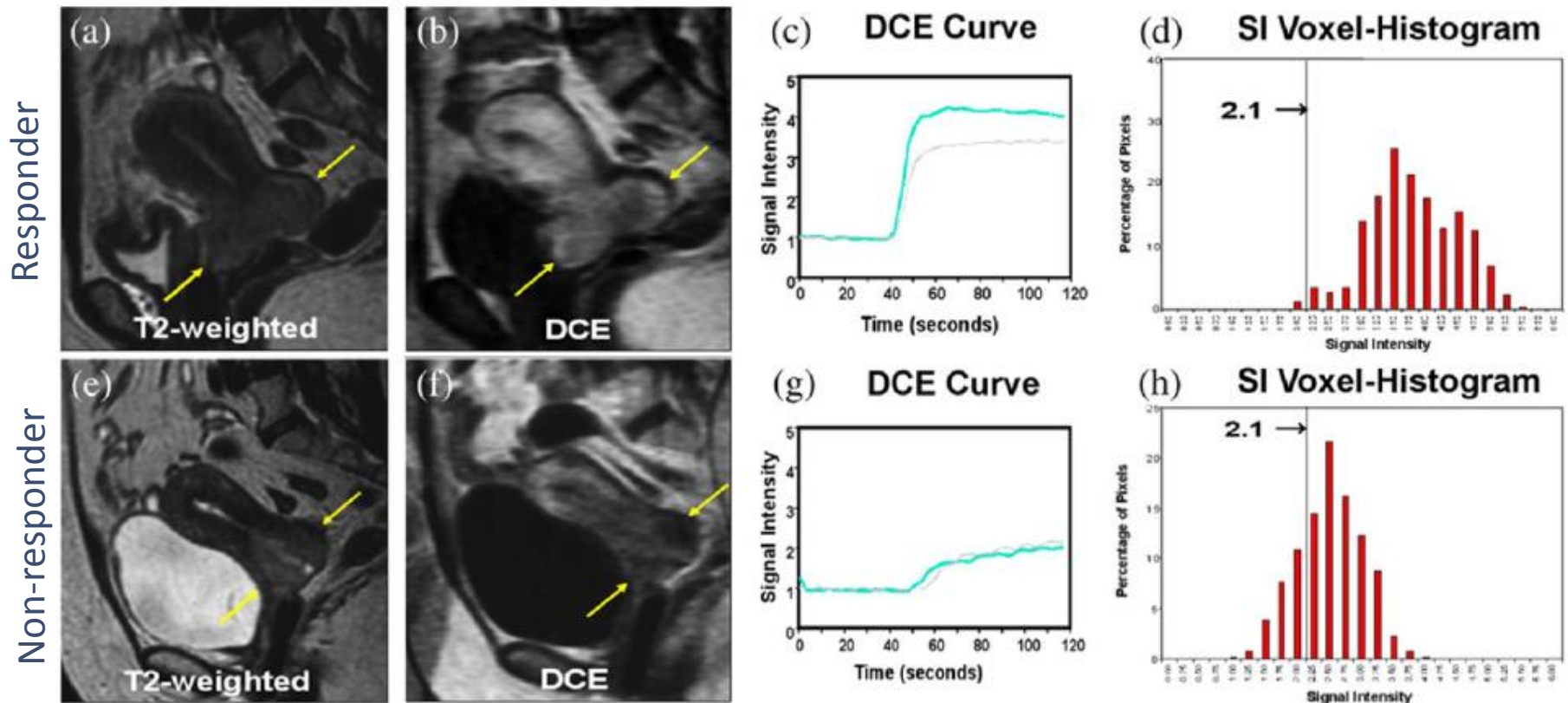


## **BIOMARKER DISCOVERY IN LOCALLY ADVANCED CERVICAL CANCER: IQ-EMBRACE**

PETRA VAN HOUDT, JESPER KALLEHAUGE, UULKE VAN DER HEIDE, KARI TANDERUP  
MARCH 23, 2018

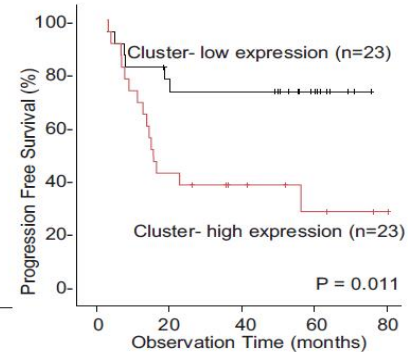
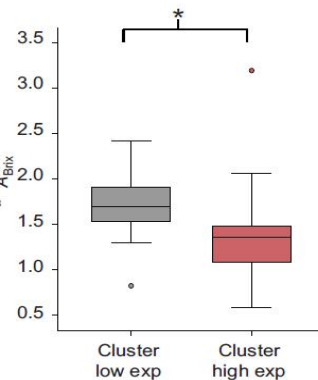
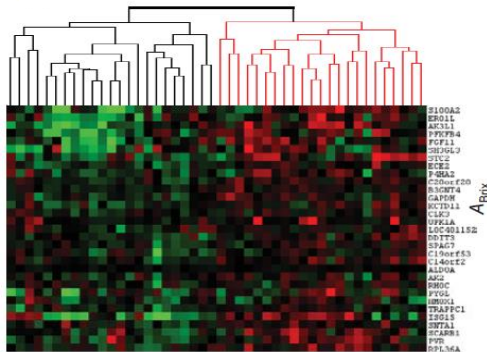
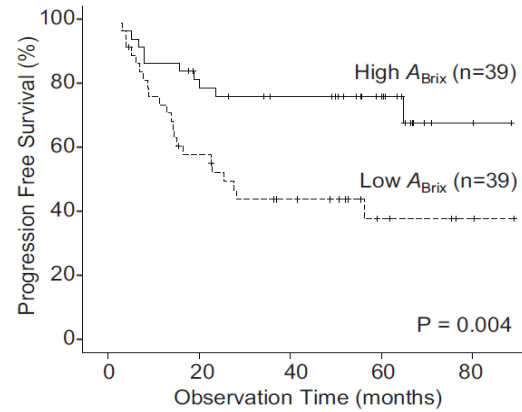
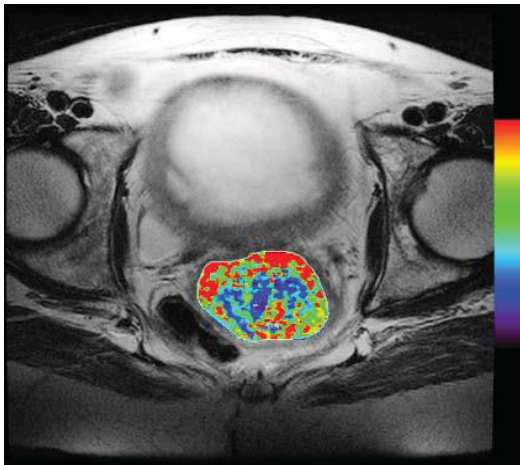
# DCE-MRI FOR PREDICTION OF TREATMENT OUTCOME

Patients with large low-enhancing volumes in tumor (i.e. low perfusion) have a less favorable outcome



# DCE-MRI FOR PREDICTION OF TREATMENT OUTCOME

## Relation between DCE-MRI parameters and hypoxia



---

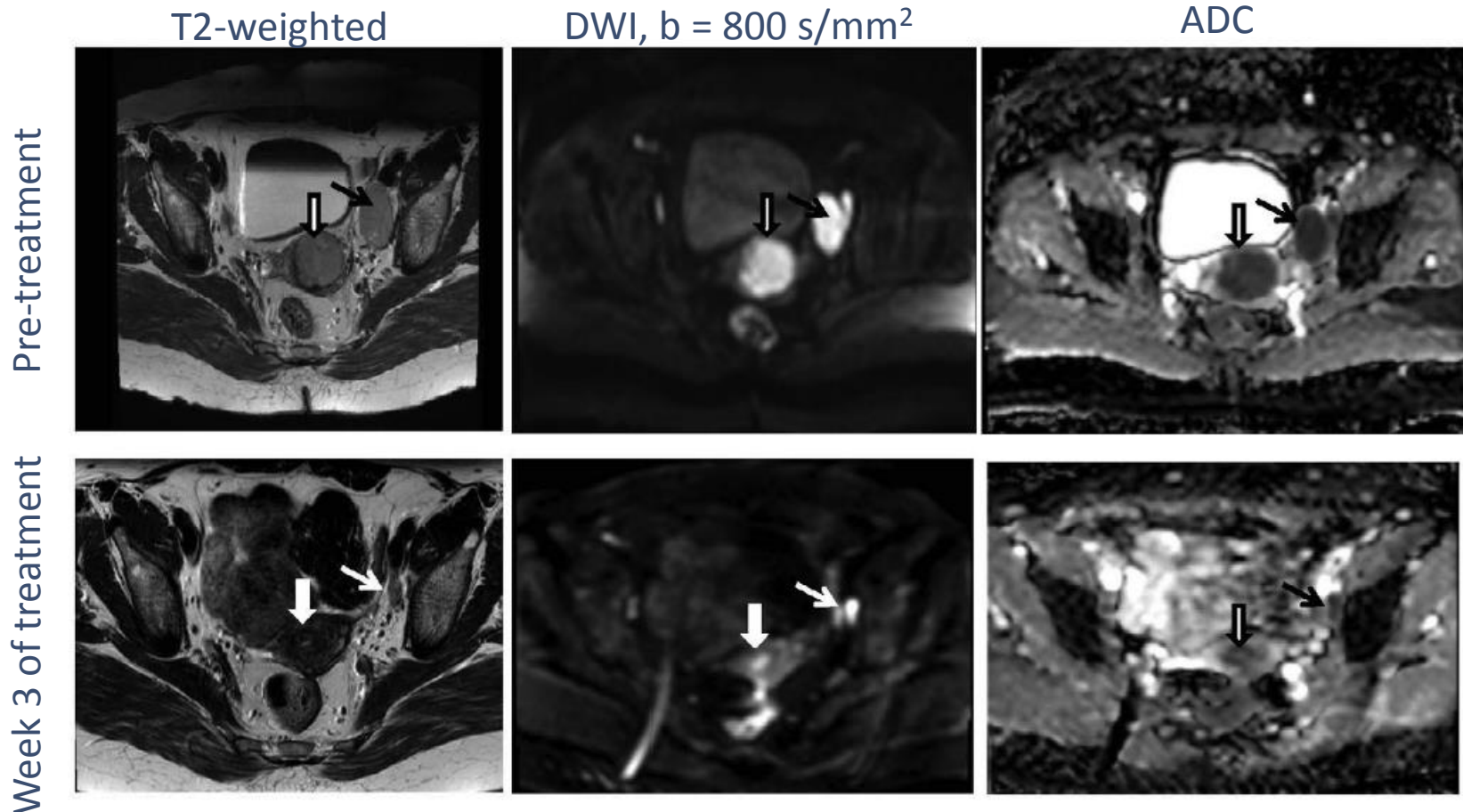
# EVIDENCE FOR PROGNOSTIC VALUE OF DCE-MRI

Review of papers published between 1996 and 2014:

- Investigate association between pre-treatment DCE-MRI parameters (e.g. Maximum uptake, Abrix, Ktrans etc.) and outcome
  - 18 papers from 10 groups
  - Median 30 patients (range 7 – 102)
  - 14 positive, 1 negative, 3 inconclusive

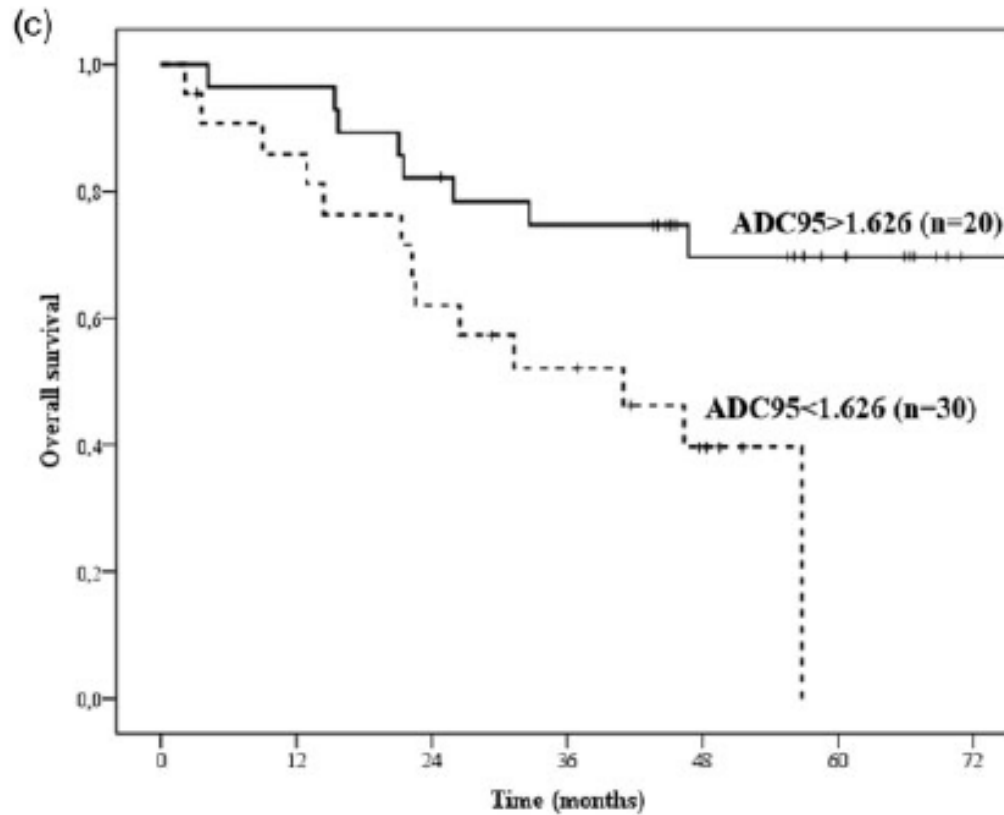
# DWI FOR PREDICTION OF TREATMENT OUTCOME

Change in ADC can be used as predictor of early pathological response



# DWI FOR PREDICTION OF TREATMENT OUTCOME

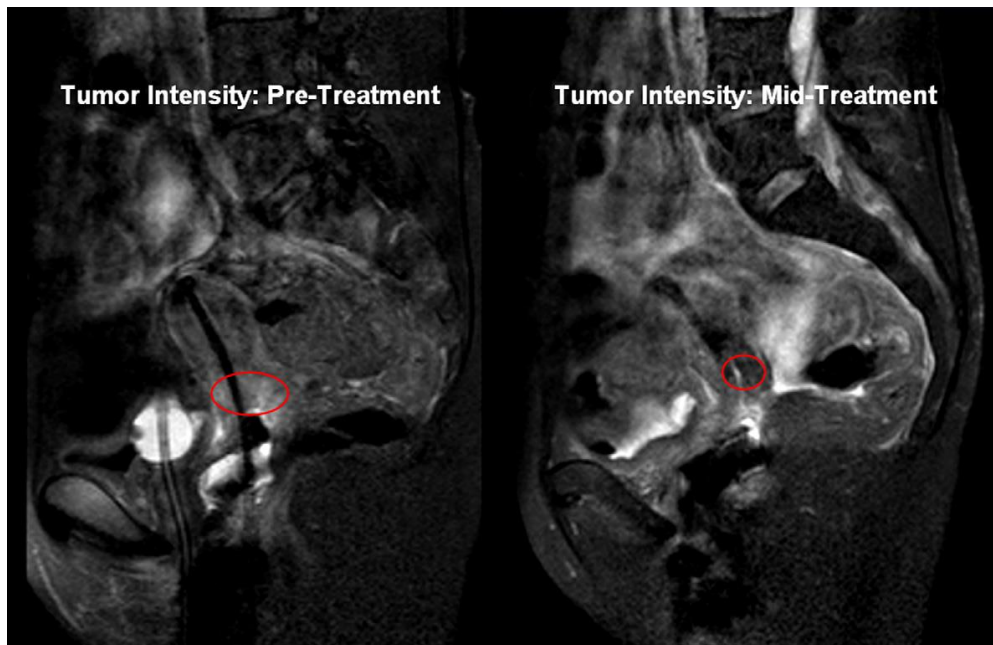
Lower maximum ADC value is associated with worse overall survival



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## POTENTIAL FOR T2 MAPPING?

Large decreases in signal intensity in T2-weighted images are correlated with a favorable outcome

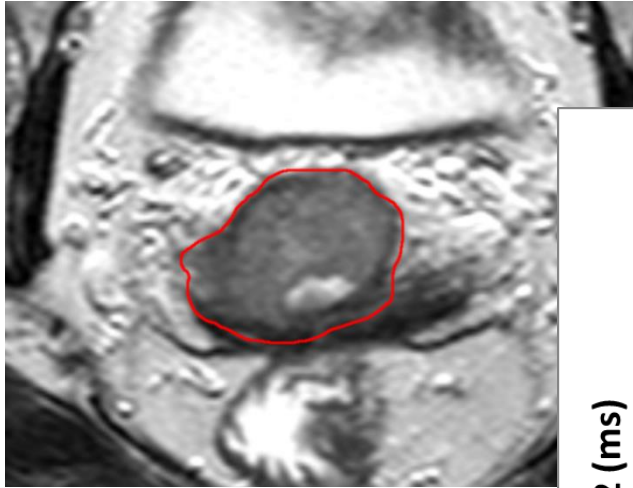




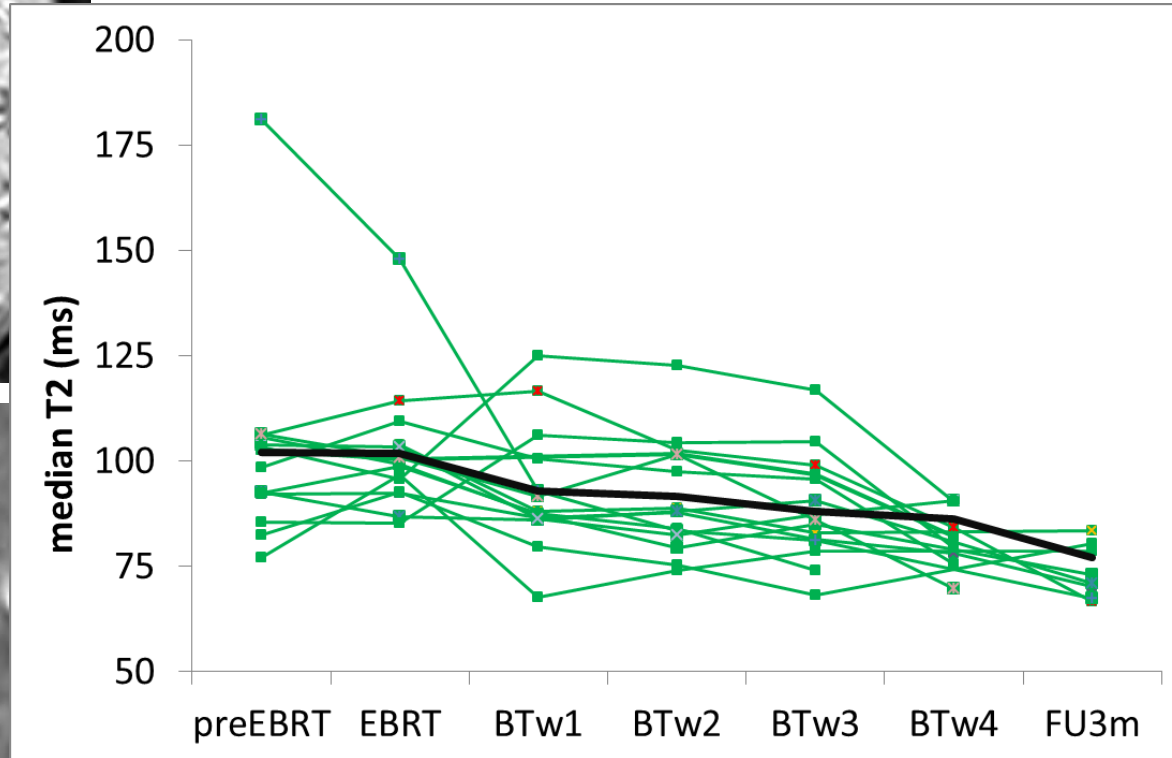
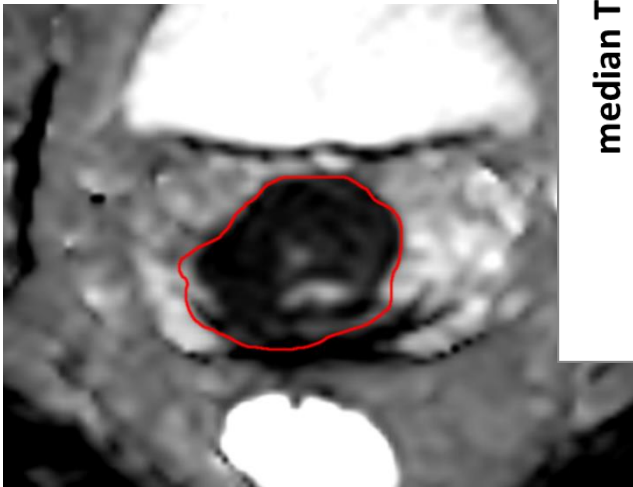
# POTENTIAL FOR T2 MAPPING? PILOT STUDY

Pre-treatment

T2w

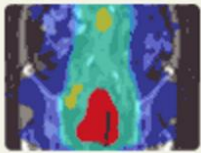


T2 map



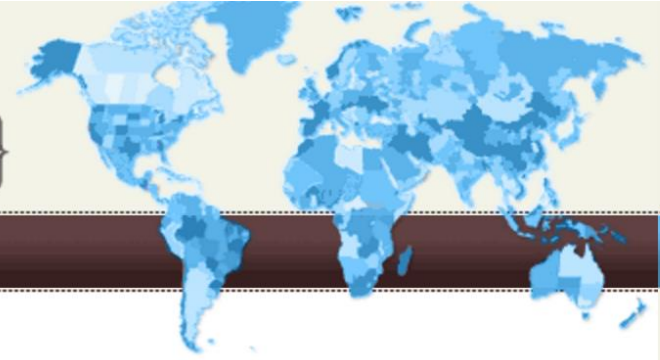
Courtesy of Sanne Wiegers





# EMBRACE-II

{ Image guided intensity modulated External beam radiotherapy and MRI based adaptive BRAchytherapy in locally advanced CErvical cancer }



[About Embrace](#) | [Contacts](#) | [Participation](#) | [Data entry](#) | [Tools](#) | [Members info](#) | [Admin](#) | [Logout](#)

## IQ-EMBRACE TRIAL

- Sub-study of EMBRACE-II
- Quantitative MRI to predict local recurrence after radio-chemotherapy of cervix cancer
- All institutes participating in EMBRACE-II who have possibility to perform additional pre-treatment MRI are eligible to participate

	standard	quantitative	
T2w			T2
DWI			ADC
DCE			$K^{trans}$

## PARTICIPATING INSTITUTES

Code	Institute	Country	Field Strength	Vendor
A	Aarhus	Denmark	1.5T	Philips Ingenia
B	AMC, Amsterdam	Netherlands	3T	Philips Ingenia
C	CHUM, Montreal	Canada	1.5T	Siemens Magnetom
D	UMC Ljubljana	Slovenia	1.5T	GE Optima
E	Leiden	Netherlands	3T	Philips Ingenia
F	Milan	Italy	1.5T	Philips Achieva
G	McGill	Canada	3T	Philips Ingenia
H	Mumbai	India		
I	NKI, Amsterdam	Netherlands	3T	Philips Ingenia
J	Oslo	Norway	3T	Siemens Skyra
K	Vienna	Austria	3T	Siemens Magnetom
L	Utrecht	Netherlands	1.5T	Philips Ingenia

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# HOW TO ACHIEVE MULTI-CENTER CONSISTENCY?

1. Develop consensus MRI protocols
  - How to deal with variations in equipment?
  - How to avoid that the oldest equipment sets the standard?
2. Optimize MRI protocols for each scanner separately, using the newest available technology
  - Accept variations in accuracy and precision

---

# QUALITY ASSURANCE PROCEDURE

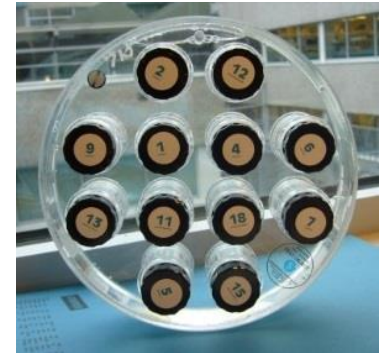
Before start of patient inclusion

1. Quantitative assessment of sequences

- Accuracy
- Precision



Phantoms

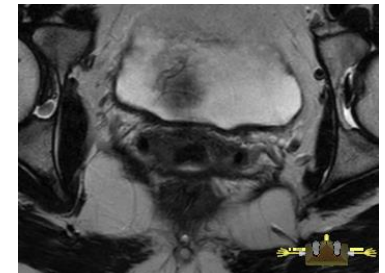


2. Qualitative assessment of sequences

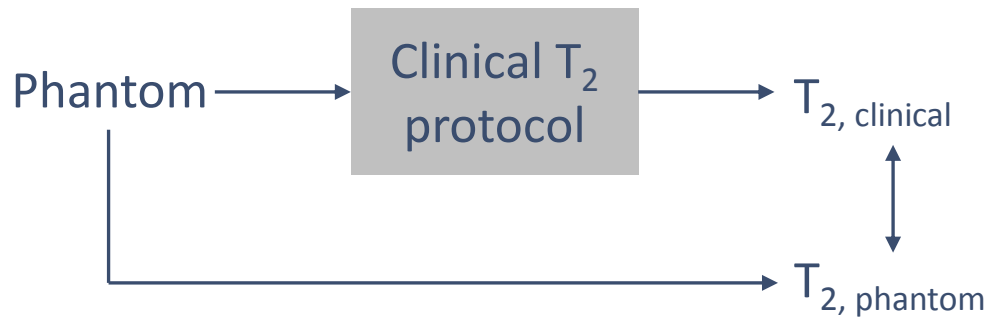
- SNR
- Check for image artifacts



Volunteers



# PHANTOM MEASUREMENTS



Large differences due to:

- Variations in protocol settings?
- System differences?



Equal on all systems

Long, slow sequences which are “gold standards”

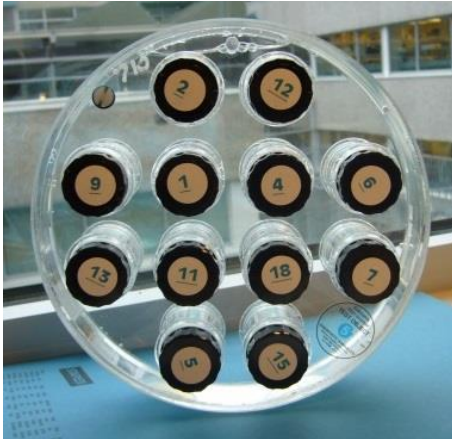
No fancy acceleration

**Not practical for clinical use**

# PHANTOMS

## T1/T2 mapping

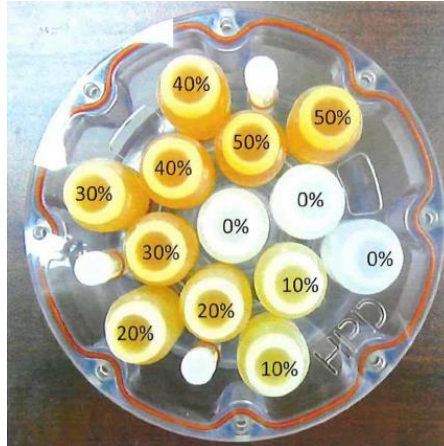
### Eurospin Phantom



T2 values: 49 – 212 ms (296 K)  
T1 values: 331 – 1615 ms (296 K)

## ADC mapping

### QIBA diffusion Phantom



## DCE-MRI

### Concentration series



Quantitative  
Imaging  
Biomarkers  
Alliance



## PROGRESS MEASUREMENTS

Code	Institute	Country	Field Strength	Vendor
A	Aarhus	Denmark	1.5T	Philips Ingenia
B	AMC, Amsterdam	Netherlands	3T	Philips Ingenia
C	CHUM, Montreal	Canada	1.5T	Siemens Magnetom
D	UMC Ljubljana	Slovenia	1.5T	GE Optima
E	Leiden	Netherlands	3T	Philips Ingenia
F	Milan	Italy	1.5T	Philips Achieva
G	McGill	Canada	3T	Philips Ingenia
H	Mumbai	India		
I	NKI, Amsterdam	Netherlands	3T	Philips Ingenia
J	Oslo	Norway	3T	Siemens Skyra
K	Vienna	Austria	3T	Siemens Magnetom
L	Utrecht	Netherlands	1.5T	Philips Ingenia



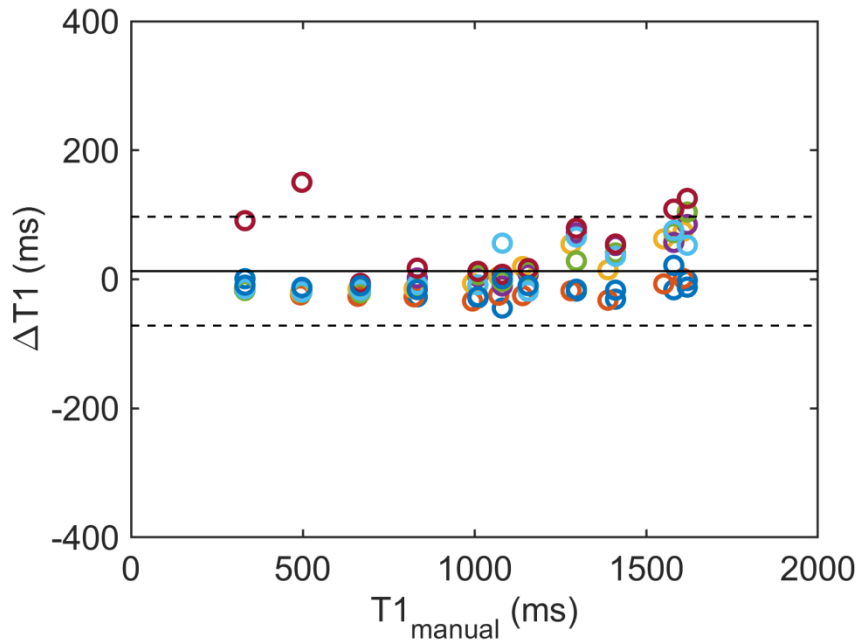
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# EVALUATION DCE

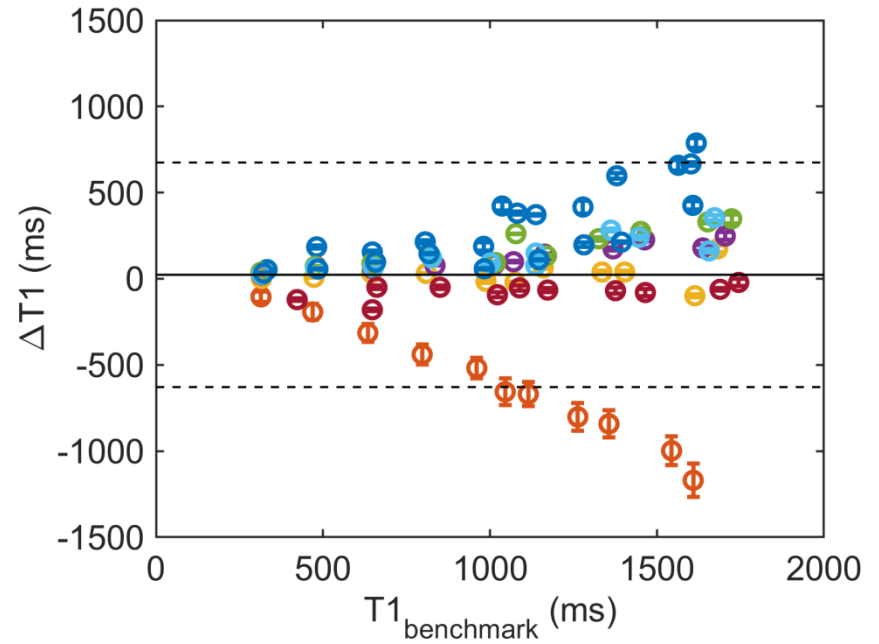
- Direct evaluation of quantitative DCE parameters (e.g.  $K^{\text{trans}}$ ) not possible
- Follow guidelines QIBA DCE-MRI profile
- Evaluate individual steps of procedure:
  1. Baseline T1 mapping
  2. Signal stability for course of measurement
  3. Signal linearity

# BASELINE T1 MAPPING

## Benchmark vs. reference values

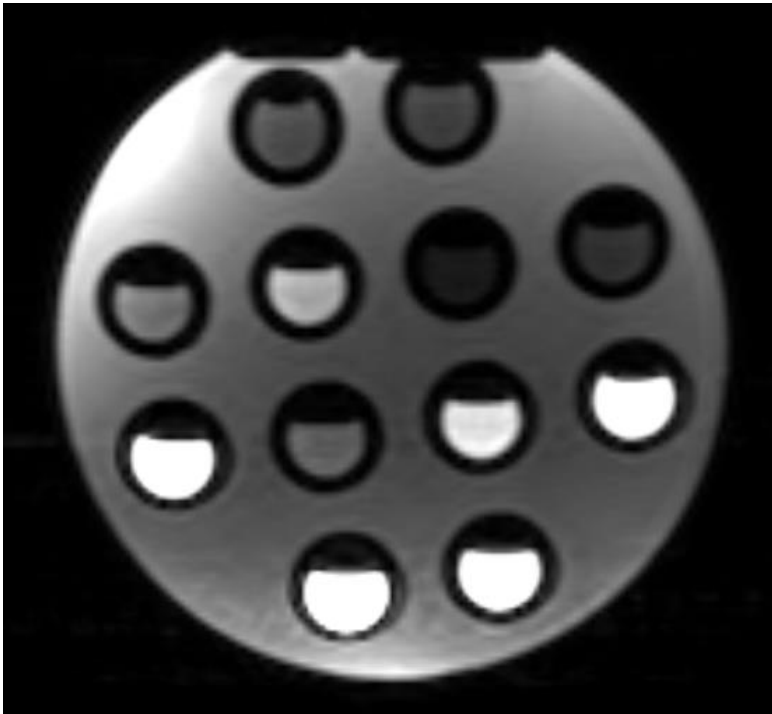


## Clinical vs. Benchmark

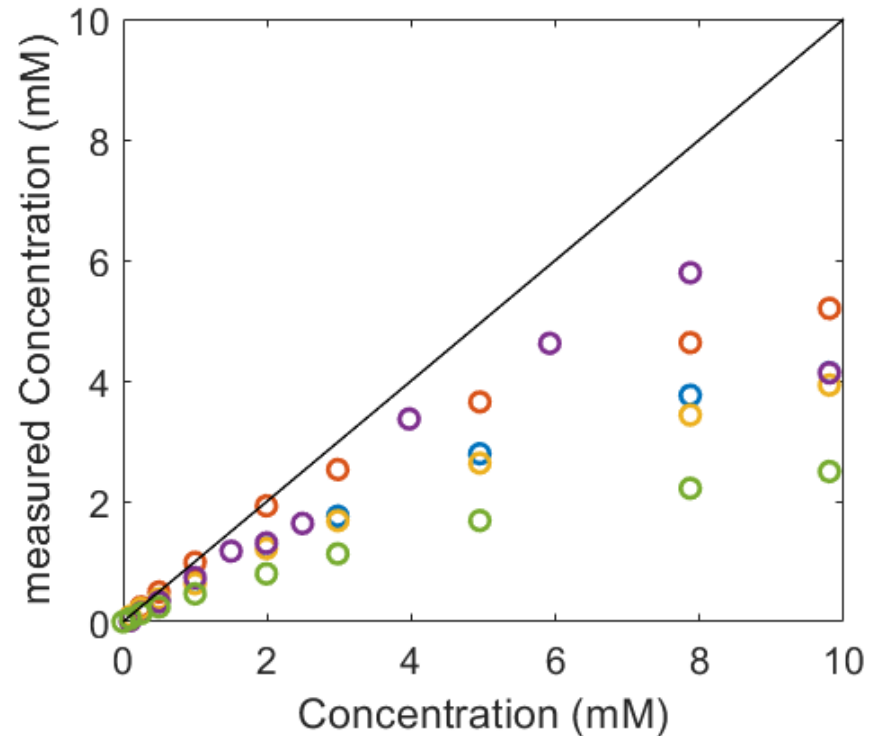


Benchmark = Inversion recovery sequence  
Clinical = variable flip angle series

# SIGNAL LINEARITY



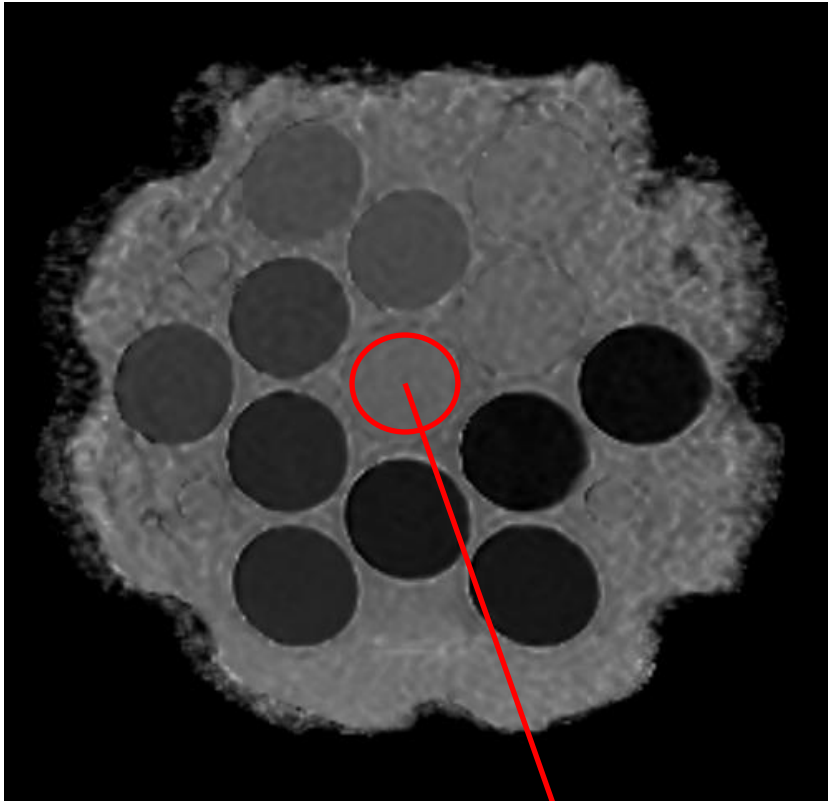
Tubes with different concentrations of gadolinium (0 – 10 mM)



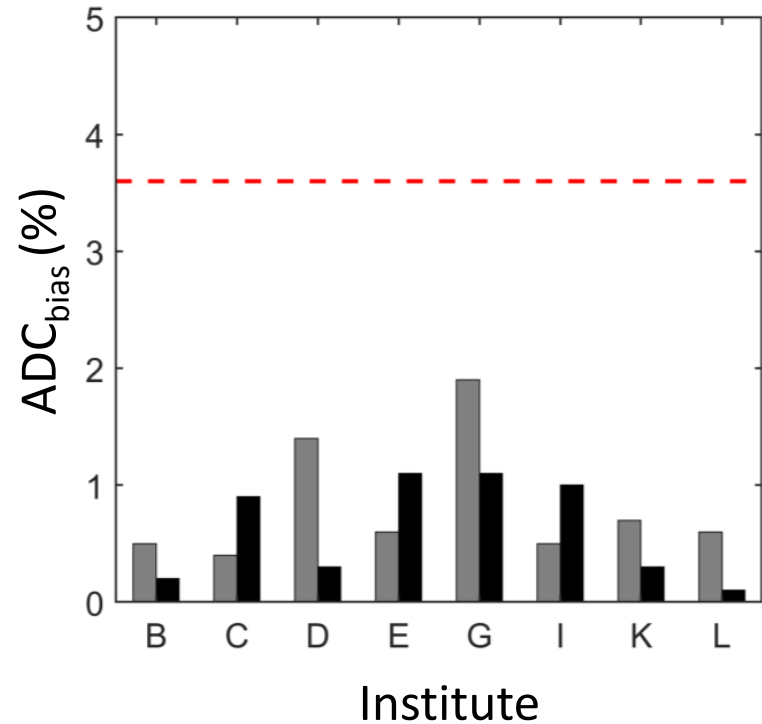
Cervical tissue ~ 1 mM

Arterial input function ~ 8 mM

# PRELIMINARY RESULTS DWI



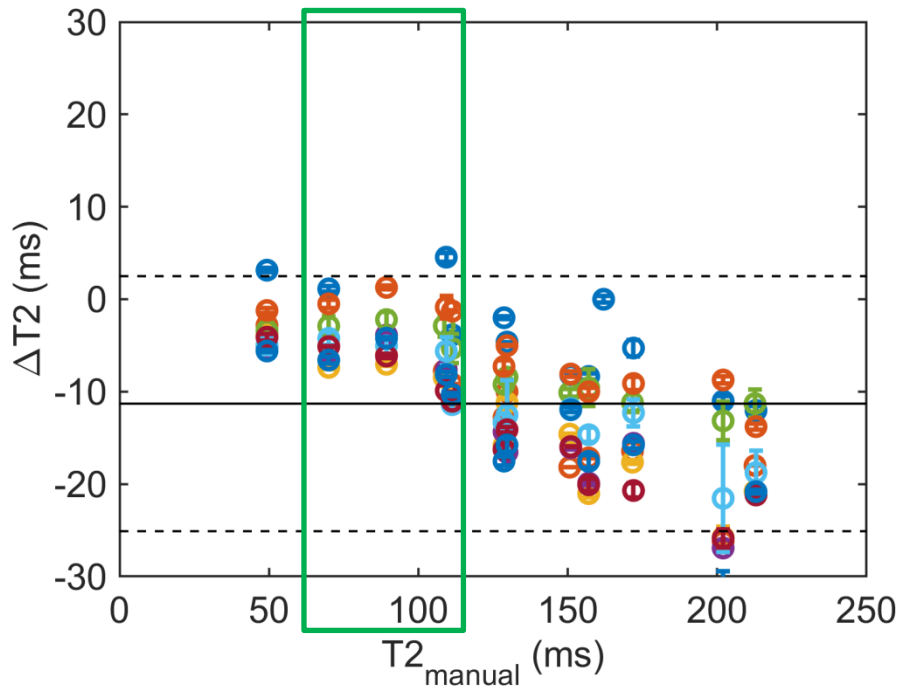
True ADC value =  $1.109 \cdot 10^{-3} \text{ mm}^2/\text{s}$



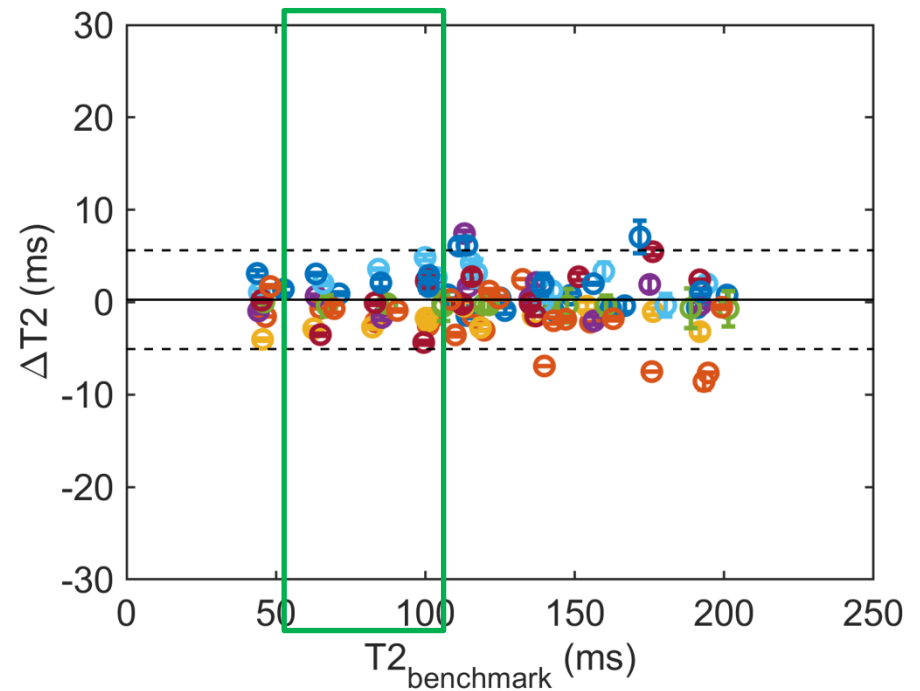
Benchmark  
Clinical  
QIBA requirements

# PRELIMINARY RESULTS T2 MAPPING

## Benchmark vs. reference values



## Clinical vs. Benchmark



T2 values in cervix tumors  $\sim 75 - 100$  ms

Benchmark = CPMG sequence  
Clinical = multi-echo spin echo sequence

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# CONCLUSIONS

- IQ-EMBRACE is a trial that prospectively collects quantitative MRI for imaging biomarker discovery in patients with cervical cancer
- With the phantom measurements we evaluate the performance of quantitative MRI sequences across institutes and correct sequences if necessary

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## NEXT STEPS

- Finish analysis of all data
- Finalize patient MRI protocols per institute
- Scan volunteer with final protocol
- Evaluate first patient data
- Monitor data quality



---

# ADVANCED IMAGE ANALYSIS WORKSHOP

Idea: workshop for participating centers about quantitative image analysis

- ADC mapping of DWI data
- Pharmacokinetic analysis of DCE-MRI
- Next EMBRACE meeting

## Requirements

- Some patient data is available
- Interest from institutes

---

# ACKNOWLEDGEMENTS

## **Radiotherapy Department**

Uulke van der Heide  
Cherita Sombroek  
Monique Bloemers

## **Aarhus University Hospital**

Kari Tanderup  
Jesper Kallehauge

## **Leiden University Medical Center**

Remi Nout  
Jordi Vonk-van Oosten  
Marieke Stammes

## **Amsterdam Medical Center**

Zdenko van Kesteren  
Henrike Westerveld

## **University Medical Center Utrecht**

Nico van den Berg  
Ina Jürgenliemk-Schultz

## **UMC Ljubljana**

Robert Hudej  
Barbara Segedin

## **AKH Vienna**

Dietmar Georg  
Michaela Daniel  
Pascal Baltzer

## **Oslo University Hospital**

Eirik Malinen  
Heidi Lyng  
Djordje Kovacevik

## **CHUM Montreal**

Cynthia Ménard  
Jean-Charles Coté

## **McGill Montreal**

Ives Levesque

## **Tata Memorial Hospital**

Supriya Chopra

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# BENCHMARK SEQUENCES

- T2 mapping
  - Multi-echo spin echo
  - No acceleration
  - TR = 2000 ms
  - Max TE = 200 ms; dTE and no. Echoes based on max TE
  - Single slice: 250x250 mm<sup>2</sup>, voxel size 2 x 2 x 4 mm<sup>3</sup>
- T1 mapping
  - Inversion recovery series
  - No acceleration
  - TR = 8000 ms
  - IR delays: 30, 50, 75, 100, 150, 200, 250, 300, 400, 500, 750, 1000, 1250, 1500, 2000, 4000 ms
  - Single slice, 2 x 2 x 4 mm<sup>3</sup>, 250 x 250 mm<sup>2</sup>
- DWI
  - QIBA EPI sequence
  - 4 b-values: 0, 500, 900, 200
  - TR = 10s; TE = 101 ms
  - Slice thickness 4 mm, 25 slices

---

# IDEAL CLINICAL PROTOCOL

Consists of:

- Anatomical sequences preferred by institute
- T2 mapping sequence
- B0 map
- DWI sequence
- B1 map (only for 3T)
- T1 mapping sequence
- DCE sequence

---

# ACCEPTABLE COMPROMISES

- Alternative for T2 mapping: separate T2-weighted images with different TE (e.g. Ljubljana)
- B1 mapping: separate scans from which a B1 map can be created with postprocessing (e.g. McGill)
- E.g. when not possible to save phase data for DCE-MRI

