

Research Opportunities in Technology for Innovation in Radiation Oncology: Oncology Informatics and Evidence Building (Highlights of the ASTRO NCI June 13-14, 2013 Workshop)

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Stanley H. Benedict, PhD

**Professor & Vice Chair of Clinical Physics
Department of Radiation Oncology**

University of California at Davis School of Medicine



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- The Radiation Oncology Department has research and development agreements with Varian Medical Technologies, Sun Nuclear, Elekta, AlignRT, and iRT Systems GmbH

Evidence Building...

**SESSION 3:
CLINICAL TRIALS: INCORPORATING AND TESTING TECHNOLOGY**

Moderators: Brian Kavanagh, MD, MPH, University of Colorado Denver and Stanley Benedict, PhD, University of California Davis Cancer Center

- **Clinical Trials That Incorporate Technology**
Robert Timmerman, MD, University of Texas Southwestern Medical Center
- **Image-guided Radiobiology Clinical Trials**
Robert Jeraj, PhD, University of Wisconsin

Timmerman: Clinical Trials Incorporating and Testing Technology

“Four Pillars” of Clinical Research

- Certainly apply to technological assessment
- 1. **Pertinence:**
 - testing important real world circumstances
- 2. **Validity:**
 - conclusions avoid bias
- 3. **Reliability:**
 - results are reproducible no matter who does the research
- 4. **Generalizability:**
 - can be taken mainstream



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Why do we do clinical trials?

- To convince decision-makers that the treatment adds real value
- Who are the decision-makers?
 - NOT the people in this room
 - Early majority (pragmatists), because they represent the:
 - Payers (patients, insurance companies, government)
- What convinces them?
 - NOT the same things that convince the people in this room



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The Phases of Oncology Clinical Trials

- Phase I: Dose finding study
 - Often the first use of the treatment in humans
 - Relates to the “volume knob” of a therapy
 - Find the ideal “therapeutic window”
- Phase II: Recognizes activity in a specific clinical scenario
 - Dose is from phase I
 - Power calculation predetermines sample size
- Phase III: More definitive study to guide care
 - Reliable comparisons of treatments



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Other Sources of Evidence

- Registries (e.g., chart reviews)
 - Databases that contain demographic, treatment, and follow-up information
 - Often incomplete datapoints (need to be 'filled in')
 - Alive/dead* is probably valid
 - Toxic/tolerated, controlled/uncontrolled, etc. ???*
 - Analysis is easily biased by selection factors and investigator motivations
- In-silico
 - Modeling the variables associated with clinical outcome
 - Strike One: NOT yet understood or embraced by pragmatists

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Clinical Trials of Technology

- Relate to two motivations/evaluations, namely techniques and new technologies (*van Loon, J, et al. Lancet, 13:e169-177, 2012*)
- Techniques
 - Variations in delivery parameters (dose, volume, etc)
 - May be enabled by a previous new technology (e.g., better imaging to allow avoidance of prophylactic treatment)
- New technologies
 - Differentiate improvements (evolution) vs novel (transfer) (*Zeitman, A, et al, JCO, 28:4275, 2010*)

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Then and now...

- Under the Technology Imperative (1950-70s)
 1. FDA approval unrelated to clinical benefit
 2. Acquire/buy an expensive technology
 3. Treat a bunch of patients
 4. Report low level but very impressive results a few years later (amaze your friends)
 - GammaKnife, protons, etc
- Current situation
 1. Government is broke, acquisition costs enormous
 2. Revenue draining procedures are highly scrutinized
 3. Payers (not FDA) INSIST on high level evidence to take innovation "mainstream"
 - SABR, RFA, etc

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Predicting outcomes in radiation oncology —multifactorial decision support systems

Philippe Lambin, Ruud G.R.M. van Stiphout, Maud H. W. Stamans, Emmanuel Rios-Velazquez, Georgi Nalbantov, Hugo J. W. L. Aerts, Erik Roelofs, Wouter van Elmpt, Paul C. Boutros, Pierluigi Granone, Vincenzo Valentini, Adrian C. Brigg, Dirk De Rysecker and Andre Dijkstra

NATURE REVIEWS | CLINICAL ONCOLOGY VOLUME 10 | JANUARY 2013 | 27

- Solve the challenge of "how to integrate diverse, multimodality information (clinical, imaging, and molecular data) in a quantitative manner to provide specific clinical predictions..."
- Scientific soothsaying
 - Put everything we know about a given patient and previous patients into a input file
 - Algorithm spits out outcomes after a variety of Rx's



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The New Frontier for Radiation Oncology

- For 100 years, we've been a "Loco-regional Therapy"
 - Mediocre for primary disease (surgery was better)
 - Pretty good for adjuvant "mop-up"
- The next 100 years, we will be a "Minimally-invasive Gross Disease Therapy"
 - For ALL stages of cancer (particularly metastatic)
 - People living longer and better (but not necessarily cured)



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Conclusions

- Clinical trials are part of a timed, sequential process intended to convince decision makers of the value of a Rx
- Prudent implementation of technology involves characterization, hypothesis driven trials, and effective communication to decision-makers
- Valid clinical testing should be considered part of legitimate R&D costs
- The key is NOT "can we do it," rather, how does it make the patient's outcome truly better



Jeraj: Image Guided Radiobiology Clinical Trials

Looking into the future...

BOTTOM-UP →

Tumor biology

1 →

Biological imaging

2 →

Bio-based prescription

3 →

Planning & delivery

4 →

Clinical outcome

← TOP-DOWN

What are the main challenges?

Where? How often? How much? Adapt? Combine?

Jeraj: Image Guided Radiobiology Clinical Trials

Radiobiology-guided RT—"TOP-DOWN"

- Most of the radiobiology targets **appear stable** through the course of therapy – **ONLY FEW MID-TX SCANS NEEDED, BUT WE NEED TO KNOW WHICH AND WHEN?**
- Tumors do **shrink** – **ADAPTATION NEEDED, BUT HOW MANY TIMES?**
- Radiobiological modulated plans can be **delivered safely** – **YES, BUT HOW MUCH CAN WE PUSH?**
- Radiobiological targeting needs **high doses**, but those are often **limited to only small areas (almost brachytherapy-like)** – **WHAT IMPLICATIONS DOES THIS HAVE FOR DELIVERY?**

Jeraj: Image Guided Radiobiology Clinical Trials

Radiobiology-guided RT—"BOTTOM-UP"

- Radiobiology-guided targeting needs to be **histology-specific** – **WHAT SHOULD WE REALLY TARGET?**
- Biology is **complex** – **WHAT OTHER BIOMARKERS BEYOND IMAGING DO WE NEED?**
- Dose prescription function is still **uncertain** – **HOW TO TRANSLATE FROM RADIOBIOLOGICAL HETEROGENEITY TO DOSE HETEROGENEITY?**
- Radiation therapy is only **part of the answer** – **WHAT DO WE COMBINE RADIATION THERAPY WITH?**

Evidence Building Summary

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.

Recommendations include:

Evidence Building Summary 1

- The next 5 years will likely see the requirement that technological innovations be assessed with approaches that have long been in place for oncology drugs. Implementation of new high technologies, including reimbursement, will require high levels of evidence demonstrating efficacy and/or effectiveness, safety, and value. Innovators and early adopters will be expected to perform formal phase I/II trials intended to define the operating characteristics and early outcome parameters.

Evidence Building Summary 1 (cont)

- 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: 1. Pertinence (testing within real world circumstances), 2. Validity (conclusions avoid bias), 3. Reliability (results are reproducible), and 4. Generalizability (can be taken mainstream).

Evidence Building Summary 2

- While established techniques in clinical research will not be completely replaced by “modern” designs, trials of new technology will require some modification of designs compared to drug discovery trials. 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 perhaps facilitate the study of more difficult clinical scenarios like the initial testing of very expensive technologies such as heavy ions or performing comparisons of existing and evolved similar technology.** Clinical trial endpoints will change from endpoints like local control, dosimetry, or performance characteristics to patient oriented endpoints like survival, patient reported toxicity and cost-effectiveness.

Evidence Building Summary 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 should/must be incorporated into the overall cost of research and development to address the new requirements of acceptance of technology.**

Evidence Building Summary 4

- Comparative effectiveness research is often performed after technological innovation has become widespread. Instead, **Integration of evidence development earlier in the innovation cycle is recommended.**

Evidence Building Summary 5

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

Evidence Building Summary 6

- Because the historical evidence base has raised concerns regarding publication bias (i.e., the propensity to publish only positive studies), **ASTRO and AAPM journals should consider modifying disclosure requests to include attestations that all relevant clinical data have been submitted for publication.**

Evidence Building 7

- Comparative studies that are available 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 and contain sufficient information on treatment protocols and devices to examine the impact of innovation on outcomes.

Evidence Building 8

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

Oncology Informatics...

PATIENT OUTCOMES AND TECHNOLOGY

Moderators: Stephen Hahn, MD, University of Pennsylvania and David Jaffray, PhD, Princess Margaret Hospital

- **Technology Assessment**
Daniel Ollendorf, MPH, ARM, Chief Review Officer, Institute for Clinical and Economic Review
- **IT Innovation Opportunities, Including Decision Support, Computer-aided Theragnostics, Bioinformatics**
John Wong, PhD, Johns Hopkins University

Wong: IT Innovation Opportunities

Big Data in Healthcare

- Not just the availability and storage of extremely large amount of data.
- *The Innovation of Big Data* requires changes in approach and utilization considerations
 - Signal vs Junk → *Unclear*
 - enable Research; Education; Decision Support
 - Collection of limited structured data vs huge amount of unstructured disparate data collected in care delivery
 - Patient privacy concerns

Wong: IT Innovation Opportunities

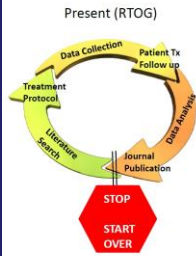
A Recognized Problem

- 2005 NIH Roadmap Workshop
 - Re-engineering the Clinical Research Enterprise
- R.A. Harrington, M.D., Duke Research Institute:
 - *“One of the greatest inefficiencies of the current model of clinical research in our country is the lack of a sustaining infrastructure (which includes shared resources, common data standards, and effective use of information technology among researchers), as well as the lack of a convenient forum to share best practices and learn from one another’s mistakes and successes.”*

OncoSpace 2008, NCI

Wong: IT Innovation Opportunities

Re-engineering the Cooperative Research Model



- < 3% of patients treated are enrolled in cooperative clinical trials
- Required data submission for QA and approval – “big problem”
- Average duration to complete a clinical trial
 - > 5years
 - outpaced by advances
- No feedback from community practice
- Data limited for re-use
 - Data/Knowledge lost

OncoSpace 2008, NCI

Wong: IT Innovation Opportunities

Initiatives in Radiation Oncology

- Three efforts:
 - The National Radiation Oncology Registry (NROR)
 - euroCAT --- Maastricht Radiation Oncology (Maastro)
 - OncoSpace --- Johns Hopkins Radiation Oncology

Wong: IT Innovation Opportunities

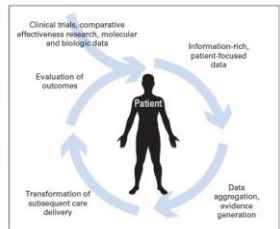
Building the National Radiation Oncology Registry

- Goal is to collect standardized information on cancer care delivery among **all** patients treated with radiotherapy in the United States
 - Primary purpose is **quality improvement**
- Supported by the ROI/ASTRO, MGH/NCI Federal Share funds
- IT infrastructure developed by HealthCare IT, Inc.
- Data transfer developed by Elekta AB, Varian Medical Systems, Inc., and Bogardus Medical Systems, Inc.
- Prostate cancer pilot scheduled to launch in Summer 2013

Wong: IT Innovation Opportunities

Rapid Learning

- Data generated through routine patient care and clinical research are fed into an ever-growing set of coordinated databases to facilitate machine learning.
- Learn from each patient to guide practice
- Validate with external datasets



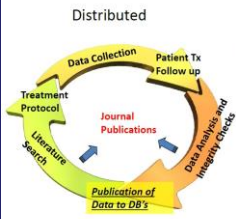
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euroCAT approach to eLearning

- "... the problem is not really technical.... Rather, the problems are **ethical, political, and administrative.**" *Lancet Oncol 2011;12:933*
- If sharing is the problem: Don't share the data
- Bring the learning application to the data
- Consequences (and contents)
 - The learning application has to be distributed
 - The data has to be readable by an application (i.e. not a human)

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JHU: Re-engineering the Cooperative Research Model



- Keep data local and available in an active database
- Send queries to data, extracting only answers
 - e.g. Validate the PTV margin prescribed for lung SBRT
- Facilitate data-reuse, decision support and education
- Promote data sharing for CER
- *Tools for data capture to populate OncoSpace*

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Conclusion

- The first applications in data-driven healthcare are likely to be for local quality and efficiency improvement.
- The healthcare industry must overcome a longstanding reluctance to re-engineer and improve processes.
- Must address information security needs for identified and de-identified data usage.
- Must accept necessary business model changes and make peace with crossing institutional and political boundaries.

Oncology Informatics Summary 1

- **Integrating radiation oncology databases with the broader domains of oncology is key.** Three notable emerging informatics efforts that shed light on this effort include (1) the National Radiation Oncology (NROR) initiative championed by the Radiation Oncology Institute (ROI) of ASTRO, (2) the euroCAT initiative for Rapid Learning at the University of Maastricht Radiation Oncology (Maastricht) in the Netherlands, and, (3) the OncoSpace initiative for data sharing and decision support at Johns Hopkins University (JHU). The approaches being explored in these efforts and the value to oncology care and research should be monitored and highlighted across the field.

Oncology Informatics Summary 2

- Integrating radiation oncology databases across the discipline will enable science and elevate the quality of care. The creation of a 'Virtual Clinical Trials Group' that enables federated databases at different institutions for the conduct of cooperative research is a consideration. Querying and sharing quality assurance queries for data integrity at each partnering institution. **Sharing practices and outcomes should enable 'high mean and tight variance' in clinical practice.**

Oncology Informatics Summary 3

- The creation of **tools** made available for the patients and physicians to discuss treatment options as recommended by Patient-Centered Outcome Research Institution. Such an approach would drive the development of meta-treatment planning systems in which one prescribes an outcome and not a treatment (e.g. I want 95% of local control rate at 5 years with 5% grade 3 or more dyspnea). What is the treatment for me? This should also expand beyond radiation oncology.

Oncology Informatics Summary 4

- Expertise in the informatics domain amongst radiation oncology professionals needs to be **developed**. The most suitable candidates whose background would require a shorter learning curve would be **medical physicists** or physicians with a strong computing background. Training grants for development of programs for oncology informatics could be used to provide these individuals the knowledge needed to support informatics research initiatives.

Oncology Informatics Summary 5

- Informatics tools to support the monitoring of the quality of oncology care at the point(s) of delivery. This 'real world evidence' approach is emerging in other domains and should be an area of focus in radiation oncology. The oft quoted value of 5% differences in dose makes a large change in TCP and NTCP, could be reinforced or challenged through collecting and sharing data from the entire clinical process.

BIG DATA Workshop: June 11-12, 2015

- A Follow-Up to the 2013 Technology Innovation Workshop.
- Big Data ASTRO-AAPM-NCI Workshop on 'Big Data'
- To be held at the NIH Campus, Porter Building on June 11-12, 2015

BIG DATA Workshop: June 11-12, 2015

- OPPORTUNITIES FOR RADIATION ONCOLOGY RESEARCH IN THE ERA OF BIG DATA
- OPPORTUNITIES FOR QUALITY ASSESSMENT IN THE ERA OF BIG DATA
- OPPORTUNITIES FOR CLINICAL CARE IN THE ERA OF BIG DATA



Thank You
