

The Road Not Taken and Choices in Radiation Oncology

C. NORMAN COLEMAN,^a ELI GLATSTEIN^b

^aRadiation Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland, USA; ^bDepartment of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

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ABSTRACT

Accomplishments and contributions in a career in radiation oncology, and in medicine in general, involve individual choices that impact the direction of a specialty, decisions in patient care, consequences of treatment outcome, and personal satisfaction. Issues in radiation oncology include: the development and implementation of new radiation treatment technology; the use of multimodality and biologically based therapies; the role of nonradiation “energy” technologies, often by other medical specialties, including the need for quality assurance in treatment and data reporting; and the type of evidence, including appropriate study design, analysis, and rigorous long-term follow-up, that is sought before widespread implementation of a new treatment. Personal choices must

weigh: the pressure from institutions—practices, departments, universities, and hospitals; the need to serve society and the underserved; the balance between individual reward and a greater mission; and the critical role of personal values and integrity, often requiring difficult and “life-defining” decisions. The impact that each of us makes in a career is perhaps more a result of character than of the specific details enumerated on one’s curriculum vitae. The individual tapestry weaved by choosing the more or less traveled paths during a career results in many pathways that would be called success; however, the one path for which there is no good alternative is that of living and acting with integrity. *The Oncologist* 2010;15:332–337

The Road Not Taken

—Robert Frost, 1874–1963

Two roads diverged in a yellow wood
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,

Correspondence: C. Norman Coleman, M.D., Radiation Research Program, 6130 Executive Boulevard, Bethesda, Maryland 20892, USA. Telephone: 301-496-6111; Fax: 301-480-5785; e-mail: ccoleman@mail.nih.gov Received November 17, 2008; accepted for publication March 3, 2009; available online without subscription through the open access option. ©AlphaMed Press 1083-7159/2010/\$30.00/0 doi: 10.1634/theoncologist.2009-S102

And both that morning equally lay
 In leaves no step had trodden black.
 Oh, I kept the first for another day!
 Yet knowing how way leads on to way,
 I doubted if I should ever come back.

I shall be telling this with a sigh
 Somewhere ages and ages hence:
 Two roads diverged in a wood, and I—
 I took the one less traveled by,
 And that has made all the difference

INTRODUCTION

The occasion of this translational research conference included the celebration of one of the author's (E.G.) 70th birthday and a tour of the new University of Pennsylvania proton treatment facility in the Perelman Center for Advanced Medicine. The American Society for Radiation Oncology (ASTRO) also celebrated its 50th birthday this year, so this is a good time to think of where we—as individuals and as the radiation oncology aggregate—are and where we are going in the world of medicine. Medicine in general and oncology in particular are facing historic opportunities and challenges with molecular and personalized medicine, a wealth of new technologies for imaging and treatment, health care costs rising in the face of a struggling economy, and many people in the U.S. who are un- or underinsured on top of the many people worldwide living with minimal to no effective cancer care. The Robert Frost poem above provides a thoughtful framework with which to look back at the five decades of radiation oncology and consider how one's choices and decisions influence how a career is pursued and how a professional life is lived.

Which road does one choose? The one more or less traveled? Is it possible to travel both of them, at least in part? How will lessons learned on one be applied farther down the road? Is the "sigh" one of relief or regret for having taken the road less traveled? And, how does one's choice and pursuit of a career "make all the difference"?

In this paper we consider career paths and choices for our specialty that we (C.N.C. and E.G.) have seen and experienced using examples from segments of our careers in common at Stanford University and the National Cancer Institute, and from 35 years of being colleagues in radiation oncology. There are, of course, many examples one could use and no doubt each reader will have their own experiences to consider.

In Figure 1, The paths we choose. . . , there are three sets of paths for radiation oncology: (a) radiation and systemic therapy, including chemotherapy and biological-based therapy; (b) technology and clinical science, including how we as a field decide on what technology to use; and (c) motivation and legacy—what drives our professional lives and how decisions now will determine the view of our careers and contributions when looking back years or decades hence.

RADIATION AND SYSTEMIC THERAPY (BLACK)

Perhaps surprisingly to most oncologists, it was not so many years ago that the ability for people to tolerate a tumoricidal radiation dose was doubted and, in fact, considered dangerous! Henry Kaplan, a teacher and mentor to both of us, demonstrated in Hodgkin's disease that large fields could be treated to high doses, and cures were seen in patients with limited stage disease. His work, and that of Vera Peters, was a watershed in radiation oncology. Moving forward with higher doses and bigger fields, however, radiation was shown to have its limits with more extensive stages of disease, so that the composite lessons were that one must achieve the necessary radiation dose to kill both gross and microscopic disease but the biology of the disease and its propensity to metastasize/spread, probably more than radiation toxicity, put a limit on very extensive field radiotherapy.

While still remaining aligned with diagnostic imaging and nuclear medicine, radiation oncology had become a separate specialty by the late 1960s, with early leaders focusing on technology development, patterns of disease spread, and cellular and tissue radiation biology. Radiation oncologists administered systemic therapy as well, a practice still prevalent in many countries. Thus, combined modality therapy (CMT) arose from radiation oncology, with the Radiation Therapy Oncology Group (RTOG) doing some of the groundbreaking work. The specialty of medical oncology was established about 35 years ago, and medical and radiation oncology may be viewed variably over the years as competitive, complementary, and collaborative. Drs. Kaplan and Rosenberg [1] and Stanford colleagues studied how to optimize drugs and radiation together. Using both Hodgkin's disease and the non-Hodgkin's lymphomas, they conducted a pioneering series of randomized trials that demonstrated the benefits of the optimal use of radiation in conjunction with combination chemotherapy, and subsequent studies by many research groups have continued to refine and tailor Hodgkin's treatment. Indeed, the issue for Hodgkin's disease once was "should treatment be radiation or CMT?" And now chemotherapy alone has emerged as a legitimate option. As an example of how an approach from the past can be relevant in the future, the "low-dose" radiation approach advocated by the very conservative radiologists 50 years ago is now a key supplemen-

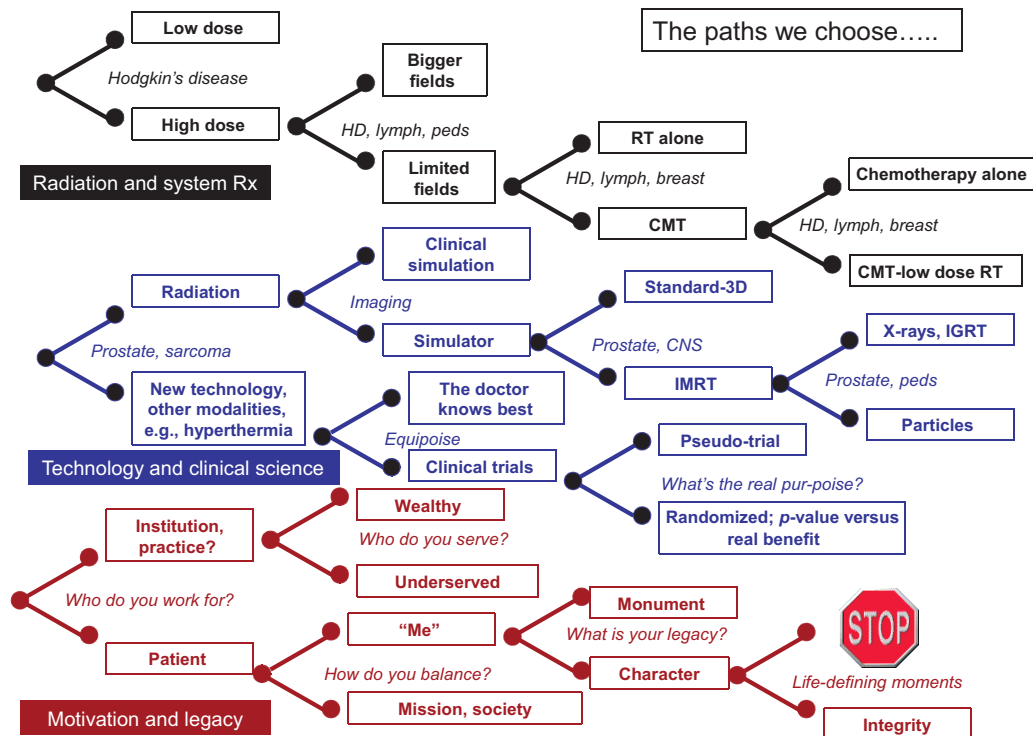


Figure 1. The paths we choose. There are numerous choices that have shaped where radiation oncology has been and where it is going. These involve: (a) radiation and systemic therapy—radiation fields and doses, and radiation modifiers, which include chemotherapy, immunotherapy and radiation sensitizers, protectors, and personalized medicine; (b) technology and clinical science—new technology involving radiation, other forms of energy, and the conduct of rigorous clinical trials to assess the new treatments; and (c) motivation and legacy—the professional and personal decisions that define who we are and what we truly accomplish. Careers are a tapestry of these various choices and pathways. In our long view, one path has no good alternative and that is the path of living with integrity.

Abbreviations: 3D, three-dimensional; CMT, combined modality therapy; CNS, central nervous system; HD, Hodgkin's disease; IGRT, image-guided radiation therapy; IMRT, intensity-modulated radiation therapy; peds, pediatrics; RT, radiotherapy; Rx, therapy.

tary ingredient to combined modality regimens that are primarily chemotherapy based.

Where are we now with regard to radiation and systemic therapy?

CMT

For most solid tumors, CMT is the only thing that has been shown to improve the survival time following surgery. Based on the fast pace of scientific developments and rapid growth in the armamentarium of new agents and innovative radiation therapy fractionation, it is necessary to complete clinical trials in a timely manner for new knowledge to reach broad clinical application.

Empiricism Versus “Science”

Translating laboratory findings to the clinic is not an easy gap to cross and requires that one test, not prove, hypotheses (“Test it, don’t tout it!”—E.G.). What works in the controlled environment of the lab, often with doses and schedules much different than are useable in patients [2], is

often not successful in the clinic, or ends up working by very different mechanisms. An example is the epidermal growth factor receptor (EGFR) inhibitor story, in which the efficacy of the inhibitor was not a result of EGFR overexpression, as initially postulated, but rather a result of specific *EGFR* mutations in lung cancer and *KRAS* mutations in colon cancer.

Radiation Biology

Classic versus modern is not a correct classification or distinction. Classic is a misnomer in that the tools and findings of “nonmolecular” research are essential to molecular biology applications, with the word “classic” too often used pejoratively. Examples include understanding the effects of molecular interventions on radiobiology assays of cell survival, DNA repair, cell cycle perturbation, and drug–radiation interaction.

Although animal models remain to be optimized for tumor-related studies, normal tissue radiation and combined

modality mechanism studies are relevant to the design of clinical trials.

Preclinical animal and cell/tissue biology studies are useful in the design of phase I and phase II CMT trials and to examine potential biomarkers for radiation and treatment effects.

Radiation and Drugs—Two Sides of the Same Coin?

Both radiation and drugs produce molecular events, with radiation being able to focus its effects in time and space (“focused biology” [3]). By using the local effects of radiation, it may be possible to enhance immunotherapy or the efficacy of chemotherapy. In that radiation can be physically targeted, depending on the biological effect desired, the cumulative radiation dose can be varied by a factor of 100 or more (10 cGy to 1,000 cGy for single-dose therapy and up to 8,000 cGy with fractionation).

TECHNOLOGY AND CLINICAL SCIENCE (BLUE)

In the second series of paths, we first consider the upper path of radiation. The requirement to use formal simulation rather than clinical setups—which was debated not as long ago as one might imagine—has led to the increasing use of imaging in radiation therapy. Clinical simulation did require a thorough understanding of the anatomical spread of tumors. Computed tomography scanning came on the scene, allowing the development of three-dimensional conformal therapy. Further development of computer technology has enabled the development of intensity-modulated radiation therapy and image-guided radiation therapy. The ability to deliver radiation with precision has led to exciting new possibilities with external-beam x-ray therapy, brachytherapy, and particle therapy with protons in the U.S. and also with carbon ions internationally.

Use of other forms of energy to treat tumors in the lower part of the “technology and clinical science” pathway has been available for three decades, starting with hyperthermia and now involving focused ultrasound, radiofrequency ablation, photodynamic therapy, and cryotherapy. An overarching theme has been the discordance between the picture of a treatment (isodose, isotherm, isoenergetic line) on a computer screen and the ability to actually deliver that treatment. All modalities are limited by target definition and by the limits of the physics and biology of imaging. Radiation is limited by inter- and intrafraction motion; hyperthermia and focused ultrasound are limited by tissue boundaries and tissue heterogeneity and by the ability of the body to dissipate heat; and cryotherapy is limited by the ability to define the boundary of the tumor and the actual physical ablation of normal tissue that is produced. These energy modalities

are occasionally used in combination, and more and more one modality is used to salvage failure by another.

Key lessons learned and learned again with these other energies are: (a) the need to define and standardize the parameters of the treatment, including the dose delivery and margin; (b) that isodoses are different for radiation than for other forms of energy that are dissipated physiologically; (c) the importance of fastidious quality assurance so a treatment in one facility can be related to treatment in another (or even another treatment in the same facility); and (d) the need for some skepticism in interpreting tumor location based on imaging. Radiation oncology has been a leader in setting standards for the clinical use of complex technology, including the RTOG, Quality Assurance Review Center [4], and Advanced Technology Consortium [5]. It is imperative that those using other forms of energy make the effort to develop and apply standards of treatment delivery and quality assurance as is done in radiation oncology.

How do physicians choose what they recommend for treatment to patients under their care (lower blue path in Fig. 1)? Perhaps one of the most challenging arguments to overcome is the acceptance of a condition of equipoise so that clinical trials are conducted before a treatment is adapted [6]. Patients are not entered in clinical trials for a variety of reasons, often eligibility criteria; however, there are those who argue that equipoise is hard (or impossible) to achieve in that the physician always “knows best.” Following that logic, randomized clinical trials are not appropriate or are even unethical. A few recent examples [7] of randomized trials for which there was considerable physician disapproval and “conventional wisdom” bias/preference for one of the treatment arms, but which turned out to not support the preference, include bone marrow transplantation for advanced breast cancer, the general use of erythropoietin in cancer patients with anemia, and the use of endovascular brachytherapy for preventing coronary artery restenosis.

For radiation oncology, the ongoing debate as to the necessity for conducting randomized trials to determine the appropriate use of proton therapy [8] is an example in which the attractive theoretical advantage (isodose on a computer screen) is a persuasive argument to some that the newer treatment is better. (Similar arguments are made for other novel radiation technologies.) Such isodose pictures do not capture concepts such as integral dose, target motion, and “marginal miss,” or the risk for radiation-induced injury or malignancy. Often single-arm and registry trials are done in place of a randomized trial, which might be the only option for rare diseases. So, at the end of the lower path in the blue section, the question may arise as to whether the purpose of the trial is to “prove” a point or test a hypothesis. Science

requires that a hypothesis be tested in a well-designed trial. A series of observations that support a preference may be interesting but are by no means proof. It seems wisest to take on the hard questions in a proper trial before widespread and possibly inappropriate implementation, and to use sensible and clinically meaningful criteria for success. A *p*-value alone may make a trial statistically significant, but the change in treatment indicated by the trial needs to be an important benefit to the patient. There are a number of recent examples of U.S. Food and Drug Administration drug approvals for differences in survival of only a few weeks [9] that have raised this issue of a statistically versus clinically meaningful result—even more concerning if the treatment comes with toxicity and great expense.

MOTIVATION AND MISSION (RED)

The final path in Figure 1 defines who and what we are. We all work for some organization or other and there are pressures to meet the goals of the institution—financial, academic, practice building, market share—that may come in conflict with what is best for the patient. The institution may serve only a sector of society, a decision that may be determined by the demographics but also by purposeful decisions of what care to provide for the underinsured. The growing number of un- and underinsured (health disparities populations) will place additional financial burden on institutions and may bring a physician in conflict with a moral obligation of service.

We all seek and need some measure of personal reward. There are the tough decisions as to what one does for one's own needs—financial, family, fame—and what one does in the service of others. Service and mission do not preclude personal benefit. From our years of observation and experience, we believe that mission to society is far more rewarding than self-interest in both the short and long term. Opportunities for service activities as part of a career are limited, and time spent in truly altruistic endeavors may even be detrimental to an academic career, sad to say.

To help provide opportunities for societal contribution, the Radiation Research Program at the National Cancer Institute (NCI) has helped develop: (a) the Cancer Disparities Research Partnership program [10], to provide opportunities for the underserved to participate in NCI clinical trials; (b) programs with the Office of the Assistant Secretary for Preparedness and Response, for radiation experts to work in terrorism and mass casualty preparedness for the country and their community [11]; and (c) the Cancer Expert Corps, a peace corps for cancer [12], which is being launched and, if successful, will provide an opportunity for experts to mentor those working in underserved areas worldwide. The goal is to raise financial support for people's time in a man-

ner analogous to a research contract or grant so that this mentoring and altruism is a predictable and sustainable part of a career and not an add-on during vacations. It would enable the establishment of important person-to-person relationships and a growing network of centers that could conduct protocol-based care and research worldwide, thereby bringing excellent stage- and resource-appropriate care to those who have little to no care available to them.

The final issue of this mission and motivation section is “what does define ‘me’?” Although having tangible rewards and recognition are of value, in our unabashed opinion, what is most important is character. The recent ASTRO 50th birthday celebration [13] was an excellent reminder of how it is the *character* of the leadership that we remember more than the specific contributions. The three initial gold medal winners are outstanding examples: Drs. DelRegato, Fletcher, and Kaplan. Although our individual accomplishments have an impact, as time goes by, it is our character and how we go about our daily life that defines each and every one of us [14].

Up to now on “the paths we choose...” one could possibly take one path or the other, even wandering back to the path left behind. Paths part but again intersect and one can weave one's own tapestry of interests and pursuits in the course of a career. At times, the path less traveled may be preferable (e.g., doing the rigorous studies before introducing a new treatment as “standard”) and at times the path less traveled may not be preferable (e.g., jumping on a bandwagon for an as yet unproven treatment in order to gain market share). What drives each and every one of us to truly make the best choice is based on individual character that on occasion leads us to decisions beyond the path of least resistance or one of group-think. It is at this last junction on this diagram that there is but one successful choice. Interestingly, the decision to live and act with integrity or not may come up when it is least expected. It may be in a visible situation during the resolution of a major issue or it may be a quiet one where the choice is to: (a) properly guide a patient for their best interest, which may mean sending them elsewhere for treatment or recommending against treatment; (b) prevent or at least hamper an institution from doing an immoral or devious action; (c) put principle ahead of profit; or (d) simply lend a quiet or anonymous hand to a situation in which only you would notice. Certainly, situations can be ambiguous, although often rationalization and a bit of self- or group delusion can obscure doing what is right.

So, the final step in the path is profound. These “life-defining moments” not only determine how you view yourself and others view you, but they allow you to *make the difference* so that when you look back on your path and

choices you will be satisfied and have a good measure of inner peace that some never seem to obtain.

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AUTHOR CONTRIBUTIONS

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