

Report from the Radiation Therapy Committee of the Southwest Oncology Group (SWOG): Research Objectives Workshop 2008

Paul Okunieff,¹ Lisa A. Kachnic,² Louis S. Constine,¹ Clifton D. Fuller,³ Laurie E. Gaspar,⁴ Daniel F. Hayes,⁵ Jean Hooks,⁶ Clifton Ling,⁷ Frank L. Meyskens, Jr.,⁸ Philip A. Philip,⁹ David Raben,⁴ Stephen R. Smalley,¹⁰ Gregory P. Swanson,³ Beverly A. Teicher,¹¹ Charles R. Thomas, Jr.,¹² Bhadrasain Vikram,¹³ Michael J. Zelefsky,¹⁴ and Laurence H. Baker⁵

Abstract Strategic planning for the Radiation Therapy Committee of the Southwest Oncology Group (SWOG) is comprehensively evaluated every six years in an effort to maintain a current and relevant scientific focus, and to provide a standard platform for future development of protocol concepts. Participants in the 2008 Strategic Planning Workshop included clinical trial experts from multiple specialties, industry representatives from both pharmaceuticals and equipment manufacturers, and basic scientists. High-priority research areas such as image-guided radiation therapy for control of limited metastatic disease, analysis of biomarkers for treatment response and late toxicity, assessment of novel agents in combination with radiation, standardization of radiation target delineation, and the assessment of new imaging techniques to individualize cancer therapy, were discussed. Research priorities included clinical study designs featuring translational end points that identify patients most likely to benefit from combined modality therapy; intervention including combination radiation with standard chemotherapy; radiation with radiosensitizing molecular-targeted therapies; and stereotactic radiation for treatment of patients with regard to asymptomatic metastasis and radiation-induced tumor autoimmunity. The Committee concluded that the future research opportunities are among the most exciting to have developed in the last decade, and work is in progress to embark on these plans. (Clin Cancer Res 2009;15(18):OF1–8)

Authors' Affiliations: ¹University of Rochester Medical Center, Rochester, New York; ²Boston University Medical Center, Boston, Massachusetts; ³University of Texas, San Antonio, Texas; ⁴University of Colorado Denver, Aurora, Colorado; ⁵University of Michigan, Ann Arbor, Michigan; ⁶BrainLab, Munich, Germany; ⁷Varian Medical Systems Inc., Palo Alto, California; ⁸University of California Irvine, Orange, California; ⁹Karmanos Cancer Institute, Detroit, Michigan; ¹⁰Olathe Medical Center, Olathe, Kansas; ¹¹Genzyme Corporation, Framingham, Massachusetts; ¹²Knight Cancer Institute, Oregon Health and Sciences University, Portland Oregon; ¹³National Cancer Institute, Rockville, Maryland; and ¹⁴Memorial Sloan-Kettering Cancer Center, New York, New York
Received 2/11/09; revised 4/30/09; accepted 7/12/09; published OnlineFirst 9/1/09.

Grant support: PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA32102, CA38926, CA11083, CA76448, CA22433, CA42777, CA27057, CA58723, CA14028, and CA46113. The views expressed herein are those of the authors and do not necessarily represent the views of the NIH or the US government.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: L.H. Baker: Chairman, Southwest Oncology Group.

Requests for reprints: Paul Okunieff, Department of Radiation Oncology, University of Rochester Medical Center, 601 Elmwood Ave., Box 647, Rochester, NY 14642. Phone: 585-275-5575; Fax: 585-275-1531; E-mail: paul_okunieff@urmc.rochester.edu.

© 2009 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-09-0357

Strategic planning for the Radiation Therapy Committee of the Southwest Oncology Group (SWOG) is comprehensively evaluated every six years in an effort to maintain a current and relevant scientific focus (1). The scientific strategy developed by the Committee provides a standard platform for future protocol concepts developed by its members. The Committee prioritizes the scientific strategy in accordance with subjects relevant to a medical oncology cooperative group. To be successful, these concepts must have a forward vision with treatment strategies and/or translational technology that does not preclude widespread national participation. Also, they must not be overly specific to a particular primary tumor site or histology and must encompass contemporary clinical trial design. Finally, the prioritized concepts must be exciting enough to compete against the many protocols being evaluated by the individual SWOG disease site committees.

A goal of cancer treatment is to improve tumor control while minimizing normal tissue toxicity. Over the past six years, advances in image-guided radiation treatment (IGRT) have exceeded most expectations, and the wide availability of these technologies has opened powerful research opportunities. For example, IGRT may be used to reduce radiation-related toxicity through improved targeting of the tumor and exclusion of

Translational Relevance

In this report, we summarize a May 2008 Strategic Planning Workshop held by the Radiation Therapy Committee of the Southwest Oncology Group to discuss scientific hypotheses relevant for national clinical and translational investigation. High-priority areas for research are image-guided radiation therapy for control of limited metastatic disease, analysis of biomarkers for response and late toxicity, assessment of novel agents in combination with radiation, standardization of radiation target delineation, and the assessment of new imaging techniques to individualize cancer therapy. The overarching purpose of this research is to advance the future management of a variety of cancers.

normal tissue. Moreover, IGRT may allow oncologists to safely irradiate tumors that were formerly difficult or unsafe to treat. Such targeting techniques now allow for high-dose radiation treatments with accuracy that was previously only available by direct surgical visualization.

New biological therapies are also becoming available, many with radiation-sensitizing profiles. It is quite possible that biological-radiation combinations could outdo or provide a further additive benefit to standard chemoradiation strategies. Many of these biological agents are already being used or are proposed for study by the disease site committees of SWOG, providing an important opportunity to concurrently evaluate their impact on radiation response. Recent preclinical investigations also suggest a role of these novel biological agents in decreasing radiation-related normal tissue toxicity (2–4). Thus, some biological agents may be of dual benefit, producing tumor radiosensitization while reducing long-term normal tissue damage by lowering oxidative stress and reducing cytokine-mediated fibrovascular complications.

The current Radiation Therapy Committee Strategic Planning Workshop was held on May 2, 2008 at the SWOG Group Meeting in Atlanta, Georgia. Participants were chosen from the SWOG leadership and included radiation oncologists with translational and/or imaging clinical experience, translational basic scientists, and individuals in industry with an understanding of radiation biology and drug/radiation interactions. The workshop participants were asked to review the relevance of the concepts chosen in 2003, and then to consider approaches to accelerate research progress. The group was also asked to make concrete recommendations to test the scientific strategies they propose. This article is a summary of the consensus of the Workshop.

Clinical Trial Design Recommendations

Randomized trials that feature arms with and without radiation have been a strong research component of SWOG and form the basis of contemporary evidence-based practice (5, 6). These phase III studies will continue to be among the most important, with the expectation that modern radiation delivery techniques might positively impact local control, side effects, and even survival. However, the initial testing of these

radiation techniques with standard or with novel agents is likely to be best accomplished through single-arm or randomized phase II trials.

In this context, Dr. Bhadrasain Vikram, Chief of Extramural Clinical Radiation Oncology at the National Cancer Institute and Keynote Speaker, suggested that in order to maximize clinical impact, the design of a phase II trial in which novel radiation delivery is added to current drug therapy should offer at least one of the following advances over standard care: (a) novel design with scientific end points, (b) incremental benefit, or (c) first in human studies with combined novel agents and radiation.

(a) Novel design with scientific end points. With advances in systemic and biological therapies, improvements in survival may be achieved in the setting of stage IV disease. Patients are often living with a low burden or single regions of metastatic spread, often referred to as an “oligometastatic” state. For these patients, novel IGRT techniques to the area of oligometastases may offer long-term disease control and impact survival. Stereotactic radiosurgery or stereotactic body radiation therapy (SBRT), in which high doses of radiation are targeted to the tumor in one to ten fractions, may be of important benefit in this regard. Data are emerging that patients with limited asymptomatic metastases may experience improved disease-free survival and quality of life after stereotactic radiosurgery or SBRT (7). Long-term disease-free survivals are seen in most single institutional SBRT studies, suggesting that some patients may in fact be cured. Because the majority of patients also had concomitant chemotherapy in these studies, one hypothesis is that chemotherapy controls micrometastatic disease leading to an oligometastatic state. The oligometastases are then consolidated by the radiosurgery (8). Other studies now suggest that the high-dose fractions of radiation associated with brain stereotactic radiosurgery or SBRT may produce a tumor-specific autoimmune effect that can optimally lead to improved disease-free survival.

As such, SWOG 0928 “Extracranial Radiosurgery for Women with a Limited Number of Known Metastases from Breast Cancer - A Limited Institution, Phase II Study” is in development. An example of a radiosurgery treatment for limited metastatic disease is depicted in Fig. 1. The proposed investigation has a primary end point of exceeding the progression-free survival of chemotherapy trials for metastatic breast cancer with the use of 10 targeted treatments of radiosurgery, each delivering 500 cGy, to the metastatic focus. Interestingly, the National Cancer Institute has recently identified the local treatment of asymptomatic metastasis as a specific area of research importance and has created a working intergroup to discuss protocol design of clinical studies. The SWOG Radiation Therapy Committee will strive to attain a leadership role in that committee. Studies similar to the above breast cancer trial are relevant in colorectal and prostate cancer patients with asymptomatic metastases.

A lack of available symptom management agents for the prevention of early or late sequella of radiation or chemotherapy is also worthy of investigation. Circulating molecular markers may identify patients at risk for the development of such therapy-related complications, allowing earlier intervention. Cooperative groups are in a particularly powerful position to evaluate these markers as secondary correlative end points. Randomized studies in which the survival outcome is found

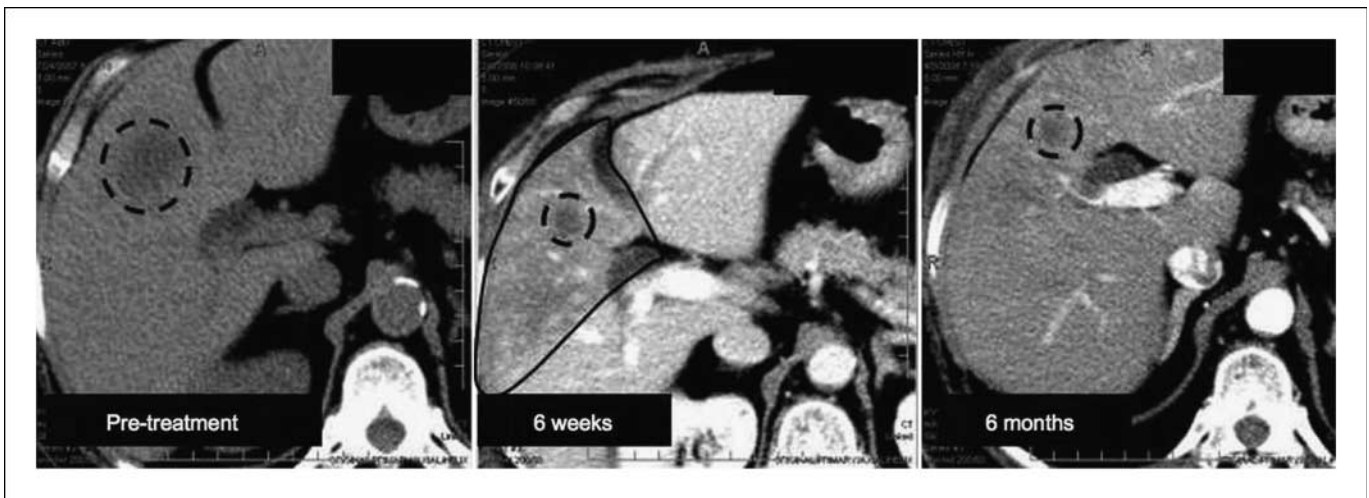


Fig. 1. A liver metastasis from breast cancer was treated to 50 Gy at 5 Gy per fraction over 12 d (hatched volume). Six weeks following irradiation there was an area of hypoperfusion (solid line) on computerized tomography and the tumor becomes necrotic. The hypoperfusion volume approximates the 37 Gy isodose contour. Six months after irradiation, the necrotic tumor area remains (hatched volume), perfusion partly recovers in the damaged liver, and the remainder of the liver undergoes compensatory hypertrophy.

to be similar in all arms, but with different toxicity profiles, are especially ripe for analysis for toxicity markers. The SWOG Radiation Therapy Committee will pursue such investigation. These studies are planned in locally advanced non-small cell lung cancer and limited small cell lung cancer.

(b) Incremental benefit. Incremental benefit trials aim to identify a subset of patients who may receive maximal benefit from a new therapy, with the least harm and expense to those unlikely to experience a benefit to treatment. To this end, one could also apply the investigation of radiosurgery compared with standard symptom management of patients with low-burden metastatic prostate cancer (9, 10). Studies that identify molecular markers for the development of metastases, or investigations that advance imaging of small metastases, will be of substantial interest in the next decade.

(c) First in human studies with novel agents and radiation. Novel agents, such as biologics, can be added to radiotherapy regimens in a similar manner as to chemotherapy regimens. Translational studies in cell culture and laboratory animals should proceed in concert with the clinical studies.

Translational Research Priorities

Using radiation to test the oligometastasis hypothesis. Many patients with metastatic disease seem to defy the dogma of the systemic nature of hematogenous metastases; they enjoy long-term stability in the number of sites and/or number of organs involved. The hypothesis “metastatic disease might be limited in scope” has been postulated for at least 40 years (11–13), and is a theoretical phenomenon that in 1995 was termed “oligometastases” (14, 15). The advent of SBRT, particularly when guided by magnetic resonance imaging and positron emission tomography, now allows for the detection and definitive treatment of very small metastatic lesions. These imaging technologies are causing a stage migration, because many patients formerly thought to have M_0 disease are now defined as M_1 . The impact this imaging has on treatment outcomes is un-

known, but may inappropriately discourage standard curative treatment regimens.

On the other hand, the ability to treat small lesions has led to more widespread acceptance of high-dose stereotactic radiation for these tumors, as well as minimally invasive surgical and invasive radiologic techniques (16–18). The benefit of these is assumed to be positive, but has not been properly tested.

Taken together, these data suggest that a patient with oligometastasis may have a better prognosis than one with more sites of disease. Although there is not yet sufficient evidence for substaging M_1 disease, our developing study, SWOG 0928, will hopefully yield a benefit and suggest subgroups of M_1 disease that benefit from local therapy. For example, in breast cancer, nearly every prognostic index developed for metastatic disease has shown that patients with lower tumor burden, as defined by number of sites of disease and/or number of metastases within a site, have substantially better survival than do those with multiple sites (19–21). Prior to initiating such large definitive randomized trials, it is of value to conduct prospective pilot and phase II studies to gain experience with the radiation techniques and to observe whether there are subgroups of patients most likely to benefit. In this regard, surrogate markers of benefit might be of value. These might include circulating soluble markers, such as carcinoembryonic antigen, CA125, circulating MUC1 (CA15-3, CA27.29), extra-cellular domain of HER2, and PSA in the respective diseases for which they have been validated. Likewise, recently reported studies have shown that circulating tumor cells can be reliably and reproducibly identified and enumerated in patients with breast, colorectal, and prostate cancers, and that changes in circulating tumor cells are strongly associated with progression-free and overall survival, suggesting that they reflect response to treatment (22).

The observation that a high-dose single fraction of radiation can produce tumor specific autoimmunity was discovered in the 1970s (23–27), and more recently has been seen in patients undergoing prostate irradiation or receiving immune adjuvants (28, 29). The use of stereotactic radiation usually includes

high-dose fractions of radiation and might induce tumor autoimmunity, partly explaining the high frequency of long-term disease-free survivals seen internationally in various clinical trials (9, 30). A high priority was placed on developing studies, including immunologic end points, that might help answer whether this phenomenon is occurring in this patient population.

Dr. Lisa Kachnic, Vice Chairperson of the SWOG Radiation Therapy Committee and SWOG Gastrointestinal Radiation Vice Chair, noted that lysyl oxidase is involved in the cross-linking of collagen and elastin, and is overexpressed by hypoxic tumor cells and by metastasis from breast cancer. Inhibitors of lysyl oxidase abrogate *in vitro* breast cancer cell invasion and lysyl oxidase seems essential for hypoxia-induced metastases (31–33). In breast cancer, high lysyl oxidase correlates with increased metastases, estrogen receptor negativity, and shorter metastasis-free and overall survival (34–36). This marker may be useful for identifying high-risk patients for the development of metastases and could provide a circulating marker indicative of a beneficial response. Molecular markers similar to lysyl oxidase are of high priority if we are to develop incremental benefit trials for patients with a low burden of asymptomatic metastases.

Combinations of radiation with DNA repair inhibitors. Defects in most, if not all, DNA repair pathways create cells that are more prone to reproductive sterilization by irradiation. In contrast, different chemotherapy drugs exhibit very specific sensitization to a more limited set of repair pathways (37). Among pathways relevant to radiation response is homologous recombination. Defects in homologous recombination proteins, prominent in the BRCA network, change the chemotherapy-sensitivity profile, rendering such cells sensitive to mitomycin C, cisplatin, tirapazamine, etoposide, and other drugs that produce complex double-strand lesions in DNA (38, 39); as well as resistance to drugs such as taxanes or navelbine (vinorelbine; ref. 40). The latter are two very important drugs for breast cancer chemotherapy. Therefore, knowledge of whether this specific DNA repair pathway is defective, as well as developing effective inhibitors of this pathway, would be valuable information in planning optimized individualized therapy.

Checkpoint kinase 1 and poly (ADP-ribose) polymerase are two proteins also involved in double-strand DNA repair (41, 42). There are many agents targeted against these proteins in development that might be employed with radiation. ABT-888, which is probably the best known (43), is a potent inhibitor of poly (ADP-ribose) polymerase, has good oral bioavailability, can cross the blood-brain barrier, and potentiates temozolomide, platinum, cyclophosphamide, and daily radiation in syngeneic and xenograft tumor models. This broad spectrum of chemopotential and radiopotential makes this compound an attractive candidate for clinical evaluation (44, 45).

Evaluation of Agents in Combination with Radiation to Reduce Late Treatment Sequellae

Combinations of radiation, cytotoxic chemotherapy, and surgery are increasingly being employed to treat local and metastatic disease. A reason for this is the current ability to better manage side effects from all treatment modalities. Until recent years, radiation following prostatectomy or surgery following

radical radiation of the pelvis was rarely done due to severe toxicity. Although the safety of these combined treatments is much better than in the past, many patients still report significant bladder toxicity, some requiring hospitalization (46–48). Much has been learned regarding the risk factors for and the mechanism of bladder-related complications after combined modality treatment, but very little has been done to clinically exploit that basic research. Bladder morbidity is hypothesized to be due to fibrovascular changes. Subendothelial proliferation, edema, and medial wall thickening may progressively deplete the blood supply to the irradiated tissue. Some agents have been evaluated in single-institution studies that could prevent toxic fibrovascular effects, which are unlikely to hinder tumor response. Included among these are curcumin (49–52), pentoxifylline (53), and statins (54, 55). Dr. Michael Zelefsky, SWOG Genitourinary Radiation Vice Chair, reviewed 871 patients treated with prostate cancer between 1994 and 2000 and noted that patients incidentally on statins seem to have reduced treatment-related complications, lower PSAs, and fewer metastases (56, 57). The mechanism for this may be related to macrophage and osteoclast reduction, subsequently causing reduced inflammation, less fibrosis (57), and a less fertile marrow microenvironment for bone metastases (58) leading to tumor suppression. The development of clinical trials with molecular correlates to evaluate such agents is of high priority.

Combinations of Radiation with Biological Modifiers

Biological modifiers currently available for national clinical testing include agents aimed at a number of cellular and physiological targets such as hypoxia, cell proliferation, apoptosis, angiogenesis, cell migration, and cellular maturation. All have potential interaction with radiation. Areas of tissue hypoxia are likely among those most resistant to radiation, a phenomenon that is physical and chemical in nature. Hypoxic regions also express angiogenesis and migration factors that promote metastasis (59, 60). Identification of hypoxia markers in the plasma or pathology specimens can therefore help in defining optimal therapy and are worth investigating as correlative markers for future incremental gain studies (61, 62). Cellular proliferation is known to accelerate during a course of radiation. "Accelerated repopulation" is likely due to increased epidermal growth factor receptor activation that can occur progressively during a course of irradiation (63–65). Inhibition of that process should improve radiation response. Epidermal growth factor receptor activation can also occur during a course of chemotherapy, reducing the potency of subsequent radiation. Thus, inhibition of treatment-enhanced tumor proliferation should also be advantageous for radiation given following chemotherapy.

Most radiation-induced cell death of adult solid tumors is an indirect consequence of reproductive inactivation (mortalization) mediated by chromosomal damage. Apoptosis is also enhanced by irradiation, and radiation predisposes both the intrinsic and extrinsic apoptotic pathways. In contrast, most chemotherapy cytotoxicity is believed to be apoptosis-mediated, and drug resistance is often attributed to resistance to apoptosis. The optimal combinations and timing of radiation and cytotoxic therapy have not been defined for many tumors.

It is likely that low-dose radiation combined with an apoptotic agent can improve chemotherapy response. This is one explanation used to explain the impact of low dose radiation in Rituxan-resistant lymphoma treated with Zevalin (66, 67). Radiation can induce apoptosis through a number of pathways, most prominently p53. Tumors with p53 mutations exhibit increased resistance to apoptosis and many systemic agents (68, 69). Radiation-induced apoptosis can also be reduced in p53 mutant cells, but local tumor control rates and reproductive inactivation following radiation are minimally impacted. Thus, p53 mutated tumors are another category of tumors that might benefit from a combined treatment approach. Marker studies for p53 may also help us to achieve more individualized therapy.

Dr. David Raben, Professor at the University of Colorado Denver, emphasized that antiangiogenesis may have an important interchange with radiation. Most antiangiogenic agents not only decrease the rate of tumor growth, but increase tumor oxygenation due to a slowing of tumor cellular oxygen consumption (70, 71). Improved oxygenation would allow tumor control at lower radiation doses. Prevention of cellular migration, and thereby elimination of new metastases, is a holy grail for local therapies. Antiangiogenesis might prevent new metastases and augment the value of local therapy. Antiangiogenic factors, like radiation, also predispose cells to apoptosis, often through indirect inactivation of nuclear factor- κ B and other growth-promoting signaling pathways. Regarding growth and angiogenesis inhibition, there are several interesting kinase and receptor inhibitors. Vanatinib (ZD6474) is a broad-spectrum inhibitor of vascular endothelial growth factor receptor with cross-reactivity on epidermal growth factor receptor signaling. *In vitro* studies suggest that kinases can work together additively. Erlotinib and bevacizumab seem to work together with vanatinib for the treatment of head and neck squamous carcinomas. To this end, collaborations with industry to study radiation interactions with novel targeted agents, and with combinations of targeted agents aimed at angiogenesis inhibition, have appeal.

Dr. Beverly Teicher, Vice President for Oncology Research at Genzyme Corporation, noted that transforming growth factor β (TGF β) inhibition is likely an exciting new approach to both reduce normal tissue fibrovascular toxicity and improve tumor response (72). TGF β causes fibroblast proliferation, is angiogenic, and promotes osteolysis. TGF β is immunosuppressive, and through its effects on T-regulatory cells, increases immune tolerance. Animal models and human studies confirm the role of TGF β in the development of radiation and drug-induced fibrovascular complications of the lung, liver, and soft tissues (73–77). Thus, TGF β suppression should doubly benefit by reducing late consequences of combined modality therapy while improving tumor response. There are several agents in development including GC1008, anti-TGF β antibody, and tumor autoimmune LY215299 (a TGF β type 1 kinase inhibitor), all meriting investigation. Regarding reduction in the number and frequency of new metastases, Sarc kinase is a pathway of great interest (77). When these agents become available for clinical study, they should be considered for assessment in patients with metastatic disease. For example, agents for the reduction of new metastases should be of particular value to patients treated for a limited number of metastases.

Combinations of Radiation with Chemotherapy

Combination chemotherapy and radiation

Most chemotherapeutic drugs cause DNA damage, prevent DNA damage repair, increase apoptosis, or alter microtubule function, thus adversely affecting the mitotic apparatus. All of these processes can interact with radiation.

Priority objectives for combinations of radiation with chemotherapy

Antitumor platinum complexes. There are three antitumor platinum complexes available (oxaliplatin, carboplatin, and cisplatin) for clinical trials. Many clinical studies have shown important interactions between cisplatin and radiation for both local control and prevention of metastases. Platinum drugs also radiosensitize cells in all phases of the cell cycle, probably due to inhibition of DNA repair by DNA adducts. Animal models show high-dose modification factors, particularly when the doses of platinum drug or radiation are individually insufficient to cause cell death (78). As an example, platinum drugs will have low concentrations in hypoxic tumor regions, but together with radiation, might meet the level needed to kill tumor cells (79–81). Cancers that respond well to platinum drugs and to irradiation include ovarian, head and neck, bladder, testis, and lung (82). Combined radiation and platinum drugs have already been proven in many SWOG protocols, and additional studies remain of interest.

Pyrimidine analogs. These drugs include 5-fluorouracil, gemcitabine, and halogenated pyrimidines. They typically have powerful independent cytotoxicity, especially to S-phase cells that are the least sensitive to radiation killing. Radiation can quickly cause up-regulation of thymidine kinase, involved in DNA repair. Inhibition of thymidine kinase by 5-fluorouracil or gemcitabine is probably an important aspect of their interaction with radiation (83). Because even sublethal doses of 5-fluorouracil are powerful radiosensitizers, dose de-escalation of either radiation or drug may be possible, and warrant study.

Topoisomerase inhibitors. Inhibition of topoisomerase activity produces a complex containing a single-strand break. Radiation induces thousands of single-strand breaks per Gray, but only about 50 double-strand breaks. Complex single-strand breaks, such as those that might occur in combination with topoisomerase inhibitors, can combine to powerfully increase double-strand breaks. This should be particularly evident in S-phase cells (84–86). Preclinical studies suggest that this group of drugs must be simultaneously present with radiation, leading to a demanding infusion schedule. For example, the local control rate of pulmonary tumors 5 years after combined modality therapy is commonly 80% to 90% when topoisomerase inhibitors are combined with radiation (87). Further improvements may be seen if the scheduling of these agents with radiation is optimized.

Taxanes. Taxanes synergize with radiation, particularly when these drugs produce a G₂-M cell cycle blockade. G₂-M synchrony can be achieved (beginning about 4 hours after exposure and continuing for as long as 72 hours) following low-dose drug exposures, such as with weekly infusions (79, 88, 89). *In vitro*, twice weekly taxane exposures can sensitize tumor cells for 5 days, allowing for daily radiation treatments (89–92). Substantial gains may be possible for tumors naturally sensitive to taxanes combined with radiation

for both adjuvant and primary treatment of a variety of solid tumors.

Advanced Imaging in Radiation Delivery

Dr. Clifton Ling, Director of Advanced Clinical Research at Varian, suggested that the various components of radiation therapy can be described as the 6 Ds, and each may be improved with advanced imaging:

1. Detection and diagnosis of the tumor.
2. Delineation of the tumor and organs at risk.
3. Determining the clinical and biological characteristics of combination therapy.
4. Dose distribution.
5. Delivery of the treatment.
6. Deciphering response to treatment.

Most critical in the era of highly conformal radiation therapy is the delineation of the tumor and organs at risk. Several studies done in recent years show that experienced physicians can disagree substantially in the definition of a radiation treatment volume even if the definitions are carefully defined in a clinical study (93). Immediate pretreatment evaluation of radiation volume and field design is therefore of increasing importance as we incorporate intensity-modulated radiation therapy and IGRT techniques into the standard of care used in national clinical trials. Furthermore, definitions of radiation treatment volumes become complicated with the addition of metabolic imaging such as positron emission tomography.

When incorporated into intensity-modulated radiation therapy and IGRT, advanced imaging techniques tailor radiation fields to cover the tumor(s) while avoiding unnecessary irradiation of noninvolved normal tissues. The promise and risk of these techniques lie in both the ability to raise the tumor dose and the requirement that the tumor be correctly delineated. New three-dimensional and metabolic and molecular imaging studies are likely to become standard (e.g., positron emission tomography, magnetic resonance spectroscopy), and their use therefore will need to be standardized. The skills and judgment of the radiation oncologist become more critical, and are harder to standardize. Incorporation of intensity-modulated radiation therapy and IGRT into clinical protocols is important to the success and relevance of national clinical trials, and is a high priority of the Committee. Indeed if this is not accomplished the future of reliable multidisciplinary cooperative group studies is at risk. Therefore, the Radiation Oncology Committees will need to develop methodologies that assure consistent and correct definitions of tumor and normal tissue when these technologies are employed.

To this end, the Radiation Therapy Committee has recently commenced a pilot study of centralized target volume delineation analysis in a sample rectal cancer case, a "Big Brother Study." Big Brother is a computerized contouring software program. The goals of this study are 2-fold: (a) to provide clinical trial quality assurance of a newly opened SWOG rectal cancer phase II study that allows for the use of intensity-modulated radiation therapy, and (b) to assess the educational benefit of a newly developed site-specific anorectal contouring atlas in improving clinical target delineation. Our hope is that Big Brother or similar methods will help to improve the radiation planning

directives for future clinical trials and increase the consistency of treatment volume definitions (93).

Additionally, there is potential for the development of agents to image for tumor features other than glucose metabolism to guide the choice of combined agents and radiation dose. These have not yet reached the level needed for national clinical testing, but are likely to progress over the next six years and are of interest to SWOG. These include 18F-fluoromisonidazole to identify areas of hypoxia (94), markers for DNA or protein synthesis (95, 96), and expression of cell surface receptors for growth and angiogenesis factors. Numerous interventions will then be possible, including hypoxic sensitizers, DNA repair inhibitors, and growth and angiogenesis factor inhibitors that might be employed based on individual tumor characteristics. Likewise, portions of a tumor can be radiation therapy-dosed in accordance with their predicted sensitivity; for example, delivery of a higher daily fraction size of radiation may be delivered to the regions of a tumor that are hypoxic or more rapidly proliferating based on imaging studies done on that day. Pilot studies of this type will deserve cooperative group investigation. Ultimately, groups like SWOG will critically evaluate these new imaging techniques and the proper incorporation of these technologies into the standard of cancer care.

Summary

The Radiation Therapy Committee Strategic Planning Workshop developed a consensus regarding high-priority areas of clinical and translational research for the future. The developing SWOG 0928 phase II study "Extracranial Radiosurgery for Women with a Limited Number of Known Metastases from Breast Cancer" will hopefully address the oligometastatic hypothesis. Additional secondary questions worthy of study are the impact of high dose per fraction radiation on antitumor immunity, the role of metastasis markers for selecting high-risk patients needed for incremental benefit trials, and the evaluation of treatment outcome.

Quality assurance remains a demanding responsibility of the Radiation Therapy Committee, particularly given the current advanced imaging and targeting techniques that are increasingly used, but which are very difficult to standardize. One of our roles is to support the Disease Site Committees of SWOG, and in doing so we will attempt to schedule and dose the radiation in accordance with temporal relationships to the radiation that maximizes benefit. By using tissue and serum collection, we will aim to better interpret the tumor and normal tissue responses to standard therapy. Most critical in the era of highly conformal radiation therapy and the incorporation of metabolic imaging, motion correction techniques (e.g., IGRT, plan adaptive and gated techniques) is the consistent and accurate delineation of the tumor and organs at risk. Our hope is that the Big Brother Study or similar methods will help to improve the radiation planning directives for future clinical trials and increase the consistency of treatment volume definitions. We are currently engaged in trials for tumor volume delineation using the Big Brother system.

There are also many opportunities to utilize molecularly targeted agents to reduce tumor growth during a course of radiation, to prevent dissemination of metastases, to increase radiation tumor response, or to prevent or ameliorate treatment-related morbidity. When feasible, the radiation interaction with

these agents should be studied as part of the combined modality therapy. Biological correlates and advanced imaging studies should prove valuable in this regard. Specimens from randomized studies that have a "no radiation arm" have particular advantage for secondary analyses.

Taken together, there are many exciting opportunities to pose critical, clinical, and scientific questions for which the Radiation Therapy Committee of the SWOG is superbly positioned. Many

of these research opportunities have the potential to change the current paradigms for the management of both local and metastatic cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

- Okunieff P, Meyn RE, Teicher BA, et al. Report from the Radiation Oncology Committee of the Southwest Oncology Group (SWOG): Research Objectives Workshop 2003. *Am J Clin Oncol* 2003;26:522-9.
- Shannon AM, Williams KJ. Antiangiogenics and radiotherapy. *J Pharm Pharmacol* 2008; 60:1029-36.
- Riesterer O, Milas L, Ang KK. Combining molecular therapeutics with radiotherapy for head and neck cancer. *J Surg Oncol* 2008;97:708-11.
- Nimmagadda S, Ford EC, Wong JW, Pomper MG. Targeted molecular imaging in oncology: focus on radiation therapy. *Semin Radiat Oncol* 2008;18:136-48.
- Macdonald JS, Smalley S, Benedetti J, et al. Postoperative combined radiation and chemotherapy improves disease-free survival (DFS) and overall survival (OS) in resected adenocarcinoma of the stomach and gastroesophageal junction: update of the results of Intergroup study INT-0116 (SWOG 9008). American Society Of Clinical Oncology Gastrointestinal Cancers Symposium #6, 2004.
- Swanson GP, Thompson IM, Tangen C, et al. Update of SWOG 8794: Adjuvant radiotherapy for pT3 prostate cancer improves metastasis free survival. *Int J Radiat Oncol Biol Phys* 2008; 72:S31.
- DiBiase SJ, Chin LS, Ma L. Influence of gamma knife radiosurgery on the quality of life in patients with brain metastases. *Am J Clin Oncol* 2002;25:131-4.
- Proceedings of the 3rd Acta Oncologica Symposium on Stereotactic Body Radiotherapy, June 15-17, 2006, Copenhagen, Denmark. *Acta Oncol* 2006;45:771-994.
- Withers HR, Lee SP. Modeling growth kinetics and statistical distribution of oligometastases. *Semin Radiat Oncol* 2006;16:111-9.
- Singh DP, Yi WS, Brasacchio RA, et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys* 2004;58:3-10.
- Rubin P, Green J. Solitary metastases. Springfield IL: Charles C. Thomas; 1968.
- French LA, Ausman JI. Metastatic neoplasms to the brain. *Clin Neurosurg* 1977;24:41-6.
- Vidne BA, Richter S, Levy MJ. Surgical treatment of solitary pulmonary metastasis. *Cancer* 1976;38:2561-3.
- Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Cancer Res* 2008;14:5255-9.
- Hellman S. Promise, promise, paradigm and prophesy. *Nat Clin Pract Oncol* 2005;2:325.
- Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol* 2008;9:621-8.
- Berber E, Tsinberg M, Tellioglu G, Simpfordorfer CH, Siperstein AE. Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis. *J Gastrointest Surg* 2008; 12:1967-72.
- Berber E, Siperstein A. Local recurrence after laparoscopic radiofrequency ablation of liver tumors: an analysis of 1032 tumors. *Ann Surg Oncol* 2008;15:2757-64.
- Swenerton KD, Legha SS, Smith T, et al. Prognostic factors in metastatic breast cancer treated with combination chemotherapy. *Cancer Res* 1979;39:1552-62.
- Clark G, Sledge G, Osborne CK, McGuire WL. Survival from first recurrence: relative importance of prognostic factors in 1,015 breast cancer patients. *J Clin Oncol* 1987;5:55-61.
- Yamamoto N, Watanabe T, Katsumata N, et al. Construction and validation of a practical prognostic index for patients with metastatic breast cancer. *J Clin Oncol* 1998;16:2401-8.
- Hayes DF, Smerage J. Is there a role for circulating tumor cells in the management of breast cancer? *Clin Cancer Res* 2008;14:3646-50.
- Suit HD, Sedlacek R, Fagundes L, Goitein M, Rothman KJ. Time distributions of recurrences of immunogenic and nonimmunogenic tumors following local irradiation. *Radiat Res* 1978;73: 251-66.
- Suit HD, Sedlacek RS, Wiggins S. Immunogenicity of tumor cells inactivated by heat. *Cancer Res* 1977;37:3836-7.
- Mendiola OA, Suit HD, Sedlacek RS. Concurrent and subsequent tumors in the same host: a model to evaluate the host tumor interaction. *Int J Radiat Oncol Biol Phys* 1980;6:193-8.
- Todoroki T, Suit HD. Therapeutic advantage in preoperative single-dose radiation combined with conservative and radical surgery in different-size murine fibrosarcomas. *J Surg Oncol* 1985;29: 207-15.
- Stone HB, Peters LJ, Milas L. Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma. *J Natl Cancer Inst* 1979;63:1229-35.
- Nesslinger NJ, Sahota RA, Stone B, et al. Standard treatments induce antigen-specific immune responses in prostate cancer. *Clin Can Res* 2007; 13:1493-502.
- Kusmartsev S, Eruslanov E, Kubler H, et al. Oxidative stress regulates expression of VEGFR1 in myeloid cells: link to tumor-induced immune suppression in renal cell carcinoma. *Immunol* 2008;181:346-53.
- Okunieff P. Design of multi-institutional and cooperative group studies of SBRT. *Acta Oncol* 2006;45:775-8.
- Kirschmann DA, Sefter EA, Fong SF, et al. A molecular role for lysyl oxidase in breast cancer invasion. *Cancer Res* 2002;62:4478-83.
- Denko NC, Fontana LA, Hudson KM, et al. Investigating hypoxic tumor physiology through gene expression patterns. *Oncogene* 2003;22:5907-14.
- Kagan HM, Li W. Lysyl oxidase: properties, specificity, and biological roles inside and outside of the cell. *J Cell Biochem* 2003;88:660-72. Review.
- Nassar A, Radhakrishnan A, Cabrero IA, Cotsonis G, Cohen C. COX-2 expression in invasive breast cancer: correlation with prognostic parameters and outcome. *Appl Immunohistochem Mol Morphol* 2007;15:255-9.
- Weise JB, Csiszar K, Gottschlich S, et al. Vaccination strategy to target lysyl oxidase-like 4 in dendritic cell based immunotherapy for head and neck cancer. *Int J Oncol* 2008;32:317-22.
- Erler JT, Bennewith KL, Nicolau M, et al. Lysyl oxidase is essential for hypoxia-induced metastasis. *Nature* 2006;440:1222-6.
- Martin LP, Hamilton TC, Schilder RJ. Platinum resistance: the role of DNA repair pathways. *Clin Cancer Res* 2008;14:1291-5.
- Treszezamsky AD, Kachnic LA, Feng Z, Zhang J, Tokadjian C, Powell SN. BRCA1- and BRCA2-deficient cells are sensitive to etoposide-induced DNA double-strand breaks via topoisomerase II. *Cancer Res* 2007;67:7078-81.
- Evans JW, Chernikova SB, Kachnic LA, et al. Homologous recombination is the principal pathway for the repair of DNA damage induced by tirapazamine in mammalian cells. *Cancer Res* 2008;68:257-65.
- Powell SN, Kachnic LA. Therapeutic exploitation of tumor cell defects in homologous recombination. *Anticancer Agents Med Chem* 2008;8: 448-60.
- O'Connor MJ, Martin NM, Smith GC. Targeted cancer therapies based on the inhibition of DNA strand break repair. *Oncogene* 2007;26:7816-24.
- Luo Y, Levenson JD. New opportunities in chemosensitization and radiosensitization: modulating the DNA-damage response. *Expert Rev Anticancer Ther* 2005;5:333-42.
- Ashworth A. A synthetic lethal therapeutic approach: poly (ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. *J Clin Oncol* 2008; 26:3785-90.
- Albert JM, Cao C, Kim KW, et al. Inhibition of poly(ADP-Ribose) polymerase enhances cell death and improves tumor growth delay in irradiated lung cancer models. *Clin Cancer Res* 2007;13:3033-42.
- Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res* 2007;13:2728-37.
- Cheng JC, Schultheiss TE, Nguyen KH, Wong JY. Acute toxicity in definitive versus postprostatectomy image-guided radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 71:351-7.
- Beckendorf V, Guerif S, Le Prise E, et al. The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. *Int J Radiat Oncol Biol Phys* 2004;60: 1056-65.
- D'Amico AV, Coleman CN. Role of interstitial radiotherapy in the management of clinically organ-confined prostate cancer: the jury is still out. *J Clin Oncol* 1996;14:304-15.
- Akpolat M, Kanter M, Uzal MC. Protective effects of curcumin against γ radiation-induced ileal mucosal damage. *Arch Toxicol* 2009;83: 609-17.
- Kunnumakkara AB, Anand P, Aggarwal B. Curcumin inhibits proliferation, invasion, angiogenesis, and metastasis of different cancers through

- interaction with multiple cell signaling proteins. *Cancer Lett* 2008;269:199–225.
51. Kunnumakkara AB, Diagaradjane P, Guha S, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor- κ B-regulated gene products. *Clin Cancer Res* 2008;14:2128–36.
 52. Okunieff P, Xu J, Hu D, et al. Curcumin protects against radiation-induced acute and chronic cutaneous toxicity in mice and decreases mRNA expression of inflammatory and fibrogenic cytokines. *Int J Radiat Oncol Biol Phys* 2006;65:890–8.
 53. Okunieff P, Augustine E, Hicks JE, et al. Pentoxifylline in the treatment of radiation-induced fibrosis. *J Clin Oncol* 2004;22:2207–13.
 54. Haydout V, Gilliot O, Rivera S, et al. Successful mitigation of delayed intestinal radiation injury using pravastatin is not associated with acute injury improvement or tumor protection. *Int J Radiat Oncol Biol Phys* 2007;68:1471–82.
 55. Williams JP, Hernady E, Johnston CJ, et al. Effect of administration of lovastatin on the development of late pulmonary effects after whole lung irradiation in a murine model. *Radiat Res* 2004;161:560–7.
 56. Moyad MA, Merrick GS, Butler WM, et al. Statins, especially atorvastatin, may improve survival following brachytherapy for clinically localized prostate cancer. *Urol Nurs* 2006;26:298–303.
 57. Moyad MA, Merrick GS, Butler WM, et al. Statins, especially atorvastatin, may favorably influence clinical presentation and biochemical progression-free survival after brachytherapy for clinically localized prostate cancer. *Urology* 2005;66:1150–4.
 58. Budman DR, Calabro A. Zoledronic acid (Zometa) enhances the cytotoxic effect of gemcitabine and fluvastatin: in vitro isobologram studies with conventional and nonconventional cytotoxic agents. *Oncology* 2006;70:147–53.
 59. Tatum JL, Kelloff GJ, Gillies RJ, et al. Hypoxia: importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy. *Int J Radiat Oncol Biol Phys* 2006;82:699–757.
 60. Vaupel P, Kelleher DK, Hockel M. Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. *Semin Oncol* 2001;28:29–35.
 61. Rankin EB, Giaccia AJ. The role of hypoxia-inducible factors in tumorigenesis. *Cell Death Differ* 2008;15:678–85.
 62. Schrijvers ML, van der Laan BF, de Bock GH, et al. Overexpression of intrinsic hypoxia markers HIF1 α and CA-IX predict for local recurrence in stage T1–T2 glottic laryngeal carcinoma treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2008;72:161–9.
 63. Lammering G, Valerie K, Lin PS, et al. Radiosensitization of malignant glioma cells through overexpression of dominant-negative epidermal growth factor receptor. *Clin Cancer Res* 2001;7:682–90.
 64. Eriksen JG, Steiniche T, Askaa J, Alsner J, Overgaard J. The prognostic value of epidermal-growth factor receptor is related to tumor differentiation and the overall treatment time of radiotherapy in squamous cell carcinomas of the head and neck. *Int J Radiat Oncol Biol Phys* 2004;58:561–6.
 65. Bentzen SL, Atasoy BM, Daley FM, et al. Epidermal growth factor receptor expression in pretreatment biopsies from head and neck squamous cell carcinoma as a predictive factor for a benefit from accelerated radiation therapy in a randomized controlled trial. *J Clin Oncol* 2005;23:5560–7.
 66. Hernandez MC, Knox SJ. Radiobiology of radioimmunotherapy: targeting CD20 B-cell antigen in non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 2004;59:1274–87.
 67. Kunala S, Macklis RM. Ionizing radiation induces CD20 surface expression on human B cells. *Int J Cancer* 2001;96:178–81.
 68. Fuster JJ, Sanz-Gonzalez SM, Moll UM, Andres V. Classic and novel roles of p53: prospects for anticancer therapy. *Trends Mol Med* 2007;13:192–9.
 69. Dahm-Daphi J, Hubbe P, Horvath F, et al. Non-homologous end-joining of site-specific but not radiation-induced DNA double-strand breaks is reduced in the presence of wild-type p53. *Oncogene* 2005;24:1663–72.
 70. Wachsberger P, Burd R, Dicker AP. Tumor response to ionizing radiation combined with antiangiogenesis or vascular targeting agents: exploring mechanisms of interaction. *Clin Cancer Res* 2003;9:1957–71.
 71. Secomb TW, Hsu R, Ong ET, Gross JF, Dewhirst MW. Analysis of the effects of oxygen supply and demand on hypoxic fraction in tumors. *Acta Oncol* 1995;34:313–6.
 72. Anscher MS, Thrasher B, Zgonjanin L, et al. Small molecular inhibitor of transforming growth factor- β protects against development of radiation-induced lung injury. *Int J Radiat Oncol Biol Phys* 2008;71:829–37.
 73. Anscher MS, Thrasher B, Rabbani Z, Teicher B, Vujaskovic Z. Antitransforming growth factor- β antibody 1D11 ameliorates normal tissue damage caused by high-dose radiation. *Int J Radiat Oncol Biol Phys* 2006;65:876–81.
 74. Anscher MS, Peters WP, Reisenbichler H, Petros WP, Jirtle RL. Transforming growth factor β as a predictor of liver and lung fibrosis after autologous bone marrow transplantation for advanced breast cancer. *N Engl J Med* 1993;328:1592–8.
 75. Okunieff P, Cornelison T, Mester M, et al. Mechanism and modification of gastrointestinal soft tissue response to radiation: role of growth factors. *Int J Radiat Oncol Biol Phys* 2005;62:273–8.
 76. Okunieff P, Wang X, Rubin P, Finkelstein JN, Constine LS, Ding I. Radiation-induced changes in bone perfusion and angiogenesis. *Int J Radiat Oncol Biol Phys* 1998;42:885–9.
 77. Finn RS. Targeting Src in breast cancer. *Ann Oncol* 2008;19:1379–86.
 78. Teicher BA, Rockwell S, Lee JB. Radiosensitization of EMT6 cells by four platinum complexes. *Int J Radiat Oncol Biol Phys* 1985;11:937–41.
 79. Choy H, Rodriguez F, Koester F, Hilsenbeck S, Von Hoff DD. Investigation of Taxol as a potential radiation sensitizer. *Cancer* 1993;71:3774–8.
 80. Kyle AH, Minchinton AI. Measurement of delivery and metabolism of tirapazamine to tumour tissue using the multilayered cell culture model. *Cancer Chemother Pharmacol* 1999;43:213–20.
 81. Minchinton AI, Wendt KR, Clow KA, Fryer KH. Multilayers of cells growing on a permeable support. An in vitro tumour model. *Acta Oncol* 1997;36:13–6.
 82. Vaupel P, Kallinowski F, Okunieff P. Blood flow, oxygen and nutrient supply, and metabolic microenvironment of human tumors: a review. *Cancer Res* 1989;49:6449–65.
 83. He Q, Skog S, Welander I, Tribukait B. X-irradiation effects on thymidine kinase (TK): I. TK1 and 2 in normal malignant cells. *Cell Prolif* 2002;35:69–81.
 84. Chen AY, Okunieff P, Pommier Y, Mitchell JB. Mammalian DNA topoisomerase I mediates the enhancement of radiation cytotoxicity by camptothecin derivatives. *Cancer Res* 1997;57:1529–36.
 85. Teicher BA, Holden SA, Khandakar V, Herman TS. Addition of a topoisomerase I inhibitor to trimodality therapy [cis-diamminedichloroplatinum(II)/heat/radiation] in a murine tumor. *J Cancer Res Clin Oncol* 1993;119:645–51.
 86. Kim JS, Amoroso GP, Pvo H, Cao Q, Choy H. Radiation enhancement by the combined use of topoisomerase I inhibitors, RFS-2000 or CPT-11, and topoisomerase II inhibitor etoposide in human lung cancer cells. *Radiation Oncol* 2002;62:61–7.
 87. Cho LC, Choy H. Topoisomerase I inhibitors in the combined-modality therapy of lung cancer. *Oncology (Huntingt)* 2004;18:29–39.
 88. Liebmann J, Cook JA, Fisher J, Teague D, Mitchell JB. Changes in radiation survival curve parameters in human tumor and rodent cells exposed to paclitaxel (Taxol). *Int J Radiat Oncol Biol Phys* 1994;29:559–64.
 89. Keng PC, Okunieff P, Chen Y. Low dose Taxol/Taxotere radiosensitization for human lung cancer cells is schedule dependent. *Int J Radiat Oncol Biol Phys* 2000;48:272–3.
 90. Chen Y, Pandya K, Raubertas R, et al. Low dose pulsed paclitaxel and concurrent radiation for thoracic malignancies: a phase I/II clinical trial based on cell cycle studies of human lung cancer cells. *Int J Radiat Oncol Biol Phys* 2000;48:326–7.
 91. Langer C, Paulus R, Ruffer J, et al. Phase II RTOG trial of weekly paclitaxel (TAX) and conventional external beam radiation therapy (EBRT) for supratentorial glioblastoma multiforme (GBM). *Proc of Am Soc Clin Oncol (ASCO)*, Atlanta, GA. *J Clin Oncol* 1999;18:139a, #534.
 92. Ruffer J, Scott C, Langer C, Movsas B, Murray K. A Phase II trial of weekly paclitaxel and conventional radiotherapy for supratentorial glioblastoma multiforme: RTOG 96-02. *Proc Am Soc Thera Rad Oncol (ASTRO)*, Phoenix, AZ. *Int J Radiat Oncol Biol Phys* 1998;42:265, #2076.
 93. Steenbakkers RJ, Duppen JC, Fitton I, et al. Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: a 'Big Brother' evaluation. *Radiation Oncol* 2005;77:182–90.
 94. Padhani A. PET imaging of tumor hypoxia. *Cancer Imaging* 2006;6:S117–21.
 95. Wei L, Easmon J, Nagi RK, Muegge BD, Meyer LA, Lewis JS. ⁶⁴Cu-azabicyclo[3.2.2]nonane thiosemicarbazone complexes: radiopharmaceuticals for PET of topoisomerase II expression in tumors. *J Nucl Med* 2006;47:2034–41.
 96. Kumar R, Dhanpathi H, Basu S, Rubello D, Fanti S, Alavi A. Oncologic PET tracers beyond [(18)F] FDG and the novel quantitative approaches in PET imaging. *O J Nucl Med Mol Imaging* 2008;52:50–65.