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Quantitative Imaging in Radiation Oncology: An Emerging Science and Clinical Service

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Radiation oncology has long required quantitative imaging approaches for the safe and effective delivery of radiation therapy. The past 10 years has seen a remarkable expansion in the variety of novel imaging signals and analyses that are starting to contribute to the prescription and design of the radiation treatment plan. These include a rapid increase in the use of magnetic resonance imaging, development of contrast-enhanced imaging techniques, integration of fluorinated deoxyglucose–positron emission tomography, evaluation of hypoxia imaging techniques, and numerous others. These are reviewed with an effort to highlight challenges related to quantification and reproducibility. In addition, several of the emerging applications of these imaging approaches are also highlighted. Finally, the growing community of support for establishing quantitative imaging approaches as we move toward clinical evaluation is summarized and the need for a clinical service in support of the clinical science and delivery of care is proposed.
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Introduction

The promise of personalized cancer medicine requires robust, quantitative measurements to stratify prognosis and predict response on a patient-by-patient basis. These measures include tissue-derived and serum-derived markers, as well as those derived from medical imaging. Furthermore, it is becoming recognized that personalization would also include assessing response and adapting an individual patient's treatment during the course of therapy.[1] Such approaches further motivate image-based techniques that can assess the state of the disease in the context of ongoing treatment. Radiation therapy (RT) has taken the lead in the integration of imaging data into the design of highly personalized cancer treatments. The initial use of computed tomography (CT) in radiotherapy was motivated by the desire to improve the accuracy of dose calculations, and the image-based approach to target and normal tissue delineation has transformed the field over the past 20 years. This includes the development of conformal and intensity-modulated techniques that are able to shape the prescribed radiation dose levels to the CT-defined anatomy of each patient. The rapid uptake of CT in radiotherapy has been enabled by the technology's intrinsic geometric accuracy and its ability to provide quantitative estimates of the attenuation coefficients of tissue within the body (or scaled relative to water to provide Hounsfield Units). Although advances in CT continue to bring benefits to radiotherapy, there is an accelerated growth in the integration of new forms of imaging data into the radiotherapy prescription and planning process.

The ever-advancing development of more sensitive and specific imaging signals from magnetic resonance imaging (MRI), positron emission tomography (PET), and

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Drs. Coolens and Keller have a patent on the flow phantom described in Figure 1 and it is licensed to Shelley Medical, London, Canada.
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single-photon emission tomography, as well as continued advances in CT, suggests that this trend is not going to slow. These new imaging signals are being used as *predictive* image-based biomarkers before treatment, for improved *delineation* of target and normal structures for treatment planning, for image-based guidance of *dose painting*, as well as anatomical and functional imaging during treatment for purposes of *adaptation*. The potential effect on RT outcomes is significant, and the challenge of bringing many new image-based signals "on-line" as reliable and quantitative inputs to an increasingly protocoled approach to radiotherapy treatment design is not a minor endeavor.

The transition from conventional staging approaches for the prognostication of a patient population outcome to the development of "biomarkers" that predict individual treatment response is occurring across the field of oncology. These biomarkers can be derived from any validated data source and do not necessarily need to be supported by mechanistic arguments.[2] Image-based data sources are an emerging and important source for new biomarker development that go beyond their conventional uses for assessing tumor size and regional progression. Some of these are based on molecular imaging techniques, such as conventional fluorinated deoxyglucose (FDG)–PET imaging of metabolic activity, or emerging data on the assessment of the microenvironment in terms of the fraction of tumor that is considered hypoxic using techniques such as ^{18}F-misonidazole (FMISO) or ^{18}F-fluoroazomycin–arabinoside (FAZA)–PET. These, among other functional imaging biomarkers for the prediction of response (eg, diffusion-weighted imaging [DWI] with MRI and MR spectroscopy [MRS]), are now positioned to directly affect the radiation prescription.

In addition to new imaging signals, the development of machine learning approaches in the field of genomics has supported the development of "radiomic" techniques that employ image features (eg, texture metrics) extracted from conventional CT images.[3] These are included in a bioinformatics framework to identify predictors of response and have demonstrated remarkable potential to isolate cohorts of differential clinical outcomes in validation studies.[3]

The accuracy of delineating target and normal tissues is critical for local control in radiotherapy. Advances in the conformality and precision of radiation dose delivery elevate the risk of being "precisely wrong" in dose placement. Numerous articles demonstrate the variability in target and normal structure delineation between practitioners.[4] This is because of the (1) variations in the practitioners understanding of the assigned task and (2) the lack of clear boundaries in the imaging signals to define the tumor or normal tissues or both. There are numerous efforts underway to increase the contrast-to-noise ratio and specificity of imaging signals used in simulations including the use of dual-energy CT, integration of MR simulators into RT planning, use of FDG-PET, and even integration of endoscopy to facilitate delineation.[5] The development of dual-energy CT techniques provides additional quantification of material properties for range estimation in particle therapy.[6] The past 5 years has demonstrated a rapid increase in the use of the MRI in the treatment planning process as a means of augmenting conventional CT simulation.[7] The use of specific MRI techniques for target and normal tissue delineation is considered to be the best practice for RT treatment planning for many treatment sites within the body, with the exception of lung cancer.[8] This trend is poised to increase with the rapid adoption rate of dedicated MRI scanners in radiation oncology departments. Geometric inaccuracy remains a persistent challenge to direct integration of MRI data into treatment planning. Geometric integrity is an important part of quantitative imaging that is often overlooked and must be considered part of quantitative imaging research efforts. A well-quantified, but misplaced, signal can hardly be considered quantitative in a treatment that is so dependent on geometric targeting.

The very nature of radiotherapy allows the clinician to prescribe nonuniform patterns of dose and therefore go beyond simple binary definitions of the target and normal tissue. The concept of dose modulation or "dose painting" explores the use of quantitative measures of either the disease burden (eg, clonogen density) or cellular radioresistance to calculate an appropriate dose to be applied on a voxel-by-voxel basis.[9] Although an elegant framing of the opportunity, the implementation is quite complex depending on the accuracy of the image-based reporter, presence of artifacts, geometric fidelity, image registration, and, of course, the quantitative performance of the imaging system. Jeraj et al have explored this topic at length and demonstrated some of the challenges associated with linking image-based measures of hypoxia and the corresponding need for dose escalation.[10] For example, using oxygen enhancement ratios determined from in vitro studies to determine dose escalation in a solid tumor in a patient is hard to justify. This is independent of the known problem of partial volume effects in PET imaging and its effect on accurate concentration recovery.[11] The same paradigm is also being explored using multiparametric MRI (mpMRI) to identify a volume for boosting of the "dominant lesion" in the prostate gland.[12] The quantification challenges here include pathology validation, as well as geometric registration of the various MRI signals, such as DW-MRI, to generate a robust composite volume for dose escalation.[13]

The gradual response of the disease to the applied radiation dose opens the powerful paradigm of *adaptation*. Adaptation involves changing the radiotherapeutic intervention as the dose is being applied to increase probability of local control, diminish normal tissue toxicity, or both. This is a powerful paradigm of personalization that integrates changes in both geometric and functional or biological information into the design of the treatment as it progresses. Advances in computational capacity, as well as delineation and deformation tools, have made this paradigm possible with several investigators exploring the potential benefit through both in silico studies[14,15] as well as clinical trials.[16] Central to the adaptation paradigm is that changes in geometry and signal are valid representations of the anatomy or functionally defined gross tumor volume (GTV). Although geometric changes are relatively straightforward (assuming consistent delineation practices and consistent imaging protocols), functional readouts are highly vulnerable to variations in patient preparation, injection, scanning protocols, and as well as the