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Lessons Learned from Radiation Oncology Clinical Trials

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Abstract

A Workshop entitled “Lessons Learned from Radiation Oncology Trials” was held on December 7–8th, 2011 in Bethesda, MD, to present and discuss some of the recently conducted Radiation Oncology clinical trials with a focus on those that failed to refute the null hypothesis. The objectives of this Workshop were to summarize and examine the questions that these trials provoked, to assess the quality and limitations of the pre-clinical data that supported the hypotheses underlying these trials, and to consider possible solutions to these challenges for the design of future clinical trials.

Several themes emerged from the discussions, including the: a) opportunities to learn from null-hypothesis trials through tissue and imaging studies; b) value of pre-clinical data supporting the design of combinatorial therapies; c) significance of validated biomarkers; d) necessity of quality assurance in radiotherapy delivery; e) conduct of sufficiently-powered studies to address the central hypothesis; and f) importance of publishing results of the trials regardless of the outcome.

The fact that well-designed hypothesis-driven clinical trials produce null or negative results is expected given the limitations of trial design, and complexities of cancer biology. It is important to understand the reasons underlying such null results however, in order to effectively merge the technological innovations with the rapidly evolving biology for maximal patient benefit, through the design of future clinical trials.

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[*]Appendix 1

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Keywords

Cancer; Null hypothesis; Radiation oncology; Radiation therapy; Randomized clinical trial

INTRODUCTION

Clinical trials involving RT for cancer are initiated to identify novel technological and biological approaches that can improve local tumor control, DFS, OS, reduce toxicity, and/or improve quality of life. The design of these trials should be based on solid preclinical evidence supporting such approaches; however, oftentimes, patients participating in the experimental arm fare no better than control subjects (1). To identify possible reasons for these negative outcomes, and to propose pathways to increase the likelihood of "success", a Workshop entitled "Lessons Learned from Radiation Oncology Trials" was held on December 7–8th, 2011 in Bethesda, MD, sponsored by the Radiation Research Program of the NCI. The objectives of the Workshop were to assess the quality, quantity, and limitations of the pre-clinical data that supported the hypotheses underlying a few recently completed trials, and to consider possible solutions. Attendees included radiation and medical oncology clinical trialists, radiation biologists, clinician-scientists, radiation physicists, statisticians, and representatives from the pharmaceutical industry. To provide common ground for dialogue, results from ten Phase III RCTs from several different malignancies were discussed (Table 1), which included the spectrum of positive, negative, and null outcomes.

SUMMARY OF CLINICAL TRIALS

Central Nervous System Tumors

Two studies focused on GBMs were presented and discussed. The RTOG 0525/EORTC 26052-22053 was an international Phase III RCT determining whether dose-intensifying adjuvant TMZ could improve OS. The overall conclusion was "no evidence for improvement", although the prognostic value of MGMT promoter methylation status was confirmed.

The second Phase I/II RTOG 0211 trial examined the addition of an EGFR TKI (Gefitinib, Iressa™) to RT for GBM patients, which failed to demonstrate any OS benefit with the combinatorial approach. In fact, tumors with elevated SRC or PTEN expression fared worse with the TKI, illustrating the complex signalling cascades underlying most GBMs.

Head and Neck Squamous Cell Carcinoma

Despite the success of the landmark Cetuximab plus RT for patients with LA HNSCC (2, 3), more recent trials have been disappointing. The RTOG 0129 asked whether AFX plus CDDP will improve OS for LA HNSCC patients (4); in fact, no difference was observed between the standard *vs*. AFX group, suggesting that CDDP likely offsets tumor cell repopulation during fractionated RT.

The TROG 02.02 trial examined the value of adding a hypoxic cytotoxic agent TPZ to CDDP-RT for LA HNSCC patients (5). Disappointingly, this study also demonstrated no difference in outcome, but underscored the importance of QA in RT delivery (6), as well as questioning the clinical importance of tumor hypoxia (7). A third trial (RTOG 0522) asked whether the addition of Cetuximab to CDDP-RT could improve progression-free survival (8); this study not only failed to demonstrated an advantage to the triple-modality, but observed greater acute toxicities. Furthermore, Cetuximab and CDDP appeared to have overlapping mechanisms of action; hence, utilizing complementary tumoricidal agents would likely be more effective.

Lung

The four-arm RTOG 0617 trial compared OS differences between high-*vs*. standard-dose conformal RT with concurrent chemotherapy (Carboplatin and Paclitaxel), with or without Cetuximab for patients with stage IIIA/IIIB NSCLC. The results demonstrated no difference in OS between the high- (74 Gy) *vs*. standard-dose (60 Gy) patients (9), even suggesting an inferior survival with the high-dose arm, possibly related to treatment-related deaths, which again underscores the importance of QA in RT planning and delivery (10).

Gastrointestinal

The RTOG 9811 Phase III RCT addressed the efficacy of substituting CDDP for MMC, in the standard 5-FU/MMC/RT regimen for anal canal carcinoma. The results demonstrated no difference in DFS between the two treatment arms, but the CDDP group experienced a significantly higher colostomy rate (11). The major design flaw related to two new hypotheses of drug and sequence, both being addressed simultaneously; the new drug being CDDP, delivered in an induction manner. Consequently, it remained unclear if the negative results were related to an ineffective drug, an ineffective sequence, or both.

The RTOG 0020 Phase II randomized trial of Gemcitabine/Paclitaxel/RT, followed by an FTI (R115777) for unresectable pancreatic cancer demonstrated that maintenance FTI failed to improve clinical outcome, yet was associated with increased toxicities, highlighting the challenges to inhibiting K-ras, an established oncogenic target in this disease (12).

Genitourinary

The RTOG 94-13 trial, a complex four-arm randomization of whole pelvis *vs*. prostate only RT, with secondary randomization of neo-adjuvant *vs*. concurrent hormone scheduling (13, 14) reported no significant difference in progression-free survival for any group. This was an under-powered 4-arm trial, and failed to address the issues of field size, or timing of androgen suppression. There might also have been an unpredicted biological interaction between concurrent androgen suppression with RT, arguing for the importance of companion translational studies to acquire biological insights.

The EORTC 22961 trial demonstrated that longer-term (total of 3 years) was marginally superior to shorter-term (6 months) androgen suppression when patients were also treated with RT (15). The effect size was small; 5-year cumulative prostate-specific mortality differed by only 2.5%, plus the majority of patients had low Gleason scores. Hence, it still remained unclear if androgen ablation is beneficial for most patients.

EMERGING THEMES

I. Pre-clinical Studies

Many reasons could account for the success of the Cetuximab plus RT RCT for HNSCC (2, 3), including: a) the universally reported prognostic value for EGFR over-expression (16–18); b) the role of EGFR in mediating radiation resistance (19–21); c) the demonstration of efficacy of EGFR inhibitors in several different pre-clinical cancer models (22–24); d) a well-designed drug (25) which was highly efficacious and well-tolerated (26); and e) a well-constructed and efficiently-executed clinical trial (2).

Based on the above success, and corroborating the framework for preclinical studies as outlined by the UK group (27), it is recommended that before any combinatorial treatments are considered with RT, a minimal expectation would be an *in vitro* clonogenic assay of novel drug-of-interest plus RT in relevant pre-clinical cancer models. The MTT and apoptotic assays are simple, but are poor substitutes for the more quantitative clonogenic

survival assays, which until demonstrated otherwise, will remain the gold standard for the evaluation of any radiation sensitizer, DNA repair modification, or combinations of RT with drug.

The Molecular Radiation Therapeutics Branch within the Radiation Research Program of the NCI (rrp.cancer.gov/aboutRRP/mrtb.htm) has already generated extensive data for multiple targeted agents combined with RT in panels of human cancer cell lines; therefore, this resource should be the first point of contact before embarking on any combinatorial therapies. Next is the generation of *in vivo* data using different human cancer xenograft models, which have their limitations by only partially reflecting human tumor heterogeneity; furthermore, the tumor micro-environment (e.g. hypoxia), stromal factors, or the human metastatic patterns are not completed recapitulated. Some orthotopic models might address such limitations (28, 29), as well as early-passaged human tumor xenografts. An alternative is the utilization of GEMMs of human cancers (30), which could be useful for lung cancer (31, 32), and soft tissue sarcomas (33).

Many of these xenograft models are readily available within the Radiation Oncology community including CNS (34); lung (35, 36), breast (37), head and neck (38), pancreas (29, 39), and cervix (28). Funding for these studies remains challenging, although some pharmaceutical companies could be interested since such data will inform the design of early-phase clinical trials. Finally, another potential solution could be the utilization of a panel of molecularly annotated first generation xenografts harbouring high and low levels of the putative target (40); this could guide clinically realistic RT and drug doses for subsequent clinical trials.

II. Biomarker Studies

Biomarkers are germane to categorizing patients into distinct risk groups for prognostic or predictive value, enriching cohorts for clinical trials, and tracking longitudinal response to therapies. With the emergence of data derived from the ICGC (www.icgc.org/) and TCGA (cancergenome.nih.gov) deep-sequencing projects, this is an opportune moment to capitalize on such resources to triage patients into genetically- or proteomically-defined groups, to identify novel targets, and actionable mutations for RT-combinatorial trials, although tumor heterogeneity will remain challenging (41). Many of the ICGC/TCGA clinical data are not yet sufficiently mature to identify robust prognostic markers; the role of RT might also be difficult to discern, if such treatment details are lacking. Consequently, the value of well-annotated biospecimens linked to RT RCTs cannot be overstated.

The landmark observation of the benefit of TMZ to RT for GBM (42) changed practice, and led to the evaluation of TMZ dose intensification (RTOG 0525), corroborating the prognostic value of MGMT methylation status. A translational study evaluating primary GBM tissues from participants in multiple clinical trials demonstrated a potential 2-gene signature (Δ*NF-kBIA* plus *MGMT* methylation), as well as suggesting a biological explanation for the lack of efficacy of Erlotinib (43), since *NF-kBIA* deletion and EGFR amplification emerged to be mutually exclusive aberrations in GBM. Similar important insights have been derived from RCT tissue studies for HNSCC, not only corroborating the superior outcome for HPV-associated HNSCC (4), but also their limited benefit by hypoxic modifiers (44), which might in part account for the negative TROG 02.02 trial (5, 7). These data clearly illustrate the value of correlative tissue studies in providing biological insights, and informing the design of future trials.

Another approach is the utilization of an adaptive design (45), which requires the analysis of multiple known mutations such as *KRAS*, *EGFR*, and *EML4-ALK* in the context of lung cancer tissues derived from RT RCTs. This is a very promising area of investigation that

should influence the design of future RT-drug trials for lung cancer. Yet another critically important consideration is the utilization of "clinical-ready" PD read-outs. Stable and validated PD assays of DNA damage such as γH2AX in tumor tissues (46), or quantifying PAR levels in PBMCs (47) might be highly applicable for RT clinical studies, as opposed to P-Akt, which is notoriously unstable. This is an area of active investigation by the Frederick National Laboratory for Cancer Research; an important resource for the Radiation Oncology research community.

III. Imaging Biomarker Studies

Tumor response assessment in clinical trials has typically been derived from longitudinal assessments of anatomically-based diagnostic images (CT, MRI), using RECIST, which could be subject to observer bias, differences in scanning techniques, or lack of quantitative rigor. In an effort to address these shortcomings, an NCI-led Quantitative Imaging Network was established, to develop robust automated and semi-automated methods for tumor identification, segmentation and characterization. Each institution in this Network has engaged teams of clinicians and researchers to develop enhanced QA methods for image acquisition and data analysis, and to improve inter-institutional reproducibility.

The ability to quantify a metabolic tumor volume on PET/CT scans across institutions will be critical, particularly for RTOG trials, to achieve an additional level of consistency. This will also expand the use of molecular imaging *via* an array of novel PET tracers, as well as application of advanced MRI methods including spectroscopy, DCE, and DWI. The synergy between the QIN and cooperative groups will be crucial for the future of RT research.

IV. Microenvironment as a Target

Over 60 years of research on hypoxia and RT tumor response can be summarized as: a) rodent and human tumors contain hypoxic cells; b) rodent tumors are more hypoxic than human tumors; thus, will model only the most hypoxic of human tumors; c) hypoxic human tumors are RT-resistant; d) methods to overcome hypoxia in human tumors are less than perfect but are beneficial (48); and e) the ideal methods to identify or treat hypoxic tumors do not yet exist.

Three limitations of the TROG 02.02 trial (5) relate to: administration of TPZ, QA of RT plans, and HPV status. The TPZ dose was sufficiently high to potentiate CDDP; however, it was administered with only 9 of 35 fractions, which could have compromised the anticipated benefit. Tumors were not selected for hypoxia, and 12% of these patients had non-compliant RT plans that adversely affected tumor control (6), which was mal-distributed to the TPZ arm. Finally, TROG 02.02 was designed before the full appreciation of HPV-associated OPC, which appear not to benefit from hypoxic modifications (44), thereby diluting the potential benefit of TPZ.

Other tumor microenvironment properties such as extracellular pH, angiogenesis, and interstitial fluid pressure, might also influence tumor response to RT, as well as targeting stromal cells, cytokines, and oxidative stress. To date however, other than hypoxia, no Phase III RCTs have evaluated such strategies with RT outcome.

In summary, hypoxia is a negative predictor in some tumors treated with RT. Despite clear benefits in multiple trials of hypoxia modifiers with RT, the results have not been sufficiently dramatic to uniformly change clinical practice (49). Improved agents are being developed (50), and will be evaluated with hypoxia imaging in order to better select the appropriate patients.

V. Importance of Radiation Therapy Quality Assurance

The critical importance of QA in RT was succinctly illustrated in the aforementioned TPZ trial, wherein deficient RT plans caused a 20% reduction in OS (6), which far outweighed any potential benefits from biologically-targeted agents. The fundamental principle is that if the tumor is not irradiated, it will not be controlled. Many international efforts have been undertaken to conduct pre-reviews of IMRT plans (51), plus QA programs for IGRT protocols (52). These are critically important endeavors to ensure patient safety, treatment fidelity, and quality of RT.

The recently completed RTOG 0617 trial for NSCLC was a null trial, failing to demonstrate a benefit for the higher-dose arm. Multiple reasons might explain this observation, but there was definitely a higher incidence of treatment-related deaths in the latter arm; posing dosimetric considerations as one possible explanation. Similarly, a review of RTOG gastrointestinal trials uncovered a significant minority of unacceptable RT plans which might also in part, account for their null results. Of note, such trials wherein unacceptable RT plans were corrected resulted in positive observations (53). By harnessing the capabilities of digital technology, pre-treatment reviews of RT plans could be undertaken in an expeditious and resource-efficient manner.

VI. Data Sharing and Publication Biases

A current challenge in our biomedical research community is a tendency towards publication bias of positive results, documented decades ago wherein meta-analyses of published data would overestimate the treatment benefit *vs*. all registered clinical trials (54). This tendency continues today, wherein more than 20% of Phase III clinical trial abstracts presented at ASCO remain unpublished after 6.5 years, or took longer than 5 years to be published (55).

The requirement to reproduce published data is a fundamental tenet to achieving true medical advances. The lack of data reproducibility is a major problem for drug development, wherein two-thirds of these studies have significant inconsistencies (56, 57). One example relates to Motexafin Gadolinium that proceeded to Phase III testing (58), despite laboratory evidence documenting its lack of radio-sensitization (59). The lack of reproducibility costs both patients, for participating in treatments which are unlikely to be beneficial, and society. Pharmaceutical companies lose time and money on pursuing academic discoveries which remain difficult to reproduce (60, 61), which can be further compounded by off-target effects with siRNAs (62, 63).

In the current era of genomic medicine, this situation becomes even more challenging (64); wherein data from only 2 of 18 micro-array publications in *Nature Genetics* could be replicated; the major problem being inaccessibility to the original raw data files (65), with potentially dire consequences for patients (64). *Science* devoted its entire Dec 2nd, 2011 issue to this very topic (66), and recommended 6 steps: 1) analytical validity (different platforms); 2) repeatability (different scientists); 3) replication (meta-analyses of different data sets); 4) external validation (consistent large-scale datasets); 5) clinical validity (can predict clinical outcome); and 6) clinical utility (actually improves clinical outcome), before any –omic data be utilized in clinical medicine. Similar guidelines have been suggested for predictive or prognostic biomarkers based on 5 levels of evidence, ranging from under-powered observational reports to prospectively-designed clinical trials examining a biomarker (67).

These recommendations have been developed to temper human nature which prefers celebratory *vs*. sobering news, the competition in science and academia, and the explosive

quadrupling growth in the number of scientific Journals from 1970 to 2011. E-Journals such as *BMC Research Notes* encourage the publication of negative data and replication of previously-reported results. Recognizing the academic and societal value of well-conducted but null or negative publications would enhance the likelihood of such studies becoming publicly available.

VII. Designs of Clinical Trials

In designing complex clinical trials, there needs to be a deep appreciation of the characteristics of the targeted population, and competing risks. For example, if the proportion of patients in a hypothetical "hypoxic cytotoxic" trial is only 15%, depending on the anticipated benefit of the intervention, up to 1000 patients might be required to demonstrate such a difference in outcome. Similarly, if the targeted population has competing risks (e.g. lung or HNSCC patients); the sample size needs to be increased significantly, if OS was the primary end-point.

Alternatively, if the design of clinical trials is complex (e.g. RTOG 94-13 had a complex 2×2 design), and if the interaction between the modalities is not fully appreciated, then this could lead to a potentially under-powered study. In the RTOG 94-13 trial, at the time of its design, the interaction of hormonal therapy with RT for prostate cancer was not yet fully elucidated (68), underscoring the importance of pre-clinical evaluations to better understand such potentially complex biology.

VIII. Consideration of an International Consortium

The clinical development of radiation modifiers is frequently a secondary path, spin-off or occasional afterthought to drug development by industry, academia or government (Fig 1). Basic discovery defines a tumor molecular target, and if the developer considers this to be useful for RT, it will be included in the developmental plans (Fig 1). In this context, the formation of an International Consortium for the Evaluation of Radiation Modifiers could be considered with pooling of resources, developed in a collaborative manner, to expedite the discovery and translation of effective agents which will enhance the curative outcomes of RT for cancer patients.

As shown (Fig 1), there could be a step-wise progression of examining molecular targets combined with RT, prioritized through a Steering Committee, with assignation of specific assays to different groups with such expertise. This will result in a pipeline of potential therapeutic candidates advancing through *in vitro*, *in vivo*, PK/PD, and Phase 0/I to II, and even RCTs, if such targets fulfill the pre-defined criteria for progression. Furthermore, the prompt publication of null, negative or positive results can be of great benefit in avoiding patient toxicity as well as the needless expense in developing a less-than-adequate drug.

CONCLUSION

Several recently-conducted Radiation Oncology clinical trials were presented and discussed at an NCI-US sponsored Workshop. By nature, clinical trials, which are resource-intensive, can often lead to null observations; hence, it behooves us to capitalize upon each opportunity, in order to maximize the derived information. To that end, important themes emerged from this Workshop, including: a) deriving robust pre-clinical data; b) conducting companion translational studies; c) designing appropriately-powered clinical trials; and d) performing expeditious real-time QA of RT plans.

The resources available through the NCI-US Molecular Radiation Therapeutics Branch, the QIN, and the Frederick National Laboratory for Cancer Research should be harnessed by the

Radiation Oncology biomedical research community before embarking on designing future RT clinical trials, particularly when combined with novel targeted agents. Exploring the establishment of an International Consortium for the Evaluation of Radiation Modifiers should be undertaken to pool resources in this important pursuit. Finally, we must all remember that the focus of all of our research efforts is the patient; our obligations are first and foremost, to them.

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ABBREVIATIONS

AFX	Accelerated fractionated radiation therapy
Akt	Serine/Threonine specific protein kinase and oncogene (protein kinase B)
ASCO	America Society of Clinical Oncology
CNS	Central nervous system
CDDP	Cisplatin
Cre	Causes Recombination
CT	Computed tomography
DCE	Dynamic contrast enhanced
DFS	Disease-free survival
DWI	Diffusion-weighted imaging
EGFR	Epidermal growth factor receptor
EML4-ALK	Echinoderm microtubule-associated protein-like 4 – ALK (anaplastic lymphoma kinase)
EORTC	European Organization for Research and Treatment of Cancer
FTI	Farnesyltransferase inhibitor
GBM	Glioblastoma multiforme
GEMM	Genetically-engineered mouse model
γ-H2AX	Gamma-histone 2AX
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
ICGC	International Cancer Genome Consortium
IDH1	Isocitrate dehydrogenase 1
IGF1R	Insulin-like growth factor-1 receptor
IGRT	Image-guided radiation therapy
IMRT	Intensity-modulated radiation therapy
K-ras	Kirsten rat sarcoma viral oncogene
LA HNSCC	Locally-advanced head and neck squamous cell carcinoma

MRI	Magnetic resonance imaging
MGMT	O-6-Methylguanine-DNA-Methyltransferase
MMC	Mitomycin-C
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NF1	Neurofibromin 1
NF-kBIA	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha
NSCLC	Non-small cell lung cancer
OPC	Oropharyngeal cancer
OS	Overall survival
P-Akt	Phosphorylated Akt
PAR	Poly-ADP-ribose
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic
PK	Pharmacokinetics
PDGFRA	Platelet-derived growth factor receptor, alpha polypeptide
PET	Positron emission tomography
PTEN	Phosphatase and tensin homolog
QA	Quality assurance
QIN	Quantitative Imaging Network
RT	Radiation therapy
RCT	Randomized clinical trial
RECIST	Response evaluation criteria in solid tumors
RTOG	Radiotherapy and Oncology Group
siRNA	Short-interfering RNA
SRC	Tyrosine kinase proto-oncogene “sarcoma”
STK33	Serine/threonine-protein kinase 33
TCGA	The Cancer Genome Atlas
TKI	Tyrosine kinase inhibitor
TMZ	Temozolomide
TPZ	Tirapazamine

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APPENDIX 1

Workshop participants

- Abrams, Jeffrey - NIH, Bethesda, MD
- Ang, Kian - MD Anderson Cancer Center, Houston, TX
- Ataman, Ozlem - AstraZeneca Corporation, Manchester, U.K.

- Bailey, Paul - Pfizer Corporation, Ney York, NY
- Ben-Josef, Edgar - University of Pennsylvania, Philadelphia, PA
- Bentzen, Soren - University of Wisconsin, Madison, WI
- Bradley, Jeffrey - Washington University, St. Louis, MO
- Bristow, Robert - Princess Margaret Cancer Centre, Toronto, Canada
- Brown, J. Martin - Stanford University, Stanford, CA
- Buatti, John - University of Iowa, Iowa City, IA
- Camphausen, Kevin - NIH, Bethesda, MD
- Chakravarti, Arnab - Ohio State University-James Cancer Hospital, Columbus, OH
- Choyke, Peter - NIH, Bethesda, MD
- Chung, Christine - Johns Hopkins Medical Institute, Baltimore, MD
- Curran, Walter - Emory University, Atlanta, GA
- Dewesse, Theodore - Johns Hopkins Medical Institute, Baltimore, MD
- Dewhirst, Mark - Duke University Medical Center, Durham, NC
- Dicker, Adam - Thomas Jefferson University Hospitals, Philadelphia, PA
- Doroshow, James - NIH, Bethesda, MD
- Efstathiou, Jason - Massachusetts General Hospital, Boston, MA
- Galvin, James - Thomas Jefferson University Hospitals, Philadelphia, PA
- Garcia-Vargas, Jose - Bayer HealthCare, USA
- Guha, Udayan - NIH, Bethesda, MD
- Ha, Chul - University of Texas Health Science Center at San Antonio, TX
- Hahn, Steve - University of Pennsylvania, Philadelphia, PA
- Hill, Richard - Princess Margaret Cancer Centre, Toronto, Canada
- Kirsch, David - Duke University Medical Center, Durham, NC
- Krishnan, Sunil - MD Anderson Cancer Center, Houston, TX
- Le, Quynh-Thu - Stanford University, Stanford, CA
- Langer, Corey - University of Pennsylvania,, Philadelphia, PA
- Liao, Zhongxiang - MD Anderson Cancer Center, Houston, TX
- Mendonca, Marc - Indiana University, Indianapolis, IN
- Machtay, Mitchell - University Hospitals Case Medical Center, Cleveland, OH
- Mehta, Minesh - Northwestern University, Chicago, Ill
- Miskel, Robin - Sanofi-Aventis Corporation, Boston, MA
- Mitchell, James - NIH, Bethesda, MD
- Pollack, Alan - University of Miami Miami,, FL
- Prasanna, Pataje - NIH, Bethesda, MD

- Teicher, Beverly - NIH, Bethesda, MD
- van der Kogel, Albert - University of Wisconsin, Madison, WI
- Wang, Dian - Medical College of Wisconsin, Milwaukee, WI
- White, Julia - Medical College of Wisconsin, Milwaukee, WI
- Willett, Christopher - Duke University Medical Center, Durham, NC
- Williams, Jackie - Rochester Medical Center, Rochester, NY
- Winter, Kathryn - American College of Radiology, Reston, VA
- Zwiebel, James - NIH, Bethesda, MD

STATEMENT OF TRANSLATIONAL RELEVANCE

Clinical trials are conducted to advance clinical outcome, by examining new technologies and novel treatments, to improve survival and quality of life for our cancer patients. Such trials are resource-intensive, for both patients and investigators; hence, it behooves us to ensure that all such studies are supported and based upon solid evidence informing the underlying hypothesis and subsequent design.

A Workshop entitled “Lessons Learned from Radiation Oncology Trials” underscored several issues, including: the importance of pre-clinical data supporting the combination of a novel molecular agent plus radiation; the value of companion translational studies; the significance of quality assurance in radiation planning and delivery; and the need for academia to acknowledge the value of publishing all results, including those with negative data.

This is the era of rapidly-advancing technological and biological platforms; we need to harness such innovations optimally, for maximal benefit for our cancer patients.

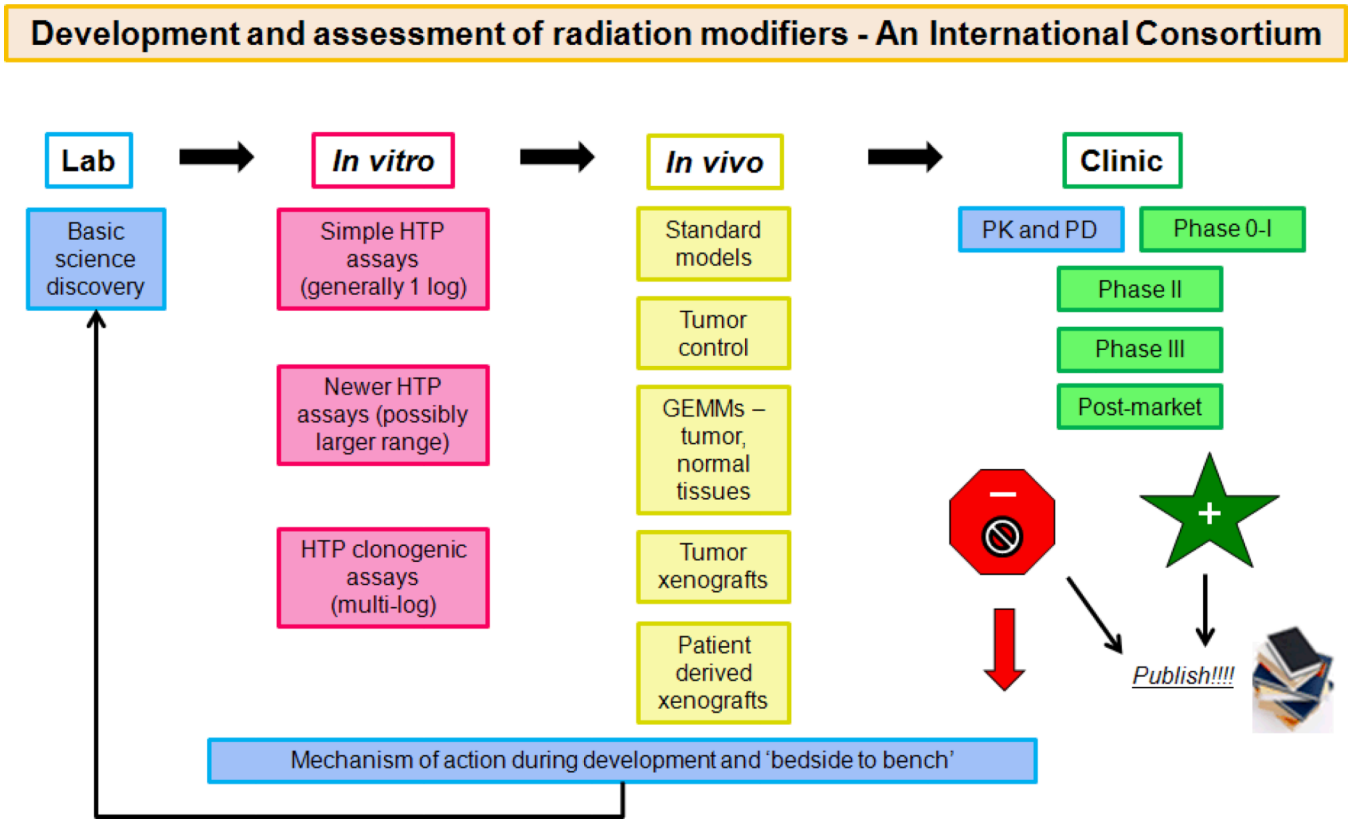

Figure 1.

Pathway of *in vitro* to *in vivo* to Phase I/II/III clinical trials. Proposed model and activities of an International Consortium whereby potential drugs can be provided from academia, industry and government, and prioritized for evaluation through a 'Steering Committee'.

Table 1

Radiation Oncology Phase III randomized clinical trials on central nervous system, head and neck, lung, gastrointestinal, and genitourinary malignancies presented and discussed by the Workshop participants

Trial	Target Tumor Site	Primary Objective (& Results)	Accrual Period	Patients Accrued (completed or randomized)	Notable Secondary Findings
RTOG 0525 **EORTC 26052-22053**	GBM	Does dose-intensifying adjuvant TMZ improve OS? (No evidence for improvement)	01/2006 to 06/2008	1173 (833)	- MGMT validated as a prognostic marker. - New prognostic markers: IDH1, G-CIMP, mRNA profiles.
RTOG 0211	GBM	Phase I/II study of EGFR TK inhibition (Iressa™) with RT (No OS benefit for patients treated with gefitinib + RT *vs*. RT alone)	06/2003 to 01/2012	Phase I: 31 Phase II: 147 (119 successfully completed therapy)	- Correlative immunohistochemical analysis of tissue for prognostic markers of survival (src, IGF1R, PTEN, AKT, EGFR, NFkB), and predictive value of these markers for gefitinib response. - Some markers (elevated Src and PTEN) predicted for poorer response with gefitinib.
RTOG-0129	HNSCC	Does accelerated RT combined with cisplatin improve survival of patients with LA HNSCC? (No evidence for improvement)	07/2002 to 05/2005	743 patients	- Cisplatin offset tumor clonogen repopulation during the course of fractionated RT.
TROG 02.02	HNSCC	Does adding a hypoxic toxin (Tirapazamine) to RT-cisplatin regimen improve survival for patients with LA HNSCC? (No evidence for improvement)	09/2002 to 04/2005	861 patients	- RT QA critical. - Need for tumor hypoxia stratification.
RTOG 0522	HNSCC	Does adding Cetuximab to the RT-cisplatin regimen improve PFS for patients with LA HNSCC? (No evidence for improvement)	11/2005 to 03/2009	940 enrolled (895 evaluable)	- Mechanism of cetuximab and cisplatin. radiosensitization may overlap. - The triplet regimen was associated with higher rates of mucositis and Cetuximab - induced skin reactions. - Effects of HPV status on response to be investigated.
RTOG 0617	NSCLC	Does higher RT dose (60 Gy *vs*. 74 Gy with CRT ± Cetuximab) confer a treatment response benefit? (No evidence for improvement)	11/2007 to 04/2011	423 enrolled	- Futility analysis resulted in closure of high-dose arms, and the standard dose of RT for Stage III NSCLC remains at 60 Gy. Surprisingly, no significant difference in treatment-related toxicity between high-dose *vs*. standard RT arms.

Trial	Target Tumor Site	Primary Objective (& Results)	Accrual Period	Patients Accrued (completed or randomized)	Notable Secondary Findings
					- RTOG has issued a Request for Proposal to conduct translational research using materials obtained from this trial.
RTOG 9811	Anal Canal	Is efficacy of cisplatin-based (experimental) therapy better than mitomycin-based (standard) therapy in treatment of anal canal carcinoma? 5FU/CDDP + RT *vs*. 5FU/MMC + RT (OS & DFS better with 5FU/MMC)	10/1998 to 06/2005	682 randomized (644 included in outcomes analysis)	- Cisplatin-based therapy resulted in a significantly worse colostomy rate.
RTOG 0020	Pancreatic Cancer	Does addition of maintenance with a farnesyltransferase inhibitor (FTI) improve gemcitabine/Taxol chemo-RT? Weekly Gemcitabine, Paclitaxel and External Irradiation (50.4 Gy) followed by the FTI R115777 (Addition of FTI demonstrated no improvement in clinical outcome, yet was associated with increased toxicities)	11/2001 to 09/2003	195 accrued (174 in analysis)	- Maintenance R115777 did not increase survival and was associated with increased toxicities. - Trial did not address potential for radiosensitization by FTI. - K-Ras was known not to be a target for FTI inhibition.
RTOG 94-13	High-risk Prostate Cancer	Does pelvic RT improve progression-free survival compared with prostate-only RT among patients with a chance of lymph node involvement? (No evidence for improvement)	04/1995 to 06/1999	1323 patients accrued (1292 enrolled)	- Study underpowered for pair-wise comparisons. - Long-term follow-up results refuted short-term benefit reported. - Similar European trial, GETUG-01, showed no difference in progression-free survival between the pelvis and prostate-only arms.
EORTC 22961	High-risk Prostate Cancer	6 months androgen-suppression followed by RT, then either observed or additional 2.5 years of androgen-suppression. (Marginal improvement in long-term outcome)	04/1997 to 11/2001	1113 patients	- Longer-term was marginally superior to short-term androgen-suppression.