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Broadening the scope of Image-Guided Radiotherapy (IGRT)

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Abstract

The recent wave of enthusiasm for image guidance in radiation therapy is largely due to the advent of on-line imaging devices. The current narrow definition of image-guided radiotherapy (IGRT), in fact, essentially connotes the use of near real-time imaging during treatment delivery to reduce uncertainties in target position and should therefore be termed IGRTD. However, a broader (and more appropriate) context of image-guidance should include: (1) detection and diagnosis, (2) delineation of target and organs at risk, (3) determining biological attributes, (4) dose distribution design, (5) dose delivery assurance and (6) deciphering treatment response through imaging i.e. the 6 D's of IGRT. Strategies to advance these areas will be discussed.

The concept of image guidance in radiation therapy is far from being new. In fact, the first use of x-ray tubes for cancer therapy involved the same kV radiation source for both imaging and treatment. Recently, image guidance has derived significant impetus from the commercial availability of advanced on-line volumetric imaging technologies that permit treatment delivery verification in near real-time. However, the commonly adopted definition of image-guided radiation therapy (IGRT) appears too narrow, primarily connoting the use of near real-time imaging for treatment delivery verification and set-up correction [1]. Thus, the above approach should be abbreviated as IGRT-D for image-guided radiation therapy delivery.

A broader and more appropriate context of IGRT should include (1) detection and diagnosis, (2) delineation of target and organs at risk, (3) determining biological attributes, (4) dose distribution design, (5) dose delivery assurance and (6) deciphering treatment response through imaging. That is, the 6 D's of IGRT. Target definition, biological attribute determination, and deciphering treatments response are the most challenging aspects of IGRT and strategies to advance these areas are needed for the benefits of IGRT to be brought to full fruition.

Detection and diagnosis

The foundation of non-invasive medical imaging can be traced back to the discovery of x-rays. Since then, an impressive armamentarium of morphological imaging techniques has been developed. Screening programs based on imaging are routinely used for the early detection of cancer. Examples of these are mammography for breast cancer [2] low-dose high resolution-CT for lung cancer [3,4] and virtual endoscopy for colon cancer [5]. It is believed that appropriate use of screening may result in improvements in cause-specific survival [6]. Of course, not only is the role of screening one of detection of the disease, but to do so at an early

stage where cure rates are significantly higher. As a consequence of early disease detection, organ- and function-sparing have increasingly become the mainstay approach for the treatment of cancer in many anatomical sites [7–10]. It is expected that the role of cancer detection and diagnosis will continue to evolve with more-thorough and effective screening programs that can establish the presence of malignancy at increasingly earlier stages when it can be effectively treated by non-invasive treatment approaches such as IGRT. The safety and efficacy of single fraction or highly hypofractionated IGRT regimens are becoming more established. Predictive assays (proteomics and genomics) may provide reliable information on the true extent of the disease, discerning between patients who may be cured with a local form of treatment only *vs.* patients likely to already harbor microscopic dissemination. Under these circumstances, IGRT may, indeed, become the quintessential tool for non-invasive tumor ablation as an alternative to surgery in many clinical settings.

Undoubtedly, with current imaging techniques many lesions continue to evade detection. Recent technological advances have brought in the clinical realm high-resolution multi-detector CT and whole-body MR imaging, whose respective roles and cost-effectiveness in oncology imaging are yet to be determined [11–13]. Positron emission tomography (PET) has been around in the research arena for many years, and only recently has it gained widespread acceptance in the clinical practice. PET with the glucose analogue ^{18}F -fluorodeoxyglucose (FDG) is now one of the standard methods for *in vivo* imaging and staging of various malignancies [14]. PET- and MR-based novel imaging probes, capable of tracking specific molecular pathways as well as tissue functions, are currently being developed and tested. Non-invasive characterization of tissue abnormalities should lead to higher accuracy in the differential diagnosis between malignant and benign lesions. Molecular probes for imaging *in vivo* gene expression (e.g. oncogenes such as *myc* or tumor suppressor genes such as *p53*) [15,16], telomerase activity, over-expressed receptors (e.g. HER-2/neu) [17,18], apoptosis [19], protease activity, hypoxia [20] and angiogenesis [21] are being scrutinized for this purpose. The next decade, therefore, will likely witness a paradigm shift in which morphological multi-modality imaging will be heavily integrated with molecular-functional imaging. Indeed, the prototype of this approach is represented by hybrid PET/CT scanners in which the relatively poor resolution and lack of anatomical detail of the PET component is rectified with the hardware-fused CT images [22]. FDG-PET/CT has clearly been shown to yield higher overall sensitivity and specificity than either modality alone [23,24]. In non-small cell lung cancer the use of ^{18}F -FDG-PET imaging has been shown to result in stage shift. Patients considered amenable to radical irradiation, based on the assessment of CT scans only, are often found to already harbor distant metastasis on PET/CT re-evaluation, changing the radiotherapy approach from a radical to a palliative one [25].

The role of novel PET tracers in the detection of primary and recurrent tumors is still largely investigational, but appears to be of promise. For instance, in the context of early biochemical relapse following radical local treatment for prostate cancer, conventional imaging modalities are of little or no value in detecting local *vs.* nodal disease. New PET tracers such as ^{11}C -choline and ^{11}C -acetate may aid early detection of local recurrences or minimal nodal involvement *vs.* distant disease, thus effectively selecting patients who may be salvaged by high-dose loco-regional radiotherapy [26,27].

Another promising integration of morphological and functional imaging is represented by MRI and magnetic resonance spectroscopy (MRS). MRS is a non-invasive technique which may provide biochemical and metabolic information associated with tumor growth and development. In the diagnosis of prostate cancer, the choline/citrate ratio measured by MRS has been frequently described as a promising tool to discriminate between benign hyperplasia and malignancy [28].

Delineation of target and organs at risk

Radiation therapy is currently going through a series of technical and conceptual revolutions that are leading to the safe delivery of radiation to unprecedented dose levels. Advances in treatment delivery accuracy (IGRT-D) currently allow safe administration of curative treatments in a single session or highly hypofractionated regimens. The resulting dose escalation to the tumor is expected to bring about both an improvement in local tumor control and in cause-specific survival with excellent morbidity profiles. Current research efforts are aimed at the incorporation of high-quality imaging in the process of target volume delineation with the specific aim to minimize uncertainties and reduce exposure to normal tissues. The sharp dose gradients and the precise dose distributions associated with highly conformal treatment plans (e.g. IMRT, stereotactic radiotherapy), in fact, are less forgiving and therefore demand more accurate delineation of the target and the surrounding critical structures at planning. Indeed, target volume delineation is likely the largest source of uncertainty in the planning phase of IGRT.

The advent of high-speed helical scanners has led to the so-called CT simulation, which, by combining the simulation and CT-scan acquisition into one single session, minimizes systematic uncertainties and produces greater operational efficiency [29]. The 3D- data set of the patient in treatment position with appropriate immobilization devices in place, may be reconstructed through dedicated software to carry out the so-called *virtual simulation*, in which digitally reconstructed radiographs (DRR's) are generated for viewing, decision-making and documentation. All of these factors make CT simulation an integral ingredient of IGRT. However, the limitations of CT imaging in the delineation of target and critical structures in many anatomical sites have become quite obvious. Concerns have been raised about the large inter- and intra -observer variability due to the uncertainties in tumor and critical organs extensions on CT images [30–34].

MRI provides improved soft tissue contrast, relative to CT, particularly for central nervous system structures, and within the abdominal and pelvic regions. MRI has, therefore, become a fundamental imaging modality for target and critical structure delineation for intracranial, head and neck, liver and pelvic tumors [35,36]. MRI by itself is not sufficient for treatment-planning purposes since it does not provide electronic densities required for dose calculations and may suffer from potential image distortion [37]. However, its inherent multi-planar capability and increased imaging functionality outweigh its drawbacks, and efficient MR distortion assessment and correction algorithms together with robust image co-registration software can overcome these limitations and permit optimal use of MRI for treatment-planning. Recently, new contrast media, such as super paramagnetic iron oxide nano-particles for abnormal lymph node identification have been developed, yielding an unprecedented diagnostic accuracy [38]. If these findings are confirmed in larger studies, this technique may turn out to be an invaluable tool in target volume delineation of involved lymph-node areas, especially in the pelvic region.

The vast potential of advanced MRI has recently led to the proposition of integrated machines coupling a high-field MRI system and a linear accelerator [39]. Indeed, this approach may usher a new era in IGRT in which advanced target localization and treatment are tightly integrated.

Recently, the advent of PET/CT devices with co-registered functional and anatomical data, has opened new exciting possibilities for target volume delineation [40]. PET/CT imaging is rapidly being embraced by the radiation oncology community as a tool to potentially improve target volume accuracy for treatment optimization [41]. A significant impact of PET-derived

contours has been observed with respect to the CT-only in studies mostly dealing with lung cancer and cancer of the head and neck [41–44].

Several studies have dealt with the feasibility of incorporating FDG-PET information into contour delineation with the aim to reduce inter-observer variability, a well-known concern in radiotherapy treatment-planning. Although still present, following target delineation with PET/CT, inter-observer variability is somehow reduced compared to conventional CT-only contouring [45,46].

PET/CT may provide improved therapeutic ratios compared to conventional CT planning. Increased target coverage and often reduced target volumes, in fact, may potentially result in PET/CT-based planning to yield better tumor control probability through dose escalation, while still complying with dose/volume constraints for normal tissues [47,48]. Although a PET-based reduction in GTV might theoretically enable more normal tissue sparing, it may also confer an undue risk of marginal miss. This approach, therefore, should be used with caution until more evidence is gathered from studies comparing PET findings with the “gold standard” histopathological assessment [49].

Despite the widespread excitement in the incorporation of PET/CT data in treatment-planning, the optimal method to accurately determine the volume and shape of the GTV using PET information still remains an unresolved issue [50–52]. Recently, studies comparing different segmentation techniques have appeared in the literature [45,53–56]. A general consensus, however, is still lacking. Notwithstanding, in the not-so-far future, tissue contouring for treatment-planning will likely become more automatic with minimal interventions from physicians, thus effectively minimizing inter-observer variability. A potential problem exists when the contours determined from different imaging modalities conflict. Computer-aided diagnosis (CAD) intelligent rules to decide which contour should be used will be required. These CAD strategies will, of course, have to rely on histopathological correlations with imaging findings [49].

Target motion due to respiration is a major concern for tumors situated in the thoracic and abdominal regions. Traditionally, a margin commensurate to the amplitude of motion is added around the CTV to account for target misplacement during delivery. The recent development of ultra-fast multi-slice CT has opened a new dimension in radio-therapy and allows time-resolved (4D) CT imaging of the patient breathing cycle [57]. Recently, the feasibility of 4D-PET/CT acquisition has also been shown [58]. The 4D approach obviously allows a significant tightening of the margin required, thereby reducing non-target dose and the risk of radiation-induced toxicity. Reproducibility issues at treatment delivery, however, still need to be resolved for this technique to become routine clinical implementation [59,60].

Determining biological attributes

Many biological factors govern the response of tumors and normal tissues to radiation. In the past, attempts to decipher the biological connotations of the tumor and the use of predictive assays to forecast the probability of successful radiation treatment were largely unsuccessful. More recently, the dawn of biological imaging has ushered in the promise that non-invasive modalities such as nuclear medicine and magnetic resonance imaging can provide biological information [61].

At present, there is much interest in tumor hypoxia in the management of cancer. Hypoxia is a well-known determinant of treatment outcome because hypoxic cells are significantly more resistant than aerobic cells to ionizing radiation [20,62]. Noninvasive PET-imaging of tumor hypoxia is a promising approach. Hypoxia-specific radiotracers have been evaluated in preclinical trials at MSKCC (^{64}Cu -ATSM, ^{18}F -FMISO and ^{124}I -IAZGP) [63–68]. Recently,

a clinical evaluation of PET imaging with ^{18}F -FMISO has been performed in patients with head and neck cancer to explore the feasibility of dose-painting hypoxic regions with IMRT [69]. The dose to the hypoxic region could be escalated by approximately 20% to a prescription dose of 84 Gy, while keeping the organs at risk at the same tolerance levels. For these hypoxic regions to be targeted appropriately by dose-painting during fractionated radiotherapy, geographic consistency over time is crucial. Evaluation of whether the pre-treatment hypoxia images were invariant over time was performed obtaining two additional PET scans separated by 3 days [70]. Significant changes in the hypoxic regions of the target were observed in a subset of patients compromising the coverage of hypoxic tumor volumes achievable by dose-painting IMRT [71].

Angiogenesis a well-known determinant of tumor growth and has recently become a key therapeutic target through anti-angiogenetic agents. The feasibility of measuring vessel-related parameters such as perfusion and microvessel density is currently being explored through MRI [72].

There is potential in applying non-invasive imaging to guide targeted therapy such as the use of anti-EGFR agents. Her2/neu antibodies and small-molecule inhibitors labeled for PET imaging have recently been developed with the aim of identifying tumors potentially responsive to EGFR-target therapies [73].

Dose distribution design

The introduction of IMRT represented a significant advance in improving the conformal dose distribution relative to the target and surrounding normal tissues. Early on following the introduction of IMRT, the optimal number of beams required and preferred beam angles were subject of intense scientific debate. In general, it was found that 5–9 beams were sufficient to produce highly conformal distributions, and that further increase in the number of beams led to diminishing returns [74].

Radiation delivery with beams from 360° , as in intensity-modulated arc therapy (IMAT) and tomotherapy, while not necessarily producing clinically superior dose distribution, obviates the need to specify the number and directions of beams [75].

IMRT has opened the doors to the concept of dose-painting, i.e. depositing dose non-uniformly within the target to improve clinical outcome. One possible application is to increase dose to hypoxic regions as described previously [76].

Recently the concept of theragnostic imaging for radiation oncology has been put forward [77]. According to this principle, advanced imaging modalities allow micro-environmental variations or cellular phenotypes that modulate the effect of radiation to be mapped in three dimensions. Dose-painting by numbers is a strategy by which the dose distribution delivered by inverse planned intensity-modulated radiotherapy is prescribed in four dimensions based on the outcomes of the imaging studies. For instance, painting by numbers based on the intensity of uptake in FDG-PET images has been proposed [78]. It must be emphasized, however, that these are hypothetical proposals that require clinical studies for validation.

Dose delivery assurance

An ideal image guidance system for radiation treatment delivery should have three essential elements: 1) 3D volumetrics of soft tissues including tumors, 2) efficient acquisition and comparison of the 3D volumetrics, and, 3) an efficacious process for clinically meaningful intervention [1]. Many of the commercially available devices fall short of these ideals. However, in the absence of an ideal system, a sub-set of the features may suffice for specific

disease sites and clinical applications. 2D MV imaging combined with a well-thought-out correction protocol may be sufficient for brain and H&N where bony landmarks can reliably determine the target position and critical organ locations. In disease sites where the target moves relative to the bony landmarks (e.g. prostate), implanted radio-opaque markers (e.g. gold seeds) provide surrogates of the target position for 2D imaging. However, bony anatomy and radio-opaque markers provide primarily surrogates of the center of the target position with less emphasis on normal tissue or changes in tumor conformation.

Assuming an ideal image guidance system such that 3D images of tumor/soft tissues can be acquired efficiently and daily comparison between the 3D images and the reference 3D volumetrics can be performed quickly prior to treatment, then both systematic and random errors would be corrected on a daily basis. Then, a margin around the target would be unnecessary, except in disease site with intra-fraction uncertainties. The complexity of IGRT-D is compounded at sites that experience motion—most commonly due to respiration [79]. Yet, respiratory control and IGRT-D are distinct processes and one does not imply the other. Eventually, the tools of IGRT-D may provide approaches to better monitor and/or facilitate respiration controlled treatment.

If image guidance during radiation delivery allows for the reduction of unnecessary dose to normal tissues, dose escalation and improved local control may ensue. Viewed in this perspective, IGRT-D is a continuation of the progress begun with 3DCRT and IMRT, processes that permit increased tumor dose while keeping normal tissue toxicity at bay. As with 3DCRT and IMRT, clinical trials would be needed to validate this hypothesis. The above is predicated upon the absence of disease outside the delineated target volume. Advanced imaging techniques are needed to validate this assumption. If advanced imaging (e.g. MRI) and treatment were combined in a single unit, then pertinent biological and physiological information (e.g. tumor cell density and hypoxia) could be used for real-time feedback and control of dose distributions using IGRT-D [39].

Deciphering treatment response

Molecular imaging is rapidly emerging as a powerful tool in the interpretation of post-irradiation treatment response. For instance, comparison of pre-treatment and post-treatment FDG-PET uptake may be used as a predictor of therapeutic response. Significant decreases in standard uptake values (SUV) SUV post-irradiation have been associated with better outcomes in various disease sites [80–82]. However, radiation-induced metabolic changes affecting FDG uptake can also be non-specific and significant increases in SUV have been observed as a result of inflammation [83]. FDG uptake has been shown to be sensitive to the microenvironment and appears to be positively correlated with hypoxia and negatively correlated with proliferation and perfusion [63]. More encouraging data will likely emerge from novel tracers. Cellular proliferation may be measured with radiolabeled nucleosides, such as ¹⁸F-fluorothymidine (FLT). In an experimental model, changes in FLT uptake post-irradiation have been shown to be more pronounced than FDG and correlate well with the proliferating cell nuclear antigen labeling index [84]. Therefore, FLT may turn out to be a useful imaging agent to monitor the early response to therapy in cancer patients.

MRI is an emerging tool to assess the effects of radiation. Studies using diffusion, perfusion and contrast uptake appear to be of great promise for quantitative evaluation of treatment effects and early prediction of outcome [85]. The apparent diffusion coefficient (ADC) measured by diffusion-weighted MRI can map the thermally induced motion of water molecules in tissues. This may provide valuable insights into tissue microstructure and enable an early assessment of response following locoregional therapy both on the tumor [86] and normal tissues [87].

The availability of reliable early surrogates of post-irradiation treatment response will likely open new avenues in the radiotherapeutic management of cancer with better disease-tailored approaches in which treatments may be modified *en-route* on the basis of the outcomes of predictive imaging studies.

Summary

Radiotherapy is an image-guided intervention and its evolution is ontogenetically linked to that of medical imaging. The commonly-adopted definition of IGRT, as the use of near real-time imaging for verifying treatment delivery, therefore, appears too narrow. A broader and more appropriate definition of image-guided radiotherapy should thus include many other key imaging steps involved in the process.

Imaging plays a pivotal role in the initial diagnostic and staging work-up of the disease. These steps are crucial for the appropriate treatment intent to be selected. The ultimate goal of IGRT is that radiation dose be delivered to an accurately-defined target volume exactly as planned. To this end, CT-based target delineation is known to be prone to considerable uncertainty. Therefore, metabolic imaging is actively being pursued with the aim to improve accuracy in target volume delineation and to minimize inter-observer variability. Biological imaging attempts to characterize the tumor in order to map regions of inherent radioresistance or of high clonogenic activity, where dose intensification (i.e. dose painting) may be required to maximize tumor control. If unaccounted for, target motion may compromise the efficacy of exquisitely-defined treatment plans. Despite all efforts to accurately define the target and to immobilize the patient for enhanced set-up reproducibility, residual uncertainties in the position of the tumor and surrounding critical structures may persist. The sharp dose gradient of dose distributions associated with highly conformal treatment plans demands for accurate target localization and guidance during treatment delivery. 3D volumetric tools for near real-time verification are now widely available and appropriate correction strategies are being developed. The availability of this new technology is paving the way for the safe implementation of high-dose single fraction or highly hypofractionated regimens, whose clinical benefits are rapidly emerging in various disease sites. Finally, imaging studies capable of predicting the ultimate outcome are actively being investigated and may eventually enable *en-route* correction of the treatment strategy. However, it must be borne in mind that IGRT, as defined above, is still in its infancy and many technical issues need to be resolved. In particular, robust tools for automatic target and normal tissue delineation, effectively removing what is likely the largest source of uncertainty in IGRT, are required.

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