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PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: REVIEW ARTICLE

Normal tissue damage: its importance, history and challenges for the future

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ABSTRACT

Sir Oliver Scott, a philanthropist and radiation biologist and, therefore, the epitome of a gentleman and a scholar, was an early Director of the BECC Radiobiology Research Unit at Mount Vernon. His tenure preceded that of Jack Fowler, with both contributing to basic, translational and clinical thought and application in radiation across the globe. With respect to this review, Fowler's name in particular has remained synonymous with the use of models, both animal and mathematical, that assess and quantify the biological mechanisms that underlie radiation-associated normal tissue toxicities. An understanding of these effects is critical to the optimal use of radiation therapy in the clinic; however, the role that basic sciences play in clinical practice has been undergoing considerable change in recent years, particularly in the USA, where there has been a growing emphasis on engineering and imaging to improve radiation delivery, with empirical observations of clinical outcome taking the place of models underpinned by evidence from basic science experiments. In honour of Scott and Fowler's work, we have taken this opportunity to review how our respective fields of radiation biology and radiation physics have intertwined over the years, affecting the clinical use of radiation with respect to normal tissue outcomes. We discuss the past and current achievements, with the hope of encouraging a revived interest in physics and biology as they relate to radiation oncology practice, since, like Scott and Fowler, we share the goal of improving the future outlook for cancer patients.

PRESERVING NORMAL TISSUE THROUGH FRACTIONATION—A BRIEF HISTORY

The history of using fractionation as a regimen for delivering radiation dates back almost to its discovery in 1895. Although the use of X-irradiation as a treatment for cancer was begun within months of Roentgen's announcement,[1] there was an almost equally fast appreciation of the profound detrimental effects that radiation can induce in involved normal tissues, leading to attempts to reduce this toxicity by spreading its administration over a more prolonged period of time.[2] However, the seemingly more pressing goal of curing cancer led radiation practitioners to wage a philosophical and internecine war over the relative superiority of using multiple *vs* a few or single fractions. This battle continued until the 1930s, when the presentation of empirical clinical findings by Coutard demonstrated the benefits in normal tissues of, what was then termed, "protracted fractionation",[3] with these revelations leading to an almost global move away from the use of large fractions. Ultimately, the combination of radiation's cytotoxic effects in tumors, together with the improved normal tissue safety, has led radiation oncologists to provide treatment to millions of cancer patients, with approximately 50% of cases now receiving irradiation at some point during their therapy.[4]

However, conventional fractionation regimens fail to completely eliminate the risk of normal tissue effects, which can span in levels of detriment from non-lethal end points, such as skin erythema and cognitive dysfunction, to potentially morbid diseases, such as radiation pneumonitis and radiogenic secondary malignant tumors. Acceptance of the risk for some level of normal tissue toxicity is seen when radiation oncologists use the concept of the "therapeutic ratio," which balances the probabilities of tumor cure against normal tissue injury to guide treatment designs. Interestingly, despite the cumulative and overwhelming volume of evidence in favor of conventional fractionation, there has been a persistent effort by some clinicians to minimize the number of delivered fractions, albeit while maintaining the

tumoricidal outcome. Thus, in the late 1950s, we saw a physicist, Larsson, working in collaboration with a neurosurgeon, Leksell, develop the first gamma knife.[5] This technology heralded the re-emergence of hypofractionation, with even greater interest being seen in the 1990s when Brenner and Hall, physicists from Columbia University, published their analysis of observational findings from prostate trials, suggesting that the α/ß ratio for prostate tumors was not the high dose normally associated with a radiation-responsive tumor.[6] When this announcement was quickly followed by supportive observations from pre-START breast trials,[7] radiation researchers were urged to find a biological justification for the use of hypofractionation.

NORMAL TISSUE DAMAGE MODELS—BIOLOGICAL AND MATHEMATICAL

Surprisingly, the performance of supportive scientific studies has consistently lagged behind the clinical implementation of novel irradiation dose and timing regimens. Prior to the 1960s, few animal studies were performed using multifraction regimens other than the early French studies performed by Regaud and Ferroux on ram and rabbit testes,[8] which were described in Hall's classic textbook,[9] a canon for radiation oncology residents in the USA. Nonetheless, those that were undertaken confirmed the utility of fractionation as a means of sparing normal tissues from late, though not early, toxicities.[10,11] However, during the 1960s, *in vitro* and *in vivo* laboratory techniques began to catch up with the clinical empirical observations. Radiation researchers, often working hand-in-hand with radiation oncology physician–scientists, became increasingly focused on deciphering the biological effects of radiation at the cellular and subcellular levels—not only in terms of cell death, but also with respect to repair mechanisms. Indeed, Fowler and his Gray Lab Research Group developed multiple *in vivo* models that were used to assess the radiation response in normal tissues, including a meticulous skin reaction system used in pigs and mice,[12–19] as well as rodent models assessing responses in lung,[20,21] kidney,[22] bladder[23–25] and the gastrointestinal tract.[26,27] These studies were performed using single, split and multifraction doses, and the derived data from this group and others were used to develop various mathematical constructs[11] that could potentially predict biological isoeffective responses in normal tissues and, therefore, provide a scientific justification for both conventional and altered clinical fractionation schedules.

It is important to note that the final solution of most, if not all, of these concepts is predicated on cell death as the major variable of interest, since that is the desired end point in tumors. Interestingly, although Fowler et al had proposed the linear–quadratic (LQ) model in the 1960s,[28,29] it was not until the 1980s, when Withers et al replotted isoeffect data using dose per fraction and demonstrated a differential between the response curves of acutely *vs* late responding normal tissues,[30,31] that it became clear that tissues that consist of predominantly slowly proliferating tissues, such as brain,[32,33] were more sensitive to changes in fraction size. Thus, the accumulation of biological data, clinical observations and mathematical modeling finally led to a full appreciation and scientific recognition that fractionated irradiation was, indeed, a means of sparing critical late tissues.

The formulae that were derived throughout this period, *e.g.* the LQ equation, Ellis' nominal standard dose,[34] and Barendsen's extrapolated tolerance dose,[35] introduced the radiation world to terminology that, in essence, constrained the physical process of DNA damage and, by inference, its biological repair within arbitrarily applied mathematical constants, including α and ß. They also established such terms as n, the extrapolation number, which suggested the apparent necessity for a critical number of hits within each cell, and D_0, the rate of cell loss per Gy. As a result, since the late 1980s, radiation scientists and clinicians alike have worked under the overarching concept of early and late responding tissues, with, in many cases, the dose thresholds for late tissue complications defining clinical organ tolerance and, therefore, radiation treatment design.[36] The formulae were, in general, developed from findings made either *in vitro* or in the limited number of highly characterized animal models developed by Fowler and his peers, and then confirmed through clinical empirical observation. But in practical terms, the mathematical concepts provided clinicians with a means of quantifying and, therefore, predicting outcomes from fractionation schedules, particularly through the use of the LQ formulation popularized by Fowler and his peers. Indeed, Fowler elegantly described the necessary calculations needed to design a successful "altered fractionation" schema through the combined use of an estimation of tumor biological effective dose (BED), a late complications BED and an acute normal tissue BED, making up what he described as the "Seven Steps to LQ Heaven".[37]

However, despite the availability of these mathematical tools and the accompanying and significant improvements made by radiation physicists in therapeutic delivery, problems with radiation-associated normal tissue effects continue to be seen in patients. Importantly, the overall increases seen in many tumor control rates has led to growing populations of cancer survivors, so that acute and, even more importantly, late toxicities that appear in normal tissues have started to take on greater importance. Long-term issues, such as cognitive dysfunction, cardiovascular disease, immune disruption, tissue remodeling, metabolic disorders and second malignant tumors, continue to haunt cancer survivors long after treatment has discontinued,[38–47] especially those treated at a younger age.[48–57] Unfortunately, with the majority of radiation-induced late outcomes, once such effects become symptomatic, mitigation and/or treatment strategies have proven to have limited efficacy. As a result, radiation oncologists have continued to explore treatment options, *e.g.* through the use of altered fractionation strategies, such as hypofractionation, with some promising results in terms of equivalent or reduced normal tissue toxicities compared to conventional fractionation outcomes seen in trials for brain, breast and prostate cancers.[58–60] But application of Fowler's "Seven Steps" to the described regimens would suggest that these findings are anomalous, bordering on the unbelievable, with respect to the reported low levels of normal tissue effects.

So, what is happening? Are the physicists and engineers truly providing radiation oncologists with the means of significantly reducing normal tissue damage? The use of image-guided and intensity modulated therapies has undoubtedly increased

the focus of imposed radiation damage within the intended target, the tumor, however, in many cases, using these newer approaches has come at the cost of increased exposure of normal tissues, albeit at a low dose. In fact, the patient's whole body can be bathed in low levels of unwanted stray radiation (about one 1/1000th of the therapeutic dose) that emanate as leakage from the treatment unit and scatter from the tumor. Given the time that it takes many late effects to become manifest, it remains currently unclear whether this low-dose "bath" is simply leading to a delay in toxicity onset, with unforeseen effects lurking over the horizon. Therefore, do radiation biologists have either the wherewithal or resources to provide a greater understanding of both tumor and normal tissue kinetics following radiation injury in the context of current clinical practice? And is such work needed in order to guide further innovation by the radiation physicists and, once more, provide clinicians with rational and scientific approaches in their search for more effective treatment paradigms?

NORMAL TISSUE TOXICITY FROM THE RADIATION PHYSICIST'S PERSPECTIVE

The successes that have been derived from radiation physics are readily seen in the clinic in terms of improved tumor outcomes and a reduction in normal tissue reactions. Indeed, physicists have provided the means to deliver therapeutic radiation with millimeter accuracy, thereby reducing normal tissue exposures through improvements in treatment delivery and planning. However, conspicuous challenges remain, especially with respect to radiation-induced toxicities in normal tissues. The prevalence and diversity of late effects in normal tissues are evident from numerous epidemiology studies of patients who have received radiotherapy.[61–63] Despite this overwhelming evidence implicating radiation exposure as one of the primary risks associated with therapy-related late effects, we do not yet routinely calculate, estimate, measure, or report most normal tissue exposures, even though, from a technical perspective, routine calculations now appear feasible. Indeed, despite enormous sums of money being spent on equipment for normal tissue dose reduction, the medical record of a typical radiotherapy patient is devoid of reliable out-of-field exposure data.

How did this situation come to be? Interestingly, we find analogies in military theory. Perusing the respective literatures reveals the use of similar terminologies: we speak of the "war" on cancer, precision interventions, surgical strikes, targets, and collateral damage. Indeed, the similarities in approaches between the wars waged on cancers and on sovereign states are profound. In his book entitled "The Art of War",[64] Sun Tzu, a soldier and scholar of ancient China, laid out the basic principles of war. Although Tzu's preferred strategy was prevention, when facing lethal threats where prevention was not feasible, he recommended using just enough force to accomplish the objective, thereby limiting collateral damage to the minimum possible amount, believing that this usually leads to a superior strategic outcome. Today, our military and cancer armamentaria are arbitrarily lethal, so that their application should require a greater consideration of their potential to cause collateral damage. However, now, as in ancient times, the neutralization of threats garners more attention than the prevention of collateral damage, creating an imbalance in the therapeutic ratio.

The logic of this argument is strong and compelling for both kinds of "war". In both endeavors, the instinctual response clearly favors action leading to survival of the most immediate existential threat. Furthermore, procurement of any type of expensive equipment requires significant financial backing and, therefore, justification is usually based on positive arguments (*e.g.* suitability for purpose; potential for success) and not on negative detractors (*e.g.* uncertain outcomes; collateral consequences). Psychologically, we also are more prone to focus on our own beneficence (*e.g.* saving someone from certain death) rather than on some vague risk of the unintended harm our actions may cause decades hence. Taken together, it could be argued that that these reasons comprise a solid rationale to continue focusing most of our attention on controlling primary cancers. However, to do so would be wrong, since this ignores the long history of treatment advancement made through the collaborative efforts of radiation physicists, oncologists and biologists. Perhaps, the most practical and compelling reason to increase research on late effects is that it will almost certainly lead to better outcomes for long-term survivors, *i.e.* fewer and less severe side effects from radiation therapy. Another reason is the burgeoning population of long-term cancer survivors, a population projected to swell to 18.1 million in the USA by 2020, a 30% increase since 2010.[65] Already, for some types of childhood cancer, second cancers cause more deaths than primary tumors,[66] with effects such as cognitive deficits,[67,68] cardiovascular disease[69,70] and skeletal abnormalities[71–73] causing profound and permanent detriments, limiting not only quality of life, but leading to long-term employment, insurance and care issues.[74] Thus, even at the financial level, economists would point out that a reduction in the prevalence of late effects would reduce healthcare costs. Notwithstanding, ethical and, perhaps, even legal arguments could be made that healthcare practitioners have a duty of care to avoid any needless exposure of healthy tissues.

A first step toward avoiding such exposures is to understand the prevalence and risk of poor outcomes.[75] Quantification requires more research in the form of long-term clinical trials with normal tissue effects as a primary end point;[76] unfortunately, even ignoring the low probability of such trials, the inherent delay in patient presentation of late toxicities means that it will be a long time, perhaps decades, before the results of such studies could be accumulated and analyzed with statistical certainly. Until then, it appears necessary to formulate parallel approaches, by expanding the scope of radiation treatment planning to include an assessment of risk of late effects. Currently, these risks are not routinely determined, mainly because radiation exposures to most of the normal tissues outside the treatment region are rarely calculated and recorded. Specifically, clinical treatment planning systems do not accurately calculate exposure, if at all, outside the high-dose "irradiated volume", where, indeed, the vast majority of second cancers ultimately appear.[77,78] New models and algorithms for such calculations are being developed.[79–81] Importantly, the prospective adoption of such capabilities at only a few major cancer centers would dramatically accelerate collection

of the high-quality dosimetry data that is needed to improve current radiation risk models.

Despite the projections for impact on cancer survivors suggesting that the duty of care should increasingly attend to managing risks of collateral damage, scientifically, the routine assessment of exposure and risk are conspicuous by their absence. Prior to the early 2010's, one could reasonably argue that the lack of this capability was justified by a combination of factors: modeling radiation exposures was difficult; stray exposures are deemed clinically insignificant; and the uncertainties in predicted outcomes are excessive. However, since that time, the ability to routinely assess exposures has become eminently more feasible for advanced technology radiotherapies,[80] including proton- and photon-beam treatments and, indeed, has been implemented in non-clinical treatment planning systems. Although the uncertainties in predicting risks of a late effect for an individual patient remain relatively large, especially when the exposure includes neutrons, several studies now have shown that these uncertainties are manageable for comparing risks to the same patient from multiple candidate treatments.[82]

In the broader context, the realm of normal tissue risk assessment has expanded rapidly in the past decade. The basic physics needed for exposure assessment is, for all intents and purposes, fully understood. However, much work is still needed to refine, generalize, and translate exposure models, as well as to integrate all of the necessary attending technologies (*e.g.* integration into the electronic medical record).[83] Of the open scientific questions in this field, those in radiation physics will likely be answered sooner and more fully, necessarily so, since they are needed in order to characterize the physical parameters found in radiation biology and epidemiology studies, which are the more difficult and lengthy in nature. However, it remains to be seen if the radiation research and medical communities will revise their agendas to deal effectively with the increasing prevalence of radiation late effects. Indeed, history suggests that the significant progress that is needed to reduce collateral damage will be slow and difficult.

NORMAL TISSUE TOXICITY FROM THE RADIATION BIOLOGIST'S PERSPECTIVE

Radiation biologists (and biophysicists, such as Fowler) have contributed to the successes seen by their physics and clinical counterparts, by enabling a greater understanding of the biological effects of treatment parameters, such as dose and fractionation. However, as with the physicists, the biologists have failed in their goal to fully realize the beneficial potential of radiotherapy by focusing predominantly on deciphering the effects of radiation on tumors. As a consequence, our understanding of the effects of radiation treatment parameters on normal tissues continues to lag behind. It must be acknowledged that there have been chronic and significant limitations placed on bench scientists in this field.[84,85] For example, the majority of *in vivo* studies make use of single doses—partly due to time (funding) constraints and the need to establish a robust end point—limiting the clinical relevance of their findings. Nonetheless, many funding agencies have shown little interest in covering the inherently more expensive fractionation studies, given the long periods of animal housing and care that are required and limited number of institutions that were capable and/or willing to provide the necessary radiation facilities for such work.[37]

But another, possibly related, factor that may now be curtailing the application of radiation biology to the clinic is the increased insular mentality of its practitioners. As Fowler freely acknowledged, his work over the decades built on that of his predecessors and peers.[37] However, nowadays, the competition for limited funding has led many laboratories to work in isolation, resulting in a loss of momentum and progress in normal tissue research. Indeed, the majority of work currently being performed in this field makes use of the same biological and mathematical models developed in the 1980s and 1990s. This is despite recurring national and international discussions as to the relevance of these models to the clinical situation,[86,87] discussions that have encompassed the applicability of many species to human pathology,[88,89] the utility and relevance of inbred *vs* outbred *vs* genetically-modified strains,[90,91] and the ability and accuracy of applying and extrapolating data derived from animal models to humans etc. For example, as with patients, heterogenic responses can be seen, even within inbred strains, with the timing and severity of events being strain, age, sex, dose and volume dependent.[92,93] Valid arguments can be made to use larger animals that better predict human responses, such as rabbits, dogs, pigs, and sheep, however, the costs involved in using statistically appropriate numbers in terms of purchase and housing, as well as significant animal rights issues, have precluded the use of many of these species in most institutions. Finally, correlations to the clinic have been limited by not only the inability of most researchers to deliver small, clinically-relevant radiation volumes to animal models, especially rodents,[94] but also by a paucity of sufficiently refined imaging tools that can detect pathological changes in small volumes of tissue. This situation has begun to improve in the last decade through the development of small animal radiation research platforms[94] and more refined imaging tools, such as microCT/PET and 2-photon imaging.

Despite these roadblocks, progress is beginning to be made towards a more thorough understanding of normal tissue radiation biology. Pathological and physiological radiation responses have been cataloged in animal models,[90,95,96] with tissue and organ differences identified between models.[89] Significantly, beyond the induction of immediate or acute cell death, the response to radiation injury in normal tissues is now seen as a highly complex series of events,[97,98] with the outcome, unlike that seen in the tumor, being only partially predicated on cell loss.[99] In addition to the physiology and architecture of the injured organ, patient-relevant characteristics, such as age and sex, as well as radiation parameters, such as quality, dose and volume, also affect the induction and progression of normal tissue effects.[99] As a result, these effects are now considered by many to be the result of not only the immediate canonical reaction to cell loss, but also a chronic disruption in homeostatic conditions, resulting in the dysregulated wound response that characterizes radiation-associated diseases.[100–102] The affected homeostatic conditions include, but are not limited to, immune status, vascular integrity, signaling (cytokine) milieu and oxidative stress levels, with

disruption in any or all contributing to microenvironmental degradation and inhibiting the innate compensatory forces that normally terminate the injury response process.

Although the importance of each homeostatic process differs between organs due to the spectrum of functions and pathologies, it should be readily apparent that multiple and, likely, organ/tissue specific approaches are needed to prevent or treat such dysregulation. Interestingly, many of these same conditions that are induced by radiation in the normal tissues are present within the tumor microenvironment and are part of the survival apparatus that leads to tumorigenesis.[100,103,104] This suggests that the two fields of tumor and normal tissue radiation biology overlap to a greater degree than has been appreciated to date and, furthermore, that care needs to be taken that the deliberate alteration of one microenvironment does not adversely affect the other in terms of treatment outcome. Indeed, much of the early work performed in tumors, such as that done in the area of the oxygen effect by Scott and others,[105–107] may now find greater resonance with normal tissue researchers and suggest "new" avenues of exploration.

The significant increase in number of contributing factors that are known now to be involved in normal tissue radiation biology suggests that most, if not all, of the mathematical concepts used to date fail to adequately accommodate the potential range of involved pathways. Greater scrutiny is needed to characterize, both quantitatively and qualitatively, the roles played by the tumor and normal tissue microenvironments in the downstream responses to radiation therapy, assessing both independent and interactive conditions. Furthermore, the likely need for developing new animal models should include the combined regimens commonly used in the clinic.

CONCLUSIONS

Despite the progress that has been made in the use of radiation therapy as a treatment modality, to a certain extent, oncologists are still being faced with the fundamental components of the therapeutic ratio: developing treatment strategies that balance tumor cure against the risk of normal tissue injury. However, at the risk of oversimplification, it would appear that, until recently, although poor survival rates have tended to drive up prescribed doses in radiation therapy, malpractice lawsuits, certainly within the USA, have tended to drive them down. So, to which side of the therapeutic ratio should we lean? Currently, the competing legal and medical factors strongly govern the increase being seen in treatment doses. However, the growing cancer survivor population is increasingly demanding better outcomes, over and above a cure of their tumor, especially with regard to quality of life issues. In order to respond, new approaches are needed that incorporate a reduction in normal tissue complication rates beyond those achieved through field size modulation. The advances being made across all scientific disciplines makes it clear that the successful interrogation of these complex radiation effects, including cognitive dysfunction, immune disruption, tissue remodeling etc. will require the incorporation of expertise from other, more specialized fields, such as neurobiology, immunology, vascular biology. However, although such an initiative should broaden the avenues of exploration and increase the probability of gaining a deeper understanding of radiation-induced normal tissue injury, care must be taken to ensure a mutual exchange of knowledge and training between disciplines, otherwise this approach may further dilute the currently limited resources available to radiation biology and physics researchers alike by diverting funds to better known and resourced scientists.

We firmly believe that, as in the past, strong collaborations between radiation biologists and physicists and other members from ancillary scientific disciplines will lead to new and improved means of treating cancer patients with higher efficacy and lower risk. However, to create these teams, greater investment will have to be made on both "sides" of the therapeutic ratio equation, and scientific integration needs to be encouraged between the involved disciplines. Examples of such avenues might include radiation biologists and oncologists working together, to firstly identify pre-treatment biomarkers that differentiate the downstream radiation responses of tumors from normal tissues, then working with physicists to target those cells through the use of current and emerging diagnostics and therapeutics, including imaging and nanotechnology delivery systems. To reduce the risks of late effects, such as secondary malignant tumors, the changes in current modeling paradigms being proposed by medical physicists[75] might take greater account of the biological variables being identified at the genomic and proteomic levels, so that the potential for personalized treatment planning finally can be realized. However, such efforts will require a fundamental change in current thinking, not only by promoting increases in basic and translational funding opportunities, but also at the institutional level, through active encouragement of collaboration and innovation. Importantly, there needs to be a return to the overarching philosophy that was the foundation of the work performed by such as Fowler and Scott: that it is only when the various arms of radiation research work together, acknowledging and appreciating our respective contributions, that our community can truly rise to the challenge of improving patient outcomes, not only with respect to the treatment of their cancers, but assuring them a full and productive life thereafter.

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