Learning Objective

- To recognize the strengths and limitations of existing normal tissue imaging biomarkers (IBs) used in the routine care of cancer patients and emerging IBs at various stages of development.

Outline

- Introduction
- IBs used in routine clinical care
  - Heart: Left ventricular ejection fraction
- IBs used as clinical research tools
  - Brain: choline-creatine ratio
  - Lung: ventilation or perfusion
  - Pelvis: 18F-FDG uptake in bone marrow
- Limitations, challenges and opportunities
- Summary

Normal Tissue IBs

- Jeraj et al. (IJROBP 2010)
- IB Roadmap for Cancer
- O’Connor et al. (Nat Rev Clin Oncol 2017)

Normal Tissue Imaging Biomarkers

Tokihiro Yamamoto, Ph.D.
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Left ventricular ejection fraction (LVEF)

- The volumetric fraction of blood ejected from the left ventricle with each contraction
- The most widely used IB to monitor the changes in cardiac function during/after chemotherapy and to detect cardiac toxicity
- Modalities: Echocardiography, scintigraphy/SPECT, MRI

Consensus Recommendations for Detection of Cardiac Toxicity

- Cancer therapeutics-related cardiac dysfunction is defined as a decrease in LVEF of >10% to a value <53% (normal reference value for 2D echocardiography).
- Different techniques use different normal reference values.
- The same imaging technique should be performed for baseline and follow-up studies.
- LVEF has low sensitivity for detection of small changes in LV function.
LVEF: Inter-Modality Variability

- International multisite study for 2,032 patients
- There was substantial inter-modality variability in LVEF between echocardiography, SPECT and MRI
- Only 43-54% of LVEF measurements agreed within 5%

[Ref: Pellikka et al. (JAMA Network Open 2018)]

LVEF vs. Cardiac Toxicity

- 2,043 patients enrolled
- 31 of 850 trastuzumab-treated patients experienced congestive heart failure
- Congestive heart failure was more frequent in patients with a reduced LVEF at baseline or after anthracyclines

[Ref: Tan-Chiu et al. (J Clin Oncol 2005)]

LVEF: Key Points

- LVEF has crossed the two translational gaps and is widely used in routine clinical care of cancer patients.
- There is an extensive literature on precision and associations with clinical outcomes of chemotherapy.
- There is little or no evidence for associations with outcomes of radiotherapy (RT).
- 2D echocardiography and scintigraphy/SPECT are more widely available and cheaper compared with 3D echocardiography and MRI.

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Brain MR Spectroscopy

Choline-Creatine (Cho/Cr) Ratio

- Increased Cho level in brain tumors
- Decreased Cho level in RT-induced brain injury
- Cr, a marker of energy metabolism, is stable under most conditions

[Ref: Plotkin et al. (J Neurooncol 2004)]

Cho/Cr: Sensitivity/Specificity

[Ref: Zhang et al. (Eur J Radiol 2014)]
Lung Ventilation or Perfusion

- Can be used to guide functional avoidance RT and to monitor the changes in lung function during/after RT
- Modalities
  - Ventilation: Biphasic/4D CT, dual-energy CT, SPECT, PET, MRI
  - Perfusion: Dual-energy CT, SPECT, PET, MRI

Ventilation vs. Pulmonary Toxicity

- A 70-patient study quantified predictive power of dose-volume and 4D CT ventilation-based dose-function metrics for grade ≥2 pneumonitis
  - Dose-function metrics had greater AUC values

Perfusion vs. Pulmonary Toxicity

- A 58-patient study quantified predictive power of dose-volume and SPECT perfusion-based dose-function metrics for grade ≥2 pneumonitis
  - Functional MLD had greater AUC value

Functional Avoidance RT Clinical Trials for Lung Cancer

<table>
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<th>Institution</th>
<th>Endpoint</th>
<th># of participants</th>
<th>Allocation</th>
<th>Modality</th>
<th>ClinicalTrials.gov ID</th>
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18F-FDG Uptake in Pelvic Bone Marrow

- 18F-FDG PET allows for measurement of metabolic activity of bone marrow
- 18F-FDG uptake in the skeleton is caused by active hematopoietic bone marrow
- Uptake pattern and amount vary with age and level of marrow function

Bone Marrow-Sparing RT Clinical Trial for Cervical Cancer

- Endpoint: Grade ≥3 neutropenia or clinically significant GI toxicity
- 83 patients enrolled at 8 sites
- 48 patients underwent CT-based IMRT
- 35 patients underwent PET-based active bone marrow-sparing IMRT
Bone Marrow-Sparing RT Clinical Trial for Cervical Cancer

Limitations and Challenges
- Little evidence from adequately powered, randomized controlled trials specifically designed to test an IB
- Limited statistical power
- Limited data on precision
- Variations in endpoints, treatment modalities, imaging modalities, image acquisition and analysis across studies

Opportunities for Progress
- Multisite reproducibility
- Standardization/harmonization to improve precision
- Multisite randomized controlled trials
- Data sharing/pooling

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Summary
- There are many published normal tissue IBs in the literature, but only a few are widely used.
  - LVEF has been used in routine clinical care.
  - There are many emerging normal tissue IBs that have great potential to improve cancer therapy or detection/monitoring of toxicity.
- Key steps for successful clinical translation include large-scale validation studies through collaboration.

Thank You!