II° CONGRESSO
Gruppo Interregionale
AIRO Piemonte-Liguria
Valle d'Aosta

"Aspetti clinici e tecnici della radioterapia nei tumori del colon-retto"

8 ottobre 2011

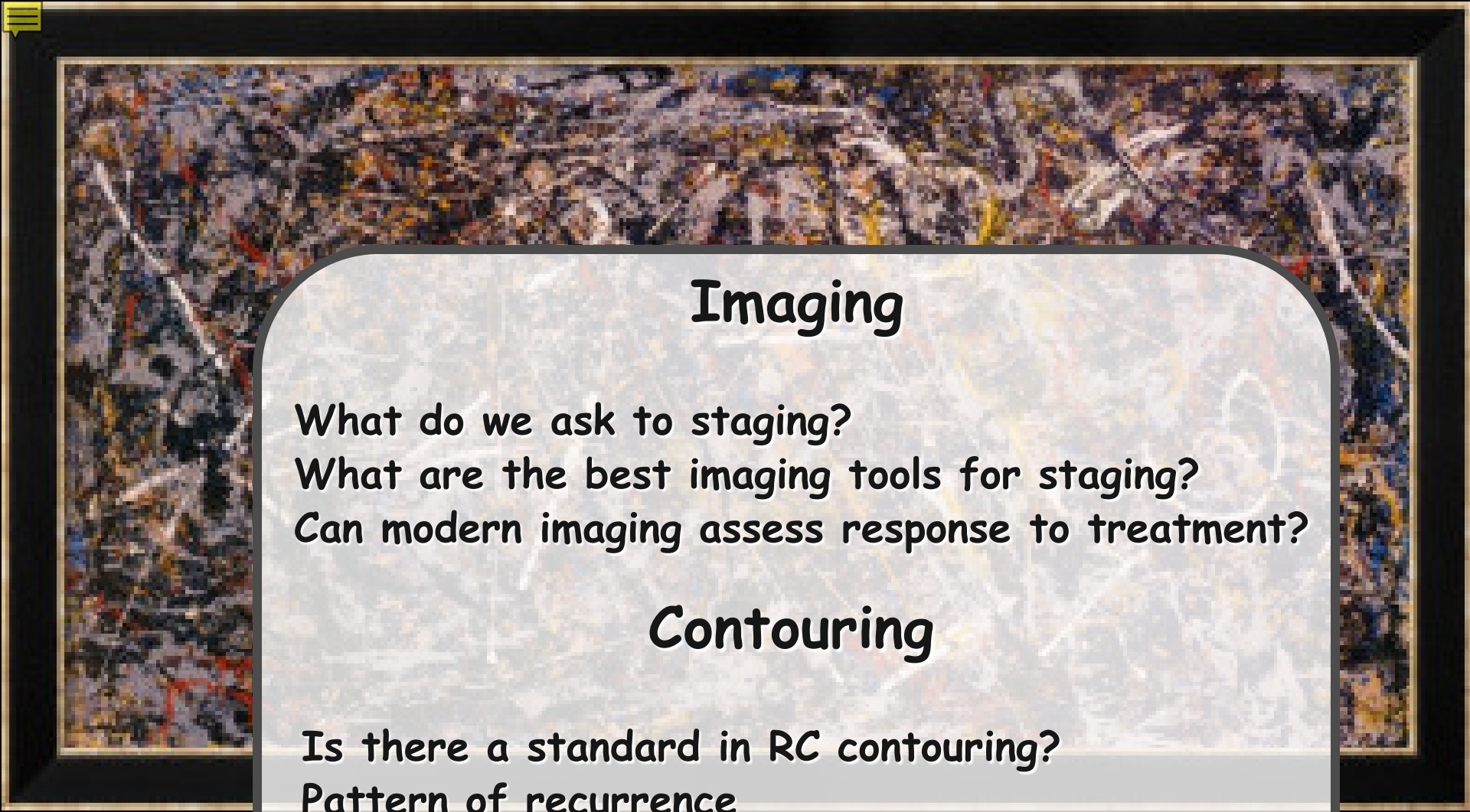
Castello di Grinzane Cavour

# *Imaging e contouring nei tumori*


G. Apicella

SCDU di Radioterapia

Azienda Ospedaliero-Universitaria "Maggiore della Carità", Novara



## Imaging

What do we ask to staging?
What are the best imaging tools for staging?
Can modern imaging assess response to treatment?

## Contouring

Is there a standard in RC contouring?
Pattern of recurrence
Can we use imaging tools for target definition?
Do we need Adaptive RT?

Alchemy, 1947 Jackson Pollock

# Treatment by stage

## T1-2 Nx M0

*with risk factors*

pT2
Grading 3
Diameter > 4 cm
Vessel invasion

Surgery

↓

RT ± Chemo

| | % 5 yy |
|---|---|
| Local control | 73-100 |
| Survival | 70-100 |
| Sphincter saving | 70-100 |

## T3-4resec or N+ M0

RT ± Chemo

↓

Surgery

↓

± Chemo

Surgery

↓

RT + Chemo

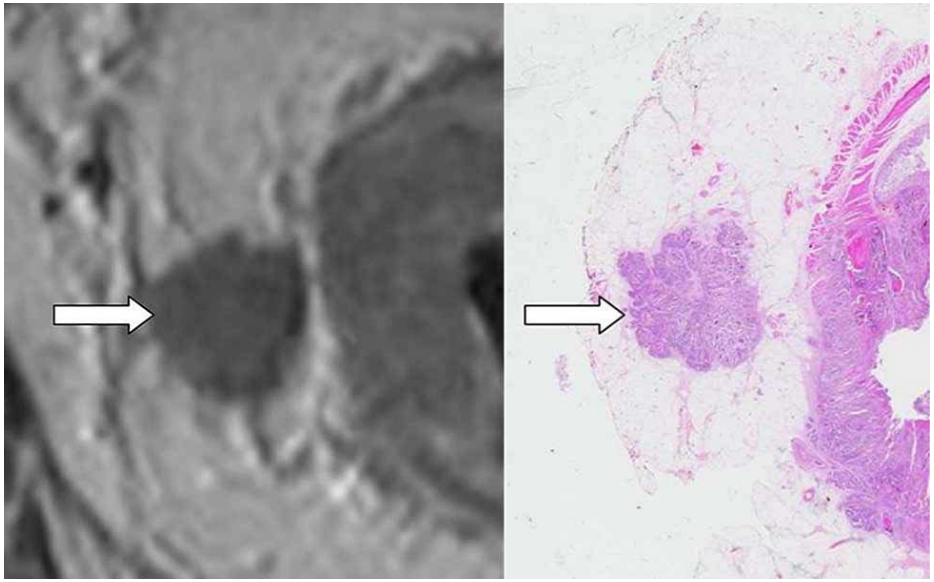
PREOP vs POSTOP

Radiobiology
> Downstaging
> Margins –
< Toxicity

Pts selection
Area at risks

# Circumferential Resection Margin

- direct tumor spread (18%-29%)
- discontinuous tumor spread (14%-67%)
- lymph node metastases (12%-14%)
- venous invasion (14%-57%)
- lymphatic invasion in 9%
- perineural tumor spread (7%-14%)



## Radial margin of ≤1 mm

→ increased risk of local recurrence (22% vs 5% n= 686) [Wibe, 2002]

→ increased risk of distant metastases (37% vs 15%)

→ shorter survival (70% vs 90% at 2 years)

**….Same implications even for < 2 mm CRM**

(16% vs 6% local recurrence for patients with radial margins 2 < mm)

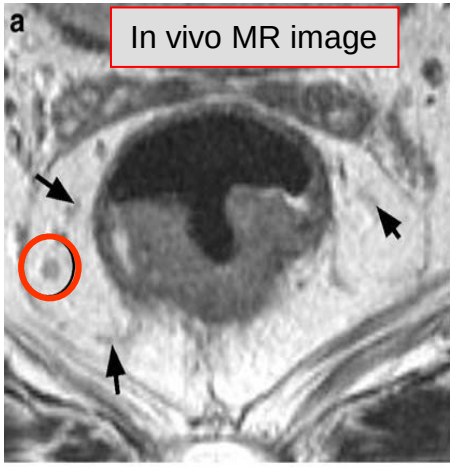
Nagtegaal, et al, Journal of Clinical Oncology, 2008

# Lymph nodes

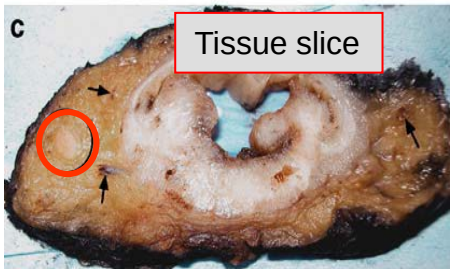
*Lymph node status probably constitutes the single most important determinant of overall survival in patients with rectal cancer*

5-year survival N+ vs N- 40% vs 68%

Cecil, et al., Dis Colon Rectum 2004





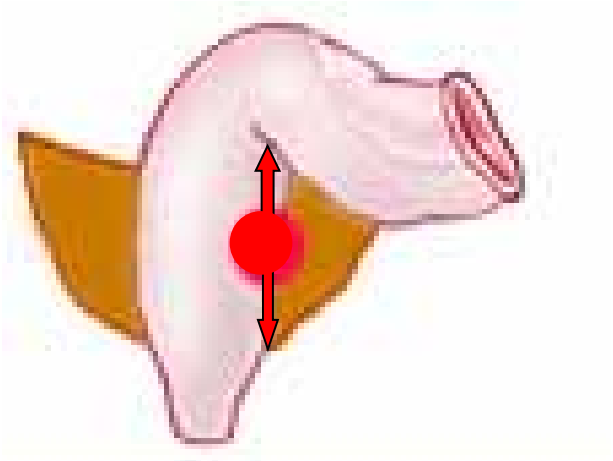



The majority of mesorectal nodes are found at the level of or **within 5 cm proximal to the tumour.**

Dominant pathway of lymphatic drainage into mesorectal nodes and upwards within the mesorectum.

Morikawa et al. Dis Colon Rectum, 1994
Parfitt, et al., J Clin Pathol, 2007

# The total mesorectal excision specimen for rectal cancer: a review of its pathological assessment



**Distal margin**

Sphincter preservation!!

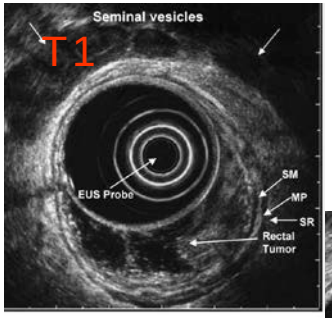
The extent of distal mesorectal spread is greater than the extent of intramural spread (3.6 cm vs 1.2 cm)

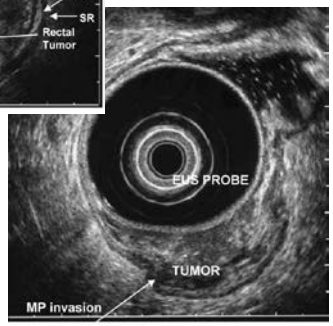
A **1.5 cm distal rectal wall** margin and a **4 cm distal mesorectal margin** are necessary to achieve adequate surgical clearance

Parfitt, et al., J Clin Pathol 2007


Joan Miró, The Hunter (Catalan Landscape)

# cT1 vs cT2




**EUS**

The most accurate imaging (T1/T2)

→ Accuracy between 69% and 97% [Bipat 2004]

→Not for high or stenosing tumors (rarely early)

[Nesbakken 2003]

**Endorectal MRI**

as accurate as EUS for staging superfi cial tumors (comparative studies)

→ less observer dependent than EUS

→ also in high located or stenosing cancers

→ more expensive

→ less comfortable for patients

**Phased array MRI**

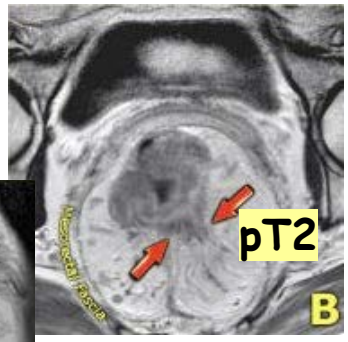
**Multispiral CTs**

Not reliable in the differentiation between T1 versus T2 [Kim 2007]

Valentini, Glimelius, Acta Oncologica, 2010

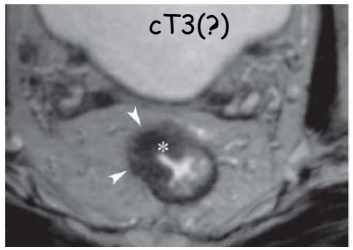
# cT2 vs cT3

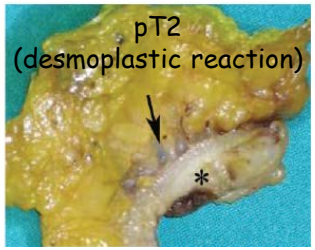
**Endorectal MRI** Differentiation of superficial (cT1/cT2) vs cT3




**EUS** MRI is equivalent to histology in measurement of extramural depth


**Phased array MRI** Not for differentiation T2 vs borderline T3




**Multispiral CTs** If with optimal bolus timing and reconstruction in multiple planes → high sensitivity and specificity for prediction of tumor penetration in the bowel wall, BUT...

→ not for low rectum located tumors.

→CT accuracy superior to EUS performed in less expert EUS centers

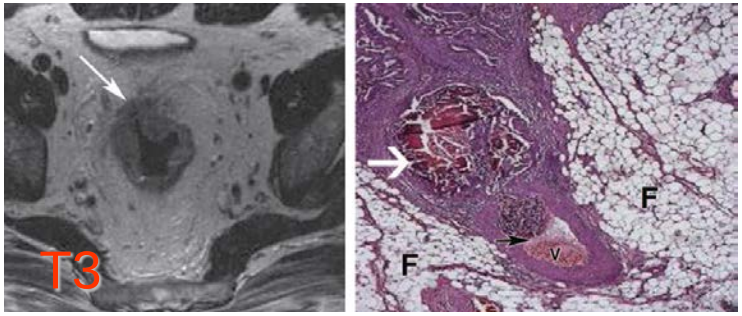
Valentini, Glimelius, Acta Oncologica, 2010

# cT3 vs cT4

**EUS** — EUS is considered not to be accurate

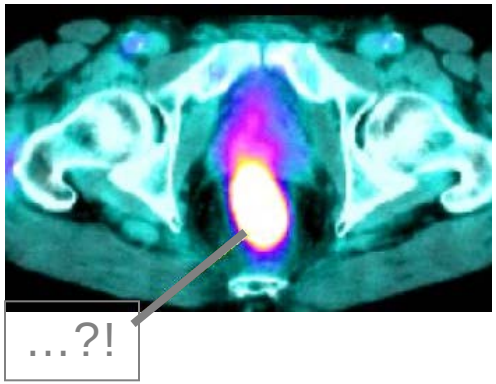
**Multispiral CTs** — is accurate for staging the advanced T3 tumors in the middle and high rectum

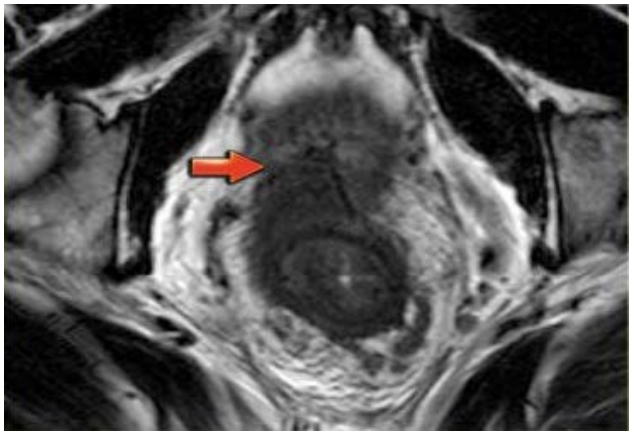
**Phased array MRI** — **To distinguish cT3 from cT4**




**FDG PET-CT**

not useful for cT staging!!!



Valentini, Glimelius, Acta Oncologica, 2010

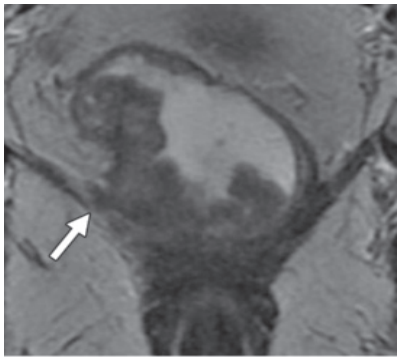
# Sphincter infiltration

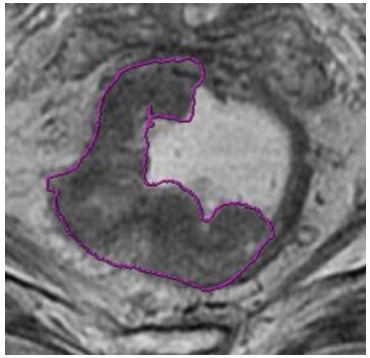
EUS

Endoanal coil MRI

Phased array MRI

Both endoanal MRI and phased array MRI are reliable in assessing sphincter infiltration






Multispiral CTs

Promising for the evaluation of the distance of the tumour to the anal sphincter (Low vs medium-high)

Valentini, Glimelius, Acta Oncologica, 2010

# CRM vs CRM-

Endorectal MRI

EUS

Conventional CT

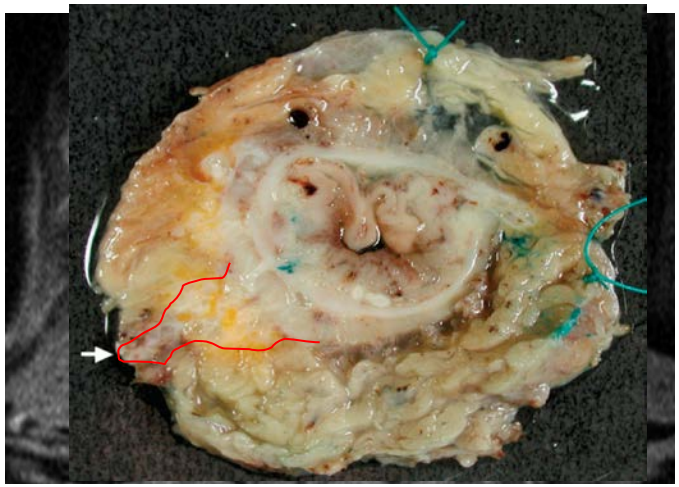
Not accurate for mesorectal fascia evaluation.

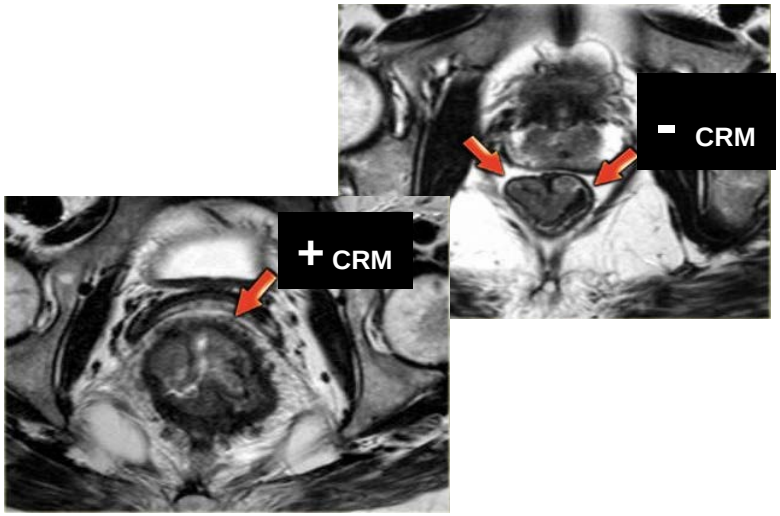
Multispiral CTs

Promising …but not in low tumors
(especially if located in the low anterior rectal wall)

Phased array MRI

**highly accurate for the prediction of CRM positivity**



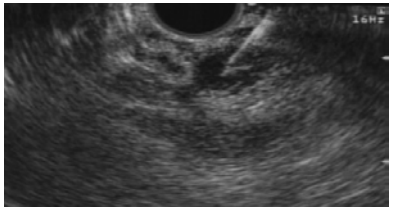



Valentini, Glimelius, Acta Oncologica, 2010

# cN0 vs cN1-2

**EUS**

EUS superior to non C.E. MRI and CT
(but the entire mesorectum not explored!)
EUS guided FNAB accuracy up to 100%

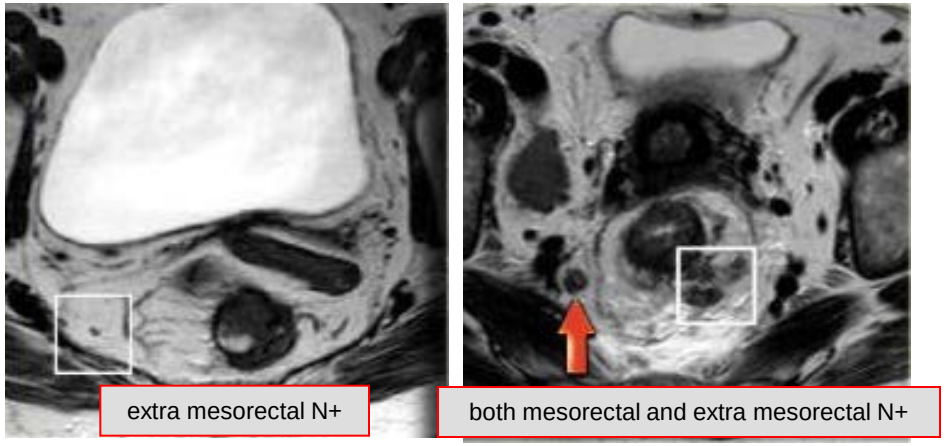


**Multispiral CTs**

New generation multislice spiral CT cannot accurately distinguish between malignant and benign lymph nodes measuring 8 mm

**Phased array MRI**

*Morphological features*
(mixed signal intensity within the lymph node and/ or irregularity of the borders due to capsular penetration by malignancy)




Accuracy rate 71% to 91%

**FDG PET-CT**

disappointing results especially in the mesorectum when bulky tumor

Valentini, Glimelius, Acta Oncologica, 2010

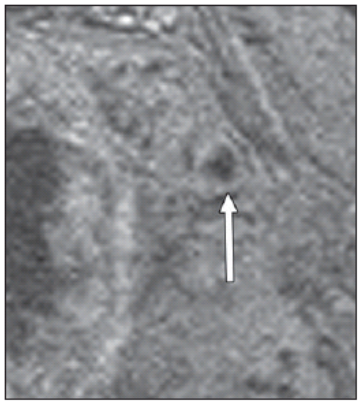
**Diagnostic Accuracy of Nodal Enhancement Pattern of Rectal Cancer at MRI Enhanced With Ultrasmall Superparamagnetic Iron Oxide: Findings in Pathologically Matched Mesorectal Lymph Nodes**

↑ interobserver agreement

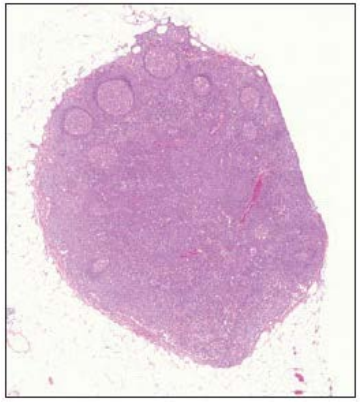
↑↑ diagnostic specificity

T2-w MR image
node classified as malignant

T2-w MR image
image with USPIO
reactive hyperplasia



reactive changes within node



…. (but the same sensitivity as morphologic MRI)

USPIO MRI

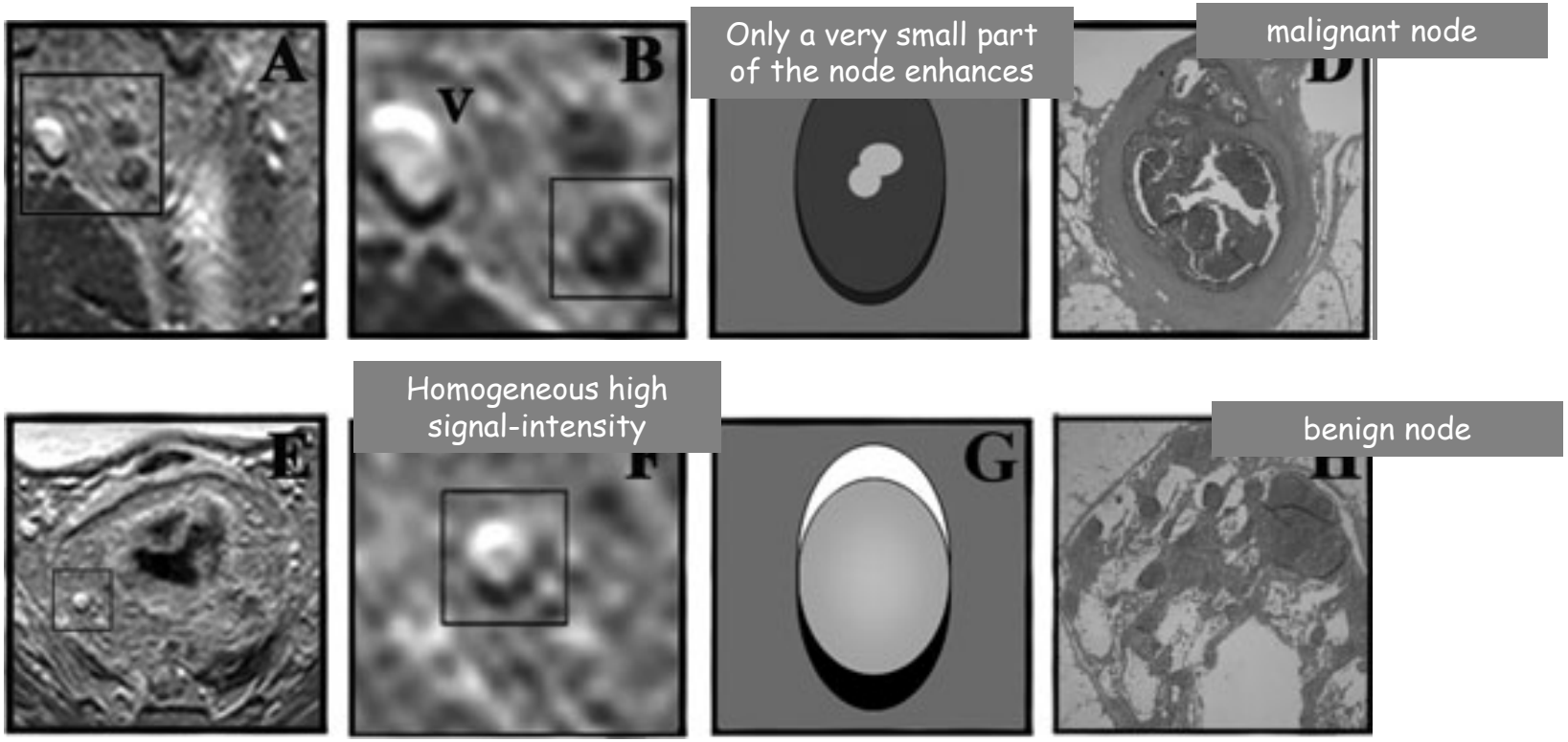
Sensitivity 91% (41% in lymph nodes ≤ 5 mm)

Specificity 98%

Dow-Mu Koh ET AL., Gastrointestinal Imaging, 2009

# Accuracy of Gadofosveset-enhanced MRI for Nodal Staging and Restaging in Rectal Cancer

Gadofosveset = blood pool MR contrast agent that binds to human albumin and is originally marketed for vascular MR imaging




Improved sensitivity 76% → 80%,

improved specificity 82% → 97%

Lambregts et al.., Annals of Surgery, 2011

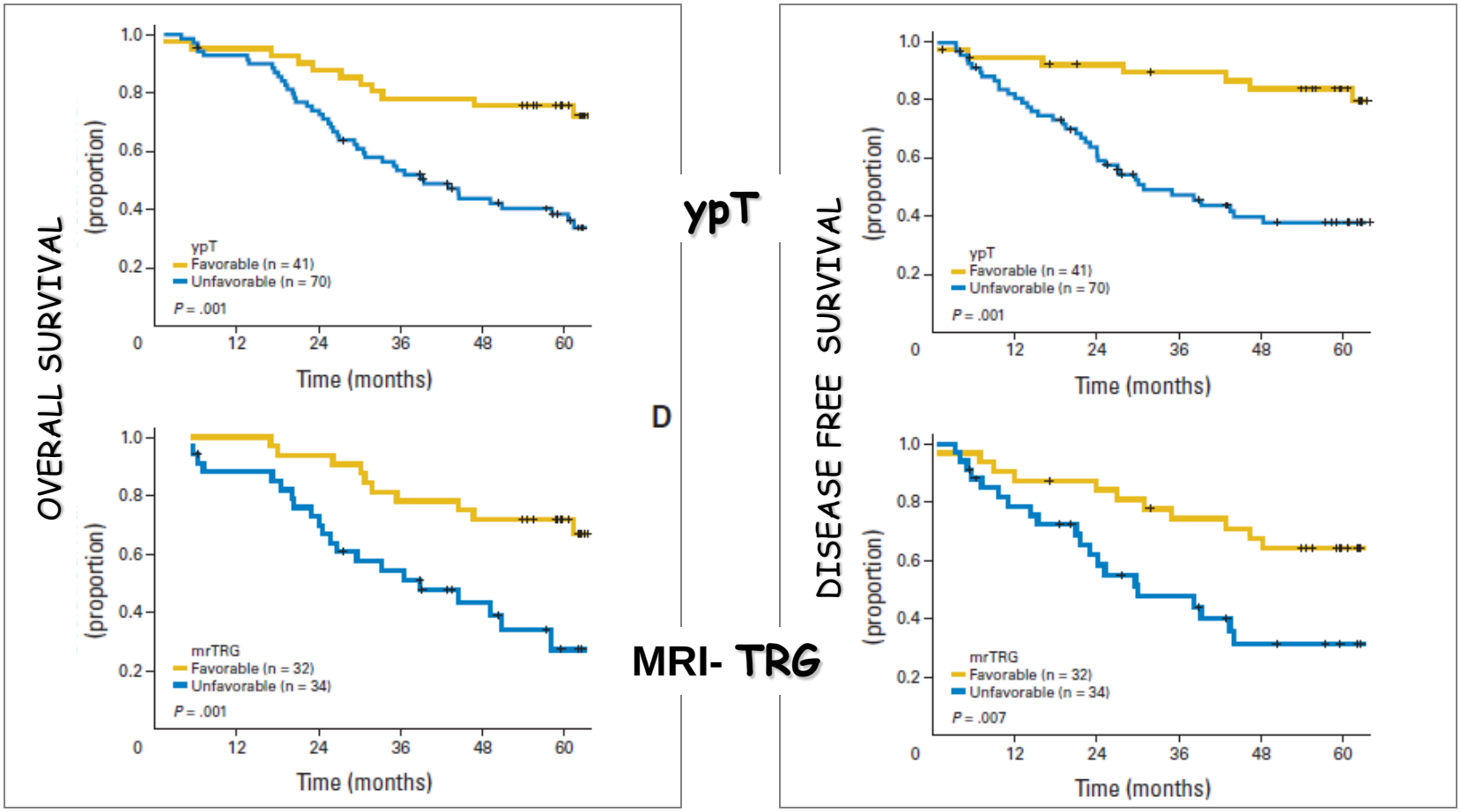
Can modern imaging assess response to treatment?

Philip Guston, Inhabiter

Magnetic Resonance Imaging–Detected Tumor Response for Locally Advanced Rectal Cancer Predicts Survival Outcomes: MERCURY Experience

**T2-weighted MRI**

## Correlation between radiologically determined tumor response and long-term outcomes

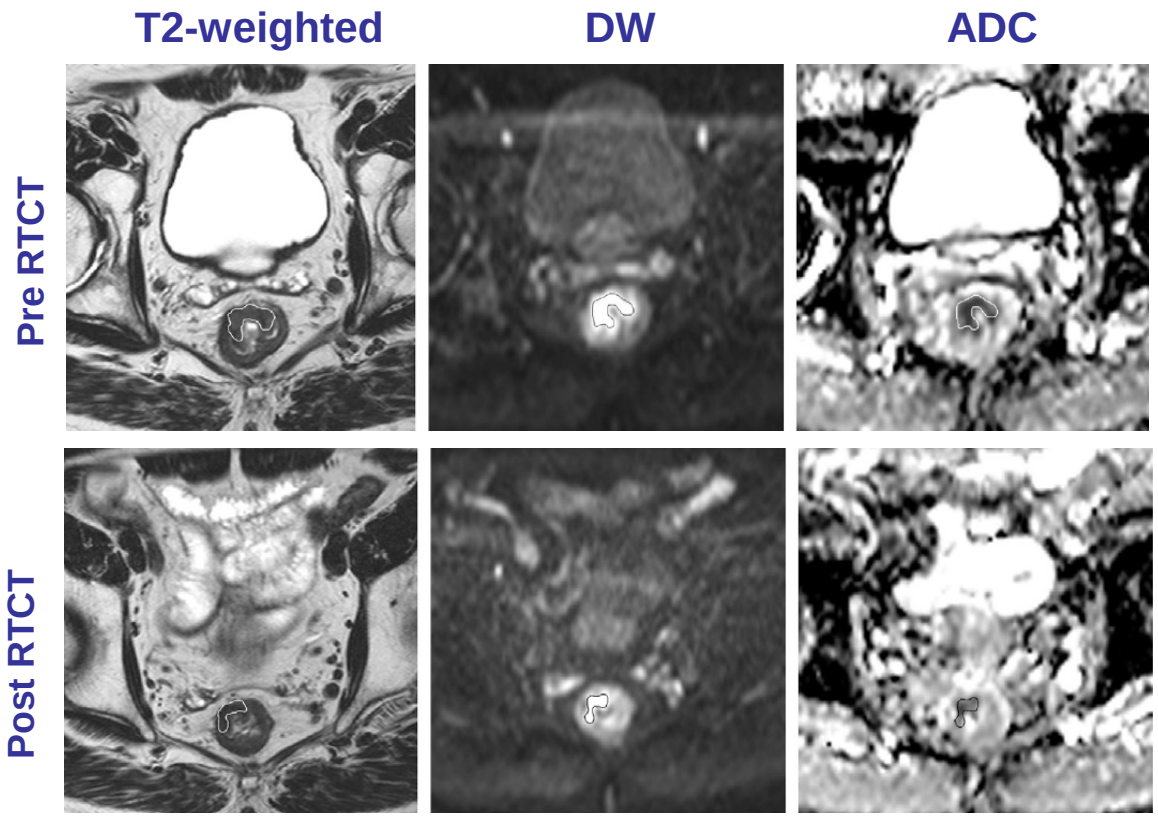



Patel et al, Journal of Clinical Oncology, 2011

**Rectal Cancer:** Assessment of Complete Response to Preoperative Combined Radiation Therapy with Chemotherapy—Conventional MR Volumetry versus Diffusion-weighted MR Imaging[1]

**Post-RTCT diagnostic performance for the assessment of a CR**

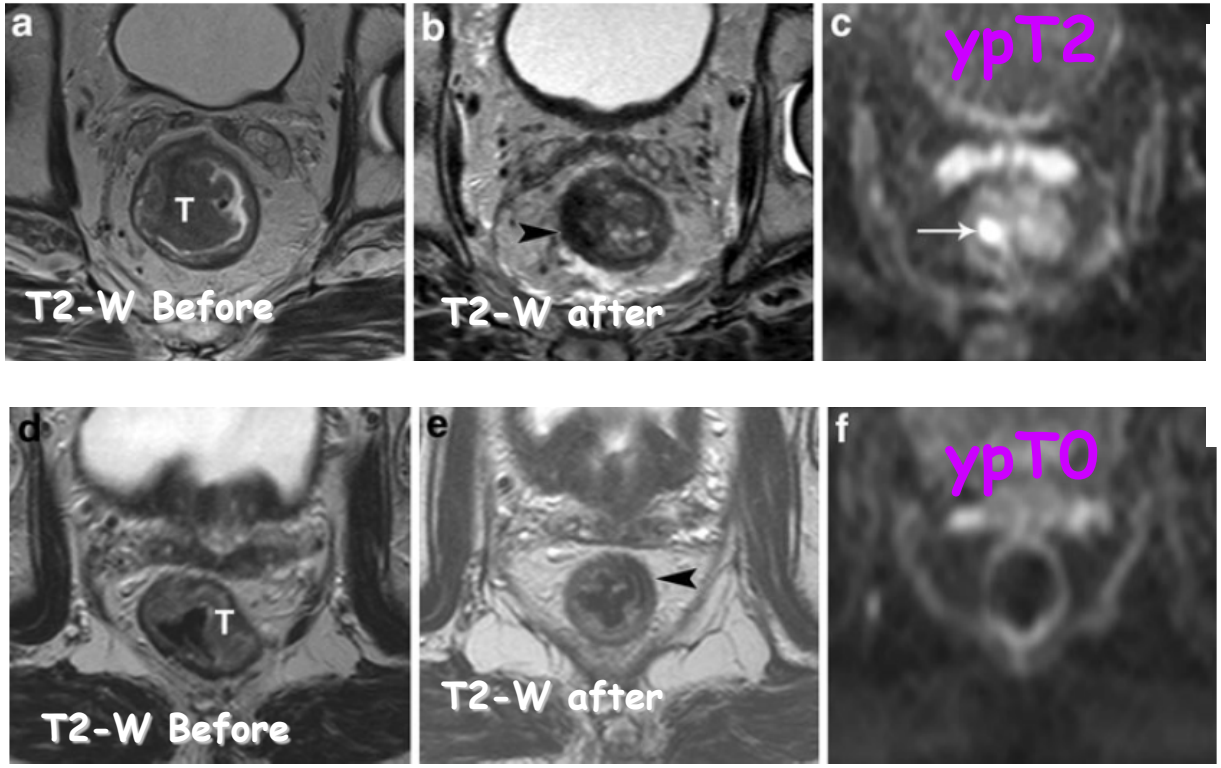
- ✓**DW MR volumetry AUC 0.93**
- ✓T2-W volumetry AUC 0.70
- ✓ADC AUC 0.54




**Difficult to differentiate TRG 1** (complete response) **vs TRG 2** (small microscopic clusters of residual tumor) **!!**

Curvo-Semedo et al, Radiology, 2011

# Diffusion-Weighted MRI for Selection of Complete Responders After Chemoradiation for Locally Advanced Rectal Cancer: A Multicenter Study

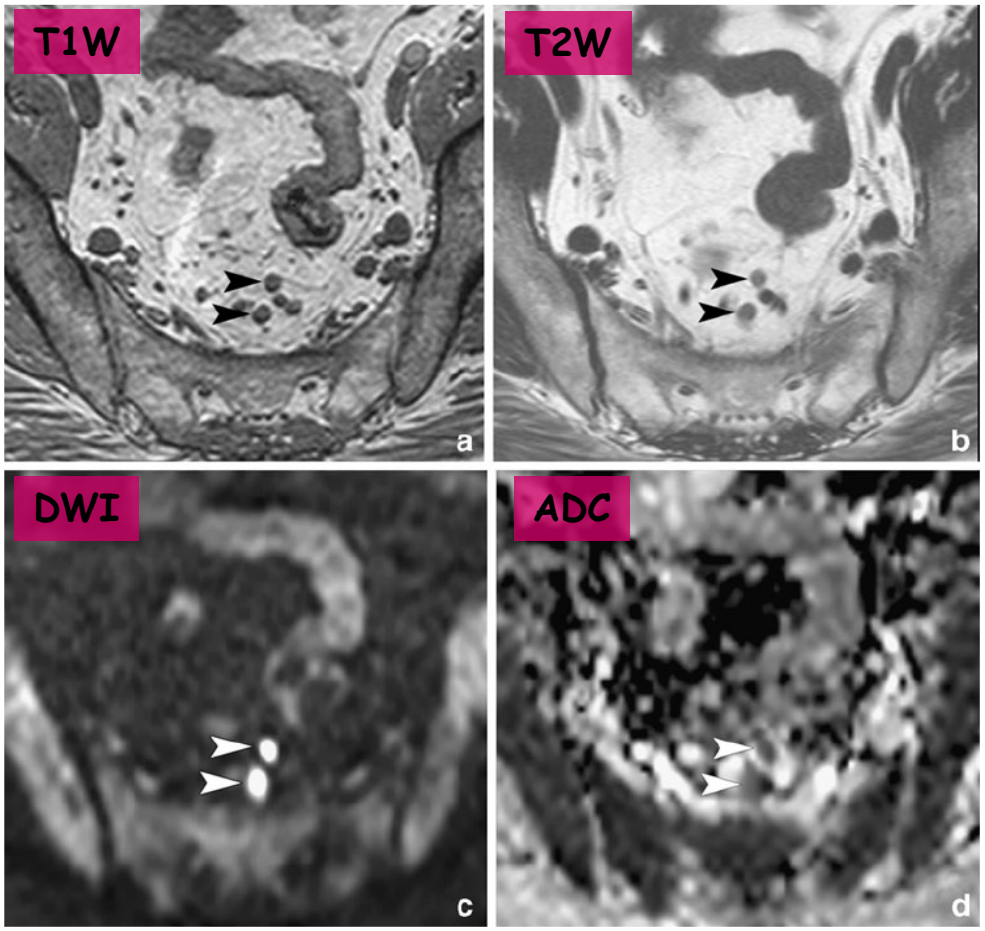



Combination MRI + DWI *promising* for more precise selection of patients eligible for minimally invasive treatments.

- ADC values are dependent on technical variations
- Results premature for clinical decision-making

Lambregts et al., Ann Surg Oncol, 2011

**Value of ADC measurements for nodal staging after chemoradiation in locally advanced rectal cancer—a per lesion validation study**




## DWI

↑ Number of lymph nodes detected (from 45% to 71%)

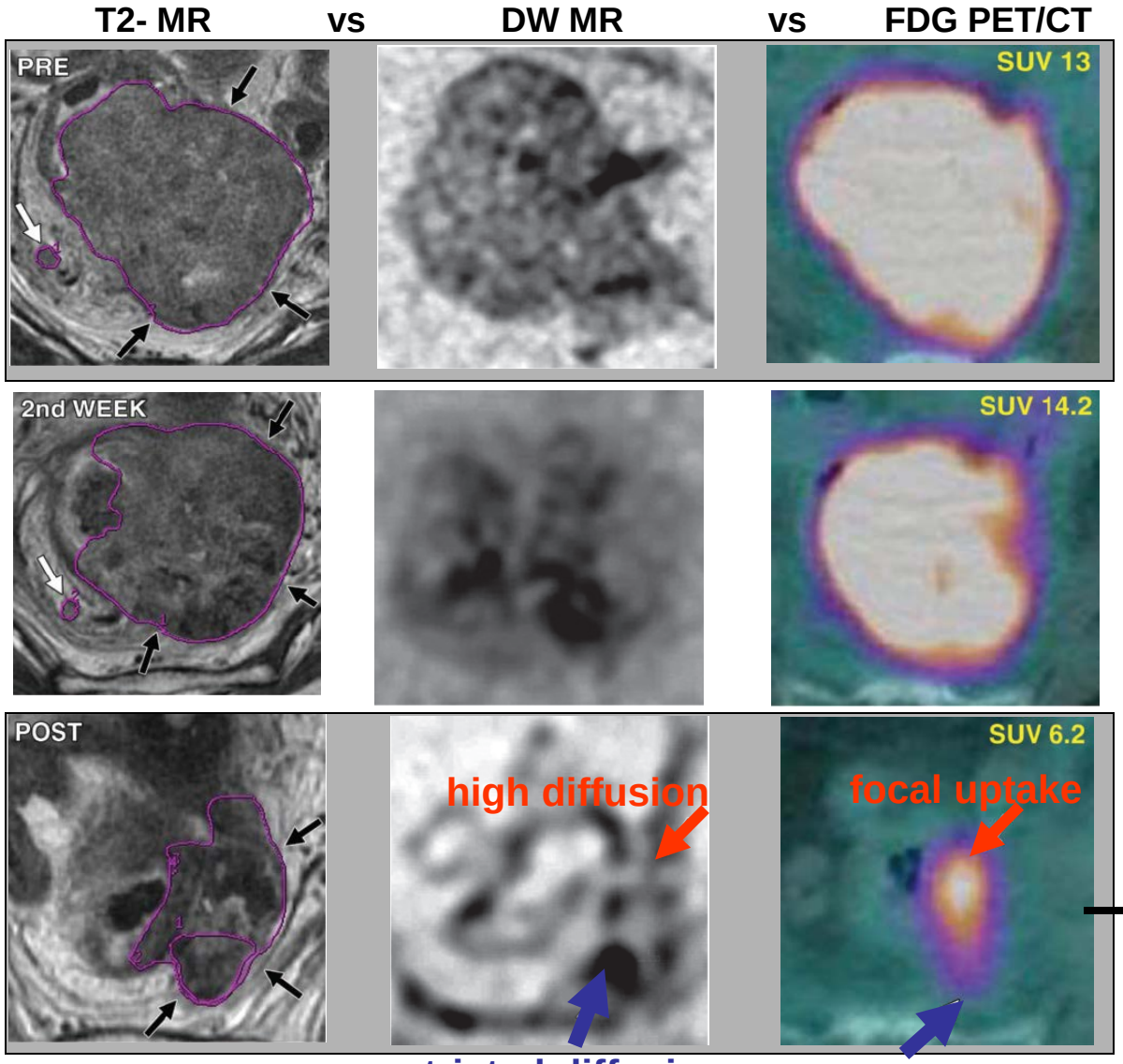
↑ PPV from ~60% to ~ 90% (reducing the overstaging errors)

↓ Not useful for iscrimination benign/metastatic nodes.

After chemoradiation, T2W-MRI on its own is already sufficient for nodal evaluation

Lambregts et al., Eur Radiol, 2011

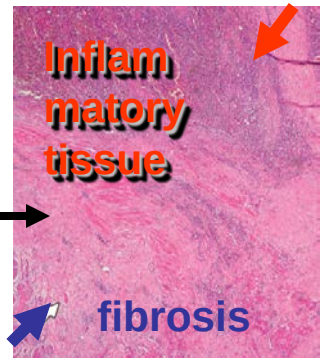
# Restaging Locally Advanced Rectal Cancer with MR Imaging after Chemoradiation Therapy




DWI MR useful for monitoring rectal cancer response after CRT

**CRM - !!**

The detection of small clusters of residual tumor cells remains a problem!



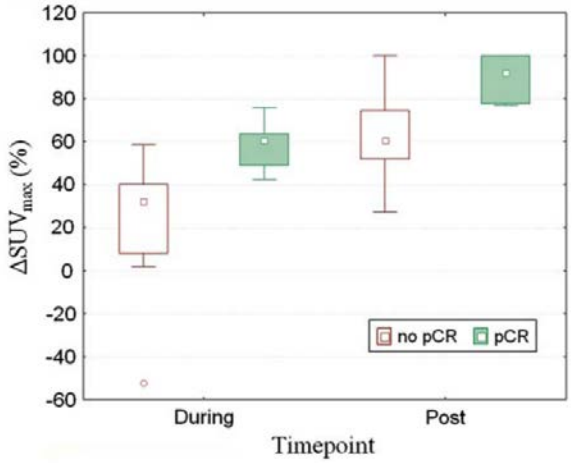

CRM-, but small cluster of residual cancer cells in the mesorectum (pT3 N0, TRG 3)

Barbaro et al., Radiographics, 2010

# The use of FDG-PET/CT and diffusion-weighted magnetic resonance imaging for response prediction before, during and after preoperative chemoradiotherapy for rectal cancer

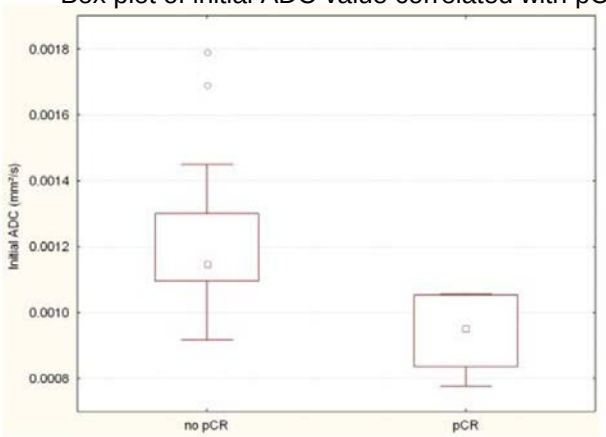
**6 pts (27%) with pCR**

Box plot of Δ SUV max during and after CRT, correlated with pCR




patients with a pCR had a mean **reduction in SUV** max of 59%

Box plot of initial ADC value correlated with pCR




**Lower initial ADC**
in patients with a pCR

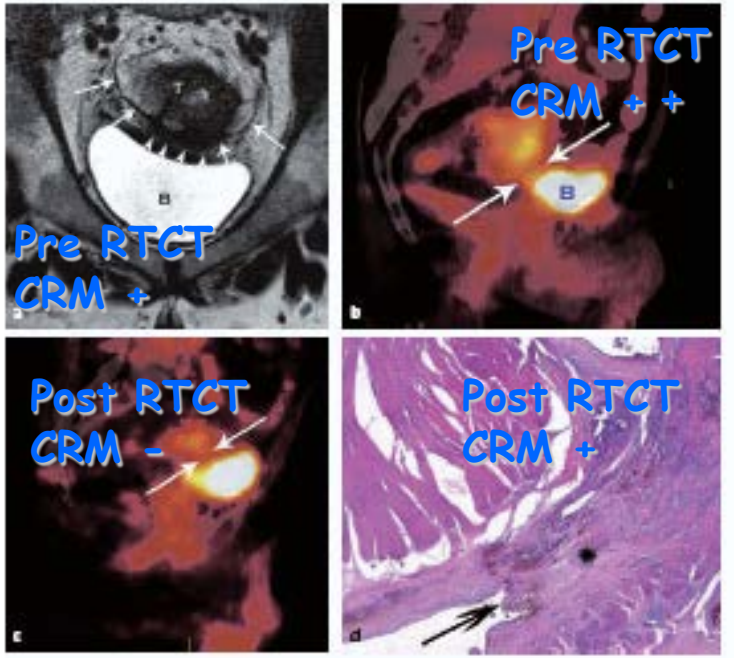
(higher ADC= edema, necrosis= radioresistence)

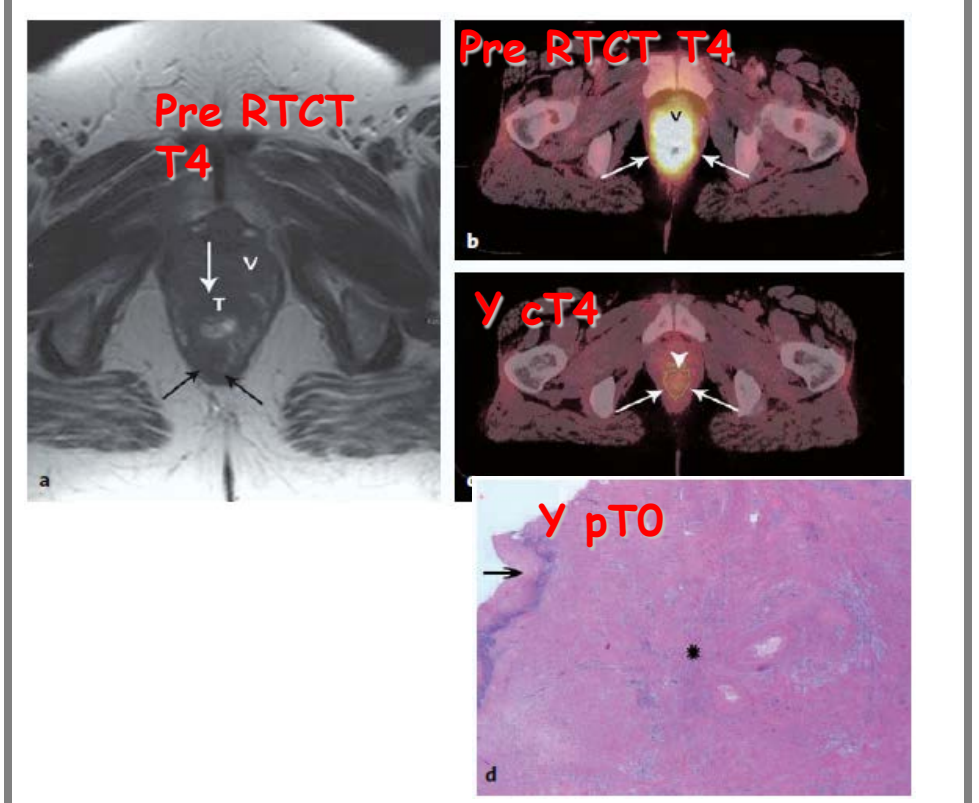
The combination of the different time points and the different imaging modalities increased the **specificity 94% and sensitivity 100%** in prediction pCR

Lambrecht et al, Acta Oncologica, 2010

# Can an FDG-PET/CT Predict Tumor Clearance of the Mesorectal Fascia after Preoperative Chemoradiation of Locally Advanced Rectal Cancer?

Autocontouring of volumes exceeding a specified threshold on PET determined by the measured signal-to-background ratio (SBR)

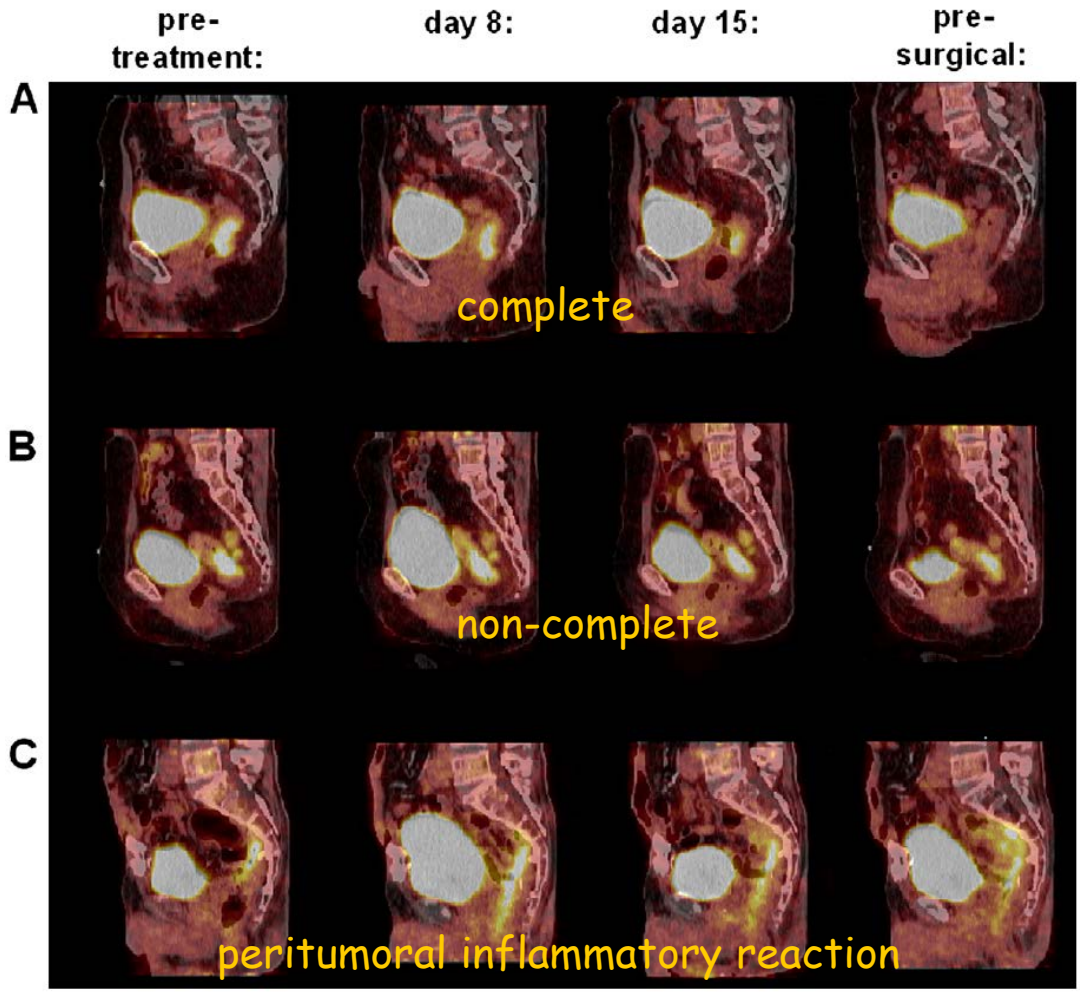



- Post-CRT PET/CT is not a useful tool for evaluating anatomic tumor changes.
- It's not accurate in predicting tumor clearance of the MRF.

Vliegen et al., Strahlentherapie und Onkologie, 2008

# ACCURATE PREDICTION OF PATHOLOGICAL RECTAL TUMOR RESPONSE AFTER TWO WEEKS OF PREOPERATIVE RADIOCHEMOTHERAPY USING $^{18}$F-FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY IMAGING




The SUVmax-based response index calculated after the first 2 weeks of RCT provided the best predictor of pathological treatment response.

…a new prognostic factor?

Peritumoral inflammatory reactions → mispredictions!!

Janssen, et al., Int. J. Radiation Oncology Biol. Phys., 2010

# Development and external validation of a predictive model for pathological complete response of rectal cancer patients including sequential PET-CT imaging

Capirci C,, et al. Long-term prognostic value of 18FFDG PET in patients with locally advanced rectal cancer previously treated with neoadjuvant radiochemotherapy. AJR Am J Roentgenol 2006

Vliegen RF, et al. Can an FDG-PET/CT predict tumor clearance of the mesorectal fascia after preoperative chemoradiation of locally advanced rectal cancer?

Amthauer H, ... of rectal cancer: correl...

Capirci C, et a... in the staging and restaging ... Int J Radiat Oncol Biol Phy...

Denecke T, et... ter multimodal preoperative ...

Guillem JG, et... ative chemoradiatio...

Kalff V, et.al, ... with locally advanced rect...

Melton GB, et... raphy for assessing prim...

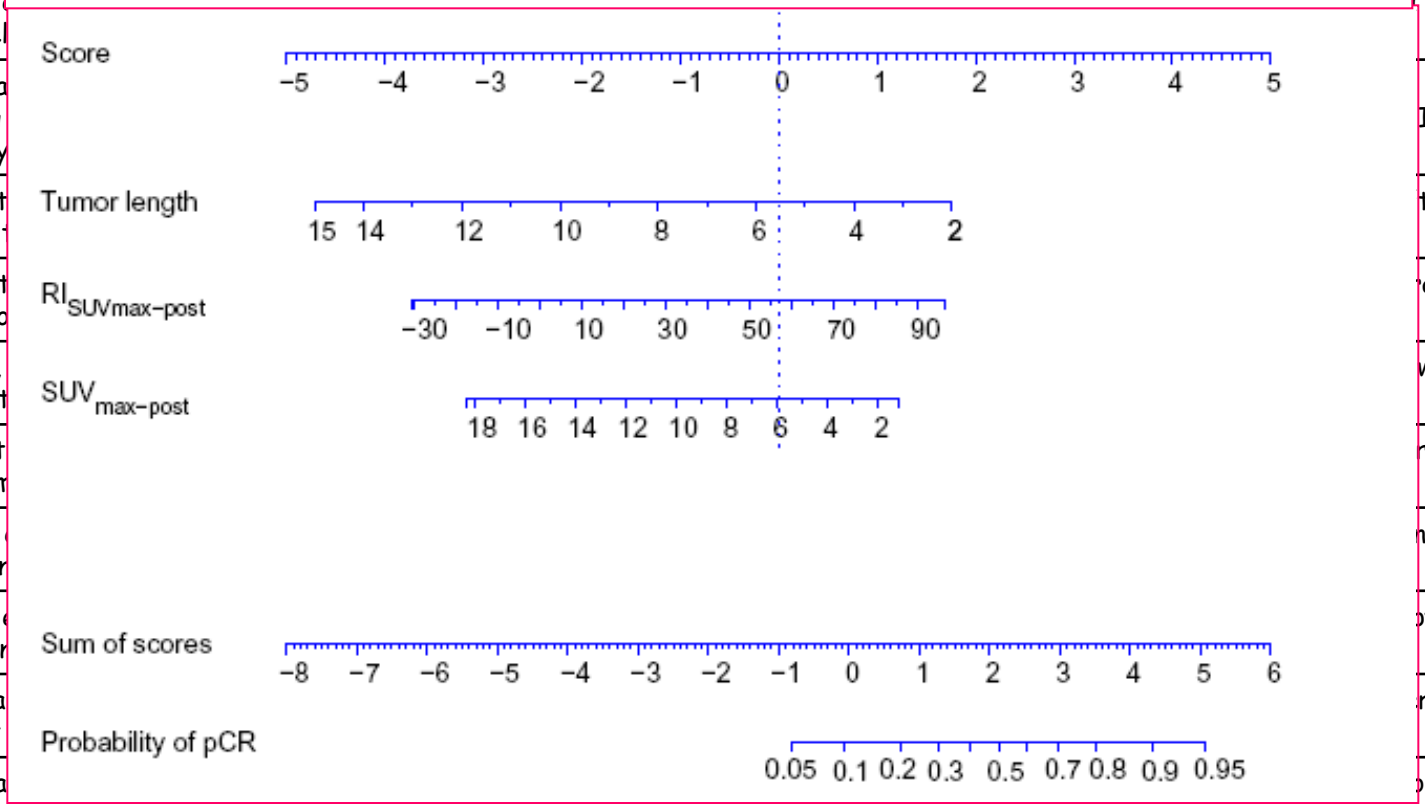
Rosenberg R, ... ncer measured by PET/CT. Ir...

Janssen MH, ... y using FDG-PET-CT imagi...

Konski A, et a... rapy and radiation. Int ...

Ollers M, et a... l 2008

## Nomogram for PET post-CRT dataset




Cascini GL, et al. 18F-FDG PET is an early predictor of pathologic tumor response to preoperative radiochemotherapy in locally advanced rectal cancer. J Nucl Med 2006

Rosenberg R, et al. The predictive value of metabolic response to preoperative radiochemotherapy in locally advanced rectal cancer measured by PET/CT. Int J Colorectal Dis 2009

van Stiphout et al, Radiotherapy and Oncology, 2011

# Contouring

Is there a standard

in RC contouring?

E. Vedova, Oltre, 1980

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 4, pp. 1129–1142, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.02.050

**CLINICAL INVESTIGATION** **Rectum**

# DEFINITION AND DELINEATION OF THE CLINICAL TARGET VOLUME FOR RECTAL CANCER

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2006

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 3, pp. 824–830, 2009

0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.08.070

**CLINICAL INVESTIGATION** **Rectum**

# ELECTIVE CLINICAL TARGET VOLUMES FOR CONFORMAL THERAPY IN ANORECTAL CANCER: A RADIATION THERAPY ONCOLOGY GROUP CONSENSUS PANEL CONTOURING ATLAS

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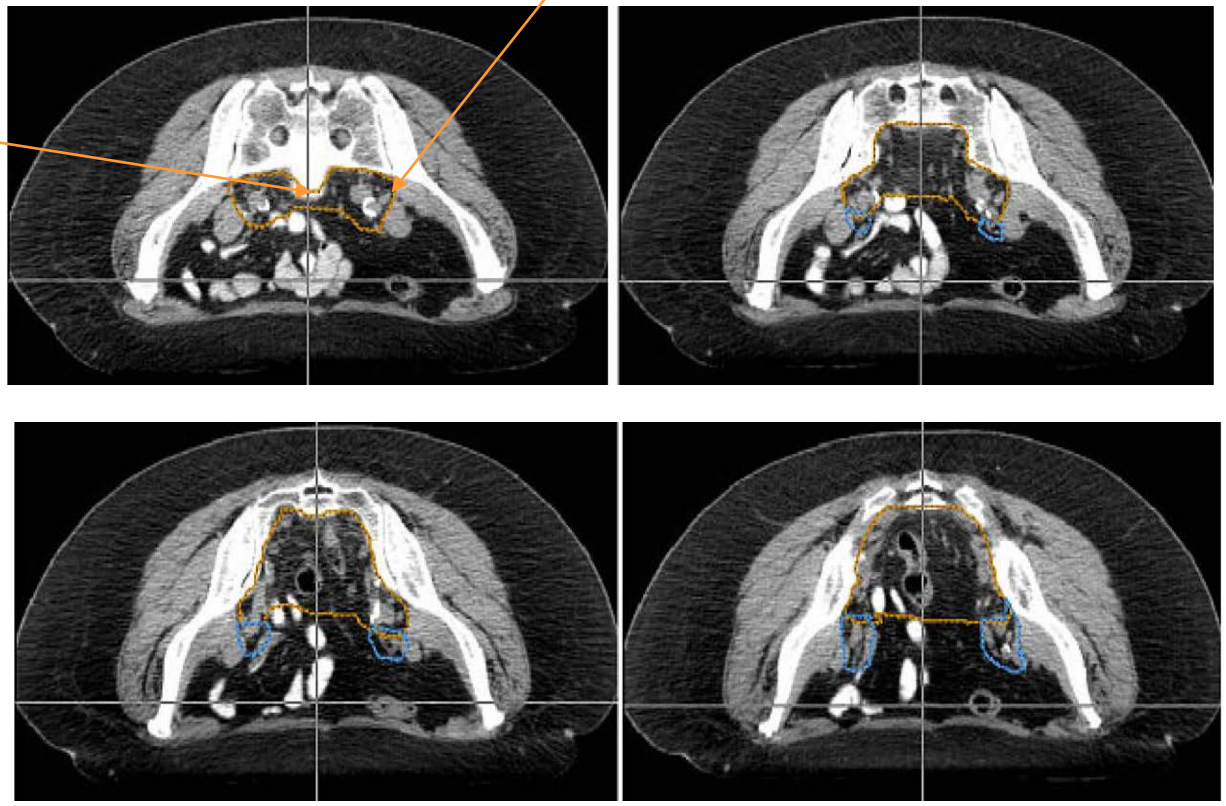
2009

Cranial edge of peri-rectal *CTVA:* rectosigmoid junction or at least 2 cm proximal to the superior extent of macroscopic disease

Where the common iliac vessels bifurcate into external/internal iliacs (approximate boney landmark: sacral promontory)

At midline at least 1cm anterior to the sacrum



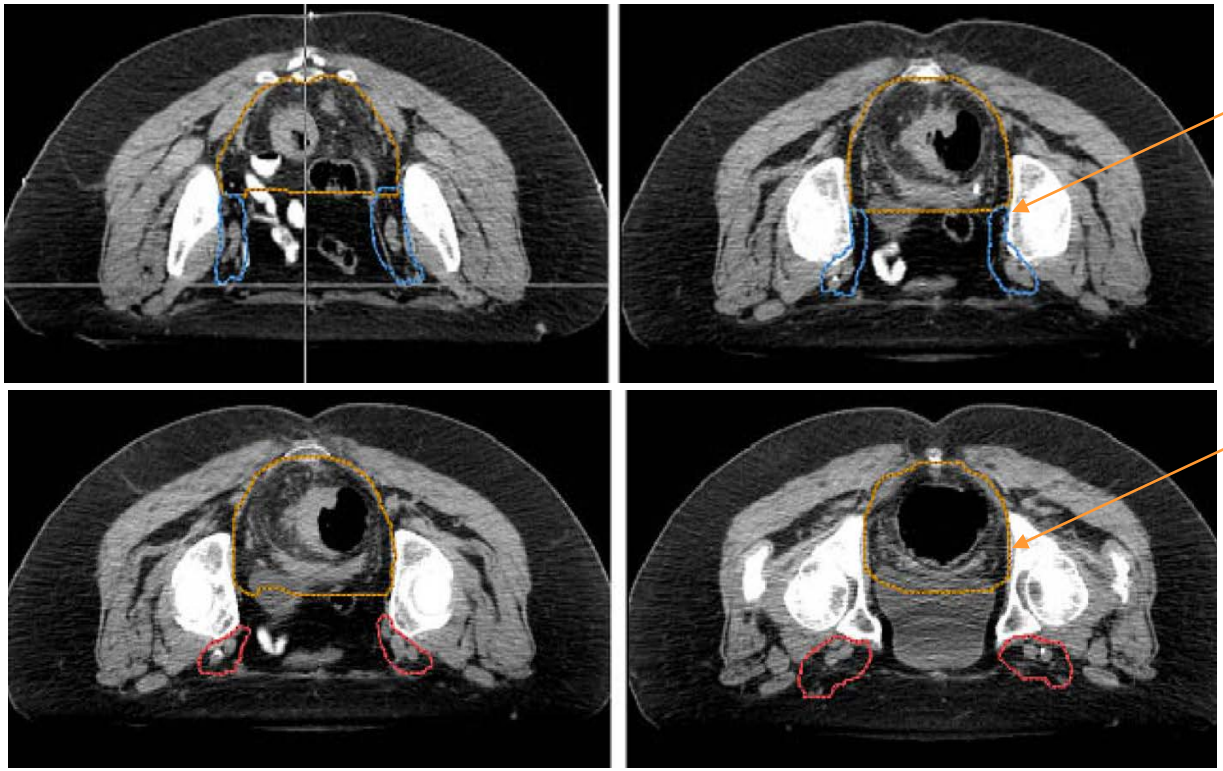
⟹ avoid contouring into uninvolved bone

⟹ avoid extending into uninvolved pelvic sidewall muscles (except for levators)

⟹ assign a uniform PTV margin and account for physiologic variability by adjusting the CTV

Myerson et al. Int J Radiat Oncol Biol Phys. 2009

# Mid pelvis



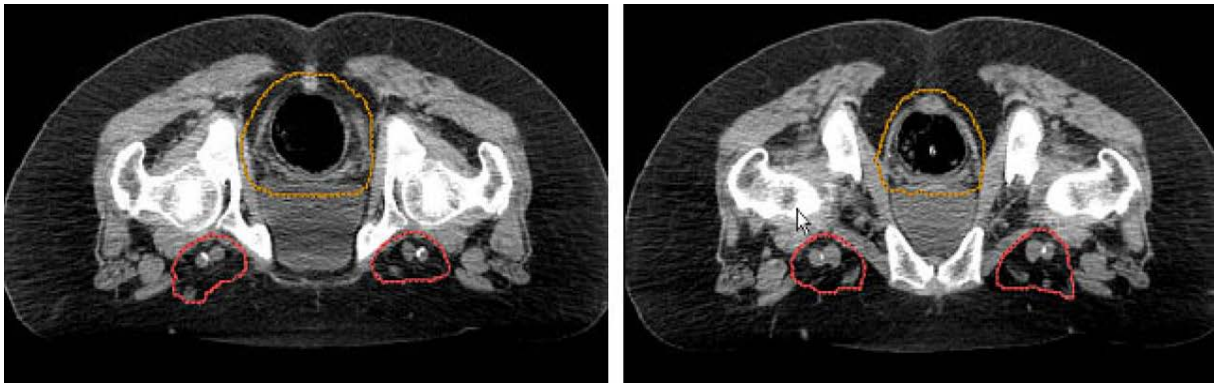
Anteriorly extend CTVA ~1 cm into the posterior bladder, to account for day-to-day variation in bladder position

The posterior and lateral margins of CTVA should extend to pelvic sidewall musculature or bone

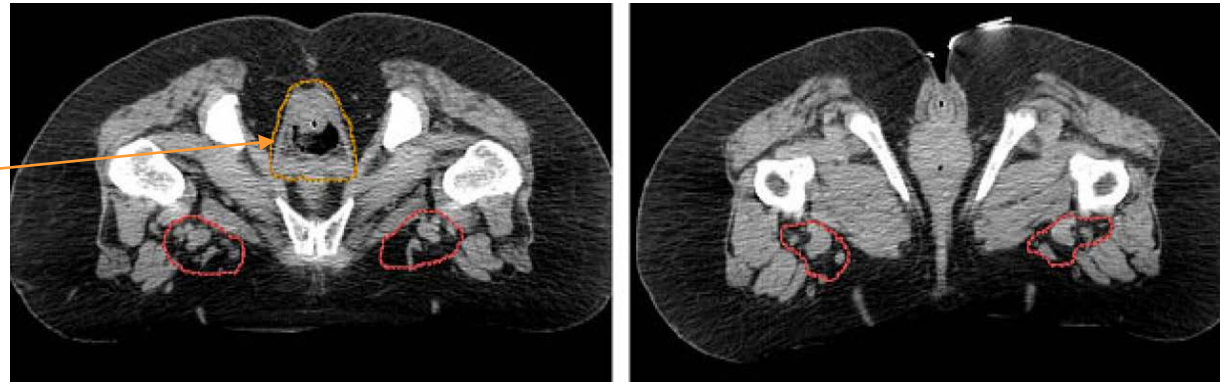
Myerson et al. Int J Radiat Oncol Biol Phys. 2009

# Lower pelvis

The caudad extent: at least 2 cm caudad to gross disease (entire mesorectum to the pelvic floor even for upper rectal cancers)



Unless there is radiographic evidence of extension into the ischiorectal fossa, CTVA does not need to go more than a few millimeters beyond the levator muscles.



- For very advanced anal or rectal cancers extending through the mesorectum or the levators add ~1–2 cm margin up to bone
- For T4 disease include a 1–2 cm margin around the identified areas of invasion of the neighboring organ
- An MRI and/or PET/CT scan is strongly recommended in such cases.

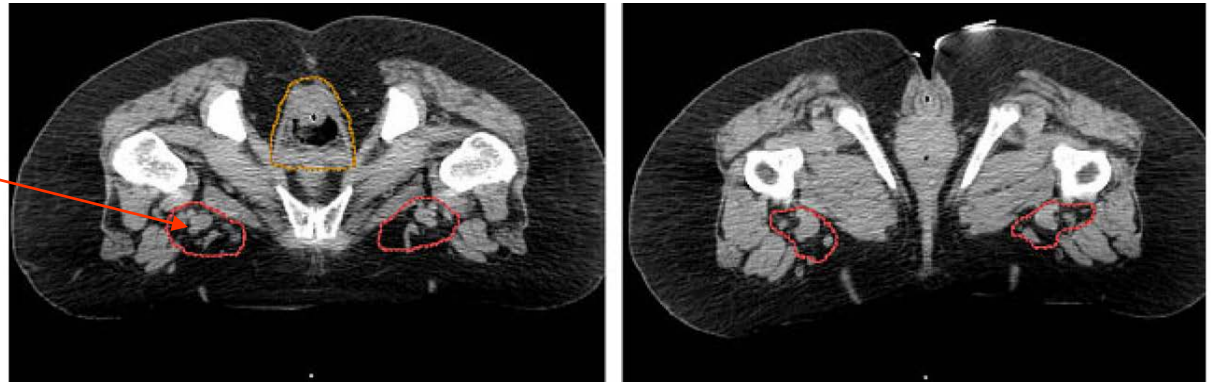
Myerson et al. Int J Radiat Oncol Biol Phys. 2009

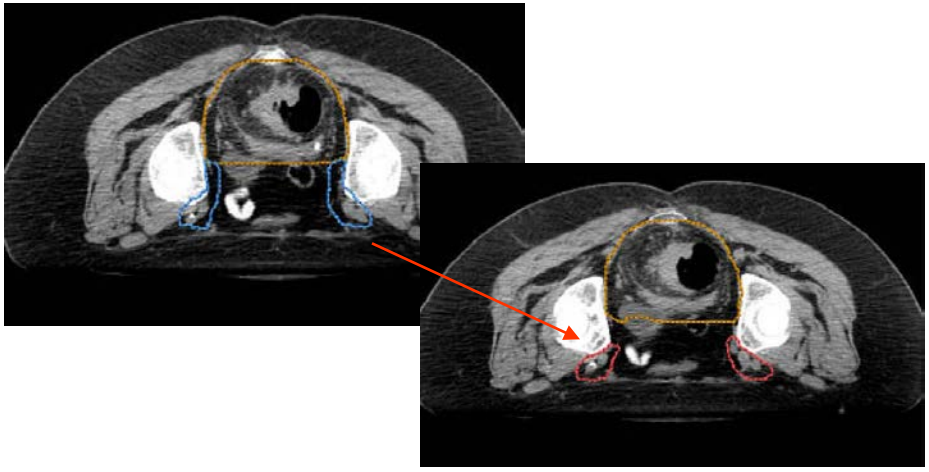
# Elective Nodal Irradiation: Indications

**External iliac** Extention into GYN or GU structures (T4) or anal canal

**Inguinal** Extention to the anal verge, peri-anal skin, or lower one-third of the vagina

Caudad extent of elective target volumes: 2 cm caudad to the saphenous/femoral junction.





The transition between inguinal → external iliac regions at the level of the caudad extent of the internal obturator vessels (approximate boney landmark: upper edge of the superior pubic rami)

Myerson et al. Int J Radiat Oncol Biol Phys. 2009

**boost CTV**

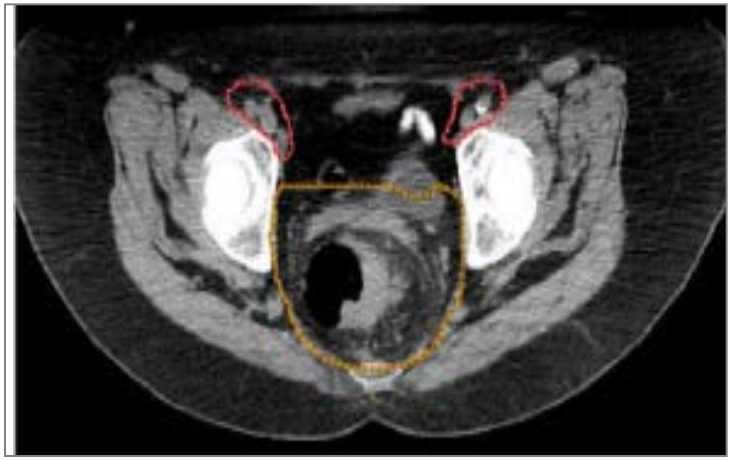
should extend to the entire mesorectum and pre-sacral region at involved levels, including ~1–2 cm cephalad and caudad in the mesorectum and ~2 cm on gross tumor within the anorectum.

**PTV margin**

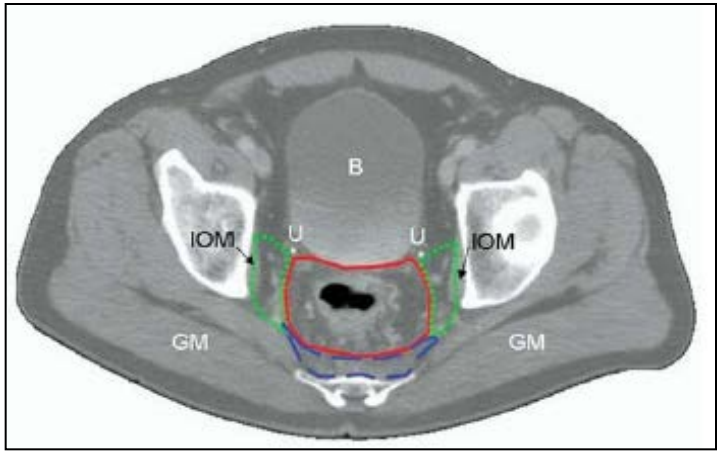
~0.7 to 1.0 cm (~2–5 mm within the skin surface).

Myerson et al. Int J Radiat Oncol Biol Phys. 2009

# Leterature disagreements: anterior border



Myerson 2009



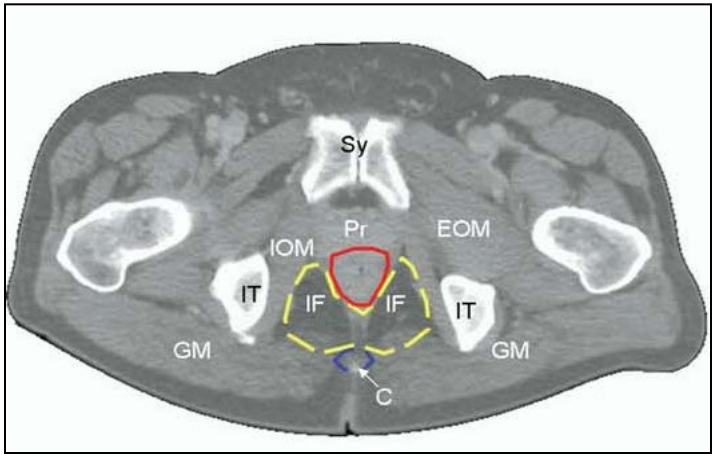

Roels 2006

The RTOG anorectal group was more generous on this border to account for day-to-day variability in the location of structures immediately anterior to the rectum

# Leterature disagreements: ischiorectal fossa

Myerson 2009

Failure in the ischiorectal fat in the absence of frank invasion on presentation was very infrequent and RTOG opted for more conformal coverage of the low anorectum.



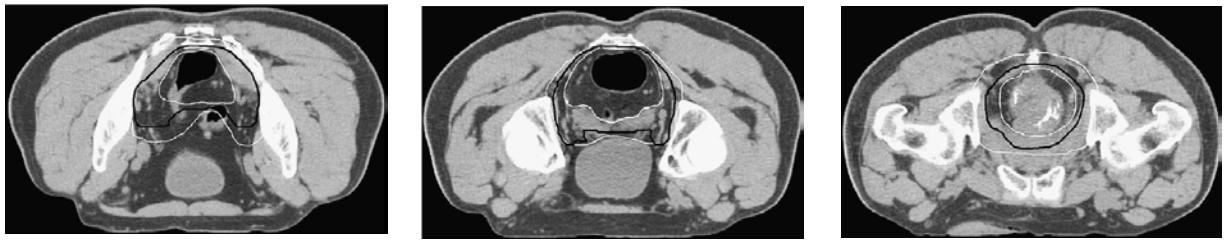

Roels 2006

If the IPS is not at risk for subclinical disease (tumor is located 6 cm above the anal margin), the external and internal sphincter with the surrounding ischiorectal fossa, should not be included in the CTV.

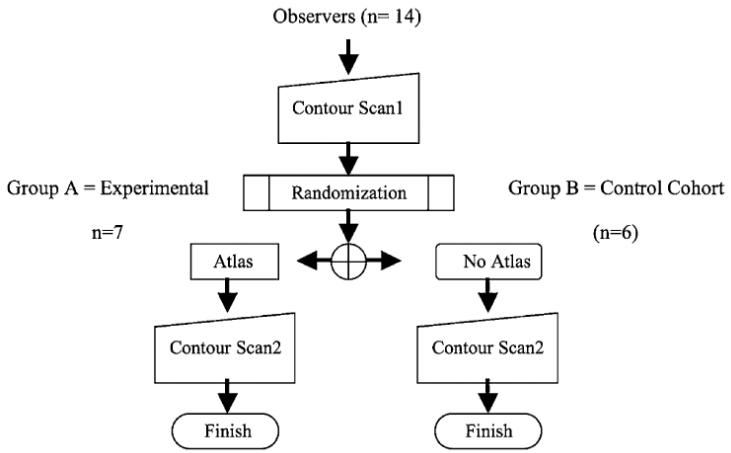
Syk 2008

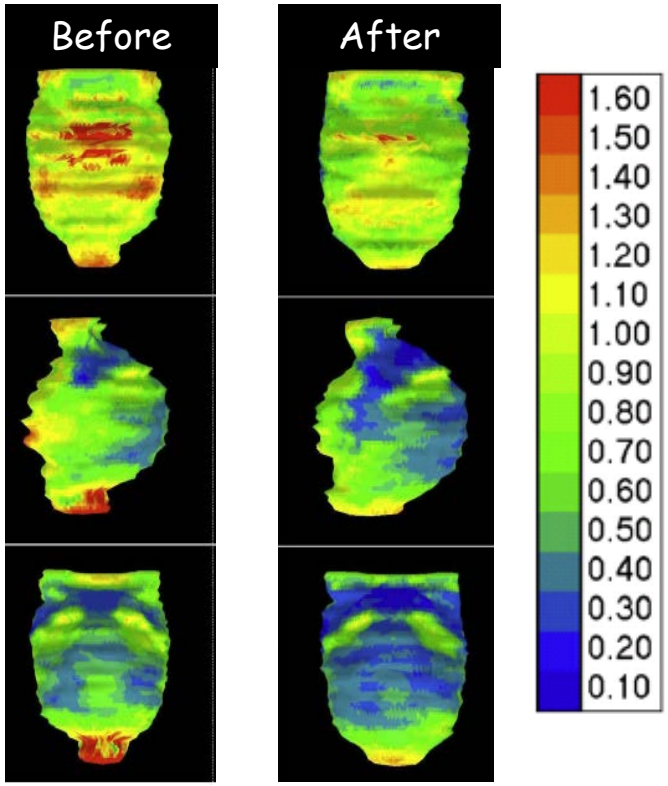
Not only the exclusion of the sphincters, but also that the levator and puborectal muscles can be spared RT if a sphincter-saving procedure has been planned.

# PROSPECTIVE RANDOMIZED DOUBLE-BLIND PILOT STUDY OF SITE-SPECIFIC CONSENSUS ATLAS IMPLEMENTATION FOR RECTAL CANCER TARGET VOLUME DELINEATION IN THE COOPERATIVE GROUP SETTING



*A representative case of rectal cancer contoured by 14 physician with and without an atlas*




- ✓ **Increased contour agreement only for CTVA**
- ✓ **GTV and CTVB, inter intra observer substantial**

Fuller et al., Int. J. Radiation Oncology Biol. Phys., 2011


Wynn Bullock, *Sunken Wreck, MOMA, NY*

*"An expert is someone who knows some of the worst mistakes that can be made in his subject, and how to avoid them"*

Werner Karl Heisenberg

# Site of local recurrence

| Pelvic subsite | First author | No. at risk (n) | No. rec. (n) | No. rec. in specified subsite (n) | Risk for rec. in specified subsite (%) | Rec in specified subsite / Total Rec. |
|---|---|---|---|---|---|---|
| Posterior | Gilbertsen | 89 | 32 | 14 | 16 | 44 |
| | Mendenhall | 90 | 40 | 18 | 20 | 45 |
| | Gunderson | 75 | 46 | 25 | 33 | 52 |
| | | 254 | | 57 | 22 | |
| | Hruby | — | 269 | 127 | — | 47 |
| | Wiig | — | 46 | 27 | — | 59 |
| | | | **435** | **211** | | **49** |
| LPS | Gilbertsen | 89 | 32 | 1 | 1 | 3 |
| Lateral | Mendenhall | 90 | 40 | 4 | 4 | 10 |
| | Gunderson | 75 | 46 | 13 | 17 | 27 |
| | Killingback | 468 | 34 | 24 | 5 | 70 |
| | | 722 | | 42 | 6 | |
| | Hruby | — | 269 | 30 | — | 11 |
| | Wiig | — | 46 | 25 | — | 54 |
| | | | **469** | **97** | | **21** |
| IPS | Gilbertsen | 89 | 32 | 5 | 6 | 16 |
| Inferior | Mendenhall | 90 | 40 | 4 | 4 | 10 |
| | Gunderson | 75 | 48 | 14 | 19 | 29 |
| | McDermott | 934 | 191 | 30 | 3 | 16 |
| | | 1188 | | 53 | | |
| | Hruby | — | 269 | 15 | — | 6 |
| | | | 580 | 68 | | **12** |
| | Gilbertsen | 89 | — | 5 | 6 | — |
| | Hruby | 100 | — | 16 | 16 | — |
| | | **189** | | **21** | **11** | |
| APS | Gilbertsen | 89 | 32 | 13 | 15 | 40 |
| Anterior | Mendenhall | 90 | 40 | 6 | 7 | 15 |
| | Gunderson | 75 | 46 | 21 | 28 | 44 |
| | McDermott | 934 | 191 | 38 | 2 | 12 |
| | | 1188 | | 63 | 5 | |
| | Hruby | — | 269 | 29 | — | 11 |
| | Wiig | — | 46 | 12 | — | 26 |
| | | | **626** | **104** | | 17 |

**49% (211/435) (five studies)**

**21% (97/469)**

**12% (68/580) (five studies)**

**17% (104/626)**

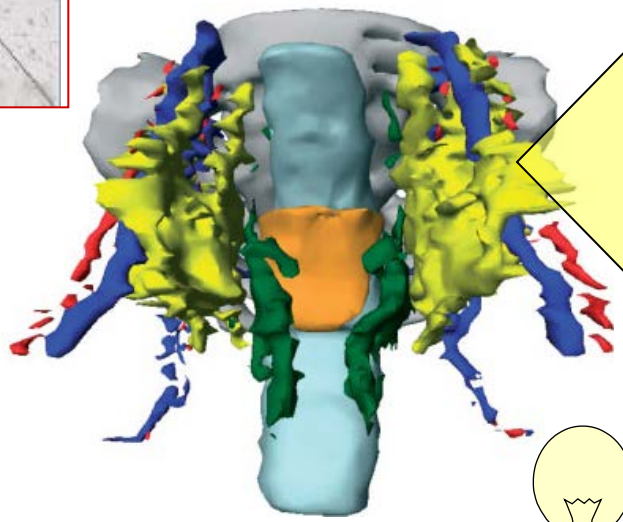
Roels et al, Int. J. Radiation Oncology Biol. Phys., 2009

# Presacral Recurrence: pathogenetic hypothesis

## Tumour recurrence might arise from lateral lymph nodes

Lymph tissue (asterisks) surrounding the middle rectal artery and vein after staining with LYVE-1 antibody.

The lymph tissue also enters the mesorectal space, together with the middle rectal artery/vein



Connections between the mesorectal and (lateral) extramesorectal lymph node system exist, located below the peritoneal reflection on the anterolateral side of the fetal rectum

**LLND** is probably not an option (….?)

If positive **lateral lymph nodes** are not suspected and thus not irradiated (IMRT) might give rise to problems…!

Kusters et al., British Journal of Surgery 2010

# Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial

**Neoadjuvant RT**

| | Patients with local recurrence | |
|---|---|---|
| | RT+ = 4.6% (36 pts) | RT- = 11% (87 pts) |
| *Age (yrs)* | | |
| Median (range) | | |
| *Sex* | | |
| Male | 23 (64) | 46 (59) |
| Female | 13 (36) | 32 (41) |
| *Distance from anus* | | |
| < 5 cm | 20 (56) | 28 (36) |
| 5–10 cm | 10 (28) | 37 (47) |
| > 10 cm | 6 (16) | 13 (17) |
| Resection type | | |
| APR | 18 (50) | 45 (58) |
| LAR | 16 (44) | 29 (37) |
| Hartmann | 2 (6) | 4 (5) |
| T-stage | | |
| T1 | – | |
| T2 | 5 (14) | |
| T3 | 28 (78) | |
| T4 | 3 (8) | |
| N-stage | | |
| N0 | 10 (28) | |
| N1 | 12 (33) | |
| N2 | 14 (39) | |
| CRM | | |
| Negative | 17 (47) | |
| Positive | 19 (53) | |

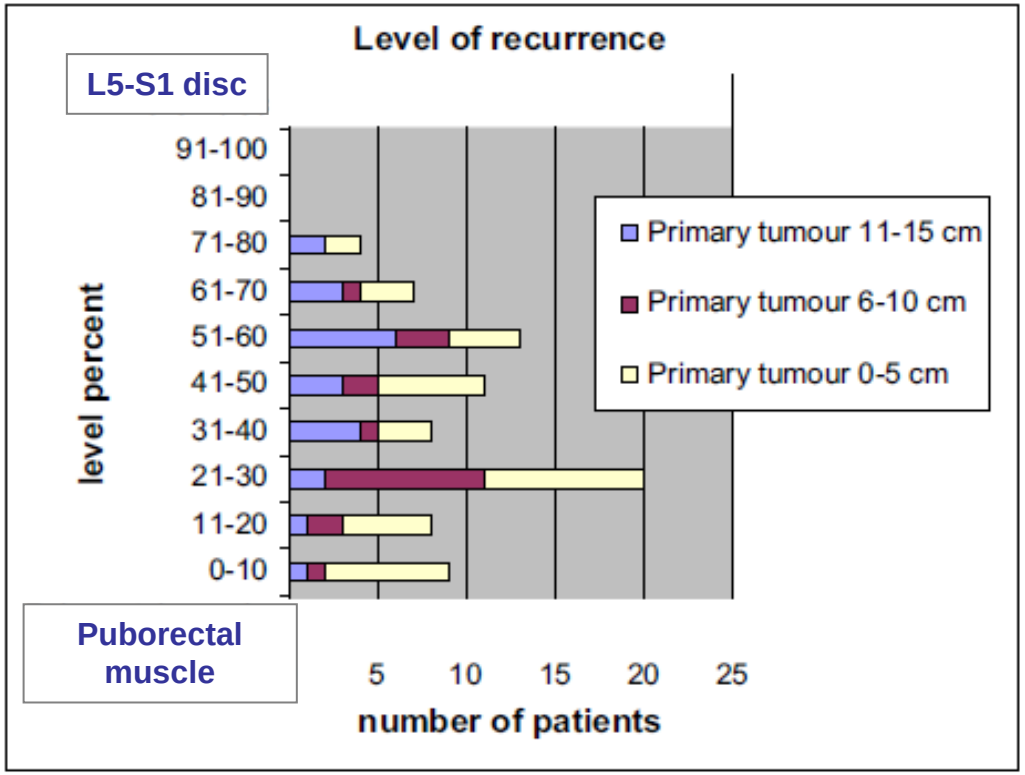
| | RT + ($n$ = 713) | RT − ($n$ = 704) |
|---|---|---|
| Presacral | 15 (2.0) | 25 (3.6) |
| Lateral | 9 (1.1) | 14 (1.9) |
| Anterior | 6 (0.7) | 14 (1.9) |
| Anastomosis | 5 (0.7) | 19 (2.7) |
| Perineum | 0 (0) | 4 (0.6) |
| Unknown | 1 (0.1) | 2 (0.3) |
| TOTAL | 36 (4.6) | 78 (11.0) |

M. Kusters et al. EJSO, 2010

# LOCAL RECURRENCE IN RECTAL CANCER: ANATOMIC LOCALIZATION AND EFFECT ON RADIATION TARGET

**100% recurences in the lower 75% of the pelvis (2/3 in the lower one-half)**

A lowering of the upper limit of the clinical target volume could be introduced




**0.3% relapse in the lowest 20% of the pelvis of pts with a mid- or high rectal cancer**

The anal sphincter complex with surrounding tissue could be excluded in patients with primary tumors > 5 cm from the anal verge

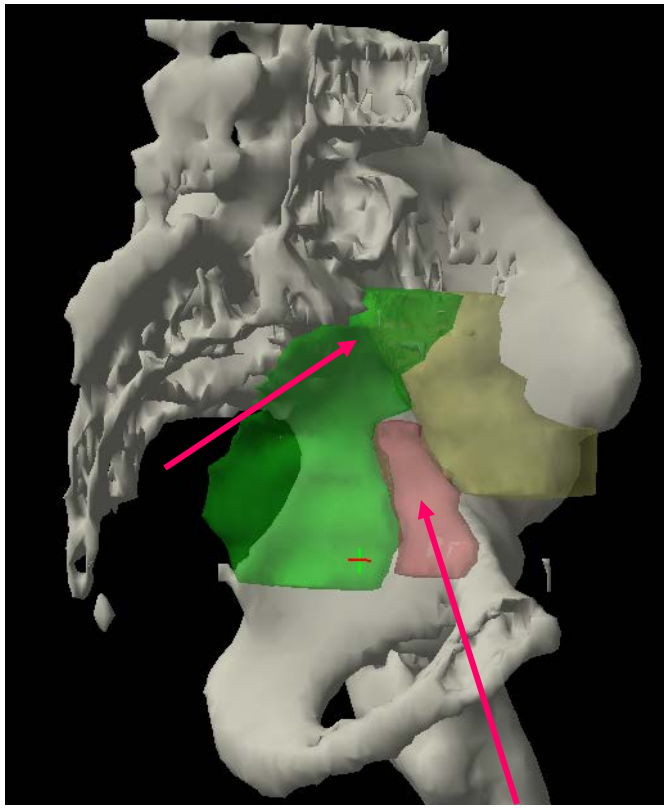
Syk et al, Int. J. Radiation Oncology Biol. Phys., 2008

# LOCAL RECURRENCE IN RECTAL CANCER: ANATOMIC LOCALIZATION AND EFFECT ON RADIATION TARGET

**Upper one-third** rectal cancer

Unnecessary irradiation of the internal iliac nodes → lowering the upper CTV border

Unnecessary irradiation of the obturator nodes → the ventral and lateral extensions in the caudal part of the CTV could be reduced

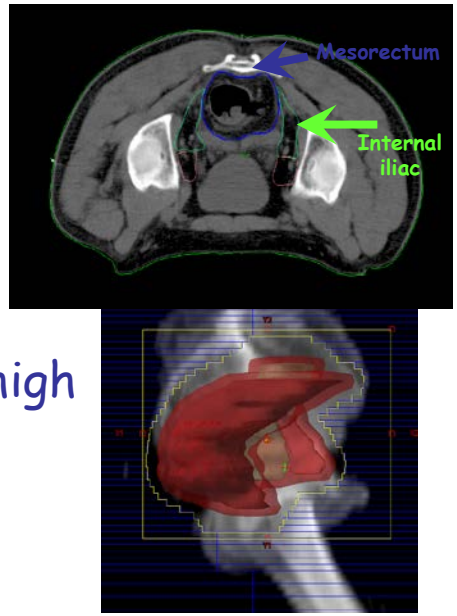


Syk et al, Int. J. Radiation Oncology Biol. Phys., 2008

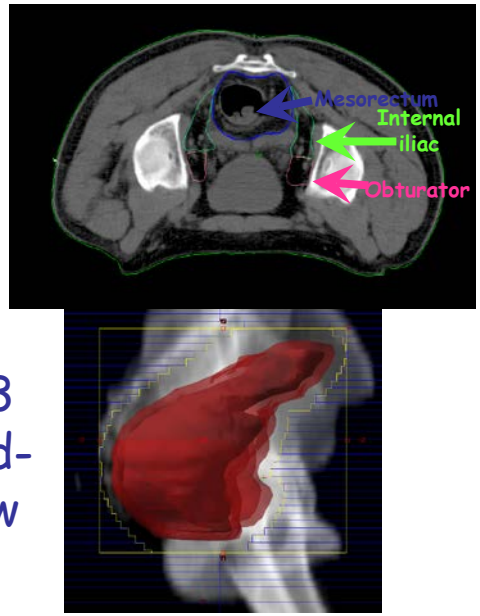
# Correlation between tumour level and lateral N+ incidence

| Tumour level | N° pts | Positive lateral Nodes |
|---|---|---|
| >6.1 cm | 308 | 2 (0.6%) |
| 5.1-6 | 72 | 1 (1.4%) |
| 4.1-5 | 69 | 6 (7.5%) |
| 3.1-4 | 65 | 6 (7%) |
| 2.1-3 | 72 | 12 (16.7%) |
| 1.1-2 | 80 | 10 (12.5%) |
| 0-1 | 98 | 29 (29.6%) |
| All | 764 | 66 (8.6%) |

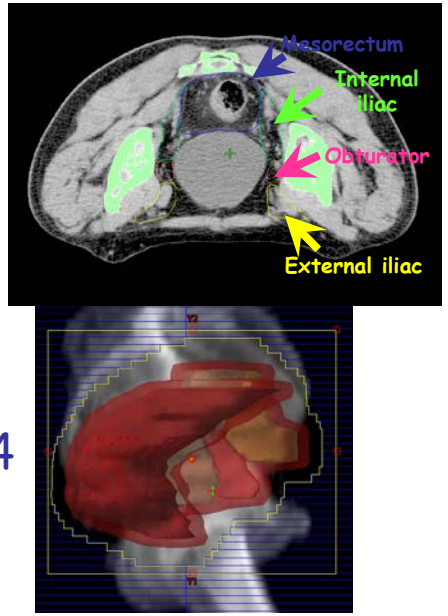
T3 high




T3 mid-low




T4



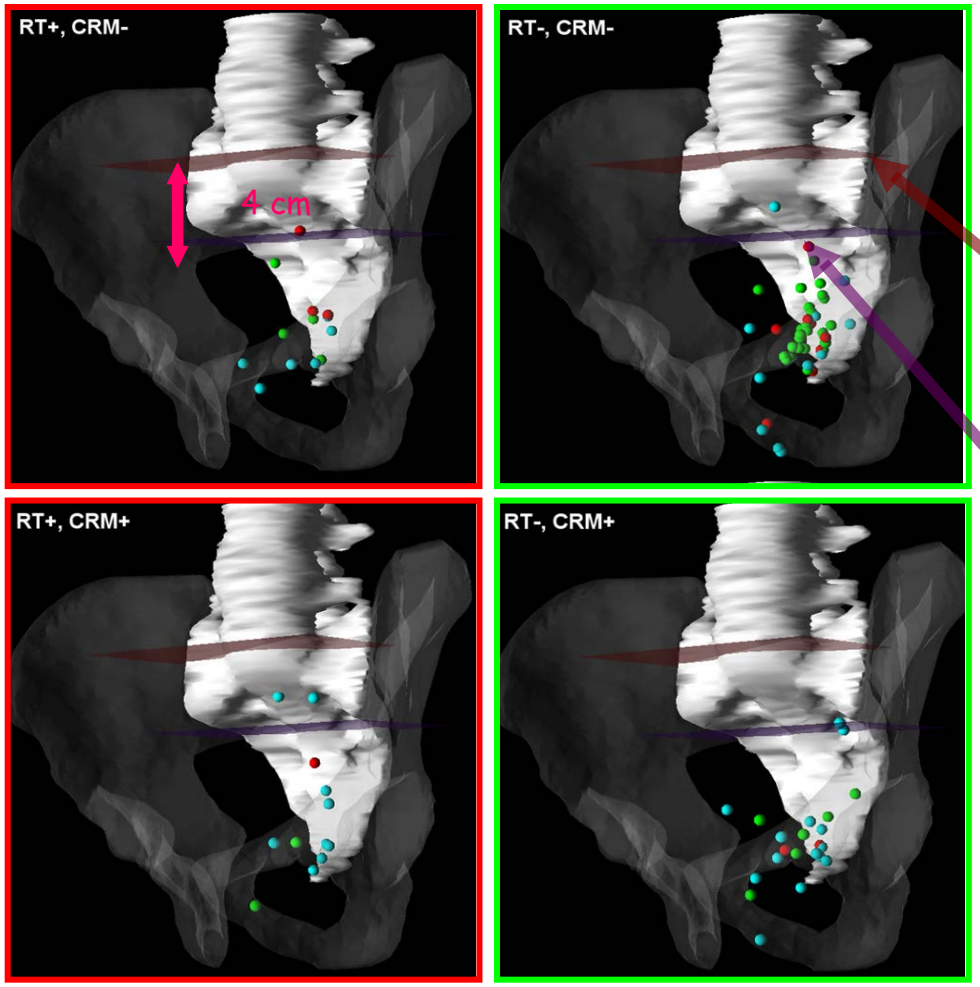

Takahashi T et al., Dis Colon Rectum 2000

# THREE-DIMENSIONAL ANALYSIS OF RECURRENCE PATTERNS IN RECTAL CANCER: THE CRANIAL BORDER IN HYPOFRACTIONATED PREOPERATIVE RADIOTHERAPY CAN BE LOWERED

**94 local recurrences analyzed**
**(69 RT-n and 25 RT+ patients)**

Primary tumor distance from the anal verge

- <5 cm
- 5–10 cm
- >10 cm

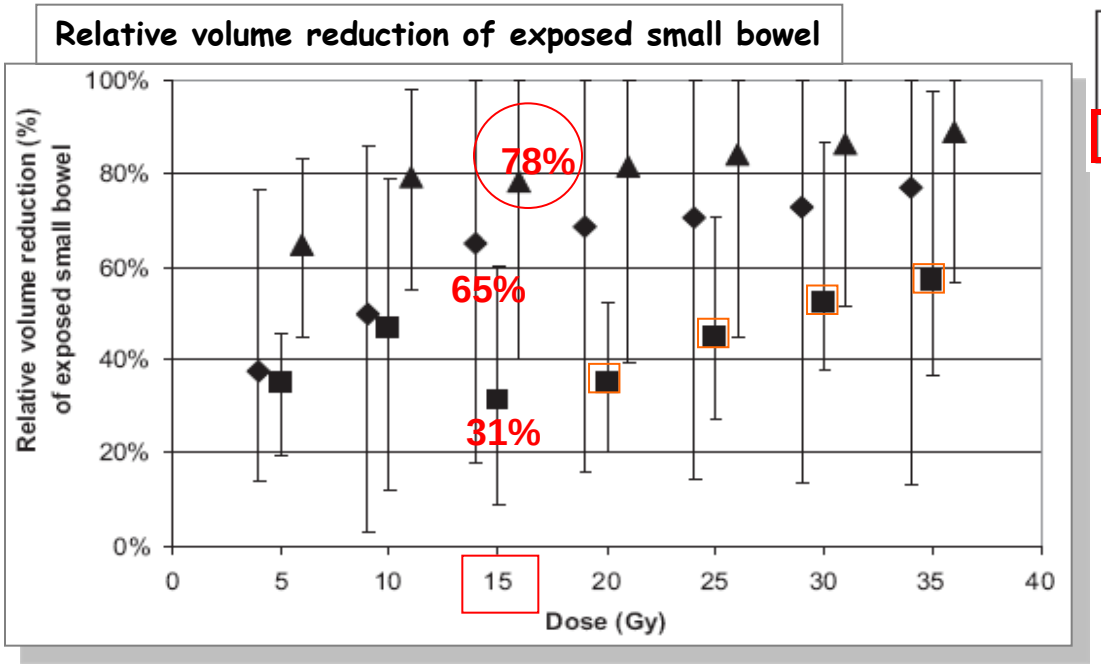


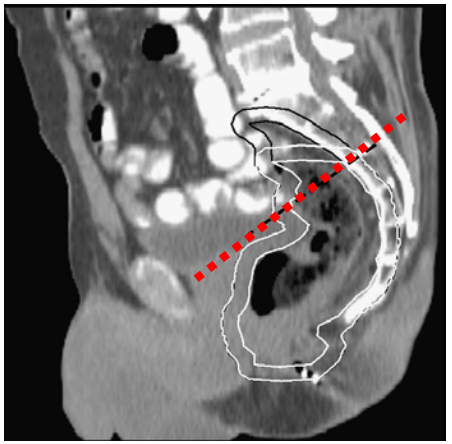

cranial border of the treatment fields used in the trial

level of the S2–S3 interspace

Nijkamp et al, Int. J. Radiation Oncology Biol. Phys., 2011

# THREE-DIMENSIONAL ANALYSIS OF RECURRENCE PATTERNS IN RECTAL CANCER: THE CRANIAL BORDER IN HYPOFRACTIONATED PREOPERATIVE RADIOTHERAPY CAN BE LOWERED



For **N -** and **CRM-** patients CTV can probably be reduced on the cranial side to the S2-S3 interspace without significantly increasing the local recurrence rate

!!!!! Identification of nodal involvement and CRM before treatment!!!!

Nijkamp et al, Int. J. Radiation Oncology Biol. Phys., 2011

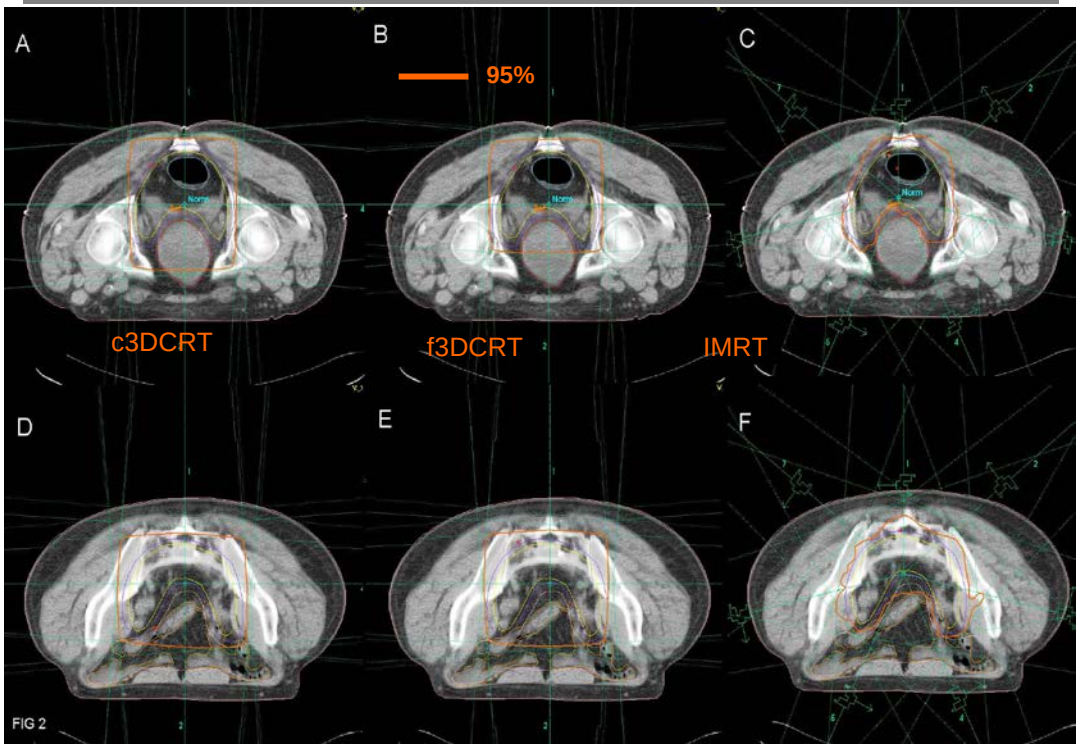
METHODOLOGY

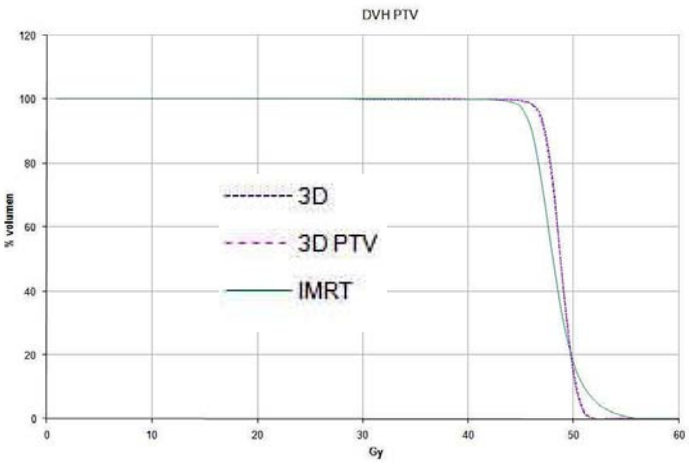
Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications

# IMRT

- ✓ decreases irradiation of the OAR
- ✓ improves target conformity…
- ✓ …increasing target heterogeneity
- ✓ more IBV at 5 Gy but less IBV ≥ 20 Gy

Isodose distribution in a patient with a uT3N+ medial rectal cancer



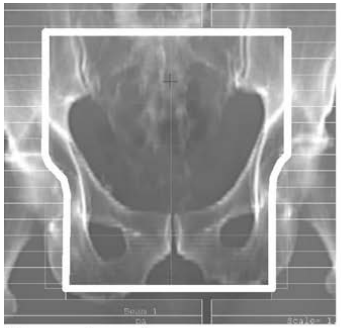



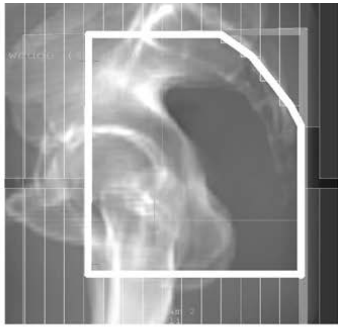

Arbea et al. Radiation Oncology 2010

# Evaluation of three different CT simulation and planning procedures for the preoperative irradiation of operable rectal cancer

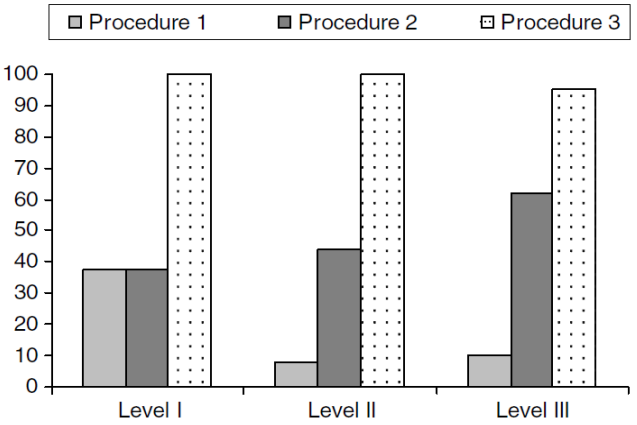
Percentage of the patient cohort in which at least 95% of the PTV is covered by the 95% isodose (PTV95%P95%)

fields based on bone anatomy on CT scans

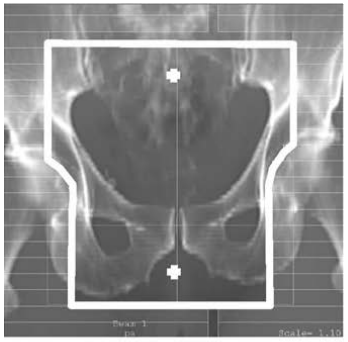


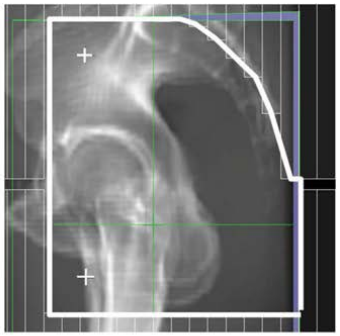


Procedure 1




Cranial, anterior and caudal extension of the CTV manually marked with a cross symbol on the CT-slices → extended by 2 cm

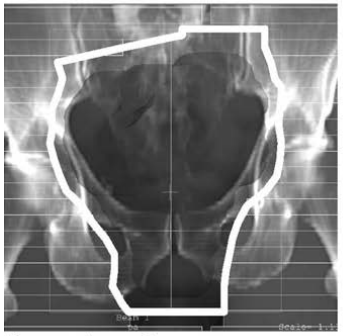


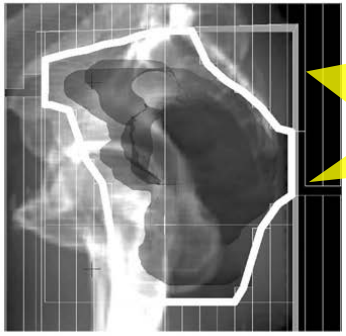


Procedure 2

87.0 (54–100) 94.0 (78–100) 99.0 (94–100)

CTVs and OARs defined on CT slices



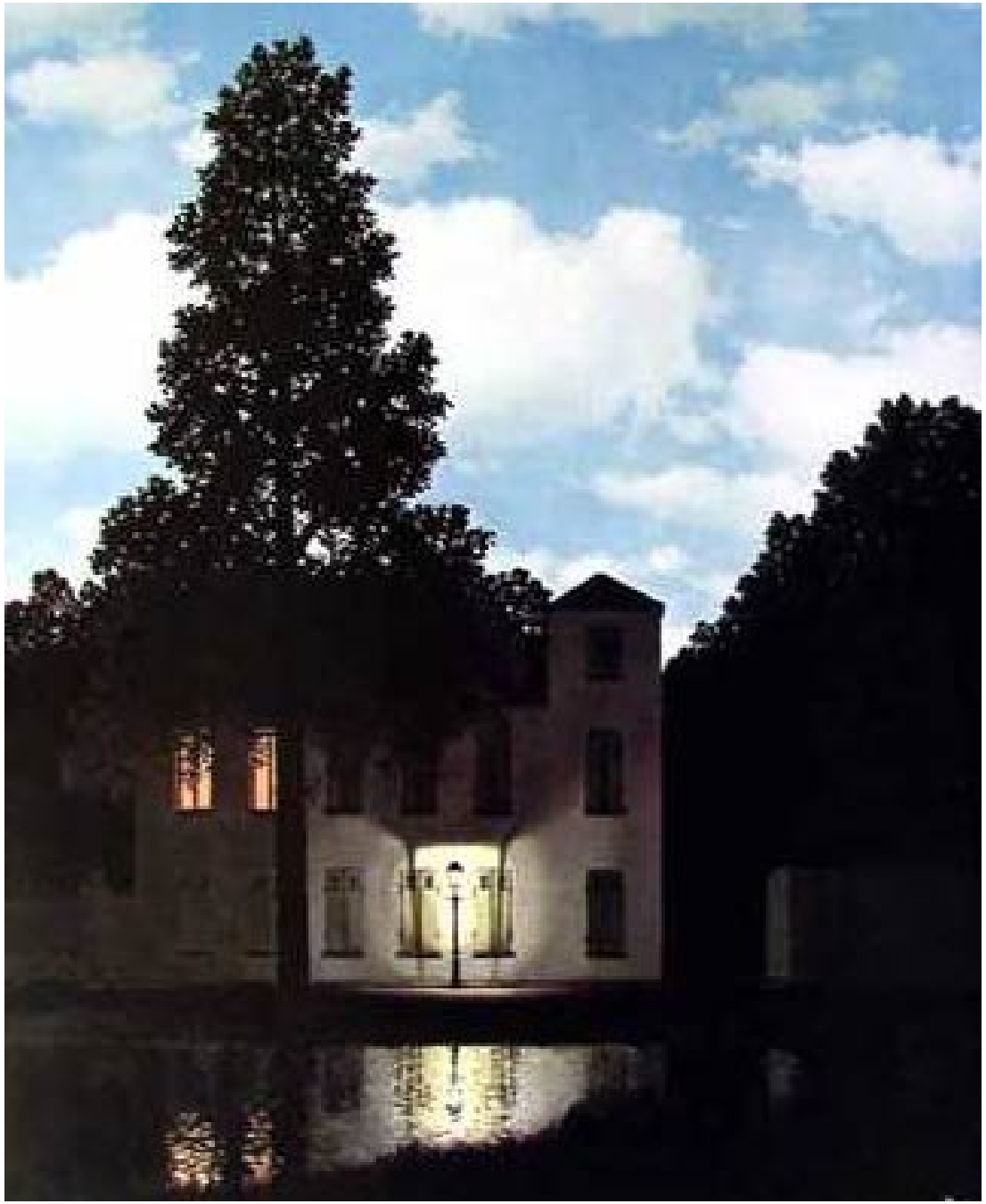


Procedure 3

**Time consuming!**

**24 vs 4 min**

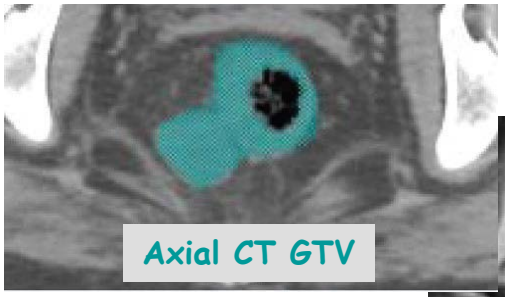
Borger et al. Radiotherapy and Oncology, 2008



Can we use new imaging tools for target definition?

René Magritte, L'empire des lumières

# MR *vs* CT imaging: low rectal cancer tumour delineation for three-dimensional conformal radiotherapy

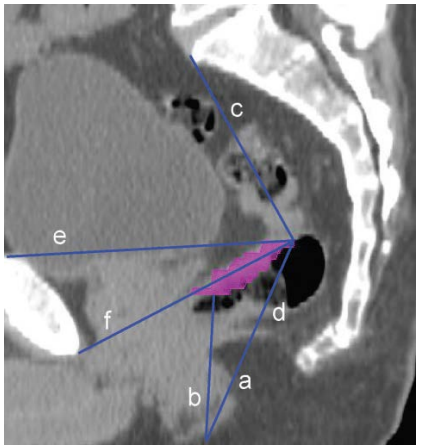




10 patients with low rectal cancer
(defined as < 6 cm from the anal verge)

*N.B. → Fusion of CT and MR data sets not attempted!!*

| Parameter measured (units) | *p*-Value |
|---|---|
| Length of tumour (cm) | 0.000 |
| Maximum width of tumour (cm) | 0.050 |
| Volume of tumour ($cm^3$) | 0.003 |
| Height of proximal tumour to anal verge (cm) | 0.003 |




All measurements were determined with a tool within the TPS

Tumour volumes defined on MRI are **smaller**, **shorter** and **more distal** from the anal sphincter than CT-based volumes

O'Neill et al, The British Journal of Radiology, 2009

# The utility of multimodality imaging with CT and MRI in defining rectal tumour volumes for radiotherapy treatment planning: a pilot study

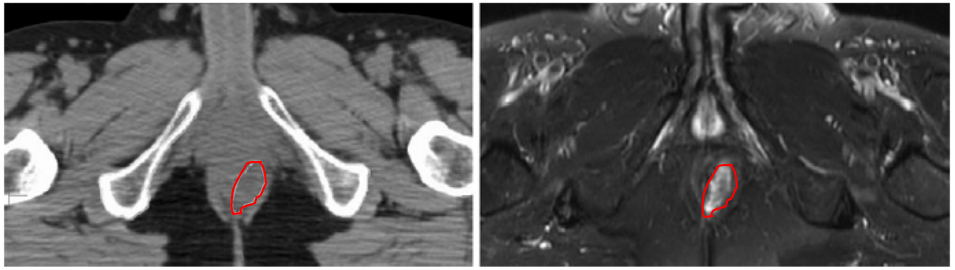
## Volumetric comparison

| Volumes | Total tumour volume |
|---|---|
| Mean CT GTV/MR-GTV ratio (range) | 1.2 (0.5to2.9) |
| Mean (ave log ratio) | 0.12 |
| Geometric mean ($e^{mean}$) | 1.13 |
| Standard deviation | 0.41 |
| Standard error of the mean | 0.11 |

*Co-registration: automated coordinate registration based upon maximisation of mutual information matching*

## Difference between reference points (cm)

| Reference points on CT-GTV–MR-GTV | Superior | Inferior | Anterior | Posterior |
|---|---|---|---|---|
| | Reasonable spatial correlation of CT / MR GTV!! | | | |
| Mean difference | 0.18 | 0.38 | –0.08 | 0.01 |
| Mean difference range | –2.0 to 4.0 | –3.0 to 4.0 | –5.7 to1.95 | –0.93 to 0.77 |
| Geometric mean ($e^{mean}$) | 1.2 | 1.47 | 0.93 | 1.01 |
| Standard deviation | 1.33 | 1.54 | 1.83 | 0.53 |
| Standard error of the mean | 0.34 | 0.4 | 0.47 | 0.14 |



MRI better definition of tumour extent (and N+)

**Staging MRI usefull**

**Simulation MRI investigational**

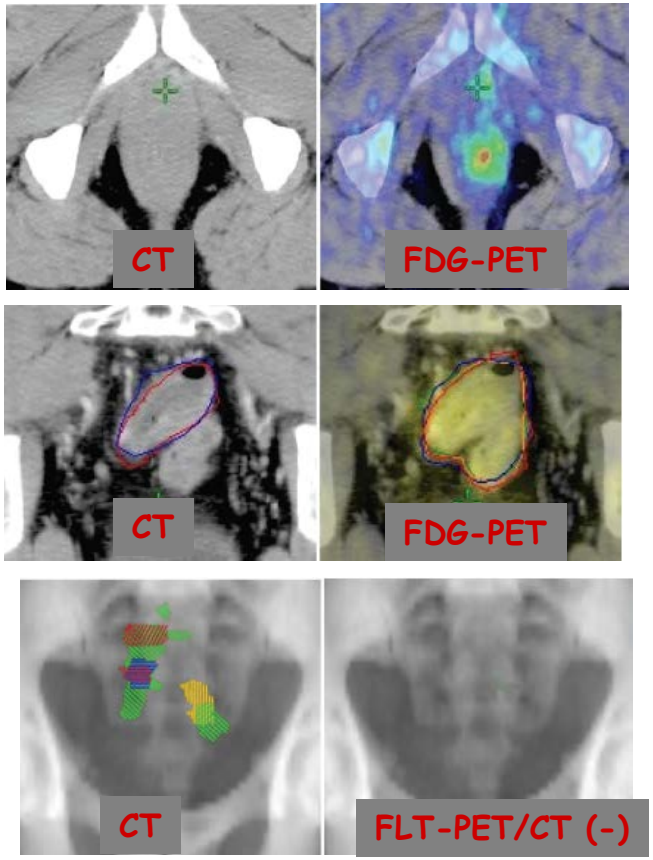
Tan et al, Journal of Medical Imaging and Radiation Oncology, 2010

PET-based
(auto) contouring?

Georges Braque, *Mandora,* 1910_

# Impact of Integrated PET/CT on Variability of Target Volume Delineation in Rectal Cancer

GTVp and GTVn PET vs CT inter-observer similarity index




**GTV Tumour**

| Modality | Estimated SI | Standard Error | | 95% CI | |
|---|---|---|---|---|---|
| CT | 0.77 | 0.03 | | 0.69 | 0.84 |
| FDG | 0.81 | 0.03 | | 0.75 | 0.870 |
| FLT | 0.80 | 0.03 | | 0.74 | 0.86 |
| **Inter-modality Difference** | **SI difference** | **Standard Error** | **P-value** | **95% CI** | |
| FDG-CT | 0.04 | 0.02 | 0.01 | 0.01 | 0.07 |
| FLT-CT | 0.03 | 0.02 | 0.09 | -0.004 | 0.06 |
| FDG-FLT | 0.01 | 0.02 | 0.54 | -0.02 | 0.04 |

**GTV Nodal**

| Modality | Estimated SI | Standard Error | | 95% CI | |
|---|---|---|---|---|---|
| CT | 0.22 | 0.12 | | -0.087 | 0.52 |
| FDG | 0.70 | 0.12 | | 0.47 | 0.94 |
| FLT | 0.70 | 0.12 | | 0.46 | 0.94 |
| **Inter-modality Difference** | **SI difference** | **Standard Error** | **P-value** | **95% CI** | |
| FDG-CT | 0.49 | 0.07 | <.0001 | 0.35 | 0.63 |
| FLT-CT | 0.49 | 0.08 | <.0001 | 0.34 | 0.64 |
| FDG-FLT | 0.001 | 0.08 | 0.98 | -0.15 | 0.15 |

- **Combined PET/CT lower inter-observer variability (N+ !)**
- **No differences between FDG and FLT**

Patel et al, Technology in Cancer Research & Treatment, 2007

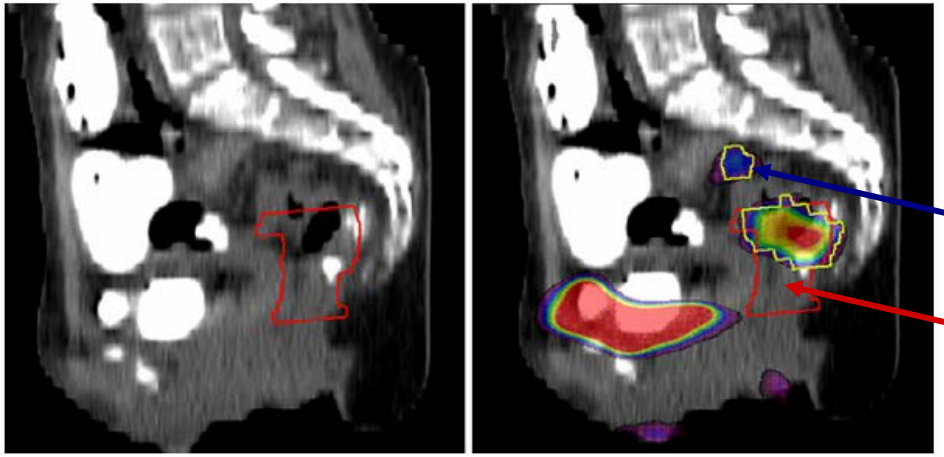
# FDG-PET/CT IMAGING FOR STAGING AND TARGET VOLUME DELINEATION IN PREOPERATIVE CONFORMAL RADIOTHERAPY OF RECTAL CANCER

| Volume of interest | Mean volume ($cm^3$) | SD |
|---|---|---|
| CT-GTV | 77.2 | 103.3 |
| PET-GTV | 56.4 | 70.0 |
| PET/CT-GTV | 96.8 | 104.5 |
| CT-CTV | 708.3 | 124.6 |
| PET/CT-CTV | 737.3 | 121.7 |

Mean increase of GTV by 25%

Mean increase of CTV by 4%

*A fixed threshold value of 40% of the maximum uptake in the lesion was chosen*

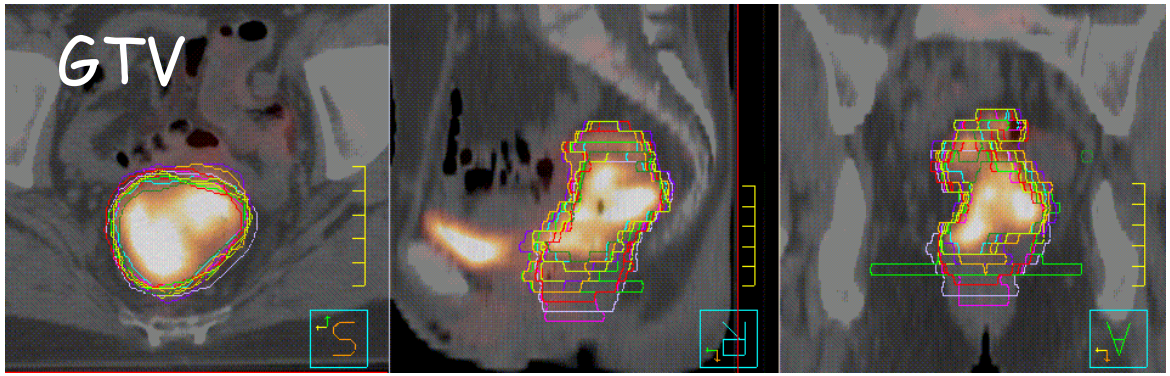



➡ Combined PET/CT information could help prevent geographic missing

➡ PET/CT can affect tumor staging or the treatment purpose

Bassi et al, Int. J. Radiation Oncology Biol. Phys., 2008

**Target volume delineation for preoperative radiotherapy of rectal cancer: inter-observer variability and potential impact of FDG-PET/CT imaging.**



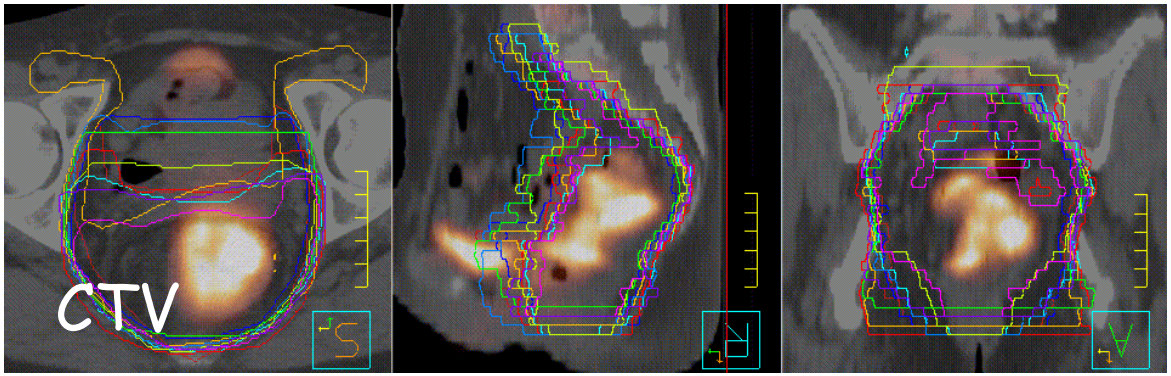

Inter-observer variability using FDG-PET for target volume delineation

10 radiation oncologists

5 on CT

5 on PET/CT

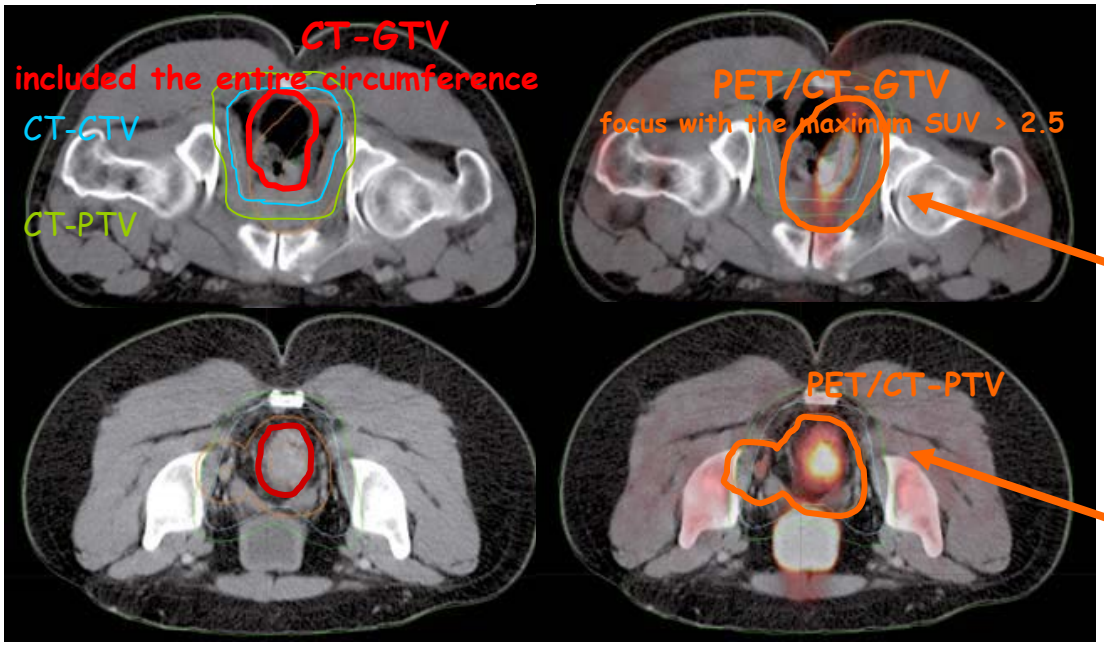
- **coefficient of variation (CV) → lower**
- **concordance index (CI) → similar or higher with PET (GTV > CTV)**




*"PET/CT may allow reducing inter-observer variability in GTV delineation"*

Krengli et al., Technol Cancer Res Treat. 2010

# Impact of $^{18}$F-FDG-PET/CT on Staging and Irradiation of Patients with Locally Advanced Rectal Cancer




PET/CT affect tumor staging and treatment purpose

Not recommend to reduce commonly accepted target volumes on the basis of metabolic information

Usefull to extend traditional volumes (CT-PTV) in high-risk areas

*PET threshold SUV > 2.5*

| | Patients with geographic miss n = 16 | | | Patients without geographic miss n = 19 | | |
|---|---|---|---|---|---|---|
| | Median | Mean | SD | Median | Mean | SD |
| CT-GTV ($cm^3$) | 140 | 193 | 141 | 126 | 137 | 46 |
| PET/CT-GTV ($cm^3$) | 58 | 92 | 94 | 35 | 37 | 24 |
| OV% | 33 | 38 | 23 | 26 | 25 | 12 |
| PET/CT-PTV outside CT-PTV ($cm^3$) | 11 | 20 | 24 | | | |

Mean Overlap Volume 31%

Brigita Paskeviciute et al, Strahlenther Onkol 2009

Focal dose escalation using FDG-PET-guided intensity-modulated radiation therapy boost for postoperative local recurrent rectal cancer: a planning study with comparison of DVH and NTCP

*PET threshold SUV > 2*

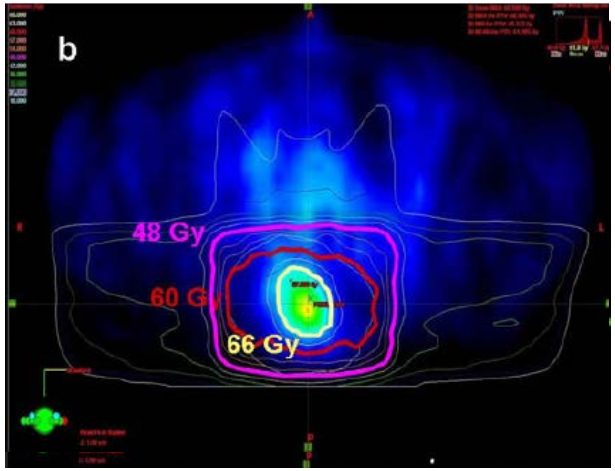
**for local recurrent rectal cancer (superior to CT and MRI)**

**Sensitivity = 94.5%**
**Specificity = 97.7%**
**Accuracy= 95.9%**

! Misalignment of the fusion of PET and CT images → on-line imaging

! Not recommend routine clinical use of focal dose escalation using FDG-PET/CT-guided IMRT

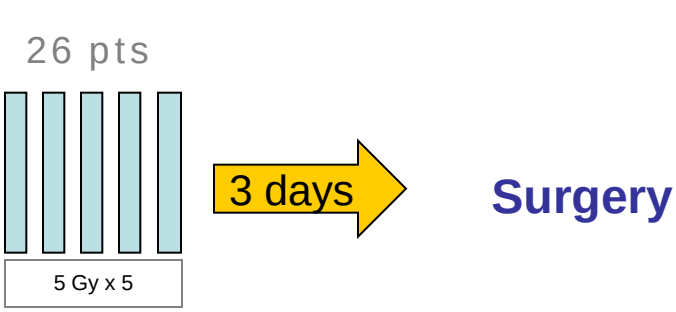
! When region of high FDG accumulation is near the OARs, careful radiotherapy planning is necessary

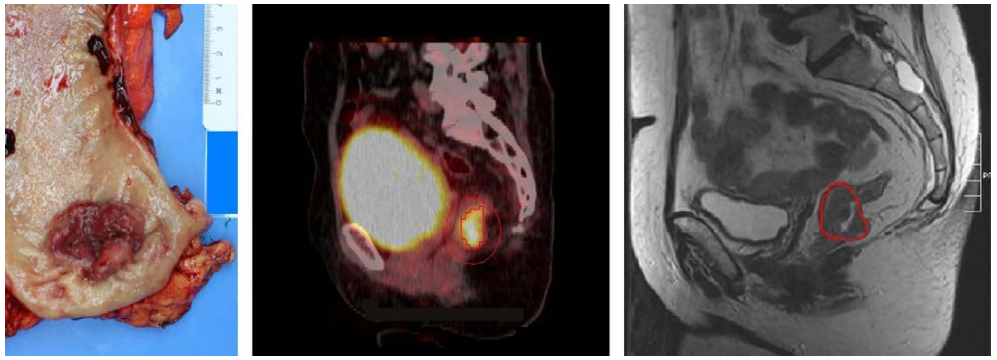



Jingu et al. BMC Cancer 2010

PET in rectal cancer

# FDG-PET provides the best correlation with the tumor specimen compared to MRI and CT in rectal cancer



Predictive performance (tumour lenght mesurement) of the different modalities

| | PET auto | PET manual | MR | CT | Endoscopy |
|---|---|---|---|---|---|
| Precision | 0.37 | 1.97 | 1.82 | 3.35 | 3.82 |
| Bias | 0.13 | 0.91 | 0.66 | 1.03 | 0.46 |
| Difference in precision (95% CI)[a] | | −1.60 (−2.71 to −0.50) | −1.45 (−2.70 to −0.19) | −2.98 (−4.00 to −1.96) | −3.45 (−7.60 to 0.70) |

**Automatically generated PET-CT based contours** show the best correlation with the surgical specimen

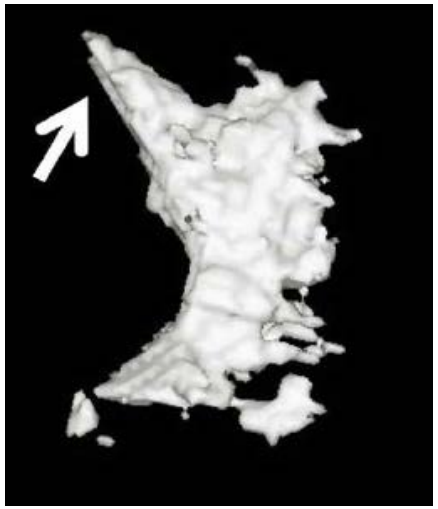
*Signal-to-background-ratio (SBR) method*

Buijsen et al., Radiotherapy and Oncology, 2011

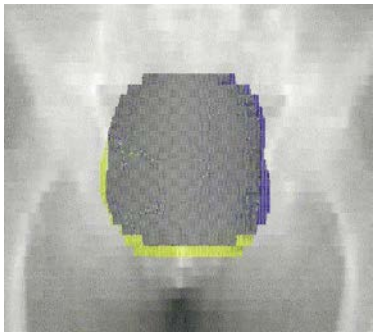
# AUTOMATED FUNCTIONAL IMAGE-GUIDED RADIATION TREATMENT PLANNING FOR RECTAL CANCER

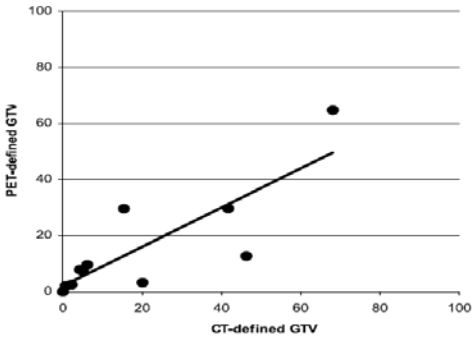
## Automatically delineated BTV

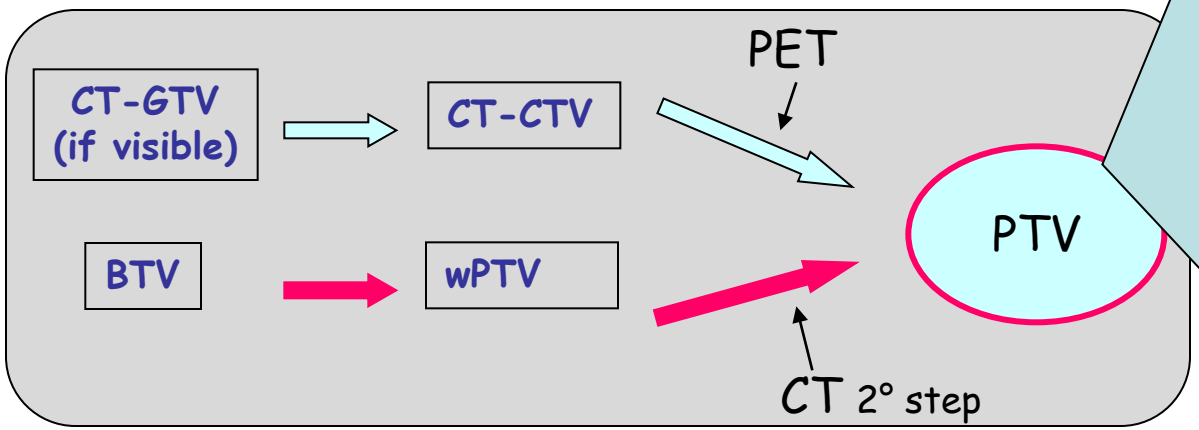
(threshold of 40% of a single signal of interest)



Correlation of the CT-derived and PET-derived PTV was sufficiently accurate ($r2$ 0.96; $p < 0.01$)



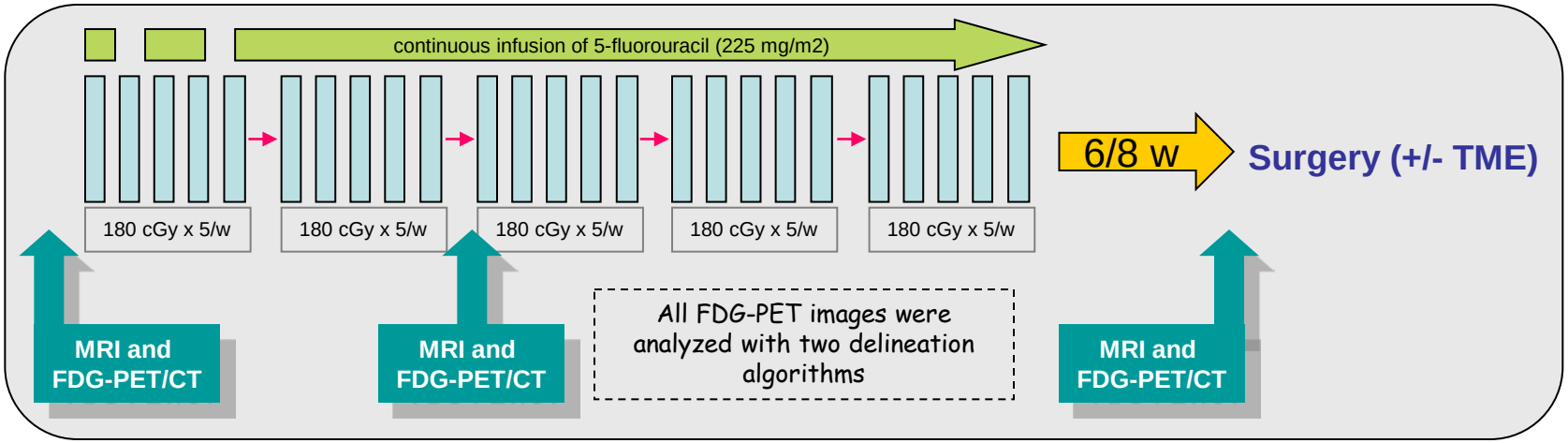



Automated BTV immediate and accurate.
Correction for anatomic precision may be applied in a second step

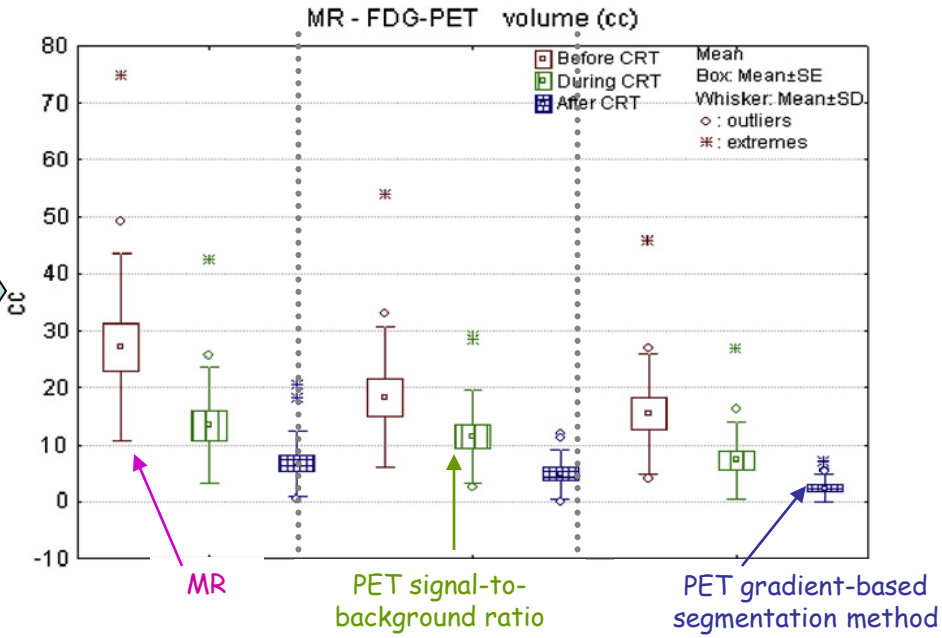
Ciernik, et al, Int. J. Radiation Oncology Biol. Phys., 2005

# BIOLOGICAL IMAGE-GUIDED RADIOTHERAPY IN RECTAL CANCER: CHALLENGES AND PITFALLS




Tumor volume analysis

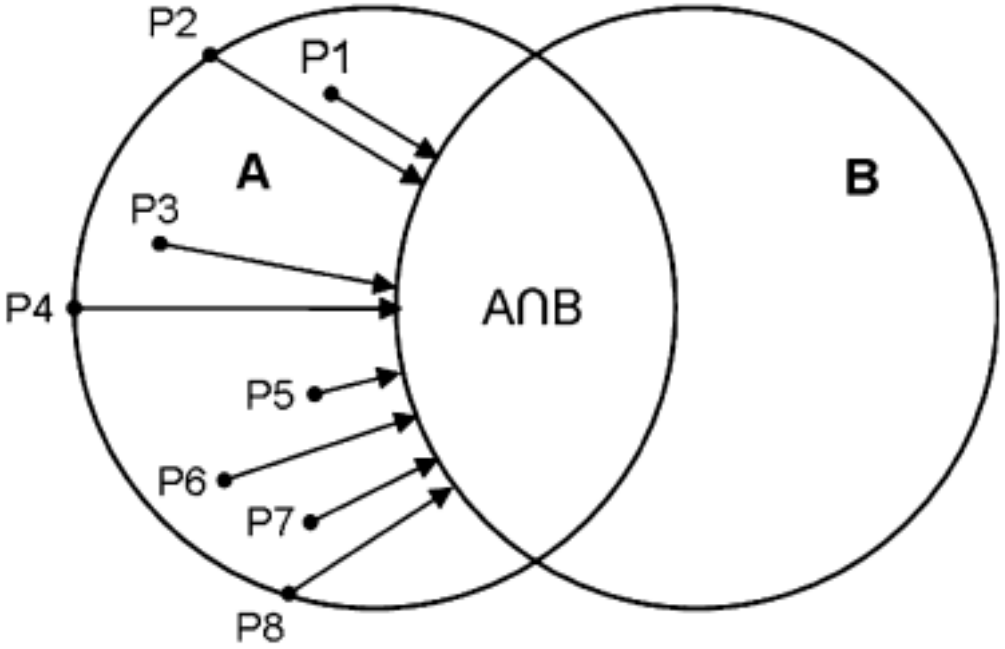
Both *MRI and FDG-PET* showed a trend toward tumor *shrinkage* during and after CRT




Roels et al, Int. J. Radiation Oncology Biol. Phys., 2009

# Image coregistration and mismatch analysis

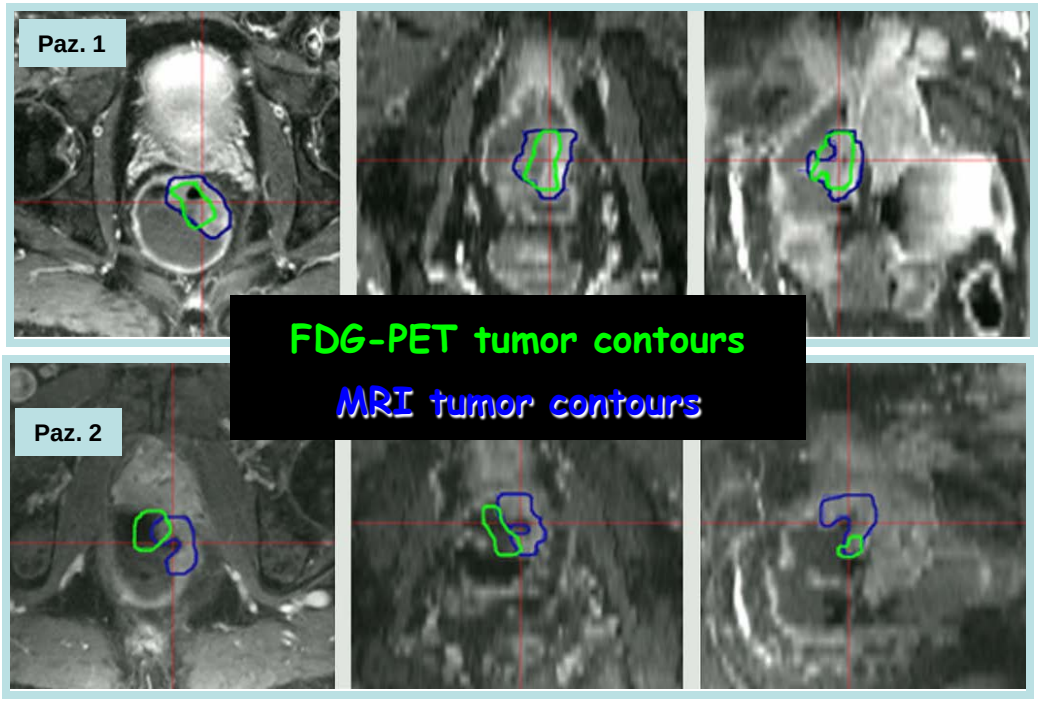
Nonrigid image registration algorithm




**Calculation limited to the region inside the mesorectum** → minimized influence from the bladder.

Roels et al, Int. J. Radiation Oncology Biol. Phys., 2009

# Correspondence mismatches between MR and FDG-PET




**Mismatches up to 70–80%**

shortest distances of 0.8 cm and a maximum value of approximately 2 cm

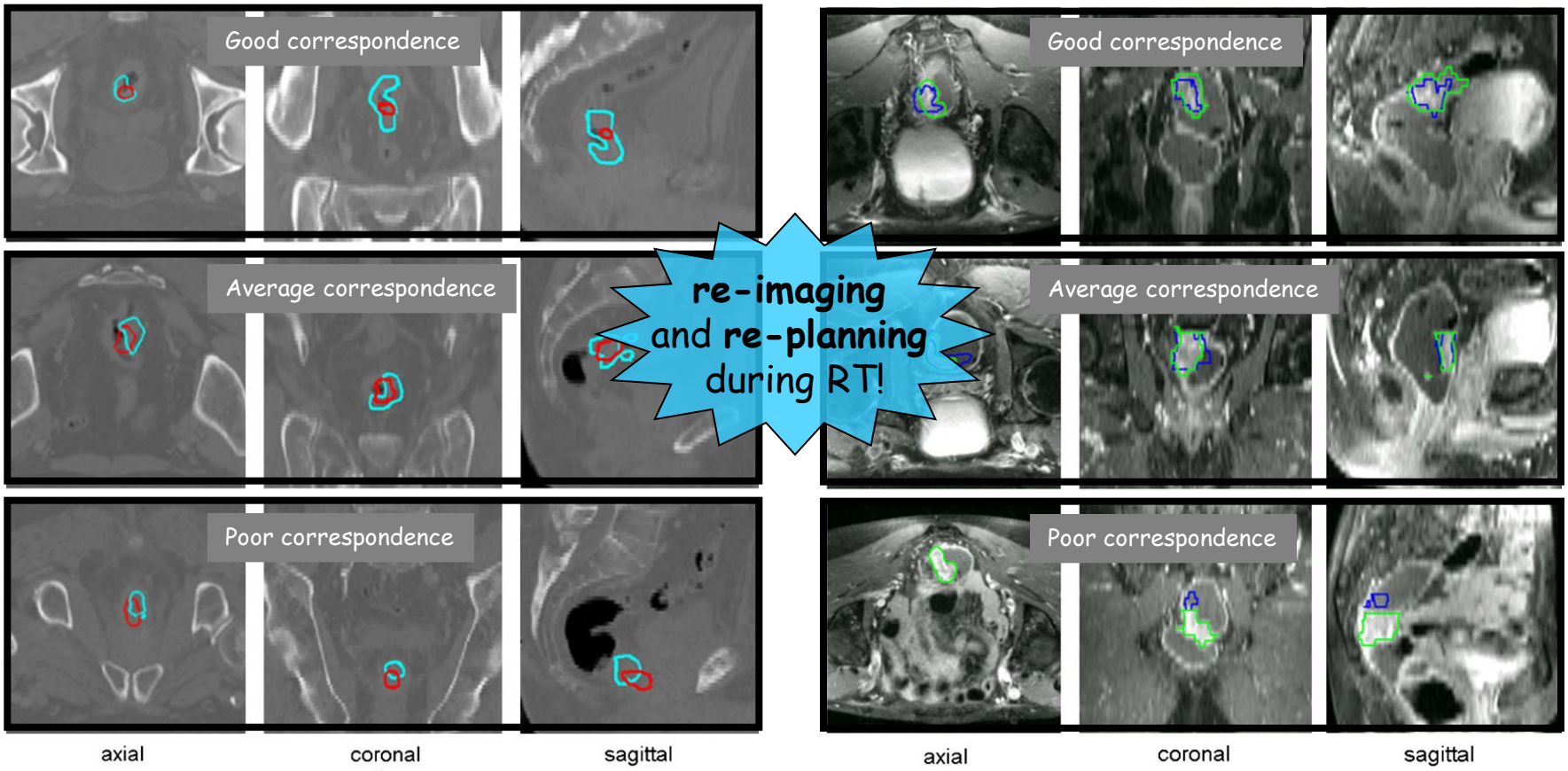
*(mainly related to the relatively large and **overestimated TV by MR**)*

Roels et al, Int. J. Radiation Oncology Biol. Phys., 2009

# Quantitative and spatial evolution

of tumor contours before and during chemo-radiotherapy

Similar reduction was measured during CRT compared with baseline




FDG-PET before / FDG-PET during: 54%

MRI before / MRI during: 53%

Roels et al, Int. J. Radiation Oncology Biol. Phys., 2009

# Responce evaluation → Correspondence imaging = pathology

| Patient no. | MRI ($cm^3$) | FDG-PET ($cm^3$) | Pathology ($cm^3$) |
|---|---|---|---|
| 1 | 7.76 | 3.54 | 1.37 |
| 2 | 5.77 | 0.53 | 0.05 |
| 3 | 20.36 | 12.95 | 11.19 |
| 4 | 8.79 | 1.02 | 0.77 |
| 5 | 7.15 | 3.61 | pCR |
| 6 | 3.59 | 0 | 0.55 |
| 7 | 6.99 | 2.92 | 0.43 |
| 8 | 3.2 | 0 | pCR |
| 9 | 18.29 | 3.18 | 2.25 |
| 10 | 3.45 | 2.05 | pCR |
| 11 | 2 | 7.09 | 0.32 |
| 12 | 4.08 | 0 | pCR |
| 13 | 0.48 | 0.35 | pCR |
| 14 | 1.32 | 0 | pCR |
| 15 | 8 | 5.4 | 0.13 |

Relationship between tumor volumes on MRI and FDG-PET acquired before surgery, with the corresponding tumor volumes on the pathologic specimen

***Gradient- based method*** *better than the threshold-based method* ***against*** *radiation-induced* ***peritumoral inflammation***

No residual FDG-PET signal in 50% of the pCR patients

All pCR patients had a positive MRI

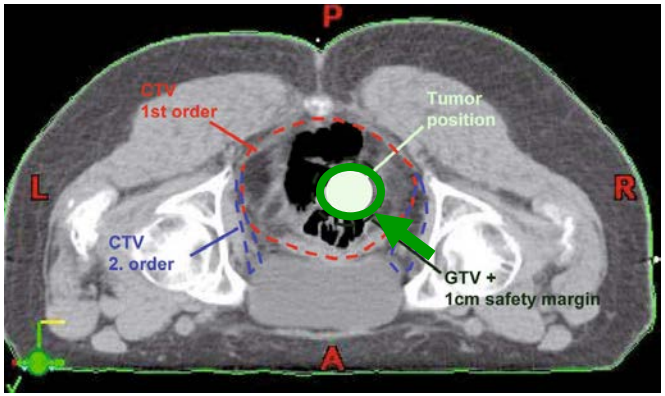
Roels et al, Int. J. Radiation Oncology Biol. Phys., 2009

# FDG PET based Planning: features

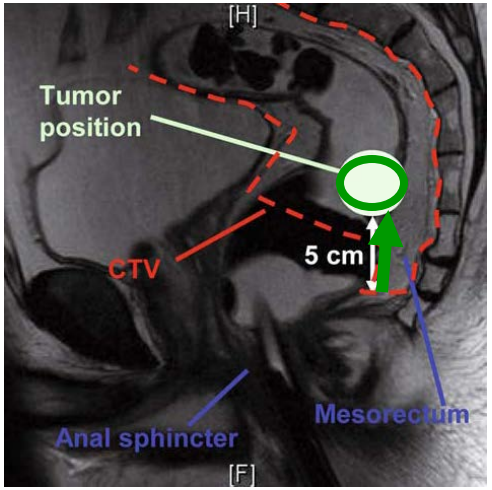
- Low spatial resolution (4 to 7 mm)
- Low sensitivity for small mesorectal N+
- Doesn't predict y CRM+/-
- Inflammatory processes in/around the tumor
- Predictive power after neoadjuvant treatment
- Automated PET-based planning for GTVs (not too small GTVs!)
- SUV threshold ? (signal-to-background ratio vs gradient-based segmentation method)
- Other tracers than FDG (hypoxia or cell-cycle turnover) for a BTV boost?


Ernst Haas , Motion Runners

# Gold Markers for Tumor Localization and Target Volume Delineation in Radiotherapy for Rectal Cancer




Mean three-dimensional deviation was 0.38 cm (± 0.99 cm)



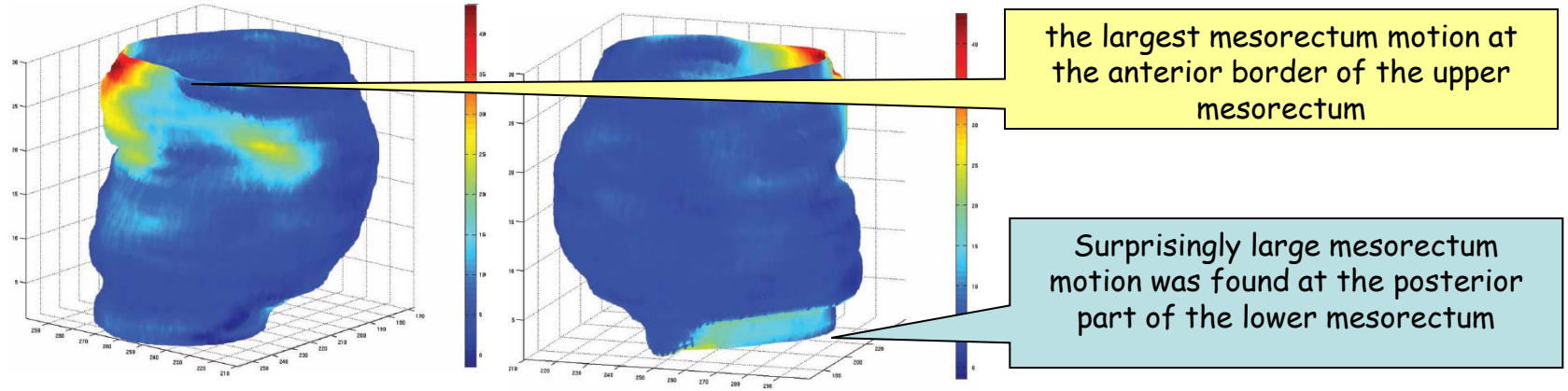

- Mean shift of markers during the treatment < 0.25 cm in all directions
- No marker loss during the radiation treatment series
- Tumor shrinkage
- Movements of the markers during restaging MRI

Vorwerk et al, Strahlentherapie und Onkologie, 2009

# IGRT in rectal cancer

| Author/ ref | Year | Topic | Comments | Rectal volume variation | Main displacement and site |
|---|---|---|---|---|---|
| Tinger [36] | 1998 | Prostate cancer | – Weekly CT+daily portal images | Mean (cc) 30±5-127±36 76±34 | |
| Stroom [37] | 1999 | Prostate cancer | – CT scans on week 2, 4, 6-laxation used in planning CT | Mean (cc) Supine: 123 Prone: 166 | |
| Nuyttens [35] | 2002 | Rectal cancer | – Weekly CT-adjuvant treatment-clips motion | | 1.5 cm Caudal |
| Muren [33] | 2003 | Bladder cancer | – Weekly CT+daily portal images | Mean (cc) 62±25-72±29 | 30 mm Anterior and left wall |
| Hoogeman [38] | 2004 | Prostate cancer | – CT scans on days 1, 2 and 3, at the 1° day and last day of the 2° week, then weekly<br>– Empty rectum | Mean (cc) 74±17 | 8 mm Anterior side |
| Fokdal [39] | 2004 | Bladder cancer | – 3 CT scan with rectal catheter filled<br>– 2 CT scan with no rectum filling | Mean (cc) 51(26-20)-185 (70-307) | |
| Stasi [40] | 2006 | Prostate cancer | – empty rectum | Mean (cc) 53±11.5 | 9.1 mm anterior wall; rectum superior half |
| Lotz [41] | 2006 | Bladder cancer | – Daily CT during 1° week; then weekly | Mean (cc) 51±8.4-243±5.3 | |

Mean 1 cm!!



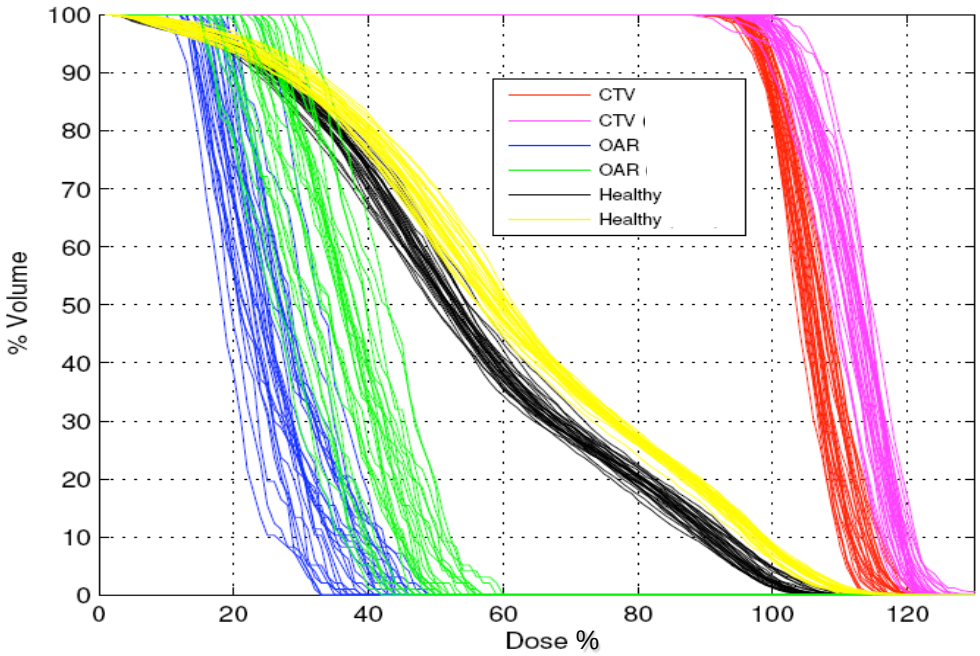

Mesorectum motion: Front view

Mesorectum motion: Back view

Ippolito et al, Acta Oncologica, 2008

# ...Do we need Adaptive RT?

incorporating geometrical and biological changes during treatment into the radiation treatment process




...not only on pre-treatment anatomical information!

Haustermans et al., Strahlentherapie und Onkologie, 2007


Toni del Tin, Ora X, 1953

# ART?

. . . . . When ?

## Imaging

What do we ask to staging? T2/3 CRM +/- N+/- Distal margin
What are the best imaging tools for staging? T2w MRI (USPIO?)
Can modern imaging assess response to treatment? DWI, FDG PET

## Contouring

Is there a standard in RC contouring? Myerson 2009
Pattern of recurrence Posterior/lower pelvis → lower CTVs (?)
Can we use imaging tools for target definition? Benefit to be proven
Do we need Adaptive RT? Yes !!

Grazie