Role of Radiotherapy in Rectal cancers

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Role of local treatment for cancer

1 : improved survival

2 : local control

3 : QOL (sphincter preservation)

Post-Op ChemoRT vs Surgery

Trial	Treatment Arms	LF	DM	OS
GITSG 7175 1975-80 202 pts	Surgery Alone RT (40-48 Gy) Chemo (MeCCNU/5FU) Chemo + RT	24% 20% 27% 11%	34% 30% 27% 26%	45% 52% 52% 67% (5-yr DFS significant)
NSABP R01 1977-86 555 pts	Surgery Alone Chemo (MOF) RT (46-47 Gy)	25% 22% 26%	26% 24% 31%	43% 53% 41% (Males: 5-yr OS significant)

Post-Op ChemoRT vs Single Modality

Trial	Treatment Arms	LF	DM	OS
NSABP R02 1987-92 694 pts	Chemo (MOF or 5FU/LV) Chemo + RT (50.4 Gy)	13% 8% (p=.02)		NS (DFS &OS)
Mayo NCCTG 1980-1986 204 pts	RT (45-50 Gy) RT + Chemo (MeCCNU/Bolus 5FU)	25% 14%	46% 29%	46% 53% (5-yr Act p=.025)

Rectal Cancers

"In contrast to colon cancer, there is a significant risk of local-regional failure as the only or first site of recurrence in patients with curative resected rectal cancer."

- *Stage I* *5% to 10%*
- *Stage II* *25% to 30%*
- *Stage III* *50% or higher*

"Combined post-op CT+ RT improves local control and survival in stage II and III patients and is recommended"

(NIH Consensus Conference on Adjuvant Therapy for Patients with Colon and Rectal Cancer, JAMA, Sept. 19, 1990)

Local-Regional Failure Characteristics

- Main prognostic determinant is Stage
- Local-Regional failure associated with significant morbidity
- Major mode of failure (+/- distant metastases)
- Most failures within 2-3 yrs and rare after 5 yrs (+/- distant metastases)
- Successful salvage is rare

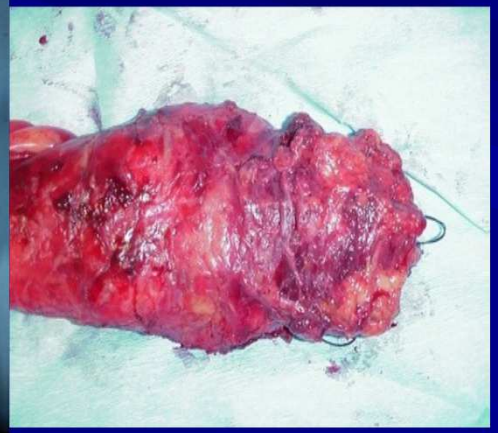
Radiation therapy and Rectal cancers

Review by Swedish council of technology Assessment in Health care (SBU) Data-42 RCT's, 3 Metaanalysis 131 scientific articles with 25,351 patients.

- Overall 5 yr survival has slowly improved compared to colon cancers.70% vs 50%
- Mortality has decreased.
- Local failure rates at 5 years after TME have decreased from 28% to 10-15%.

Local recurrences in rectal cancer has in populations decreased from above 30% to about 8%

Improved surgery

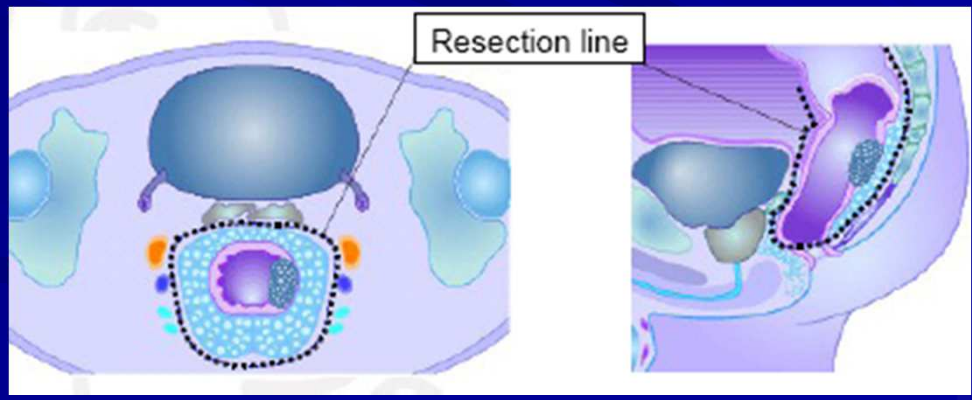


and radiotherapy

Developments in 1980's

In Sweden: preoperative RT
5x5 Gy
local recurrence ↓
survival ↑

Heald: TME surgery
local recurrence ↓



Heterogeneity in rectal cancers

Rectal cancer represents a broad spectrum of Disease requiring tailored treatment regimens to maximize the outcome

M.Mohiuddin - IJROBP - 1993

The heterogeneity problem

- The Good

  stage I

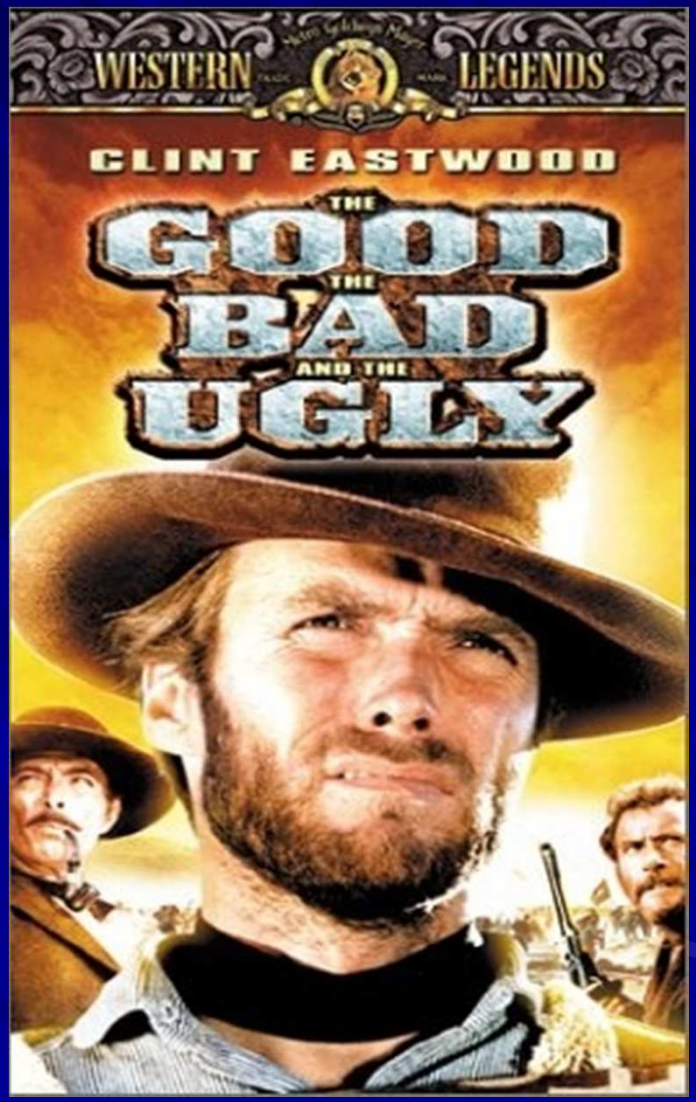
- The Bad

  stage II-III

- The Ugly

Unresectable

Recurrent



Courtesy Dr V Valentini

Treatments- Early tumours

cT2 rectal cancers and
cT1 with high risk factors
are adequately treated
with TME alone
the nodes are negative
(N0).

RT in treatment of early tumors

- pT1 with adverse pathologic factors
- pT2 without adverse factors
- Patients with co-morbidity or refuse surgery can be treated with local excision and postoperative radio(chemo)therapy

The bad tumors- Treatment of stage II -III tumors

Randomized trials after 2000

		Winner
Short ERT		
Dutch Trial	Short RT+TME vs TME	Short RT
MRC C07	Short RT+TME vs TME	Short RT
Long ERT		
EORTC 22921	Long RT vs Chemo RT	
FFCD 9203	Long RT vs Chemo RT	
Polish Trial	Short RT vs Chemo RT	
TROG Trial		
Scandinavian	Long RT vs Chemo RT	

Issues

- Preop or postop?
- TME Alone or TME + RT?
- Short or long course?
- With or without chemotherapy
- +/- targeted drug?
- What target?

Pre-op RT

- To increase the probability of tumor control in the pelvis and to increase the frequency of sphincter preservation.
- To stop further dissemination of metastatic clonogens pending removal of the primary tumor.

From Nelson and Sargent, 2000.

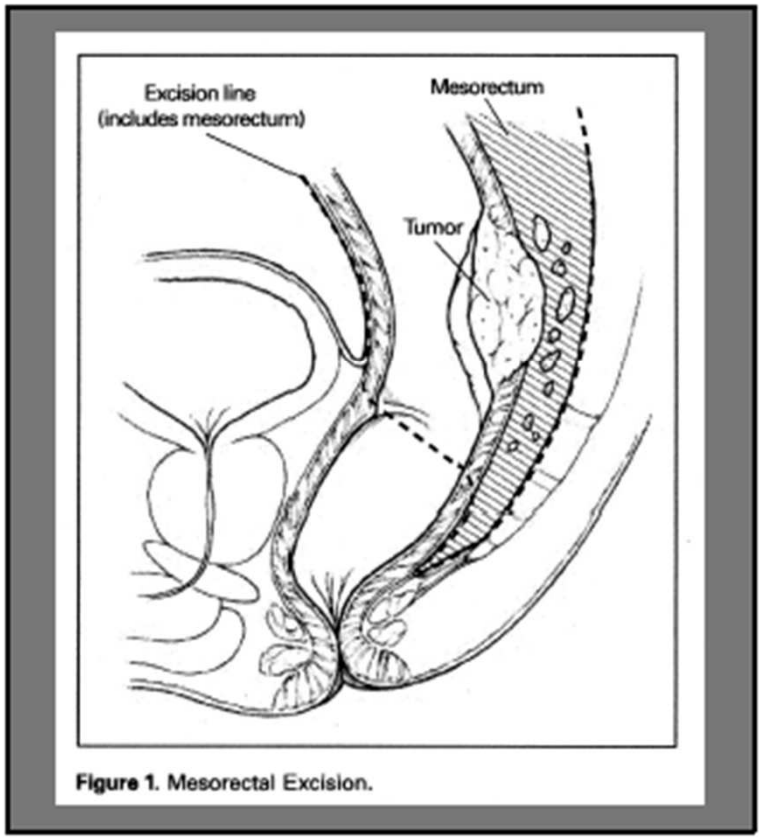
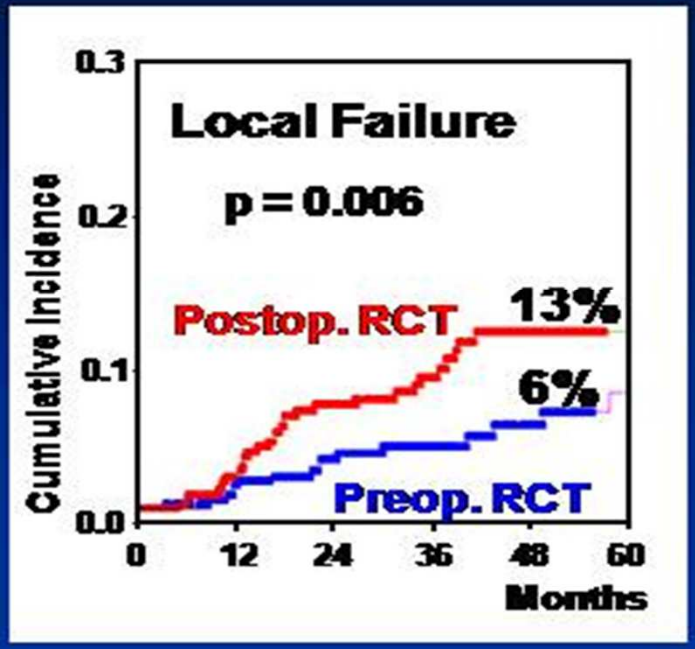


Figure 1. Mesorectal Excision.

CAO/ARO/AIO *Sauer et al., NEJM 2004*

50.4 Gy + 5 FU preop **vs** 55.8 Gy + 5 FU postop

CAO/ARO/AIO-94



Preop. RCT:

- Local Control +
- Toxicity +
- Compliance +
- Sphincter +

- Risk: overtreatment (UICC I) -

Sauer R et al., N Engl J Med 2004

No survival benefit

Standard of care

Pre- vs Post-operative RT

Randomized studies

	Pts	Survival Pre – Post 5y %		Local control Pre – Post 5y %	
UPPSALA Trial	471	42 - 38	ns	86 - 77	0.02
NSABP R03	254	75 - 66	ns*	89 - 89	ns
CAO/ARO/AIO 94	823	74 - 76	ns	94 - 85	0.006
Korean Trial	240	76 - 74	ns	95 - 94	ns
MRC C07	1350	70 - 68	ns	96 - 89	0.0001

* DFS p=0.011

Pahlman L et Al – Ann SUrg - 1990
Sauer R et Al – NEJM – 2004
Sebag-Montefiore D et Al - Lancet – 2009
Roh MS et Al – JCO - 2009
Park J et Al – Cancer - 2011

Pre- vs Post-operative RT

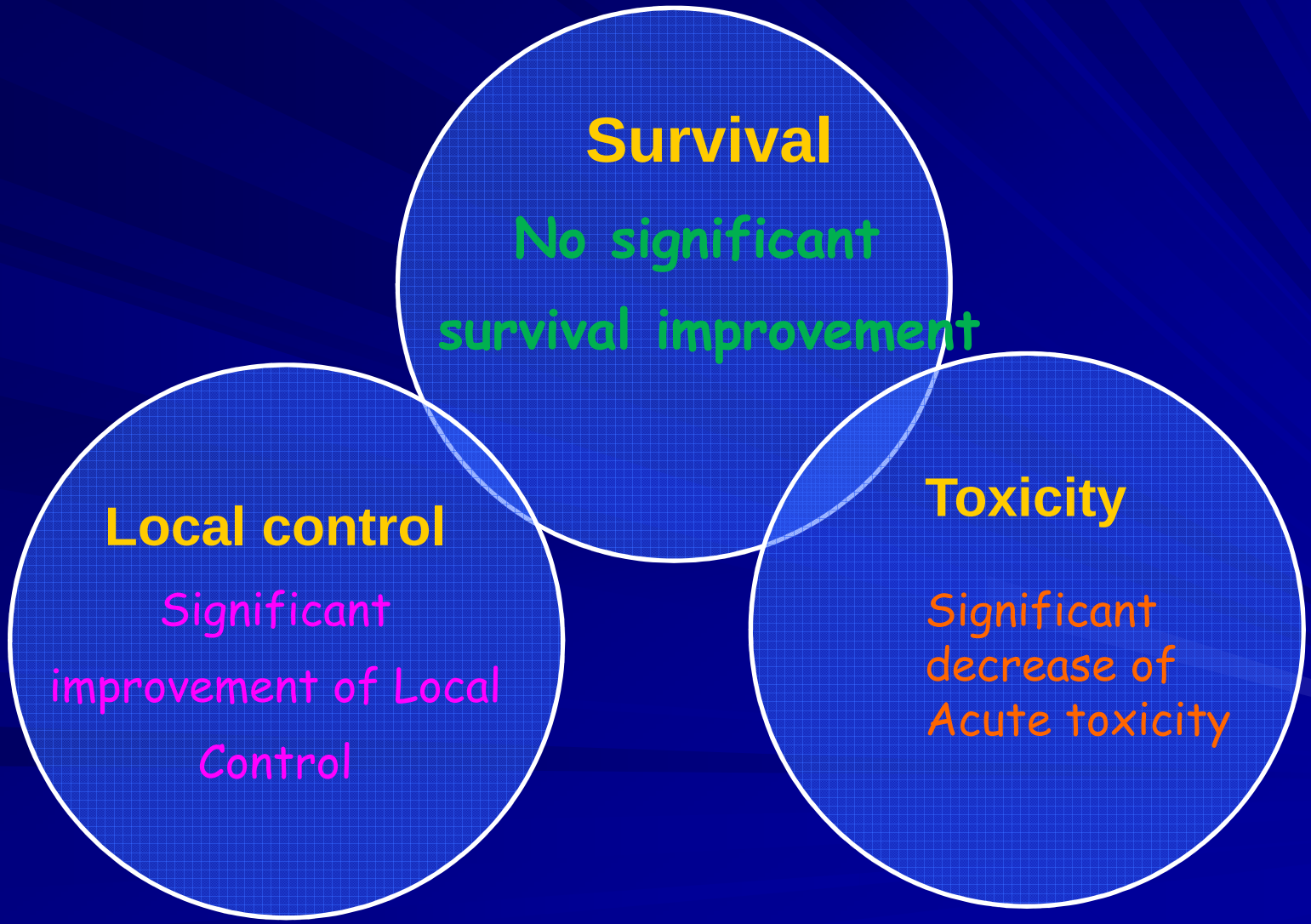
Randomized studies

	Pts	Sphincter Sav. Pre – Post %		Grade 3 Tox Pre – Post %	
UPPSALA Trial	471	59 - 58	ns	20 - 41	0.03
NSABP R03	254	44 - 34	ns	52 - 49	ns
CAO/ARO/AIO 94	823	39 - 20	0.004	28 - 39	0.005
Korean Trial	240	68 - 42	0.008°	15 - 16	ns
MRC C07	1350	61 - 63	ns	na - na	-

° 0-5 cm
na = not available

Pahlman L et Al – Ann SUrg - 1990
Sauer R et Al – NEJM – 2004
Sebag-Montefiore D et Al - Lancet – 2009
Roh MS et Al – JCO - 2009
Park J et Al – Cancer - 2011

Randomized trials after 2000



Consensus

All patients with cT3 rectal cancer
who require additional therapy
(chemoradiation or short course radiotherapy)

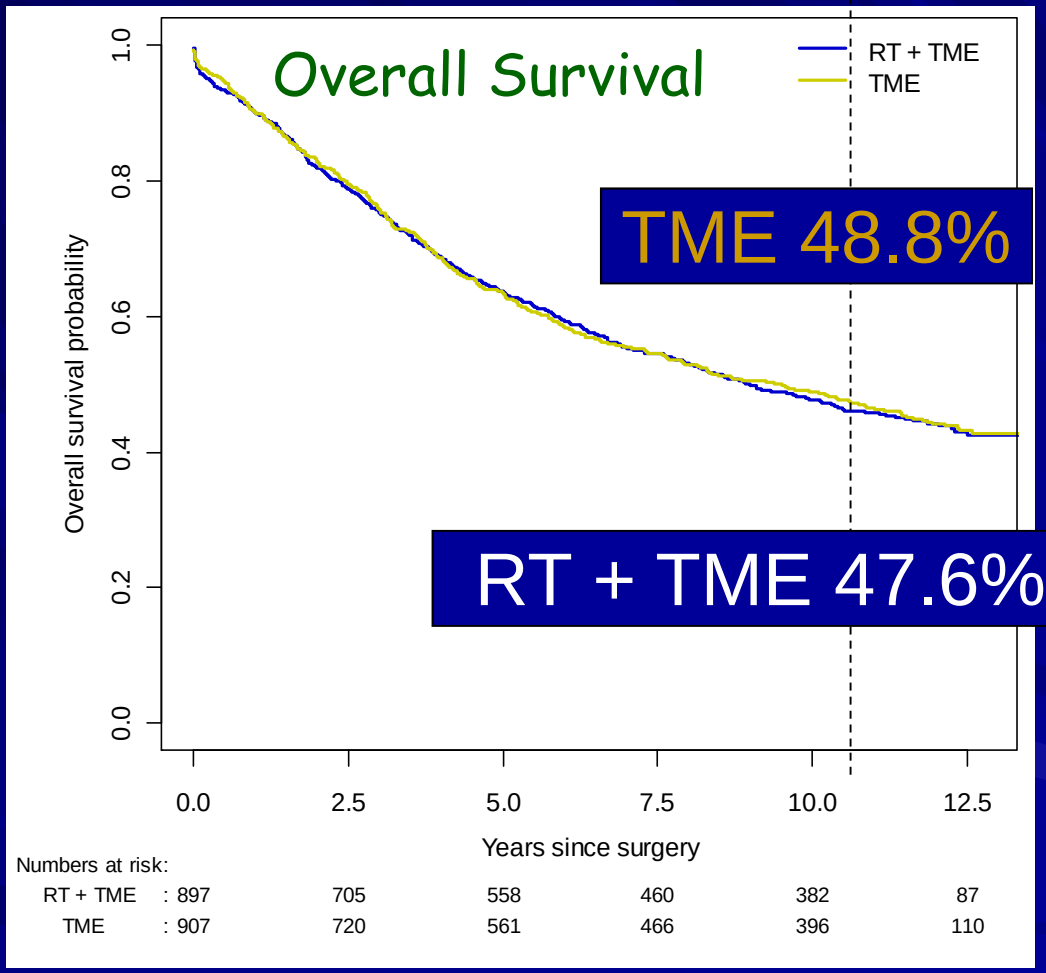
should receive it preoperatively

Issues

- Preop or postop? - Preop better
- **TME Alone or TME + RT?**
- Short or long course?
- With or without chemotherapy
- +/- targeted drug?
- What target?

Treatment - Intermediate

12 years Update of Dutch Trial



P = 0.891

By the courtesy of C. Van de Velde

Treatment - Intermediate

12 years Update of Dutch Trial

Cause of death	RT + TME (295)	TME (298)
Rectal cancer	40.3%	51.0%
Other	59.7%	49.0%

P = 0.01

By the courtesy of C. Van de Velde

Quality of TME

- Commented by Pathologist
- Minimal 12-15 lymph nodes retrieval a must during grossing
- Reporting on CRM

Short or long course?

Preop RT - Short or long course?

RT alone
5 Gy x 5# (1 week Mon – Fri)

↓

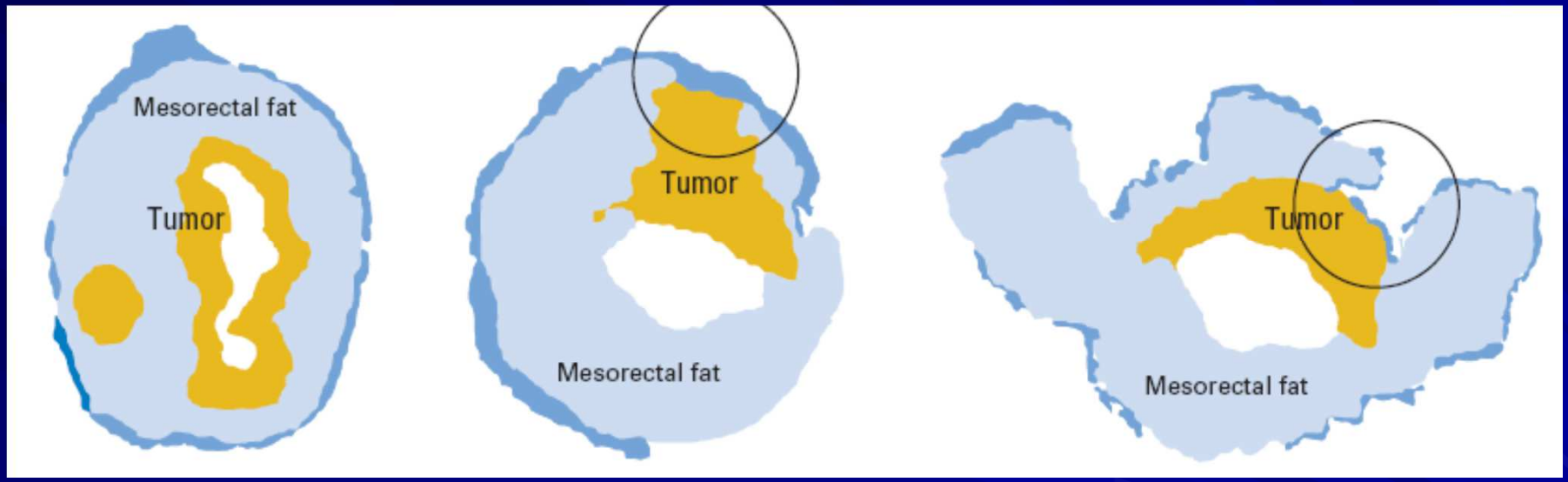
Surgery TME (Next week)

Chemoradiation 50Gy / 25#
+ Capecitabine

↓

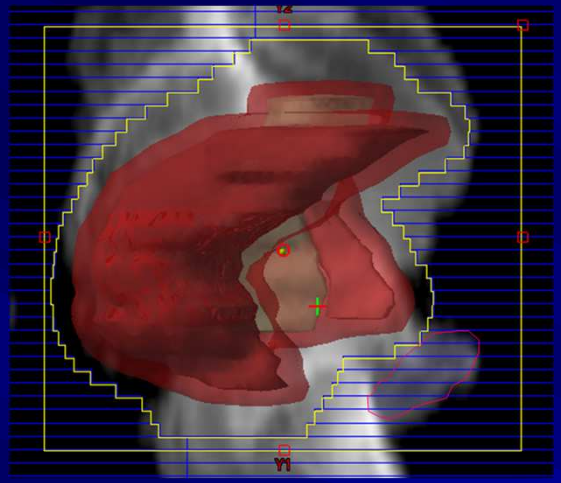
Response assessment after
6 weeks and surgery

Circumferential Resection Margins

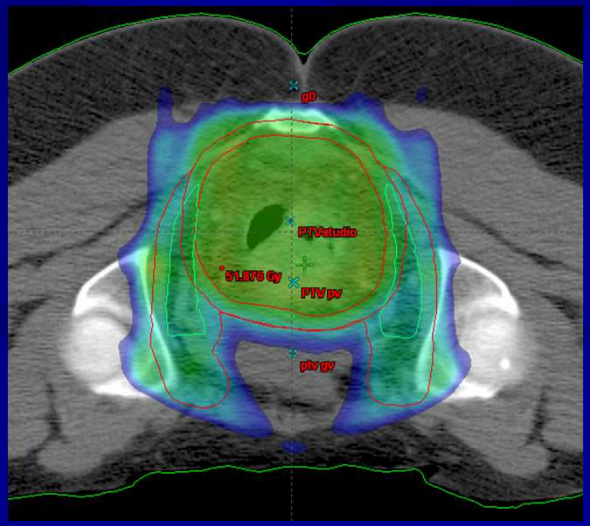


Nagtegaal I et Al - *JCO* – 2008

Optimized RT



+



Circumferential Resection Margins

	Preop Short RT	Preop Long RTCHEM
CRM +	13 %	4 %

P= 0.001

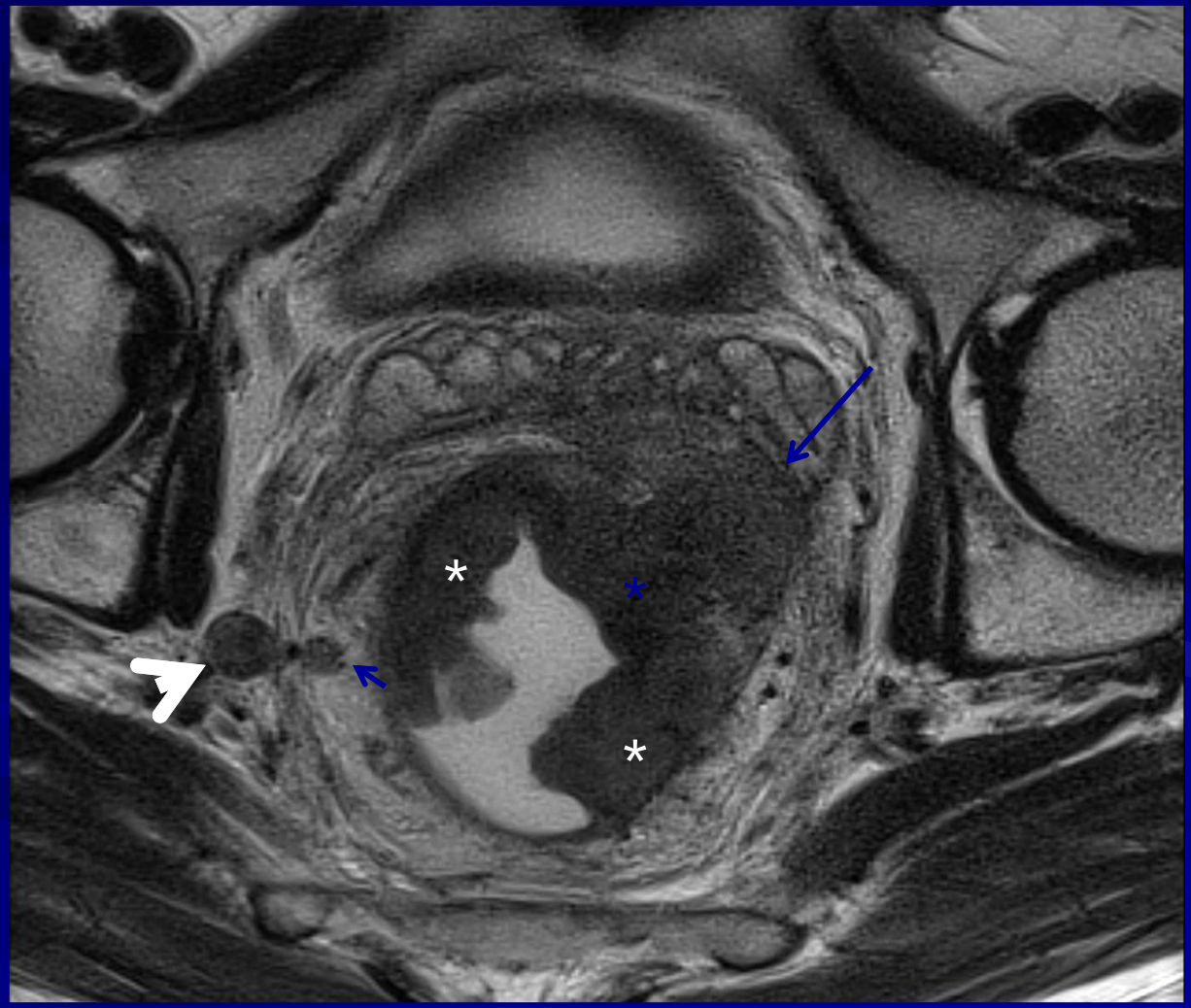
Bujko K et Al - *Radioth Oncol* – 2004

CT or MRI?

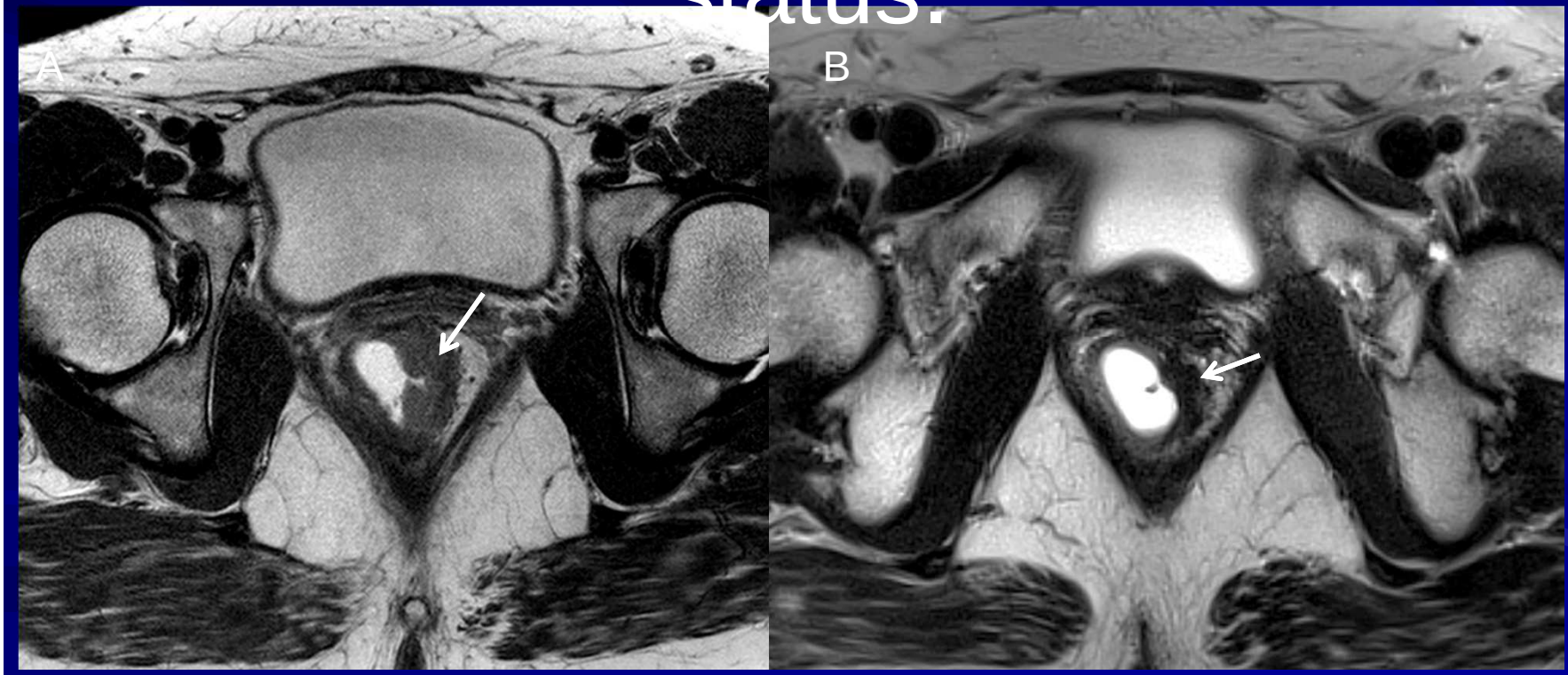
- MDCT has enabled thin sections and high quality reformats
- Yet MRI has shown superiority over MDCT for T staging and CRM status
- Current recommendation is MRI pelvis for local staging & MDCT chest and abdomen for distant workup.
- However in resource constrained environments, one can use MDCT with reformations.

Mesorectal fascia free(arrow)= CRM negative
Tumor reaches into perirectal fat , T3 CRM -

Rectal tumor(*) reaching MRF on left (white arrow) →T3
CRM +
Right internal iliac node (arrowhead)
Small arrow –right perirectal node touching MRF



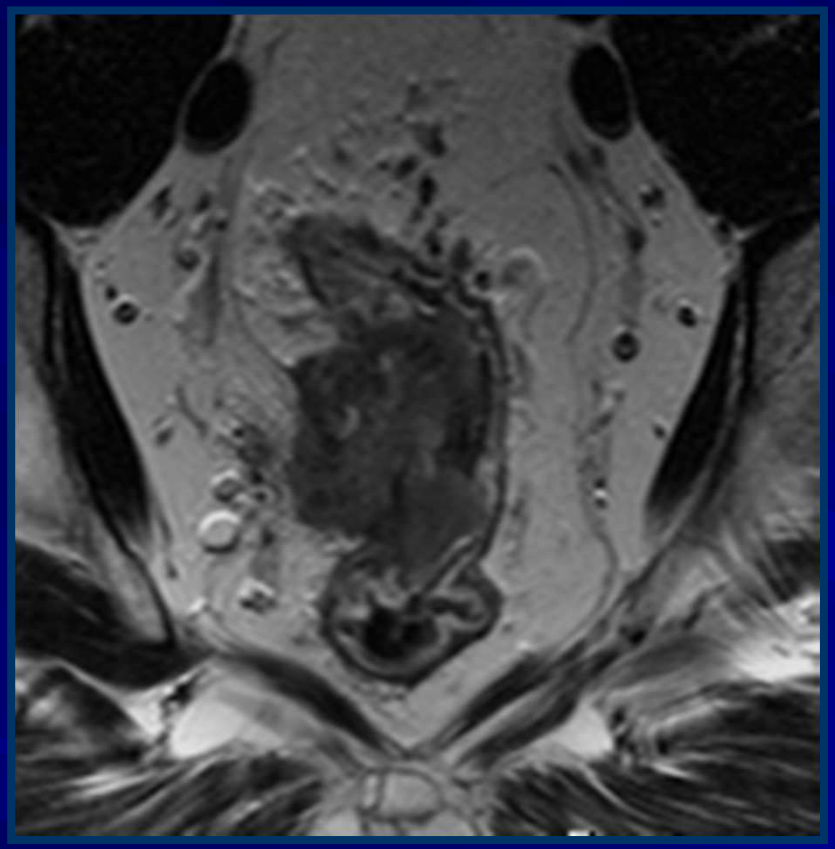
A.Pre-chemoradiotherapy & B.postchemoradiotherapy status.



Replacement of intermediate signal intensity in A by dark hypointensity is s/o fibrosis.

Circumferential Resection Margins

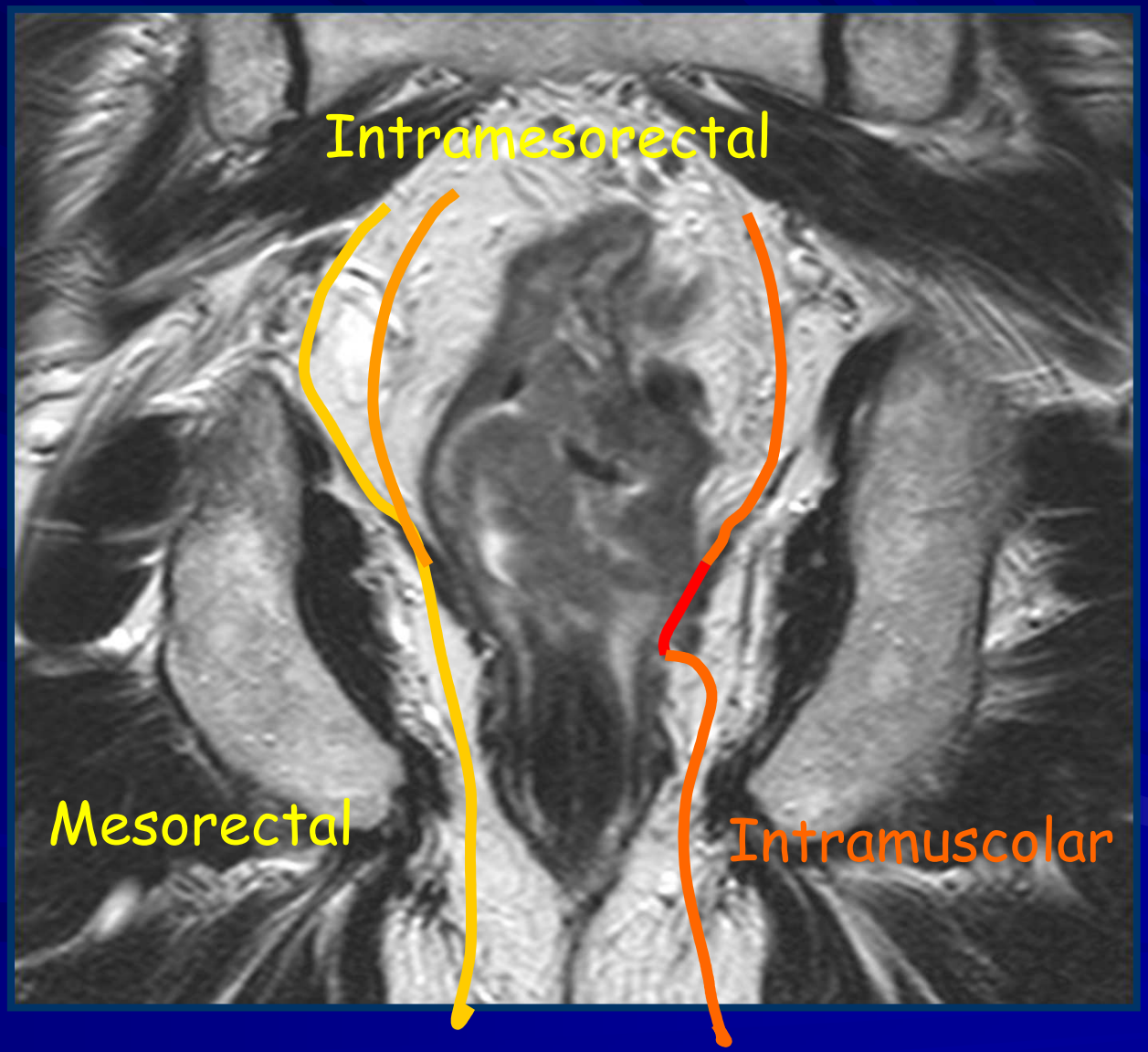
CRM- vs CRM+



EURECA 2 C.C.

Phased array MRI is highly accurate to predict CRM

Circumferential Resection Margins



Quirke P et Al - *Lancet* – 2009

Therefore:
tailored treatment

- “small” T3 short-term RT and TME
- “large” T3 long-term CRT and TME
- T4 long term CRT and TME

? With or without chemotherapy

? RTCT rather than RT pre- or postoperatively

- If prolonged course RT (45-50 Gy), we have

  good evidence that

  RTCT is superior to RT alone

  both pre- and postoperatively

RTCT rather than (the same) RT pre- or postoperatively?

- Old US postop trials (GITSG, NCCTG) + Cafiero
- Old negative preop trials (all inop T4)
- Three modern preop trials

Locally advanced (90% cT3, 10% op cT4):

- EORTC 1011 pts (Bosset et al NEJM 2006;355;1114-23)

- FFCD 762 pts (Gerard et al JCO 2006;24:4620-5)

Inoperable cT4:

- Nordic LARCS 209 pts (Braendengen et al JCO Aug 2008;)

Which Chemotherapy

- • 5-FU explored in the randomised trials (oral likely equivalent)
- Capecitabine - convenient

- • Now ”everyone” use combinations (numerous publications)

All claim superiority, pCR considered an important endpoint (Glynne-Jones Red J 2006;66:319-20), all recognize more toxicity

More studies: for locally advanced tumors

Local failure

	CRT 25x1.8 + chemo	RT 25x1.8 - chemo	p
FFCD 9203	8.1%	16.5%	<0.05
EORTC 22921	7.6-9.6%*	17.1%	<0.05

Gerard, JCO 2006
Bosset , NEJM 2006

Issues

- Preop or postop? - Preop better
- TME Alone or TME + RT?
- Short or long course? - "small" T3 short-term RT+TME
  "large" T3+T4 long-term CRT and TME
- With or without chemotherapy – CTRT better
- +/- targeted drug?
- What target?

RTCT with targeted drug?

- • Experimental evidence (but this can be found in at least one system for virtually everything)
- Explored clinically (and as usual, ”promising” activities in the phase I/II trials)
- At least one randomised phase II trial, EXPERT-C, accrual completed, n=164)
- **Should not be used**, but of course explored properly

All phase II trials!

- **What target?**

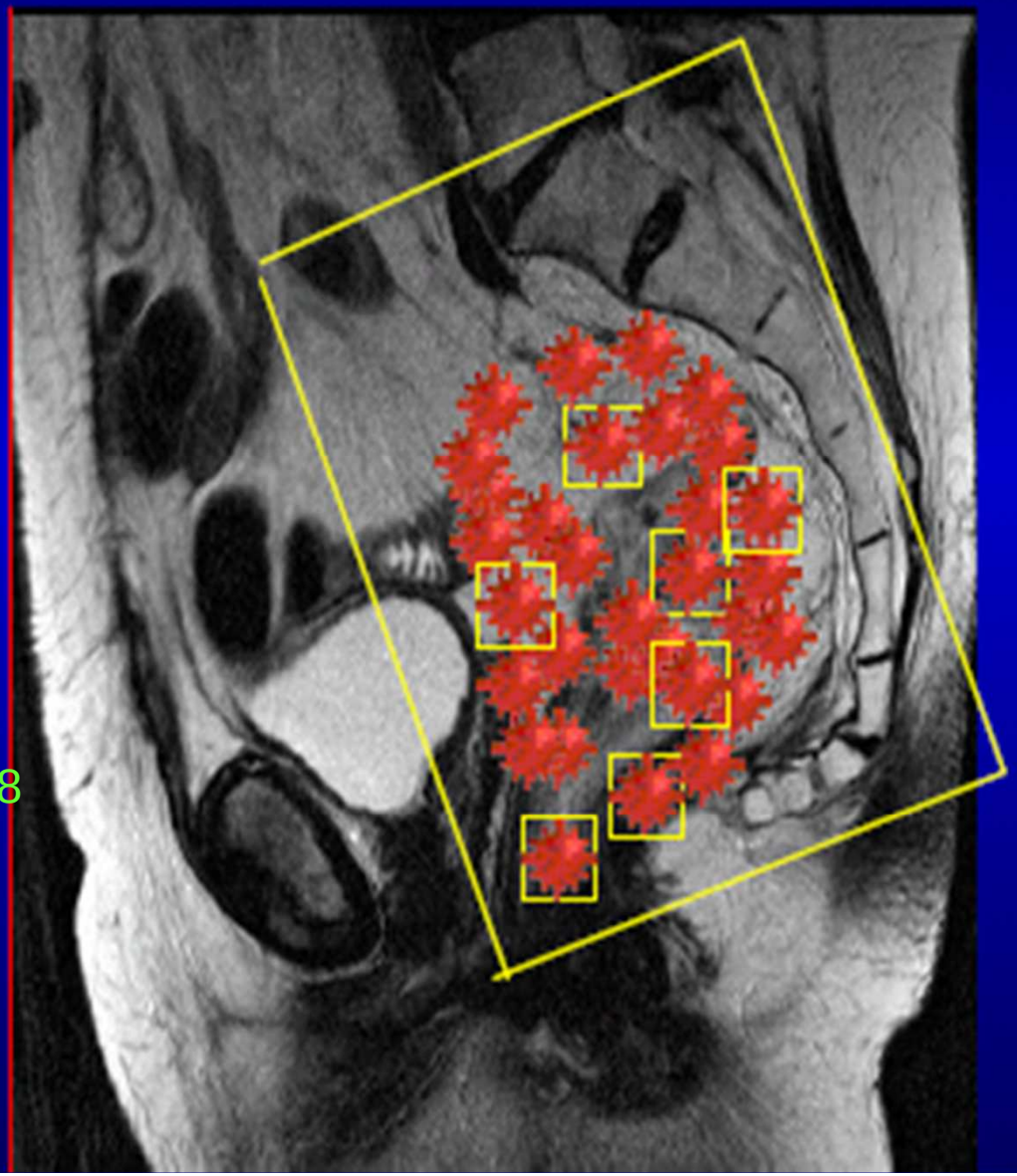
Why local failure in spite of TME or, what should be irradiated?

- • Poor surgery due to incomplete TME?
- • Remaining tumour cells in tissues not removed, e.g. in the lateral nodes?
- Population-based study in Stockholm 1995-2004, 2495 pts, 2315 resections and TME, 155 recurrences (65(4%) RT+, 90(12%) RT-) Most recurrences anastomotic (high, non-RT pts), few from the lateral nodes

- Syk et al, Br J Surg 2006;93:113-9, Int J Radiat Biol Phys

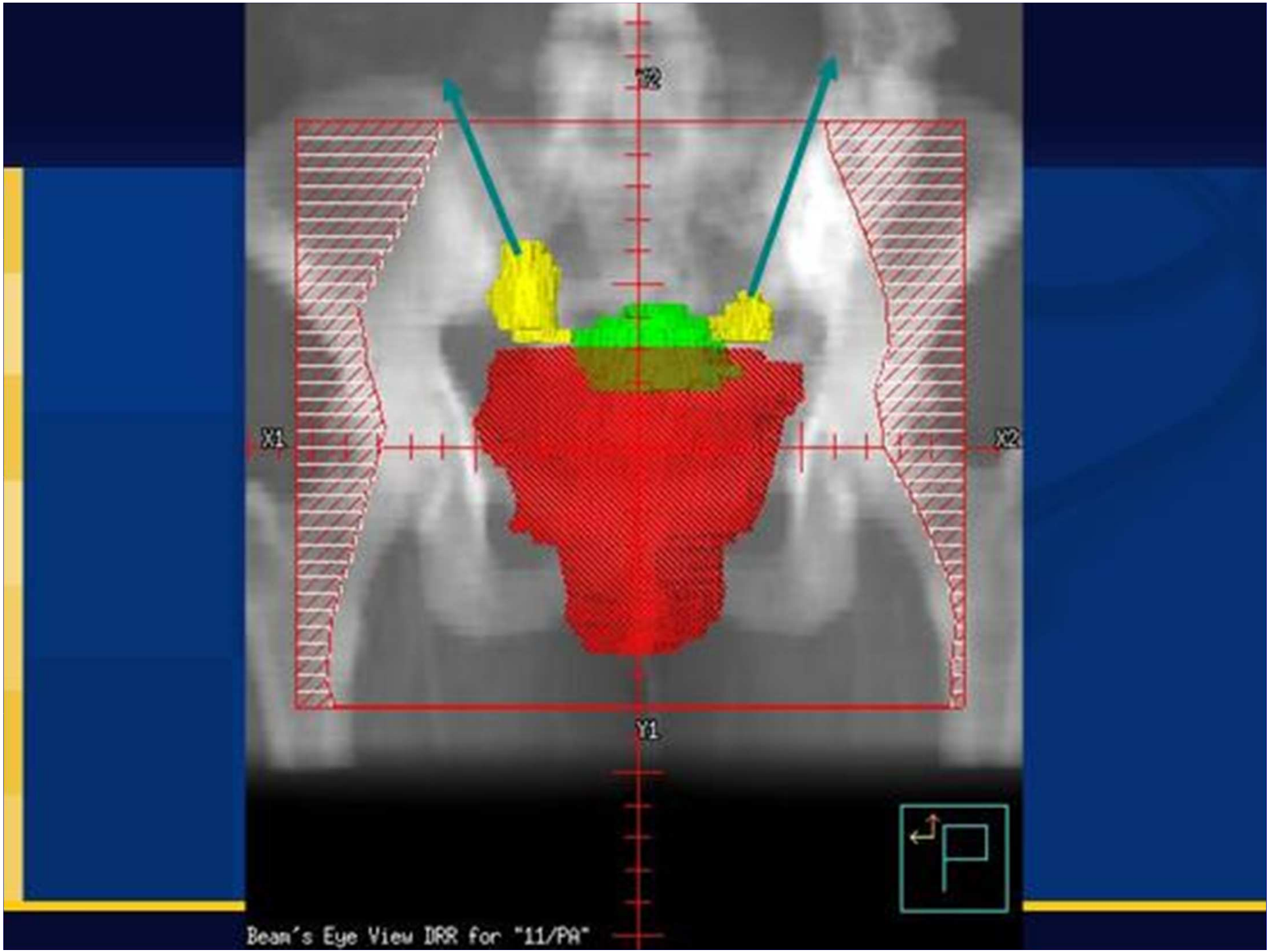
Location of the local failures (n=83)

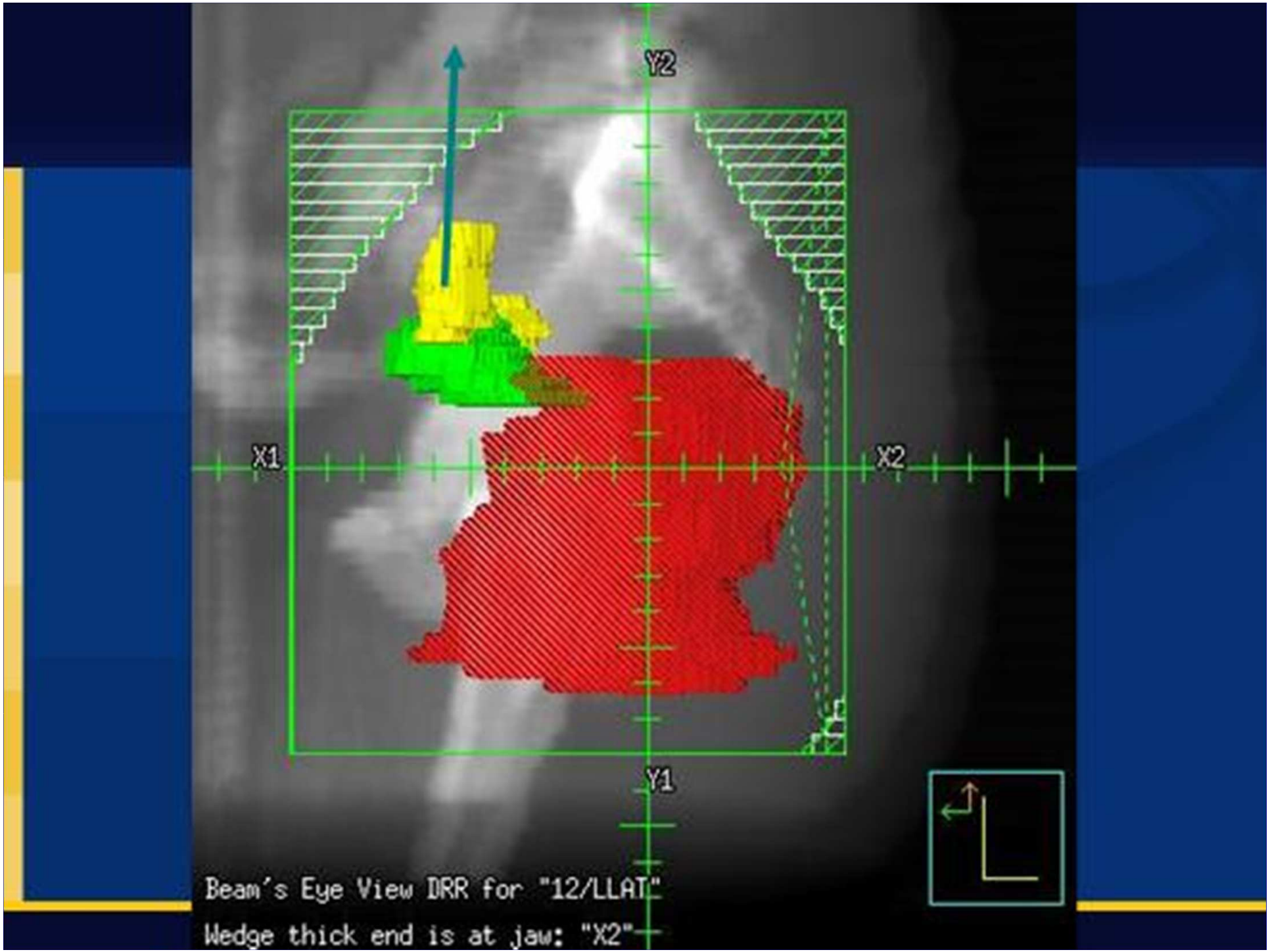
Indicates that the target can be slightly modified, i.e. decreased



Syk et al IJROBP 2008
Br J of surgery 2009

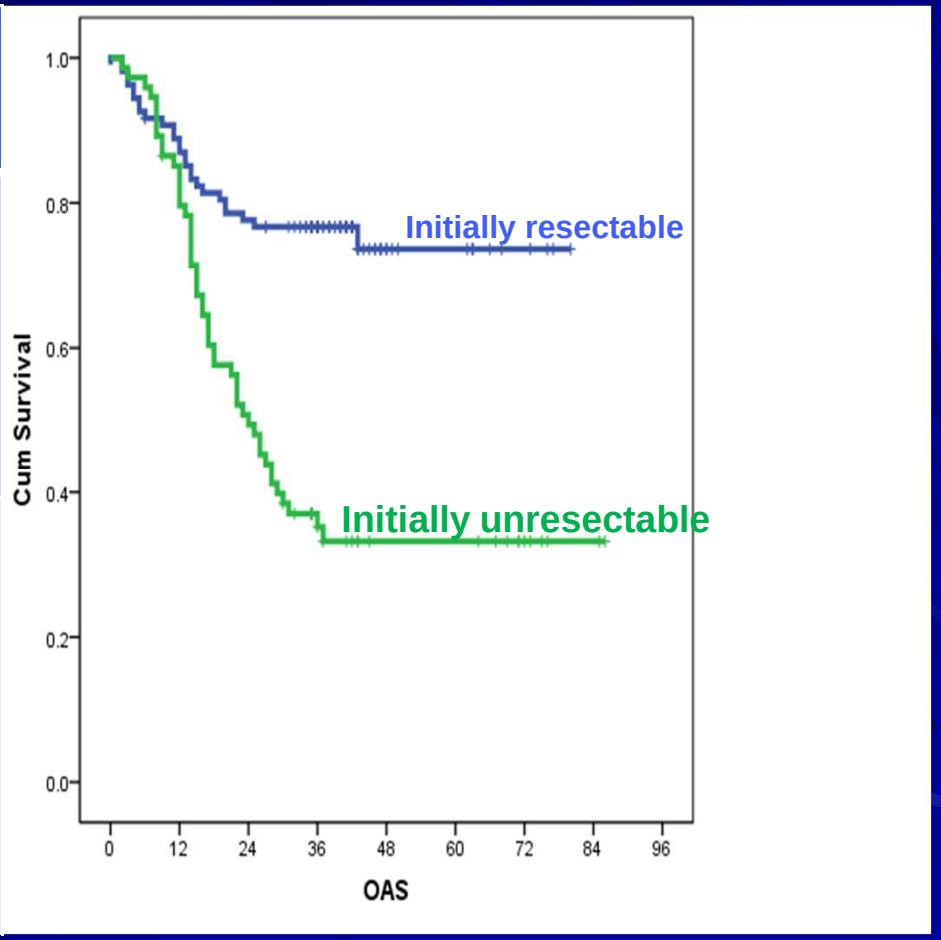
The yellow box shows beam limits


Y2
X1
X2
Y1
P
Beam's Eye View DRR for "11/PA"


Y2
X1
X2
Y1
Beam's Eye View DRR for "12/LLAT"
Wedge thick end is at jaw: "X2"

Rectal receiving NACTRT at TMH
July 2006 Dec 2010 N=182

Disease at presentation	Underwent surgical resection	Reasons for not undergoing surgical resection
Resectable (n=108)	R0: 88 (81%) R1: 4 (3.7%)	6- Refused Surgery 5 – D.M 1- Died post CRT 4- Local progression
Unresectable (n=74)	R0: 33 (44.5%) R1: 6 (8%)	3- Refused Surgery 25- Locally unresectable post CRT 6 - D.M 1- Died post CRT

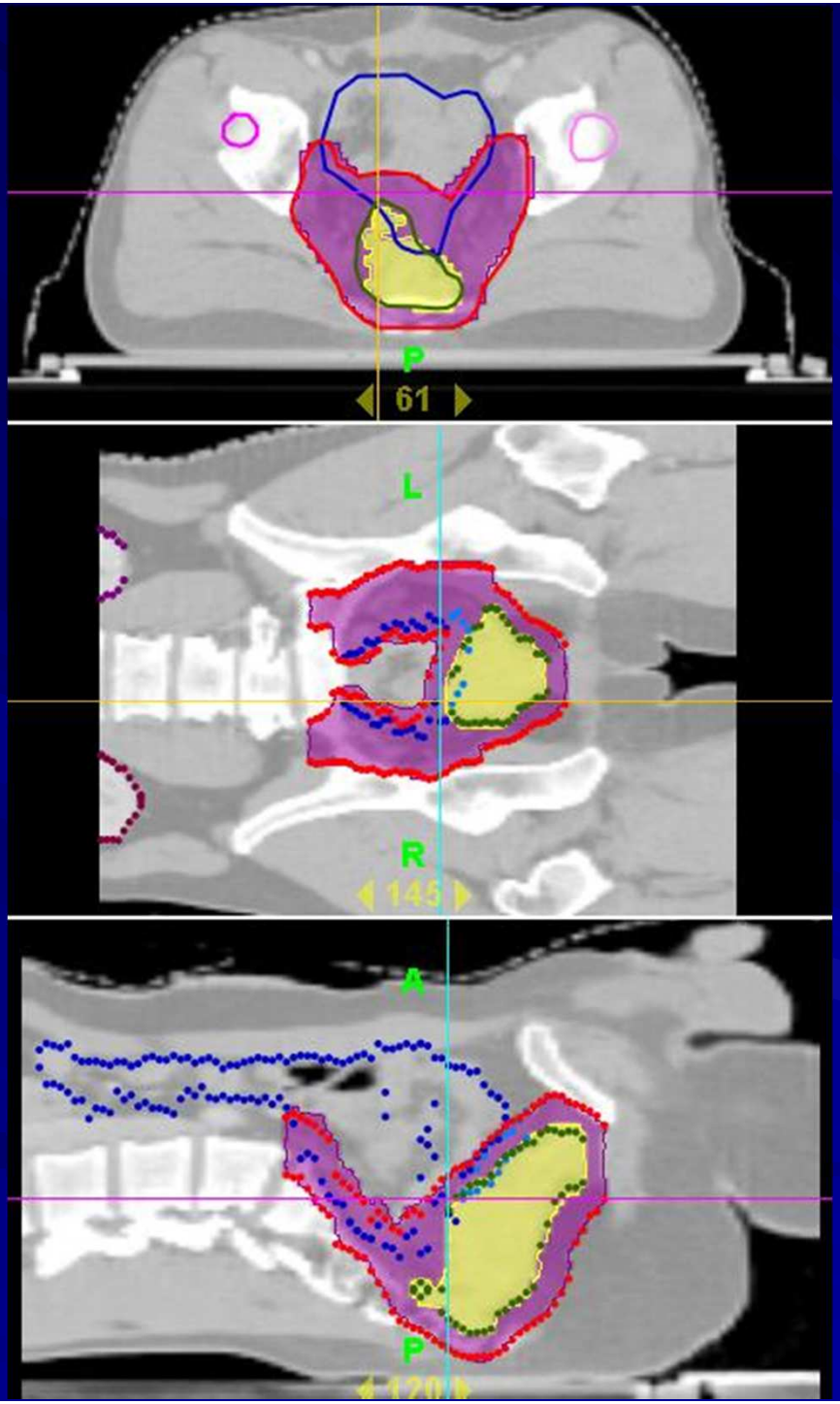


pCR rate - 21%

Multivariate analysis for factors affecting DFS and OAS

	DFS	OAS
Initially resectable vs. Unresectable	(p=0.001)	(p=0.01)
pT stage	(p=0.16)	(p=0.01)
pN stage	(p=0.002)	(p=0.01)
pretreatment CEA levels more than 5ng/ml	(p=0.05)	(p=0.003)
signet ring cell carcinoma	(p=0.05)	(p=0.01)
TRG ≤3 >3	(p=0.33)	(p=0.04)

IMRT plan for rectal cancer

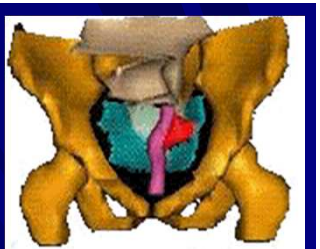


5x5 Gy with delayed surgery as an alternative to radiochemotherapy

- • Much simpler, but has it the same tumour
- down-staging and down-sizing effect?
- • The simple answer is that we don´t know
- • Many have successful anecdotal patients
- • Retrospective study in Uppsala (Radu et al.,
- Radiother Oncol. Aug 2008;87:343-9)

Local recurrence

Retreatment: Storm 97.03



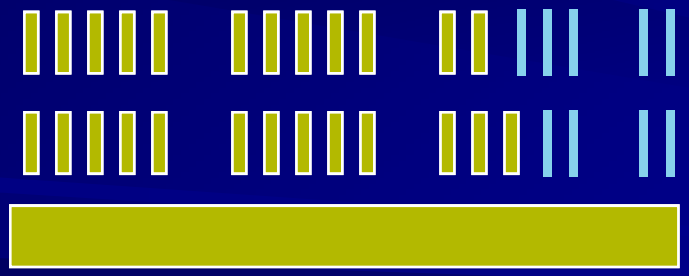
59 pts

Patients Selection

Pelvic Recurrence F0-3, M0,

Previous ERT (45-54 Gy)

Study Schema :



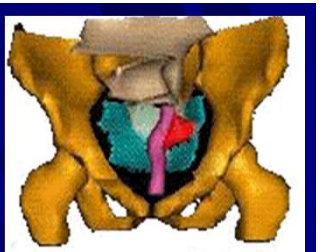
ERT 30+10 Gy

(120 cGy b.i.d.)

5FU 225 mg/m2 PVI

Valentini V et Al - IJROBP – 2006

Retreatment: Storm 97.03



	59 pts %
R0 surgery	36
pCR	8.5
Local Control (5y)	39
DFS (5y)	29
OS (5y)	39
Overall late toxicity	12

Median follow-up: 3 years

Wait & Watch only post CRT

- Chemoradiation

Complete clinicoradiological response

No surgery only Wait & Watch policy ??

EMERGING CONCEPT – Only for research

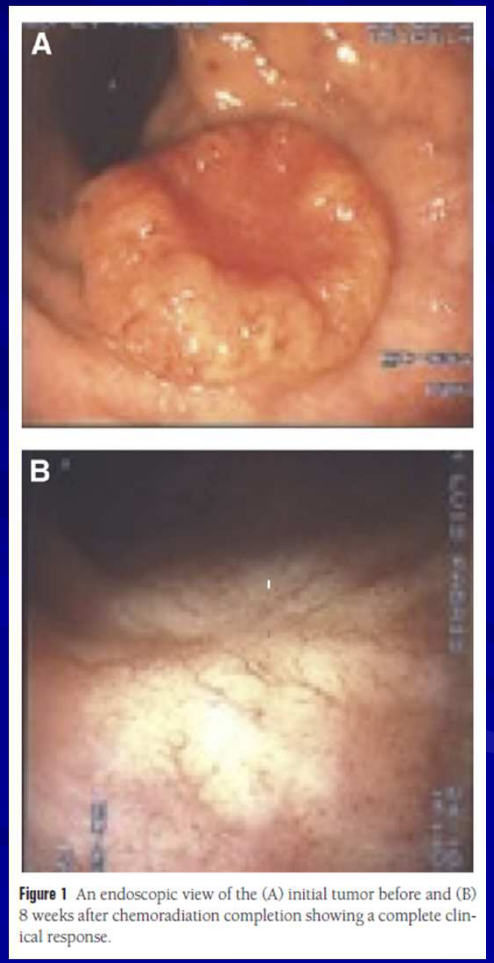


Figure 1 An endoscopic view of the (A) initial tumor before and (B) 8 weeks after chemoradiation completion showing a complete clinical response.

Semin Radiat Oncol 21:234-239 © 2011

Semin Radiat Oncol 21:234-239 © 2011

Habr Gama et al

173 patients

Stage II 63% Stage III 21% (tumor within 7 cm ofanal verge)

↓

RT 50.4 – 54 Gy + Inj 5FU
Assessment for surgery at 8 weeks

↓

67 (39%) Complete response

↓

Strict follow up
4- Local rec
- 3- local excision
- 1- Brachytherapy
- 1- APR at 16 months

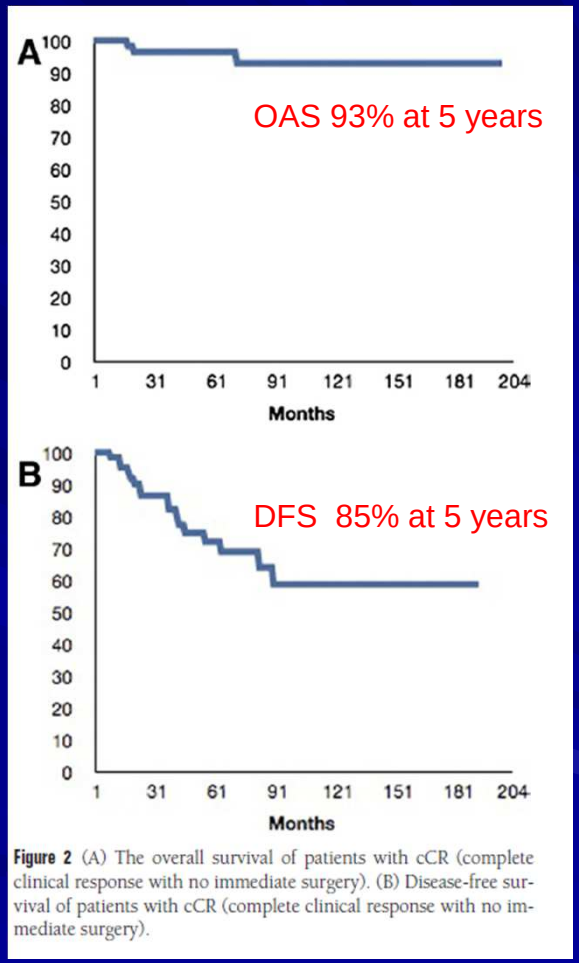


Figure 2 (A) The overall survival of patients with cCR (complete clinical response with no immediate surgery). (B) Disease-free survival of patients with cCR (complete clinical response with no immediate surgery).

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Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer

Monique Maas, Regina G.H. Beets-Tan, Doenja M.J. Lambregts, Guido Lammering, Patty J. Nelemans, Sanne M.E. Engelen, Ronald M. van Dam, Rob L.H. Jansen, Meindert Sosef, Jeroen W.A. Leijtens, Karel W.E. Hulsewé, Jeroen Buijsen, and Geerard L. Beets

192 patients
CRT 50.4 Gy/ 28# + capecitabine.

↓

Assessment of response 6- 8 weeks

↓

Complete clinicoradiolocal response
21 patients

10 of 21 patients (48%) spared APR/colostomy

Cumulative probability of 2-year DFS - 89% (95% CI, 43% to 98%), and OS is 100%.

Compliance to NACTRT and surgery

- Proper counselling by the surgeon and the Radiation Oncologist
- If good response wait of >6weeks
- More attempt for sphincter saving surgeries like LAR and ISR

TAKE HOME

- • Preoperative RT preferred + TME
- • Small tumors 5x5 Gy
- • Large tumors: CRT
- Reduced local recurrenceSome studies survival benefit!
- Locally recurrent cancers can be treated with reirradiation +/- Sx
- Mutidisciplinary team