e-session 573

The role of image-guided radiotherapy in cancer care

Expert: **Prof Daniel Zips**, University Hospital and Medical Faculty, Tübingen, Germany

Discussant: **Prof Pierfrancesco Franco**, University of Eastern Piedmont, Novara, Italy

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Department for Radiation Oncology

The role of image-guided radiotherapy in cancer care

European School of Oncology

Daniel Zips

17.5.2021

EBERHARD KARLS UNIVERSITÄT TÜBINGEN
Universitätsklinikum Tübingen

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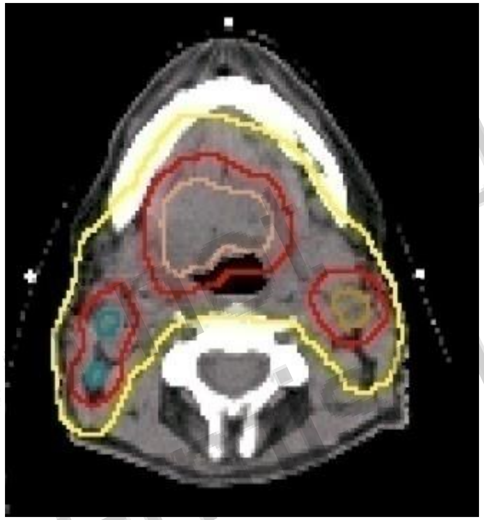
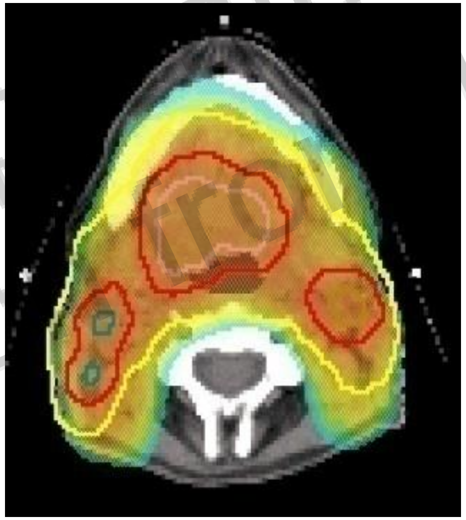
- PTW Freiburg
- Dr. Sennewald
- Siemens

Overview: IGRT today

- image guided in all steps
- precise, effective and tolerable
- Image-based approach towards personalized radiation oncology



Target Volumes



Dose Distribution

IGRT review free full text Mol Oncol 2020, 14:1470

Molecular Oncology

FEBS PRESS

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REVIEW

Image guidance in radiation therapy for better cure of cancer

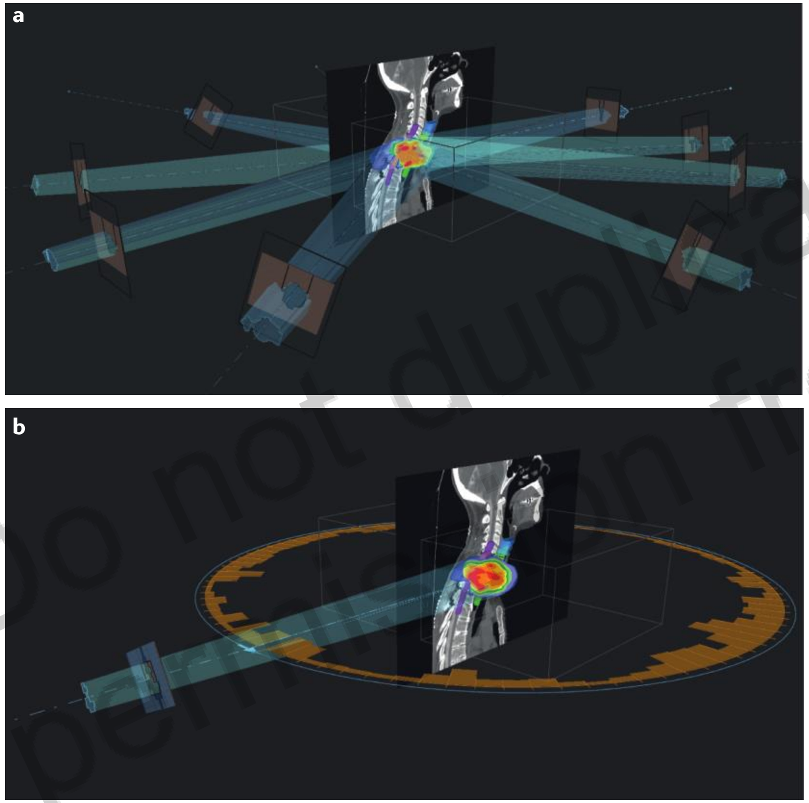
Vincent Grégoire[1], Matthias Guckenberger[2], Karin Haustermans[3], Jan J. W. Lagendijk[4], Cynthia Ménard[5], Richard Pötter[6], Ben J. Slotman[7], Kari Tanderup[8], Daniela Thorwarth[9], Marcel van Herk[10,11,12] and Daniel Zips[13]

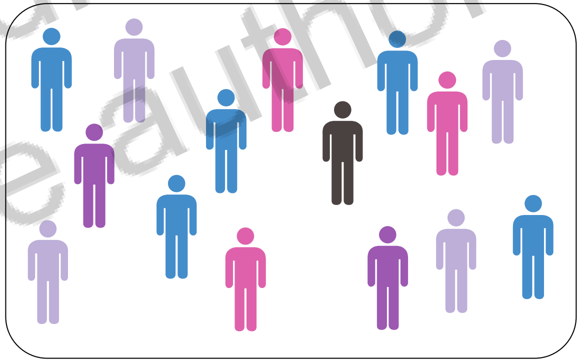
Imaging is the basis for precision radiation oncology

Radiation oncology in the era of precision medicine

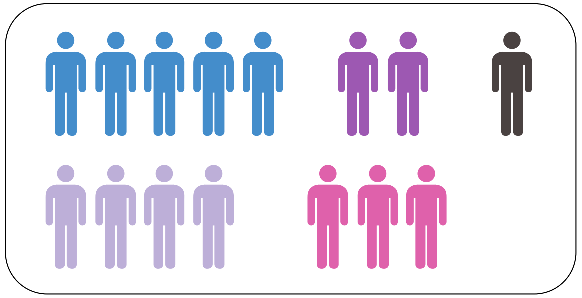
Michael Baumann[1–6], Mechthild Krause[1–6], Jens Overgaard[7], Jürgen Debus[5,8–11], Søren M. Bentzen[12], Juliane Daartz[13], Christian Richter[1–5], Daniel Zips[5,14,15] and Thomas Bortfeld[13]

NATURE REVIEWS | CANCER VOLUME 16 | APRIL 2016 | 235



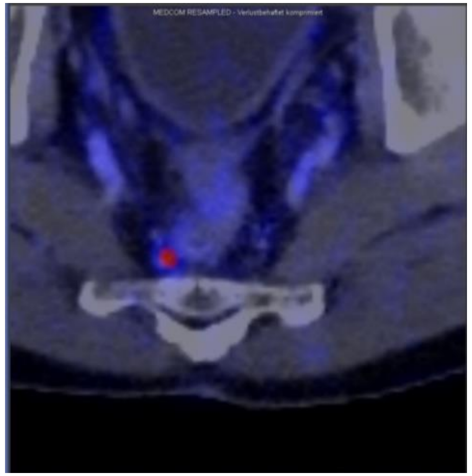


- Patients with the same tumour disease and stage have typically received similar treatments
- Large clinical trials possible

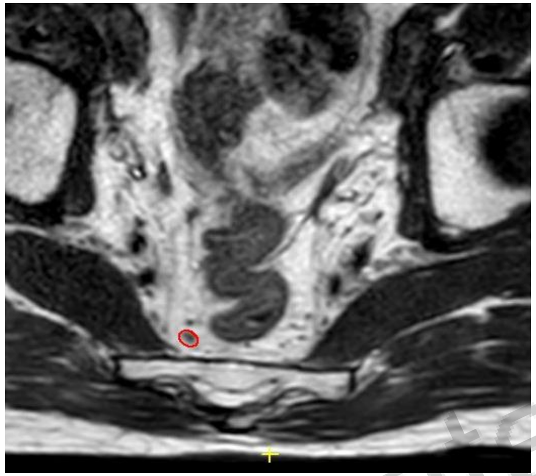


- Biomarkers allow stratification into small subgroups
- Trials for treatment individualization

Anatomical imaging: towards online adaptive RT

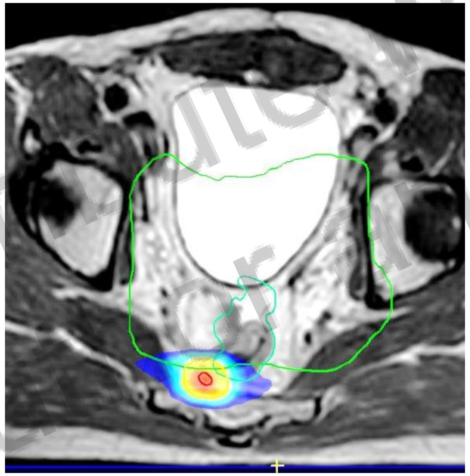


PSMA PET CT



MRI at 1.5 T MRL

CBCT

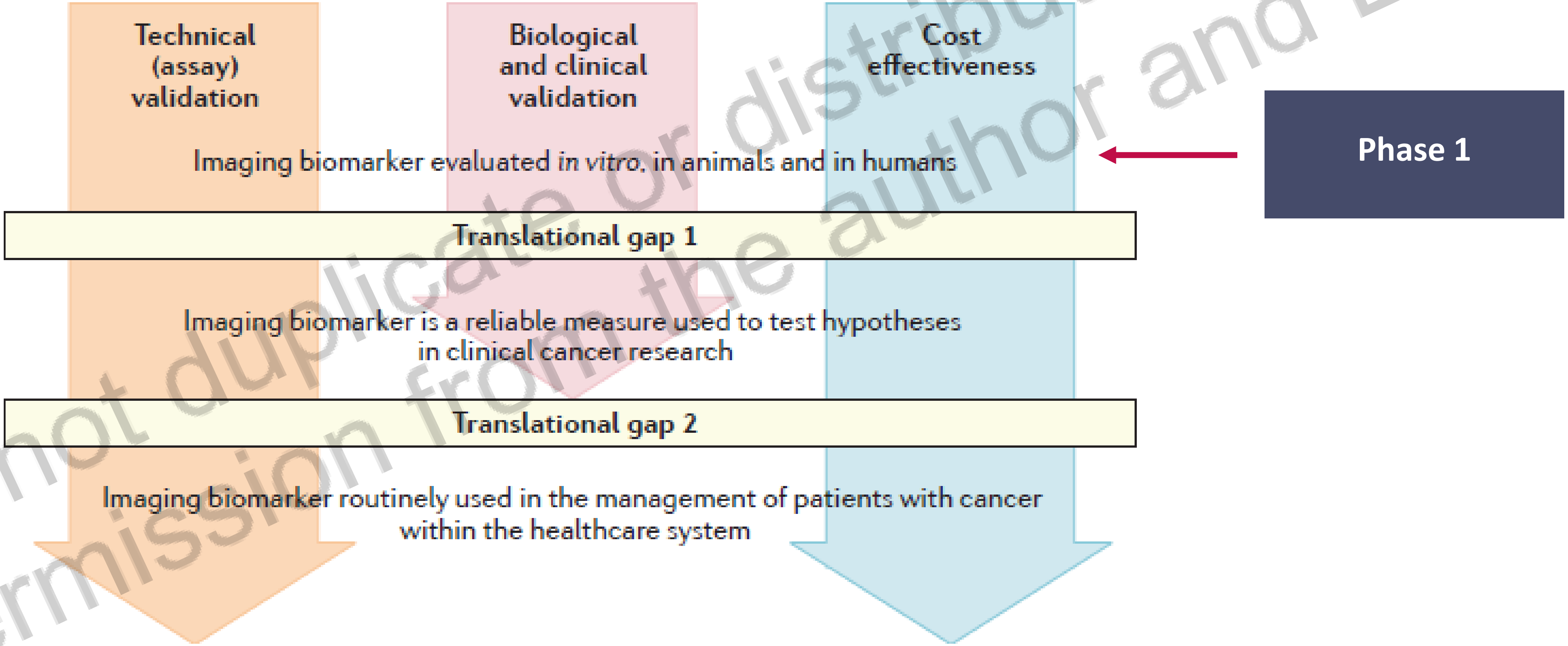


s&s IMRT (8 Beams, min. segment size: 3 cm^2, min. MU/ segment: 10)

motion monitoring

Imaging Biomarker Roadmap for Cancer Studies

O'Connor JPB, et al. Nat Rev Clin Oncol 2017; 14(3): 169-86.



Functional imaging may allow to discriminate risk groups

PET

- **^{18}F-FDG** metabolism
- **^{18}F-FMISO/FAZA** hypoxia
- **^{18}F-FLT** proliferation
- …

MRI

- **DCE** perfusion
- **DWI** cellularity
- **T1-/T2-mapping** relaxometry
- **ASL** perfusion
- …

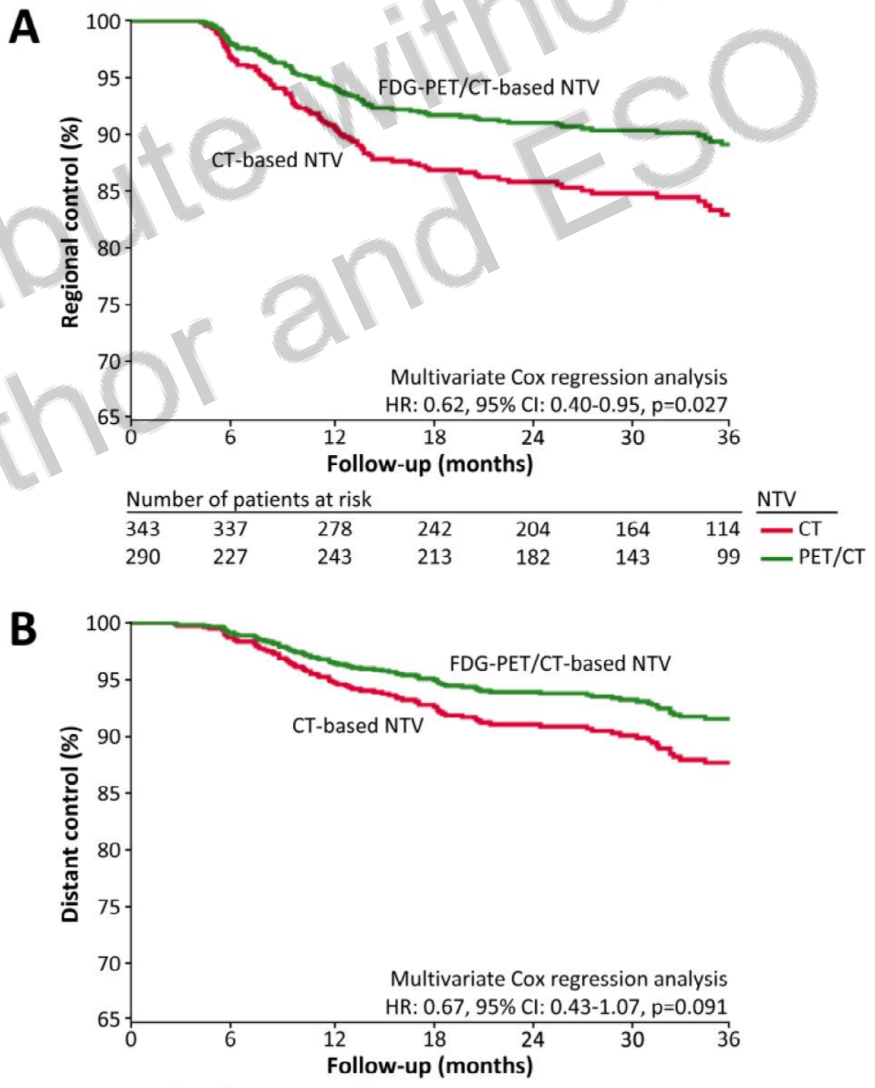
CT

- **DCE** perfusion
- **Radiomics** Tissue characteristics

FDG PET/CT based RT planning improves local control in HNC

Van den Bosch S, et al. Radiother Oncol 2020; 142: 107-14.

- FDG PET/CT based nodal target volume (NTV) definition vs. conventional CT based
- N=633 head-and-neck cancer (HNC) patients
- 46% with PET/CT based NTV definition
- PET based NTV definition improved local control (HR: 0.33, p=0.026)
- High potential von FDG PET based NTV definition for personalized target delineation/ dose prescription concepts in HNC RT

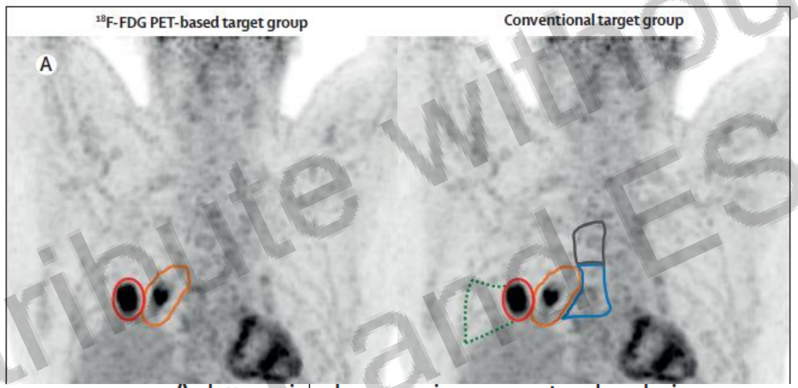


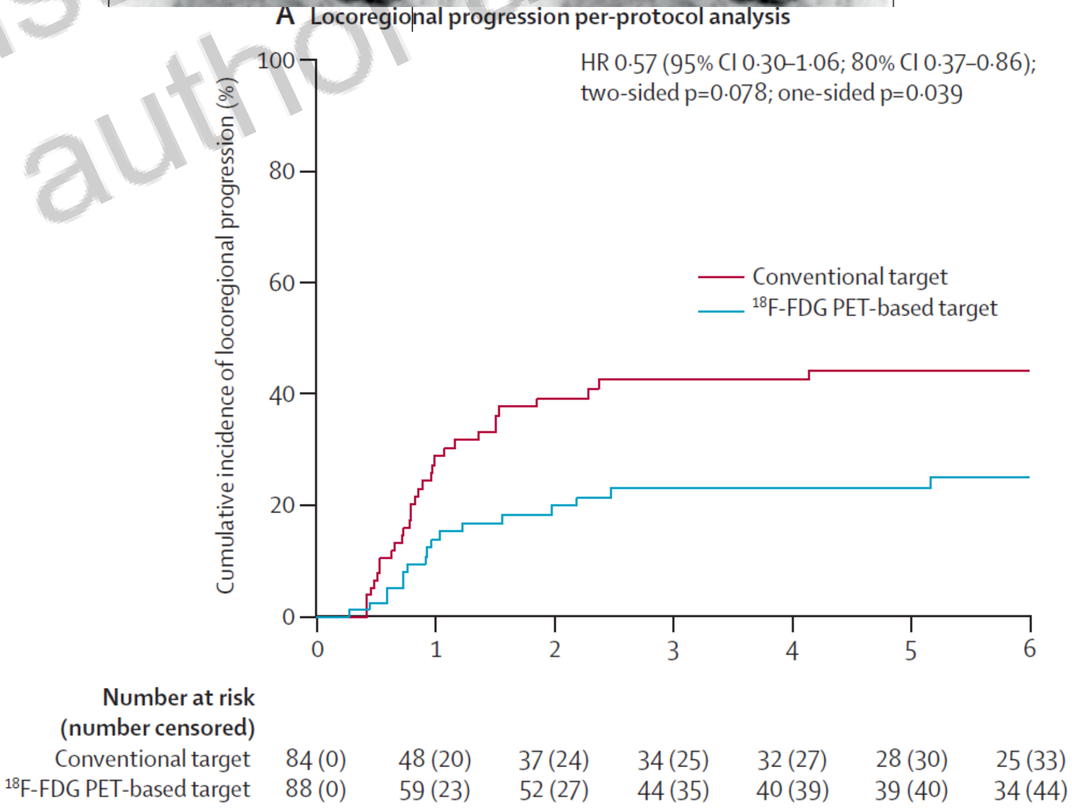
FDG PET based target volume delineation allows personalized RT dose escalation

Nestle U, et al. Lancet Oncol 2020; 21(4): 581-92.

Randomized PET-Plan study:

- FDG PET only based target vs. PET plus CT-based target and elective node delineation
- N=205 non-small cell lung cancer (NSCLC) patients
- Dose escalation (60 – 74 Gy) in 2 Gy fx
- Primary endpoint: Time to local progression (non-inferiority)
- Risk of locoregional progression 14% vs. 29% at 1 year, HR 0.57

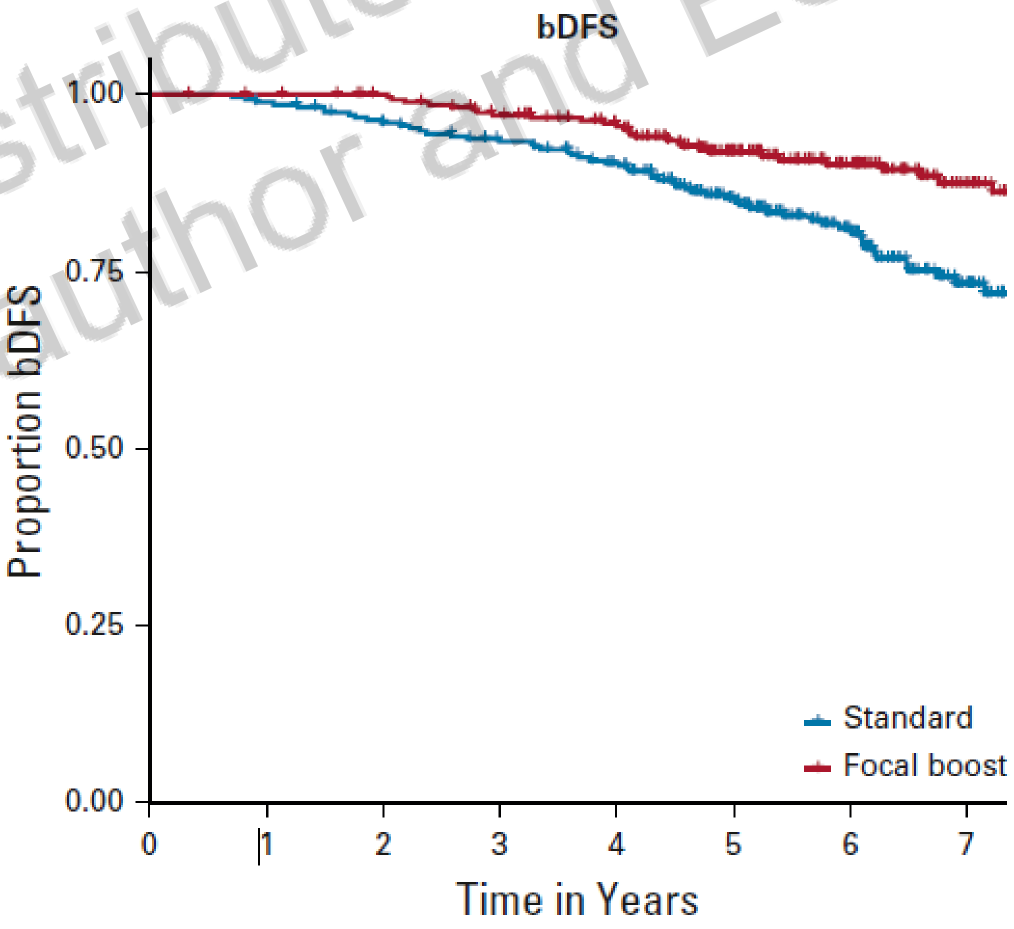




Focal MRI-guided RT dose escalation in prostate cancer: The FLAME trial

Kerkmeijer LGW, et al. J Clin Oncol 2021; 39: 787-96.

- N=571 intermediate- and high-risk prostate cancer patients
- Standard treatment: 77 Gy (2.2 Gy/ fx)
- Focal boost: up to 95 Gy to the intraprostatic lesion defined on multi-parametric MRI.
- Significantly higher biochemical disease-free survival (bDFS) in focal boost arm ($p<0.001$)
- 5-year bDFS: 92% vs. 85%

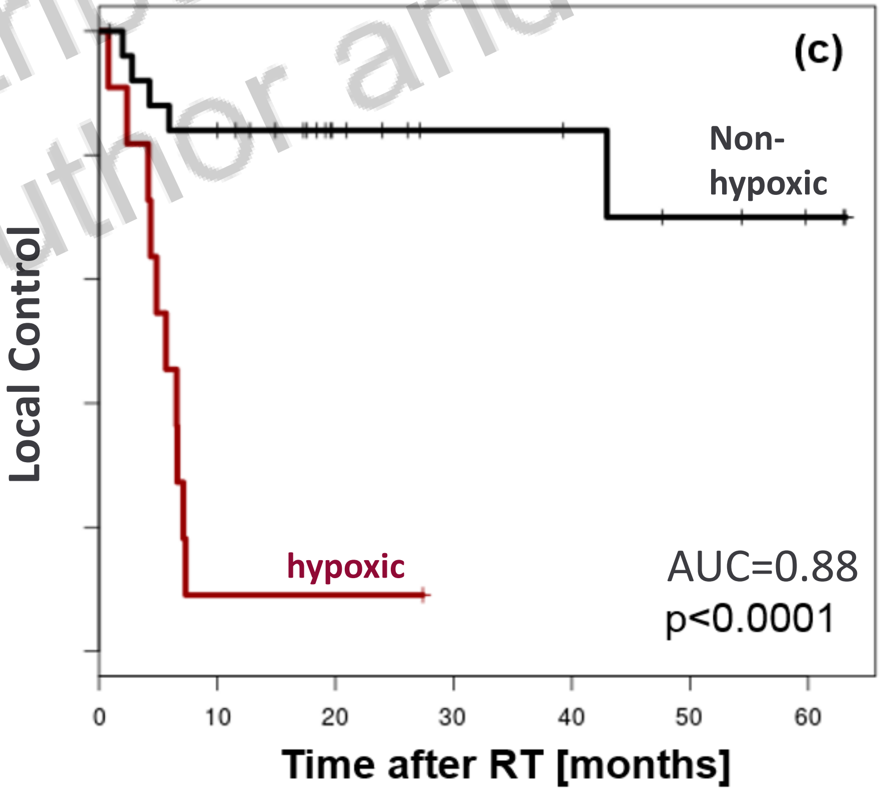


Hypoxia PET has prognostic value in HNC

Thorwarth D, et al. J Nucl Med 2019; 60(12): 1698-1704.

- Dynamic FMISO PET/CT (0 – 4 h pi)
- 2-parameter signature of dyn. FMISO analysis is prognostic for local control (LC) after HNC RT
- Independent validation in n=33 patients
- Potential basis for RT personalization!

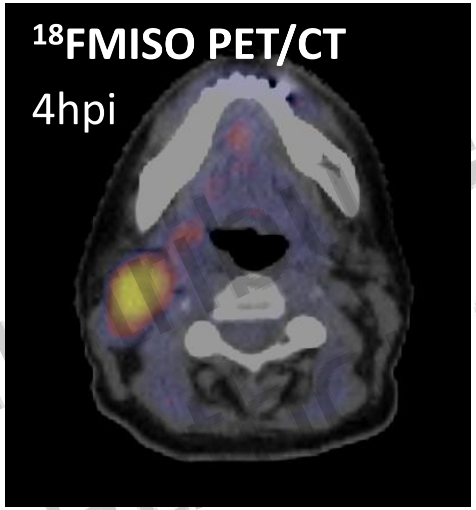
- FMISO is a non-standard PET tracer, low SNR
- Complex image acquisition and analysis protocol

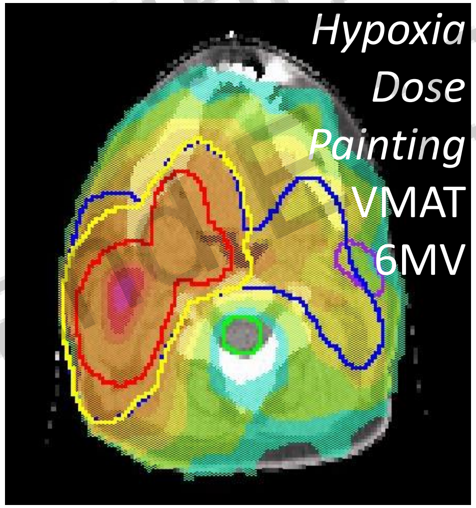


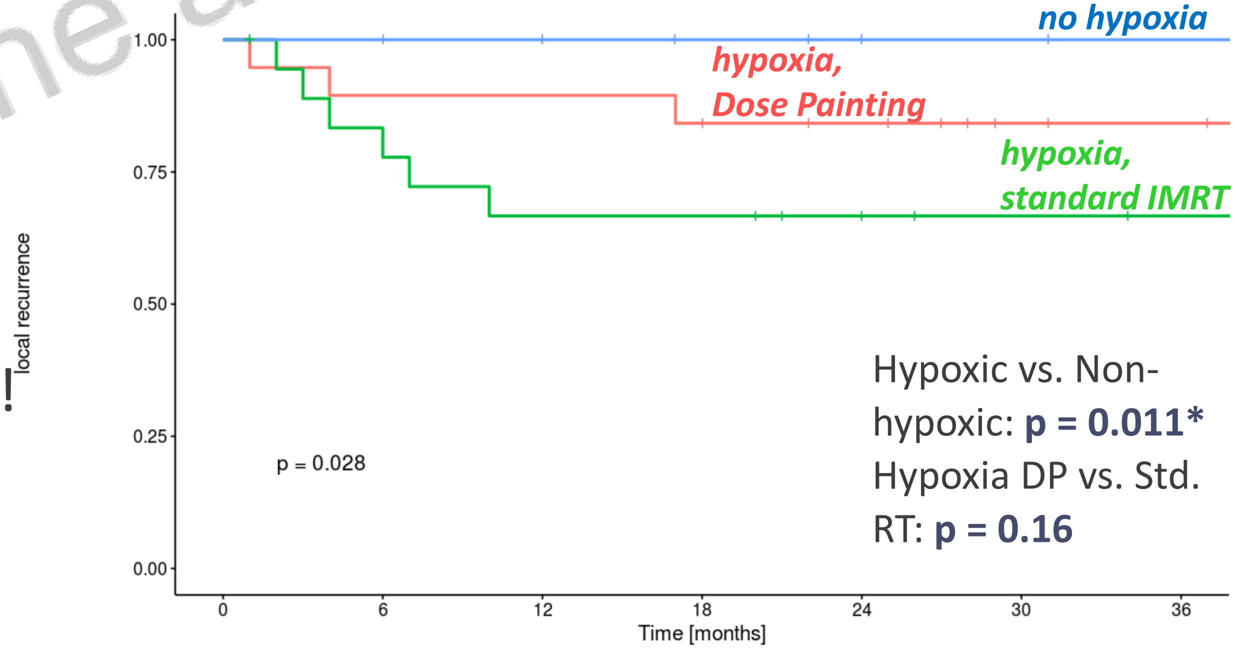
Hypoxia Dose Painting – a single-center randomized trial

Welz S, Thorwarth D, et al. 2021 (in preparation).

- Randomized phase II trial (NCT 02352792)
- N=54 HNC patients
- Hypoxic patients randomized into dose escalation (77Gy) vs. standard RT (70 Gy)
- Slow accrual (12/09 – 03/17)
- Complex moelcular imaging and logistics
- Premature closing
- Hypoxia dose painting is clinically feasible!
- Non-significant improvement of LC



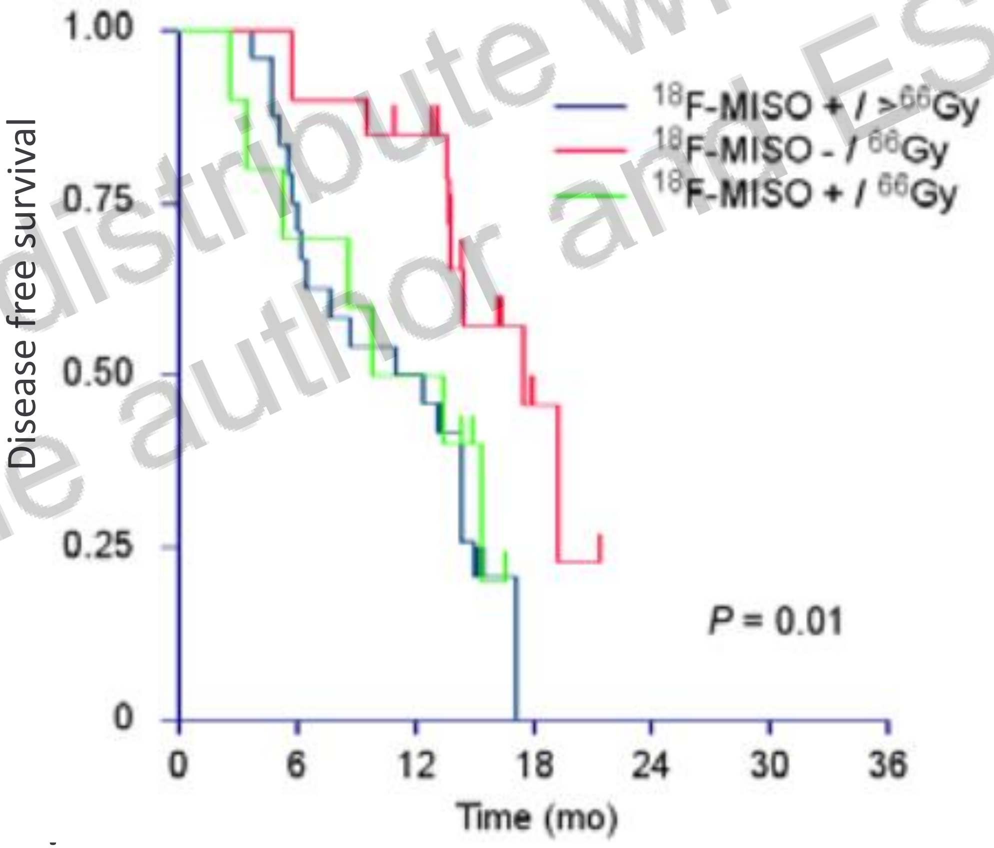




Dose escalation based on FMISO PET in NSCLC

Vera P, et al. J Nucl Med 2017; 58: 1045-53.

- n=54/79 patients
- FMISO PET
- FMISO- 66Gy
- FMISO+ up to 78 Gy
- Dose escalation to HV
- HV defined by SUV≥1.4



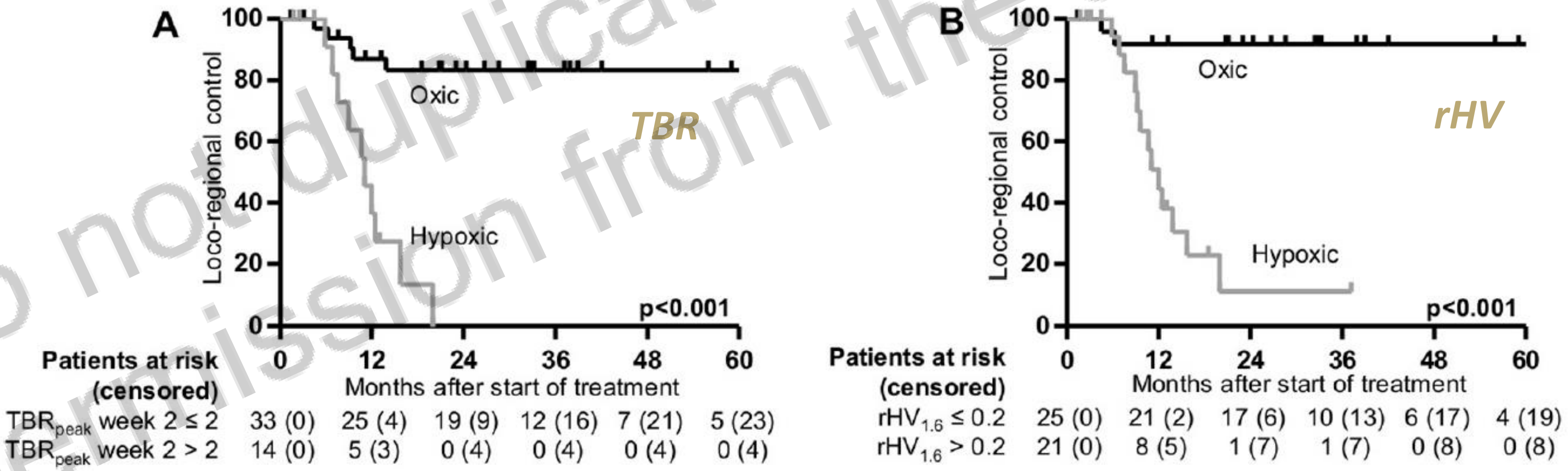
- FMISO strongly associated with poor prognosis
- No effect of DE on LC

Prognostic value of hypoxia PET/CT in HNC before and during RT

Löck S, et al. Radiother Oncol 2017;124:533-40.
Zips D, et al. Radiother Oncol 2012;105:1-8.
Zschaeck S, et al. Radiother Oncol 2020; 149: 189-96.

- Exploration trial (n=25) and validation study (n=25)
- [^{18}F]-FMISO PET/CT before and after 2 weeks of RT
- Assessment of different image parameters

- **Highest prognostic value: FMISO TBR assessed after 2 weeks of RT**
- Or: residual hypoxic volume (rHV)



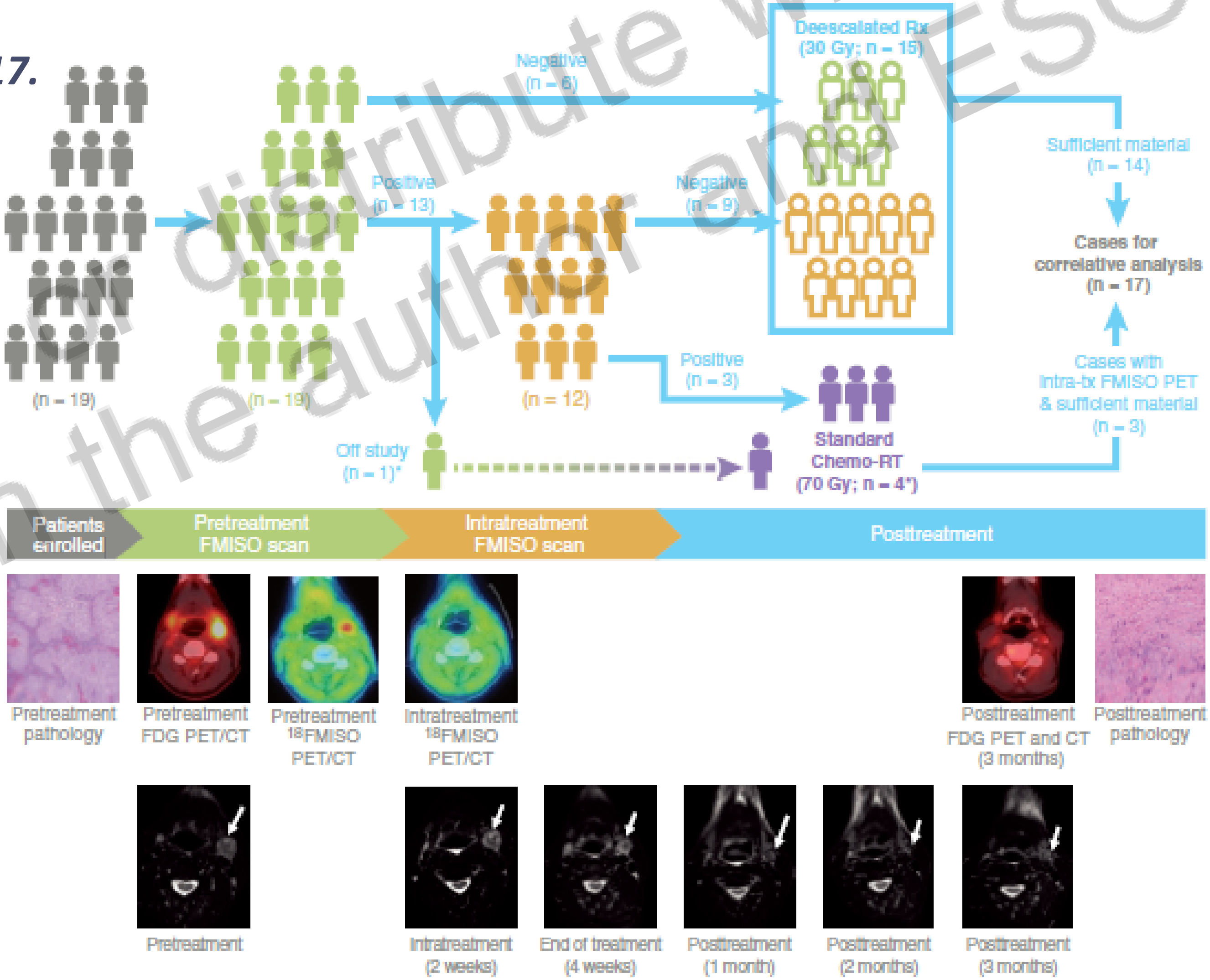
RT personalization through FMISO-based dose de-escalation

Riaz N, et al. J Natl Cancer Inst 2021; epub.
Lee N, et al. Int J Radiat Oncol Biol Phys 2016;96:9-17.

In HPV+ oropharyngeal patients without FMISO detectable hypoxia at baseline or in week 1 of RT (n=15/19):

- Dose de-escalation to 30 Gy to gross nodal desease and post-operative tumor bed

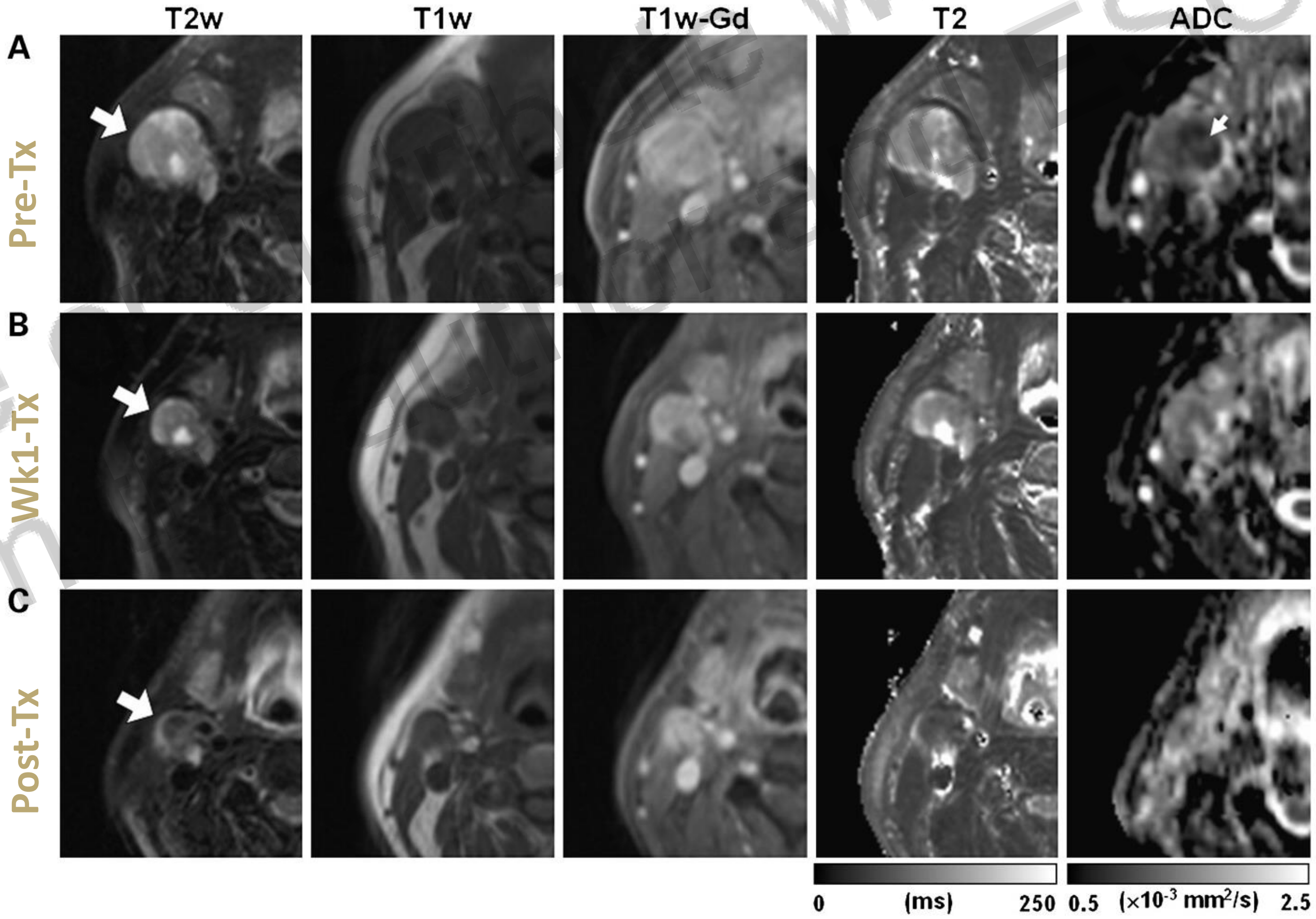
Excellent local control in dose de-escalation group: 94%.



DW-MRI during RT

Kim S, et al. Clin Cancer Res 2009;15:986-94.

- N=40 HNC patients
- DW-MRI before, during and after RT
- Pre-Tx ADC lower in CR compared to PR (p<0.05)
- Significant prognostic value of ADC in week 1 for CR (p<0.01)



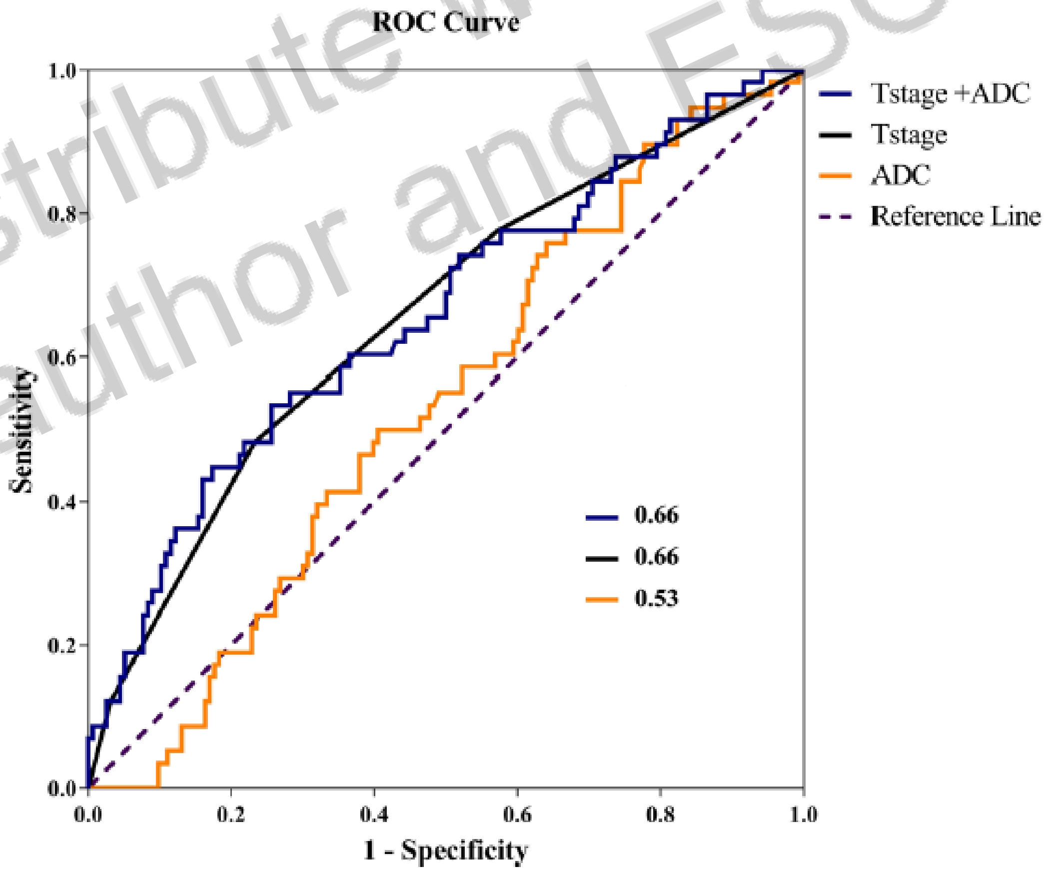
Clinical Cancer Research

AACR American Association for Cancer Research

The prognostic value of ADC in HNC is controversially discussed

Peltenburg B, et al. Eur Radiol 2020; 30:1228-31.

- N=217 HNC patients treated with (chemo-)RT
- Pre-treatement DW-MRI
- Similar median ADC values in patients with and without recurrence
- No significant association between ADC and recurrence (p=0.09)
- T-stage was independent predictor of local recurrence.



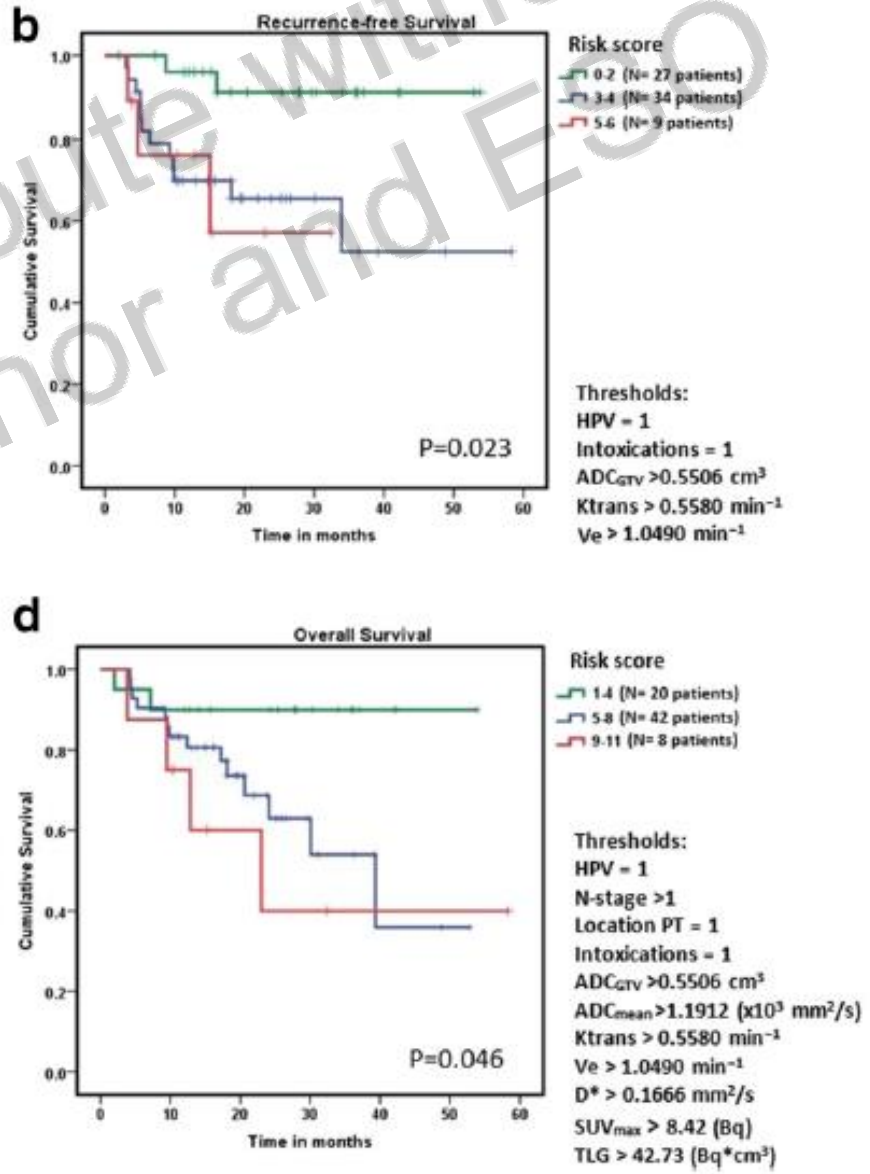
Driessen JP, et al. Eur J Radiol 2019; 111: 62-7.

- Similar diagnostic accuracy of DW-MRI and FDG PET.

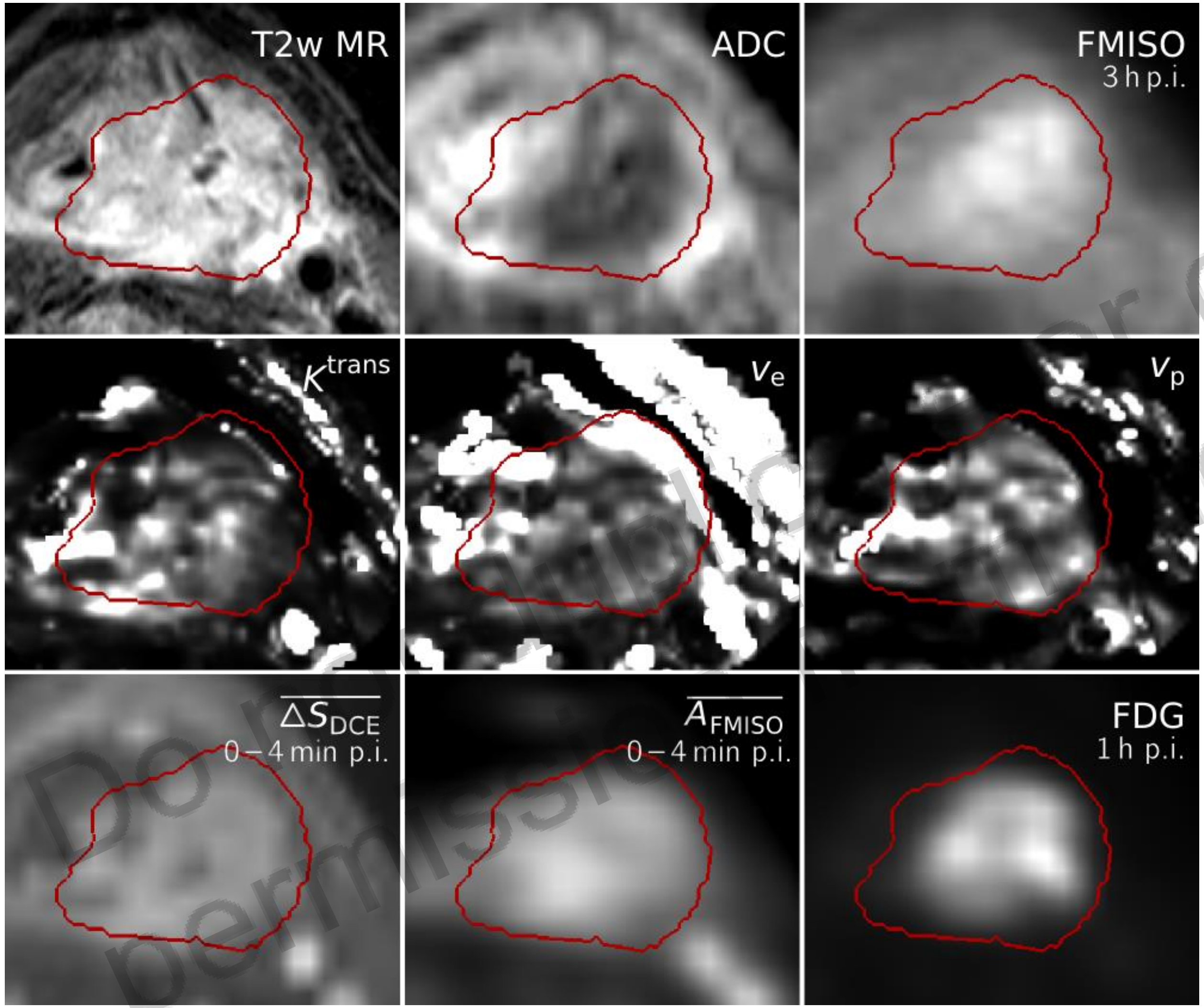
Combination of PET- and MRI-parameters allows patient stratification

Martens RM, et al. Eur Radiol 2021; 31: 616-28.

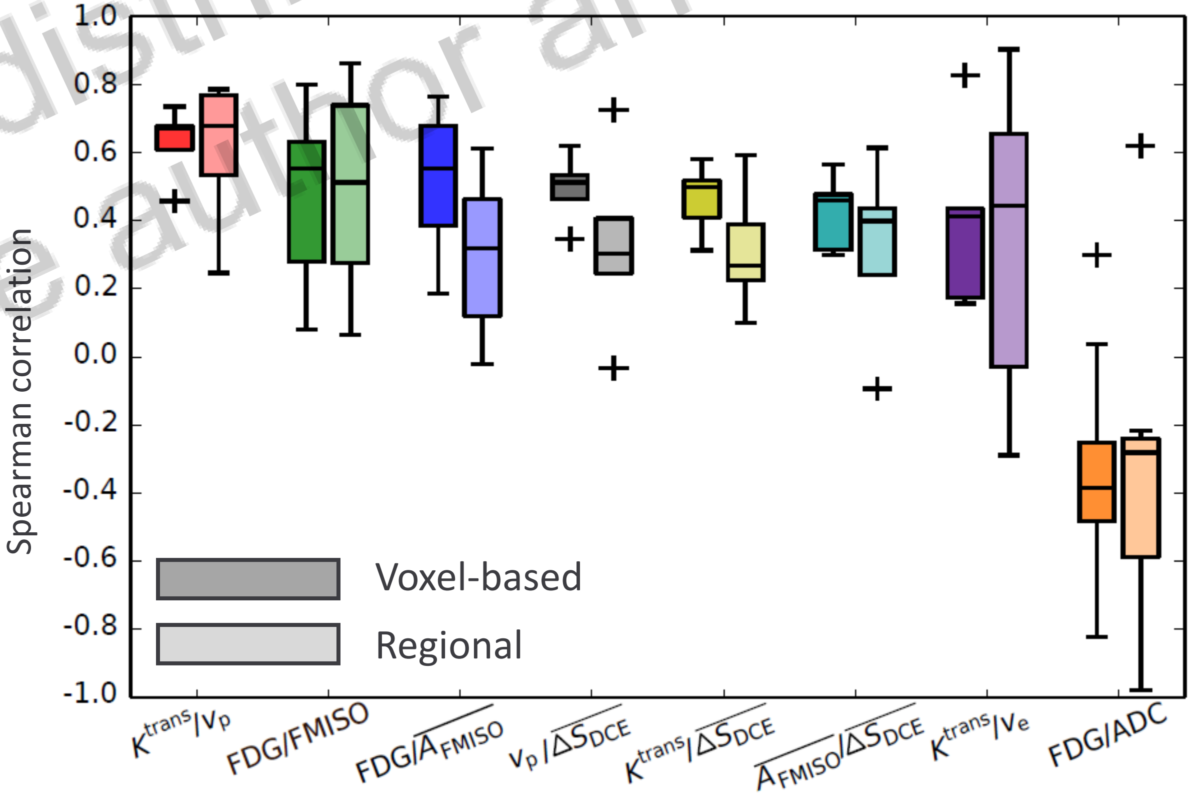
- N=70 HNC patients treated with curative chemo-RT
- Baseline imaging:
  - (IVIM) DW-MRI
  - DCE-MRI
  - FDG PET
- Significant correlation between FDG PET and ADC
- Combination of HPV, intoxications, ADC, K_{trans} and v_e was predictive for locoregional recurrence free survival
- Functional imaging techniques yielded complementary value in capturing tumor characteristics.



Investigation of functional imaging parameters in HNC: FMISO PET/CT, FDG PET/MR, DW-MRT, DCE-MRT



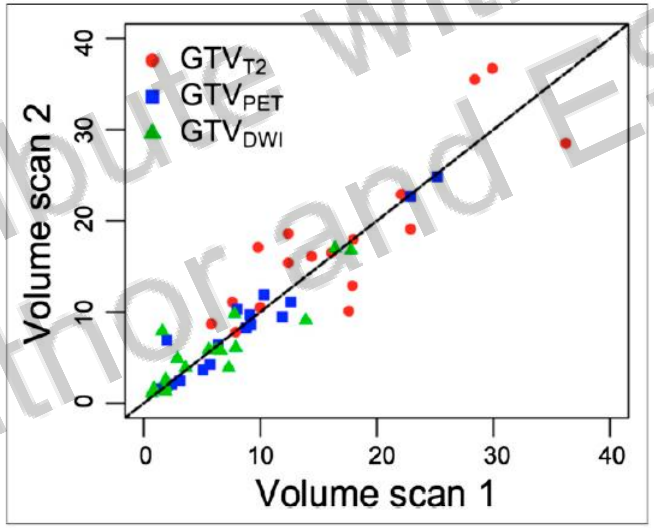
Leibfarth S et al. EJNMMI 2016; 43(7):1199-208.



Multi-parametric imaging using combined PET/MRI

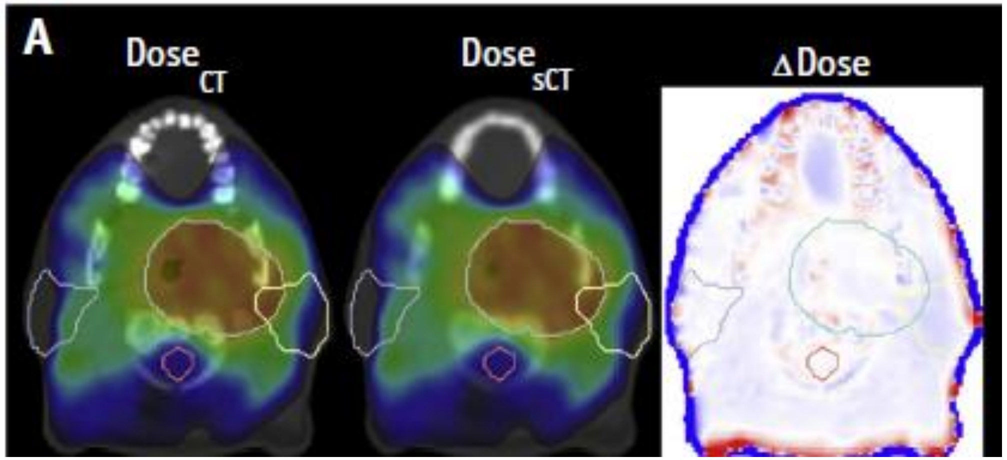
Rasmussen JH, et al. J Nucl Med 2017; 58: 69-74.

- N=21 HNC patients
- Prospective scan-rescan study
- Assessment of overlap between ADC- and FDG-based RT target volumes



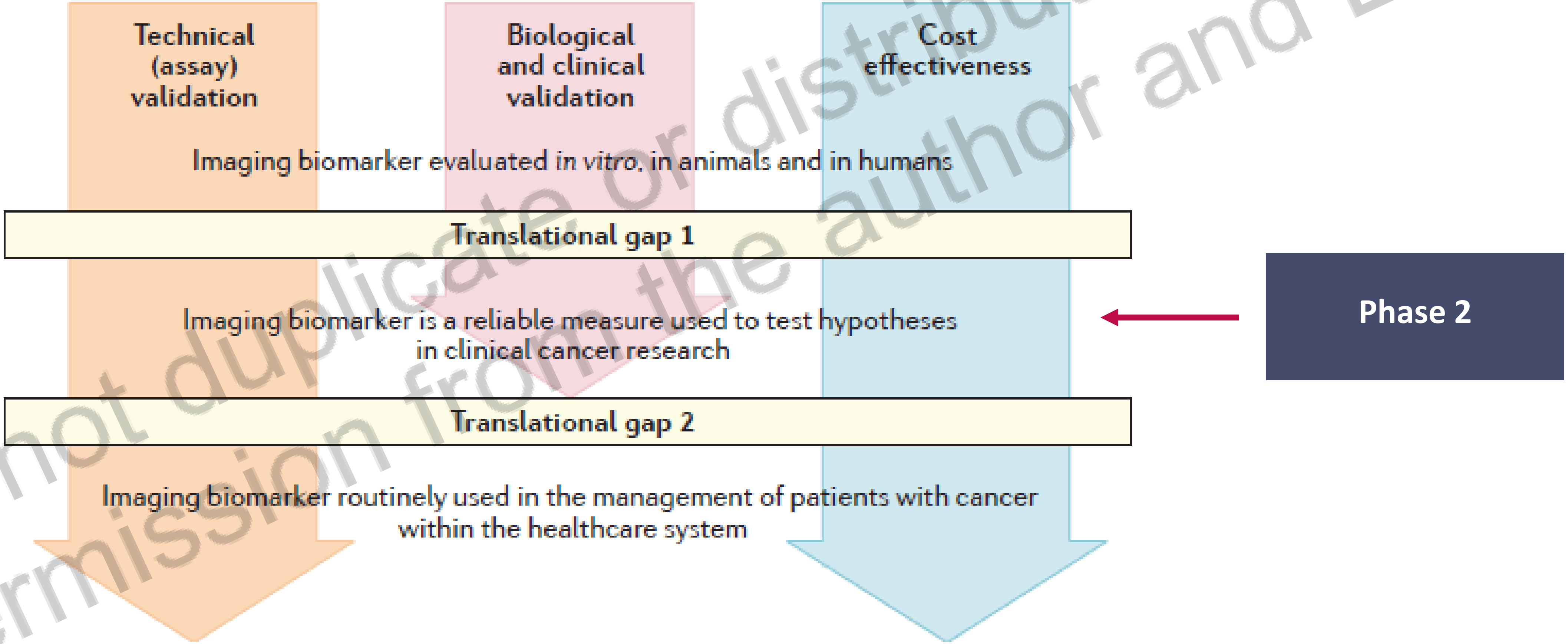
Olin AB, et al. Int J Radiother Oncol Biol Phys 2020; 108: 1329-38.

- N=11 HNC patients
- Direct usage of PET/MRI for RT planning investigated
- Synthetic CT determined from Dixon-MRI, comparison to PET/CT



Imaging Biomarker Roadmap for Cancer Studies

O'Connor JPB, et al. Nat Rev Clin Oncol 2017; 14(3): 169-86.



Technical Requirements for using Quantitative Imaging in RT

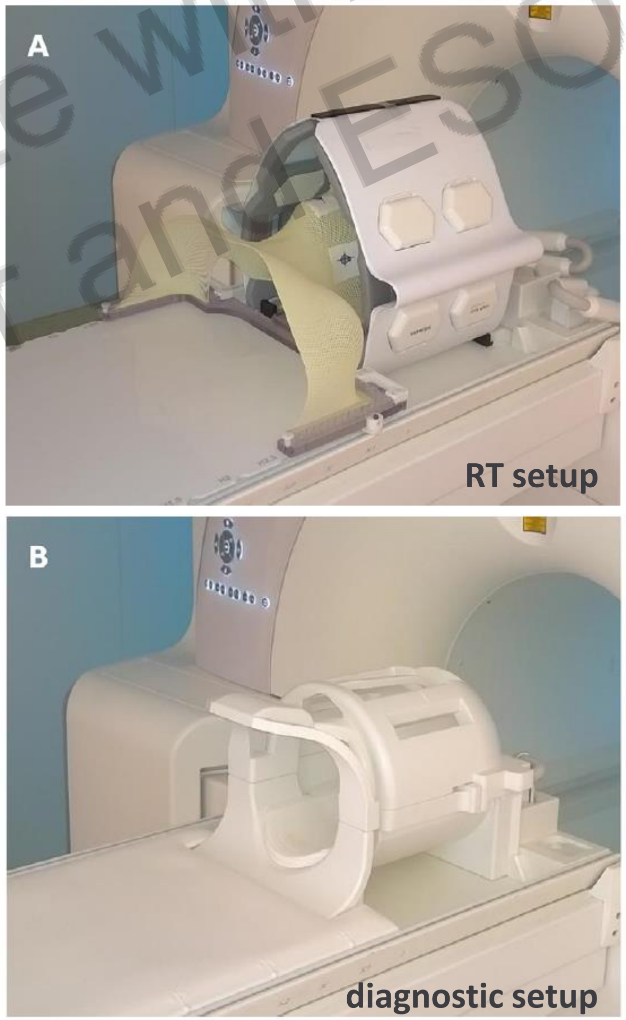
Gurney-Champion O, et al. Radiother Oncol 2020; 146: 66-75.

- Imaging in RT position!
  - Dedicated positioning aids and coils needed
  - Eventually image registration in addition helpful
- Geometrical accuracy is a prerequisite for functional imaging based RT personalization
- Quantitative imaging information required
  - Reproducible measurement of quantiative information
  - Image processing and analysis
- Technical requirements depend on the level of intervention
  - Contouring
  - Dose prescription
  - Dose painting

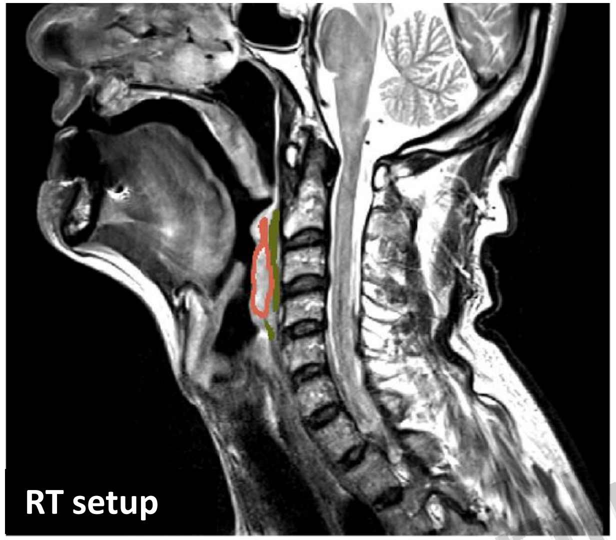
Development of a dedicated hardware solution for RT-patient positioning during hybrid PET/MR imaging

Prototype of table overlay and coil holder for Biograph mMR (Siemens), in cooperation with

- **RT table overlay:**
  - Above spine coil
  - RT indexing system
- **RT mask fixation:**
  - Add-on to table overlay
- **RF coil holders (CH):**
  - Fixation for flexible coils (6-channel body matrix)
  - Patient positioning with mask fixation possible

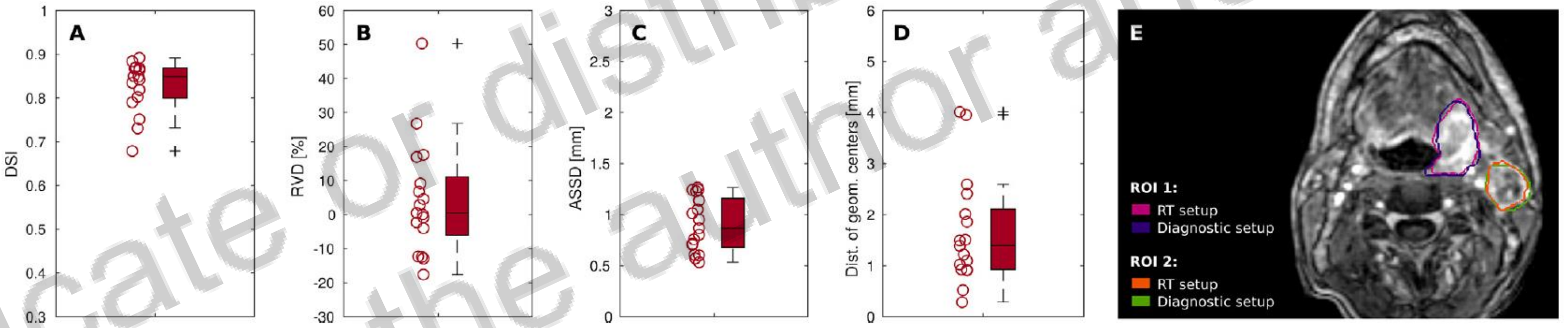


PET/MR imaging in RT position yields excellent PET and MR image quality for radiotherapy planning



Winter R, et al. Radiother Oncol 2018; 128(3):485-91.

Assessment of MR image quality for RT contouring:



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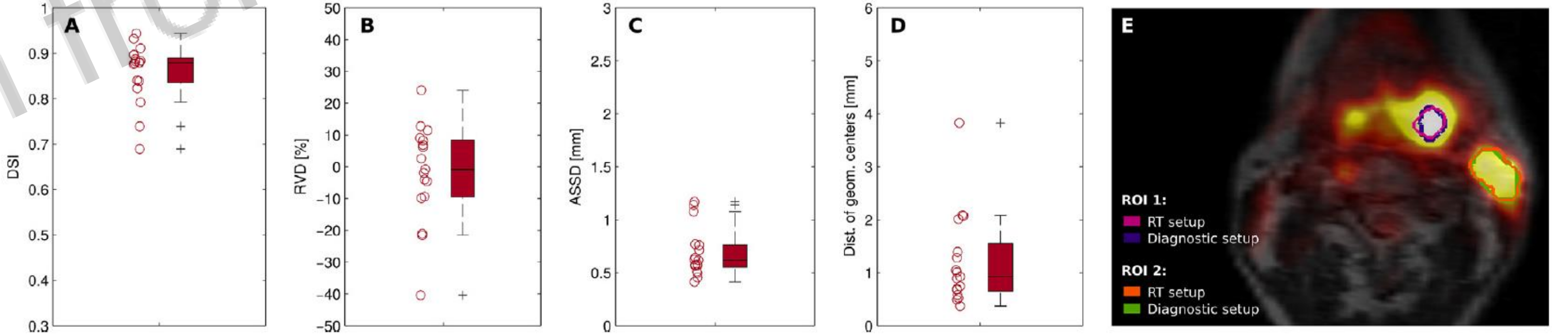
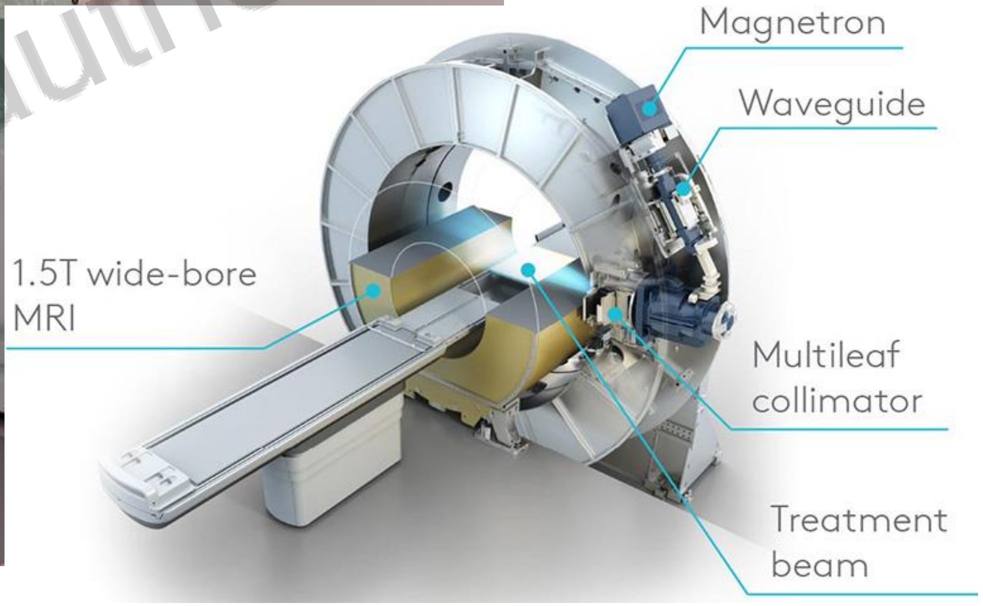


Implementation of a RT-simulation protocol on a 3 T MRI for HNC

- Patient positioning in RT mask
- Flat table top incl. mask fixation
- Flexible coil (18-channel)
- RT simulation protocol on a 3 T MRI (~20 min):
  - T2w TSE (1.3x1.3x4 mm^3)
  - DWI EPI RESOLVE (3x3x5 mm^3, IVIM, 8 b-vaues)
  - DCE (GRASP, 1.1x1.1x2 mm^3)
  - High resolution T1w post contrast (1x1x1 mm^3, VIBE + Dixon fat sat)

Hybrid MR-Linacs offer optimal basis for RT personalization

Unity, Elekta AB, Sweden



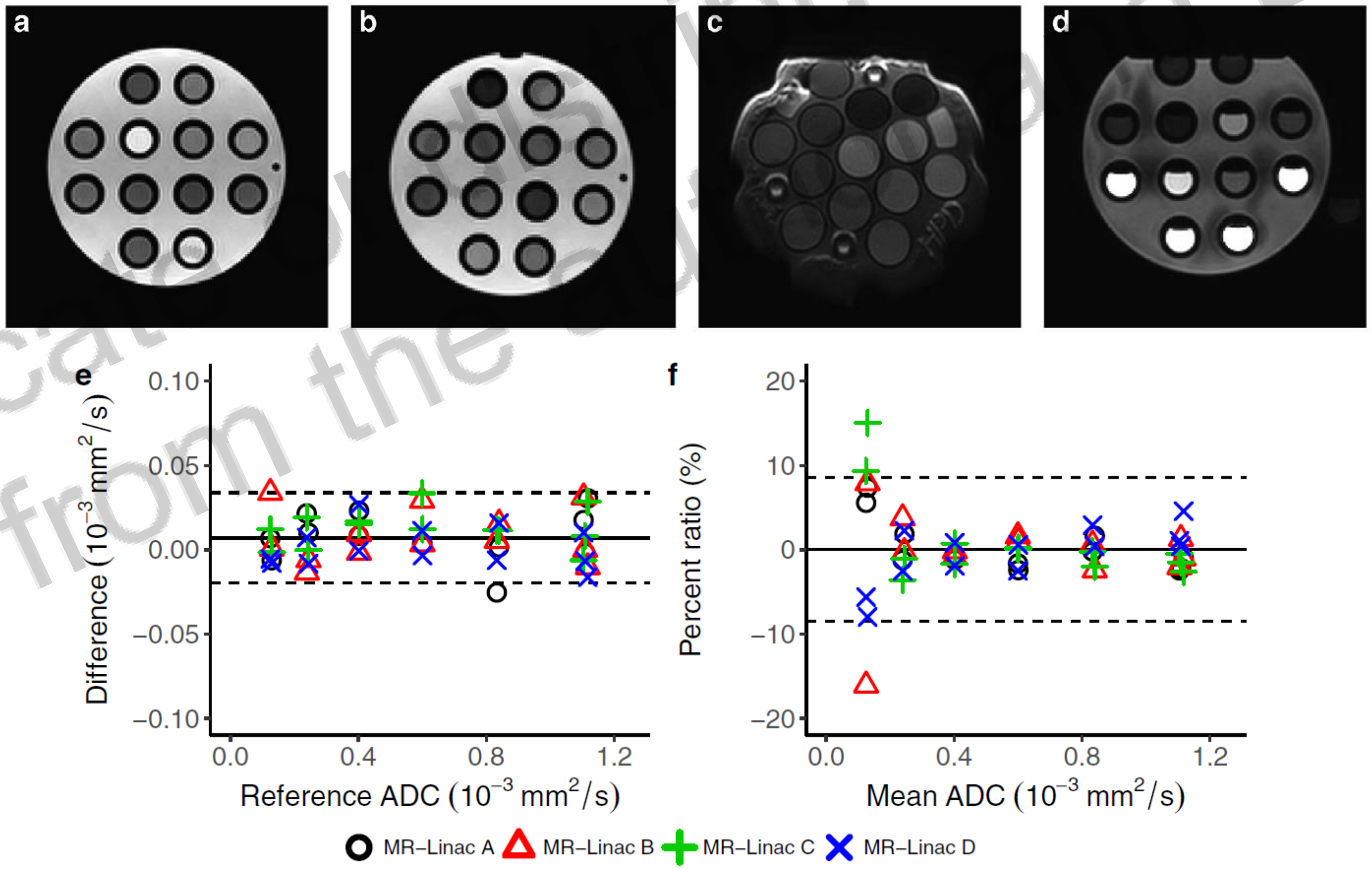
Source: www.elekta.com

Hybrid MR-Linacs offer optimal basis for RT personalization

…but also for functional image acquisition

- Investigation of quant. MR-imaging (qMRI) on MR-Linacs
- Determination of accuracy, reproducibility and repeatability of **T1, T2, ADC and DCE**
- Acquisition of qMRI using hybrid 1.5 T MR-Linacs is possible

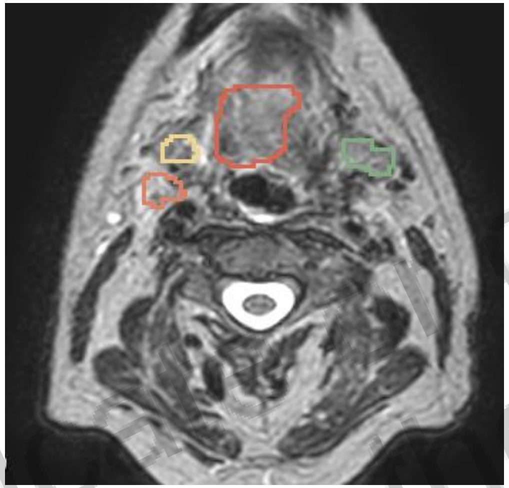
Kooreman E, et al. Radiother Oncol 2019; 133:156-62.

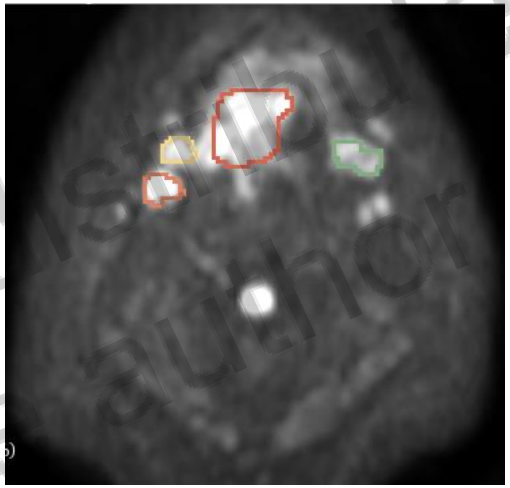


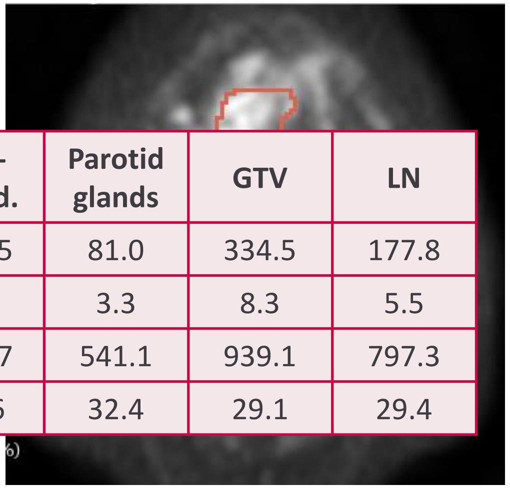
QIBA-Phantom

Test/re-test study on the 1.5 T MR-Linac to assess repeatability of ADC measurements in HNC

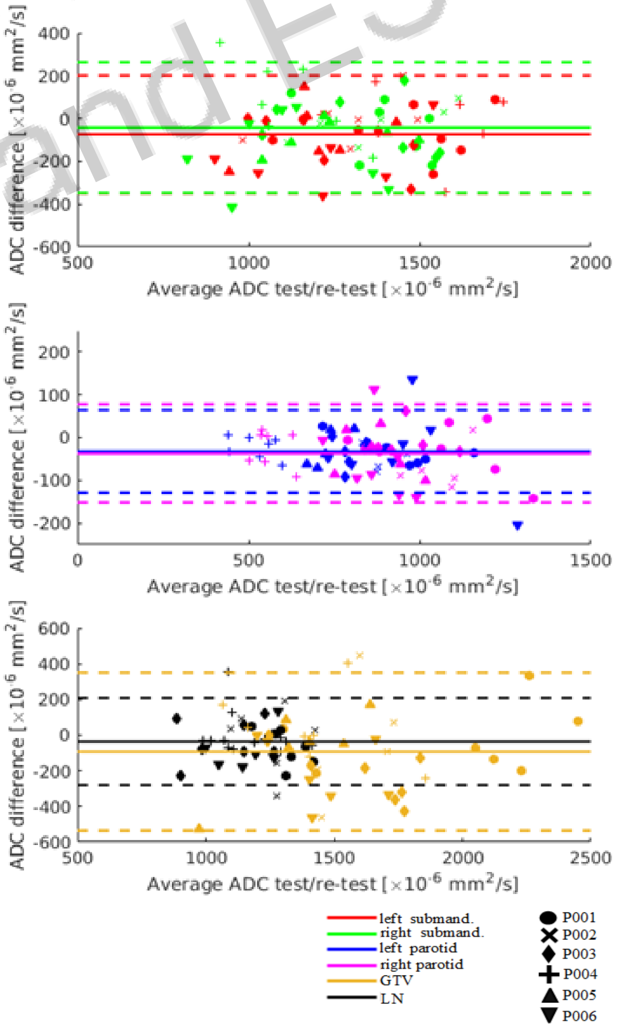
- HNC patients treated (35 fx) on the 1.5 T MR-Linac
- DW-MRI 1x/week
- Test/re-test before and after RT fraction
- Delineation of GTV, LN, submandibular and parotid glands
- Assessment of repeatability coefficient (RC) and within-subject coeff. Of variation (wCV) on volume- and voxel-level







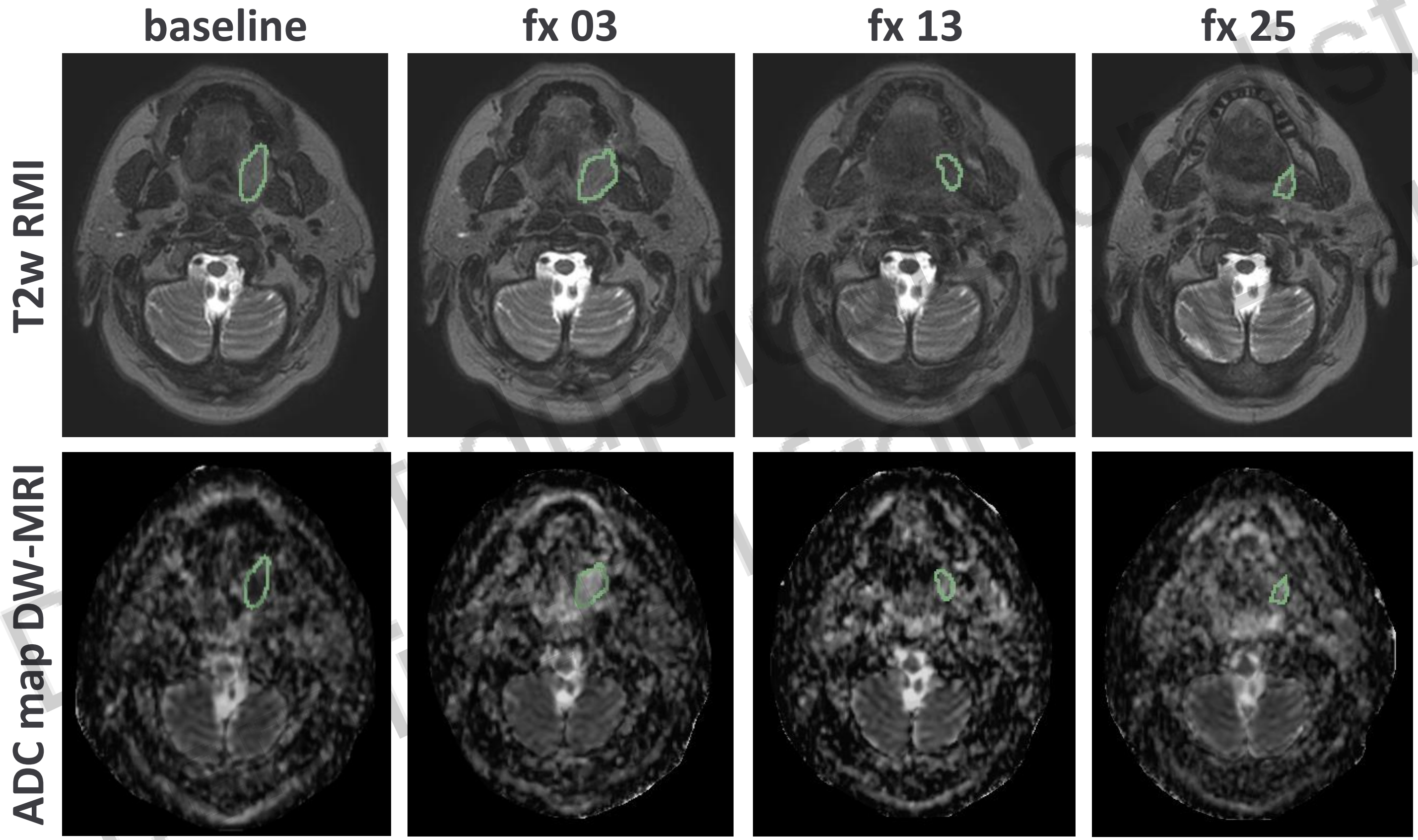
		Sub-mand.	Parotid glands	GTV	LN
VOI	RC [10^{-6} mm²/s]	217.5	81.0	334.5	177.8
	wCV [%]	6.2	3.3	8.3	5.5
Voxel-level	RC [10^{-6} mm²/s]	695.7	541.1	939.1	797.3
	wCV [%]	23.6	32.4	29.1	29.4

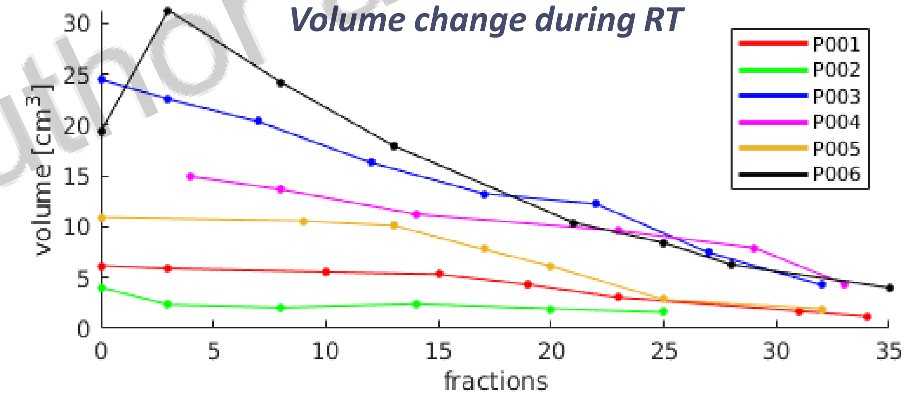


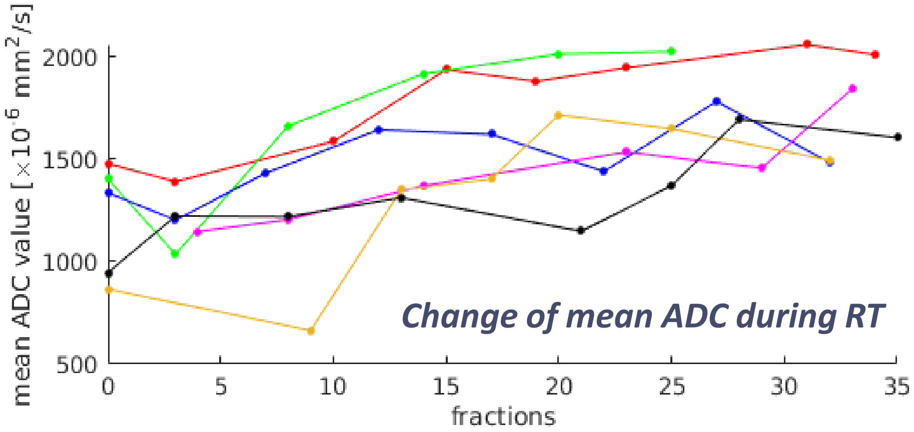
Work in progress, University of Tübingen

Sequential functional MRI during RT on the MR-Linac

Sequential DW-MRI in HNC during fractionated RT







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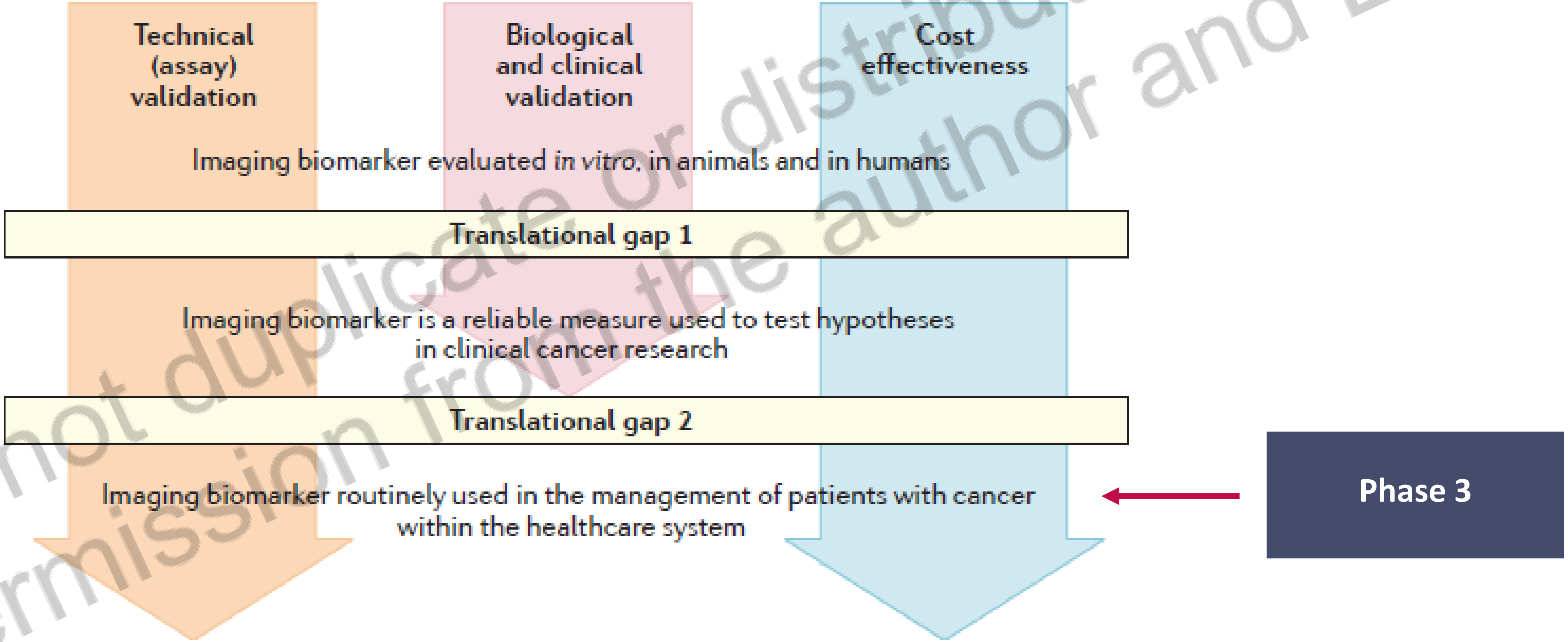
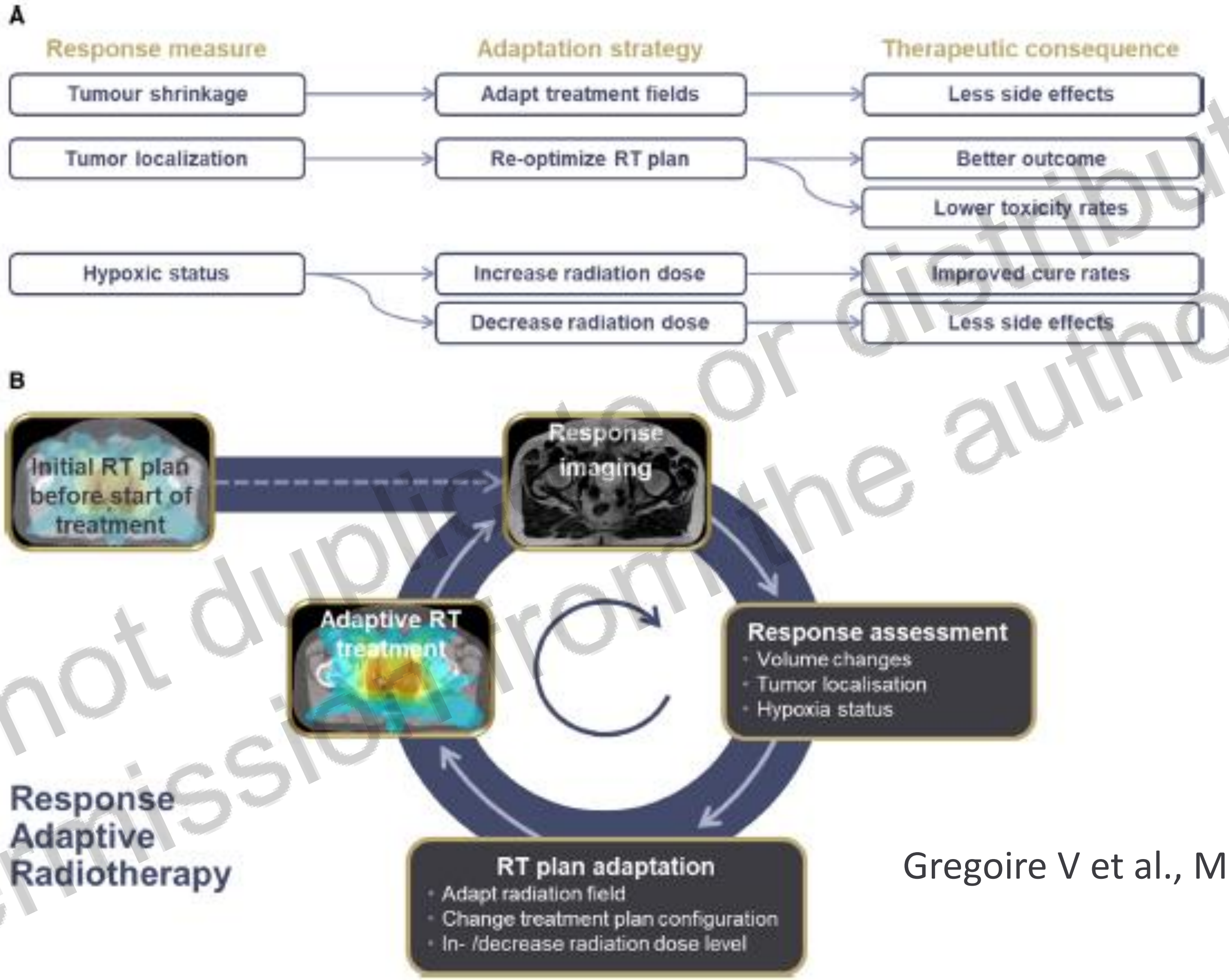
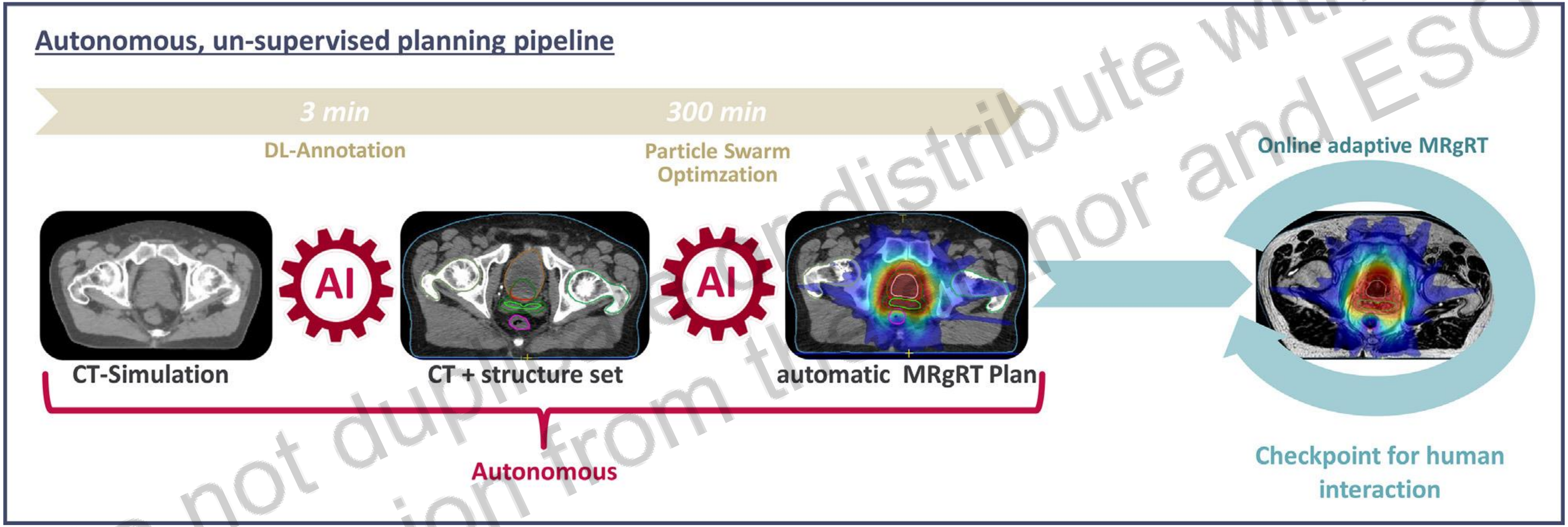


Future of IGRT: Response adaptive IGRT



Gregoire V et al., Molecular Oncology 14 (2020) 1470–1491

Future of IGRT: Automation and AI-driven



Künzel LA et al., Radiother Oncol 2021; 159:197-201

Conclusions

1. High-resolution IGRT has become a mainstay of modern RT.
2. IGRT has widened the therapeutic window: it allows to safely deliver radiation dose with tumor coverage and sufficient radiation dose while sparing normal tissue
3. IGRT is a major contribution of radiation oncology for cancer medicine for virtually all patients
4. IGRT will remain a driving force for research and development
5. IGRT is a core technology towards Precision (Personalized) Radiation Oncology

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The next e-ESO Session

will take place next Monday,
24th May 2021, at the same time

e-session 573001

Neuroendocrine breast cancer - neuroendocrine or breast cancer?

Expert: **Dr Joana Ribeiro**, Champalimaud Clinical Center, Lisbon, Portugal

Discussant: **Dr Assia Konsoulova Kirova**, Complex Oncological Center, Burgas, Bulgaria

Thank you!

for participating in this
e-session
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