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Perspectives

Clinical Cancer Research

Report from the SWOG Radiation Oncology Committee: Research Objectives Workshop 2017

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Abstract

The Radiation Therapy Committee of SWOG periodically evaluates its strategic plan 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 2017 Strategic Planning Workshop included leaders in cancer basic sciences, molecular theragnostics, pharmaceutical and technology industries, clinical trial design, oncology practice, and statistical analysis. The committee discussed high-priority research areas, such as optimization of combined modality therapy, radiation oncology–specific drug design, identification of molecular profiles predictive of radiation-induced local or distant tumor responses, and methods for normal tissue-specific mitigation of radiation toxicity. The following concepts emerged as dominant questions ready for national testing: (i) what is the role of radiotherapy in the treatment of oligometastatic, oligorecurrent, and oligoprogressive disease? (ii) How can combined modality therapy be used to enhance systemic and local response? (iii) Can we validate and optimize liquid biopsy and other biomarkers (such as novel imaging) to supplement current response criteria to guide therapy and clinical trial design endpoints? (iv) How can we overcome deficiencies of randomized survival endpoint trials in an era of increasing molecular stratification factors? And (v) how can we mitigate treatment-related side effects and maximize quality of life in cancer survivors? The committee concluded that many aspects of these questions are ready for clinical evaluation and example protocol concepts are provided that could improve rates of cancer cure and quality of survival. *Clin Cancer Res; 24(15); 3500–9. ©2018 AACR.*

Introduction

As part of the SWOG Spring 2017 Group Meeting (April 26–29, 2017), the Radiation Therapy Committee held a Strategic Planning Symposium in radiation research to identify the most pertinent questions ready for evaluation by a national cooperative group. Strategic planning for the Radiation Therapy Committee of SWOG is comprehensively evaluated periodically in an effort to maintain current and relevant scientific focus and to provide a standard platform for future development of protocol concepts (1, 2). SWOG committee members, including members of the Radiation Therapy Committee, are chosen from the general

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SWOG group membership. Committee members attend semiannual committee meetings and participate in protocol and manuscript reviews as necessary. For the symposium, selected Radiation Therapy Committee participants included leaders in cancer basic sciences, molecular theragnostics, pharmaceutical and technology industries, oncology practice, clinical trial design, and statistical analysis. Topics of discussion involved a spectrum of strategies to increase the therapeutic ratio of radiotherapy, including optimization of combined modality therapy with a focus on the immunotherapeutic interactions of radiotherapy, radiation oncology–specific drug design, identification of molecular profiles advantageous or detrimental to radiation-induced local or distant tumor response, novel imaging strategies to guide therapy and enhance the prediction of tumor response, and methods for normal tissue-specific mitigation of radiation toxicity. Suggestions for future directions were also taken from the audience at this interactive meeting.

Symposium participants were challenged not only to identify an essential unanswered question in their respective areas of expertise but also to design a study or class of studies that could answer a clinical and/or translational research question and lead to an improved therapeutic index for cancer patients over the next five years. The following five concepts emerged as dominant issues that are ready for clinical evaluation and likely to improve cancer cures and therapeutic index:

1. Evaluating the role of radiotherapy in the treatment of oligometastatic, oligorecurrent, and oligoprogressive diseases.
2. Tailoring combined modality therapy to enhance systemic and local responses.
3. Validating and optimizing liquid biopsy and other biomarkers (e.g., novel imaging) to supplement current response criteria to guide therapy selection and clinical trial design endpoints.
4. Overcoming features of randomized trials that delay discovery, including choice of trial endpoints, accrual criteria and trial size, and identification of valid surrogate markers of survival.
5. Evaluating approaches to mitigate treatment-related side effects and maximize quality of life in cancer survivors.

These clinical and scientific questions have the potential to change the paradigm of clinical trial development and implementation while also improving our utilization of radiation within combined modality therapies (Fig. 1).

Role of radiotherapy in the treatment of oligometastases and oligoprogression

At a previous SWOG symposium in 2008, we proposed that combined modality therapy employing new stereotactic body radiotherapy (SBRT) techniques led to long term, disease-free survival for patients with five or fewer metastases (1). At that time, evidence showed that patients with chemotherapy-responsive disease further benefited from localized treatments, including surgery and/or radiation (3–5). These results suggested that systemic therapy could control subclinical disease, thereby allowing aggressive local treatment to potentially eradicate primary disease. More recent studies have observed that patients with mixed chemotherapy response appear to benefit from local therapy targeting stubborn, nonresponsive lesions (i.e., oligoprogression; refs. 6, 7). Oligoprogression, the progression of a few cancer sites despite the response of most lesions to systemic therapy, may be attributed to microenvironmental factors (e.g., hypoxia, perfusion, and pH), tumor clonogenic heterogeneity, and differences in immune activation and/or accessibility of activated immune cells. We discussed using noninvasive liquid biopsy technologies and imaging to identify these causes of oligoprogression and developed relevant recommendations for clinical study design.

Oligometastasis, a subset of oligoprogression, occurs earlier when only a few metastases exist and clonogenic variation is still low. This represents a subset of metastatic patients that may have prolonged disease-free interval and are potentially curable (8). Patients with oligorecurrence, a total systemic response followed by recurrence in an area of previous disease, also appear respond to local therapy with prolonged responses and some apparent cures. A recent randomized phase II study of aggressive local therapy compared with maintenance therapy alone demonstrated improved progression-free survival (median PFS 11.9 vs. 3.9 months, respectively, $P = 0.005$) among oligometastatic non-small cell lung cancer (NSCLC patients; ref. 9). The current phase II/III NRG LU002 randomized study assesses whether aggressive local therapy of oligometastatic NSCLC results in an overall survival advantage. Common approaches to surveillance for patients at high risk for metastases, however, often fail to detect these lesions early enough to institute comprehensive combined modality care. The development of early approaches to detect these metastases is now realistic given advances in liquid biopsy and metabolic imaging (10–14). The concept is agnostic to cancer type and holds promise for most solid tumor types, including node-positive breast, prostate, and colon cancers; early-stage lung

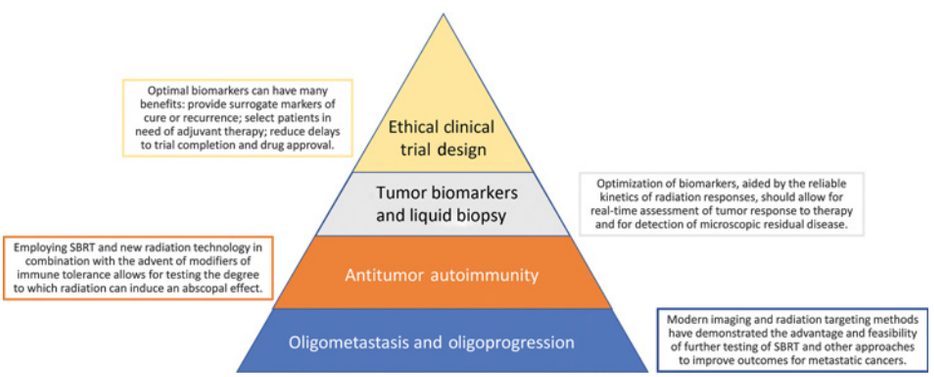

Figure 1.
Understanding the mechanisms of tumor progression and breakthrough responses to targeted therapies is poorly suited to traditional randomized clinical trial design. It is considered necessary to establish surrogate markers based on sound scientific principles to aid in efficient design and conduct of valid clinical trials.

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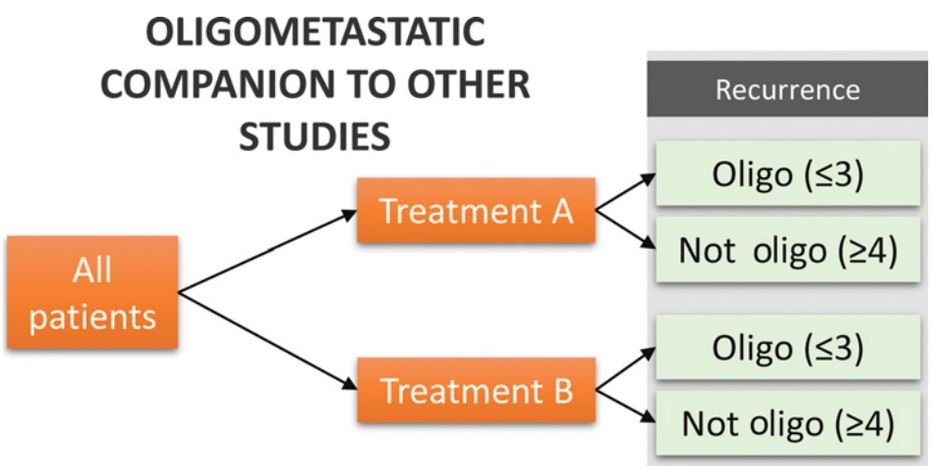

Figure 2.
Management of patients with oligoprogression and oligometastases varies between institutions, impacting the results of any clinical trial. Standardizing the treatment of patients who progress in a standard randomized study has many scientific and administrative advantages. For example, patients who have less than a threshold number of metastases may be offered locally aggressive therapy in companion trials.

and upper digestive tract cancers; and any nonmetastatic cancers associated with a high rate of metastatic relapse. It likewise holds promise for therapy and correlational science for patients with oligoprogression. For example, retrospective studies now suggest improved survival in many cancer types for which irradiation of one or more metastases was included in the palliative regimen (15–18). Image-targeted radiotherapy allows for better and more specific theragnostics, more effective use of hypoxic sensitizers and DNA repair inhibitors, and testing and optimization of liquid biopsy techniques. Specific potential has already been seen in breast, prostate, and colon cancers, and perhaps soft tissue sarcoma (Fig. 2).

Imaging is critical to accurate targeting of these lesions for localized therapy. H.C. Manning, Director of the Vanderbilt Center for Molecular Probes and Molecular Imaging Research at the Vanderbilt-Ingram Cancer Center (Nashville, TN; ref. 19), discussed using advanced imaging techniques with markers specific for tumors and tumor response. He gave examples of amino acid analogue PET reagents with improved capacity to detect tumors compared with fluorine-18-deoxyglucose, including tumors in the liver, lung, and brain. As imaging reagents become more widely available and reimbursement for their implementation improves, tumor-specific imaging should be integrated into trial design for at least a subset of patients in national clinical trials; indeed, advanced radiographic and functional imaging may improve detection and, therefore, outcomes of oligometastatic patients.

Tailoring combined modality therapy to enhance systemic and local responses

The role radiation plays as an antitumor immune adjuvant therapy has been an area of basic (20–24) and clinical (25, 26) researches for at least five decades. Indeed, early clinical observations of abscopal or "away from the target" responses were noted in prominent early textbooks (27). In the intervening decades, fractionation using standard daily doses of approximately 2 Gy for most tumor types (and reduced use of brachytherapy implants) has likely led to a reduction in these apparently random abscopal responses. The recent increase in SBRT use as well as the advent of checkpoint-inhibiting agents and modern immunologic monitoring capabilities has led to a resurgence of interest in the subject of abscopal effects. J. Welsh, a radiation oncologist at the University of Texas MD Anderson Cancer Center (Houston, TX), discussed the still enigmatic role that radiation plays in triggering these effects in the presence or absence of immune stimulatory agents and the potential for radiation to beneficially or detrimentally affect lymphocyte numbers and subsets (28). High-dose radiation plays a known role in damaging cell membranes and exposing antigens, which is a process used to improve viral capsid antigenicity in vaccines; thus, radiation may create the vaccine antigen exposure *in situ*. H. Enderling, a specialist in integrated mathematical oncology and cancer biology from Moffitt Cancer Center (Tampa, FL), discussed the potential opportunities to optimize the SBRT target (e.g., lymph node metastases vs. bone metastasis vs. soft tissue metastasis vs. brain metastasis) and scheduling of radiation (e.g., pretreatment, concurrent, or delayed) as well as checkpoint inhibitor or other immune adjuvant therapies (Fig. 3). Using mathematical modeling, he suggested several approaches to advance identification of the best target metastasis, dose, and drug sequencing in clinical studies. The targeted metastasis was discussed in some detail. Viral vaccines injected directly into lymph nodes can produce immunity at vaccine doses several orders of magnitude lower than for subcutaneous injection, suggesting nodes as an optimal target. However, lymphocytes required for immune effects may be permanently depleted by radiation, preventing immune response, if a tumor node is targeted. Liver tumors are known to be very hypoxic and might not be ideal as a radiation target for the generation of immunity. Thus, identifying the "best" radiation target to induce antitumor autoimmunity should be examined in clinical trials. Finally, local and systemic radiation alters cytokine production and stem cell maturation (29). M. Brown, a cancer biologist in the Department of Radiation Oncology at Stanford University (Palo Alto, CA), discussed the role of direct radiation-induced antiangiogenic effects and the compensatory macrophage and bone marrow progenitor response to induce stem cells and angiogenesis. He also presented preclinical and early clinical data demonstrating the role that SDF-1/CXCR4 inhibition may play in sequence with radiation to prevent an angiogenic response, thereby improving radiation response (30).

Energy deposition of the particle beam Bragg peak yields a substantially different set of membrane damage, DNA damage, and cytokine response parameters that could likewise be used to augment immune responses (31–35). A study of the biological differences, and not just the dosimetric differences, of particle beams was judged an area of novel opportunity

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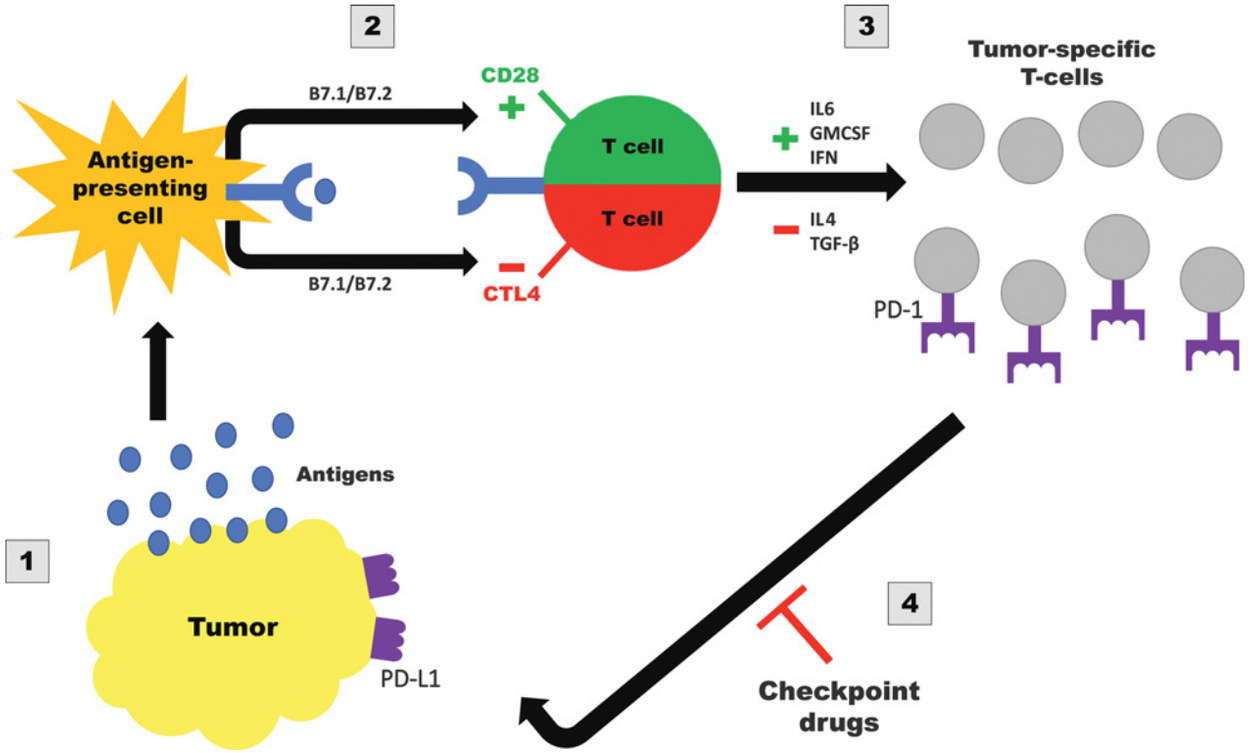

Figure 3.

Immune responses include several processes that change over time and which must occur for checkpoint inhibitors to inhibit tolerance. Thoughtful use of radiation can aid at every step. Radiation improves tumor antigen presentation although membrane damage and other death processes (Step 1); increases (and/or reduces) T-cell activation in a time- and dose-dependent manner (Step 2); and alters cytokine expression also in a similar dose- and time-dependent manner (Step 3). Thus, in many clinical and research designs, radiation has proven to be a powerful adjunct or even a critical component of immune therapy. Poorly designed studies have the potential to yield a deleterious outcome.

given the increasing number of SWOG sites capable of offering proton therapy.

Committee members observed that the number of clinical trials aimed at improving immunotherapy using radiotherapy to prime the immune system is growing rapidly; however, a substantial weakness of all studies to date is the lack of validated immune response biomarkers. Nonetheless, great progress has been made in this field, and there are excellent opportunities to work with industry partners. Notably, the Blue Ribbon Panel for the NIH Cancer Moonshot recommended an emphasis on the identification of immune response biomarkers (36). Radiotherapy gives us the unique opportunity to potentially reactivate the immune response in patients who are no longer responsive to immunotherapy. Therefore, biomarkers relevant to response should rebound in the responders, validating those markers. In addition to monitoring antitumor immune responses, biomarkers are also needed to help identify those patients most likely to benefit from immunotherapy and radiotherapy combined treatment. S. Knox, a radiation oncologist studying novel solid tumor therapies at Stanford University (Palo Alto, CA), discussed prognostic and therapeutic immune biomarkers. She recommended blood tests for assessment of cytokines, global immunocompetence, immunophenotyping of T-cell subsets (including tests to determine T cells specific for tumor antigens), and antibody titers to tumor-specific antigens (before, during, and after treatment). She also discussed the pivotal role of tumor biopsies in correlating response with changes in tumor histology, IHC, RNA expression, immunophenotyping of immune cell subsets in tumors, and cellular immune functions. Notably, this list is exhaustive but the logistics of the specimen requirements fit with many existing and planned studies, and the tests could be performed in order of priority on increasingly smaller specimen sizes.

S. Galbraith, the head of Oncology IMED at AstraZeneca (Cambridge, UK), discussed the portfolio of agents being developed by the pharmaceutical industry. These include a number of immunotherapy checkpoint inhibitors and a collection of DNA damage response (DDR) inhibitors, cell-cycle modification agents, and proliferation modifiers, including PARP-1, Wee-1, ATR, and ATM inhibitors (37). Regarding the DDR inhibitors, benefit for individual patients is dependent on the specific deficiency in the DDR present in tumors. For example, radiosensitization to olaparib is increased in BRCA-deficient cell lines and *in vivo* models due to deficiency in homologous recombination, and hypoxia can increase radiosensitization even in BRCA wild-type cells due to hypoxia-induced relative deficiency in homologous recombination capacity. ATM inhibition produced particular radiosensitization in p53-mutated glioblastoma cell lines and *in vivo* models (38). This presents an opportunity to use precision medicine approaches for the development of such agents in combination with radiotherapy (Table 1). The sequencing and dosing of radiation and drugs could be very important. For example, lowering both the radiation and drug doses, personalized for specific

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Table 1. Types of agents expected to interact with radiation and for which validated surrogate response markers could accelerate clinical research

	Opportunity for drug interaction		
Radiation biology	**Class**	**Molecular targets**	**Mechanism**
Creates DNA damage	DNA damage repair inhibitors	PARP, ATR, Chk1, and DNA-PK	Reduce cellular DNA repair and enhance synthetic lethality
Decreases proliferation	Growth factor inhibitors	EGFR and MAPK	Prevent tumor repopulation and improve apoptosis
Releases tumor cell antigens	Immunotherapy	CTLA-4 and PD-1	Enhance immune response to tumor antigens
Decreases angiogenesis	Antiangiogenic agents	VEGF	Alter the microenvironment and reduce metastagenesis
Disrupts local invasion and metastasis	Anti-invasive agents	Kinase, chemokine, and integrins	Alter the microenvironment and reduce repopulation
Selects for resistant hypoxic cell populations	Antihypoxia agents	HIF-1α, CA9, and UPR	Reduce hypoxia mediated radioresistance
Selects for resistant population/stem cells	Survival inhibitors	mTOR, BRaf, PI3K, and NF-κβ	Reduce resistant cell population and repopulation
Least benefit to S phase	S-phase agents	Most systemic chemo	Time to achieve best impact on all cell-cycle phases
Modulates metabolism	Metabolic inhibitors	MCT1 and MCT4	Alter cellular energetics

NOTE: Adapted from Sharma et al., Nat Rev Clin Oncol 2016;13:627–42.

tumor DDR requirements, could provide synergistic toxicity against the tumor while reducing normal tissue toxicity. S. Galbraith illustrated the importance of examining effects of such combinations on normal tissues as well as on tumors directly. She also discussed using some of these agents in combination with radiation in a tumor-specific approach, including SBRT, as a noninvasive tumor vaccine wherein the high dose is restricted to the tumor volume. Proton therapy may play a similar role with different immune and DNA repair agents (35, 39).

Use of circulating tumor DNA (liquid biopsy), biomarkers, and noninvasive imaging methods to guide adjuvant therapy

Although many biomarker products are advanced daily into the market, and new technologies are currently under development, each has significant unknowns with regard to interpretation, implementation, and utility. DNA sequencing of the primary tumor, for example, has become standard for many tumors and provides an opportunity (the ground truth) to test the promising field of liquid biopsies. The optimal liquid biopsy should be:

1. Extremely tumor specific (negligible false positive) and sensitive (negligible false negatives).
2. Capable of quantitatively measuring tumor size and response to therapy even if disease is subclinical.
3. Rapidly available and able to use easily acquired specimens.
4. Inexpensive and easily deployable to Clinical laboratory improvement amendments–approved (CLIA) laboratories nationwide.

A fully personalized liquid biopsy technique could logically replace death and imaging–based PFS as the endpoint of clinical efficacy trials. While such a technique is not yet on the market, many are ready for more substantial testing in this regard.

Although, one often thinks of tumor DNA or circulating tumor cells (CTC) when using the term "liquid biopsy," some tumor size–related and response-related circulating proteins nearly achieve the definition. For example, prostate-specific antigen is relatively specific for prostate cancer (especially after prostatectomy) and is reliable and quantitative with low detection limits and may be easily deployed. These features are necessary in a quality personalized marker for other cancers. Recently, SWOG has taken a leadership role in increasing our understanding of CTCs for breast cancer (40, 41). Although, CTCs should constitute evidence for occult metastasis, accurately detecting and counting these cells has presented technical and operational challenges. Notably, the numbers of cells in circulation appear to be rare even in patients with known active disease, currently making it necessary to examine large specimens or use pheresis. Nevertheless, there is prognostic benefit to some existing assays, and FDA and Centers for Medicare and Medicaid approvals have been obtained for some tests allowing them to be employed in national studies (42–48). Finally, new technologies that can more accurately identify and detect tumor cells in the circulation are being developed.

A second example of a new personalized technology for liquid biopsy is cell-free circulating tumor DNA (ctDNA), which may be examined for tumor-specific mutations and epigenetics by screening the patient's specific mutation (or panel of mutations; ref. 49). Unfortunately, DNA in the circulation is a mixture of wild-type and tumor DNA, and the vast majority of oncogenic mutations are difficult to detect point mutations, insertions, or deletions. In a patient with occult disease, the wild-type to tumor DNA ratio may be overwhelming; thus, ctDNA assays require stringent elimination of false positives (50–52). Nevertheless, many new approaches using mathematical models (incorporating the known tumor sequencing data) allow detection of tumor in the blood from reasonably sized specimens, and some are already CLIA ready and easily deployable. Although less than for CTC assays, the specimen size must still be substantial for reliable detection of small tumors given an estimated 420 ng of DNA requirement for a 1-gm tumor (6 pg/genome $\times$ 70 kg body weight/1 g tumor weight; plasma contains $\approx 20 \pm 10$ ng/mL cell-free DNA). P. Okunieff, Chair of the Department Radiation Oncology at the University of Florida, discussed a method for personalized quantitative liquid biopsy that prevents PCR amplification of genes with no point mutations. This method and other similar approaches have the potential to measure residual tumor mass, allow early detection of tumor progression, and permit immediate estimation of chemotherapy or radiation sensitivity (e.g., the morning after infusions or the first radiation dose). More correlative studies are needed, as circulating tumor markers, and cfDNA in particular, are subject to a number of physiologic and biological variables.

F. Feng, Director of Translational Research for the Department of Radiation Oncology at the University of California (San

Francisco, CA), and R. Bristow, Director of the Manchester Cancer Research Centre (Manchester, UK), discussed the role that gene expression arrays, if collected along with patient outcome information, may play the selections of the optimal therapeutic modality for an individual's cancer. The size and success of historic collections of combined genomic and clinical information from randomized studies means that such analyses are now possible. As an example of an approach ready for testing, F. Feng discussed a prognostic expression pattern originally defined for luminal A and luminal B breast cancer, which he used with prostate cancer to determine the extent of benefit with the addition of androgen deprivation with radiotherapy (53). R. Bristow noted this field is rapidly growing and that other expression patterns have been defined that might help identify patients likely to develop metastases or who will have ineffective or deleterious responses to specific therapies (54–59). To stay at the forefront of research related to biomarker incorporation into clinical trial design, we suspect that initial studies will include integrated biomarkers where analysis of the utility and predictive power of a putative biomarker is performed *post hoc* and its presence or change is not utilized in the trial for clinical decision making. Once more mature data are available, possibly from these integrated biomarker trials, we would then be poised to embark on integral biomarker trials in which clinical management is predicated on the presence or absence of a biomarker or its alteration during treatment.

Overcoming deficiencies of randomized trials in an era of increasing molecular and technical stratification factors (discovery of rapidly available, validated, and surrogate markers for survival)

The randomized clinical trial (RCT), with overall survival and disease-specific survival as endpoints, is the gold standard for evaluation of a new therapeutic approach. As RCTs are usually required for drug approvals, they are sought after by industry. Insurers likewise emphasize level one evidence, which is often defined as a systematic overview of RCTs. However, it has become increasingly clear that effective therapies are sometimes inappropriately invalidated because many patients on the study do not have the required biology for a response. Similarly, large studies may be positive ($P < 0.05$) primarily because they are large, not because the benefit is substantial. Given the expanded number of molecularly directed therapies that require increasing patient stratification, these trials are increasingly impractical and unrealistically expensive, which has in turn increased drug development costs, health care costs, required sample size, and the time it takes for lifesaving therapies to become clinically available. Therefore, we determined that a 5- to 10-year goal should be the identification of liquid biopsy or other biomarker-driven surrogate endpoints that are sufficiently robust to allow for reduced reliance on death as an endpoint in RCTs, both with regard to agent approval by the FDA and payment by insurers. An arena of particular interest to radiation oncology trialists is that of utilizing quantitative imaging tools to immediately assign patients to therapies that may be beneficial (i.e., trial enrichment via careful but not overly restrictive patient selection), stratify patients based on predicted likelihood of good or poor outcomes (i.e., risk stratification), or modify therapy based on alteration in an imaging parameter during the course of treatment (i.e., adaptive treatment modification). The routine use of images for radiation treatment planning, the increasing utilization of cone-beam CT, CT on rails, and integrated magnetic resonance X-ray technologies may hasten the adoption of such biomarker-driven imaging clinical trial designs. Biomarkers have been used previously as alternatives to standard RCTs for the approval of some agents (60); hence, this approach has historical precedent (Fig. 4). G. Yothers, Professor in the Department of Biostatistics, University of Pittsburgh Graduate School of Public Health, and Director of the Division of Biostatistics and Science, NRG Oncology Statistics and Data Management Center (Pittsburgh, PA), discussed the importance of collecting these objective molecular and imaging response endpoints to assure secondary analyses are possible upon completion of a clinical trial. The dividends for smaller, faster future studies with endpoints as valid as survival, make the addition of many of these tests more economical, even in large clinical studies. G. Yothers commented that this latter approach is not just a logistical imperative but will also greatly reduce unnecessary human suffering associated with overtreatment and undertreatment on an otherwise much longer and larger RCT. In addition, where trials specifically randomizing the radiation intervention are not feasible, SWOG supports the careful conduct of observational comparative effectiveness analyses. Such trials may allow for the generation of new hypotheses. For example, in the ongoing SWOG 1418 trial evaluating pembrolizumab and radiotherapy in patients with high-risk triple-negative breast cancer, patients are randomized to pembrolizumab, and radiotherapy is offered concurrently or sequentially at the discretion of the treating physicians to allow for exploration of the interaction of radiation and immunotherapy in that context. Opportunities for the conduct of correlative studies in this setting are also critically important.

Patient-centered priorities

The potential for improved clinical trial endpoints to reduce patient suffering and achieve more rapid advancement of new treatments as well as the need to outperform current randomized trial designs has strong patient support. Priorities regarding reduction of the burden of radiation and combined treatment–induced side effects were also importantly judged by patient advocates. S. Finkelstein, Director of the Bay Regional Cancer Center/Advanced Urology Institute (Panama City, FL), discussed the role that simple nutritional modification may have on alleviation of the side effects of therapy. He presented a study featuring nutritional intervention for combined modality-related gastrointestinal toxicity, including patient-reported outcomes with a composite symptom endpoint and performed in a community-based practice. Patient advocates had enthusiasm for medical foods as a component of active and symptom control interventions. The committee views the collection and rigorous evaluation of patient-reported outcomes to be a priority in studies that include radiotherapy as a modality, especially because its impact often relates to meaningful changes in quality of life rather than in survival exclusively.

Summary

A strategic planning symposium that included leaders in cancer basic sciences, molecular theragnostics, pharmaceutical and technology industries, clinical trial design, oncology practice, and statistical analysis identified a number of priority questions ready for study and advancement. These research opportunities have the potential to greatly advance cancer care, lead to novel therapeutic combinations, and identify new radiation biomodifiers. The

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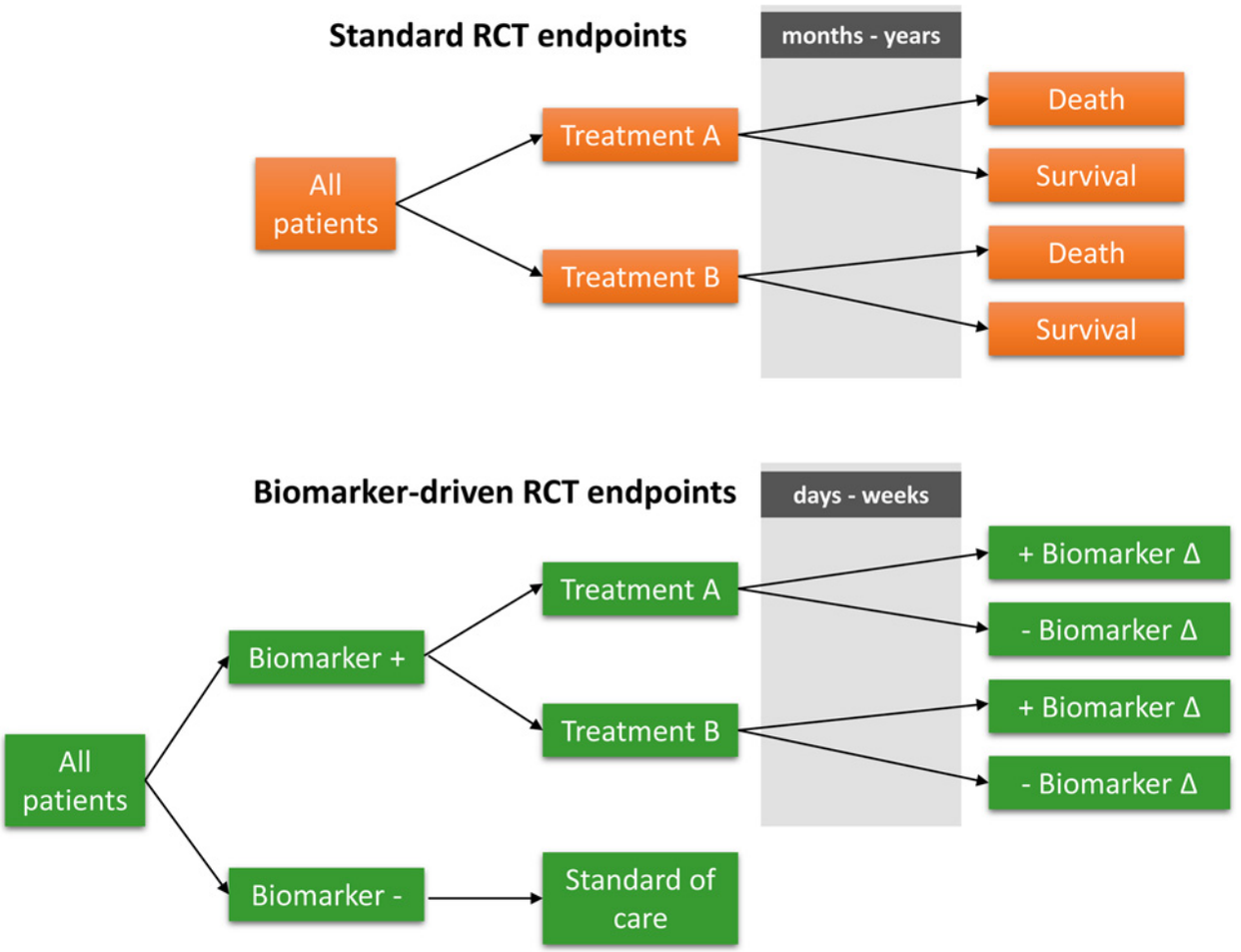

Figure 4.

A biomarker that measured tumor kill in the first day after the first dose of radiation or chemotherapy could powerfully aid in optimization of personalized therapy and would be a welcome solution to the present imaging-based studies. Similarly, quantitative liquid biopsies that accurately measure tumor burden with minimal false negative values could replace the expensive and demanding studies of disease-specific survival.

Radiation Therapy Committee reached consensus on five high-priority areas with example clinical trial designs to answer the proposed hypotheses:

1. Oligometastasis/oligoprogression: does SBRT received in combination with systemic therapy for gross disease improve survival for patients with oligoprogression or oligometastasis? Does surveillance imaging of high-risk patients to detect early resistant tumors aid in successful salvage after adjuvant chemotherapy (e.g., high-risk breast cancer and node-positive colon cancer)?
2. Systemic and local radiomodifications: does radiation enhance systemic immune response in drug-resistant cancer? If so, what target lesions (lung vs. liver vs. lymph node) and radiation doses and fractionations achieve the best response? Studies using DDR agents to enhance local control could be used for tumor types with poor local control or to allow reduction of radiation dose for sites with high radiation morbidity.
3. Liquid biopsy and molecular panels: should radiation be withheld for patients with panels demonstrating poor radiation response? Should radiation be used for preoperative vaccination of patients with biomarker panels suggesting benefit from immune therapy? Can liquid biopsies be used to select patients who will benefit most from the addition or deletion of adjuvant radiation? Biomarker, Imaging, and Quality of Life Studies Funding Program (BIQSFP) specimens suitable for analysis should be collected prospectively in order to develop increasingly sophisticated panels.
4. Improve RCT efficiency with surrogate endpoints and bias correction: although, RCTs are classically assumed to be the best method for validating new therapies, the high associated costs, limited pragmatic relevance of their design, slow accruals, and delayed agent approvals greatly slow clinical progress. Therefore, we support the controversial belief that the current standard of RCTs needs revision. Validated biomarker panels that genuinely mirror or even outperform

survival endpoints have great potential to shorten the time for development of new agents. Future clinical trials both within SWOG and by component SWOG institutions should include robust biomarker and liquid biopsy panels aimed at identifying surrogate markers for determination of quality-adjusted life years (QALY).

5. Patient-centeredness: side effects are more severe with combined modality therapy and may be unexpected when employing molecularly driven agents. Toxicity data collection and patient-reported outcomes should accompany tumor response data, and like tumor response will require predictive and surrogate markers to allow QALY calculations.

The Committee believes that advances in the proposed areas can be achieved economically with existing technologies as secondary aims on many of the existing and proposed clinical trials at SWOG. The concepts are generally agnostic to the anatomic origin of the tumor and are relevant for patients with localized or metastatic disease; as such, we believe that many aspects of these questions may be ready for clinical evaluation and are likely to critically improve cancer cure rates and the quality of survival.

Disclosure of Potential Conflicts of Interest

P. Okunieff reports receiving commercial research grants from DiaCarta, and holds ownership interest (including patents) in and is a consultant/advisory board member for Entrinsic Health and DiaCarta. C.C. Pinnix is an employee of MD Anderson Cancer Center and reports receiving commercial research grants from Merck and Co. J.W. Welsh is an employee of Healios, MolecularMatch, and OncoResponse; reports receiving commercial research grants from Varian, Merck, Calithera, Checkmat Pharmaceuticals, OncoResponse, and Incyte; and is a consultant/advisory board member for Reflexion Medical and Mavu. S.J. Knox reports receiving commercial research grants from Ludwig/Bristol, Myers, Squibb. F.Y. Feng is an employee of PFS Genomics; reports receiving commercial research grants from Varian; and is a consultant/advisory board member for Medivation/Astellas, Janssen, Sanofi, Bayer, Dendreon, Ferring, EMD Serono, Clovis, and Reflexion. S.M. Galbraith is an employee of AstraZeneca. A.A. Solanki reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Blue Earth Diagnostics. M. Daly reports receiving commercial research grants from EMD Serono. T.J.C. Wang reports receiving other commercial research support from Abbvie, Merck, and Novocure; reports receiving speakers bureau honoraria from Elekta; holds ownership interest (including patents) in Doximity; and is a consultant/advisory board member for AstraZeneca and Wolters Kluwer. D.T. Marshall is a consultant/advisory board member for FirstString Research, Inc. D. Raben is a consultant/advisory board member for Merck, Nanobiotix, AstraZeneca, and Genentech. No potential conflicts of interest were disclosed by the other authors.

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