Outcome modeling & response prediction: the promise and challenges

X. Sharon Qi, PhD
Dept. of Radiation Oncology,
UCLA School of Medicine, Los Angeles, CA

Understanding the underlying biology of cancer response to treatment

Design of new clinical trials

Development of clinical decision support for personalized treatment

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

- Potential variables → Predictive algorithms → Predictive modeling
- Data selection → Model evaluation → Prediction model
- A clinical question → Clinical Implementation?

Factors for outcome modeling & prediction in RT

- Inputs:
  - Clinical features
  - Dosimetric metrics
  - Radiomics
  - Radiogenomics

- Complex relationship

- Outputs:
  - Outcome: Survival (OS), Tumor control, OAR toxicity, Local recurrence, Metastasis

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
Prediction of overall survival for Malignant Glioma


MG: Grade III+IV GBM

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

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

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

Personalized treatment planning guided by functional/biological images

Grade III:
\[ \alpha = 0.11 \]
\[ \alpha / \beta = 5.8 \]

Grade IV:
\[ \alpha = 0.04 \]
\[ \alpha / \beta = 5.6 \]

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

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
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

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.
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.


- 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

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.

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.
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)
  - ...

Effectiveness of Data sample

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

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

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 heterogeneous (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 (TRIPD) guidelines

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

- Multimodal imaging of improving rectal pCR prediction

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 signature that predicts time-to-event treatment outcomes
- Integration of clinical variables + radiomics features in Deep Profiler to derive an individualized dose (iGray)

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

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 most frequent treatment dose can reduce treatment failure probability.
• Voxels localized to the peritumoral regions are predictive of local failure.


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!

Thank you!