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**Image-Guided Radiation Therapy: the potential for imaging science research to improve cancer treatment outcomes<sup>1</sup>**

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The role of medical imaging in the planning and delivery of radiation therapy (RT) is rapidly expanding. This is being driven by two developments: Image-guided radiation therapy (IGRT) and biological image-based planning (BIBP). IGRT is the systematic use of serial treatment-position imaging to improve geometric targeting accuracy and/or to refine target definition. The enabling technology is the integration of high-performance three-dimensional (3D) imaging systems, e.g., onboard kilovoltage x-ray cone-beam CT, into RT delivery systems. IGRT seeks to adapt the patient's treatment to weekly, daily, or even real-time changes in organ position and shape. BIBP uses non-anatomic imaging (PET, MR spectroscopy, functional MR, etc.) to visualize abnormal tissue biology (angiogenesis, proliferation, metabolism, etc.) leading to more accurate clinical target volume (CTV) delineation and more accurate targeting of high doses to tissue with the highest tumor cell burden. In both cases, the goal is to reduce both systematic and random tissue localization errors (2-5 mm for conventional RT) conformality so that planning target volume (PTV) margins (varying from 8 to 20 mm in conventional RT) used to ensure target volume coverage in the presence of geometric error, can be substantially reduced. Reduced PTV expansion allows more conformal treatment of the target volume, increased avoidance of normal tissue and potential for safe delivery of more aggressive dose regimens. This presentation will focus on the imaging science challenges posed by the IGRT and BIBP. These issues include: *Development of robust and accurate nonrigid image-registration (NIR) tools:* Extracting locally nonlinear mappings that relate, voxel-by-voxel, one 3D anatomic representation of the patient to differently deformed anatomies acquired at different time points, is essential if IGRT is to move beyond simple translational treatment plan adaptations. NIR is needed to map segmented and labeled anatomy from the pretreatment planning images to each daily treatment position image and to deformably map delivered dose distributions computed on each time instance of deformed anatomy, back to the reference 3D anatomy. Because biological imaging must be performed offline, NIR is needed to deformably map these images onto CT images acquired during treatment. *Reducing target and organ contouring errors:* As IGRT significantly reduces impact of differences between planning and treatment anatomy, RT targeting accuracy becomes increasingly dominated by the remaining systematic treatment-preparation errors, chiefly error in delineating the clinical target volume (CTV) and organs-at-risk. These delineation errors range from 1 mm to 5 mm. No single solution to this problem exists. For BIBP, a better understanding of tumor cell density vs. signal intensity is required. For anatomic CT imaging, improved image reconstruction techniques that improve contrast-to-noise ratio, reduce artifacts due to limited projection data, and incorporate prior information are promising. More sophisticated alternatives to the current concept fixed boundary anatomic structures are needed, e.g., probabilistic CTV representations that incorporate delineation uncertainties. *Quantifying four-dimensional (4D) anatomy:* For adaptive treatment planning to produce an optimal time sequence of delivery parameters, a 4D anatomic representation, the spatial trajectory through time of each tissue voxel, is needed. One