Improving the Predictive Value of Preclinical Studies in Support of Radiotherapy Clinical Trials

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Abstract

There is an urgent need to improve reproducibility and translatability of preclinical data to fully exploit opportunities for molecular therapeutics involving radiation and radiochemotherapy. For in vitro research, the clonogenic assay remains the current state-of-the-art of preclinical assays, whereas newer moderate and high-throughput assays offer the potential for rapid initial screening. Studies of radiation response modification by molecularly targeted agents can be improved using more physiologic 3D culture models. Elucidating effects on the cancer stem cells (CSC, and CSC-like) and developing biomarkers for defining targets and measuring responses are also important. In vivo studies are necessary to confirm in vitro findings, further define mechanism of action, and address immunomodulation and treatment-induced modification of the microenvironment. Newer in vivo models include genetically engineered and patient-derived xenograft mouse models and spontaneously occurring cancers in domesticated animals. Selection of appropriate endpoints is important for in vitro studies; for example, regrowth delay measures bulk tumor killing, whereas local tumor control assesses effects on CSGs. The reliability of individual assays requires standardization of procedures and cross-laboratory validation. Radiation modifiers must be tested as part of clinical standard of care, which includes radiotherapy for most tumors. Radiation models are compatible with but also differ from those used for drug screening. Furthermore, the mechanism of a drug as a chemotherapeutic agent may be different from its interaction with radiation and/or radiochemotherapy. This provides an opportunity to expand the use of molecular-targeted agents. Clin Cancer Res; 22(13): 3138–47. ©2016 AACR.

Disclosure of Potential Conflicts of Interest

M. Baumann reports receiving a commercial research grant from Merck. D.G. Kirsch reports receiving a commercial research grant from GlaxoSmithKline. M.W. Dewhirst reports receiving commercial research grants from Aeglio Therapeutics, BioMimetix Pharmaceutical, and Janssen, has ownership interest in Celoxon, and was a consultant/advisory board member for EMD Serono. No potential conflicts of interest were disclosed by the other authors.

Editor’s Disclosures

The following editor(s) reported relevant financial relationships: J.R. Grandis—None.

CME Staff Planners’ Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the strategies currently under investigation to improve the preclinical development of drugs to enhance the efficacy of radiotherapy. These strategies include high-throughput screening approaches and assessing drugs in clonogenic survival assays in vitro and in animal models in vivo. Issues both in common with and in comparison with drug screening can facilitate innovative drug-radiotherapy combinations, including drug repurposing.

Acknowledgment of Financial or Other Support

This activity does not receive commercial support.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-16-0069

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**Introduction**

The era of personalized and precision medicine has emerged with a multitude of molecularly targeted drugs, immune modifiers, and new classifications of cancer based on biologic/genomic characteristics in addition to the organ of origin. Appropriate preclinical studies are critical to optimize targeted therapeutic strategies and clinical trial design to benefit the patients and also enhance the return on investment in translational research.

Approximately 60% of patients with cancer in the developed world receive radiotherapy, often combined with systemic agents. Radiotherapy is a critical component of comprehensive cancer treatment in the developing world (1). It is effective and often curative but would be more so if radiosensitizers, radio protectors, and predictive biomarkers of patient and tumor radiation sensitivity were employed (2, 3). Radiation modifiers have been reviewed recently (4–8), as has the potential for radiotherapy to enhance the effectiveness of immunotherapeutics (9–11) to improve local tumor control as well as to induce abscopal effects that result in concomitant responses in distant metastases (12, 13).

One impediment to drug development has been the irreproducibility of preclinical data (14). A 2012 NCI Radiation Research Program (RRP) workshop examined six randomized clinical trials from the Radiation Therapy Oncology Group that resulted in null outcomes (15). This result may be due, in part, to the quality and validity of the preclinical data. Stone and colleagues (16), after examining the details of 125 reported in vivo and in vitro preclinical studies on radiation modifiers, concluded that future preclinical studies must include (i) use of appropriate preclinical models that best represent the clinical setting of extant 'standard-of-care' multimodality cancer therapy; (ii) fastidious calibration and dosimetry of radiation sources (17); (iii) detailed and accurate descriptions of experimental methodology and results; and (iv) clinically relevant drugs, doses, schedules, and assay conditions. Of critical importance is the recognition that the mechanism of action of a molecular-targeted drug may be different when it is used by itself to target a specific tumor pathway compared with how it affects combination therapy that includes radiation.

Here we review issues that could enhance the strength of preclinical models of radiation-modifying drugs in leading to early-phase clinical trials. This review includes specific aspects of in vitro assay systems and in vivo rodent and companion canine tumor models with the goal of identifying critical steps, gaps, and new approaches toward enhancing the use of rapidly emerging discoveries in cancer treatment with radiotherapy. Recommendations are presented with the recognition of substantial ongoing changes in cell lines and models for screening drugs for cancer treatment moving from the NCI-60 cell lines (18) to patient-derived xenografts (PDX; ref. 19). While the radiation-modifying drugs could enhance the immune response through the radiation-induced changes in the tumor cell, this review does not include discussion of models for screening and assessing immunotherapy. Radiation-induced immunomodulation is a major topic in itself now under active development, including novel animal models with functioning humanized immune systems (20).

**Focus Areas: Preclinical Radiobiological Assays**

Key components of the workflow of preclinical radiobiological assays (Fig. 1A) and potential avenues to enhance standards and quality (Fig. 1B) are discussed. There is general agreement that the ability of a treated cell to form a colony, as measured by the “clonogenic assay” (21), should be considered the gold standard for testing radiation modifiers, although a number of commercial and short-term assays likely will be required for initial screening of drugs followed by clonogenic assays for confirmation of results wherever possible. The clonogenic assay does not work for all cell lines, and this is currently problematic for patient-derived in vitro models (18, 22, 23). In the future, it is envisioned that short-term assays using patient-derived cell lines and 3D models will be benchmarked against the gold-standard clonogenic assay, using cell lines that are amenable to this endpoint.

**In vitro radiosensitivity screening assays**

Higgins and colleagues (24) reported two types of screening assays for determining new radiosensitization targets including a DNA damage readout and a medium/high-throughput clonogenic assay. The DNA damage readout assay (Fig. 2A) was used with an siRNA library targeted against 200 DNA damage response (DDR) genes. Screening of both tumor and normal cell lines identified polymerase theta (POLQ) as a tumor-specific radiosensitization target.

The medium/high-throughput clonogenic assay (Fig. 2B) uses an automated 96-well plate colony-counting platform with the cell kill measurable to 2 logs (0.01) surviving fraction (25). Screening 10,000 genes in HeLa cells in 8 months identified several new targets. One of these is thiamin pyrophosphokinase (TPK1). The radiosensitizing effects of TPK1 knockdown were subsequently investigated in several other cell lines and confirmed to radiosensitize tumor but not normal cell lines. Work in progress includes evaluating suitability of other cells for this assay system, using drugs in addition to gene knockdowns and validation of hits in in vivo models.

Lin and colleagues (26) describe a novel high-content clonogenic survival assay that is similar in concept to that of Higgins and colleagues (24). This assay performed well, compared with a traditional clonogenic assay with an upper radiation dose limit of 6 Gy (26). This assay was used in a drug screen to identify trametinib as a sensitizer for K-RAS–mutant tumor cells. Like the assay developed by Higgins and colleagues (24), the latter assay has a range of SF limited to 2 logs of kill, but notably, both assays measure cell killing rather than inhibition of proliferation as in most short-term viability/proliferation assays.

Liu and colleagues reported an automated high-throughput (HTS) drug screening platform (Fig. 3; ref. 27) on the basis of short-term cell proliferation/survival assays (3–5 days of incubation). These assays were used to derive a short-term radiosensitization factor at 2 Gy (SRF2Gy), which correlates with standard dose enhancement factors (DEF) derived from clonogenic survival assays using radiation doses up to 8 Gy. The correlation between the SRF2Gy and the DEF at SF of 0.1 (DEF0.1) had a sensitivity and specificity of more than 80%. Drug-induced short-term radiosensitization was accompanied by changes in the mode of cell death such as senescence or apoptosis, thus providing a mechanistic basis explaining why short-term endpoints could effectively predict radiosensitization in a clonogenic assay. The results obtained with this assay underscored the impact of genomic heterogeneity among tumors and the need to examine the activity of a targeted drug in a broad range of tumors. Further development of this automated platform would allow...
high-throughput initial screening of drugs against tumors from a range of established and patient-derived cell lines with defined genomic backgrounds for establishing drug–biomarker–radio-sensitization relationships.

In vitro: Endpoints and 3D models

Short-term assay endpoints include growth inhibition (analysis of cell number after 2–4 days of exposure to an agent by assays such as MTT or XTT), cell viability analysis (trypan blue

Figure 1.
A, workflow of preclinical radiobiology experimental tasks from the discovery phase to clinical trials. The critical steps are the clonogenic assay and regrowth delay assay using a clinically relevant model that includes the extant standard of care that may include systemic agents. Initial drug screening may be high/moderate throughput automated assays or more targeted clonogenic screening. The options for in vivo assays include mouse xenograft models and patient-derived assays. Additional studies may be needed to address mechanism of action, normal tissue toxicity, target cells and microenvironment, such as TCD50 using genetically engineered mouse models (GEMM), or canine companion models. B, steps for assay development to improve quality control and quality assurance for the preclinical radiobiology assays. Developing and standardizing assay procedures are critical steps for the broad clinical application of the assays beyond the research laboratories in which the concept is initially discovered and developed.
exclusion), and measures of apoptosis. The results of short-term assays do not always correlate with those from long-term assays that measure tumor clonogens (clonogenic assay and human tumor stem cell assays). For example, Brown and Wouters showed that while differences in genetic makeup (p53 mutation status) can change the frequency of apoptosis (a short-term assay) induced by radiation or chemotherapy (28), it plays little or no role in clonogenic survival that captures all mechanisms of cell death (29). In contrast, a positive impact of p53 mutation on increased cell sensitivity to DNA-damaging agents was detected by short-term assay in the NCI-60 cell line panel (30). Thus, it is important to understand the mechanism by which cancer cells die (31) and its impact on the endpoint measured in the various assays.

Significant differences exist between 2D and 3D cell culture systems. For example, Eke and colleagues showed that cells cultured in a 3D extracellular matrix are more radio- and chemoresistant compared with cells grown under 2D cell culture conditions (32). A coculture assay platform was developed for drug screening via high-content analysis that could further mimic in vivo systems (33). Our conclusion is that clonogenic or similar long-term assays are essential tools for validating and standardizing the testing of radiation modifiers in HTS assays. While HTS is feasible with
certain cells using a clonogenic survival endpoint, patient-derived tumor models will likely require nonclonogenic endpoints. Three-dimensional systems, including those with extracellular matrix and with coculture with normal cells, represent approaches for initial screening of a limited number of compounds as well as for secondary screens of lead compounds identified in initial 2D screens. Validating the effects of novel radiation modifiers by examining their effects on a relevant panel of tumor and normal cell lines is key to establishing their clinical relevance.

No in vitro cell culture assays will be able to fully assess the efficacy of agents that work through the microenvironment, such as improved tumor oxygenation, altered immune cell infiltration, or altered tumor vasculature.

**In vivo Approaches**

**Tumor control dose assay.** Baumann and Krause (34) have reported extensively on the use of tumor control dose (TCD<sub>50</sub>) assay (i.e., the radiation dose that results in a 50% probability of tumor control) as a cancer stem cell (CSC, also referred to as “tumor-initiating cells” or “CSC-like”)-related endpoint in preclinical tumor models. Hill and Milas (35) demonstrated the importance of CSC number and tumor control in the TCD<sub>50</sub> assay (ref. 34; Fig. 4). They showed an inverse linear correlation between their TD50 (take dose 50, i.e., the cell number necessary to achieve tumor growth in 50% of the host animals) and the TCD<sub>50</sub> after single-dose irradiation under homogeneous hypoxia (35–37). The importance of inactivation of CSCs by radiotherapy for local tumor control is supported by a number of further experiments (38) and recent clinical data, for example, use of the putative CSC marker CD44 for patients with early-stage laryngeal cancer (36, 39). CSC number was correlated with permanent local tumor control. In line with this result, a multicenter retrospective analysis of postoperative radiochemotherapy in HPV-negative high-risk head and neck small cell cancer (HNSCC) revealed a significant correlation between high levels of CD44 protein expression as well as mRNA expression of other putative CSC markers and low locoregional tumor control after radiochemotherapy (40). A further example is the observation that low 26S proteasome activity, which leads to CSC-like phenotype with higher self-renewal capacity and higher tumorigenicity, correlates with locoregional control in HNSCC (41). Similar correlations have also been found for other tumor types investigated using a variety of putative CSC markers (42). It is important to note that so-called CSC markers do not directly indicate a single CSC but rather correlate with enrichment of CSCs in a subpopulation. In addition, remarkable plasticity has been recognized between the non-CSC and CSC phenotype in tumor cells (43, 44). For example, therapeutic interventions including fractionated irradiation may lead to epigenetic reprogramming of non-CSC to CSC-like tumor cells (45). Despite these important limitations, the clinical and preclinical observations described above indicate that surrogate markers of CSC density and number (36) are significantly correlated with the probability of local tumor control after radiotherapy, supporting the need for in vivo assays to reflect CSC inactivation.

Results from tumor growth delay assays may not always be consistent with the results of TCD<sub>50</sub> assays (46). However, growth delay experiments are useful for gaining mechanistic insights and also because shrinkage and growth delay provide clinical benefit. Thus, an unresolved issue is whether there is an optimal series of in vivo assays that should be done before proposing a clinical trial. TCD<sub>50</sub> assays are performed much less commonly than growth delay assays because of the larger number of animals required and higher cost. Nevertheless, before clinical trials with curative endpoints are initiated, TCD<sub>50</sub> assays, which better reflect CSC inactivation, should be considered to reduce the chance of a negative trial. This effort may require cooperation between specialized laboratories for practical reasons. While the TCD<sub>50</sub> assay has been widely used in radiotherapy studies, the same arguments for its use can also be made for other therapeutic interventions when their curative potential is tested (38).

**Genetically engineered mouse models.** Genetically engineered mouse models (GEMM) allow for the generation of primary...
tumors that develop in a mouse with an intact immune system and within a native microenvironment. Therefore, GEMMs may be particularly useful in modeling the response of cancer to radiation and immunotherapy. Because GEMM cancers can be generated in a temporally and spatially restricted manner (47, 48), these models can be used to study the response of cancer to chemoradiotherapy in vivo. One of the most attractive features of GEMMs is the ability to use different recombinases to mutate genes in specific cell types for mechanistic studies. Kirsch and colleagues (48) have used a dual recombinase GEMM to answer a fundamental question in radiobiology: Is tumor sensitivity defined by the tumor cell or host stromal components? Figure 5 outlines the results of these studies published in an article by Moding and colleagues (49). With the development of Flp-regulated CreER alleles (50), dual recombinase technology can also be applied for sequential mutagenesis within tumor cells to investigate mechanisms of tumor maintenance and response to radiotherapy. These approaches could be expanded to include newer gene technologies such as CRISPR/Cas9.

Other animal models. Companion animal studies, primarily in dogs, are a focus of the Comparative Oncology Program at the NCI. Increased interest in these models is highlighted in a recent report by the Institute of Medicine, summarizing a 2-day workshop held in 2015. A summary of this conference has recently been published (51). These models offer unique opportunities for drug and chemoradiotherapy development (52). Canine tumors are genetically diverse, grow relatively slowly, exhibit spatiotemporal heterogeneity and diversity, are amenable to imaging studies, and can help assess cost-effective treatment choices (53). In addition, they are not subject to HIPAA regulations, allowing for greater flexibility in conducting retrospective tissue analyses. An example of the type of data from a canine trial is provided in Supplementary Fig. S1.

*In vivo* Biomarkers and other endpoints

Other potential confounders and considerations should be taken into account when using the results of a screening assay for a combined radiochemotherapy clinical trial. These confounders include (i) the differential impact of the drug on the CSC and non-CSC compartments; (ii) the effect of the tumor microenvironment on radiation response (e.g., hypoxia) or the other components of the microenvironment as noted above; and (iii) the fate of various cell populations following fractionated irradiation. The impact of multifraction irradiation on altering the cellular molecular phenotype has been reviewed by Makinde and colleagues (54). Radiation-inducible targets may be exploitable for immunotherapy and molecular-targeted therapy. A comprehensive discussion of biomarkers is beyond the scope of this article, but biomarker development is an essential part of drug development and treatment selection. The γ-H2AX biomarker is frequently used for assessing the impact of therapy (55). Other DNA damage and tumor biomarkers will provide enhanced and potentially early predictive information. Opportunities exist to use tumor radiation resistance/sensitivity biomarkers to escalate/de-escalate radiation...
Figure 5. Illustration of utility of GEMM in the investigation of mechanism for stereotactic body radiotherapy (SBRT). A, dual recombinase (Flp + Cre recombinases) technology can be employed to dissect the mechanism of tumor response to SBRT. Genetically engineered mice were generated so that injection of an adenovirus-expressing Flp initiates primary cancer development (47). The mice also express Cre recombinase specifically from stromal cells (49). B, deleting ATM specifically in endothelial cells sensitized tumor endothelial cells to radiation. This increased growth delay after SBRT (49) but with high-dose SBRT, which was capable of achieving local control in some mice, sensitizing endothelial cells to radiation failed to improve local control (72). A, adapted from "Generation of primary tumors with Flp recombinase in FRT-flanked p53 mice," by Lee et al. (47). © 2012, Published by The Company of Biologists Ltd. This figure is licensed under a Creative Commons Attribution 3.0 Unported License, which permits unrestricted noncommercial use, distribution, and reproduction in any medium provided that the original work is properly cited and all further distributions of the work or adaptation are subject to the same Creative Commons License terms. (Continued on the following page.)
dose and to spare normal tissue toxicity. Biomarkers that assess tumor characteristics are being used for making treatment choices in clinical trials (56–58).

Other Considerations
In addition to the radiobiological issues outlined above, several general points should be considered. Gene expression patterns can vary on the basis of the location of the tumor cells in a tissue culture or the location of implantation in a rodent model— xenograft versus orthotopic (59). Gene silencing is often used to study the effect of targeting a specific molecular pathway with drugs in an experimental model. However, John-Aryankalayil and colleagues showed that the gene expression pattern can be substantially different when the target gene is silenced in comparison with the pattern seen when a pathway is drugged. They also reported that drug concentrations in excess of what is clinically relevant can lead to mechanisms of action that may be irrelevant in the clinic (60).

Spatiotemporal heterogeneity within tumors during tumor evolution, at the time of initial biopsy and profiling, and over time during and after treatment is another key and highly complex consideration. The provocative report in renal cell cancer by Gerlinger and colleagues demonstrated the heterogeneity in tumors present de novo and the likelihood of adaptation/evolution during therapy (25). The complexity of heterogeneity includes genomic heterogeneity, epigenetic changes in tumor phenotype, environmental and metabolic influences on treatment outcome, normal tissue–tumor cell interaction, including cell-to-cell signaling, and immunologic responses (61). In vivo organoid models (62) may mimic the hypoxic aspects of heterogeneity, as the 3D models (32, 33) can reproduce cell–matrix interaction. The move to patient-derived tumor xenografts (PDF) addresses certain aspects of heterogeneity (63), but many important factors relating to treatment outcome as well as evolution under the treatment conditions will not be accounted for in a pretreatment xenograft (64, 65). While this area of research remains speculative, given the ability to target radiation dose to specific volumes, radiotherapy may be a very useful 'drug' with which to alter tumor behavior in a way that makes treatments more effective, in addition to the cell killing by radiation itself (54, 66).

Toward Improved Preclinical Models of Radiation Modifiers
A pathway for the development of radiation modifiers reported in a recent publication (8, 67) suggests modifications to address the new biology; however, time-honored assessments often referred to pejoratively as "classical" remain critical to both drug and radiation clinical trials (66). While animal normal tissue models may provide only limited information, normal tissue injury remains an integral part of preclinical development (67, 68). The need for studies will depend on the size of the treatment field, as highly focused radiation fields in some regions are designed to be at tissue-damaging doses to limited volumes and thereby minimizing clinically significant late effects.

Critical issues raised about translation of preclinical study results to clinical trials are being addressed (69, 70). Recognizing the rapid evolution in tumor biology and model systems and our reluctance to be prescriptive in such a complex field, a general approach to preclinical assessment of radiation modifiers may be as follows (see Fig. 1A):

Step 1
HTS screens need to be harmonized for 2D cultures so that comparable results can reliably be obtained by different laboratories. The techniques themselves can be varied as long as the results are reasonably compatible and/or differences understood. In settings in which a limited number of compounds are being tested, the initial screening may be Step 2.

Step 2
When clonogenic assays are possible, these should be conducted as they measure cell killing down to 3 to 4 log kill and not just growth inhibition. Notably, few drugs are subject to a clonogenic assay, and cell survival below 1 log is rarely assessed in short-term viability/proliferation assays. In vitro assays should consider CSC-like cells that are relevant for radioresistance, for example through the use of tumor spheres. Furthermore, 3D models can help approximate some microenvironmental factors. Before going into animal models, Step 2 may also include assessing the impact of concurrently given chemotherapeutics on radiosensitizing drug effects. The inclusion of patient-derived tumor models is recommended if the initial screen was done on established cancer cell lines. In general, Step 2 narrows down the number of compounds that will undergo the next step in testing.

Step 3
Assessment of efficacy in murine models should include treatment regimens that are clinically relevant. These regimens will include combinations of radiation plus drugs that are the standard of care and an appropriate radiation schedule. While regrowth delay assays may not necessarily correspond to local tumor control, they are useful for evaluating drug–radiation interaction, mechanisms of action, and microenvironmental effects. The initial models may be xenografts like those used now or newer models from patient-derived tumors with the models selected on the basis of their utility for predicting clinical results (16).

Step 4
At this point, expansion of in vivo systems beyond growth delay should be selectively applied on the basis of the specific mechanistic issues being addressed and also on the aim of assessing local control as a clinically relevant endpoint, such as with the TCD50 assay. GEMMs can help determine mechanisms of action and which cells are the "target," and companion canine models have all the components of spontaneous human tumors, as well as providing needed care to the animals. It may also be equally important to study normal tissue toxicity to critical organs in tumor-bearing animal models to determine the overall risk–benefit ratio.
Figure 1 summarizes the workflow sequence for radiation modifier preclinical development. It also shows the hierarchy of steps to be followed with increasingly stringent laboratory protocols for preclinical radiobiology assays to ensure rigorous quality control, assure validity of preclinical data to conduct clinical studies, and then provide broad application beyond the single laboratory that developed the assay. Such attention to detail is a key issue for the FDA for laboratory-developed tests (71).

Conclusions

Rapid advances in cancer biology are uncovering many potential targets for cancer treatment. These developments have led to a need to screen potential drugs/treatments with accuracy and efficiency so that subsequent assessments have higher chances of identifying effective treatments. Establishing biomarkers that can be used to select the optimal treatment and monitor its effects will facilitate this process.

Cancer researchers and physicians, while working to improve the knowledge in their specific fields, enhance the efficacy, and reduce normal tissue toxicity, need to be cognizant that the best treatment for a given patient may not necessarily be contained within their particular area of interest/research focus. To help with treatment selection, results across preclinical studies need to be comparable, which requires fastidious assay development and cross-platform comparisons. In this context, we stress the continued importance of well-done preclinical trials that are comparable between laboratories and platforms. The continued utility of “classic” methodologies in chemotherapy and radiotherapy, including clinically relevant drug doses, schemes, and assay conditions, should not be overlooked in these trials.

It is expected that the relationship between the “new biology” and advancing clinical care will involve complex multimodality care requiring knowledge of the initial tumor characteristics, biomarkers of tumor response, and adaptation to treatment before treatment resistance arises. The potential for radiotherapy as curative and palliative treatment (1) provides unique opportunities to exploit the technological advances in radiation together with molecular-targeted and immunomodulating agents. The potential exists to use a spectrum of radiation treatments, including highly focused, broad field/whole body, or systemic radiation at specified doses and dose rates, which will open up possibilities for combination treatments requiring careful development, implementation, and ongoing assessment. These are the “next steps” for novel biologically based radiation oncology.

Grant Support

H. Willens is supported by the American Cancer Society (123420RSG-12-224-01-DMC).

Received January 8, 2016; revised March 18, 2016; accepted March 21, 2016; published OnlineFirst May 6, 2016.

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Clinical Cancer Research

Improving the Predictive Value of Preclinical Studies in Support of Radiotherapy Clinical Trials


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Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-16-0069

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