



**CDDF SPRING
CONFERENCE 2021**

08 - 10 February 2021
Virtual Conference

Current and future challenges
of innovative oncology drug
development



Radiology Imaging in neuro-oncological trials

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Erasmus MC, Rotterdam, The Netherlands





Disclosures

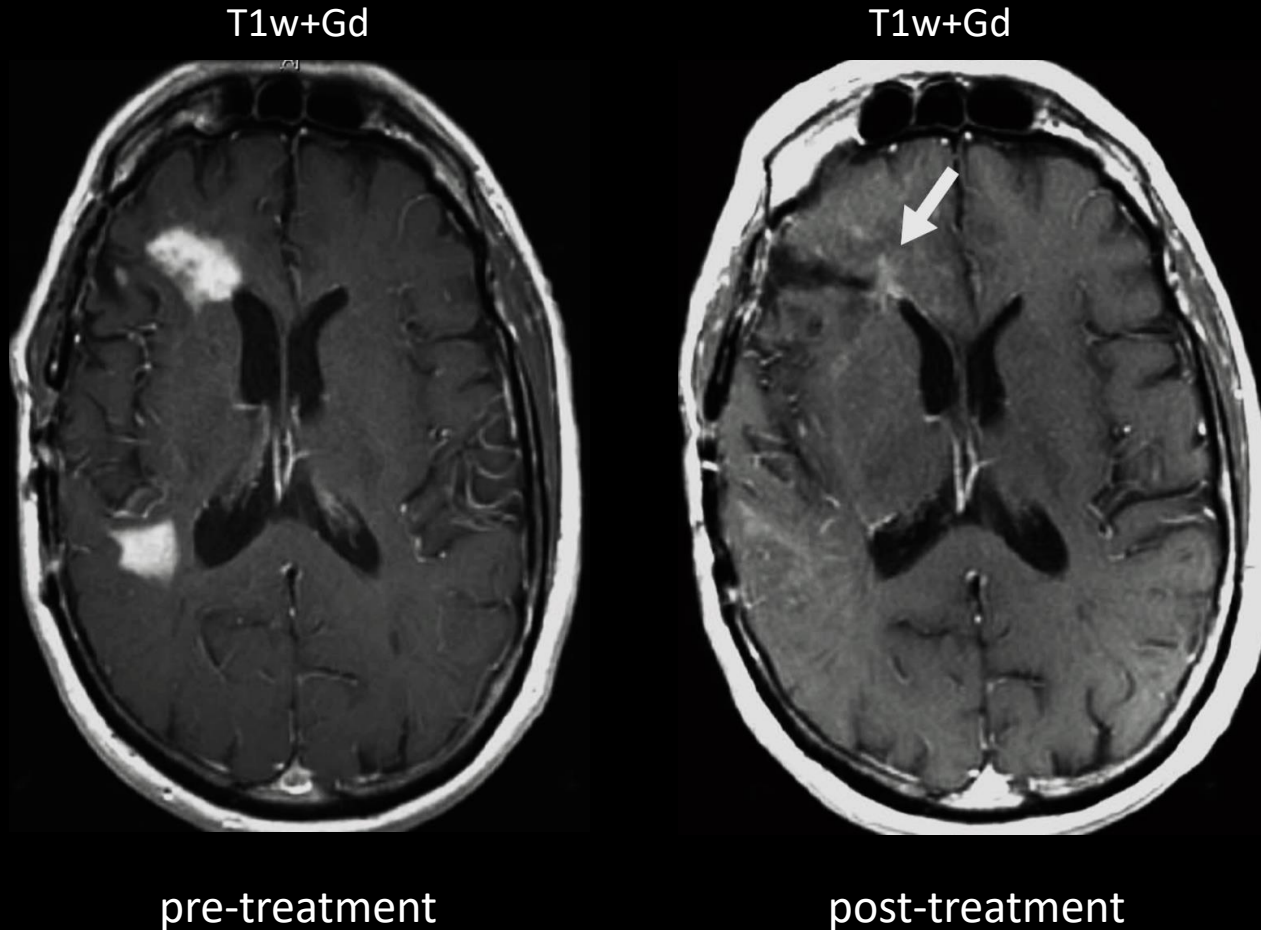
relevant positions

- Chair of the Imaging Group and BTG-Imaging Committee | EORTC
- Past President | European Soc of Magnetic Resonance in Medicine and Biology (ESMRMB)
- Steering Committee on brain tumour imaging standardisation | NBTS
- Chair of Publications, Executive Council | Eur Soc of Radiology (ESR)
- Dutch guideline committees on glioma, brain metastasis, and neuro-oncological quality of care | Dutch Soc of NeuroOncology (LWNO)

financial (paid to institution)

- Independent reviewer (EORTC-1410) | Parexel Intl. Corp.
- Speaker fees | GE Healthcare

Response assessment in glioblastoma



Response !

⇒ accelerated approval (FDA, 2009)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 20, 2014

VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

CONCLUSIONS

First-line use of bevacizumab **did not improve overall survival** in patients with newly diagnosed glioblastoma. Progression-free survival was prolonged but did not reach the prespecified improvement target. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00884741.)

? Response assessment with imaging

ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren Mason, M.D., Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishikawa, M.D., Antoine F. Carpentier, M.D., Ph.D., Khe Hoang-Xuan, M.D., Ph.D., Petr Kavan, M.D., Ph.D., Dana Cernea, Ph.D., Alba A. Brandes, M.D., Magalie Hilton, M.Sc., Lauren Abrey, M.D., and Timothy Cloughesy, M.D.

CONCLUSIONS

The addition of bevacizumab to radiotherapy–temozolomide **did not improve survival** in patients with glioblastoma. Improved progression-free survival and maintenance of baseline quality of life and performance status were observed with bevacizumab; however, the rate of adverse events was higher with bevacizumab than with placebo. (Funded by F. Hoffmann–La Roche; ClinicalTrials.gov number, NCT00943826.)



Imaging in neuro-oncology trials

Historically no involvement of Radiology

- imaging performed according to local protocols
- wide variety of scanning equipment and implementation
- generally no 'advanced' imaging
- no quality assurance.

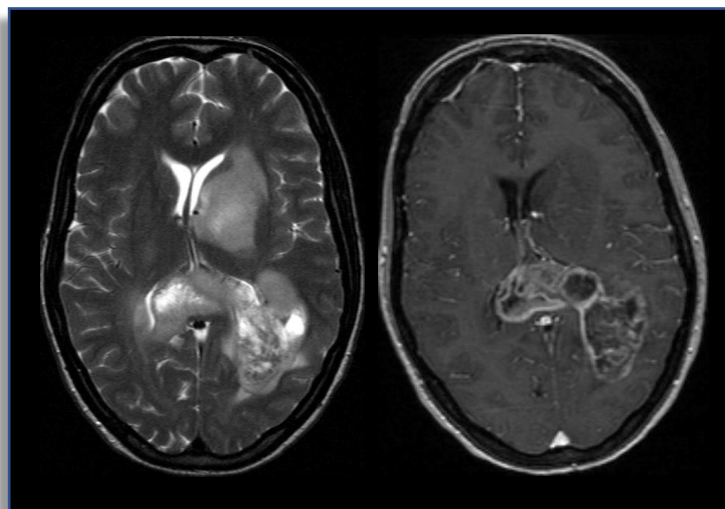
⇒ Considerable variations in patient selection/outcome assessment.

⇒ Limited diagnostic accuracy.



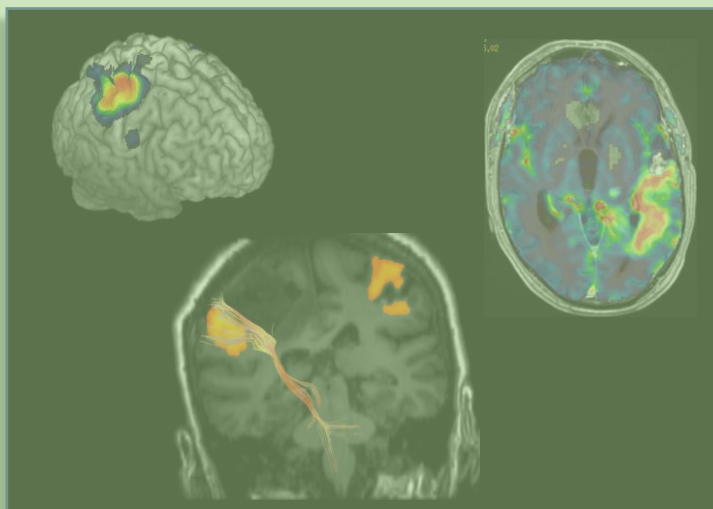
Imaging in neuro-oncology

clinical trials



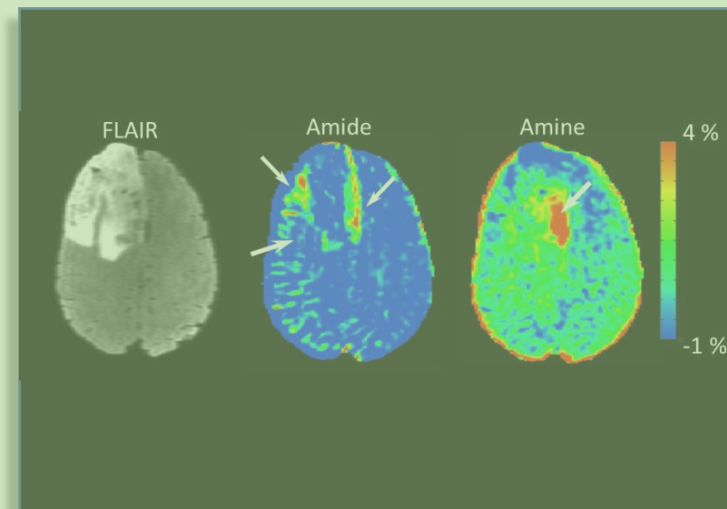
⇒ enhancing tumour size
(in 2 dimensions)

brain tumour centre



⇒ tumour size (3D)
 ⇒ cellularity (DWI)
 ⇒ blood volume (perfusion MRI)
 ⇒ metabolism (MRS)
 ⇒ function

the 'MRI lab'



in vivo mapping of tumour biology
 ⇒ vascular architecture
 ⇒ oxygenation/oxygen extraction
 ⇒ metabolism and pH
 ⇒ protein (amide/amine) content
 ⇒ white matter infiltration
 ⇒ ...



Imaging in neuro-oncology trials

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

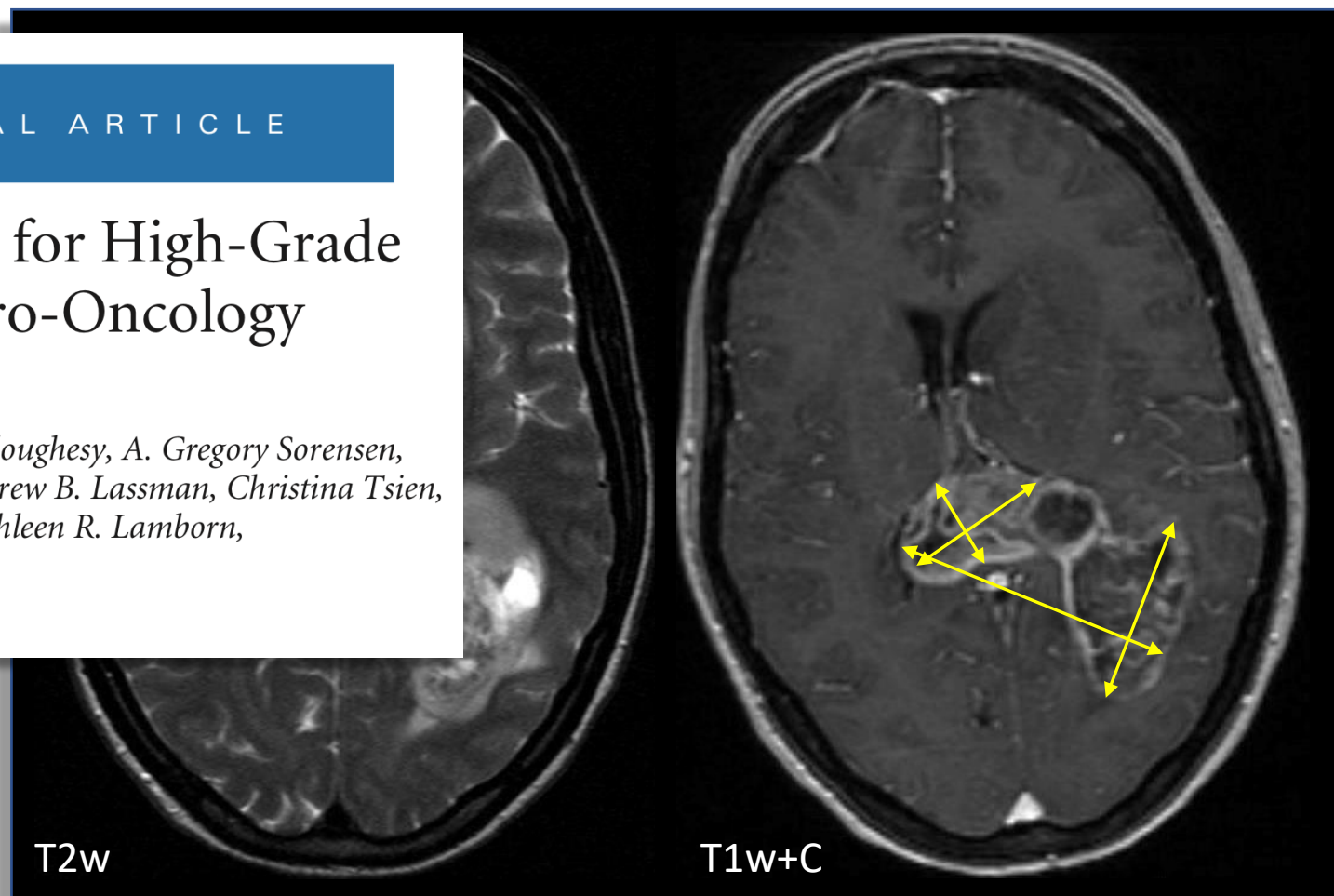
Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

Patrick Y. Wen, David R. Macdonald, David A. Reardon, Timothy F. Cloughesy, A. Gregory Sorensen, Evanthia Galanis, John DeGroot, Wolfgang Wick, Mark R. Gilbert, Andrew B. Lassman, Christina Tsien, Tom Mikkelsen, Eric T. Wong, Marc C. Chamberlain, Roger Stupp, Kathleen R. Lamborn, Michael A. Vogelbaum, Martin J. van den Bent, and Susan M. Chang

bidimensional measurement of solid enhancement

⇒ **no accurate reflection of tumour size**

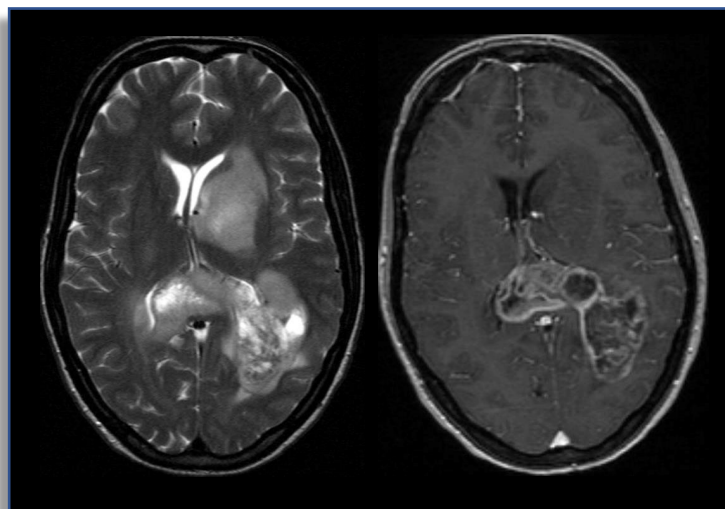
⇒ **substantial inter-rater variability**





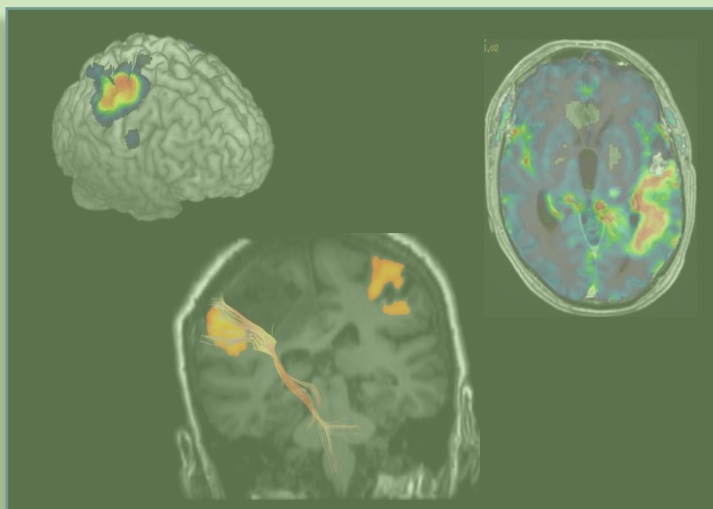
Imaging in neuro-oncology

clinical trials



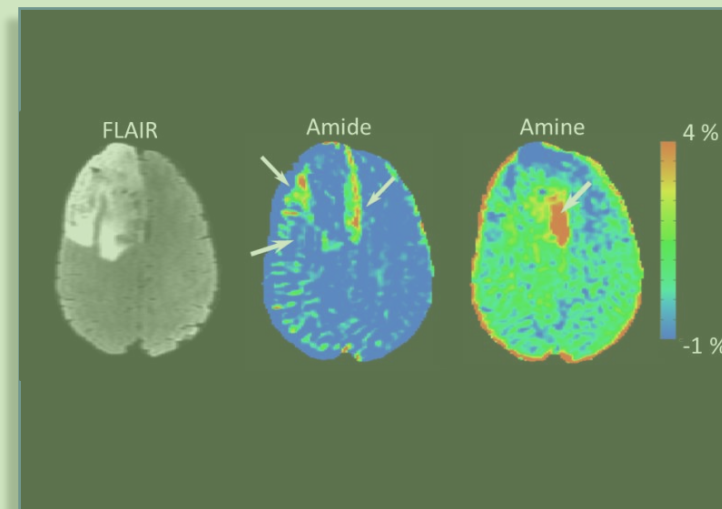
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Imaging in neuro-oncology trials

Neuro-Oncology

19(6), 853–861, 2017 | doi:10.1093/neuonc/now311 | Advance Access date 13 February 2017

Comparison of 2D (RANO) and volumetric methods for assessment of recurrent glioblastoma treated with bevacizumab—a report from the BELOB trial

Renske Gahrman, Martin van den Bent, Bronno van der Holt, René Michel Vernhout,
Walter Taal, Maaike Vos, Jan Cees de Groot, Laurens Victor Beerepoot, Jan Buter,
Zwenneke Hendrieke Flach, Monique Hanse, Bas Jasperse, and Marion Smits

With (automated) 3D methods:

- ⇒ improved sensitivity to progression
- ⇒ reduced inter-rater variability

! currently not the standard

Lancet Oncol 2019

Automated quantitative tumour response assessment of MRI in neuro-oncology with artificial neural networks: a multicentre, retrospective study

Philipp Kickingereder*, Fabian Isensee*, Irada Tursunova, Jens Petersen, Ulf Neuberger, David Bonekamp, Gianluca Brugnara, Marianne Schell,
Tobias Kessler, Martha Foltyn, Inga Harting, Felix Sahm, Marcel Prager, Martha Nowosielski, Antje Wick, Marco Nolden, Alexander Radbruch,
Jürgen Debus, Heinz-Peter Schlemmer, Sabine Heiland, Michael Platten, Andreas von Deimling, Martin J van den Bent, Thierry Gorlia,
Wolfgang Wick, Martin Bendszus†, Klaus H Maier-Hein†

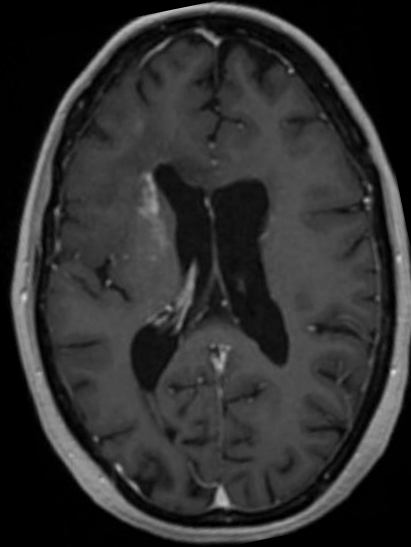


Treatment monitoring challenges

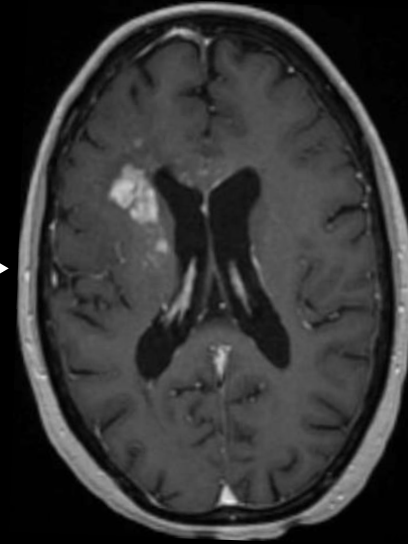
- Pseudoresponse
 - anti-angiogenic agents: normalisation of vasculature
 - ⇒ tumour appears to disappear
 - ⇒ T2-abnormalities: unspecific (tumour, oedema, gliosis).
- Pseudoprogression
 - radiation, chemo-, immunotherapy
 - ⇒ enhancement and oedema indistinguishable from tumour
 - ⇒ inaccurate patient **selection** and trial **endpoints**.

Pseudoprogression

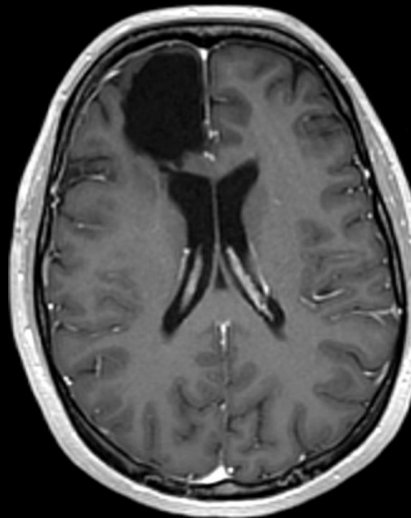
pat1 after
chemorad



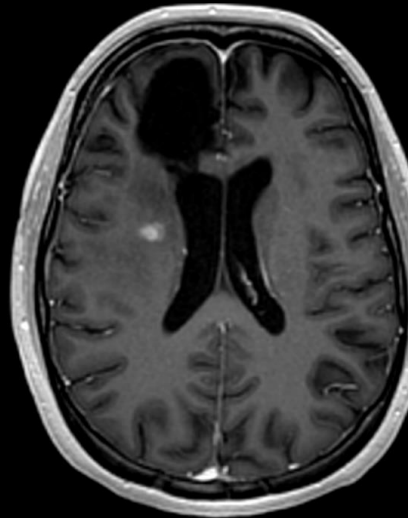
3 months



pat2 after
chemorad

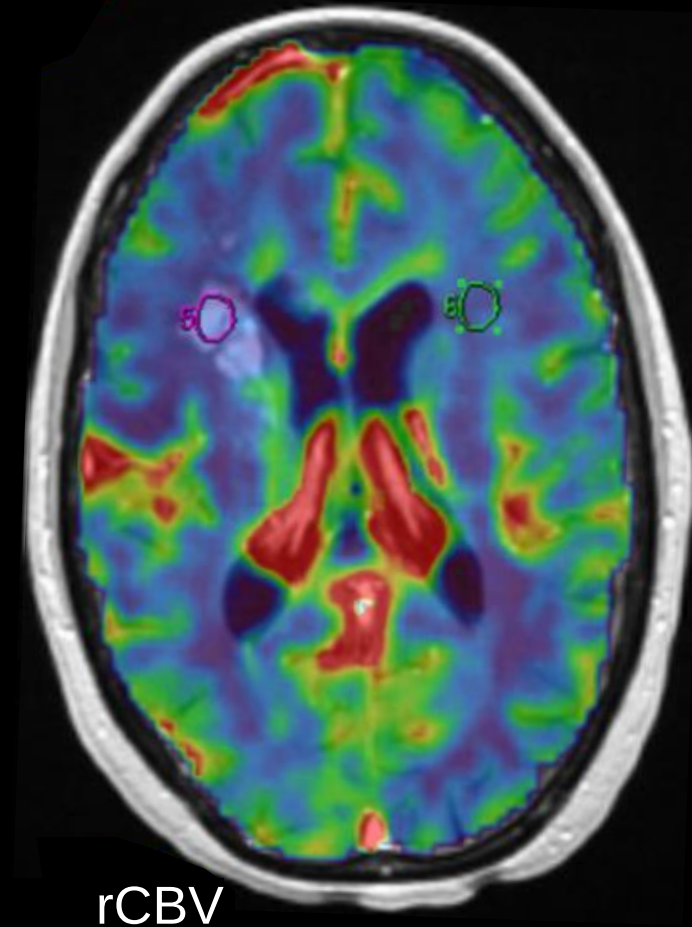
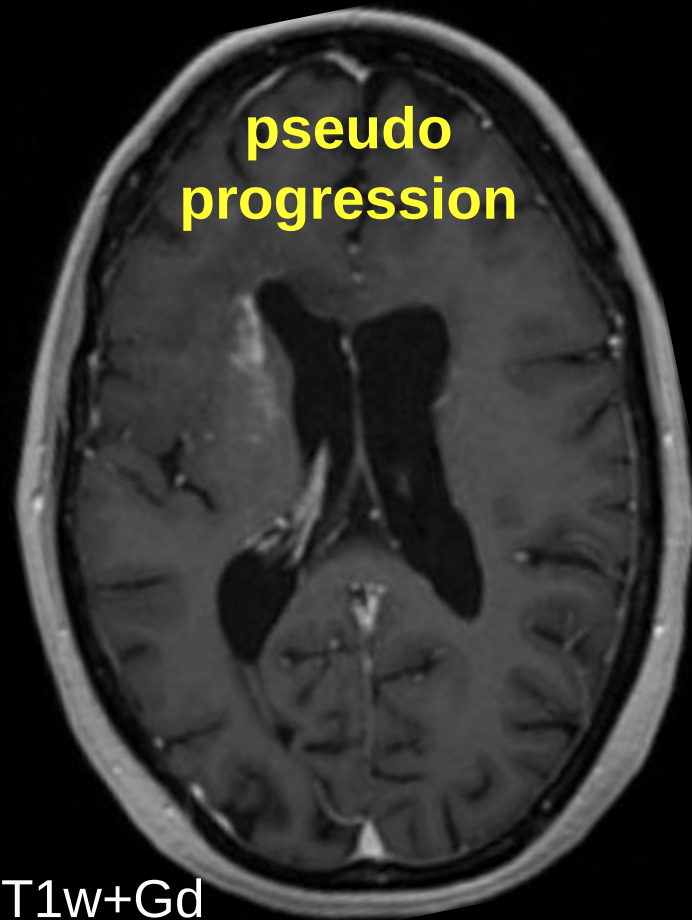


3 months



**tumour progression
or
pseudoprogression
???**

Perfusion MRI



Perfusion MRI

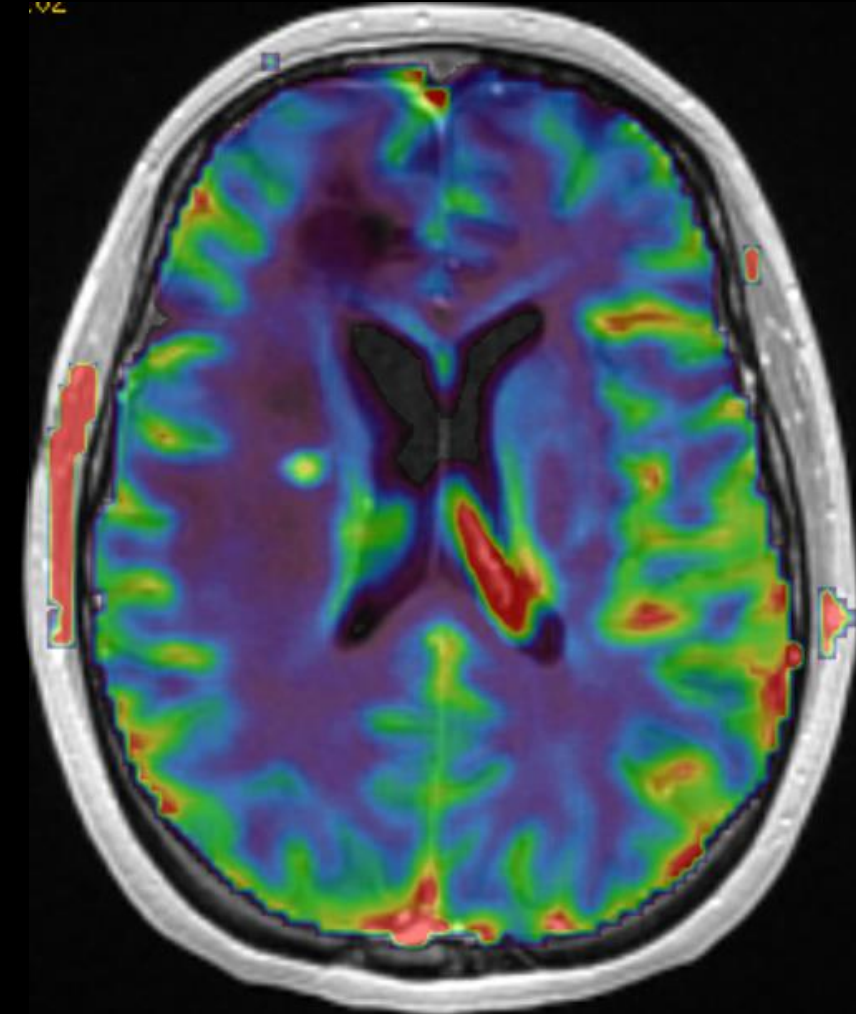
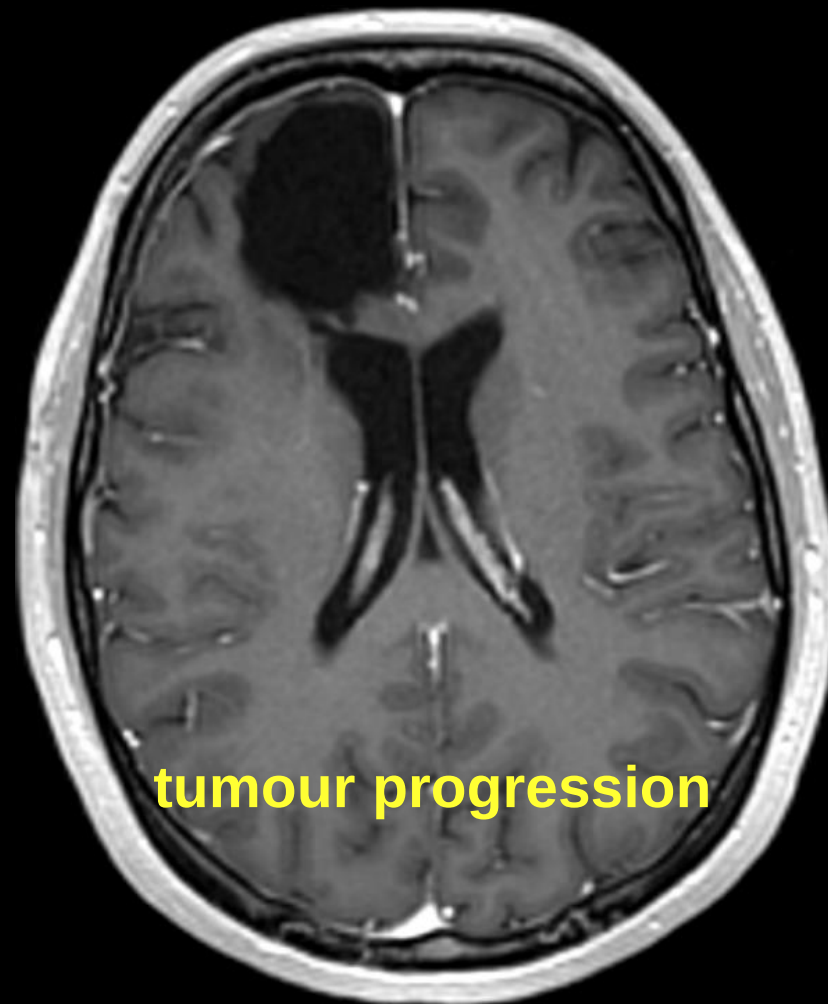
van Dijken et al. Eur Radiol 2017, Patel et al. Neuro Oncol 2017

pooled sensitivity

- 87% (0.82-0.91)
- 90% (0.85-0.94)

pooled specificity

- 86% (0.77-0.91)
- 88% (0.83-0.92)





Perfusion MRI in clinical trials?

- Improved assessment of treatment response.
- Accurate patient inclusion (true progression).
- Timely patient inclusion.
- Takes $\pm$ 2 min scanning time.
- Performed at >80% of institutions in Europe.

! currently not the standard

Thust et al. Eur Radiol 2018:3306



Perfusion MRI in clinical trials?



European Journal of Cancer

Volume 114, June 2019, Pages 89-96



Original Research

Repeatability and reproducibility of relative cerebral blood volume measurement of recurrent glioma in a multicentre trial setting

Marion Smits^a , Martin Bendszus^b, Sandra Collette^c, Linda A. Postma^d, Frederic Dhermain^e, Rogier E. Hagenbeek^f, Paul M. Clement^g, Yan Liu^c, Wolfgang Wick^b, Martin J. van den Bent^a, Sabine Heiland^b

1262

Neuro-Oncology

22(9), 1262–1275, 2020 | doi:10.1093/neuonc/noaa141 | Advance Access date 9 June 2020

Consensus recommendations for a dynamic susceptibility contrast MRI protocol for use in high-grade gliomas

Jerrold L. Boxerman, Chad C. Quarles, Leland S. Hu, Bradley J. Erickson, Elizabeth R. Gerstner, Marion Smits, Timothy J. Kaufmann, Daniel P. Barboriak, Raymond H. Huang, Wolfgang Wick, Michael Weller, Evanthia Galanis, Jayashree Kalpathy-Cramer, Lalitha Shankar, Paula Jacobs, Caroline Chung, Martin J. van den Bent, Susan Chang, W.K. Al Yung, Timothy F. Cloughesy, Patrick Y. Wen, Mark R. Gilbert, Bruce R. Rosen, Benjamin M. Ellingson, and Kathleen M. Schmainda and the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee

the time is ripe !

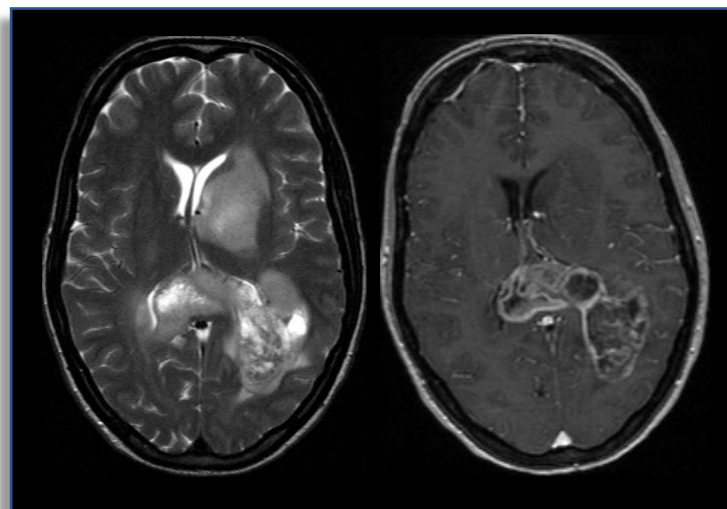


Imaging in neuro-oncology

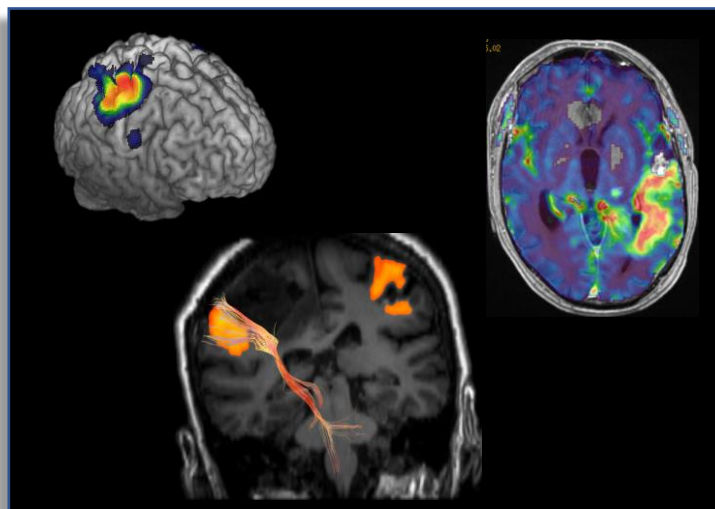
clinical trials

brain tumour centre

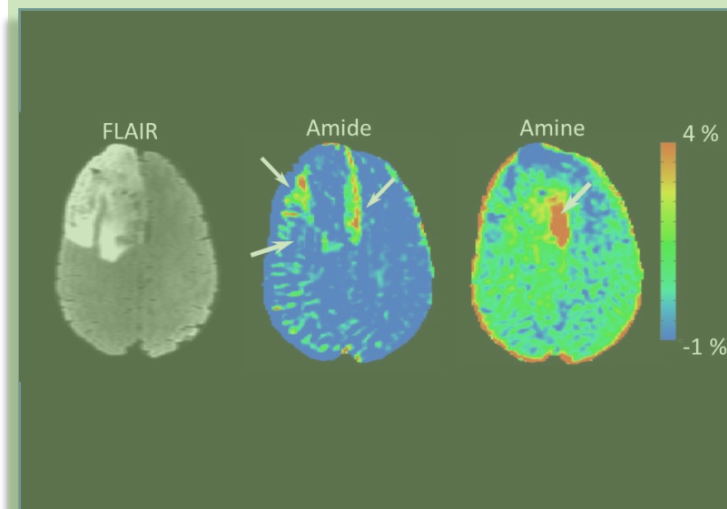
the 'MRI lab'



⇒ enhancing tumour size
(in 2 dimensions)



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in vivo mapping of tumour biology

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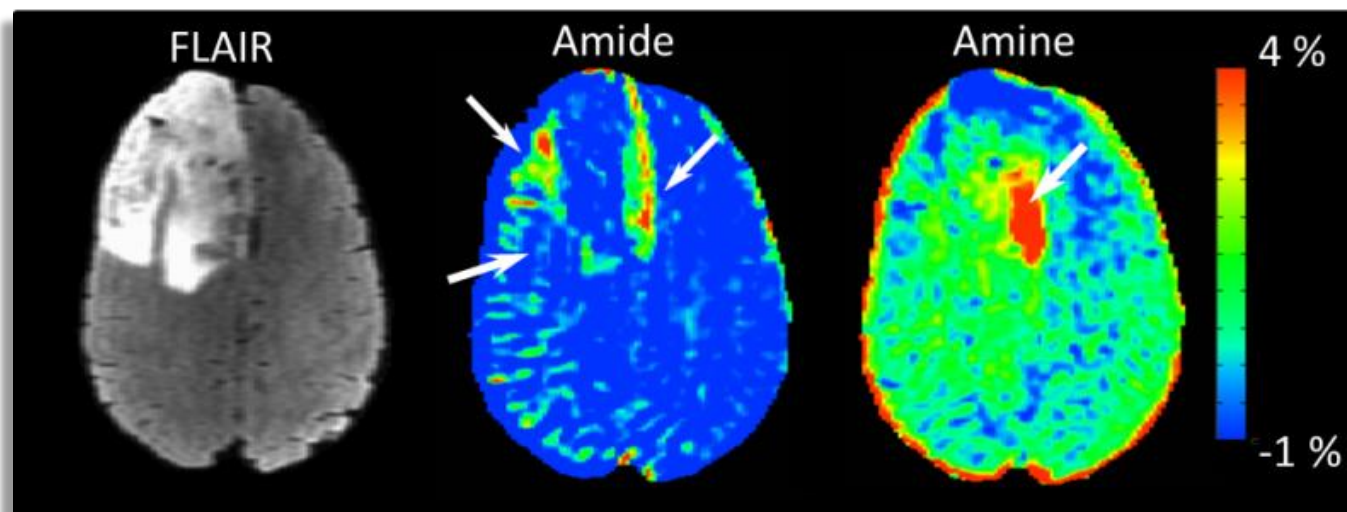
Linking with the MRI lab

- Advances in imaging.
- Advances in image analysis.
- Imaging (bio)marker development.



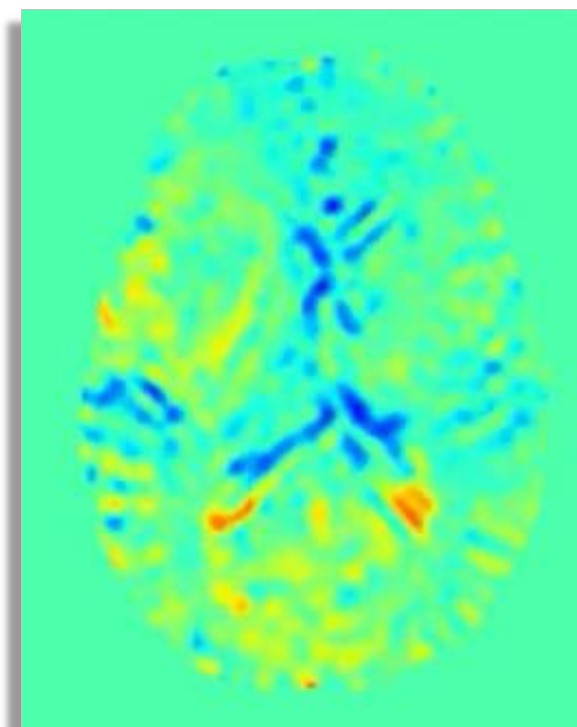
Novel MR imaging sequences: CEST

protein content



images courtesy Esther Warnert

glucose dynamics

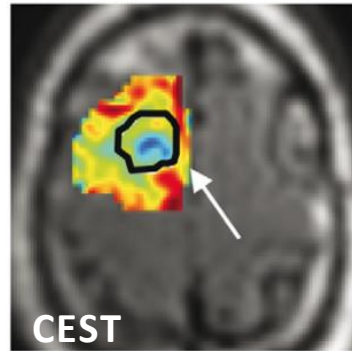
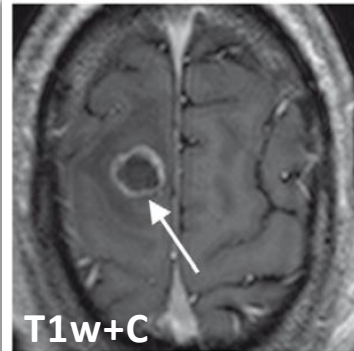


Johns Hopkins Medical Center

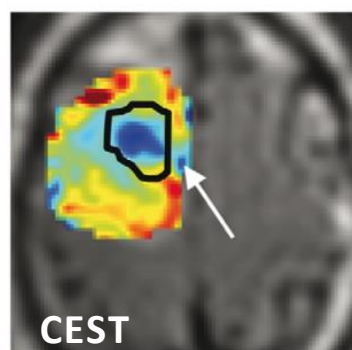
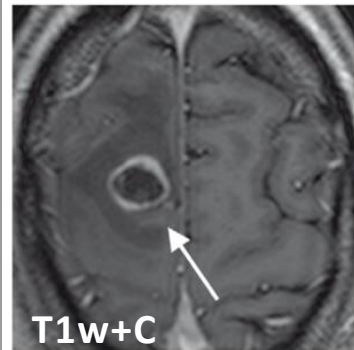
CEST for SRS treatment response

Desmond et al MRM 2017:1110-20

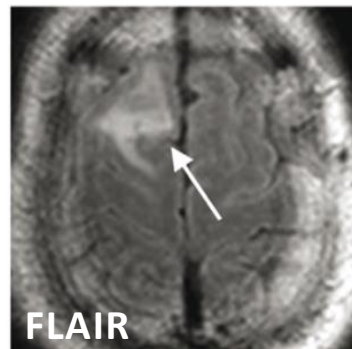
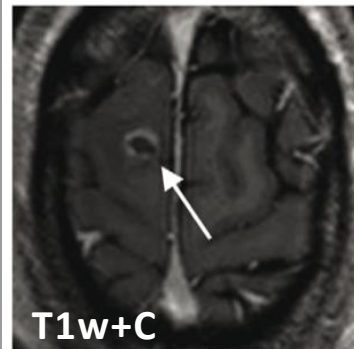
RESPONSE



baseline

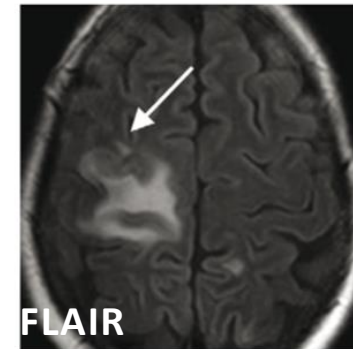
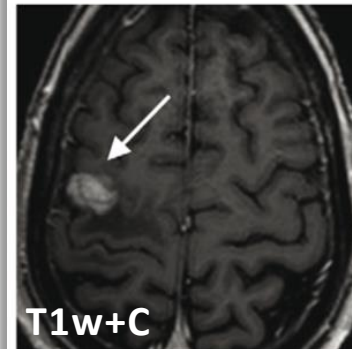
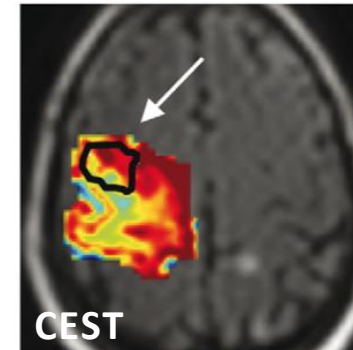
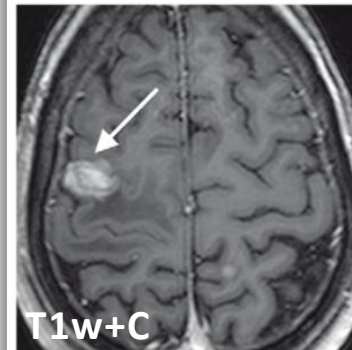
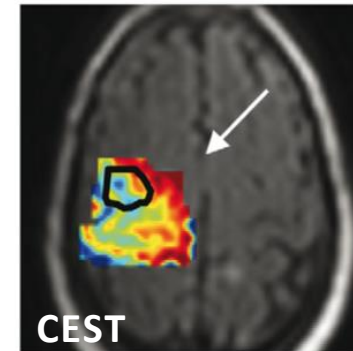
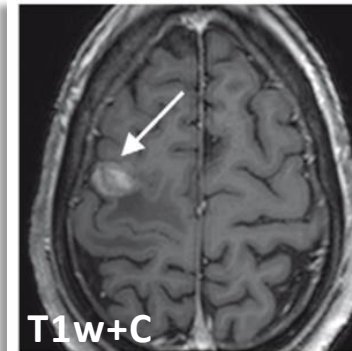


1 week



1 month

NO RESPONSE

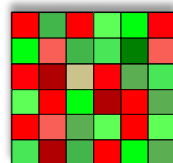




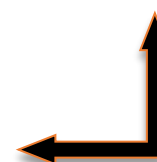
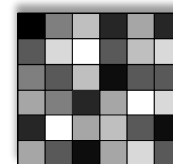
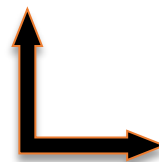
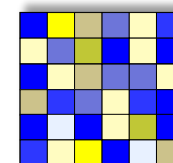
Advances in image analysis: radio(geno)mics

premise: there exists a correlation between medical image features and underlying biological information.

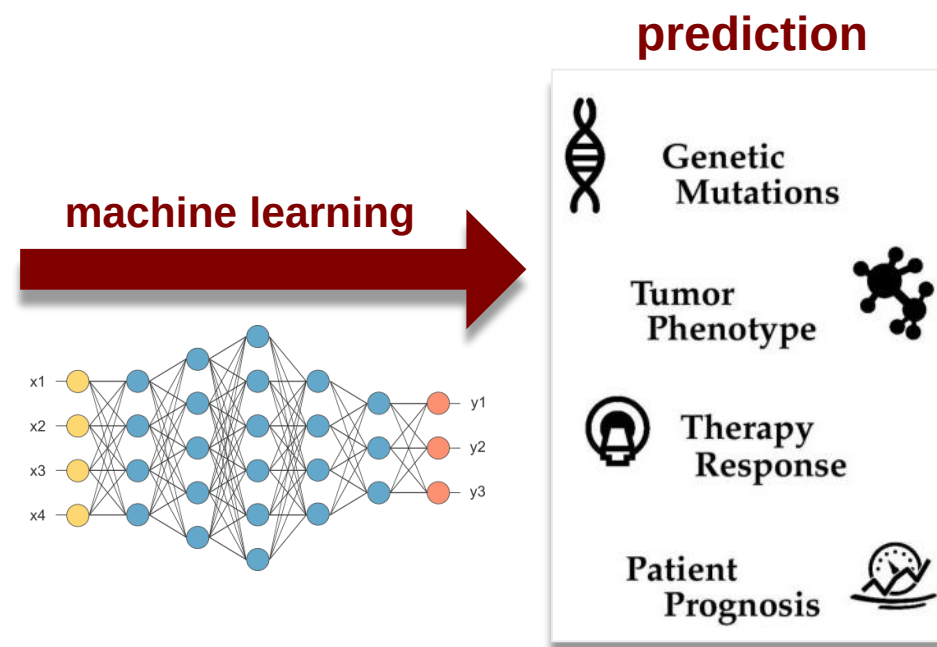
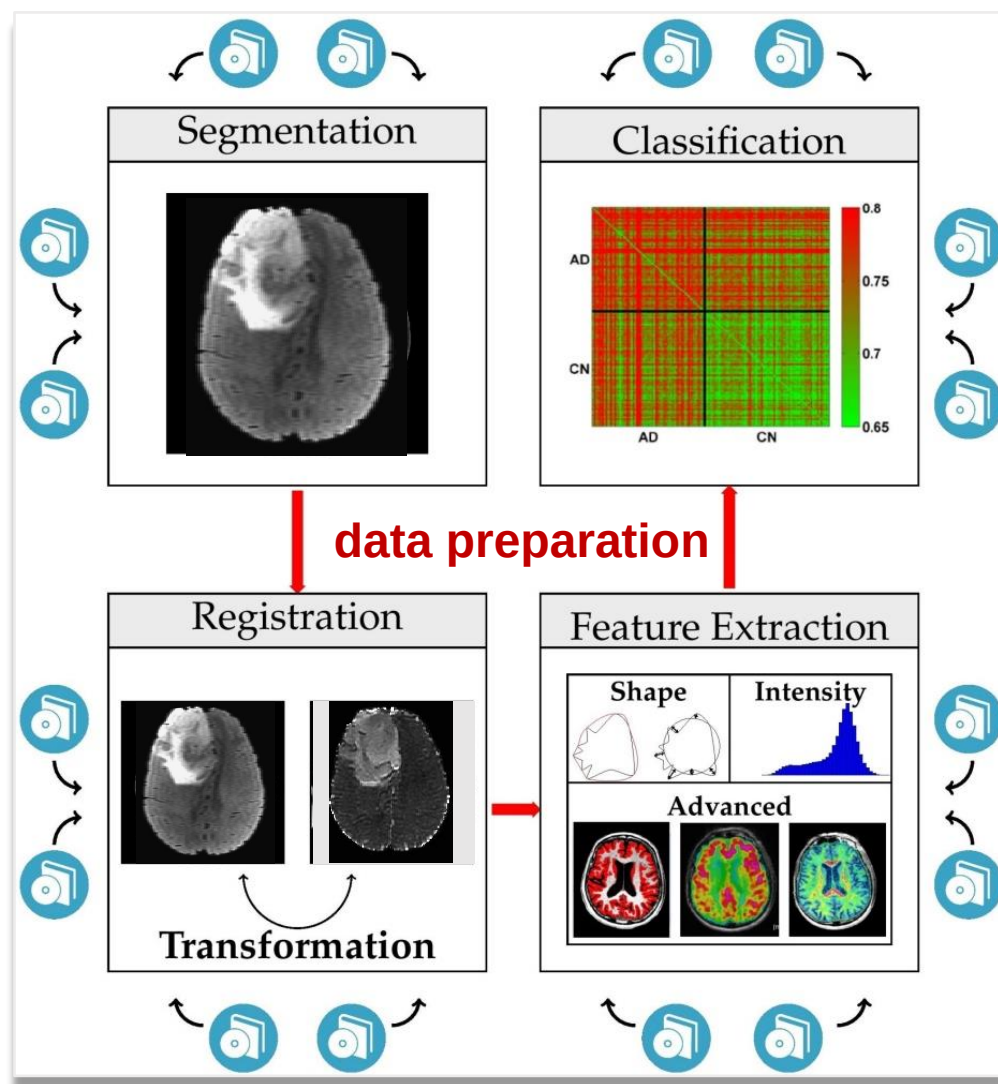
genomic data



radiomics (imaging) data



clinical data



figures courtesy of
Biomedical Imaging Group Rotterdam



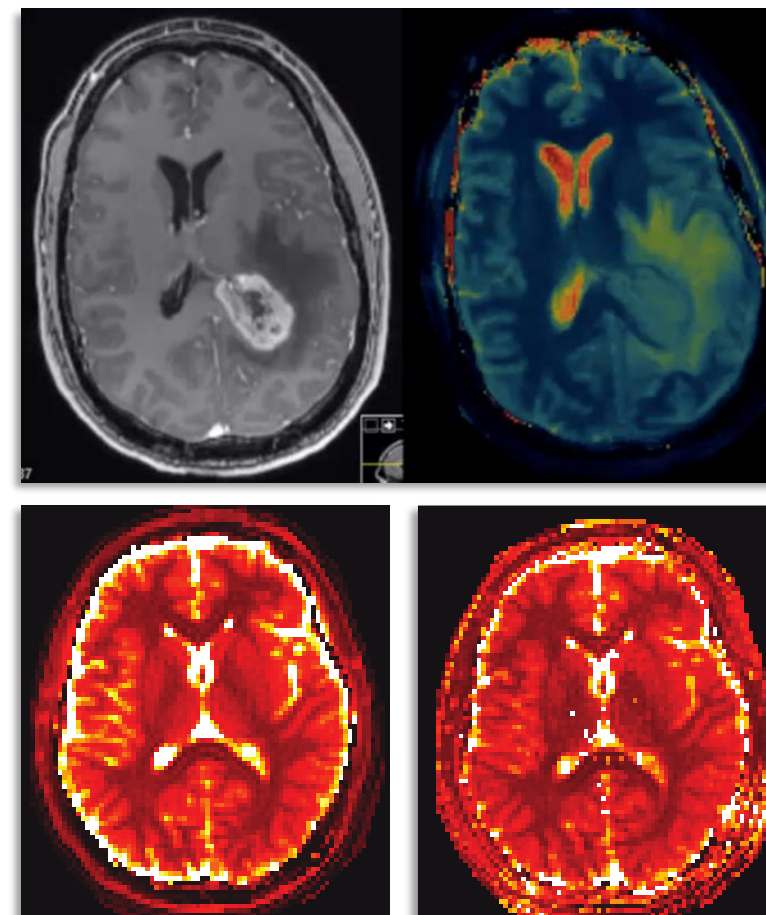
Imaging (bio)markers



MR Fingerprinting

Ma et al. Nature 2013;495:187

fully quantitative MRI < 1 min scan time





With the advancement of precision medicine

there is an immense clinical need for

- accurate diagnosis of various phenotypes
- early detection of disease (changes)
- close and precise monitoring of disease/treatment response
- early prediction of response to treatment
- wide availability of – advanced – diagnostic tools.



Conclusions

- Challenges for response assessment with MRI
 - due to current and future therapeutic regimes
 - conventional MRI practically meaningless.

At present no reliable MR imaging marker of response in clinical trials
for assessing high-dose radiotherapy/immunotherapy/anti-angiogenic agents

- Perfusion MRI is ready for use.
- New imaging techniques on the horizon.
- Involvement of imaging experts in clinical trials essential.



Thank you for your attention

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