



UMC Utrecht

Image guided response assessment to neoadjuvant chemoradiation in esophageal cancer patients

Where are we today?

Gert Meijer

University Medical Center Utrecht



ATLANTIC
CONSORTIUM



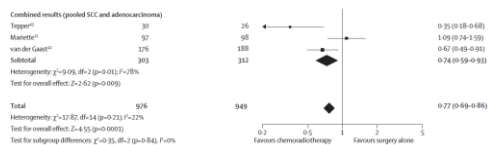
Esophageal cancer

480,000 new diagnoses annually

400,000 deaths annually

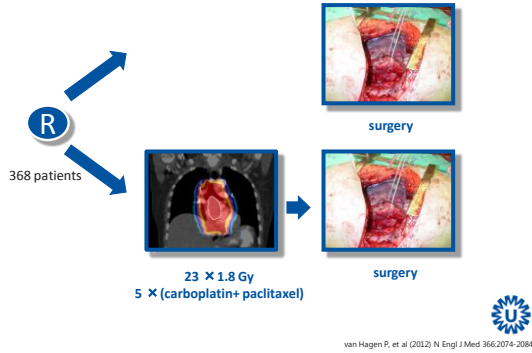
8th most common cancer type world wide

traditionally surgery cornerstone of curative treatment, but....

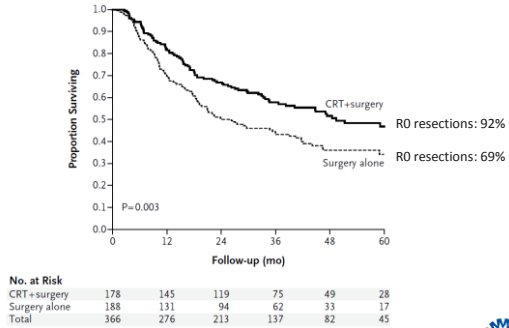


Spiegel, et al (2011) Lancet Oncology 2011.

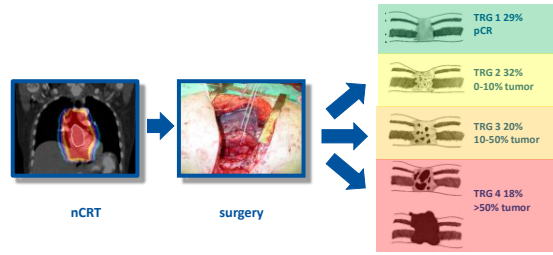
CROSS trial



Survival According to Treatment Group

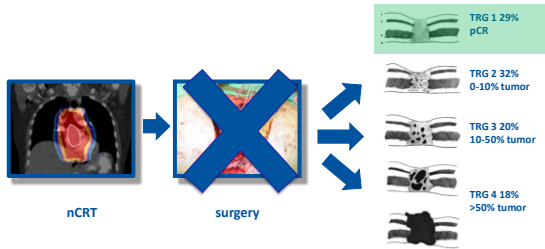


Pathologic outcome



Can we identify response during or after nCRT?

Pathologic outcome

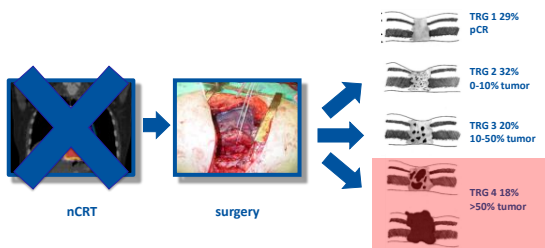


Can we identify response during or after nCRT?



van Hagen P, et al (2012) N Engl J Med 366:2074-2084.

Pathologic outcome



Can we identify response during or after nCRT?



van Hagen P, et al (2012) N Engl J Med 366:2074-2084.

Aim of response prediction is two-fold

- Predict pathologic complete response
 - Why:** omission of surgery
 - When:** before surgery
 - How:** test(s) with **high NPV**
- Predict pathologic poor response
 - Why:** modification or discontinuation of nCRT
 - When:** (before or) early during nCRT
 - How:** test(s) with **high PPV**



Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS?
2. FDG-PET?
3. DW-MRI / DCE-MRI?
4. A combination of modalities?

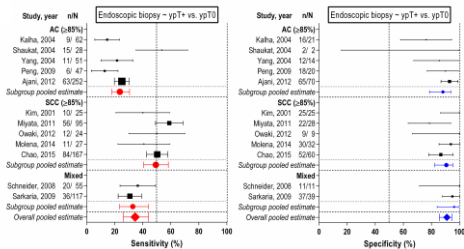


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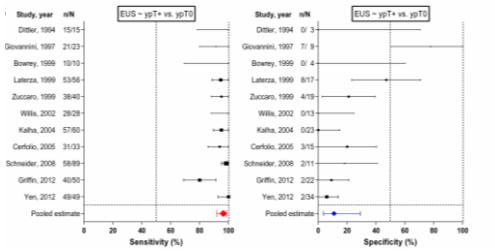
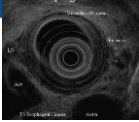


Results – Endoscopic biopsy



Van Rossum, et al. Manuscript under construction

Results – EUS ~ ypT+ versus ypT0



Van Rossum, et al. Manuscript under construction

Implications of findings in CROSS-setting

Cohort of 1000 patients

		endoscopic biopsy	EUS
test positive	true positive <i>justified surgery</i>	210 per 1000	588 per 1000
	false positive <i>unnecessary surgery</i>	35 per 1000	347 per 1000
test negative	true negative <i>justified omission of surgery</i>	355 per 1000	43 per 1000
	false negative <i>unjustified omission of surgery</i>	400 per 1000	22 per 1000

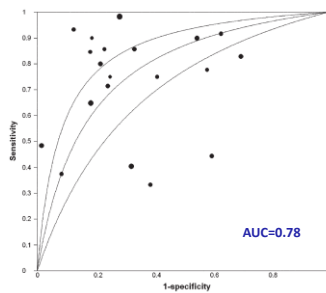
Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? NO
2. FDG-PET?
3. DW-MRI / DCE-MRI?
4. A combination of modalities?



Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? **NO**
2. FDG-PET?
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ROC curves show sensitivities and specificities of individual studies in ROC space with sROC and 95% CI.

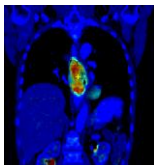


R. Kwee Radiology 2010

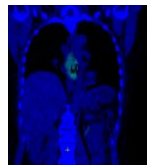
What can FDG-PET really add to prediction of pathCR?

Retrospective diagnostic (prediction) study, MD Anderson

n=217



pre nCRT



post nCRT

Results – Clinical characteristics

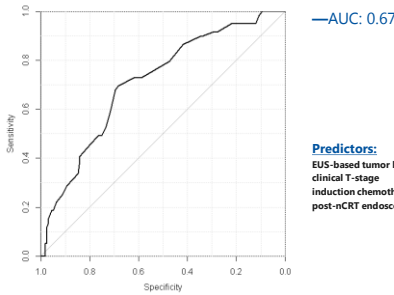
Table 1 Clinical baseline and treatment-related characteristics.

Characteristic	PathCR (n=59)	No pathCR (n=158)	p value
Male gender	54 (91.5)	148 (93.7)	0.558
Age (y)	58.8 ± 12.3	60.1 ± 9.9	0.440
Tumor location			0.324
Middle third of esophagus	2 (3.4)	1 (0.6)	
Distal third of esophagus	52 (88.1)	143 (90.5)	
Gastro-esophageal junction	5 (8.5)	14 (8.9)	
EUS-based tumor length (cm)	5.0 ± 2.4	5.9 ± 2.7	0.034*
Histologic differentiation grade			0.055
Moderate	34 (57.6)	68 (43.0)	
Poor	25 (42.4)	90 (57.0)	
Signet ring cell adenocarcinoma	5 (8.5)	30 (19.0)	0.061
Clinical T-stage			0.006*
cT2	14 (23.7)	15 (9.5)	
cT3	45 (76.3)	143 (90.5)	
Clinical N-stage			0.450
cN0	18 (30.5)	58 (36.7)	
cN+	39 (66.1)	98 (62.0)	
Missing	2 (3.4)	2 (1.3)	
Induction chemotherapy	28 (47.5)	50 (31.6)	0.031*
Post-chemoradiation endoscopic biopsy			0.023*
No residual cancer	55 (93.2)	126 (79.7)	
Residual cancer	4 (6.8)	32 (20.3)	
Days from completion CRT to surgery	61.5 ± 20.4	58.3 ± 19.3	0.285



Van Rossum, et al. Radiology (submitted)

Model 1: Clinical predictors only



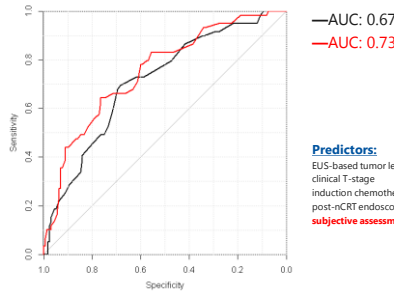
Predictors:

EUS-based tumor length
clinical T-stage
induction chemotherapy
post-nCRT endoscopic biopsy



Van Rossum, et al. Radiology (submitted)

Model 2: Clinical predictors + subjective PET



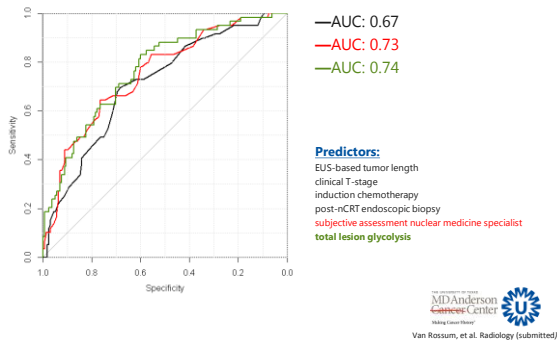
Predictors:

EUS-based tumor length
clinical T-stage
induction chemotherapy
post-nCRT endoscopic biopsy
subjective assessment nuclear medicine specialist

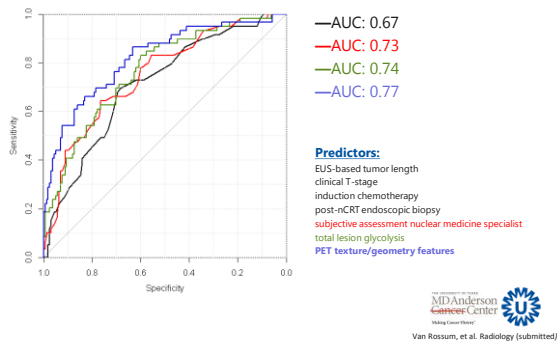


Van Rossum, et al. Radiology (submitted)

Model 3: Model 2 + quantitative PET



Model 4: Model 3 + PET texture/geometry features



Conclusions FDG-PET

- FDG-PET provides statistical benefit in terms of discrimination.
- However, clinical relevance of this benefit is limited.



Overview

Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? **NO**
2. FDG-PET? **NO**
3. DW-MRI / DCE-MRI?
4. A combination of modalities?



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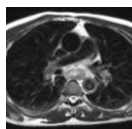
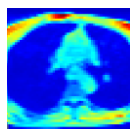
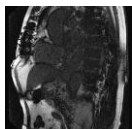


MRI in esophageal cancer

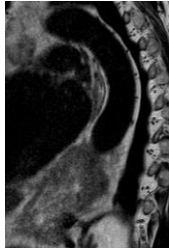
challenging because of:

motion

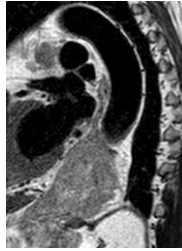
magnetic field inhomogeneities



Optimization study



no triggering
free breathing

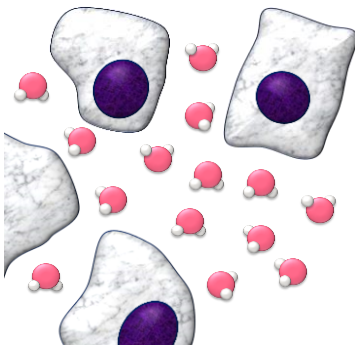


cardiac triggering
breathhold



van Rossum et al. *Eur Radiol*, 2013.

DW-MRI: diffusion weighted MRI

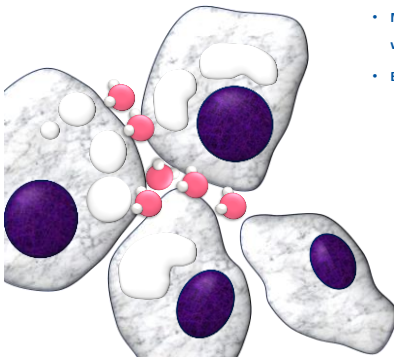


- Microscopic mobility of water
- Brownian motion:
 - viscosity
 - cellular environment



courtesy Nicola Dinapoli

DW-MRI: diffusion weighted MRI

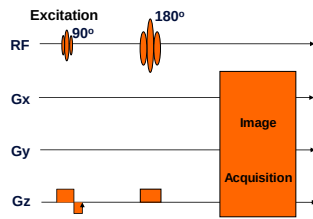


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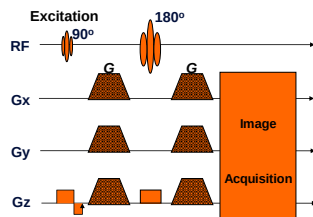


courtesy Nicola Dinapoli

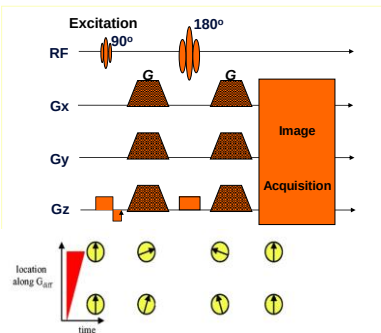
Pulse Sequence: Spin-Echo



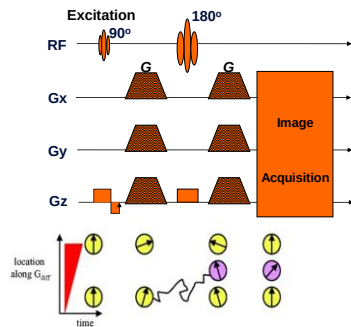
Pulse Sequence: Spin-Echo Diffusion Weighting



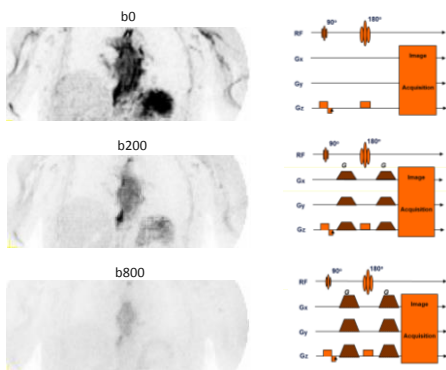
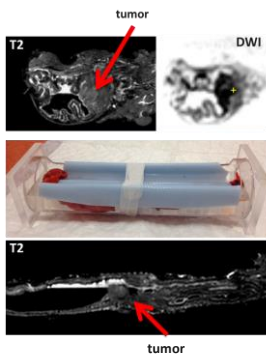
Pulse Sequence: Spin-Echo Diffusion Weighting

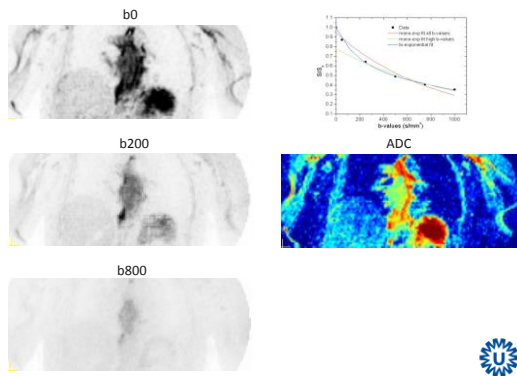


diffusion gradient

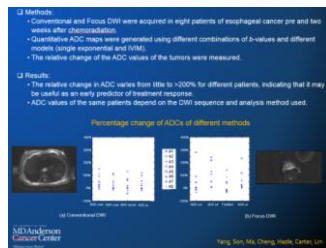


Ex vivo 3T MRI





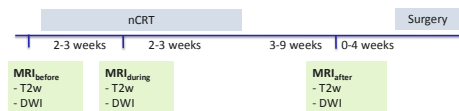
Quantitative ADC Measurement of Esophageal Cancer Before and After Chemoradiation



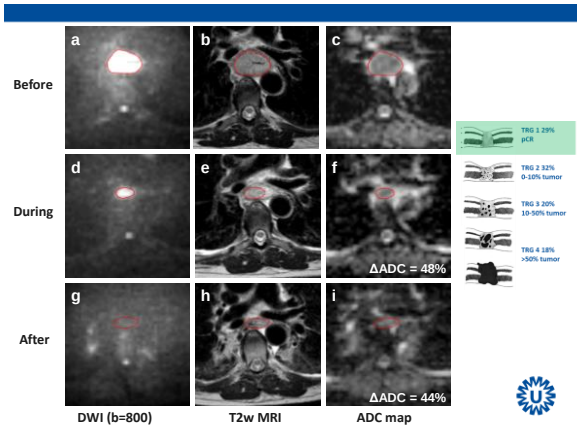
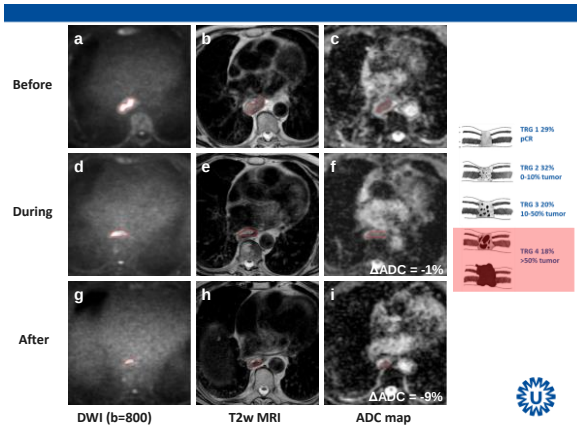
Yang L, Son JB, Ma J, Cheng S, Hazle J, Carter BW, Lin S.

MO-F-CAMPUS-1-05

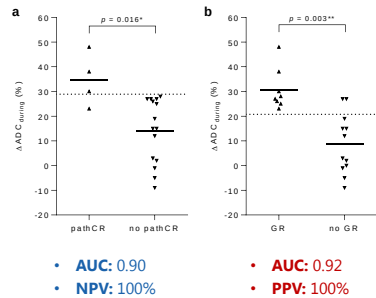
Methods – DWI response assessment study



N=20



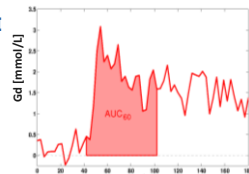
Results – ΔADC measurements vs. response



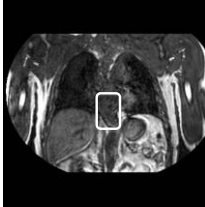
van Rossum, et al. *Radiother Oncol.* 2015

Dynamic Contrast Enhanced MRI

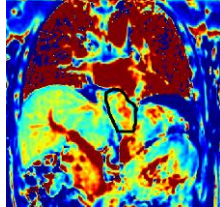
- Area under the curve (AUC)
- Start after inflow of contrast in artery
- Integral of 60 seconds on concentration time-curve



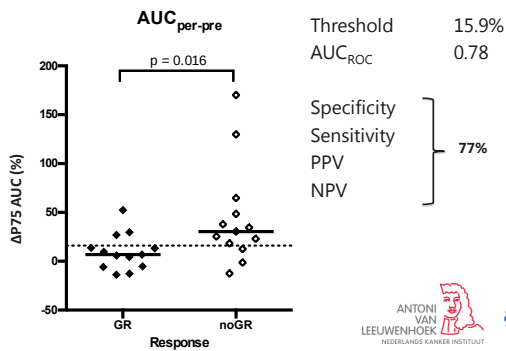
DCE-MRI



AUC



DCE-MRI for predicting response



Overview

Can we accurately predict pathologic response using:

1. Endoscopic biopsy or EUS? **NO**
2. FDG-PET? **NO**
3. DW-MRI / DCE-MRI? **MAYBE**
4. A combination of modalities?



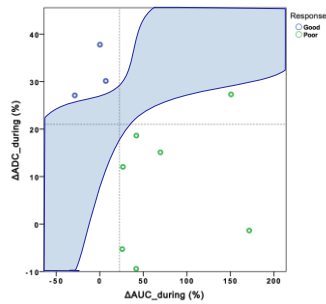
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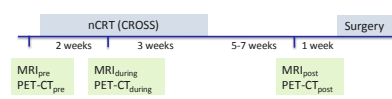
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Hot off the press

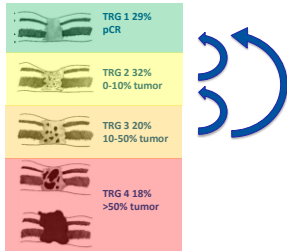


Ongoing research collaboration

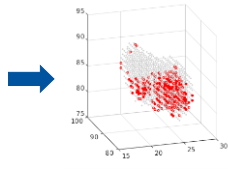
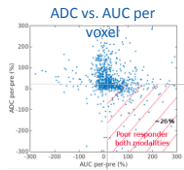
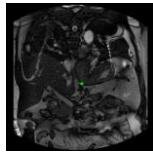
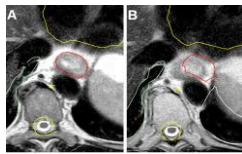


- Multi center response assessment trial at **MDACC, AvL and UMCU**:
n=90 patients, so far n=50

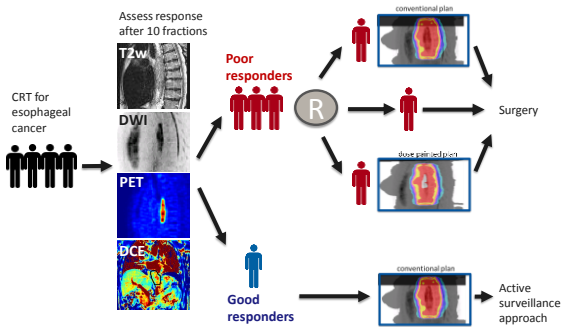




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Personalized adaptive treatment approach?





UMC Utrecht

Dept. of Radiotherapy:

Gert Meijer
Onne Reerink
Jan Lagendijk
Astrid van Lier
Sophie Heethuis
Peter van Rossum
Lucas Goense
Marco van Vulpen
Alexis Kotte
Rien Moerland
Nico van den berg
Marielle Philippons

Dept. of Surgery:

Richard van Hillegersberg
Jelle Ruurda

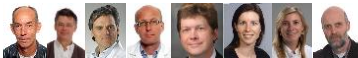
Dept. of Radiology/Nucl Med:

Marnix Lam
Maarten van Leeuwen
Frank Wessels
Manon Braat



Dept. of Radiation Oncology:

Steven Lin
Laurence Court
Lifei Zhang
Jingfei Ma



Dept. of Radiotherapy:

Francine Voncken
Marlies Nowee
Marcel Verheij
Berthe Aleman
Uulke van der Heide