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Image-based Biomarkers in Clinical Practice

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Abstract

The growth of functional and metabolically informative imaging is eclipsing anatomic imaging alone, in clinical practice. The recognition that MR and PET-based treatment planning and response assessment are essential components of clinical practice and furthermore offer the potential of quantitative analysis is important. To extract the greatest benefit from these imaging techniques will require refining the best combinations of multimodality imaging through well designed clinical trials that employ robust image-analysis tools and require substantial computer based infrastructure. Through these changes and enhancements, image-based biomarkers will enhance clinical decision making and accelerate the progress that is made through clinical trial research.

Introduction

Departments of radiation oncology were recently well recognized divisions within radiology departments. Because of increasing complexity, substantial separation of residency training requirements and its unique focus on therapeutic endeavors for cancer, as opposed to diagnostics, the vast majority of radiation oncology divisions are now independent departments. While this is a positive development in the recognition and development of our field, we paradoxically find ourselves increasingly engaged in the application and evaluation of imaging for staging (and hence decision making), treatment, targeting and determination of response to therapy.

The rapid proliferation of functional and metabolically informative imaging agents goes far beyond the common standards of fluoroscopic simulation that comprised the image-based training of many active radiation oncologists. The adoption of computed tomography (CT)-

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based and megavoltage portal image-planning in the 1990's, has given way to the common recognition that magnetic resonance (MR) based planning is an advantage for many sites of disease (the brain for example) and most recently that positron emission tomography (PET) based imaging and functional MR may have an even greater impact. This, along with the growth of both functionally relevant MR techniques and new molecular imaging agents makes imaging an essential component of clinical practices.

The potential of imaging to directly impact our practical decision making for our patients has never been greater. This complexity requires enhanced training for the radiation oncologist and invites important paradigm shifting studies that utilize the potential of image-based therapy and decision making. While clinical acumen remains vital, the impact of image-based staging, treatment targeting and response assessment are becoming paramount to our future success.

Prognostics To Assess The Need For/Value Of A Given Therapy

Positron Emission Tomography—Fluorodeoxyglucose (FDG)-PET imaging is commonly used to demonstrate the indication for radiation therapy. Many patients receive a FDG PET/CT prior to surgery and find evidence of previously unidentified metastatic disease, resulting in their being upstaged and no longer a surgical candidate. Other patients are identified as candidates for radiation therapy once PET/CT imaging demonstrates they are not responding to chemotherapy. Scientific literature has many examples of several disease sites where this is true, including non-small cell lung cancer, small cell lung cancer, tumors of the head and neck, esophageal cancer, and pancreatic cancer. This imaging modality has become the preferred method for staging and decision making in several disease sites.

Patients who are being planned for radiation therapy can also benefit from molecular imaging; this is seen clearly in patients being treated for lymphoma. In a prospective multi-institutional study, Pommier *et al*⁽¹⁾ considered the impact of pre-radiation therapy FDG-PET in the management of lymphoma patients. Eight institutions collected images from a combination of 16 children and 108 adult patients and found significant modifications of the treatment strategy in nearly 1 of 6 patients, ranging from modifications to the plan (13% of patients) to cancellation of radiotherapy (5% of patients). Those patients cancelling radiation therapy did so predominately due to inadequate response, but also from patient refusal following complete response detected by PET/CT. Furthermore, several recent trials make clinical decisions based on response to chemotherapy indexed by PET/CT or Single Photon Emission Computed Tomography (SPECT), (COG 0532/HD protocol). Initial PET volumes are identified as treatment targets in other patients. Radiation therapy modifications included changes to the CTV volume by more than 25% (4% patients) or number of CTVs (5% patients), beam configurations used to create the desired dose distribution (5% patients), and the total dose prescribed by more than 10% (9% patients). Robertson *et al*.⁽²⁾ retrospectively reviewed the role of FDG-PET in 30 pediatric Hodgkin's lymphoma patients treated over a nearly 5 year period and concluded that this functional imaging approach influenced the initial staging and treatment volume. Although the majority of the 546 regions analyzed were in agreement (86%), extranodal sites were found to be problematic.

Regions that were discordant were most likely PET positive and CT negative. PET imaging resulted in a change in staging in 15 (50%) patients, and modifications to in-field radiation therapy volumes in 21 (70%) patients (32 sites added and 15 excluded).

Reviews by Belkacemi *et al.*⁽³⁾ and Saleem *et al.*⁽⁴⁾ succinctly summarize studies in which the role of PET imaging can indicate tumor radiosensitivity. Labeled amino acids (F-DOPA, CII – methionine) can identify cell proliferation and protein synthesis. Labeled nucleosides directly test cell proliferation and DNA synthesis. Several agents now being studied demonstrate tissue hypoxia via either selective or reduced uptake in hypoxic cells (F-Misonidazole, Cu-ATSM, HX-4). Hormones, EGF, and R-EGF show cell proliferation and through either intracellular incorporation or cell fixation the presence of specific receptors and/or growth factors (Octreotide, prostate specific membrane antigen, somatostatin analysis). Other agents directly measure necrosis and apoptosis. Although many remain promising, evaluation of the radiosensitivity of a tissue prior to radiotherapy exposure requires further research.

Magnetic Resonance Imaging (MRI)—Magnetic resonance spectroscopic imaging (MRSI) enables analysis at the metabolic level. Crehan *et al.*⁽⁵⁾ in a retrospective review, showed that MRSI can identify both the tumor volume as well as metabolic activity in prostate cancer. Metabolic imaging data from 72 men who were stratified by risk (low=26, medium=24, high=22) were acquired at 3T using a phased array coil, obviating the need for an endorectal coil that distorts patient anatomy. They found the MRSI based tumor volumes were significantly different from anatomic volumes ($p=0.03$) and correlated with increased PSA levels ($p=0.012$). MRSI is also an effective prognostic tool for evaluating gliomas. In a study of 72 patients with glioma, Li *et al.*⁽⁶⁾ found that a high choline-to-creatine ratio, a high choline to N-acetyl aspartate ratio, a high lactate and lipid concentration and a low creatine to N-acetyl aspartate ratio, were all associated with poor prognosis, when evaluated with proton MRSI. In pediatric brain tumors, Warrant *et al.*⁽⁷⁾ found a low choline to N-acetyl aspartate ratio was predictive of a good prognosis ($P < 0.0067$). They also showed ^{31}P MRSI to be a useful prognostic tool for bone sarcoma, where 20 patients demonstrated a high nucleoside-tri-phosphate to inorganic phosphate ratio conferred with a good prognosis ($P < 0.003$).

In addition to being used as a prognostic tool, MRSI may be useful in revealing metabolically active tumors that extend beyond the morphological mass typically identified on a T1 or even T2 weighted image. In a retrospective review of 15 glioma patients Muruganandham *et al.*⁽⁸⁾ found significant differences between morphologically defined tumor volumes (T1 and T2) and metabolic tumor volumes identified by MRSI. An example is shown in figure 1, where the choline-to-N-Acetyl aspartate ratio of 2.0 is shown as a thermal colorwash superimposed on the treatment planning CT, T1-contrast enhanced MRI, and T2 weighted 2D turbo spin echo MRI. The MRSI data was acquired at 3T (Siemens Trio TIM) using point resolved spectroscopy. This example is representative of all patients within the study, where two common characteristics were seen: 1) metabolic tumor volumes were consistently smaller than those defined by morphological imaging, and 2) metabolically active volumes typically extended beyond both the gross tumor volume and even the clinical target volume. The implications for successful radiation therapy are clear.

Several investigators have used dynamic contrast enhanced (DCE) MRI to predict prognosis but have had limited success, due to insufficient patient numbers and follow-up. Nevertheless, a few reports have associated certain quantitative MRI criteria with tumor characteristics having prognostic value. Alonzi and Hoskin⁽⁹⁾ provide a review article that summarizes the role of functional MRI in several cancer types: central nervous system, prostate, lung, breast, kidney, cervix, rectum, and metastatic disease. In breast cancer, DCE is being used to differentiate between fibrocystic disease, ductal carcinoma *in situ* (DCIS) and invasive cancer. DCE MRI was used to differentiate between high- and low-grade lesions in a study of 39 patients⁽¹⁰⁾, and to successfully predict the presence of axillary lymph node metastases ($P<0.01$)⁽¹¹⁾. In cancer of the cervix⁽¹²⁾ and prostate⁽¹³⁾ DCE MRI has been used to identify angiogenesis, which correlates with outcome.

In addition to DCE and MRSI, blood-oxygen level dependent (BOLD) MRI is a functional imaging technique that indirectly measures the oxygenated state of the blood. BOLD MRI has been used in prostate to identify extra-capsular spread⁽¹⁴⁾. BOLD MRI is being evaluated as a tool to assess hypoxia⁽¹⁵⁾, which reduces the sensitivity of tumors to radiation therapy. O'Connor *et al.*⁽¹⁶⁾ used BOLD to measure induced changes in tissue oxygenation concentration in a series of 10 patients with cervical, hepatocellular, and metastases from ovarian and colorectal carcinoma. While competing with many PET agents to understand hypoxia, BOLD MRI is a non-radiographic means that may provide new momentum into studying the temporal and spatial maps of hypoxia within tumors. Challenges to BOLD MRI include the relative nature of the measurement, and its dependence on blood volume, flow, and pH.

Diffusion weighted imaging is a method of measuring the Brownian motion of water molecules which tends to differ in tumors due to loss of tissue structure, disrupted cell membranes, and a reduction in interstitial pressure. The flow of water molecules between tissue compartments is quantified by the apparent diffusion coefficient (ADC). This technique has been used to differentiate between malignant and benign tumors in the parotid⁽¹⁷⁾ and prostate⁽¹⁸⁾, and has been used to distinguish between recurrent gliomas and necrosis⁽¹⁹⁾. Finally, ADC maps were found to be predictive of response in a series of 14 patients with colorectal cancer receiving chemoradiation⁽²⁰⁾.

Early Assessments To Stop Or Alter The Course Of A Given Therapy

Functional and molecular imaging techniques can be used to evaluate the response of either the tumor or the normal tissues during the course of therapy. This information could be used to adapt treatments as the tumors and normal tissues change during therapy, alter the course of treatment when no response occurs, or potentially reduce toxicity by withholding additional dose once complete response has occurred. As such, many investigators are looking to functional and molecular imaging to provide metrics that can be correlated with outcomes.

In a prospective study of 20 cervical cancer patients Harry *et al.*⁽²¹⁾ showed diffusion-weighted magnetic resonance imaging (DWI) as an early response indicator. DWI was carried out prior to chemoradiation, repeated after 2 weeks of therapy, and again at the conclusion of therapy. Both the ADC values and their change after 2 weeks of therapy

showed a significant correlation with eventual MR response ($p < 0.05$) and clinical response ($p < 0.03$). Retrospectively, Mayr *et al.* ⁽²²⁾ utilized DCE to show that longitudinal tumor perfusion changes during RT correlate with ultimate treatment outcome. When analyzing DCE-MRI in 98 patients they found persistently low perfusion (prior to RT, following 2 weeks of RT, and following 5 weeks at 10 Gy/week) indicated high risk of treatment failure, while those with initially high perfusion or more importantly, substantial improvement had favorable outcomes ($p=0.003$). FDG-PET imaging has also been used to show treatment response in cervical cancer. Schwarz *et al.* ⁽²³⁾ found complete metabolic response during radiation therapy for a 6 of 36 patients studied, while 26 had a partial metabolic response and 4 had stable or increased tumor metabolic activity. The median time to complete response was 29.5 days for those having a complete response.

Menda *et al.* ⁽²⁴⁾ reported using fluorothymidine (FLT)-PET to assess tumor response after the first week of chemoradiotherapy. An image of one subject is shown in figure 2. These images show that an index of proliferation can be used to assess outcome both pre-therapy and at early timepoints. Preliminary data suggest initial low proliferation may be an indicator of ultimate failure to control disease chemoradiotherapy.

Muruganandham *et al.* ⁽²⁵⁾ has shown a positive correlation between MRSI changes in tumor metabolic activity at 3 weeks of treatment and disease control in glioma patients. Data from one subject is presented in figure 3. This data suggests that the initial change in a choline-NAA ratio after 3 weeks predicts early failure versus more sustained local control. This combined with previously discussed implications on targeting makes new approaches to therapy based on MRSI intriguing.

Ding *et al.* ⁽²⁶⁾ utilized 4DCT to compute pulmonary function changes. An example is shown in figure 4, where the subject's pulmonary function was determined from a 4DCT scan acquired prior to therapy, and again once the subject had received 13 of 37 prescribed fractions (23.4 Gy of 66.6 Gy prescribed). The first and second column show a colorwash display of pulmonary function, while the third column is the difference between the two. The final column shows the planned radiation dose distribution after 13 fractions of therapy. During the third week of radiation therapy, changes in pulmonary function were observed. Analysis for correlation to rethink the outcome is pending. Such studies illustrate that even 4DCT may be a means of obtaining important regional lung function information that could also be used for treatment planning (ie, deposit more radiation through less functional areas of lung to avoid long term sequelae).

Post-Treatment Assessment To Gauge Treatment Effectiveness

FDG has been proven a useful tool in assessment of radiation therapy treatment effectiveness in head and neck cancer. Yao *et al.* ⁽²⁷⁾ have shown the accuracy and prognostic significance of post-treatment FDG-PET in squamous cell carcinoma after radiotherapy in a retrospective study of 188 head-and-neck patients. Based on a median follow up after RT of 32.6 months, they found patients with positive post-RT PET findings had significantly worse 3-year overall survival (42.5% vs 70.5%, $p<0.001$) and disease-free survival (57% vs. 73.6%, $p=0.005$). Patients were imaged at 15 weeks post-RT (median). They reported the sensitivity, specificity, positive predictive value, and negative predictive

value for FDG-PET in the assessment of the treatment response in the neck / primary site to be 86% / 86%, 97% / 86%, 71% / 32.4%, and 99% / 98.7%, respectively. The greatest challenge was interpreting the primary site, where two false negative findings were reported in 151 patients, and 25 false positive were reported in 37 patients with positive FDG-PET findings.

In an earlier retrospective study of 53 head-and-neck patients spanning 5 years, Yao *et al.*⁽²⁸⁾ showed the ability of FDG-PET to indicate the need for post-RT neck dissection. Of the 42 patients who had no evidence of residual lymphadenopathy and a negative FDG-PET scan 12 weeks after definitive radiation, the negative predictive value of PET was 100%. They concluded in these cases neck dissection can be safely withheld, even in cases in which residual lymphadenopathy remains. This has substantially altered the general approach to manage the neck following chemotherapy.

Kamel *et al.*⁽²⁹⁾ showed that for patients with hepatocellular carcinoma receiving TACE, tumors decreased in size and enhancement with increasing ADC values.

Marcus *et al.*⁽³⁰⁾ provides an overview of Dynamic Contrast Enhanced (DCE)-MRI, DCE-(CT) and DCE-ultrasonography (US) as techniques for evaluating and monitoring treatment responses. Price *et al.*⁽³¹⁾ investigated the ability of functional imaging to quantify the effects of radiation therapy damage to normal brain tissue.

Infrastructure Needs To Support These Efforts

Quality Assurance—Few institutions perform quality assurance on their imaging systems with the intent of using the images for quantitative analysis. Rather the focus is on reading images for diagnosis. In this regard several protocols have been established that identify quality assurance (QA) procedures, test frequencies, and action levels. Both NEMA NU 2-2001⁽³²⁾ and ACR Technical Standards for PET/CT⁽³³⁾ are outstanding documents for evaluating PET system performance in the context of diagnosis. Two American Association of Physicists in Medicine (AAPM) Task Groups are currently performing work that will also contribute to these efforts. TG-126⁽³⁴⁾ is charged with establishing acceptance testing and routine QA of PET/CT scanners, while TG-145⁽³⁵⁾ will establish phantoms and test procedures for assuring consistent and quantitatively accurate metrics from PET/CT scanners. Recently the International Atomic Energy Agency (IAEA) published a detailed guide of QA for PET & PET/CT (2009) which contains a comprehensive list of practical tests to be performed. Bergman⁽³⁶⁾ followed the NEMA protocol to assess image quality variation between 15 scanners using the International Electrotechnical Commission body phantom containing 6 spheres of varying diameter and activity concentrations relative to background. They found considerable differences in image quality, calling into question the clinical interpretation of images and measurement of quantitative indices such as the standardized uptake value.

Ultimately, the RFP specifications and QA appropriate for PET/CT in RT is dependent on how the system is to be utilized. A parallel example is provided by Nichols⁽³⁷⁾ who described the QA process followed for PET/CT systems utilized in cardiology. In RT, Xing⁽³⁸⁾ described QA directed towards PET/CT where in addition to general system

performance assessment and QA he considered issues surrounding image acquisition and data transfer, consistency of SUV, multimodality image fusion, system integration, and respiratory motion management. The frequency and action levels of system testing have been investigated for many systems⁽³⁹⁻⁴¹⁾, with an emerging philosophical shift being introduced by Task Group 100⁽⁴²⁾ of the AAPM. The TG-100 approach utilizes “Failure Modes and Effects Analysis” (FMEA) to better implement QA programs based on institutional procedures. One could easily understand the implications of erroneous conclusions from insufficiently validated and monitored quantitative imaging propagating through the decision process of precision adaptive therapy, and thus the need for such systems level failure analysis incorporating metabolic and physiologic imaging uncertainties is evident.

Education—Balter *et al.*⁽⁴³⁾ reported on the findings of an intersociety workshop discussing imaging opportunities in Radiation Oncology. A major theme of this workshop was the need for formal training requirements in diagnostic imaging for the radiation oncology trainee.

Recognition of this need has existed for several years. In 2005, Coleman *et al.*⁽⁴⁴⁾ described the conclusions of a working group comprised of representatives from the American College of Radiology, the Society of Nuclear Medicine, and the Society of Computed Body Tomography and Magnetic Resonance. They too identified the growing utilization of functional and molecular imaging to necessitate a greater review of image acquisition protocols, supervision, interpretation, professional qualifications, and patient/staff safety.

In 2007 Li and Hendee⁽⁴⁵⁾ identified the lack of knowledge and/or training by radiation oncology physicists to successfully integrate the emerging utilization of medical imaging into radiation oncology. They encouraged enhancement of knowledge through self-learning, on-the-job training, interactions with diagnostic radiology and nuclear medicine physicists and physicians, and educational opportunities made available by professional societies and vendors.

Shortt *et al.*⁽⁴⁶⁾ provided the perspective of The IAEA, who recognized the necessary coupling between medical radiation imaging and radiotherapy, especially in the context of advanced technologies being implemented in current radiation oncology departments.

Requirements for Broad Adoption of Molecular and Functional Imaging in the Community Setting

Efforts must be made to establish reimbursement for functional imaging. Ideally, results from the clinical trials would provide information needed to construct business plans that allow Radiation Oncology and Radiology departments to afford the equipment and imaging time required for molecular and functional imaging. Once departments can be reimbursed they can hire the professional and technical staff trained with the required skills to perform these studies in routine clinical practice.

A literature review reveals thousands of peer-reviewed publications showing the utility of molecular and functional imaging. Almost 10 years ago this very journal dedicated an entire

volume (volume 11, number 1, 2001) to “Functional Imaging and Its Application to Radiation Oncology,” yet one decade later we have made little progress in adopting these approaches in the community setting. Why the disconnect? Academic institutions must demonstrate efficacy in well-defined prospective clinical trials, leading to multi-institutional clinical trials following rigorous and prescriptive quality assurance. One effort to standardize quantitative imaging is being developed by the National Cancer Institute under a contract with multiple institutions, known as the Quantitative Imaging Network (QIN). The ability to use functional imaging quantitatively should enable the objective and mathematically robust determination of treatment targets for therapy and for treatment response assessment. Developing tools and methods to address these needs are substantial.

Medical imaging analysis has been thwarted by a lack of standardization. Image processing software is primarily written by scanner vendors, third party developers, and university researchers. Algorithms vary, interfaces vary, and even calculation methodologies vary. Software is often proprietary and prohibitively expensive. This problem makes it difficult to compare response assessment data in a multi-center clinical trial.

Another obstacle is the reliability of input data. As such, the QIN is also addressing the lack of uniformity and consistency in data acquisition. The imaging data to be analyzed is subject to uncertainties introduced during the data collection process. These variations may manifest from many different sources including the scanning system, image acquisition and post-processing protocols, and/or physiological or biochemical patient changes. Consistent protocols must be established and followed to make results from quantitative imaging studies reproducible.

With robust imaging data for analysis, quantitative image assessment tools must have interoperability across platforms. Specifically, the tools must be : i) developed to operate on standardized platforms (DICOM WG-23 compliant) so that they are accessible in an open environment, ii) validated by evaluation against large databases of patient data where ground truth is known, iii) shared directly with the scientific community for utilization in the community setting, and iv) open to further development by investigators.

Establishing a framework to enable quantitative imaging for tumor response assessment will require coordinating an interdisciplinary team of oncologists, imaging clinicians, imaging and therapy physicists, computer scientists, bioinformatics experts, as well as corporate scientists. A major initiative of the QIN is to link together large imaging databases with outcomes databases. Once automated and semi-automated quantitative imaging tools are developed to identify tumors and quantify their changes in subsequent imaging studies, the imaging/outcomes database will serve as the ground truth for evaluating the quantitative tools. This requires a substantial effort in bioinformatics.

Figure 5 illustrates the software architecture being developed within the University of Iowa as a part of the QIN. A key enabling element is the caBIG/caGRID infrastructure, which is the result of 5 years of investment by the NCI in building this community-driven enterprise, and represents the ‘digital backbone,’ for caGRID protocols and developer tools. To harmonize imaging protocols, data acquisition, tool development and validation, imaging

analysis and QA requires interconnection of the multiple nodes of the QIN itself and establishment of an open-source, open access fabric that enables all parties and stakeholders (including industrial partners) to contribute tools and enhancements.

One example of resources becoming available within the QIN includes a dataset of all H&N cancer patient PET/CT studies acquired at the University of Iowa since 2003 (U of Iowa IRB-01 200503706). The dataset has already proven to be a useful resource, leading to multiple retrospective studies that have contributed significantly to the utilization of PET/CT as a highly predictive tool for patients with H&N cancer and significant nodal disease. Using an SUV > 3, we found that a PET/CT, 3 months post-radiation had a negative predictive value of 97% and a positive predictive value of 32-57%. Such studies illustrate the potential of molecular imaging to affect clinical decision making, as we now routinely defer surgery in patients with even initially large lymph nodes when their PET/CT is negative, using this criteria, 3 months following chemoradiotherapy. In contrast, positive scans are frequently false positives, outlining the need for more rigorous quantitative analysis to improve and then be further tested. This extensively studied dataset of more than 250 patients' imaging and clinical outcomes is an ideal test-bed for tool development and sharing.

All new quantitative image analysis tools and decision support tools developed for the QIN are intended to be shared with the cancer treatment and research communities via an open source approach in addition to the deployment of tools such as caGRID-enabled applications. Applications developed within this environment will most likely be built on the eXtensible Imaging Platform (XIP). XIP is an open source framework and platform where common infrastructure functions used by most applications (such as data management) are separated from analysis/processing chores (which are typically task specific). It is designed for rapidly developing medical imaging applications that are 'plug-and-play' across multiple computing environments. XIP was developed out of the caBIG initiative, and is the application hosting initiative of DICOM WG-23. XNAT will serve as a conduit for uploading all QIN-Iowa imaging data into the National Biomedical Imaging Archive (NBIA) as shown in figure 5. The NBIA will be the primary repository allowing for open sharing of all data resources to the cancer community.

Validation of the quantitative imaging tools (for semi-automated tumor identification and quantitative metric calculation) developed by imaging researchers requires merging longitudinal imaging data with annotation and bioinformatics. The Algorithm Validation Toolkit (AVT) project brings the new Annotation and Image Markup (AIM) standard into the XIP development environment, allowing statistical assessment tools developed through AVT and collaboration with statistical, bioinformatics, and machine learning researchers. Once the stand-alone modules have been assessed and validated they can readily be integrated within any DICOM WG-23 compliant host; ideally applications could be distributed and run using a web browser.

Variance of measurement equipment—A common source of variation in functional and metabolic imaging is found within the imaging device itself. The performance of a given scanner can be verified by executing consistent quality assurance. Figure 6 shows a slice-by-slice evaluation of the mean SUV within a cylindrical liquid phantom filled with known

concentrations of FDG. Data were acquired monthly; each data point represents the slice-specific SUV averaged over 14 months. Although all slices should identify an SUV of unity, substantial daily variation occurs. Furthermore, variations can be seen when comparing data between slices. Finally, a systematic shift of 2.7% is clearly present, which is likely due to inaccurate knowledge of the true activity within the phantom used to for daily cross-calibration of counts into bequerels. Additional sources of uncertainty are the dose calibrator ($\pm 0.5\text{-}1\%$), the concentration of the injected solutions within the dose calibrator ($\pm 1\%$), and the variation by slice ($\pm 2\%$). When summed in quadrature, this produces nearly 4% uncertainty, simply due to the imaging equipment.

Temporal variance of functional metric within a given human subject is also a substantial issue for evaluating response to therapy. Biological variability within a given subject adds further to the overall uncertainty of the measurement, having a further negative influence on the power of a trial to identify changes caused by therapy. The sensitivity of the response assessment approach to physical/biological variation can be determined from experiments where imaging is repeated in a very short interval, under the assumption no change has occurred. These “coffee break” studies allow investigators to quantify combined sources of uncertainty.

Conclusions

In conclusion, image-based biomarkers offer critical and objective decision making tools that will change our practice. Refining the best combination of multimodality imaging remains a significant challenge. Multi-institutional efforts are underway to design tools that operate across many platforms, provide an infrastructure for image analysis and tool validation against large clinical databases with longitudinal studies and complete annotation, and establishment of prospective clinical trials. In combination, the broad adoption of advanced imaging into clinical practice will further require enhancing the imaging skills typically accessed by the Radiation Oncology community. The promise of mathematically defined image-based targets from well qualified and harmonized imaging protocols is profound in that it finally enables true consistency in target definition and response assessment. The impact on our ability to perform high quality clinical trials will be dramatic.

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Figure 1.

Comparison of conventional CT and MR-based gross tumor volume (GTV), clinical target volume (CTV) with MRSI derived Choline-to-NAA maps. MRSI fused with CT (left), T1-contrast enhanced MRI (middle), and T2-MRI of rim enhancing GBM lesion (pt 3).

Contours: Purple, Cho:NAA = 2.0; Red, GTV; Green, CTV. Note a significant portion of metabolically active tumor falls outside both GTV and CTV.

Baseline FLT PET scan

5 days post-therapy FLT PET scan

Figure 2.

Fluorothymidine (FLT)-PET to assess tumor response after the first week of chemoradiotherapy. Proliferation within the tumor is shown to be reduced at an early time point and may be used to assess outcome and/or modify therapy.

Figure 3. Metabolite ratio (Cho/NAA) color maps and corresponding MR spectral array from a representative case.

Figure 4.

The pulmonary function change compared to the planned radiation dose distribution. The dose map, pulmonary function, and pulmonary function change are overlaid on the free breathing CT. The first column is the pulmonary function before RT. The second column is the pulmonary function after RT. The third column is the pulmonary function change from the subtraction of the previous two images. The fourth column is the planned radiation dose distribution. In the third column, the red arrows show regions with decreased pulmonary function, and the blue arrows show regions with increased pulmonary function.

Figure 5.
Informatics system architecture as related to the Quantitative Imaging Network (QIN).

Figure 6.
Mean SUV within a cylindrical liquid phantom filled with known concentrations of FDG.
Data were acquired monthly; each data point represents the slice-specific SUV averaged
over 14 months of data collection.