The Clinical Research Center: A Vital Part of the ACR Mission

Howard B. Fleishon, MD, MMM[a], Christoph Wald, MD, PhD[b], Ron Korn, MD, PhD[c], Seth Rosenthal, MD[d], Nancy Fredericks[e]

The ACR's mission statement identifies five pillars of excellence. One of its pillars is research. ACR is recognized by many as supporting one of the premier research endeavors sponsored by a professional medical society of which the ACR Clinical Research Center is the largest component. The center is comprised of four entities: ACRIN®, RTOG®, QRRO®, and ACR Image Metrix™. The Clinical Research Center encompasses personnel with extensive clinical trial expertise, a state-of-the-art IT infrastructure, and an imaging and radiation oncology core laboratory. This research enterprise supports a global network of researchers in the conduct of medical imaging and radiation oncology clinical trials. This paper's focus is on the Clinical Research Center's value to the radiology and radiation oncology professions, to the practices engaged in the clinical research, and to our patients.

Key Words: Clinical research center, ACR research, radiology research

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RESEARCH: A PILLAR OF THE ACR

The ACR's mission statement identifies 5 areas of excellence. The activities of the government relations and economics departments are widely reported. Through the accreditation, standards and guidelines, and Appropriateness Criteria® programs, the ACR's quality and safety programs have become prominent. The online ACR Campus and new state-of-the-art Education Center have highlighted the education component of the ACR's mission. The fifth, less recognized pillar of the ACR's mission is research, the largest component being the ACR Clinical Research Center in Philadelphia.

Clinical research programs and initiatives are a vital aspect of the ACR's mission. Most important, they have direct clinical and economic implications for imaging and radiation oncology practices. The goal of the Clinical Research Center is to study the efficacy of diagnostic and therapeutic applications and to provide the scientific basis for establishing those that deliver the best clinical care for our patients. This goal complements the much discussed "comparative effectiveness" initiative in the recent health care debate. The center's clinical research is designed to obtain data within a multicenter framework to answer questions needed to bring new modalities and applications from the bench to the clinical setting, making them available to all of our practices.

THE CLINICAL RESEARCH CENTER'S STRUCTURE

The 4 Research Entities

The size and scope of the ACR Clinical Research Center are unique for a medical professional society. The center is composed of a complex construct of services built around 4 organizations. ACRIN®, RTOG®, and QRRO® are the 3 nonprofit entities funded, in large part, by the National Cancer Institute (NCI), with ACRIN and RTOG being 2 of the 10 NCI Clinical Trials Cooperative Group Program members. The ACR's Image Metrix™, launched in 2007, is the commercial imaging contract research organization (CRO) that competes for business within the pharmaceutical, biotechnology, and medical device sectors.

The Research Network

The clinical research groups each encompass a network of investigators at more than 350 facilities in the United States and abroad. They represent a variety of settings, from large teaching institutions and tertiary care hospitals to freestanding imaging and treatment centers. The affiliated researchers cover a wide spectrum of medical specialists, including diagnostic radiologists, nuclear medicine physicians, radiation oncologists, medical oncologists, physicists, pathologists, surgeons, and clini-

[a]North Mountain Radiology Group, Phoenix, Arizona.

[b]Lahey Clinic, Burlington, Massachusetts.

[c]Scottsdale Medical Imaging Ltd Scottsdale, Arizona.

[d]Radiology Associates of Sacramento, Sacramento, California.

[e]ACR Clinical Research Center, Reston, Virginia.

Corresponding author and reprints: Howard B. Fleishon, MD, John C. Lincoln North Mountain Hospital, 250 E Dunlap Avenue, Phoenix, AZ 85020; e-mail: hbf@cox.net.

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cians from other specialties who have an interest in medical imaging and radiation oncology clinical trials.

The research of the 3 NCI-funded groups originates from scientific committees. Study concepts may be proffered by committee members or introduced by external clinicians and scientists. It is within these scientific committees that study concepts are vetted for how well they address both the group's overarching research strategy and the committee-specific goals. Other criteria, such as a trial's complexity, cost, and potential impact on patient care, are also factored into prioritization. Each group has a decision-making body that considers the research priorities across all committees and determines which trials to fund, so as to maintain a balanced portfolio of trials related to the groups' research goals.

Supporting these investigators and committees is a cadre of research professionals located at the ACR Clinical Research Center. Statisticians, data managers, regulatory staff members, technologists, dosimetrists, project managers, and administrative personnel all play a critical role in implementation of the clinical trials, from the development of an initial research concept to recruitment, data collection and analysis, and manuscript preparation. The specific research services provided include protocol development, study design, data forms development, site recruitment and qualification, regulatory compliance, image quality review, radiation therapy quality assurance, and statistical analysis and reporting.

The ACR Image Metrix shares the infrastructure in place for the NCI-funded groups to conduct its CRO operations. It uses the information technology capabilities of the center, such as the clinical trials database, image management and archive applications, and state-of-the-art image-viewing workstations. In addition, the imaging CRO engages experts from the extensive network of clinical trial investigators and content specialists involved in ACRIN, RTOG, and QRRO research to carry out commercial projects.

The Core Laboratory

An important shared center resource is the imaging and radiation oncology core laboratory. First established in 2000 to manage imaging archival and transmission services for large clinical trials, the core laboratory has evolved to support a wide range of functions and services, including advanced image data extraction and quantification, investigator and reader training, and the standardization of new imaging and radiation treatment planning techniques.

Reader studies are an integral part of many ACRIN trials and ACR Image Metrix commercial projects. Experts from around the country use the laboratory to compare centralized image interpretation with local interpretation and to evaluate disease status both quantitatively and qualitatively. The laboratory's environment controls for blind reads and standardizes image evaluation. For example, the core laboratory facilitated a 3-day blinded reader study that involved tumor analysis with measurements for the ACRIN 6673 trial, A Multicenter Feasibility Study of Percutaneous Radiofrequency Ablation of Hepatocellular Carcinoma in Cirrhotic Patients, which is estimating the proportion of participants undergoing radiofrequency ablation whose livers have no identifiable tumors on CT at 18 months.

HISTORY AND GROWTH

The Clinical Research Center has historical roots dating back to 1968, when Simon Kramer, MD, at Jefferson Medical College, received a grant from the NCI to study patterns of care in radiation oncology and approached the ACR to support the project. This small project, with 7 employees and a budget of $500,000, has developed into a multifaceted research operation encompassing more than 180 staff members, with an annual operating budget of more than $40 million in 2009, 46% of the College's annual budget. The operations of the NCI-funded research groups are primarily supported by grant dollars and supplemented through foundation, industry, and other governmental sources. The College also receives payment to cover the operations indirect costs.

Most recently, ACRIN, RTOG, and QRRO have pursued supplementary grant funding from the NCI that has been made available through the American Recovery and Reinvestment Act (ARRA). As of November 2010, the center has submitted more than 16 grant applications to the NCI for ARRA-funded projects and has been awarded more than $17.5 million to date. Efforts are ongoing to secure additional funding as new ARRA grant opportunities are announced.

Additional center funding sources, such as the ACRIN Fund for Imaging Innovation, the RTOG Foundation, and Pennsylvania's Commonwealth Universal Research Enhancement program, have facilitated the implementation of novel projects and new research foci.

For example, ACRIN Fund for Imaging Innovation funding allowed ACRIN to expand beyond cancer research with the establishment of cardiovascular and neuroscience committees. The ACRIN Cardiovascular Committee has launched two clinical trials investigating unique applications of CT angiography with Commonwealth Universal Research Enhancement funding and a grant from the Agency for Healthcare Research and Quality.

A significant portion of the grant funding is distributed to participating research sites as case reimbursement for each study participant enrolled. ACRIN and RTOG distributed nearly $175 million to participating institutions from 1999 to 2009.

SITE PARTICIPATION IN CLINICAL RESEARCH

Although academic institutions represent a significant percentage of sites that participate in the Clinical Research Center's trials, private practices have elected to participate as well. One such example is Scottsdale Medical Imaging, Ltd (SMIL), in Arizona. ACRIN provided the group the opportunity to combine its interests in

research with the practical realities of a private practice enterprise.

SMIL has participated in the National CT Colonography Trial [1] and the MRI of the Contralateral Breast study [2]. Through these research opportunities, SMIL learned that the compensation per participant enrolled was sufficient to employ the necessary research staff members to conduct these studies.

Although current ACRIN studies have smaller accrual targets, the ACRIN protocols allow the practice access to investigational protocols and imaging agents, which in turn, allows them to uniquely serve their communities and patients. As a direct result of its participation in ACRIN, SMIL has distinguished itself as a radiology private practice group that can support a dedicated research department.

Another example is Radiological Associates of Sacramento (RAS). RAS has been a full member of RTOG since the 1970s. Over the past 3 decades, more than 1,600 patients have been accrued by RAS physicians to RTOG trials.

Clinical research has provided the group with a methodology to help introduce innovations in cancer care to its patients. In addition to furthering its mission of advancing oncology care in the Sacramento community, participation in clinical research has had tangible benefits to the practice as a whole, including recruitment and marketing.

Participation in RTOG trials and the associated credentialing has helped RAS introduce new technologies into clinical practice with the rigid and strict credentialing, quality assurance, and institutional review board structures required for patient care on RTOG trials. RTOG has external credentialing procedures for specialized radiation therapy techniques, such as intensity-modulated radiation therapy, prostate brachytherapy, and stereotactic body radiation therapy. These external and independent activities, in addition to RTOG's routine quality assurance activities, treatment plan, and chart reviews, provide a level of external quality assurance that has helped RAS physicians introduce new techniques into the practice according to strict protocols, while adhering to national guidelines and safeguarding patient safety.

The radiation oncology practice at the Medical College of Wisconsin is 1 of the 40 practice groups that participated in QRRO's national survey project, launched in August 2008, that has gathered extensive data about the delivery of radiation oncology care in the clinical setting. By participating in the QRRO survey, the Medical College of Wisconsin's radiation oncologists and medical physicists had the opportunity to contribute to QRRO's database of care delivery and outcomes data, which facilitates research about whether improved treatment approaches documented in phase 3 clinical trials are being adopted in actual clinical practice. For example, data being collected related to cervical cancer treatment will provide important information about the use of chemotherapy with radiation, radiation planning for brachytherapy insertion, and radiation dose with combined brachytherapy and external-beam radiation. These data will serve as a benchmark for radiation oncology practices and practitioners around the country.

The recent designation of QRRO participation as a Practice Quality Improvement initiative by the ABR provides the Medical College of Wisconsin's radiation oncologists with a significant additional participation benefit. PQI is 1 of 4 requirements for maintenance of certification required for diplomats graduating after 1995 (and soon to be obligatory for all physicians). Using the site data collected by the QRRO survey, individual doctors can design their own PQI projects.

VALUE PROPOSITION

Through its mission of "providing a multicenter and state-of-the-art clinical trials, management, consulting, and survey service dedicated to improving patient care by advancing the science and practice of both imaging and radiation oncology," the Clinical Research Center has had significant impact on the practice of imaging and radiation oncology. Hundreds of scientific papers reporting its clinical trial results appear in peer-reviewed journals each year, along with presentations at major scientific meetings. It is through this information dissemination that clinical guidelines are changed, improved clinical practices are adopted, and new therapies and procedures are reimbursed.

CONTRIBUTIONS TO CLINICAL PRACTICE

ACRIN Research Highlights

Since its inception in 1998, ACRIN has established a clinical trials infrastructure and implemented numerous protocols. One of the first ACRIN endeavors was the Digital Mammographic Imaging Screening Trial to determine the efficacy of digital vs standard film mammography [3]. Important papers are still being published today using the rich source of data collected for the trial.

In September 2008, publication of the National CT Colonography Trial [1] confirmed CT colonography as an effective colon cancer screening tool. The trial enrolled 2,600 study volunteers at 15 sites across the country. Secondary analyses, such as elaboration of CT colonographic results in the study subpopulation older than 65 years of age (targeting Medicare beneficiaries), detection rates of flat colonic lesions, and performance analysis of computer-aided detection for CT colonography, are all under way. These secondary publications are expected to provide data that will further support the broadening of insurance coverage for this procedure and ultimately result in more people being screened for colorectal cancer.

Initial results of the National Lung Screening Trial, a randomized trial that compared the effects of lung cancer

screening with low-dose CT and x-ray on lung cancer mortality, were announced in November 2010. Investigators reported that 20% fewer lung cancer deaths were found among trial participants screened with low-dose helical CT. The results were announced before publication at the direction of the National Lung Screening Trial's Data and Safety Monitoring Board. ACRIN and the NCI's Lung Screening Study Group conducted the trial that enrolled more than 53,000 current and former heavy smokers aged 55 to 74 at 33 US-based sites. Publication of the trial's full primary aim results is expected in 2011, followed by a wide range of secondary publications.

When CMS put out a request for applications to establish its first "coverage with evidence" program to help guide coverage determination for PET/CT scans, ACRIN was selected as the organization to manage the National Oncologic PET Registry (NOPR). After a collaborative work effort by leaders in the field of outcomes research, nuclear medicine imaging, and oncology, NOPR was launched in May 2006.

Under this program, participating PET/CT facilities were reimbursed for previously uncovered PET scan indications if prescan and postscan surveys were submitted to NOPR. The survey data collected resulted in an extensive national database for PET applications. Subsequently, studies published analyzed data from more than 72,000 NOPR cases [4]. The results led to change in cancer management of nearly 40% of patients. Approximately 10% of all Medicare-covered PET scans in 2007 were performed under the auspices of NOPR [4].

On the basis of the evidence of the effectiveness of PET/CT for the management of cancer patients' care, provided in large part by NOPR, CMS has expanded coverage of PET/CT for the vast majority of indications [4].

RTOG Research Highlights

RTOG activated its first clinical trial in 1968, a randomized trial evaluating the addition of concurrent methotrexate to radiation for patients with squamous cell carcinoma of the head and neck region [5]. The study formed the baseline for many of the clinical investigations in the area of head and neck cancer. RTOG continues as an international leader in systematically testing novel radiotherapy approaches and evaluating the integration of optimized radiotherapy with new classes of anticancer therapies. As evidence of the group's research leadership, RTOG investigators presented research findings of 20 RTOG clinical trials at the 2010 American Society of Radiation Oncology meeting. RTOG enrolled 403 participants with locoregionally advanced cancer of the cervix in a study between September 1990 and November 1997 to compare the effects on survival of treatment with extended-field radiation and treatment with pelvic radiotherapy and concurrent chemotherapy with fluorouracil and cisplatin (RTOG 9001).

An interim analysis of the data conducted shortly after the completion of participant enrollment demonstrated sufficiently compelling results that the trial's data monitoring committee recommended the early results publication. Published in April 1990 [6], the results demonstrated that the inclusion of chemotherapy substantially reduced both local and distant recurrences of cervical cancer, leading to higher overall and disease-free survival rates. A subsequent 2004 publication of mature data [7] confirmed the benefit of concurrent administration of chemotherapy with radiation, as a 51% reduction in the risk for recurrence and a 52% reduction in the risk for death were documented. This improvement was accomplished without any increase in the rate of serious late effects of radiation.

In another RTOG clinical trial with research results directly transferable to clinical care, 333 participants from 55 participating RTOG institutions were enrolled in the first multi-institutional randomized trial to compare whole-brain radiotherapy with or without stereotactic radiosurgery for patients with 1 to 3 brain metastases (RTOG 9508).

The study found a significant survival benefit in patients with a single unresectable brain metastasis randomized to the whole-brain radiotherapy and stereotactic surgery group, with no associated toxicity [8]. In addition, improved survival performance was demonstrated in all patients who had whole-brain radiotherapy and stereotactic radiosurgery, suggesting that both treatments be considered for patients with 2 or 3 brain lesions.

QRRO Research Highlights

The data collected by QRRO surveys (previously Patterns of Care Surveys) have demonstrated practice changes in radiation oncology over time. An analysis of Patterns of Care Survey data published in 2004 was undertaken to compare the changes in the practice of brachytherapy and multimodality therapy for patients with cancer of the cervix using data from the 1992-1994 and 1996-1999 surveys and to discern practice pattern differences between small and large facilities [9]. Data from 383 patients collected at 55 institutions of varying sizes and types were analyzed.

The results demonstrated a significant difference in practice between small and large radiation therapy facilities and that these disparities had increased.

Although the study did not detect an overall increase in the use of concurrent chemotherapy between the 1992-1994 survey and the 1996-1999 survey, a dramatic increase in the use of chemoradiation was evident in the last year of the survey. The increase corresponded with the dissemination of information from several randomized clinical trials [9], indicating that new treatment practices were rapidly being adopted.

RESEARCH INITIATIVES

ACRIN Case Study

ACRIN trial results highlight the importance of imaging for improving patient care and serve to inform peers, policymakers, regulators, and patients. As an example, ACRIN recently completed protocol development for a new trial that will conduct a prospective, multicenter comparison of multiphase contrast-enhanced CT and multiphase contrast-enhanced MRI for the diagnosis of hepatocellular carcinoma in context with liver transplant allocation (ACRIN 6690). The trial tests the ability of both imaging modalities to correctly diagnose presence and stage of liver cancer using a new draft policy of the United Network for Organ Sharing, which governs solid organ transplantation in the United States. Results are expected to provide the evidence base to either affirm this new policy in its current form or provide a knowledge base for necessary amendments. Through its investment in ACRIN, radiology is highlighted as taking the lead in developing and evaluating new methodologies.

RTOG Case Study

During the past decade, a concerted effort to recruit RTOG participating sites outside of North America has resulted in a significant international representation, with 11 countries now participating in RTOG trials. Collaboration with the European Organization for Research and Treatment of Cancer has also expanded RTOG's international reach. The RTOG 0525 study, Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma, opened in 2006 with European Organization for Research and Treatment of Cancer brain and radiotherapy groups enrolling nearly 200 of the 1,173 study participants.

QRRO Case Study

At the 2010 American Society for Radiation Oncology meeting, 7 abstracts incorporating data from the recently completed QRRO survey were reported that demonstrate the value of the QRRO benchmarking data. One such presentation reported a review of radiotherapy treatment of 384 patients from 42 institutions and found excellent adherence to published treatment guidelines on the basis of clinical trials among practicing radiation oncologists [10]. These data are particularly insightful given the many reports of radiation overexposure published in the mass media during 2010.

Image Metrix Case Study

The imaging CRO designs, implements, and conducts proprietary clinical trials for which imaging is an important endpoint. In early phase trials, this often means using imaging to help further knowledge of a drug's mechanism of action, obtain early insight of effectiveness, and aid in the decision of whether to pursue a drug into expensive later phase trials. Early phase trials may use conventional imaging or, increasingly, novel imaging methods such as dynamic contrast-enhanced MRI or PET using innovative radionuclides. Later phase trials typically use conventional imaging methods as a biomarker of surrogate endpoint for effectiveness in support of an application to the FDA for drug approval.

Future Endeavors

The clinical research carried out within the ACR Clinical Research Center continues to pursue research questions for which the groups are uniquely positioned to address by the broad participation of investigators and participating sites and its robust infrastructure. The current trials under way hold promise to continue reporting discoveries that translate into improved patient care. Trials investigating imaging biomarkers and using biomarkers to determine the most appropriate treatment are at the forefront of cancer research.

In March 2010, a study commissioned by the NCI and carried out by the Institute of Medicine was published that assesses the current state of the NCI's Clinical Trials Cooperative Group Program. The report presents an in-depth evaluation of the program and makes broad recommendations for change. As the newly appointed NCI director, Harold Varmus, MD, works with his leadership team to translate the report into an action plan, the ACR Clinical Research Center's affiliated investigators look forward to changes that will build on and bolster their research efforts.

CONCLUSION

The Clinical Research Center is the axis of the research pillar of the ACR mission. Although not as frequently highlighted as other areas in the College, the center is a unique hub of innovation for a medical subspecialty society. The ACR's seed investments have spiraled to build a highly sophisticated and internationally recognized research network supported by various funding sources. Its size and structure have evolved over 4 decades to support value-added research for radiologists, radiation oncologists, and our patients. The process, along with the results of the investigations, provides tangible benefits not only to patient care but also to ACR members and our practices.

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