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Technology for Innovation in Radiation Oncology

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Abstract

Radiotherapy is an effective, personalized cancer treatment that has benefited from technological advances associated with growing ability to identify and target tumors with accuracy and precision. As these advances have played a central role in the success of radiation therapy as a major component of comprehensive cancer care, the American Society of Therapeutic Radiation Oncology (ASTRO), the American Association of Physicists in Medicine (AAPM) and the National Cancer Institute (NCI) sponsored a workshop entitled “Technology for Innovation in Radiation Oncology”, which took place at the National Institutes of Health (NIH) in Bethesda, MD, on June 13-14, 2013. The purpose of this workshop was to discuss emerging technology for the field and recognize areas for greater research investment. Expert clinicians and scientists discussed innovative technology in radiation oncology, in particular as to how they are being developed and translated to clinical practice in the face of current and future challenges and opportunities. Technologies encompassed topics in functional imaging, treatment devices, nanotechnology, as well as information technology. The technical, quality, and safety performance of these technologies were also considered. A major theme of the workshop was the growing importance of innovation in the domain of process automation and oncology informatics. The technologically-advanced nature of radiation therapy treatments pre-disposes radiation oncology research teams to take on informatics research initiatives. In addition, the discussion on technology development was balanced with a parallel conversation regarding the need for evidence of efficacy and effectiveness. The linkage between the need for evidence and the efforts in informatics research were clearly identified as synergistic.

Introduction

Innovative technology plays a vital role in improving the quality of care and outcomes for patients receiving radiation therapy. Technological advances in radiation oncology, and the associated ability to accurately target tumors with highly focused radiation, have led to improvements in local control and survival for certain types of cancers. Recent examples include the use of stereotactic body radiation therapy (SBRT) for the treatment of early stage, non-small cell lung cancer (NSCLC), where the hypofractionated dose regimens delivered in ≤ 5 fractions have significantly improved local control and overall survival (1). Indeed, it has been argued that the success associated with SBRT-based treatment of early stage NSCLC might well be due to the substantially high, ablative doses delivered to tumors under image-guided radiation therapy (IGRT), which has enabled highly focused and accurate targeting (2). The success of SBRT for early stage lung cancers and the emergence of this treatment paradigm for other treatment sites might well have an important influence on current and future clinical practice (3).

In light of the positive influence of innovative technology in radiation oncology, the American Society of Radiation Oncology (ASTRO), the American Association of Physicists in Medicine (AAPM), and the National Cancer Institute (NCI) convened a workshop entitled ‘Technology for Innovation in Radiation Oncology.’ The workshop focused on the challenges posed by new technologies, addressed the state of the science for several disease sites, discussed clinical trials for advanced technology, and reviewed the future promise and potential pitfalls of emerging, innovative technologies.

The goal of the workshop was to help guide innovative technology-based research for radiation oncology. The following topics were included: (a) Innovative treatment delivery technology, (b) Advances in imaging for quantitative and validated treatment design, (c) Oncology informatics, and (d) Evidence building. While there are several other novel research topics being investigated in the field of Radiation Oncology, the goal of this article is to provide a summary of the central themes covered during the lectures of the workshop.

Innovative Treatment Delivery Technology—Innovative technology is an important element in improving the performance and quality of care in radiation oncology. Examples of innovations in delivery technology include advancements in hardware, improvements in software and algorithms to facilitate fast computations and enable automation, and the development of information technologies. Hardware advances enable new multi-modal machines that fuse high performance imaging modalities and advanced radiation delivery methods, such as in-room, coupled MRI and treatment delivery systems, which allow for real-time monitoring of dose delivery to the target and normal tissues. Such devices offer the potential to further reduce planning margins and potentially escalate the dose to the target, thereby improving the therapeutic ratio. There are also emerging technologies, such as targeted nanoparticle systems, and other therapies focused on patient-specific “personalized” biological targets, that have been shown to work synergystically with radiation to increase tumor cell kill (4,5). Summaries relevant to the key treatment delivery technologies are presented.

1. *Computational Advances*: Technological advances in software and hardware, focusing on high-speed calculations and automation of processes will improve the efficiency and quality of patient treatments. The use of “fast physics” calculations implemented through the use of graphics processor units (GPU's), cloud-based methods, and parallel processing will facilitate: rapid computation and accumulation of dose in deforming structures for efficient treatment adaptation, prediction of X-ray scatter, modeling of electron transport in magnetic fields, etc. (6). Advances in interface technologies which bury the underlying complexity of these computations, serves as a pillar for automation. Studies have shown that the development of automated interfaces, which minimize the need for manual, human-driven interaction at the treatment console reduces human errors and improves treatment quality (7). Automation of treatment planning processes has been shown to result in clinically acceptable plans at significantly reduced times, offering the potential for reduced effort, complexity and cost associated with more advanced, manual techniques (8). The emergence of programming and communication constructs, in addition to DICOM RT (e.g. extensible markup language (XML)), will facilitate better integration of planning, delivery and patient electronic medical record systems (EMR), and will enable advanced computer-controlled delivery, incorporating “on the fly” plan changes (6). The adoption of open source models for innovation (9), i.e. automation and integration of human, software, and machine processes will likely lead to a future generation of treatment systems viewed as specialized computers, rather than the current model comprising delivery devices with attached computers. Tools for automation and reduction in complexity will need to be properly validated before they are used routinely in the clinic.

2. *High Performance IGRT Systems*: Machines incorporating multi-modal, treatment and imaging functionalities, e.g. MRI, to perform real-time imaging during treatment (MRgRT) are likely to improve the precision and accuracy of treatments (10). Soft tissue contrast with MR imaging is inherently better than that with CT. Low field strength MR imaging (0.35 T) coupled with $^{Co}60$-based treatment sources is clinically available and MR imaging enabled-linacs are being developed. Integrated MRI, in addition to being a non-ionizing imaging modality, allows for real-time management of tumor motion and other geometric changes during treatment, and subsequently “dose of the session” computation at the treatment console (10). Challenges to the development of these technologies include geometric distortions due to the system as well as patient (susceptibility and chemical shift artifacts), influence of the magnetic field on dose deposition due to the recoil of electrons in a magnetic field, as well as safety related to proper patient screening (11).

3. *High performance particle therapies*: Machines utilizing particles (e.g. protons or heavier ions) reduce the total energy deposited in the patient (for the same treatment dose) compared to other types of external beam photon treatments independent of any planning or delivery technique (12, 13). While we do not fully understand the clinical consequence of the reduced integral dose, evidence suggests that particle therapies are clinically beneficial for pediatric patients and young

adults, and in patients who have tumors of the CNS (14). Opportunities for future research include the following areas: (a) Reduction of range uncertainties through the use of Monte Carlo-based dose calculation methods (15), combined with better imaging for planning (e.g. dual energy CT or proton CT (16); (b) Robust treatment planning using intensity modulated particle therapy (IMPT), which will make plans less sensitive to uncertainties (17); (c) In-vivo range verification, currently being performed using positron emission tomography (PET) or employing prompt gamma detection methods (18); (d) Biological effectiveness of protons and heavy ions with respect to tumors and normal tissues (12); (e) Clinical studies which assess the effectiveness and/or efficacy of protons (14) and carbon ions (19) compared with photons for different treatment sites (17).

4. *Nanotechnologies*: Nanoparticle therapies for combination with radiation are being developed to increase the effectiveness of radiation and thereby enhance tumor cell kill (20). Research is centered in the following areas: (a) Image-guided drug delivery to radiation-induced receptors, in which different peptides, antibodies and adenovirus-mediated gene vectors are coupled with nanoparticle systems to perform simultaneous imaging and targeting of cancers (21). (b) Deep-penetrating triggered release nanoparticles as tumor radiosensitizers, in which delivery of nanoparticles using thermo-sensitive liposomes has been shown to enhance deep penetration of nanoparticles when triggered by hyperthermia (22). (c) Gold Nanoparticles (GNP) as vascular-disrupting agents during external beam radiation therapy - it has been hypothesized that MV irradiation of targeted GNP will cause localized destruction of tumor blood vessels (endothelium) leading to subsequent disruption of tumor viability (23, 24).

   Despite the promise afforded by nanoparticle systems, challenges exist (25): (i) toxicity is a concern and nanoparticles (even gold-based systems) will need to be extensively tested for safety and biocompatibility prior to human trials; (ii) stability in size and form of nanoparticles or their delivery vehicles – if particles lose their form or cluster together in circulation and are opsonized by plasma proteins, their delivery to tumors and targeting efficiency may be significantly dampened; (iii) potency – the amount of agent taken up in the target to observe an improvement in therapy needs to be validated; (iv) distribution: tissue penetration of the stimulating agent – if the nanoparticle stimulating agent does not penetrate deeply in tissue, the clinical feasibility may be severely limited except for those applications that do not require tissue penetration (e.g. targeting tumor vasculature); (v) targeting specificity - while passive targeting, relying on intrinsic enhanced permeability and retention (EPR) properties of tumors is an effective method for preferential nanoparticle accumulation in the tumor, active targeting via ligands, peptides or other methods has been shown to provide greater specificity for some situations; (vi) feasibility –clinical workflow and costs, among other factors, will need to be addressed.

Advances in Imaging—The role of imaging and, in particular, the transition from anatomical to functional imaging for better assessment of the target and sparing of

surrounding organs, represents a major technological innovation in radiation oncology (26). The concept of the biological target volume (BTV), as proposed by Ling *et al.* (5), provides rationale for the development of functional/molecular imaging relevant to tumor response to radiotherapy. Ling *et al.* (5) hypothesized that the BTV can be derived from images that reflect biological processes and that their use may improve target delineation and direct non-uniform dose delivery. Functional imaging of tumors and normal tissues using MRI, PET and other modalities is likely to play a central role in this regard. The integration of imaging and panomics or totalomics (a term used to refer to the range of molecular biology technologies including genomics, proteomics, metabolomics, transcriptomics, etc., or the integration of their use) in combination with radiation therapy is an area of research likely to facilitate tailored therapies in support of personalized cancer medicine (27). Summaries relevant to the pivotal role of imaging are provided.

1. The role of PET technology is central to the following areas: (i) localization of the gross tumor volume (GTV) in radiotherapy treatment planning; (ii) characterization of tumor sites, particular for features such as hypoxia that may impact treatment response, and can therefore be incorporated into a BTV (5); (iii) measurement of response to radiotherapy early in the course of treatment and therapy adaptation, as appropriate, based upon early response. Key areas for the development and application of new PET biomarkers/probes will be to: (a) develop and implement probes to detect and localize cancers (such as prostate cancer) not well visualized by FDG-PET (examples include, labeled choline agents and amino acid tracers) (28); (b) measurement of regional tumor hypoxia to construct BTVs that can be used to direct treatment planning based upon hypoxia (examples include, ^{18}F-FMISO and ^{18}F-EF5) (29); (c) measurement of cellular proliferation to assess early response to treatment (examples include, ^{18}F-FLT, ^{18}F-FMISO) (30); (d) imaging of normal tissues using specific biomarkers (e.g. indocyanine green for assessment of radiation-induced liver damage) to incorporate healthy tissue functional reserve into adaptive RT models (31). Proper validation and quantification of these probes as tools for directing radiotherapy will be essential prior to initiation of prospective multi-center clinical trials (28). Cooperative group clinical trials using concurrent chemo-radiation for patients with locally-advanced stage lung cancer (27, 28), among others, have been initated to investigate the role of imaging during treatment. These trials utilize FDG PET/CT imaging to assess tumor response during treatment and subsequent plan adaptation, with the goal of iso-toxic dose escalation to the tumor.

2. MRI plays an important role during patient simulation because of enhanced soft tissue contrast relative to CT. Patient models are likely to be improved with MRI due to more accurate delineation of tumor margins and identification of normal tissue boundaries, which will potentially lead to better planning margin design (32). Consequently, it will be possible to generate treatment plans with higher therapeutic ratios. Challenges to enable wide spread implementation of MR simulation include, generation of electron density distributions for dose calculations, planar reference images for localization using bony landmarks, and improvement of spatial integrity (32, 33). MRI has also been demonstrated to be an

effective modality for evaluation of early and late stage tumor response and the effects of radiation on normal tissue toxicity (34). This information can in turn be used to adapt treatment plans to optimize the therapeutic ratio over the course of therapy. Key areas for development include: (a) Careful consideration of the timing of image acquisitions due to dynamic tumor changes, which occurs over the course of treatment (35); (b) Development of more sensitive imaging tools to enable cancer stem cell imaging (36); (c) Investigation of image monitoring protocols of acute and chronic normal tissue toxicity over time by scanning with appropriate and pre-designated intervals, which would allow for earlier intervention for long-term preservation of tissue function.

3. Personalized Cancer Medicine and Radiation Therapy: Several opportunities exist in the field of panomics, and assimilation of imaging and panomics to quantify the involvement of the functions, structures, and interactions of DNA-level molecules in the development of cancer. The integration of panomics into radiation medicine will make possible adaptation of therapy for individual patients, and thereby improve clinical outcomes. Examples include the improvement in outcome and potential to de-escalate radiation therapy for HPV+ patients with oropharyngeal cancers (37), and the ability to personalize radiation treatments based on sub-typing (e.g. Luminal A, B and Her-2-neu status) for patients with breast cancers (38).

Oncology Informatics

In Radiation Oncology, we have been collecting digital, structured patient information for use in learning and advancing care through ‘big data’ initiatives. Our existing electronic infrastructure captures much of the dosimetric and outcome data, which theoretically could be retrieved and aggregated for analysis. With additional efforts on integrating structured data collection into the clinical workflow, there is a great opportunity to generate complete datasets about the care delivered to patients and their outcomes.

A major hurdle confronting the effective use of the ‘big data’ sets is the enormous volume which impedes analyses and data exchange. With clinical data, one must try to identify the types of questions that researchers might ask in the future, the type of data required, and balance data collection efforts with practicality in the clinical workflow. Given the advances in imaging and detection technologies in the laboratories and clinics, the Big Data challenges will only intensify in the future. There is a lack of infrastructure to support and sustain efficient learning from one's own experience or that from other institutions. The need for new informatics approaches to address Big Data is evident in the new initiatives by the NIH (39), NSF (40), and others as well as this technology-focused, translational research workshop sponsored by NCI/ASTRO/AAPM. In response to these efforts, a fundamentally new informatics infra-structure and methodology to promote data sharing, decision support and data re-use is needed for a data sharing model that more seamlessly supports continuous quality improvement and comparative effectiveness research (41).

These developments in medical and bioinformatics demonstrate an important and well-aligned research area critical to advancing the role of radiation therapy in cancer control. Integrating radiation oncology databases with the broader domains of oncology is a key

element. Three notable emerging informatics efforts that shed light on this effort include: (a) the National Radiation Oncology Registry (NROR) initiative championed by ASTRO (42), (b) the euroCAT initiative for Rapid Learning (43), and (c) the OncoSpace initiative for data sharing and decision support (44). The approaches being explored in these efforts and the value to oncology care and research should be monitored and highlighted across the field. The following areas of oncology informatics have been identified as having the greatest potential for impact on the scientific, clinical research, and on-going technology development in radiation oncology.

1. Integrating radiation oncology databases across the discipline will facilitate science and elevate the quality of care (45). The creation of a 'Virtual Clinical Trials Group' that enables federated databases at different institutions for conducting cooperative research is a consideration. Sharing practices and outcomes will permit 'high mean and tight variance' in clinical practice and will improve quality (46).
2. Tools need to be created and made available for patients and physicians to discuss treatment options, as recommended by the Patient-Centered Outcome Research Institution. Such an approach will drive the development of meta-treatment planning systems, in which one prescribes an outcome and not a treatment (e.g. specification of a 95% local control rate at 5 years with 5% grade 3 or more dyspnea) (6, 47). This could also be expanded beyond radiation oncology.
3. Expertise in the informatics domain amongst radiation oncology professionals needs to be developed (6). The most suitable candidates with the appropriate skill sets and multi-disciplinary knowledge to succeed in this space are likely medical physicists or physicians with strong computational backgrounds. Training grants for development of programs for oncology informatics will provide these individuals with the knowledge needed to support informatics research initiatives.
4. Informatics tools need to be developed to support the monitoring of the quality of oncology care at the point(s) of delivery (48). 'Real world-based evidence' approaches are emerging in other domains and will also benefit the field of radiation oncology. The often quoted statements that 5% differences in dose result in significant changes in tumor control and normal tissue complication probabilities will be reinforced or challenged through collecting and sharing data from the entire clinical process.

Methods of Building Evidence

The field of radiation oncology needs to innovate in our approach to harnessing the power of technological innovation, while also building evidence. Innovative approaches to demonstrate clinical efficacy and effectiveness, and safety were identified as an important area of research to be included during the discovery and testing of new technologies. The following recommendations were provided.

1. The next 5 years will likely see the requirement that technological innovations are assessed with approaches that have long been in place for oncology drugs. Implementation of new technologies, including reimbursement, will require high levels of evidence demonstrating efficacy and/or effectiveness, safety, and value

(49). Innovators and early adopters will be expected to perform formal phase I/II trials intended to define the operating characteristics and early outcome parameters. For technologies further along in the pipeline, pragmatic early majority users will be required to perform high level phase III comparative trials. In cases where such trials cannot be practically performed, other methodologies including observational studies extracting information from large electronic medical record databases will be necessary. In general, these trials must maintain the "4 pillars" of legitimate clinical research: (a) Pertinence (testing within real world circumstances), (b) Validity (conclusions must avoid bias), (c) Reliability (results must be reproducible), and (d) Generalizability (results can be considered mainstream).

2. While established techniques in clinical research will not be completely replaced by "modern" schemes, trials of new technology will require some design modification compared to drug discovery trials (50). For example, phase I trials may require a higher number of patients per dose level, and some may require a phase I/II design that simultaneously studies toxicity and efficacy. *In-silico* trials will facilitate the study of more difficult clinical scenarios, such as the initial testing of very expensive technologies (e.g. heavy ions), or the comparison of existing and evolved similar technology (51). Clinical trial endpoints will change from traditional metrics, such as local control, dose indices, or performance characteristics to patient-oriented endpoints, such as survival, patient reported outcomes (PRO's) and cost-effectiveness.

3. Equipment vendors have historically developed and implemented technology in conjunction with physicists and limited early adopters at academic centers with studies ending at performance/use evaluations. Similar to the "pipeline" of new pharmaceuticals, the costs of clinical testing must be incorporated into the overall cost of research and development to address the new requirements of acceptance of technology (52).

4. Comparative effectiveness research is often performed after a technological innovation has become widespread. Instead, integration of evidence development earlier in the innovation cycle, *in silico* is recommended (53).

5. Radiation therapy has its own unique set of evidentiary challenges. For one, the historical evidence base has consisted mainly of case-based series from single research centers. Increasing use of randomized controlled trials, particularly pragmatic trials, and high-quality comparative observational designs are therefore recommended (54), particularly in clinical areas where there remains sufficient equipoise around the best treatment option, such as prostate cancer (55).

6. Because the historical evidence base has raised concerns regarding publication bias (i.e., the propensity to publish only positive studies), Radiation Oncology-related journals should consider modifying disclosure requests to include attestations that all relevant clinical data have been submitted for publication. Examples of approaches to reduce publication bias during the review process have also been reported (56).

7. Comparative studies are often short-term in nature and tend not to capture the impact of technical innovation. ASTRO and AAPM should continue (and expand, if necessary) their support of the development of multicenter registries to capture standardized clinical and economic data over the longer term. Such registries will garner the necessary wealth of information on treatment protocols and devices to examine the impact of innovation on outcomes (57).

8. Evidence building to measure efficacy and effectiveness for radiation therapy is clearly linked to oncology informatics (41), and in the long term, broader oncology efforts should be included (58), such as radiomics, genomics, radiogenomics (59), molecular targeted therapy, and next generation pathology, etc.

Summary

Technological advances and the linkage to improving patient outcomes within radiation oncology were the topics highlighted during the NCI/ASTRO/AAPM-sponsored workshop on “Technology for Innovation in Radiation Oncology”. In addition to the more traditional domains of dose delivery, advances in imaging, nanotechnology, and more recently, oncology informatics and evidence building, were identified as potential areas for further research investment. Continued progress in the development of imaging of biomarkers, the field of panomics and the integration of these studies with innovative technological advances in radiation oncology, will likely accelerate the development of personalization and adaptation of cancer therapy. This, in concert with data collection and analysis through advances in oncology informatics, will enable us to build evidence and answer important questions about the impact of the technology, for instance by using novel *in silico* approaches, which assess effectiveness during the development phase. In summary, progress in the field of radiation oncology demonstrates that technological advances can lead to improvement in patient outcomes, and further investment is needed in medical physics and radiation oncology research to address major challenges. The field is encouraged to broaden its efforts in technological development to embrace the powerful field of informatics such that these innovations can be placed in the broader context of personalized cancer medicine and evidence building.

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Appendix

Workshop Lectures and Participants

Lecture Title	Presenter/s	Moderator/s
Impact of Technology on RT Field: Current Status	Stephen Hahn, MD	Stephen Hahn, MD, and David Jaffray, PhD
Impact of Technology on RT Field: Vision for the Future	David Jaffray, PhD	

Lecture Title	Presenter/s	Moderator/s
Session 1: Image-based Metrics [Biomarkers] for Planning and Response		Yue Cao, PhD, and Nancy Lee, MD
Molecular/Functional Imaging [PET]	David Mankoff, MD	
Functional MRI Imaging	Brian Ross, PhD	
Session 2: Novel High-performance RT Systems		Indrin J. Chetty, PhD
MR Simulators, MR-treatment Machines	Daniel Low, PhD	
High-performance Particle Therapy	Harald Paganetti, PhD	
Will Tomorrows' RT Devices (Photon) Be Open Standards Platforms for Innovation?	Ramon Alfredo Siochi, PhD	
Session 3: Clinical Trials: Incorporating and Testing Technology		Brian Kavanagh, MD, MPH, and Stanley Benedict, PhD
Clinical Trials That Incorporate Technology	Robert Timmerman, MD	
Image-guided Radiobiology Clinical Trials	Robert Jeraj, PhD	
Session 4: Patient Outcome and Technology		Stephen Hahn, MD, and David Jaffray, PhD
Technology Assessment	Daniel Ollendorf, MD, MPH	
IT Innovation Opportunities, Including Decision Support, Computer Aided Theragnostics, Bioinformatics	John Wong, PhD	

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