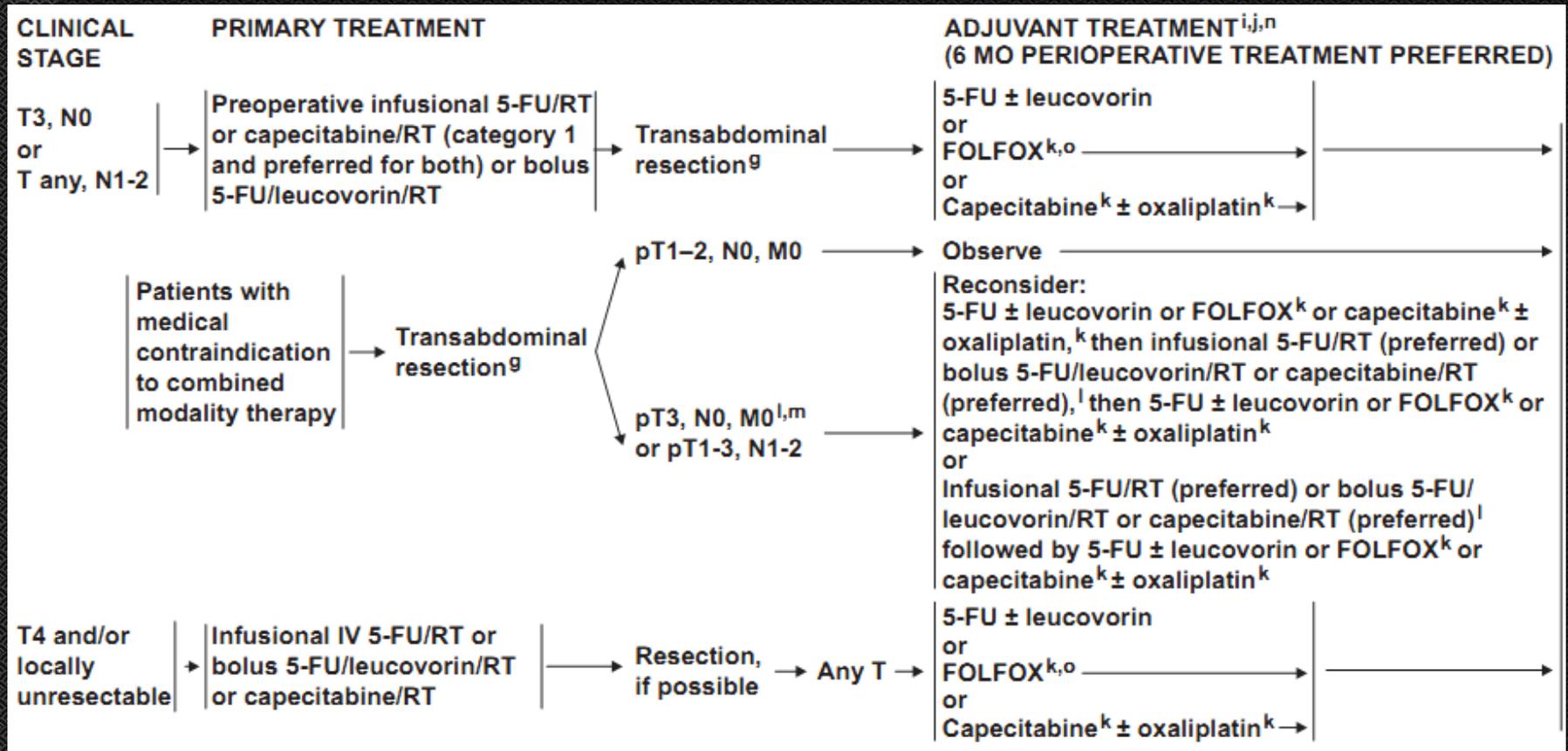


# Pre-OP CCRT better than Post-OP



- ✓ Large German randomized trial
- ✓ Pre-OP CCRT improve local control, sphincter preserving, and reduce toxicity

# NCCN for stage II/III rectal cancer



Pre-OP CCRT → OP

# CCRT vs SCRT



TABLE II – SUMMARY RESULTS OF THE 4 INCLUDED TRIALS

Study	Period	Treatment	N	RT dose (Gy) total/per fraction	Chemo	pCR	SPS	LR @ 5 years	OS @ 5 years	DFS @ 5 years	Incidence of distant metastases
EORTC (Bouliswassif) <sup>18</sup>	1972–1976	CRT	126	34.5/2.3	5-FU	4.8%	10.5%	15.1%	54%	–	30% overall
		RT	121	34.5/2.3	–	2.5%	5%	14.9%	41.3%	–	
EORTC 22921 (Bosset) <sup>19,32,34</sup>	1993–2003	CRT	506	45/1.8	FUFA	13.7%	52.8%	8.7% <sup>1</sup>	65.8%	56.1%	34.4% overall
		RT	505	45/1.8	–	5.3%	50.5	17.1% <sup>1</sup>	64.8%	54.4%	
FFCD 9203 (Gérard) <sup>20,35</sup>	1993–2003	CRT	375	45/1.8	FUFA	11.4%	52.7%	8.1%	67.4%	59.4%	–
		RT	367	45/1.8	–	3.6%	51.8%	16.5%	67.9%	55.5%	–
Polish trial (Bujko) <sup>21,36–38</sup>	1999–2002	CRT	157	50.4/1.8	FUFA	16%	55.4%	14.2%	66.2% <sup>2</sup>	55.6% <sup>2</sup>	34.6%
		RT	155	25/5	–	1%	56.1%	9%	67.2% <sup>2</sup>	58.4% <sup>2</sup>	31.4%

# CCRT vs SCRT



CCRT vs SCRT		
	Favor CCRT	No significance
★ Local recurrence	V	
★ pCR	V	
sphincter preservation		V
PFS		V
OS		V
★ Gr III and IV acute toxicity	V	
postoperative morbidity		V
postoperative mortality.		V

# ESMO for stage I/II/III rectal cancer



Risk group	TN substage	Therapeutic options
Very early	cT1 sm1 (-2?) N0	Local excision (TEM). If poor prognostic signs (sm $\geq$ 2, high grade, V1), resection (TME) (or possibly CRT)
Early (good)	cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT <sup>a</sup> . (CRT with evaluation, if cCR, wait-and-see, organ preservation)
Intermediate (bad)	cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited cT4aN0	<u>Preop RT (5 x 5 Gy) or CRT followed by TME.</u> (if CRT and cCR, wait-and-see in high risk patients for surgery)
Advanced (ugly)	cT3mrf+, cT4a,b, lateral node+	<u>Preop CRT followed by</u> surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 x 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT

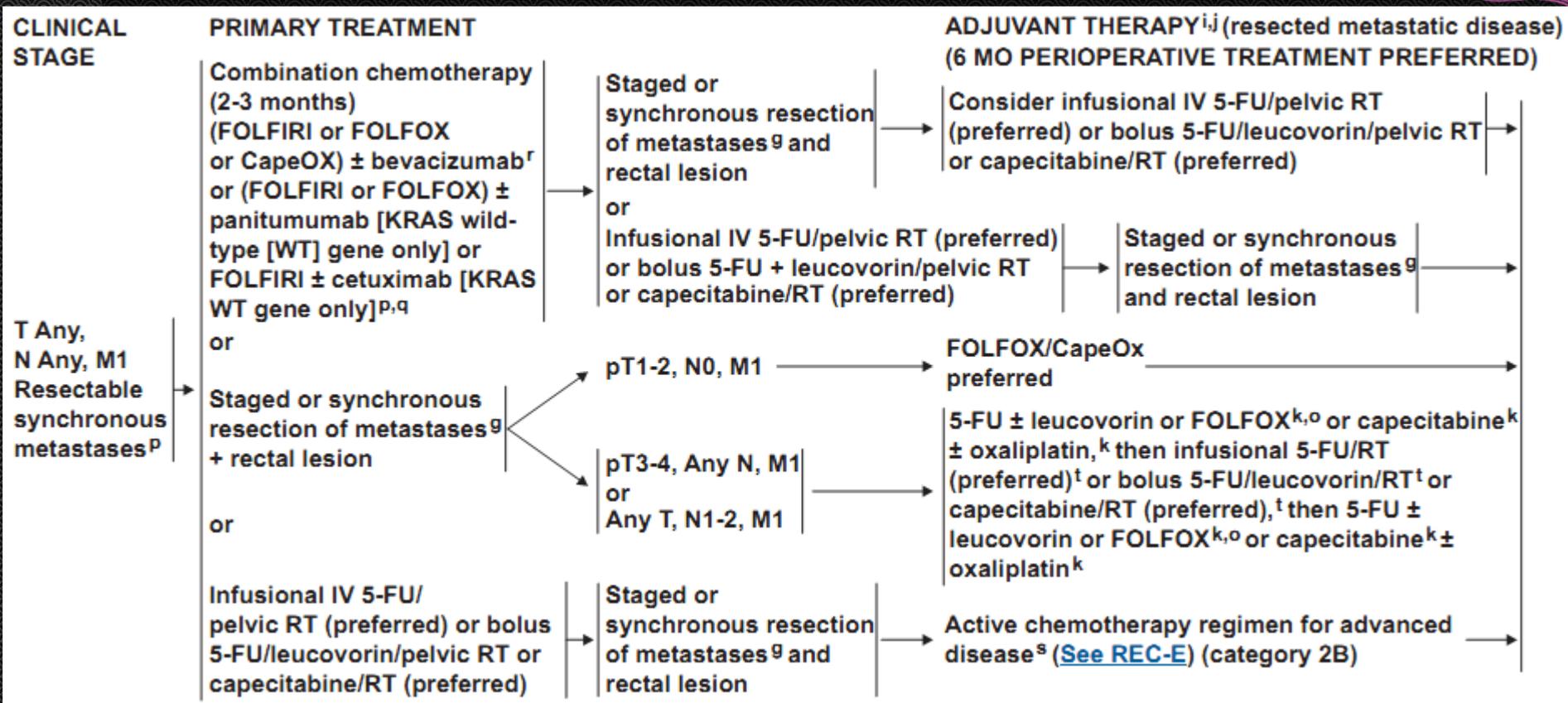
# Stage IV Rectal Cancer



# Stage IV Rectal Cancer



# NCCN for stage IV rectal cancer



# ESMO for stage IV rectal cancer



mRC	resectability		
Primary	+	+ & advanced risk	Down-size
Metastasis	+	+	Down-size
Tx	SCRT→→C/T	SCRT→ D11-18 C/T	SCRT→ D11-18 C/T C/T→PR→SCRT→OP
C/T duration	Pre- and post-op C/T up to 6 months	Pre- and post-op C/T up to 6 mo	Pre- and post-op C/T up to 6 mo

CCRT is almost never indicated as upfront treatment in synchronous metastases.



*Annals of Oncology* 24: 1762–1769, 2013

doi:10.1093/annonc/mdt124

Published online 22 March 2013

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# Methods



- ◆ Open-label, single-arm, phase II clinical study
- ◆ 2006-2010, in seven centers in The Netherlands
- ◆ 50 patients with primary stage IV rectal cancer
  
- ◆ Primary end point: patient (%) receiving R0 resection of all tumor sites
- ◆ Secondary end point: 2-yr survival, 2-yr recurrence rate, treatment-related toxicity

# Methods



## Inclusion Criteria

Age > 18 years,

Histologically confirmed rectal adenocarcinoma

**Resectable or ablatable metastases in liver or lung**

( $\leq 6$  metastatic lesion, requiring  $\leq$  trisegmentectomy in either lobe, adequate liver reserve)

ECOG = 0 or 1

Adequate marrow function (WBC  $> 3000$ , PLT  $> 10^5$ )

Adequate hepatic function (bilirubin and ALT/AST  $< 1.5 \times$  UNL)

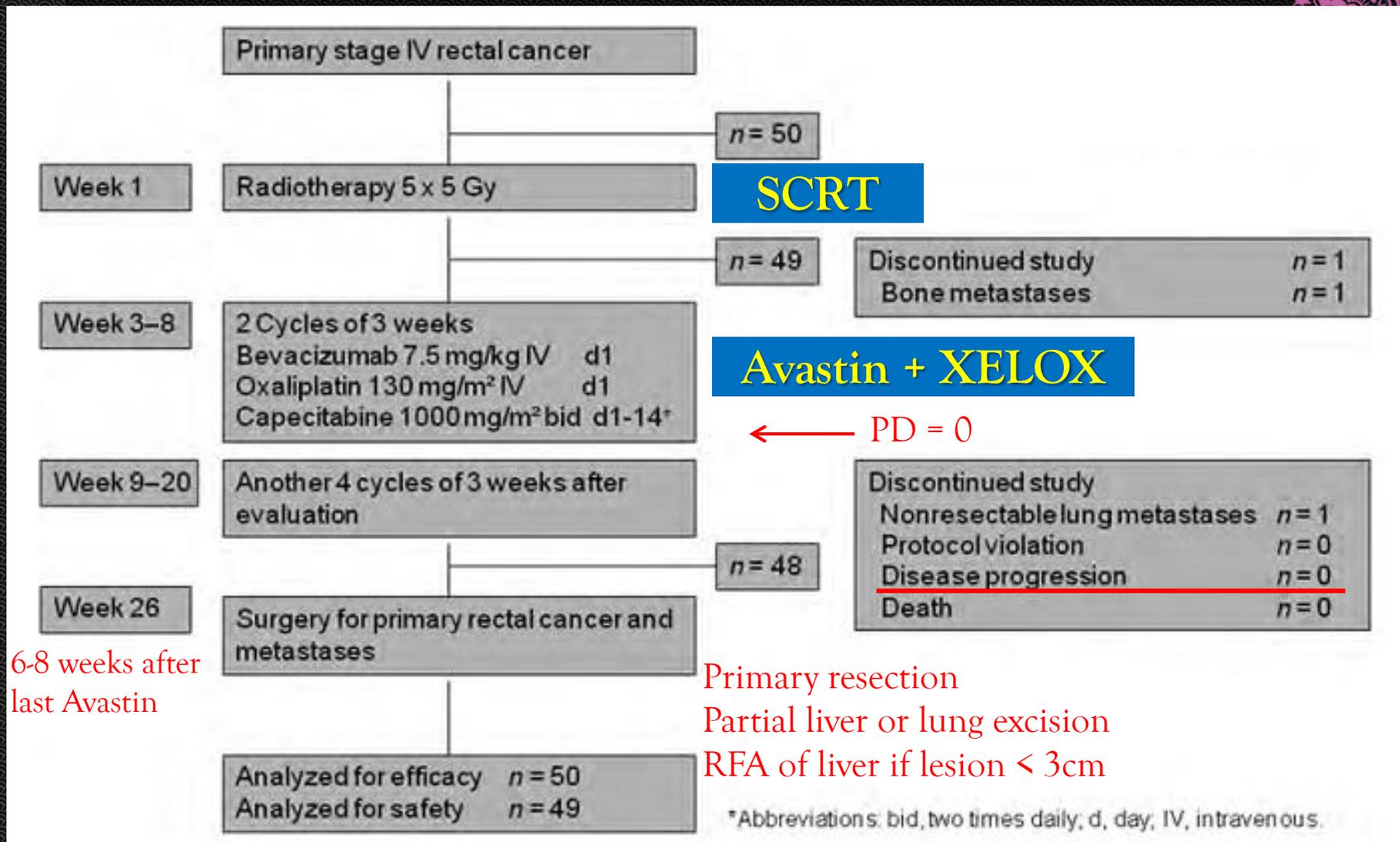
Adequate renal function (Ccr  $> 50$ )

## Exclusion criteria

Extrahepatic or extrapulmonary metastases

Previous pelvic R/T, 5-FU based C/T

Presence of any malignancy



No adjuvant C/T after R0 resection

F/U every 3 months during first 3 years: CEA, image

Median F/U: 32 months

# Baseline Characteristics



Characteristic	Results <sup>a</sup> (N = 50)
Sex	
Men	27 (54)
Women	23 (46)
Age (years)	
Median	59
Range	(35-75)
Clinical tumor category	
T2N0	0 (0)
T2N1	4 (8)
T3N0	6 (12)
T3N1-2	32 (64)
Substaging <sup>b</sup>	
T3a (<1 mm)	7 (14)
T3b (1-5 mm)	23 (46)
T3c (5-15 mm)	8 (18)
T4N0	1 (2)
T4N1-2	7 (14)
Perforation into visceral peritoneum	4 (8)
Invasion of other organs	3 (6)
T3-4N2	13 (26)

Characteristic	Results <sup>a</sup> (N = 50)
Tumor localization	
Low (0-5 cm)	23 (46)
Middle (5-10 cm)	21 (42)
High (10-15 cm)	6 (12)
Metastatic site	
Liver	42 (84)
Lung	5 (10)
Lung and liver	3 (6)
Liver metastases	
Unilobar	21 (47)
Bilobar	24 (53)
1-3	36 (72)
>3	9 (18)
Lung metastases	
1	5 (10)
>1	3 (6)

# Primary End Point



Radical surgical treatment: 72% of the 50 patients

Characteristic	Results <sup>a</sup> (N = 50)	Total no.
Patients who had surgery with curative intent		48
Radical operation at all tumor sites (R0)		36
Rectum		
Hartmann procedure	19 (53)	
Abdominoperineal resection	11 (30)	
Low anterior resection	6 (17)	
Metastases		
Liver resection	8 (22)	
Liver resection (>3 segments)	11 (30)	
Liver resection and radiofrequency ablation	7 (20)	
Radiofrequency ablation alone	4 (11)	
Lung resection	5 (14)	
Liver and lung resection	1 (3)	

72%

# Primary End Point



Characteristic	Results <sup>a</sup> (N = 50)	Total no.
Primary rectal tumor resection <sup>b</sup>		43
Resection type		
R0 resection of primary tumor <sup>c</sup>	39 (91)	
R1 resection of primary tumor	4 (9)	
Response		
Pathologic complete response	11 (26)	
Pathologic near-complete response	7 (16)	

ypCR: 26%

		Initial imaging of rectal cancer <sup>a</sup>			
		All <sup>b</sup> (n=43)	T2 (n=4)	T3 (n=32)	T4 (n=7)
Pathologic staging after surgery					
	ypT0	11 (26)	1 (25)	8 (25)	2 (29)
	ypT1	0 (0)	0 (0)	0 (0)	0 (0)
	ypT2	8 (18)	2 (50)	5 (16)	1 (14)
	ypT3	22 (51)	1 (25)	18 (56)	3 (43)
	ypT4	2 (5)	0 (0)	1 (3)	1 (14)
	<b>T downstaging</b>	<b>20 (47)</b>	1 (25)	13 (41)	6 (86)
	T progression	2 (5)	1 (25)	1 (3)	0 (0)



- ◆ **72%** R0 resection of primary and metastatic lesion
- ◆ **No** PD during pre-OP period
- ◆ **Comparable or better** ypCR rate
  - prognostic marker of better DFS



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  - prognostic marker of better DFS

**SCRT→Avastin+Xelox,  
effective pre-OP Tx in stage IV rectal cancer**

# Primary End Point



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Resection type		
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Response		
Pathologic complete response	11 (26)	
Pathologic near-complete response	7 (16)	
Nonradical treatment/irresectable disease		14
R1 resection rectum		
Tumor at circumferential resection margin	3 (21)	
Tumor at distal resection plane	1 (7)	
Incurable/irresectable disease		
Peritoneal carcinomatosis	2 (14)	
Liver metastases	5 (37)	
Lung and liver metastases	1 (7)	
Incurable disease before surgery	2 (14)	

Initial stage: T3N2 (n=2)  
 T3N1 (n=1)  
 T4N1 (n=1)

# Primary End Point



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Incurable disease before surgery	2 (14)	

# Secondary End point



Characteristic	Results <sup>a</sup> (N = 50)	Total no.
Results of treatment		
Overall		50
2-year overall survival <sup>d</sup>	40 (80)	
After R0		36
2-year recurrence rate after R0 <sup>e</sup>	23 (64)	
Local recurrence, rectum, after R0	2 (6)	
Distant recurrence after R0	21 (58)	
Liver	10 (28)	
Lung	7 (19)	
Liver and lung	2 (6)	
Other/diffuse	2 (6)	

# Secondary End point



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Liver	10 (28)	
Lung	7 (19)	
Liver and lung	2 (6)	
Other/diffuse	2 (6)	

# Safety and Compliance



Variable	Patients exposed to treatment, N	Total no.
Grade 3–4 toxicity (radiotherapy)	0	50
Timing of initiating bevacizumab and CapeOx <sup>a</sup>		49
As planned, within 2 weeks after radiotherapy	38	
Delayed 1 week because of grade 2 toxicity <sup>b</sup>	7	
Delay >1 week <sup>c</sup>	4	
Compliance bevacizumab and CapeOx		49
Six cycles	42	
Four cycles	3	
Three cycles	3	
One cycle	1	
Grade 3–4 toxicity bevacizumab and CapeOx	19	49
Gastrointestinal	6	
Vascular	6	
Pain (tumor)	4	
Dermatologic	1	
Infection	1	
Other	1	

Proctitis, Diarrhea,  
Pain, Ileus

# Safety and Compliance



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Six cycles	42	
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One cycle	1	
Grade 3–4 toxicity bevacizumab and CapeOx	19	49
Gastrointestinal	6	Diarrhea,
Vascular	6	Pulmonary embolism
Pain (tumor)	4	
Dermatologic	1	
Infection	1	
Other	1	

# Safety and Compliance



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Gastrointestinal	6	
Vascular	6	
Pain (tumor)	4	
Dermatologic	1	
Infection	1	
Other	1	

**84% completing SCRT+C/T without major delay**

# Safety and Compliance



Variable	Patients exposed to treatment, N	Total no.
Surgical complications within 60 days after surgery		48
Infection/abscess	12	
Wound	6	
Abdominal cavity	3	
Perineal	2	
Thorax	1	
Anastomotic leak	1	
Rectal stump leak	1	
Bleeding	1	
Death	0	
Reoperation		48
1	4	
≥2	6	
Radiological intervention	5	

**Similar post-OP morbidity  
even under Avastin in neoadjuvant regimen**

# Safety and Compliance

- ◆ High tolerability of the pre-OP regimen
- ◆ Similar surgery-related morbidity



# Conclusion



- ◆ SCRT followed by Pre-OP Avastin+Xelox for stage IV rectal cancer with resectable metastasis
  - ✓ effective and potential curative
  - ✓ enhance local control and treat metastatic disease



- ◆ Sequence of C/T and R/T ?
- ◆ What chemoregimen ?
- ◆ Survival benefit ?

