Challenges on Assessment of Treatment Response for Physiologically Adaptive Radiation Therapy

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A tumor target volume could be defined and segmented as multiple biological target subvolumes.
The subvolumes defined by multiple physiological imaging studies should be prognostic or predictive indicators.
Biological Target Volume, Tx Predictor, Dose Adaption

Dose sculpting of multiple biological target subvolumes and adaptation based upon early response could lead to better outcome.

Imaging for Tx Assessment

Physiological adaptation

Dose sculpting & adaption

Ling, IJROBP, 2000

Cao AAPM 2013 5
How to Establish an Imaging Biomarker for Therapy Assessment

- Reproducibility
  - Separation of a true change from variation

- Sensitivity and specificity
  - Clinical end points, specific for tumor and therapy types

- Utility
  - Biomarker associated with failure/progression
  - Adaptive therapy for intensification or toxicity reduction
Heterogeneous Subvolumes in GBM

Post-Gd T1W

FLAIR

ADC

CBV/CBF

Vascular Permeability

C^{11}MET PET
Heterogeneous therapy response of a tumor could be primarily due to biological heterogeneity in the tumor.

The most aggressive or resistant sub-volume in a tumor could predominantly determine therapy response or outcome of a treatment to the whole tumor.

**Aims:** Extract the physiological imaging–defined tumor sub-volume that is:

- Predictive for treatment response
- Highly reproducible
- A candidate to be a boost target
High CBV: Prognostic Indicator in High-grade Gliomas

Small fractional TV w High-CBV

Great fractional TV w High-CBV

P=0.002

Cao, IJROBP, 2006
Change in high-CBV During RT

Pt A

Pre RT  Week 3

Pt B

Boost Volume?

Decrease  Little Change

Better OS  Worse OS
These early studies show that certain features of a tumor, and their changes during RT, which are identified by physiological imaging, are associated with outcome, or failure, and thereby can be candidates for radiation boosting or adaptation.
How to extract sub-volumes from a heterogeneous tumor

Feature (parameter) space

f1

f2

Bad features

Quantitative metric:
Subvolumes of the tumor with the “bad” features

Whether “bad” features decrease after receiving treatment?

Pre RT

3 wk during RT

Cao ARS 2013 12
Advanced HNC: ChemoRT

Study aim: To test whether the poorly perfused subvolume of the tumor that persists during the early course of RT is associated with LR failure.
Poorly Perfused Sub-Volumes in Advanced HN Cancers

Blood Volume (BV)

Local Failure

Local Control

Poorly perfused Subvolume

The large sub-volumes of the tumors with low BV (blue color) pre-Tx is significantly associated with LF. Wang, et al Med Phys 2012
The large sub-volumes of the tumors with low BV (blue color) pre-Tx and persisting during the early course of CRT (2 weeks) are significantly associated with LF.
Prediction of Local Failure


85% sensitivity and 91% specificity
Association with Pattern Failure

Poorly-perfused Subvolume of the Tumor pre RT

FDG 3 moths post RT
Subvolumes of a Tumor

- A physiological imaging defined response-induced subvolume of a tumor is a better predictor for outcome and could be a candidate for an intensified therapy target.
- Our approach can be applied to other physiological/metabolic imaging parameters.
- Our method does not depend upon voxel-level accuracy of registration of a pair of images acquired over a period of therapy.
- Our method produces metrics robust to image noise and other random factors.
Additive Value of Diffusion Imaging in HNC

Subvolume with low BV (poor perfusion) and low ADC (high cellularity) -> Outcome?
Subvolume of the tumor with high Cellularity

ADC map pre-RT

Prediction for local and regional failure

3.2x10^{-3} \text{ mm}^2/\text{s}

GTV

Low ADC

TPR (Sensitivity)

FPR (1-Specificity)

pre RT

Wk2
Aim: Test whether a decrease in the subvolume of the tumor with elevated CBV and high vascular permeability at the end of RT is associated with post-RT response.
Brain metastases (Farjam 2013)

Create a single metric, a subvolume of a tumor with high CBV, $K^{\text{trans}}$, or both, for assessment of response.
Does the tumor subvolume with high CBV predict response?

- **End point**
  - Post-RT radiographic response
    - $\Delta \text{GTV}_{\text{post}} = \text{GTV}_{1\text{m post}} - \text{GTV}_{\text{preRT}}$
    - Non-responsive: $\Delta \text{GTV}_{\text{post}} < -25\%$

- **Early prediction for non-responsive tumors**
  - A change in the subvolume with high CBV, high $K^{\text{trans}}$, or both at the end of WBRT
Sensitivity and Specificity

Prediction for non-responsive tumors

AUC

0.86 ± 0.06
0.80 ± 0.07
0.70 ± 0.08
0.66 ± 0.08
0.61 ± 0.08

Farjam, et al
Red J 2013
Intrahepatic Cancer: RT

Aim: Test whether an increase in the subvolume of the tumor with elevated hepatic arterial perfusion after receiving 60% of treatment of RT is associated with progression.
Perfusion in Hepatic Cancer

Normal liver: ~20% arterial perfusion and ~80% portal venous perfusion

Intrahepatic cancer: elevated arterial perfusion and decreased portal venous perfusion
Hepatic cancer: high arterial perfusion subvolume

Wang, AAPM 2013
Sensitivity and Specificity

Prediction of progression

![Graph showing sensitivity and specificity](image-url)
Adaptation: targeting the active residual tumor

SBRT Standard course
55 Gy (5 Fx)
NTCP: 10%

SBRT Adaptive course
80 Gy (5 Fx)
NTCP: 10%

M. Matuszak, M. Feng, 2013
Summary

- Imaging-defined response-derived subvolume
- Dose adaption & boosting
MET Uptake is associated with Patterns of Failure (Lee & Tsien, 2009)
Permeability: Prognostic indicator for high-grade gliomas

- Large vascular leakage volume, reflecting angiogenesis, was associated with worse OS
- Post-Gd T1 or FLAIR GTV failed to predict OS

Cao, Cancer Research, 2006
Poorly Perfused Subvolumes in HNC

Pre RT

2 Wk during RT
Fuzzy-Subvolume Model

Cluster analysis:
PMF({f}, class_1)
...
PMF({f}, class_j)
...
{f}: a set of parameters

Joint histogram of a set of tumors

New tumor

PMF({f}, {class})

Probability belonging to the low BV class