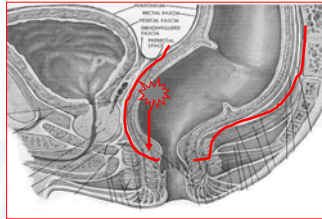


Radiotherapy for rectal cancer

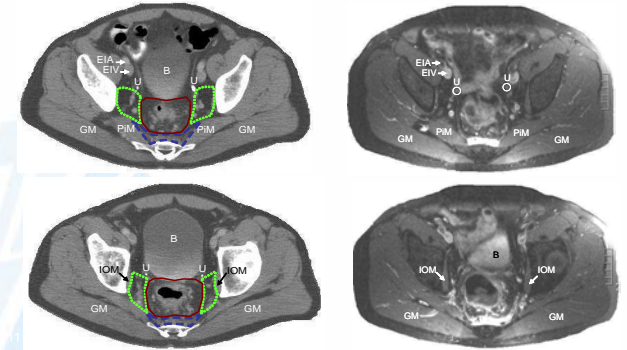
Karin Haustermans
Radiation Oncology
Leuven Cancer Institute

Introduction



- Increase CRM
- Increase sphincter preservation
- Decrease LR and DM
- Organ preservation?

Clinical Target Volume (CTV)

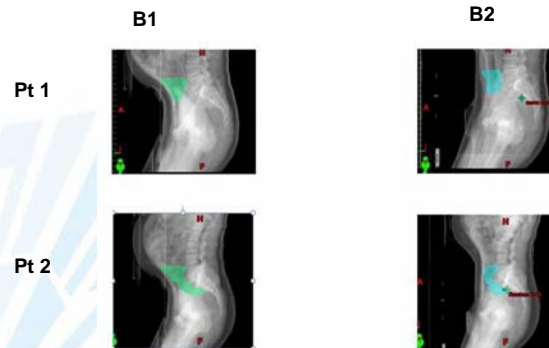


Belly board (B1)



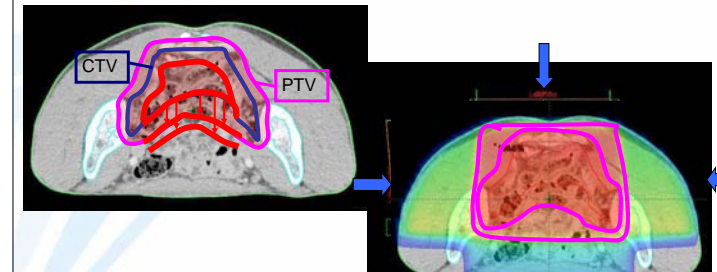
Belly board (B2)

B1 versus B2



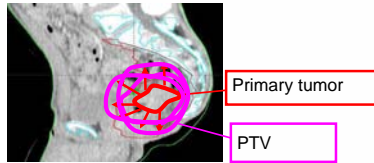
Conventional RT treatment plan

- 3-beam set-up: posterior - left - right
⇒ homogeneous dose distribution !



When is re-imaging important?

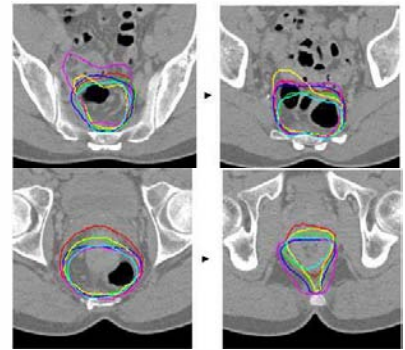
- IMRT treatment plan: steep dose-gradients outside PTV
 ↓
 risk of "missing" the tumor region
- Dose-escalation: relative small boost volumes



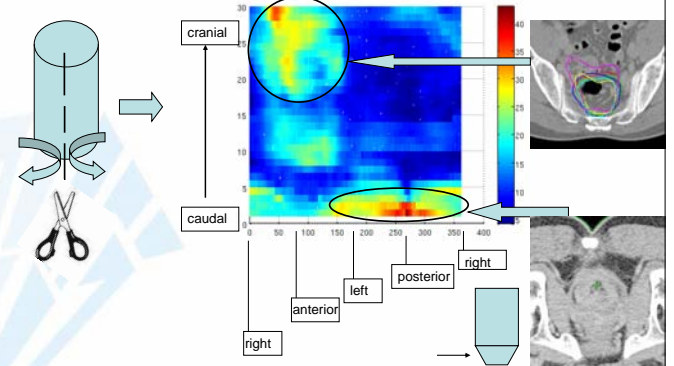
Delineation example in one patient

Bony anatomy registration of repeat CT 's to CT 1

red = CT1
 green = CT 2
 dark blue = CT 3
 yellow = CT 4
 magenta = CT 5
 light blue = CT 6



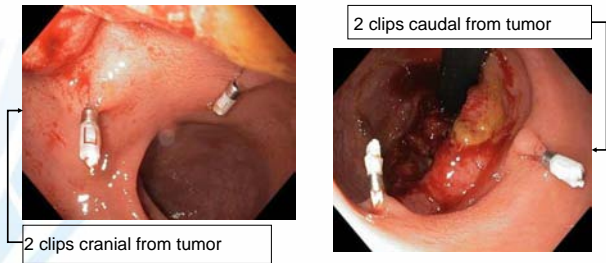
Motion/shape variation in one patient



- Main problem: image quality of CBCT not good enough to delineate rectal tumor

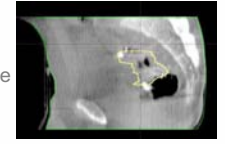


- Attempt to better visualize the tumor = placement of fiducial markers (Olympus HK-610-090)



Fiducial markers

- Cranio-caudal tumor motion can be markers stay in place
- 82% of the markers stay in place from the planning CT till the last day of RT!



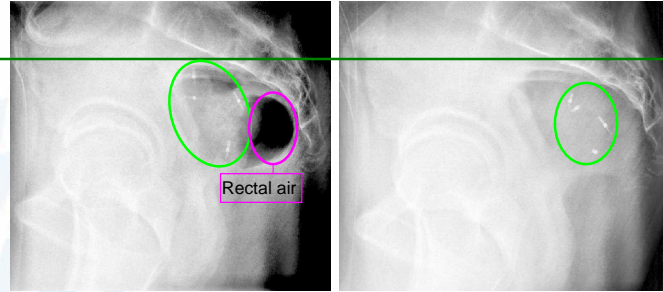
	ENDOSCOPY			LAST DAY RT
	CRANIAL	CAUDAL	LATERAL	TOTAL
patient 1	2	impossible		1
patient 2	1	1	2	4
patient 3	2	2		4
patient 4	2	2		1
patient 5	2	impossible		2
patient 6	2	2	2	6
	22 markers			18 markers

Fiducial markers

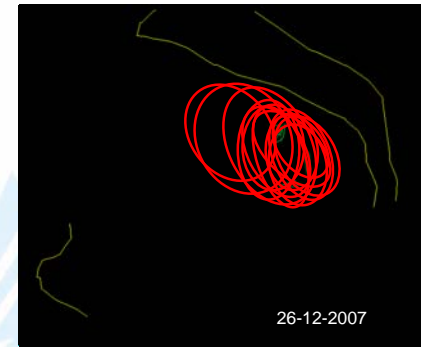


Proximal markers
Lateral markers
Distal markers

IGRT with kV-EPID

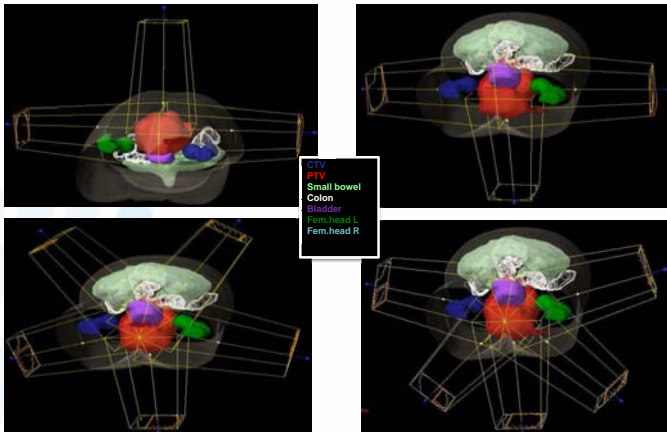


IGRT with kV-EPID

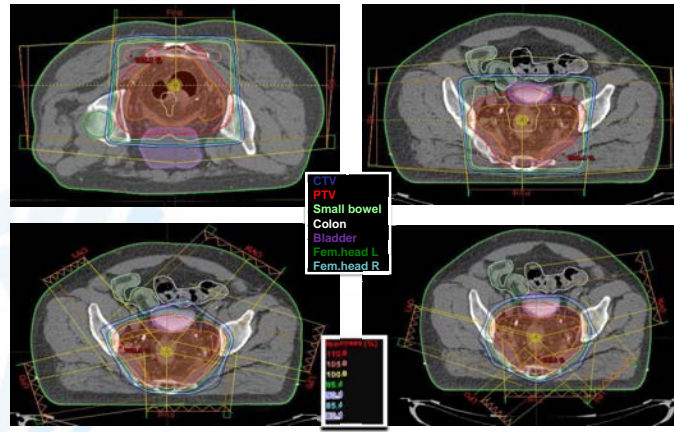


Inter-fraction motion

Beam arrangements



Dose distribution



Conclusion

- Prone position better sparing of the small bowel using only 3D-CRT
 - Sparing is more dependent on individual patients using the belly board device (50% higher SD for prone, than for supine)
- IMRT Lat (in supine position) can better spare the small bowel than the currently used 3D-CRT in prone position

- RT with TME surgery?
- Neoadjuvant or adjuvant RT?
- 5 x 5 Gy or long-course CRT?
- RT with new drugs?
- Selection of patients?

Swedish Rectal Cancer Trial

	Preop RT	Surgery	P - value
Local Failure	12 %	27 %	< 0.001
5-Yr Survival	58 %	48 %	0.04

NEJM, 1997

TME-Trial: RT+TME vs. TME

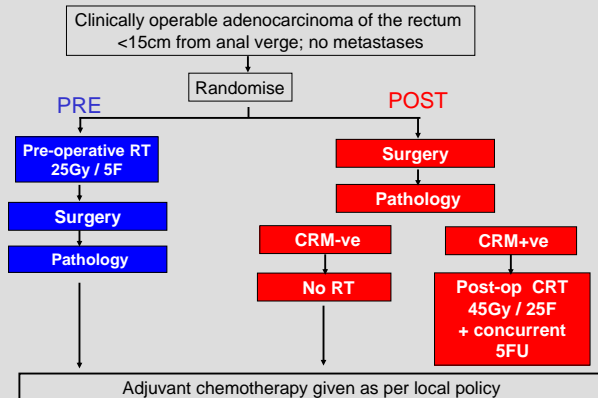


Local Failure at 5 years:

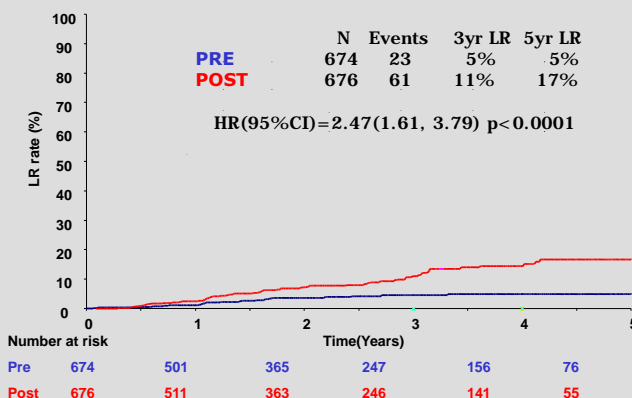
RT+TME: 5.6%
TME: 10.9%
p < 0.001

Kapiteijn E et al., N Engl J Med 2001;345: 638-46
Peeters K et al., Ann Surg 2007;246:693-701

Trial Design



LR by treatment (ITT)



LR by distance from the anal verge



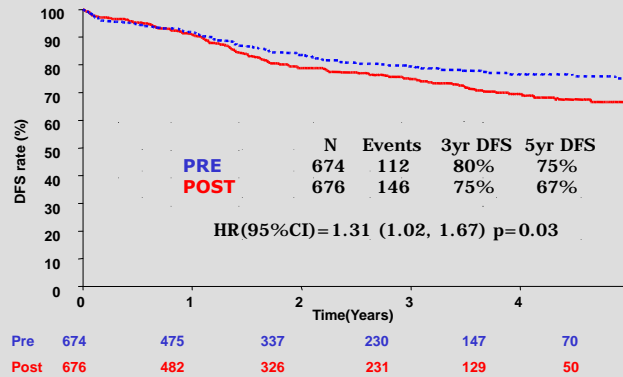
Distance from anal verge	Events/N	3yr		5yr		HR (95%CI)
		PRE	PRE	POST	POST	
0-5cm	29/444	6%	7%	10%	17%	2.0 (0.97,4.15)
> 5-10cm	39/674	5%	5%	10%	16%	2.14 (1.14,4.02)
> 10-15cm	15/204	1%	1%	16%	19%	4.94 (1.79,13.64)

LR by TNM Stage



TNM Stage	Events/N	3yr		5yr		HR (95%CI)
		PRE	PRE	POST	POST	
I	4/315	0%	0%	3%	6%	12.19 (1.64,90.41)
II	16/370	2%	2%	8%	12%	3.47 (1.29,9.35)
III	56/526	9%	10%	17%	25%	2.02 (1.20,3.42)

DFS by treatment (ITT)



- RT with TME surgery?

YES! But some subgroups may not benefit

- Neoadjuvant or adjuvant RT?

- 5 x 5 Gy or long-course CRT?

- RT with new drugs?

- Selection of patients?

- RT with TME surgery?

YES! But some subgroups may not benefit

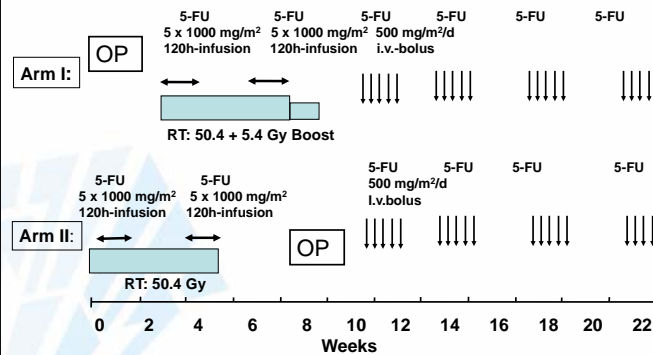
- Neoadjuvant or adjuvant RT?

- 5 x 5 Gy or long-course CRT?

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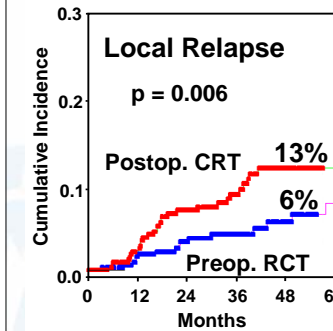
- Selection of patients?

CAO/ARO/AIO-94



Sauer R et al., N Engl J Med 2004; 351:1731-40

Pre vs. Postop. RCT: CAO/ARO/AIO-94



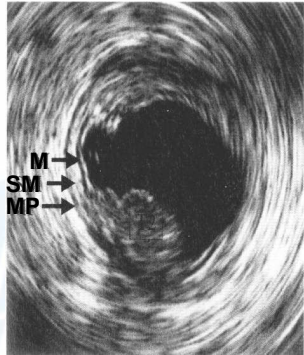
Preop CRT:



- Downstaging
- Compliance
- Local control
- Toxicity
- Sphincter

Sauer R et al., N Engl J Med 2004; 351:1731-40

Pathological Stage



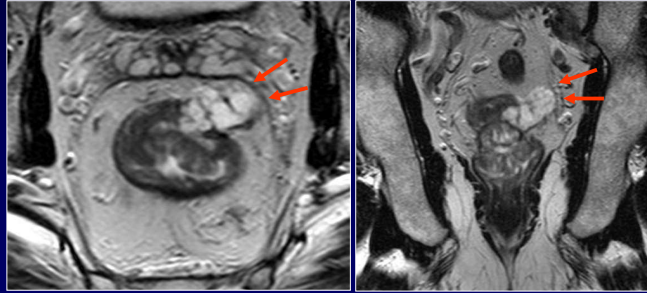
Postop. CRT
CAO/ARO/AIO-94

UICC-I	18 %
UICC-II	29 %
UICC-III	40 %
UICC-IV	7 %
Missing	6 %

Risk of "Overtreatment"

Sauer R et al., N Engl J Med 2004; 351:1731-40

Selection of patients!



- RT with TME surgery?

YES! But some subgroups may not benefit

- Neoadjuvant or adjuvant RT?

Neoadjuvant! But need for improved staging (MRI)

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- RT with new drugs?

- Selection of patients?

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YES! But some subgroups may not benefit

- Neoadjuvant or adjuvant RT?

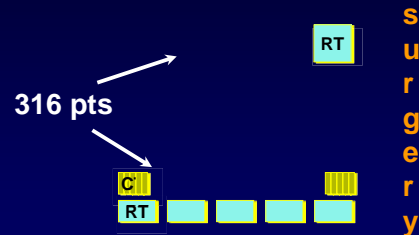
Neoadjuvant! But need for improved staging (MRI)

- 5 x 5 Gy or long-course CRT?

- RT with new drugs?

- Selection of patients?

Polish trial



Bujko et al, Radiother Oncol 2004



	5x5 Gy n=148	50.4 Gy + CT n=138	P
Sphincter-preserved	61%	58%	0.57
T-Category			
ypT0	1%	16%	<0.001
ypT1	2%	9%	
ypT2	37%	37%	
ypT3-4	60%	38%	
N-Category			
ypN0	52%	68%	0.007
ypN1	48%	32%	
CRM +	13%	4%	0.017

Bujko et al. Radiother Oncol 2004;72:15-24

**Preoperative
R(C)T**

**Preoperative
5x5Gy**

- (+) Biologic effective dose
- + Combination with CT
- + Downsizing
- Acute toxicity
- (+) Late toxicity
- Compliance
- Costs

- (+)
- +
- +

• **RT with TME surgery?**

YES! But some subgroups may not benefit

• **Neoadjuvant or adjuvant RT?**

Neoadjuvant! But need for improved staging (MRI)

• **5 x 5 Gy or long-course CRT?**

Risk-adapted! If downsizing required: CRT or wait

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• **Selection of patients?**

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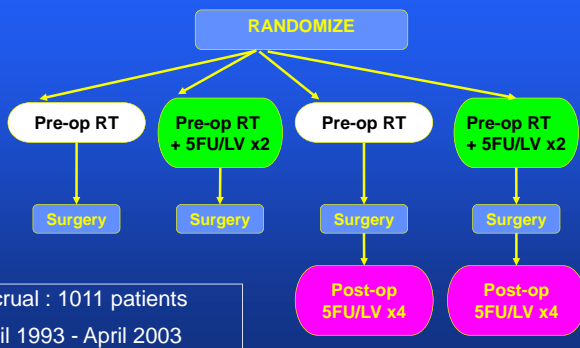
Risk-adapted! If downsizing required: CRT or wait

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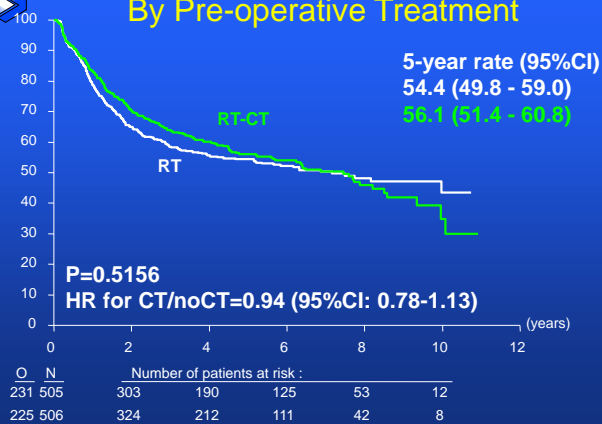
• **Selection of patients?**



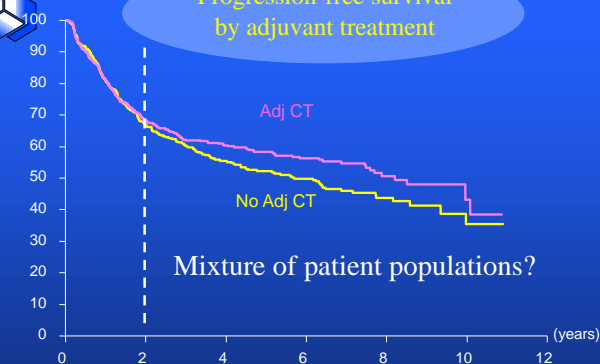
Rectal cancer T3/T4 NX M0 (UICC 1987) by DRE or EUS
Considered resectable, WHO PS 0-1, Age ≤ 80 y



**Progression-free survival
By Pre-operative Treatment**



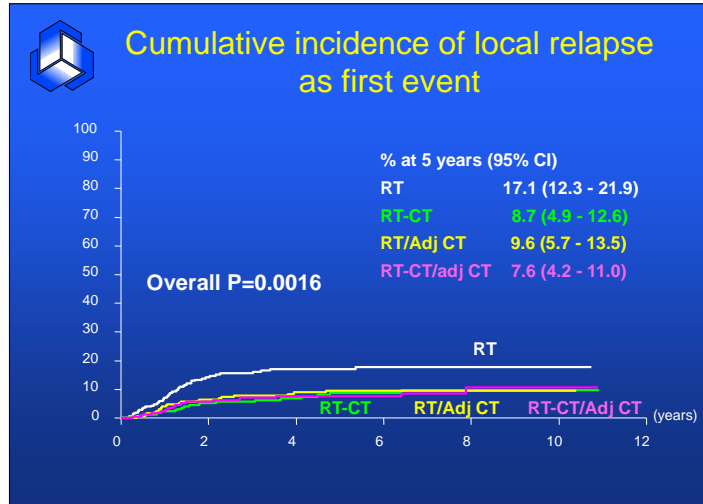
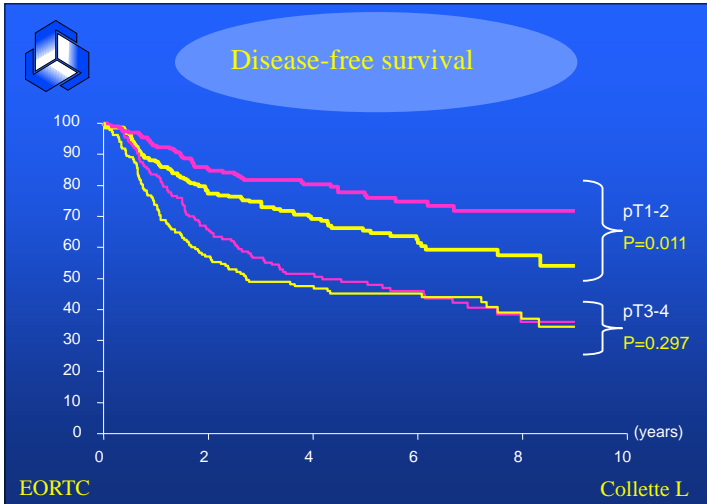
**Progression-free survival
by adjuvant treatment**



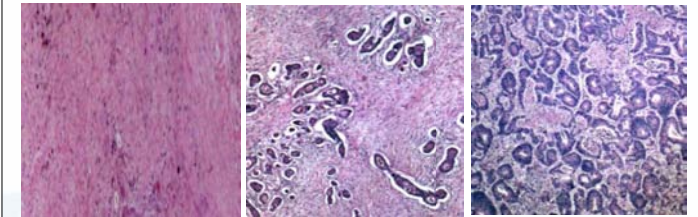
Bosset et al. ASCO 2005

Collette L

EORTC



Tumor-Regression-Grading: TRG



	CAPOX-RT (n=104)	5-FU-RT (n=385)
Complete Regression (100%)	19%	8%
Good Regression (> 50%)	55%	51%
Moderate Regression (25-50%)	11%	15%
Minimal Regression (< 25%)	11%	19%
No Regression (0%)	3%	7%

CAO/ARO/AIO-04

**RT 50.4 Gy + 5-FU
Week 1 and 5**

(Better Arm CAO/ARO/AIO-94,
Sauer R et al., N Eng J Med 2004)

**RT 50.4 Gy +
FOLFOX**

T
M
E

**5-FU
4#**

**FOLFOX
4#**

PETACC-6

RT 45 Gy + XELODA

825 mg/m² days 1-33
w/o weekends

RT 45 Gy + XELOX

Xeloda: 825 mg/m² days 1-33 w/o
weekends
Oxaliplatin: 50 mg/m² weekly

T
M
E

**6 cycles:
XELODA**

1250 mg/m²
d 1(e)-15(m)

**6 cycles:
XELOX**

Xeloda: 1000 mg/m²
d 1(e)-15(m)
Oxaliplatin: 130 mg/m² d1

• RT with TME surgery?

YES! But some subgroups may not benefit

• Neoadjuvant or adjuvant RT?

Neoadjuvant! But need for improved staging (MRI)

• 5 x 5 Gy or long-course CRT?

Risk-adapted! If downsizing required: CRT or wait

• RT with new drugs?

Promising! Ongoing phase III trials

• Selection of patients?

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Promising! Ongoing phase III trials

• **Selection of patients?**

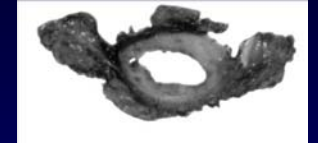
Quality of surgery: definitions



Complete mesorectum:

No defect deeper than 5 mm
Smooth circumferential margin

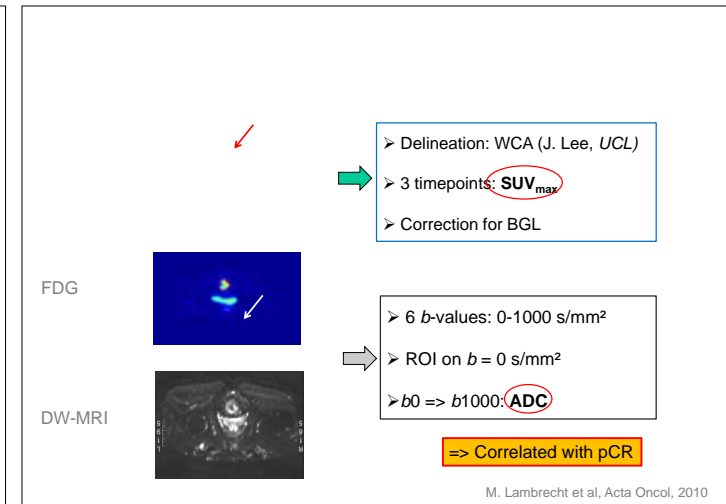
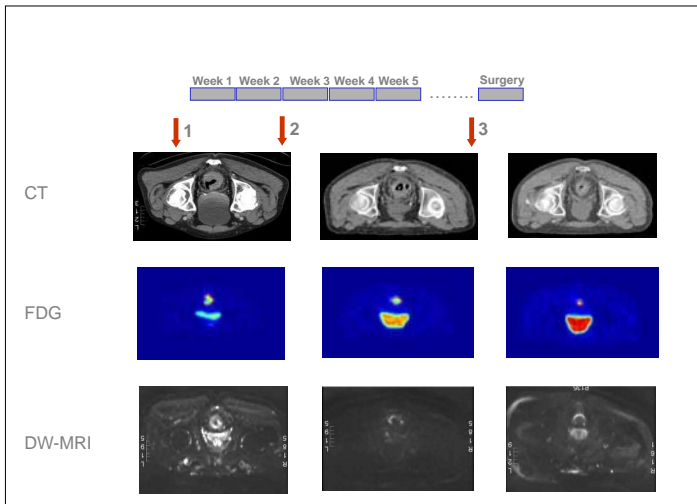
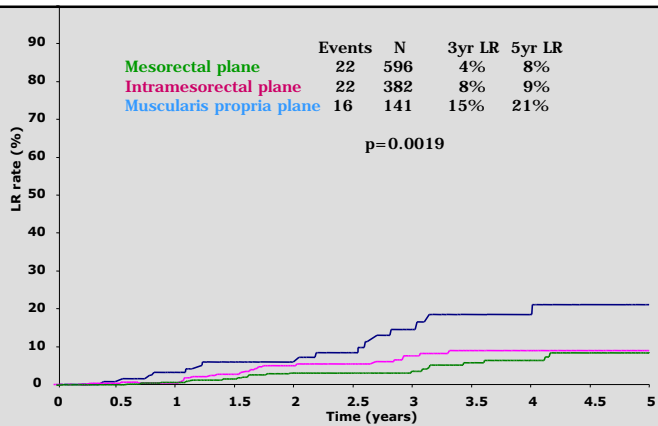
Quality of surgery: definitions



Incomplete mesorectum:

Defects down onto muscularis
Irregular circumferential margin

LR by plane of surgery



Combination?



Combining imaging: Accuracy↑?

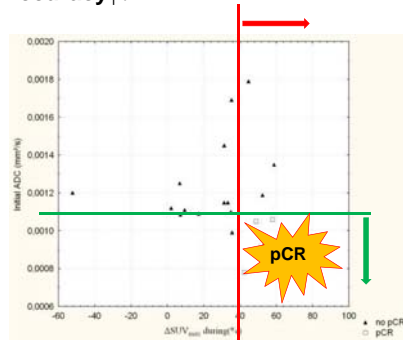
• 22 patients

• Thresholds:

➢ $\Delta\text{SUV}_{\text{max}}$: 40 %

➢ ADC: 1.06 mm²/s

• Sensitivity: 100%
• Specificity: 94%



S
U
M
M
A
R
Y

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Neoadjuvant! But need for improved staging (MRI)

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Risk-adapted! If downsizing required: CRT or wait

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Promising! Ongoing phase III trials

• Selection of patients?

YES! Before and during ...

