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 7–8, 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 preclinical 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: (i) opportunities to learn from null-hypothesis trials through tissue and imaging studies; (ii) value of preclinical data supporting the design of combinatorial therapies; (iii) significance of validated biomarkers; (iv) necessity of quality assurance in radiotherapy delivery; (v) conduct of sufficiently powered studies to address the central hypotheses; and (vi) 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, to effectively merge the technologic innovations with the rapidly evolving biology for maximal patient benefit through the design of future clinical trials. Clin Cancer Res; 19(22); 6089–100. ©2013 AACR.

Introduction
Clinical trials involving radiotherapy (RT) for cancer are initiated to identify novel technologic and biologic approaches that can improve local tumor control, disease-free survival (DFS), and overall survival (OS); reduce toxicity; and/or enhance quality of life. The design of these trials should be based on solid preclinical evidence supporting such approaches; however, often, patients participating in the experimental arm fare no better than control subjects (1). A similar trend is currently being reported for drug patients with cancer, through the methodical conduct of high-impact clinical trials.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

CME Staff Planners’ Disclosures
The members of the planning committee have no real or apparent conflict of interest to disclose.

Learning Objectives
Upon completion of this activity, the participant should have a better understanding of the lessons learned from null or negative clinical trials in radiation oncology and how to improve the design of radiation oncology clinical trials in the future.

Acknowledgment of Financial or Other Support
This activity does not receive commercial support.

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This article is dedicated to the memory of Dr. Kian Ang, a leader in radiation oncology, who was continuously improving outcome for our patients with cancer, through the methodical conduct of high-impact clinical trials.

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doi: 10.1158/1078-0432.CCR-13-1116
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combination trials (2). 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 7–8, 2011, in Bethesda, MD, sponsored by the Radiation Research Program of the National Cancer Institute (NCI; Bethesda, MD). The objectives of the workshop were to assess the quality, quantity, and limitations of the preclinical data that supported the hypotheses underlying a few recently completed trials and to consider potential improvements in methods generating these trials. 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 10 recently completed clinical trials 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 glioblastoma multiforme were presented and discussed. The Radiotherapy and Oncology Group (RTOG) 0252/EORTC 26052-22053 was an international phase III randomized clinical trials (RCT) determining whether dose-intensifying adjuvant temozolomide could improve OS (3). The overall conclusion was “no evidence for improvement,” although the prognostic value of MGMT (O-6-methylguanine-DNA-methyltransferase) promoter methylation status was confirmed.

The second phase I/II RTOG 0211 trial examined the addition of an EGF receptor (EGFR) tyrosine kinase inhibitor (TKI; gefitinib) to radiotherapy for patients with glioblastoma multiforme, which failed to show any OS benefit with the combinatorial approach (4). In fact, tumors with elevated SRC or PTEN expression fared worse with the TKI, illustrating the complex signaling cascades underlying most glioblastoma multiforme.

Head and neck squamous cell carcinoma

Despite the success of the landmark cetuximab plus radiotherapy combination for patients with locally advanced squamous cell carcinoma of the head and neck (LA HNSCC; refs. 5, 6), the results of more recent trials have been disappointing. The RTOG 0129 asked whether accelerated fractionated radiotherapy (AFX) plus cisplatin (CDDP) would improve OS for patients with LA HNSCC (7); in fact, no difference was observed between the standard versus AFX group, suggesting that CDDP likely offsets tumor cell repopulation during fractionated radiotherapy.

The TROG 02.02 trial examined the value of adding a hypoxic cytotoxic agent, tirapazamine, to CDDP-RT for patients with LA HNSCC (8). Disappointingly, this study also showed no difference in outcome, but its results underscored the importance of quality assurance in radiotherapy delivery (9), as well as raising questions about the clinical importance of tumor hypoxia (10). A third trial (RTOG 0522) asked whether the addition of cetuximab to CDDP-RT could improve progression-free survival (PFS; ref. 11); this study not only failed to show an advantage to the triple modality but also observed greater acute toxicities. Furthermore, cetuximab and CDDP seemed to have overlapping mechanisms of action; hence, using complementary tumor-cidal agents would likely be more effective.

Lung malignancies

The four-arm RTOG 0617 trial compared OS differences between high- versus standard-dose conformal radiotherapy with concurrent chemotherapy (carboplatin and paclitaxel), with or without cetuximab for patients with stage IIIA/IIIB non–small cell lung carcinoma (NSCLC). The results showed no difference in OS between the high- (74 Gy) versus standard-dose (60 Gy) patients (12), even suggesting an inferior survival with the high-dose arm, possibly related to treatment-related deaths, which may underscore the importance of quality assurance in radiotherapy planning and delivery (13).

Gastrointestinal malignancies

The RTOG 9811 phase III RCT addressed the efficacy of substituting CDDP for mitomycin C (MMC), in the standard 5-fluorouracil (5-FU)/MMC/RT regimen for anal canal carcinoma. The results showed no difference in DFS between the two treatment arms, but the CDDP group experienced a significantly higher colostomy rate (14). The major design flaw related to two new hypotheses of drug and sequence, both being addressed simultaneously, with the new drug being CDDP, delivered in an induction manner. Consequently, it remained unclear whether 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 a farnesyltransferase inhibitor (FTI; R157777) for unresectable pancreatic cancer, showed that maintenance of FTI failed to improve clinical outcome and yet was associated with increased toxicities, highlighting the challenges to inhibiting K-ras, an established oncogenic target in this disease (15).

Genitourinary malignancies

The RTOG 94-13 trial, a complex four-arm randomization of whole pelvis versus prostate-only radiotherapy, with secondary randomization of neoadjuvant versus concurrent hormone scheduling (16, 17) reported no significant difference in PFS for any group. This was an underpowered four-arm trial that failed to address the issues of field size or timing of androgen suppression. There might also have been an unpredicted biologic interaction between concurrent androgen suppression with radiotherapy, supporting an argument for the importance of companion translational studies to acquire biologic insights.

The European Organisation for Research and Treatment of Cancer (EORTC) 22961 trial showed that long-term androgen suppression (total of 3 years) was marginally superior to short-term treatment (6 months) when patients were also...
<table>
<thead>
<tr>
<th>Trial</th>
<th>Target tumor site</th>
<th>Primary objective (and results)</th>
<th>Accrual period</th>
<th>Patients accrued (completed or randomized)</th>
<th>Notable secondary findings</th>
</tr>
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<tbody>
<tr>
<td>RTOG 0525EORTC 26052-22053</td>
<td>Glioblastoma multiforme</td>
<td>Does dose-intensifying adjuvant temozolomide improve OS? (no evidence for improvement)</td>
<td>January 2006 to June 2008</td>
<td>1,173 (833)</td>
<td>— MGMT was validated as a prognostic marker. (3) — New prognostic markers were revealed: IDH1, G-CIMP, mRNA profiles.</td>
</tr>
<tr>
<td>RTOG 0211</td>
<td>Glioblastoma multiforme</td>
<td>Is the combination of EGFR TK inhibition (Iressa) with RT safe and efficacious? (no OS benefit for patients treated with gefitinib + RT vs. RT alone)</td>
<td>June 2003 to January 2012</td>
<td>Phase I: 31 Phase II: 147 (119)</td>
<td>— Correlative immunohistochemical analysis of tissue for prognostic markers of survival (src, IGF-IR, PTEN, AKT, EGFR, NF-kB), and predictive value of these markers for gefitinib response — Some markers (elevated Src and PTEN) predicted for poorer response with gefitinib.</td>
</tr>
<tr>
<td>RTOG 0129</td>
<td>HNSCC</td>
<td>Does accelerated RT combined with CDDP improve survival of patients with LA HNSCC? (no evidence for improvement)</td>
<td>July 2002 to May 2005</td>
<td>743 (721)</td>
<td>— CDDP offset tumor clonogen repopulation during the course of fractionated RT</td>
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<tr>
<td>TROG 02.02</td>
<td>HNSCC</td>
<td>Does adding a hypoxic toxin (tirapazamine) to RT-CDDP regimen improve survival for patients with LA HNSCC? (no evidence for improvement)</td>
<td>September 2002 to April 2005</td>
<td>861 (853)</td>
<td>— RT quality assurance is critical. (8) — Need for tumor hypoxia stratification.</td>
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<tr>
<td>RTOG 0522</td>
<td>HNSCC</td>
<td>Does adding cetuximab to the RT-CDDP regimen improve PFS for patients with LA HNSCC? (no evidence for improvement)</td>
<td>November 2005 to March 2009</td>
<td>940 (895)</td>
<td>— Mechanism of cetuximab and CDDP. 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</td>
</tr>
<tr>
<td>RTOG 0617</td>
<td>NSCLC</td>
<td>Does higher RT dose (60 vs. 74 Gy with conformal RT ± cetuximab) confer a treatment response benefit? (no evidence for improvement)</td>
<td>November 2007 to April 2011</td>
<td>≈500 (423)</td>
<td>— 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. — RTOG has issued a request for proposals to conduct translational research using materials obtained from this trial.</td>
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<tr>
<td>Trial</td>
<td>Target tumor site</td>
<td>Primary objective (and results)</td>
<td>Accrual period</td>
<td>Patients accrued (completed or randomized)</td>
<td>Notable secondary findings</td>
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<tr>
<td>RTOG 9811</td>
<td>Anal canal</td>
<td>Is efficacy of CDDP-based (experimental) therapy better than mitomycin-based (standard) therapy in treatment of anal canal carcinoma? 5-FU/CDDP + RT vs. 5-FU/MMC + RT</td>
<td>October 1998 to June 2005</td>
<td>682 (644)</td>
<td>— No difference in DFS between the two arms, but CDDP-based therapy resulted in a significantly worse colostomy rate.</td>
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<tr>
<td>RTOG 0020</td>
<td>Pancreatic cancer</td>
<td>Does addition of maintenance with an FTI improve gemcitabine/paclitaxel chemo-RT? Weekly gemcitabine, paclitaxel, and external irradiation (50.4 Gy) followed by the FTI R115777; addition of FTI showed no improvement in clinical outcome, yet was associated with increased toxicities.</td>
<td>November 2001 to September 2003</td>
<td>195 (174)</td>
<td>— 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.</td>
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<tr>
<td>RTOG 94-13</td>
<td>High-risk prostate cancer</td>
<td>Does pelvic RT improve PFS compared with prostate-only RT among patients with a chance of lymph node involvement? (no evidence for improvement)</td>
<td>April 1995 to June 1999</td>
<td>1,323 (1,292)</td>
<td>— Study underpowered for pairwise comparisons. — Long-term follow-up results refuted short-term benefit reported. — Similar European trial, GETUG-01, showed no difference in PFS between the pelvis and prostate-only arms.</td>
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<td>EORTC 22961</td>
<td>High-risk prostate cancer</td>
<td>Does longer duration of androgen suppression improve long-term outcome? (marginal improvement in long-term outcome)</td>
<td>April 1997 to November 2001</td>
<td>1,113 (970)</td>
<td>— Long-term was marginally superior to short-term androgen suppression.</td>
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Abbreviations: HPV, human papillomavirus; IDH, isocitrate dehydrogenase 1; IGF-IR, insulin-like growth factor-I receptor.
treated with radiotherapy (18). The effect size was small; 5-year cumulative prostate-specific mortality differed by only 2.5%, and the majority of patients had low Gleason scores. Hence, whether long-term androgen ablation is beneficial for most patients or not remained unclear.

Emerging Themes

Table 2 summarizes the emerging themes and recommendations from the workshop.

Preclinical studies

Many reasons could account for the success of the cetuximab-plus-radiotherapy RCT for HNSCC (5, 6), including (i) the universally reported prognostic value for EGFR over-expression (19–21); (ii) the role of EGFR in mediating radiation resistance (22–24); (iii) the demonstration of efficacy of EGFR inhibitors in several different preclinical cancer models (25–27); (iv) a well-designed drug (28), which was highly efficacious and well-tolerated (29); and (v) a well-constructed and efficiently executed clinical trial (3).

On the basis of the above success, and corroborating the framework for preclinical studies as outlined by Harrington and colleagues in the UK (30), it is recommended that before any combinatorial treatments are considered with radiotherapy, one must start with an in vitro clonogenic assay of the novel drug of interest plus radiotherapy in relevant preclinical cancer models. The MTT and apoptotic assays are simple but are poor substitutes for the more quantitative clonogenic survival assays, which until otherwise shown, will remain the gold standard for the evaluation of any radiation sensitizer, DNA repair modification, or combinations of radiotherapy with drug.

The Molecular Radiation Therapeutics Branch within the Radiation Research Program of the NCI (rrp.cancer.gov/aboutRRP/mrtb.htm) has already generated data for multiple targeted agents combined with radiotherapy 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 microenvironment (e.g., hypoxia), stromal factors, or the human metastatic patterns are not completely recapitulated. Some orthotopic models might address such limitations (31, 32), as well as early-passaged human tumor xenografts. An alternative is the use of genetically engineered mouse models (GEMM) of human cancers (33), which could be useful for lung cancer (34, 35) and soft tissue sarcomas (36). Recently, Guerin and colleagues at the Sunnybrook Research Institute (Toronto, ON, Canada) developed a clinically relevant murine model of postsurgical advanced:

<table>
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<th>Table 2. Summary of recommendations from the workshop</th>
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<tr>
<td><strong>Emerging themes</strong></td>
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<tr>
<td>Preclinical studies</td>
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<tr>
<td>• Must conduct at least in vitro clonogenic assay</td>
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<tr>
<td>• Contact the Radiation Research Program at NCI, which is coordinating the preclinical and clinical studies for multiple targeted agents combined with RT in panels of human cancer cells before embarking on combinatorial therapies</td>
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<td>• Generate in vivo data using different human cancer xenograft models</td>
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<td>Biomarkers</td>
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<tr>
<td>• Develop and validate tumor microenvironment predictive biomarkers</td>
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<td>• Develop and validate predictive biomarkers of sensitivity to molecular-targeted therapies</td>
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<tr>
<td>• Use &quot;clinical-ready&quot; pharmacodynamic read-outs</td>
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<tr>
<td>• Need for robust imaging methods for tumor identification, segmentation, and characterization across institutions</td>
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<td>Clinical trial design</td>
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<tr>
<td>• Simple</td>
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<td>• Ensure study statistically powered (i.e., sufficient sample size)</td>
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<td>• Consider use of adaptive trial design</td>
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<td>Quality assurance</td>
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<td>• Conduct expeditious real-time quality assurance of RT plans</td>
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<td>Publication bias</td>
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<tr>
<td>• Publish results of trials regardless of the outcome</td>
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<td>• Public sharing of raw data</td>
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<td>International consortium</td>
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<tr>
<td>• Establish a consortium for the evaluation of radiation modifiers to expedite the discovery and translation of effective agents that will enhance the curative outcomes of RT for patients with cancer</td>
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metastatic breast cancer, which could be an improved model on evaluating efficacy of antiangiogenic agents (37). This effort and other similar work highlight the need to focus on developing and using better preclinical models, which in turn might lead to higher success rates in clinical trials.

Many of these xenograft models are readily available within the radiation oncology community, including the central nervous system (38), lung (39, 40), breast (41), head and neck (42), pancreas (32, 43), and cervix (31). Funding for these studies remains challenging, although some pharmaceutical companies could be interested as such data will inform the design of early-phase clinical trials. Finally, another potential solution could be the use of a panel of molecularly annotated first-generation xenografts harboring high and low levels of the putative target (44); this could guide clinically realistic radiotherapy and drug doses for subsequent clinical trials.

Microenvironment as a target

Over 60 years of research on hypoxia and radiotherapy, tumor response can be summarized in the following manner: (i) rodent and human tumors contain hypoxic cells; (ii) rodent tumors are more hypoxic than human tumors and thus will model only the most hypoxic of human tumors; (iii) hypoxic human tumors are radiotherapy resistant; (iv) methods to overcome hypoxia in human tumors are less than perfect but are beneficial (45); and (v) the ideal methods to identify or treat hypoxic tumors do not yet exist.

Three limitations of the TROG 02.02 trial (8) relate to administration of tirapazamine, quality assurance of radiotherapy plans, and human papillomavirus (HPV) status. The tirapazamine dose was sufficient high to potentiate CDDP; however, it was administered with only nine of 35 fractions, which could have compromised the anticipated benefit. Tumors were not selected for hypoxia, and 12% of these patients had noncompliant radiotherapy plans that adversely affected tumor control (9), and these patients were disproportionately distributed to the tirapazamine arm. Finally, TROG 02.02 was designed before the full appreciation of HPV-associated oropharyngeal cancer, which seems not to benefit from hypoxic modifications (46), thereby diluting the potential benefit of tirapazamine.

Other tumor microenvironment properties, such as extracellular pH, angiogenesis, and interstitial fluid pressure, might also influence tumor response to radiotherapy, 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 radiotherapy outcome.

In summary, hypoxia is a negative predictor in some tumors treated with radiotherapy. Despite clear benefits in multiple trials of hypoxia modifiers with radiotherapy, the results have not been sufficiently dramatic to change clinical practice (47). Improved agents are being developed (48) and will be evaluated with hypoxia imaging conducted at critically important times (49), which will help to improve selection of appropriate patients for such therapeutic strategies and hopefully improve the likelihood of positive clinical trials.

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 International Cancer Genome Consortium (ICGC; www.icgc.org) and The Cancer Genome Atlas (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 and to identify novel targets and actionable mutations for radiotherapy-combinatorial trials, although tumor heterogeneity will remain challenging (50). Many of the ICGC/TCGA clinical data are not yet sufficiently mature to identify robust prognostic markers; the role of radiotherapy might also be difficult to discern if such treatment details are lacking. Consequently, the value of well-annotated biospecimens linked to radiotherapy RCTs cannot be overstated.

The landmark observation of the benefit of temozolomide to radiotherapy for glioblastoma multiforme (51) changed practice and led to the evaluation of temozolomide dose intensification (RTOG 0523), corroborating the prognostic value of MGMT methylation status. A translational study evaluating primary glioblastoma multiforme tissues from participants in multiple clinical trials showed a potential two-gene signature ($\Delta$NF-$kBIA$ plus $MGMT$ methylation), as well as suggesting a biologic explanation for the lack of efficacy of erlotinib (52), as $NF-kBIA$ deletion and EGFR amplification emerged to be mutually exclusive aberrations in glioblastoma multiforme. Similar important insights have been derived from RCT tissue studies for HNSCC, not only corroborating the superior outcome for HPV-associated HNSCC (7), but also their limited benefit by hypoxic modifiers (46), which might in part account for the negative TROG 02.02 trial (8, 10). These data clearly illustrate the value of correlative tissue studies in providing biologic insights, and informing the design of future trials.

Another approach is the use of an adaptive trial design (53); in these trials, data gathered during trial progression are used to change an aspect of the trial midway. In the Biomarkers-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, 40% of the patients were randomly assigned to receive one of four treatments during the first phase of the trial (54). In the second adaptive phase, treatments were based on the results of previous biomarker testing during the first phase. This trial highlighted the potential advantage of an adaptive design, especially during complex trials that assess multiple drugs and biomarkers, and require tissue collection and biomarker analysis (33). This is a very promising area of investigation that should influence the design of future radiotherapy–drug trials for lung cancer, which requires...
the analysis of multiple known mutations such as KRAS, EGFR, and EML4-ALK.

Yet another critically important consideration is the use of "clinical-ready" pharmacodynamic read-outs. Pharmacodynamic assays of DNA damage such as γ-H2AX in tumor tissues (55) or quantifying poly-ADP-ribose (PAR) levels in peripheral blood mononuclear cells (PBMC; ref. 56) might be highly applicable for radiotherapy clinical studies, as opposed to phosphorylated Akt (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.

**Imaging biomarker studies**

Tumor response assessment in clinical trials has typically been derived from longitudinal assessments of anatomically based diagnostic images [computed tomography (CT) and MRI], using Response Evaluation Criteria in Solid Tumors (RECIST), which could be subject to observer bias, differences in scanning techniques, or lack of quantitative rigor (57). In an effort to address these shortcomings the NCI established the Quantitative Imaging Network (QIN) as a means to develop robust automated and semiautomatic methods for tumor identification, segmentation, and characterization. Each institution in this network has engaged teams of clinicians and researchers to develop enhanced quality assurance methods for image acquisition and data analysis and to improve interinstitutional reproducibility.

The ability to quantify a metabolic tumor volume on PET/CT scans across institutions will be critical to provide biologic information and achieve an added level of consistency. These changes would also expand the use of molecular imaging with an array of novel positron emission tomography (PET) tracers, as well as application of advanced MRI methods including spectroscopy, dynamic contrast enhanced, and diffusion-weighted imaging. The synergy between the QIN and cooperative groups will be crucial for the future of radiotherapy research.

**Design 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 1,000 patients might be required to show a difference in outcome (as hypothesized by Dr. Quynh-Thu Le, Stanford University, Stanford, CA). Similarly, if the targeted population has competing risks (e.g., patients with lung cancer or HNSCC); the sample size needs to be increased significantly if OS is the primary endpoint.

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 underpowered study. In the RTOG 94-13 trial, at the time of its design, the interaction of hormonal therapy with radiotherapy for prostate cancer was not yet fully elucidated (58), underscoring the importance of preclinical evaluations to better understand such potentially complex biology.

**Importance of radiotherapy quality assurance**

The critical importance of quality assurance in radiotherapy was succinctly illustrated in the aforementioned tirapazamine trial, wherein deficient radiotherapy plans were associated with a 20% reduction in OS (9) that 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 prereviews of intensity-modulated radiotherapy plans (59, 60) and quality assurance programs for image-guided radiotherapy protocols (61, 62). These are critically important endeavors to ensure patient safety, treatment fidelity, and quality of radiotherapy.

The recently completed RTOG 0617 trial for NSCLC was a null trial, failing to show a benefit for the higher-dose radiotherapy arm. Multiple reasons might explain this observation, but there was a higher incidence of treatment-related deaths in the latter arm (discussed during the workshop), posing dosimetric considerations as one possible explanation. Similarly, a review of RTOG gastrointestinal trials uncovered a significant minority of unacceptable radiotherapy plans (discussed by Dr. Chris Willott, Duke University Medical Center, Durham, NC), which might also in part, account for their null results (63). Importantly, in trials in which unacceptable radiotherapy plans were corrected, positive results were then observed (63). By harnessing the capabilities of digital technology, pretreatment reviews of radiotherapy plans could be undertaken in an expeditious and resource-efficient manner. Several reports have highlighted that radiotherapy quality assurance is a critically important step in the clinical trial process that should result in improved clinical outcomes (64–66).

**Data sharing and publication bias**

A current challenge in our biomedical research community is a tendency toward publication bias of positive results, documented decades ago wherein meta-analyses of published data would have overestimated the treatment benefit versus results from registered clinical trials (67). This tendency continues today, wherein more than 20% of phase III clinical trial abstracts presented at the annual meeting of the America Society of Clinical Oncology (ASCO) remain unpublished after 6.5 years, or took longer than 5 years to be published (68).

The requirement to reproduce published data is a fundamental tenet to achieve true medical advances. The lack of data reproducibility is a major problem for drug development, wherein two thirds of these studies have significant inconsistencies (69, 70). One example relates to motexafin gadolinium, which proceeded to phase III...
testing (71) despite laboratory evidence documenting its lack of radiosensitization (72). The lack of reproducibility has costs to patients, for participating in treatments that are unlikely to be beneficial, and to society. Pharmaceutical companies lose time and money on pursuing academic discoveries that remain difficult to reproduce (73, 74), which can be further compounded by off-target effects with siRNAs (75, 76).

In the current era of genomic medicine, this situation becomes even more challenging (77); data from only two of 18 microarray publications in *Nature Genetics* could be replicated. The major problem is inaccessibility to the original raw data files (78), with potentially dire consequences for patients (77). *Science* devoted its entire December 2, 2011, issue to this very topic (79) and recommended six steps: (i) analytic validity (different platforms); (ii) repeatability (different scientists); (iii) replication (meta-analyses of different datasets); (iv) external validation (consistent large-scale datasets); (v) clinical validity (can predict clinical outcome); and (vi) clinical use (actually improves clinical outcome) before any -omic data be used in clinical medicine. Similar guidelines have been suggested for predictive or prognostic biomarkers based on five levels of evidence, ranging from underpowered observational reports to prospectively designed clinical trials examining a specific biomarker (80).

These recommendations have been developed to temper human nature, which prefers celebratory versus 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.

**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 potentially useful in combination with radiotherapy, 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 as a means to pool resources developed in a collaborative manner to expedite the discovery and translation of effective agents, which will enhance the curative outcomes of radiotherapy for patients with cancer.

As shown in Fig. 1, there could be a stepwise progression of examining molecular targets combined with radiotherapy, prioritized through a steering committee, with assignment 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*, pharmacokinetics/pharmacodynamic, and phase 0/I to II, and even RCTs, if such targets fulfill the predefined 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.

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Figure 1. Pathway of *in vitro* to *in vivo* to phase III clinical trials. Proposed model and activities of an international consortium through which potential drugs can be provided from academia, industry, and government, and prioritized for evaluation through a steering committee. HTP, high throughput; PD, pharmacodynamic; PK, pharmacokinetics.
Conclusions

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 to maximize the derived information. To that end, important themes emerged from this workshop, including (i) deriving robust preclinical data; (ii) conducting companion translational studies; (iii) designing appropriately powered clinical trials; and (iv) conducting expeditious real-time quality assurance of radiotherapy 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 the design of future radiotherapy clinical trials, particularly when combined with novel targeted agents. The possibility of an international consortium for the evaluation of radiation modifiers should be explored as a means to pool resources in this important pursuit. Finally, we must remember that the focus of our research efforts is the patient; our obligations are first and foremost, to them.

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Grant Support

This work has been supported by funds from the NCI.

Received April 23, 2013; revised August 6, 2013; accepted August 10, 2013; published online November 15, 2013.
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Clin Cancer Res; 19(22) November 15, 2013 6099
Lessons Learned from Radiation Oncology Clinical Trials

Fei-Fei Liu, for the workshop participants, Paul Okunieff, et al.


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