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● *Special Feature*

EVOLUTION AND ACCOMPLISHMENTS OF THE RADIATION THERAPY ONCOLOGY GROUP

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Purpose: The Radiation Therapy Oncology Group (RTOG) recently completed its first quarter century as a cooperative clinical cancer research organization. It is timely and appropriate to document its origins, evolution, and accomplishments.
Methods and Materials: The historical review of the RTOG called upon written and oral documentation.
Results: The RTOG is the most enduring product of the Committee for Radiation Therapy Studies (CRTS). Although not one of the original 17 clinical trials groups developed by the National Cancer Institute in 1956, the RTOG has pursued trials suggested by laboratory findings including the oxygen effect, intrinsic radiosensitivity, proliferation kinetics of normal and tumor cells, and interactions with other cytotoxic agents. Improvements in survival have been demonstrated for patients with carcinoma of the esophagus and cervix, and nonsmall cell carcinomas of the lung. The national and international radiation oncology communities have benefitted from standards and quality control/assurance guidelines for established and new modalities. A growing number of institutions in North America participate in RTOG trials.
Conclusion: The RTOG is an important clinical research resource, which has contributed to improved outcome for patients with many forms of cancer. It has become increasingly productive and widely adopted and endorsed by oncologists throughout North America.

Clinical trials, Radiation therapy, Radiation Therapy Oncology Group.

INTRODUCTION

The Radiation Therapy Oncology Group (RTOG) is the most enduring product of the Committee for Radiation Therapy Studies (CRTS). The formal organization of the RTOG began in 1968, a year of great intellectual and political upheaval in the United States and Western Europe. It might have been given birth to more than a decade earlier had there been full appreciation of the uniqueness of ionizing radiations as an anticancer agent, rather than the often-held view of it as just another "single agent" along with cytotoxic drugs.

In 1956, the Cancer Chemotherapy Service Center was established under the governance of the National Cancer Institute (NCI) as a result of a specific congressional appropriation (11). The National Cancer Institute leaders had recognized that comparative clinical trials were necessary to advance cancer treatment and single institutions, large as they might be, could not accrue sufficient numbers of patients in a reasonable period of time to answer important questions. Seventeen clinical cooperative groups were organized and received funds at that time. The Radiation Therapy Oncology Group was not one of them.

Several national leaders of the fledgling discipline of radiation oncology, encouraged by Kenneth M. Endicott, Director of the NCI, somewhat grudgingly agreed to collaborate to provide advice to him based on consensus rather than individual viewpoints. Fifteen of the 111 physicians in the United States who confined their practice to the therapeutic uses of ionizing radiations convened and adopted the name *Committee for Radiation Therapy Studies* (CRTS); they selected Gilbert H. Fletcher as chair of the committee and his colleague from the M.D. Anderson Hospital and Tumor Institute, Nora duV. Tapley, as the Executive Secretary. In 1963, Endicott secured funding to permit this group to convene regularly and to provide advice to him and other leaders of the NCI.

One of the earliest activities recognized as important by the CRTS was the conduct of clinical trials addressing radiation therapy questions. Comparative clinical trials in cancer had begun in England in the 1940s and hypotheses

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relating to radiation therapy were among the first studied (31, 32). Comparative trials that included randomization and concurrent control groups were considered essential in medicine because it had been demonstrated that subjectivity and bias influenced the interpretation of uncontrolled trials.

EARLY CLINICAL TRIALS

The members of the CRTS had a conceptual framework that differed from that of their colleagues in hematology, who naturally viewed malignant neoplasia as a systemic disease. Radiation oncologists considered tumors to be localized unless demonstrably disseminated, so CRTS members assumed that there is the potential to cure patients with cancer if the local-regional tumors could be eradicated.

Two early clinical trials were endorsed by the CRTS as important studies that could lead to improved treatment of patients with cancer. A trial comparing extended irradiation vs. localized "involved-field" irradiation for Hodgkin's disease was encouraged by Henry S. Kaplan of Stanford University, a member of the CRTS. Because Kaplan would not commit to enrolling Stanford patients in the study, James J. Nixon, also a CRTS member, chaired the steering committee that developed the trial. Collaborators were recruited, a statistical office was formed, and investigators began enrolling patients in The Cooperative Hodgkin's Disease Clinical Trial in 1967 (22, 30). Six years later, 467 patients had been enrolled, but the results per se did not greatly influence practice. First, because of the effective educational efforts of Kaplan and his hematologist colleague, Saul Rosenberg, the question was considered by many to have already been answered. Second, the definition of extended field was changed midway through the study because there were frequent transdiaphragmatic failures when only supradiaphragmatic irradiation was given. Third, the unanticipated adoption of laparotomy as a staging procedure for abdominal disease resulted in disqualification in the later years of the study of many patients who had involvement of the paraaortic nodes and spleen, thus rendering their tumors pathologic Stage III.

A cooperative trial of adjuvant hormone therapy for adenocarcinoma of the prostate also received the blessing of the CRTS. Juan A. del Regato, a member of the CRTS and Secretary of the American Club of Therapeutic Radiologists, had provided one of the earliest observations of the value of megavoltage radiation therapy for carcinoma of the prostate (10). Within 2 years of publication of the first series of patients so treated (1), a group of investigators was recruited to study the effectiveness of irradiation for this disease. This group involved a different cadre of investigators than the Hodgkin's trial. Although the study enrolled 411 patients between 1967 and 1973 (virtually all of whom were followed for 20 years or until death) (12), the question of the possible benefit of adjuvant hormonal therapy with pelvic irradiation could not be answered due to the slow accrual rate and problems with documentation of long-term compliance with the hormonal treatment.

GENESIS OF THE RTOG

When yet another member of the group, Simon Kramer, proposed a trial comparing radiation therapy alone with radiation therapy and concurrent methotrexate for advanced cancer of the upper aerodigestive tract, the CRTS supported the development of a cooperative group, not only to perform this study but to undertake a series of clinical trials using the same operations and statistical centers and the same support personnel in the participating institutions. Kramer applied to the NCI for support and an award was made to the Jefferson Medical Center in July 1968 to establish the RTOG. Marvin Zelen, Ph.D., was recruited to lead the statistical office, which was first located in Buffalo at the State University of New York and subsequently, at the Harvard School of Public Health.

It proved difficult to coordinate multiinstitutional clinical trials from an academic medical center. Demands for space and finances by the Thomas Jefferson Medical Center vied with the needs of the RTOG. Because the financial support provided by the NCI for conduct of the clinical trials did not then and never has fully reimbursed the cost of such trials, different solutions were sought. John J. Curry, now Executive Director of the American College of Radiology (ACR), was hired by Kramer in 1970 by virtue of funds provided by the NCI grant to serve as departmental administrator and coordinator of the RTOG: He was instrumental in moving the operations office to a storefront at 926 Walnut Street in Philadelphia (with a church upstairs), then to offices at 130 S. 9th Street that had been purchased by Jefferson from the Philadelphia Electric Power Company. When it became apparent to Kramer and Curry that much greater computing capability was required for the RTOG, arrangements were made to secure support from the ACR. In 1975, with the blessing of the Jefferson administration, the ACR became the grantee for the RTOG, a successful relationship that has endured to the present. The office was moved again in 1977 to the Pennsylvania Manufacturers Association Building at 925 Chestnut and a decade later to the 14th floor of the Aramark Building at 11th and Market Streets.

The ethics of medical practice and especially of clinical trials have been debated for 90 years (40). The responsibility of the physician/investigator to provide the best-known treatment is in tension with the reality that known treatments for cancer are far from satisfactory. Alternative treatments rarely differ so much that results are obvious and incremental advances are the best that may be expected; thus, there is a necessity for controlled clinical trials. The need for an Institutional Review Board (IRB), previously satisfied by the one at Jefferson, led to the establishment in 1975 of an IRB for the Philadelphia

office of the ACR in anticipation of its becoming the grantee. Thus, the RTOG became the first and, to this day, one of the very few clinical cooperative groups with an independent review of its protocols with regard to ethics, patient safety, and informed consent, separate from and in addition to reviews by the NCI and the individual collaborating institutions.

Fifteen clinical trials were activated by the RTOG during its first 5 years, in addition to Kramer's methotrexate trials. The architects of these trials were Frank Hendrickson of Chicago, Luther Brady of Philadelphia, Philip Rubin of Rochester, NY, Victor Marcial of San Juan, Puerto Rico, Morton Kligerman of New Haven, CT, Carlos Perez of St. Louis, and Chu Chang of New York City. A total of 6992 patients were enrolled in these trials (an average of 437 patients per trial), amply demonstrating the ability of a collaborative group to address questions because this number of patients was unattainable in even the largest single institution. One trial from the latter part of this early period was a milestone in the evolution of clinical investigations: It represented the first collaboration between two cooperative clinical trial groups—the RTOG and the Eastern Cooperative Oncology Group (ECOG)—to study a question of common interest, namely combined modality treatment of malignant glioma (RTOG 74-01/ECOG 1374) (24).

RTOG RESEARCH STRATEGIES

The research strategies of the RTOG have been predicated on laboratory findings from the beginning; protocols were developed specifically to address questions posed or thought to have been answered in the laboratory. Several of the fundamental research questions of the early studies continue to be of major interest to laboratory and clinical investigators. The availability of oxygen during the interactions of ionizing radiations and biological systems is considered one of the most important influences on cellular radiosensitivity and, therefore, tumor control probability. Hyperbaric oxygen was studied in a comparative trial for cancer of the cervix (2). Radiotherapy delivered following the breathing of carbogen (95% oxygen and 5% CO_2) was studied in a randomized trial for advanced carcinomas of the upper respiratory and digestive tracts (35). More recently, a series of drugs that were shown to sensitize hypoxic cells to radiations *in vitro* were studied in comparative trials.

Dose intensification was considered important from the outset because the intrinsic radiosensitivity of tumor cells was not predictable. Escalating total doses with standard fractionation (2.0 Gy per fraction) were studied in non-small cell carcinoma of the lung in Protocol 73-01 (33). *Altered fractionation* was investigated in several trials, but the paradigm changed over the years. The *fractionation paradigm* at the time the RTOG began was that of isoeffect formulae derived from laboratory studies and acute effects in human skin, which suggested that a smaller number of large-size fractions was equivalent both in tumor control and late effects to standard fractionation—2.0 Gy per fraction—given more frequently. The early emphasis was on split-course radiation therapy (27) to achieve reoxygenation of tumors (and best use of existing equipment). A linear-quadratic paradigm prevails at present, reflecting the fact that large-sized fractions have greater late effects in normal tissues than previously recognized (16). Moreover, the kinetics of repopulation of tumor cells and normal cells may render prolonged intervals between treatments disadvantageous. Randomized dose-searching studies with hyperfractionation were prominent in the 1980s.

At the present time, dose escalation permitted by *three dimensional conformal radiation therapy* (3DCRT) is a major objective of the RTOG and the Radiation Research Program of the NCI. The emphasis is on standard fractionation, but altered fractionation with 3DCRT is a possibility if the initial results are promising.

The complexities of the several classes and modes of action of *cytotoxic drugs and hormones* have resulted in empirical approaches to clinical studies of their interactions with ionizing radiations; laboratory studies have provided less guidance than had been hoped for. Nonetheless, combined modality trials were considered important from the beginning of the RTOG. The very first RTOG trial sought enhanced control of advanced carcinomas of the upper aerodigestive tract by interactions of radiations with concurrent methotrexate (23). The first glioma trial also studied the interaction of systemic chemotherapy and irradiation (24).

Even more remote from the laboratory, but compelling clinically, is *surgical adjuvant radiation therapy.* This combination of modalities was first studied by the RTOG for resectable carcinomas of the upper aerodigestive tract (39).

Studies of palliative irradiation for metastasis to the brain (20) and skeletal system (42) were undertaken to seek the most effective fractionation regimen. These efforts demonstrated the difficulties inherent in investigating palliative end points, especially in an era before formalized quality-of-life instruments were available.

Disappointments

It should not be surprising that studies of the intractable types of cancer investigated by the RTOG should have produced negative results. This has been a disappointment for the investigators and a sad reality for many patients. Fortunately, in the midst of the blind alleys, many benefits were realized from these studies by the radiation oncology community in North America. Standards were established for conducting and recording radiation therapy (17). The means of communicating these standards widely throughout the community (18), quality control of calibration and dosimetry (41), and quality assurance programs (43) were also established.

In response to a request by the CRTS that the American Association of Physicists in Medicine (AAPM) solve the

problem of possible errors in measurement and calculation when treating patients by interinstitutional protocol, the Radiological Physics Center (RPC) was established in Houston under the direction of Robert J. Shalek, Ph.D. (19). Over the 25 years of its existence, the RPC has made measurements on well over half the treatment units in the United States, thus reducing the already small risk of misadministration due to calibration error.

Disappointments have occurred in three major areas (5): radiation sensitizers, biologic response modifiers, and hyperthermia. In each case, laboratory investigations provided a compelling rationale for the clinical trials. In the case of *radiation-sensitizing drugs,* especially the electron-affinic nitroimadazoles, the reason for failure in clinical applications is partially understood. It did not prove possible to achieve drug concentrations in hypoxic cells *in vivo* as high as those achieved in the laboratory. Hope still remains for a beneficial effect of the more hydrophilic compound, etanidozole, but the preliminary reports from Europe are not encouraging (4).

A series of *biologic response modifiers* (BRMs), especially immune modulating or restoring agents, has thus far not proved beneficial. While other groups studied bacillus Calmette-Guerin (BCG) and the methanol-extractable residue of this bacillus to no avail, the RTOG first studied levamisole in combination with radiation therapy. Not only were the results not superior to those of radiation therapy alone, but there was a suggestion of an adverse effect. More recent studies of thymosin have not yielded better results. In the last few years, a previously unimaginable array of biologic molecules has been discovered, but there has been no consistent suggestion from the laboratory that any of them would have a favorable interaction with ionizing radiations. A single clinical experience has again raised the hope that BRMs could enhance radiation effects; a Phase III trial of beta-interferon is underway for patients with nonsmall cell carcinoma of the lung who have an especially unfavorable prognosis (28).

Very compelling laboratory data for favorable interactions of *hyperthermia* with radiations led to the funding of a vast research program by the Radiation Research Program of the NCI, and the initiation of several clinical trials by the RTOG. Problems with thermal dose distribution and measurement, and the inability to focus heat sufficiently in humans, have impeded these investigations and led to the RTOG's decision to discontinue research plans for this modality.

In spite of these negative trials, the benefits of an increasingly rigorous quality assurance program within the RTOG almost certainly enhanced the care of tens of thousands of patients in the participating institutions throughout North America. As new modalities were introduced in cooperative clinical trials, guidelines were developed for them and were made widely available. These guidelines provided assistance to physicians applying these modalities in the community beyond the needs specific to clinical investigations.

Dose–response studies

Studies seeking to determine the most effective total dose of radiation therapy were pursued in some of the earliest trials of the RTOG. One of the most influential studies was a dose-escalation trial for nonsmall cell carcinoma of the lung, chaired by Carlos Perez, which has already been noted (33). Using standard fractionation, the study showed a dose–response relationship for local control and survival at 2 to 3 years. As a result of this study, a total dose of 60 Gy in 30 fractions became a standard treatment throughout the United States.

The wide range of total doses permitted in Simon Kramer's original methotrexate trial, 55 Gy to 80 Gy in 5 to 10 weeks, reflected the inability to achieve consensus at that time as to the best total dose for unresectable squamous cell carcinomas arising in the upper aerodigestive tract. The split-course studies of Victor Marcial served to standardize the total dose at 66 Gy with 2.2 Gy per fraction. Allowing for somewhat smaller fraction sizes, total doses were permitted in the range of 66 Gy (2.2 Gy per fraction) to 72 Gy (1.8 Gy per fraction) for several years.

At disease sites where dose–response relationships had been shown with standard fractionation (lung [nonsmall cell carcinomas], head and neck, and brain [glioma]), higher total doses were studied with hyperfractionation (13), with the goal of greater tumor control without more severe effects on normal tissue. These studies did indeed provide evidence of a further dose response, improving local control or prolonging survival with total doses 7 to 20% above those considered to be the maximum tolerated with standard fractionation. In cases of advanced carcinoma of the upper aerodigestive tract, 72.0 Gy provided better tumor control than 67.2 Gy, both given with fractions of 1.2 Gy twice daily (9). The optimal total dose for patients with malignant gliomas proved to be 72 Gy (29); 69.6 Gy proved superior to 60.0 and 64.8 Gy for nonsmall cell carcinoma of the lung (6). In each of these three disease types, higher total doses than 69.6 to 72.0 Gy did not result in a further improvement in outcome, either local control or survival. In two of the three disease sites, the lung (7) and the upper aerodigestive tract (8), delays in completing the total dose resulted in a loss of tumor control or shortening of survival. This suggested that the total dose per se was important, but that the period of time over which it was administered was even more important. These findings are consistent with the hypothesis that proliferation of tumor cells during the course of treatment affects outcome.

Integration of chemotherapy and radiation therapy

The very first study of the RTOG was an attempt to achieve effective integration of chemotherapy and radiation therapy (23). This and many subsequent trials over the last 25 years showed no benefit to this integration. As more effective single agents and combinations of drugs were developed, however, the potential to combine

radiation therapy with combination chemotherapy in an effective manner continued to justify the search for an effective strategy for integrating these modalities.

A growing number of successful efforts in combining radiation therapy and chemotherapy has taught us lessons that may be applied to future strategies. The most dramatic benefit from this integration has been for patients with inoperable carcinoma of the esophagus. These patients were randomized (Protocol 85-01) to receive the standard treatment—high-dose radiation therapy of the esophagus (64 Gy in 32 fractions in 6.5 weeks)—or chemotherapy with 5-fluorouracil and cisplatin concurrent with radiation therapy at a lesser dose (50 Gy in 25 fractions in 5 weeks) (21). After a planned interim analysis, randomization was stopped because of the highly significant difference in survival in favor of the combined modality arm. The 2-year survival rate was 10% in the radiation therapy group whereas that in the combined therapy group was 38%. At 5 years, one-fourth of the patients in the combined modality group were still alive, while only a single patient from the radiation therapy group was alive.

Similar benefits have been observed in patients with carcinoma of the anal canal. The prognosis for this disease overall is far better than that for inoperable carcinoma of the esophagus. Indeed, results from the most recent RTOG study (Protocol 87-04) showed that approximately 80% of patients were alive 2 years after treatment (15). This study addressed the value of adding mitomycin-C to a combination regimen of radiation therapy plus 5-FU. The first end point was complete response based on biopsy at the site of the primary tumor. This indicated the need for additional treatment with further radiation therapy and chemotherapy and possible salvage adominoperineal resection with permanent colostomy. The colostomy-free survival rate for the group that received radiation therapy and 5-FU was 65% at 3 years, whereas that for the group that also received mitomycin was 78%.

The RTOG coordinated an intergroup trial (Protocol 88-08) for nonsmall cell carcinoma of the lung, which compared standard radiation therapy (60 Gy in 30 fractions in 6 weeks), induction chemotherapy with cisplatin and vinblastine for 7 weeks prior to the same radiation therapy, and hyperfractionated radiation therapy with 69.6 Gy in 58 fractions of 1.2 Gy given twice daily for 6 weeks) (37). Patients who received induction chemotherapy had statistically significant survival, better than the two groups of patients who received radiation therapy alone, corroborating the results of a prior Cancer and Leukemia Group B (CALGB) trial (14). Treatment failure patterns have not yet been analyzed in detail, but the CALGB trial and a French study of *induction* chemotherapy (25) did not suggest any improvement in local tumor control. The French trial demonstrated a reduction in the frequency of distant metastasis in the induction chemotherapy group, and a randomized study by the European Organization for Research and Treatment of Cancer (EORTC) (38) showed a significant improvement in local control and survival with *concurrent* cisplatin and radiation therapy for nonsmall cell carcinoma of the lung.

Three pilot studies have built upon these results. Each sought to enhance local tumor control by concurrently administering the two modalities, and to eliminate distant metastatic disease by using the most effective combination chemotherapy. These trials studied induction chemotherapy plus concurrent cisplatin and standard radiation therapy (Protocol 88-04) (36), concurrent hyperfractionated radiation therapy, vinblastine, and cisplatin (Protocol 90-15) all beginning the first day of treatment (3), and concurrent therapy similar to that just mentioned but substituting oral etoposide for vinblastine (Protocol 91-06) (26). The evidence strongly suggests that concurrent intensive chemotherapy and radiation therapy both enhances local tumor control and diminishes the frequency of distant metastasis (similar to that which was accomplished with esophageal cancer) and thus deserves very thorough evaluation. A Phase III trial (Protocol 94-10) is now comparing induction vinblastine and cisplatin plus radiation therapy using 60 Gy in 6 weeks (now the standard treatment for favorable patients with inoperable nonsmall cell carcinoma of the lung) vs. cisplatin and vinblastine given concurrently with the same radiation therapy vs. an oral etoposide with concurrent hyperfractionated irradiation.

Trials are underway with combinations of chemotherapy and radiation therapy for carcinomas of the larynx (Protocol 91-11) emphasizing laryngeal preservation, carcinomas of the cervix (Protocol 90-01), and carcinomas of the nasopharynx (Protocol 88-17).

Finally, a conceptually similar study has been completed in patients with locally very advanced adenocarcinomas of the prostate (Protocol 86-10). Patients were randomized to receive high-dose radiation therapy alone or 2 months of induction hormone therapy with goserelin and flutamide, followed by concurrent hormone and radiation therapy and then discontinuation of hormones until there was evidence of progressive disease. Preliminary results of this study indicate that the hormone regimen yielded a highly statistically significant benefit in local tumor control and progression-free survival, but overall survival rates do not yet differ (34).

PERSPECTIVE

After the retirement of Simon Kramer as chair of the RTOG, the first election for chair was held in 1981 and Luther Brady was chosen to lead the group. During his tenure as chair, the RTOG initiated some of its most important studies. After serving as Vice-Chair for Research Strategy, James Cox was elected the third chair of the group in 1987.

The radiation oncology community in North America has adopted the RTOG with increasing enthusiasm. While the long-term planning survey of the American Society for Therapeutic Radiology and Oncology in 1991 showed

that 39% of members participated in RTOG studies, the number of institutions participating in the RTOG has increased from 125 at that time to over 200. The statistical office of the RTOG, which relocated to RTOG Headquarters in Philadelphia and has been led by Thomas F. Pajak, Ph.D., since 1981, has become recognized for its work in identifying prognostic factors, describing methodologies for chemoprevention and quality-of-life studies, and refining statistical methods for estimating local tumor control. The semiannual meetings have become more exciting and more widely attended each year. Surgical and medical oncologists have developed committees for each disease site, tumor biologists and pathologists lead considerations of correlative studies and translational research, and keynote speakers and plenary scientific sessions point to future strategies. Formal training in biomedical ethics has been instituted to increase the awareness of all participants in issues of scientific misconduct and conflicts of interest. Finally, because the medical schools of the United States and Canada have abrogated their responsibilities for the training of clinical scientists, a formal program in clinical trials methodology is under development to assure an even more effective future for the RTOG.

REFERENCES

1. Bagshaw, M. A.; Kaplan, H. S.; Sagerman R. H. Linear accelerator supervoltage radiotherapy. VII. Carcinoma of the prostate. Radiology 85:121–129; 1965.
2. Brady, L. W.; Plenk, H. P.; Hanley, J. A.; Glassburn, J. R.; Kramer, S.; and Parker, R. G. Hyperbaric oxygen therapy for carcinoma of the cervix—Stages IIB, IIIA, IIIB and IVA. Results of a randomized study by the Radiation Therapy Oncology Group. Int. J. Radiat. Oncol. Biol. Phys. 7:991–998; 1981.
3. Byhardt, R. W.; Scott, C. B.; Ettinger, D. S.; Curran, W. J.; Doggett, R. L. S.; Coughlin, C. C.; Scarantino, C.; Rotman, M.; Emami, B. Concurrent hyperfractionated irradiation and chemotherapy for nonsmall cell lung cancer. Preliminary report of a Phase I/II Radiation Therapy Oncology Group (RTOG) trial. (Abstr) Proc. Am. Soc. Clin. Oncol. 12:327; 1993.
4. Chassagne, D.; Charreau, I.; Sancho-Garnier, H.; Eschwege, F.; Malaise, E. First analysis of tumor regression for the European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. Int. J. Radiat. Oncol. Biol. Phys. 22:581–584; 1992.
5. Cox, J. D. Clinical application of new modalities. In: Cox, J. D., ed. Moss' Radiation Oncology, Rationale, Technique, Results. 7th ed. St. Louis, MO: CV Mosby Company; 1994:971–986.
6. Cox, J. D.; Azarnia, N.; Byhardt, R. W.; Shin, K. H.; Emami, B.; Pajak, T. F. A randomized Phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: Possible survival benefit with ≥69.6 Gy in favorable patients with RTOG Stage III nonsmall-cell lung carcinoma: Report of RTOG 83-11. J. Clin. Oncol. 8:1543–1555; 1990.
7. Cox, J. D.; Pajak, T. F.; Asbell, S.; Russell, A. H.; Pedersen, J.; Byhardt, R. W.; Emami, B.; Roach, III, M. Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable nonsmall cell carcinoma of the lung: Analysis of 1244 cases from three Radiation Therapy Oncology Group (RTOG) trials. Int. J. Radiat. Oncol. Biol. Phys. 27:493–498; 1993.
8. Cox, J. D.; Pajak, T. F.; Marcial, V. A.; Coia, L.; Mohiuddin, M.; Fu, K. K.; Selim, H. M.; Byhardt, R. W.; Rubin, P.; Ortiz, H. G.; Martin, L. Interruptions adversely affect local control and survival with hyperfractionated radiation therapy of carcinomas of the upper respiratory and digestive tracts. New evidence for accelerated proliferation from Radiation Therapy Oncology Group Protocol 83-13. Cancer 69:2744–2748; 1992.
9. Cox, J. D.; Pajak, T. F.; Marcial, V. A.; Hanks, G. E.; Mohiuddin, M.; Fu, K. K.; Byhardt, R. W.; Rubin, P. Dose response for local control with hyperfractionated radiation therapy in advanced carcinomas of the upper aerodigestive tracts. Preliminary report of Radiation Therapy Oncology Group protocol 83-13. Int. J. Radiat. Oncol. Biol. Phys. 18:515–521; 1990.
10. del Regato, J. A. Cancer of the genitourinary tract. In: Acerman, L. V., del Regato, J. A., eds. Cancer: Diagnosis, Treatment and Prognosis. 3rd ed. St. Louis, MO: Mosby; 1962; 859.
11. del Regato, J. A. Reports to the Clinical Studies Panel: Suggestions for incorporating studies using radiotherapy into clinical studies of the Cancer Chemotherapy National Service Center. Cancer Chemother. Rep. 7:47–49; 1960.
12. del Regato, J. A.; Trailins, A. H.; Pittman, D. D. Twenty years follow-up of patients with inoperable cancer of the prostate (Stage C) treated by radiation therapy: Report of a national cooperative study. Int. J. Radiat. Oncol. Biol. Phys. 26:197–201; 1993.
13. Diener-West, M.; Pajak, T. F.; Bauer, M.; Cox, J. D. Randomized dose searching Phase ILE/II trials of fractionation in radiation therapy for cancer. J. Natl. Cancer Inst. 83:1065–1071; 1991.
14. Dillman, R. O.; Seagren, S. L.; Propert, K. J.; Guerra, J.; Eaton, W. L.; Perry, M. C.; Carey, R. W.; Frei, E. F.; Green, M. R. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in Stage III nonsmall cell carcinoma of the lung. N. Engl. J. Med. 323:940–945; 1990.
15. Flam, M. S.; John, M. J.; Peters, T.; Hoffman, J,; Savage, D.; Petrelli, N.; Myerson, R.; Rotman, M.; Mesic, J.; Swift, P.; Coia, L.; Cooper, J.; Gunderson, L. Radiation and 5-fluorouracil vs. radiation , 5-fluorouracil, mitomycin-C in the treatment of anal canal carcinoma; preliminary results of a Phase III randomized RTOG/ECOG intergroup trial. (abstr). Proc. Am. Soc. Clin. Oncol. 12:192; 1993.
16. Fowler, J. F. Radiobiological principles in fractionated radiotherapy. Semin. Radiat. Oncol. 2:16–21; 1993.
17. Glicksman, A. S.; Wasserman, T. H.; Bjarngard, B.; Laurie, F. The structure for a radiation oncology protocol. Int. J. Radiat. Oncol. Biol. Phys. 23:1079–1082; 1992.
18. Grundy, G.; Turner, M.; Germano, F. Computerized reporting system to compile participation data on medical studies. Sixth Conference on Computer Applications in Radiology and Computer Aided Analysis of Radiological Images. 37–45; 1979.
19. Hanson, W. F.; Shalek, R. J.; Kennedy, P. Dosimetry quality assurance in the United States: The experience of the radiological physics center. Proceedings of an American College of Medical Physics Symposium. SSDL Newsletter #30. IAEA/WHO. Vienna, Austria. pp. 255–282; 1991.
20. Hendrickson, F. The optimum schedule for palliative radio-

therapy for metastatic brain cancer. Int. J. Radiat. Oncol. Biol. Phys. 2:165–168; 1977.
21. Herskovic, A.; Martz, K.; Al-Sarraf, M.; Leichman, L.; Brindle, J,; Vaitkevicius, V.; Cooper, J,; Byhardt, R.; Davis, L.; Emami, B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N. Engl. J. Med. 326:1593–1598; 1992.
22. Hutchison, G. B. Radiotherapy of Stage I and II Hodgkin's disease: A collaborative study. Cancer 54:1928–1942; 1984.
23. Kramer, S. Methotrexate and radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx and hypopharynx (preliminary report of a controlled clinical trial of the Radiation Therapy Oncology Group). Can. J. Otolaryngol. 4:213–218; 1975.
24. Kramer, S. Radiation Therapy Oncology Group and Eastern Cooperative Group study of patients with malignant gliomas. Monogr. Natl. Cancer Inst. 46:237–238; 1977.
25. Le Chavalier, T.; Arrigada, R.; Tarayre, M.; Lacombe-Terrier, M.; La Planche, A.; Quoix E.; Ruffie, P.; Martin, M.; Douillard, J.-Y. Significant effect of adjuvant chemotherapy on survival in locally advanced nonsmall cell lung cancer. J. Natl. Cancer. Inst. 84:58; 1992.
26. Lee, J. S.; Scott, C.; Komaki, R.; Fossella, F.; Dundas, G. S.; McDonald, S.; Palmer, M.; Curran, W. J.; Byhardt, R. W. Concurrent chemoradiation therapy with oral VP-16 and cisplatin for locally advanced inoperable nonsmall cell lung cancer (NSCLC): RTOG Protocol 91–06. (abstr). Proc. Am. Soc. Clin. Oncol. 13:363; 1994.
27. Marcial, V. Unconventional time-dose-fractionation in radiotherapy of cancer. In: Moore, M., ed. Advances in Medical Oncology Research and Education. New York: Raven Press; 1979:265–266.
28. McDonald, S.; Chang, A. Y.; Rubin, P.; Wallenberg, J.; Kim, I. S.; Sobel, S.; Smith, J.; King, P.; Muhs, A. Combined betaseron R (recombinant human interferon beta) and radiation for inoperable nonsmall cell lung cancer. Int. J. Radiat. Oncol. Biol. Phys. 27:63–69; 1993.
29. Nelson, D. F.; Curran, W. J.; Scott, C.; Nelson, J. S.; Weinstein, A. S.; Ahmad, K.; Constine, L. S.; Murray, K.; Powlis, W. D.; Mohiuddin, M.; Fischbach, J. Hyperfractionated radiation therapy and bischlorethyl nitrosouria in the treatment of malignant glioma—Possible advantage observed at 72.0 Gy in 1.2 by bid fractions: Report of RTOG Protocol 8302. Int. J. Radiat. Oncol. Biol. Phys. 25:193–207; 1993.
30. Nickson, J. J. Hodgkin's disease clinical trial. Cancer Res. 26:1279–1283; 1966.
31. Paterson, R. Clinical trials in malignant disease. I. Principles of random selection. J. Faculty Radiol. 9:80–83; 1958.
32. Paterson, F; Russell, M. H. Clinical trials in malignant disease. III. Breast cancer: Evaluation of postoperative radiotherapy. J. Faculty Radiol. 10:175–180; 1960.
33. Perez, C. A.; Pajak, T. F.; Stanley, K.; Rubin, P.; Simpson, J. R.; Mohiuddin, M.; Brady, L.; Perez-Tamayo, R.; Rotman, M. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy: Report by the Radiation Therapy Oncology Group. Cancer 59:1874–1881; 1987.
34. Pilepich, M. V.; Krall, J.; Al-Sarraf, M.; Roach, III, M.; Doggett, R. L. S.; Sause, W.; Lawton, C. A.; Abrams, R. A.; Rotman, M.; Rubin, P.; Shipley, W. U.; Cox, J. D. A Phase III trial of androgen suppression before and during radiation therapy (RT) for locally advanced prostatic carcinoma: Preliminary report of RTOG Protocol 86-10. Urology 45:616–623; 1995.
35. Rubin, P.; Hanley, J.; Keys, H.; Marcial, V.; Brady, L. Carbogen breathing during radiation therapy. The Radiation Therapy Oncology Group Study. Int. J. Radiat. Oncol. Biol. Phys. 15:1337–1346; 1988.
36. Sause, W. T.; Scott, C.; Taylor, S.; Byhardt, R. W.; Banker, F. L.; Thomson, J. W.; Jones, T. K.; Cooper, J. S.; Lindberg, R. D. Phase II trial of combination chemotherapy and irradiation in nonsmall cell lung cancer, Radiation Therapy Oncology Group 88-04. Am. J. Clin. Oncol. 15:163–167; 1992.
37. Sause, W.; Scott, C.; Taylor, S.; Johnson, D.; Livingston, R.; Komaki, R.; Emami, B.; Curran, W.; Byhardt, R.; Fisher, B.; Turrisi, A. RTOG 88-08 ECOG 4588; Preliminary analysis of a Phase III trail in regionally advanced unresectable nonsmall cell lung cancer. (abstr). Proc. Am. Soc. Clin. Oncol. 13:325; 1994.
38. Schaake-Koning, C.; van den Bogairt, W.; Dalesio, O.; Festen, J.; Hoogenhout, J,; van Houtte, P.; Kirkpatrick, A.; Koolen, M.; Maat, B.; Nijs, A. Effects of concomitant cisplatin and radiotherapy on inoperable nonsmall cell lung cancer. N. Engl. J. Med. 326:524–530; 1992.
39. Snow, J. B.; Kramer, S.; Marcial, V. A.; Gelber, R.; Davis, R. D.; Lowry, L. W.; Lowry, R. D. Evaluation of randomized preoperative and postoperative radiation therapy for supraglottic carcinoma. Ann. Otolaryngol. Rhinol. Laryngol. 87:686–691; 1978.
40. Sperry, K. Informed consent: Ninety years of debate. RTOG Report, May–June; 1994.
41. Suntharalingam, N.; Johansson, K. A. Quality assurance/physics/dosimetry. Int. J. Radiat. Oncol. Biol. Phys. 14:S21–S24; 1988.
42. Tong, D.; Gillick, L.; Hendrickson, F. The palliation of symptomatic osseous metastases. Cancer 50:893–899; 1982.
43. Wallner, P. E.; Lustig, R. A.; Pajak, T. F.; Robinson, G.; Davis, L. W.; Perez, C. A.; Seydel, H. G.; Marcial, V. A.; Laramore, G. E. Impact of initial quality control review on study outcome in lung and head/neck cancer studies—Review of the Radiation Therapy Oncology Group experience. Int. J. Radiat. Oncol. Biol. Phys. 17:893–900; 1989.

APPENDIX I

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APPENDIX II

Radiation Therapy Oncology Group Steering Committee

Group Chair:	James D. Cox, M.D.	Vice Chair for Publications:	Jay S. Cooper, M.D.
Deputy Chair:	Walter J. Curran, M.D.	Vice Chair for Membership:	William T. Sause, M.D.
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