Outcome modeling & response prediction: the promise and challenges

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The needs of outcome modeling & response prediction in radiation therapy:

- Understanding the underlying biology of cancer response to treatment
- Design of new clinical trials
- Development of clinical decision support for personalized treatment

Outcome prediction and personalized treatment

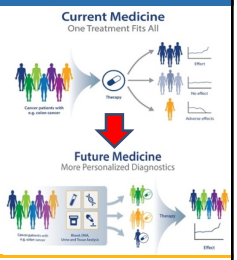
Current one-size-fits-all treatment is NOT optimal

- Inter-/intra- patient heterogeneity
- Inter/intra- tumor heterogeneity

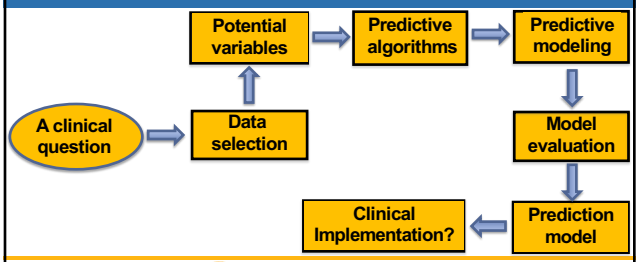
Personalized treatment to improve outcome

- To tailor therapy with the best response and highest safety margin to ensure better patient care.

Predicting the expected outcome is a critical step towards personalized treatment.



Building a prediction model: a schematic overview



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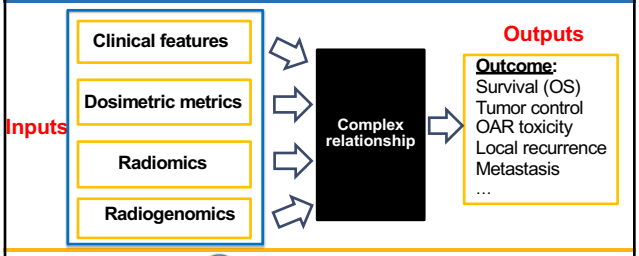
Factors for outcome modeling & prediction in RT



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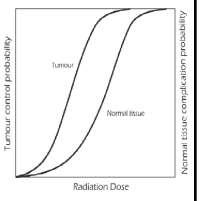
Outcome prediction: analytical approach

Analytical (mathematical) approach

- quantitative or computational in nature
- **known** underlying principles to predict clinical endpoint, i.e., LQ model, TCP/NTCP
- a set of mathematical equations
- overfitting with increasing model complexity
- certain simplifying assumptions

Sigmoidal shapes (S-curved)



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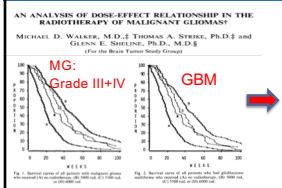
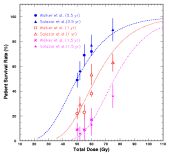
Prediction of overall survival for Malignant Glioma



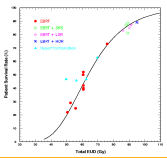
Rx dose: A) no RT; B) 5000 rad, C) 5500 rad; D) 6000 rad.

Walker et al, IJROBP 1979;5:1725-31.



Training datasets:
Walker et al., 632 pts
Salazar et al., 243pts

Validation datasets:
EBRT+SRS,
EBRT+LDR,
EBRT+HDR,
Hyperfractionation



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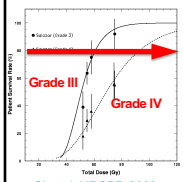
Qi et al, IJROBP, 2006; 64(5):1570-80.

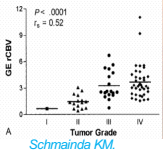
Personalized treatment planning guided by functional/biological images

Tumor Radiosensitivity | Perfusion MR images (rCBV) | Personalized RT

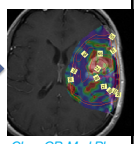


Grade 3:
$\alpha = 0.11 \pm 0.10\ Gy^{-1}$
$\alpha/\beta = 5.8 \pm 11.8$ Gy
Grade 4:
$\alpha = 0.04 \pm 0.06\ Gy^{-1}$
$\alpha/\beta = 5.6 \pm 9.4$ Gy

Qi et al, IJROBP, 2006.



Schmainda KM. Am J Neuroradiol 2004.



Chen GP. Med Phys 2007.

Tumor heterogeneity captured by functional/biological images to design personalized (non-uniform) treatment plan.

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Outcome modeling & prediction: data-driven approach

Data-driven approach (ML/DL)

- Dictated by the analysis of data to identify trends and correlations in Big data
- Underlying principles are **unknown** or **uncertain**
- Ideal for **high-dimensional** classification for prediction problems
- To build very predictive model, which can guide underlying (mechanism) insights

INPUT → [redacted] → OUTPUT

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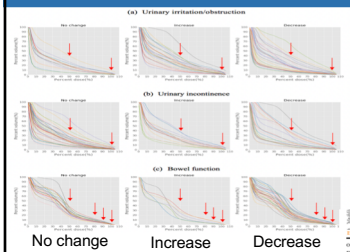
Dosimetric predictors of patient-reported toxicity after prostate SBRT treatment



- Training cohort: 86 pts
- Rx dose: 8Gy x 5
- Patient reported outcome (PRO): EPIC-26 score changes at baseline and 3- (acute toxicity), 12-months (subacute toxicity)
- Minimum important difference (**MID**) of 5/6/4 scores for (*Skolarus TA, et al, Urology 2015*)
  - (a) Urinary irritation
  - (b) Urinary incontinence
  - (c) Bowel function

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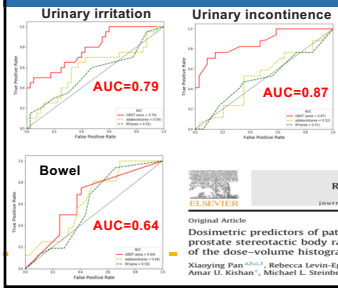
Prediction of patient-reported toxicity after Prostate SBRT: data-driven approach



- Ensemble ML methods
- **INPUTs:**
  - Patient-specific full bladder/rectal DVH (in 10 cGy increment)
  - Other dosimetric quantities from Eclipse TPS
- QOL score changes at 3- and 12- months
- Validated with an independent cohort of 26 pts

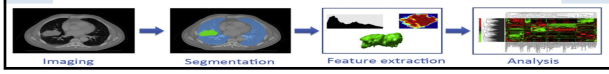
Radiomics: a high throughput approach to convert images to minable data

- Quantitative information from multi-imaging modalities: CT, PET, MRI, could be related to **biological** and **clinical endpoints**
- The imaging derived phenotypes can be linked with **genomic** data to **understanding underlying biology**.

Radiomics: Extracting more information from medical images using advanced feature analysis

Philippe Lambin [a,*,c,f], Emmanuel Rios-Velazquez [a,c], Ralph Leijenaar [a,c], Sara Carvalho [a,c], Ruud G.P.M. van Stiphout [a,c], Patrick Granton [a,c], Catharina M.L. Zegers [a,c], Robert Gillies [b,c], Ronald Boellard [c,e], André Dekker [a,c], Hugo J.W.L. Aerts [a,d,c]

P. Lambin et al. / European Journal of Cancer 48 (2012) 441–446



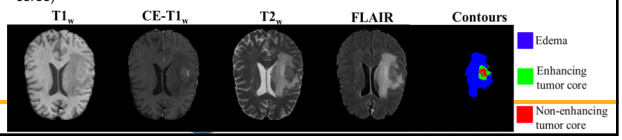
Subregion based radiomics analysis for survival prediction of GBM

Hypothesis 1: The existence of spatial heterogeneity (or regional variations) within a tumor.

Hypothesis 2: Auto GBM subregion segmentation is less sensitive to large inter-observer variations and may achieve the more accurate prediction.

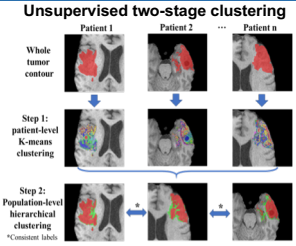
Dataset: 101 GBM patients from 2019 BraTS challenge - *Menze, B. H., et al (2014).*

- Four pre-operative MR images (T1w, CE-T1w, T2w, FLAIR)
- Manual contours of the three tumor subregions (edema, enhancing, and non-enhancing tumor cores)



Subregion-based radiomics analysis for improving GBM survival prediction

Unsupervised two-stage clustering



Two-stage clustering method for acquiring auto subregions:

- **Patient level**: K-means clustering method was applied on voxel intensity vectors to generate supervoxels. The mean intensity vector of each supervoxel was calculated.
- **Population level**: A hierarchical clustering method was applied on mean intensity vectors to generate auto subregion contours from the supervoxels. The optimal number of subregions was determined using the Calinski and Harabasz score.

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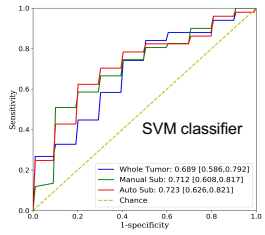
Fu, J, et al. AAPM 2020 Oral

Subregion-based radiomics analysis improving GBM survival prediction



Key results:

- Subregion-based radiomic features derived from manual or auto contours of GBM subregions achieved more accurate risk prediction than whole tumor-based ones.
- Auto subregion-based features achieved the best performance.
- Our study demonstrated the potential of using subregion-based features for improving survival risk prediction for GBM.

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Challenges for outcome prediction - Data

Quality, Quantity, Consistency, Standardization, Availability

- Useful/reliable data
- Data variation & inconsistency (i.e., reasonable to combine data)
- Unbiased data
- Data integration and interpretation
  - Heterogeneity of data types, sources, information content
  - Different formats across various information systems: EMR, PACS, patient reports, clinical notes, etc.
- Unbalanced data (i.e., smaller # of positive events)
- Incomplete data (i..e., not all data sources is available for all patients)
- …

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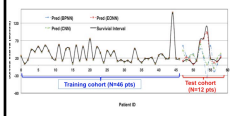
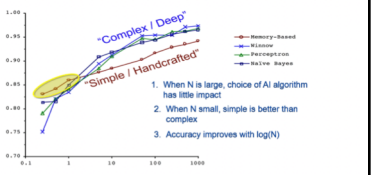
Effectiveness of Data sample

Prediction of overall survival for a cohort of 60 H&N patients (*Pan et al., AAPM 2017*)



The Unreasonable Effectiveness of Data



Courtesy of R. Gillies

Banko & Brill, Transactions of the Association for Computational Linguistics, 2001

UCLA Health | Dr. P. Lambin, AAPM webinar 2018

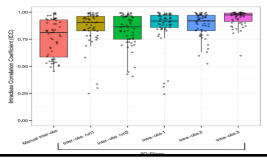
Challenges for predictive modeling - Radiomics

- Robustness and reproducibility of radiomics features
  - Imaging scanner type and manufacture
  - Imaging protocol: acquisition and reconstruction
  - Feature definition and extraction platform - **standardization**
  - ROI definition:

    Manual segmentation
    - User dependent
    - Large intra-observer variabilities

    Auto-segmentation algorithms:
    - Atlas based segmentation
    - Deep learning based segmentation

Parmar C, et al. PloS One. 2014; 9:e102107.



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Challenges for predictive modeling - Radiomics

- Model validation
  - Risk of overfitting
    - Number of imaging features >> number of patients
    - Feature selection/reduction to improve robustness, stability, reproducibility
  - Cross-validation (or bootstrapping)
  - External/independent patient cohort
    - Multi-institution studies often very heterogenous (i.e., PET>MR>CT)
    - Similar image quality and patient characteristics
    - Standardizing the validation process by adopting Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines

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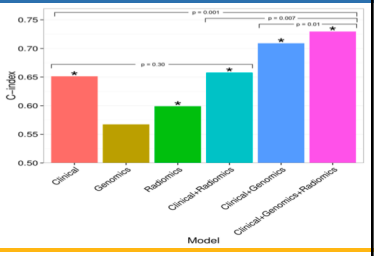
Overall survival prediction for Lung: combining radiomics with genomics and clinical signatures

Multimodal imaging of improving rectal pCR prediction



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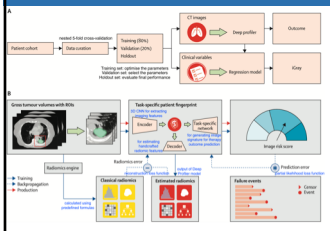
Grossmann, P et al. eLife 2017;6:e23421.

An image-based deep learning framework for Individualizing RT dose



- 944 Lung SBRT patients from multiple institutions
  - Training cohort: **847** pts
  - External validation cohort: **95** pts
- Pre-therapy lung CT images into a multi-task deep neural network (Deep Profiler) to generate an image singiture that predicts time-to-event treatment outcomes
- Integration of clinical variables + radiomics features in Deep Profiler to derive an individualized dose (iGray).

Lou B, et al. The Lancet Digital Health 2019

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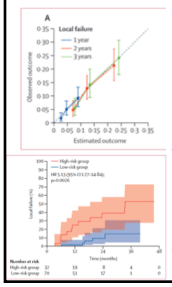
An image-based deep learning framework for Individualizing RT dose



Key clinical findings:

- Local failure can be significantly reduced as a function of dose
- iGray had a wider range, great variance than actual dose delivered, suggesting dose de-escalation in a subset of patients.
- Incremental increases in the the most frequent treatment dose can reduce treatment failure probability.
- Voxels localized to the peritumoral regions are predictive of local failure.

Lou B, et al. The Lancet Digital Health 2019

Summary

- With emerging AI/ML techniques and big data platforms, outcome modeling is transitioning from population-based into **individualized** response prediction.
- **Integration** of radiation (physics), biology (genomics), and imaging (radiomics) enable better understanding and prediction radiation response and personalized treatment.

Big Data is here to stay

Outcome modeling & response prediction is here to help improve our clinical decision making!

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2020 JULY 12–16 VIRTUAL EASTERN TIME (GMT-4) JOINT AAPM | COMP MEETING

Thank you !

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