Technology, Biology and Traffic

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The purpose of the Nobel Conference 2000 'From the cellular response and DNA damage to biological optimization of radiation therapy' was to consider research extending from biophysics and molecular cell biology to clinical physics in order both to explain and improve treatment of malignant disease by radiation. The fact that I, a physician, was asked to give the Keynote Address testifies to the orientation of the meeting. The conference was convened not only for the discussion of science at many levels, but also in order to focus on improving the treatment of cancer patients. Medicine is an amalgamation of basic science, applied science and that special relationship between the physician and patient which results in determining the nature of illness and an appropriate plan of management. It is within the context of all three that one should consider radiation therapy. This medical specialty—radiation oncology—is a particular recipient of the advances of technology, the molecular biologic revolution and the understanding of the complex self-regulating cybernetic system that is the human body faced with a malignant disease. How to evaluate the individual clinical circumstances is benefited by molecular, anatomic and physiological knowledge of the particular patient and the tumor.

Technology, molecular and cell biology, and an understanding of complex systems all offer opportunities for improvement in radiation treatment, but before discussing these areas, I would like to put the importance of the local treatment of cancer in an appropriate prospective. It is often stated that local-regional treatment of cancer is not a critical factor in the cure of cancer. Although it is important today, it will be supplanted by effective systemic therapies which will eradicate local disease as well as distant metastases, the latter thought to be the dominant cancer problem. This trivializing of the importance of the primary tumor and the regional lymph nodes does not conform to present knowledge of malignant disease. Perez & Brady, in their textbook *Principles and Practice of Radiation Oncology*, review the data from the 1990 American Cancer Society Facts and Figures and estimate that in the United States, of the approximately 440000 cancer deaths that year, 127000 were due to local-regional disease alone and that an additional 170000 were due to both local-regional and distant disease. Collectively, therefore, two-thirds of those patients who died had local-regional tumor as a significant component of their disease, distant metastasis only being the site of disease in only one-third. It is also worth considering the importance of local-regional treatment in those patients with a high probability of occult distant metastases. Two recent studies reported considered whether improved local-regional control was important in breast cancer patients treated with modified radical mastectomy who were treated with adjuvant chemotherapy to destroy occult microscopic disease. In both of these prospective randomized trials the addition of radiation therapy to mastectomy improved local-regional control, as expected, but in addition there was an important improvement in survival. The magnitude of this improvement in survival of about 10 absolute percentage points is equivalent to that found in randomized trials of adjuvant chemotherapy alone. Adjuvant treatment with systemic agents and with local-regional radiation is at least additive. It also suggests that as we develop more effective systemic treatment for subclinical metastases in other types of cancer locoregional control will become even more important. While we all hope that a single effective therapy will completely eradicate tumor at all locations, until such a panacea is found we must address both distant and local-regional sites of cancer.

It is interesting that the most recently promulgated systemic therapy—which is designed to prevent the angiogenesis induced by cancer—seems to be most effective when combined with local-regional treatment. I conclude that radiation therapy will have an expanded role in cancer treatment for the foreseeable future.

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TECHNOLOGY

In our enthusiasm for the truly astounding advances in molecular biology, we may neglect the changes in medicine resulting from technological advances. At the beginning of my medical education the art of medicine was primarily in determining the appropriate diagnosis, with the medical history and physical examination playing the most prominent role. Today, I believe that the diagnosis is largely established by technological means while medical practice is more concerned with the treatment of the disease. This improvement in diagnosis is due to a variety of laboratory instruments but most importantly to the imaging revolution. Imaging advances are being applied to local treatment and will play an increasingly important role in radiation oncology. Advances in computed tomography applied to the patient in the treatment position will greatly reduce uncertainty, resulting in increased accuracy and reproducibility of treatment.

Magnetic resonance improves tumor imaging greatly and—like computed tomography—its digital format and software allow integration of these images. Magnetic resonance spectroscopy and positron emission tomography enable imaging of the anatomy of tumor physiology both initially and during treatment. Such functional imaging will also allow the identification of occult tumor as well as increasing our accuracy in separating tumor from non-malignant tissue. A major focus of tumor imaging will be accurate estimation of the extent of the tumor. Accurate anatomic identification of all tumor cells might even be possible. Alternatively, one might use imaging methods to determine the concentration of tumor cells within a unit volume of tissue. This I call 'tumor density'. It can be combined with the probability of tumor cells within a defined volume based on the known proclivities of individual tumors for invasion and metastases. All of these determinations will radically change our understanding of what the treatment volume should be.

Not only is imaging important for locating the tumor and identifying its physiology, but these representations of the tumor can be linked to treatment delivery. Such computer-controlled radiation therapy has been suggested for at least 25 years, but it is only in more recent times that technology has allowed this to have widespread clinical application. Intensity-modulated radiation therapy and tomotherapy are but two current examples of computer-controlled radiation therapy. These approaches require reconsideration of the fundamental paradigm of treatment. This paradigm urges uniform irradiation of tumor while minimizing the dose to the normal tissues. Computer control of treatment with accurate anatomically presented physiologic data and tumor density information offer the opportunity to 'paint' the dose in conformity with tumor cell distribution, oxygenation and other important physiologic characteristics. Reductions in the uncertainty of tumor extent and improvement in treatment precision will allow significant reduction in the target volume.

Feedback and control of the radiation treatment is now being employed utilizing simple gating techniques. However, software has already been developed which could be applied to assure the appropriate radiation delivery while compensating for patient motion or physiologic organ motion. This feedback and control will greatly reduce unnecessary irradiation and will also improve the likelihood of treating the entire tumor to the planned dose. These techniques also depend on an assessment of how to distribute the unwanted radiation administered to traversed normal tissues. Such 'dose dumping' depends on understanding the sequelae of organ-specific dose distribution, the biology of which will be discussed later. Improved software should also provide a reconsideration of particle radiation to further restrict radiation to the tumor. Protons are on the immediate horizon and it will be interesting to see whether the theoretic advantage of such particle radiation will have practical consequences in more than very limited circumstances.

BIOLOGY

The rapid developments in molecular cell biology are advancing our understanding of the effects of ionizing radiation on biologic material. While this begins with damage to and repair of the genome, it also includes the recently discovered important cytotoxic effects of ionizing radiation on non-genomic structures such as the cell membrane and even a bystander effect resulting in the death of adjacent cells. In association with radiation damage to cells, there is a cascade of cytokines released which may play a role in further tumor cell kill as well as contributing to damage to normal tissues.

The importance of oxygen concentration to cellular radiation sensitivity has been noted for more than half of the last century, yet therapy designed to exploit this has been limited. With the anatomic determination of local differences in oxygen concentration within tumors and the availability of new modifiers of the oxygen effect or agents specifically toxic to hypoxic cells, we should finally be able to take advantage of this large effect.

Perhaps the most intensely studied phenomenon in cell biology is the cell cycle and those changes associated with cell birth and cell death. Intimately bound with the cell cycle are those checkpoints at which damage is evaluated and either repaired or the cell committed to programmed cell death. Evaluation of these mechanisms in individual tumors and their manipulation offer the possibility of optimizing and individualizing radiation therapy. The aberrations of the cell cycle checkpoints and of cell kinetics in each individual malignancy will determine appropriate treatment strategies. Determining the importance of apoptosis as well as how one stimulates or increases terminal differentiation will offer new therapeutic opportunities.

Tumors require the acquisition of four important phenotypes: growth, invasion, metastases and angiogenesis. The ability to induce a new blood supply is essential in order for tumors to grow both locally and in distant sites and so I add angiogenesis to the usual triad of malignant behavior. Tumor angiogenesis provides a new target for therapy. Studies of anti-angiogenic agents are extremely promising in the laboratory and are beginning to be used in the clinic. What perhaps would be most useful would be to combine anti-tumor agents such as radiation with anti-angiogenic agents. Possibly some of the current effectiveness of radiation may be due to its effect on tumor vessels. Cytotoxic agents currently used in cancer treatment, if used with quite different time-dose configurations than those designed for anti-tumor effects, may be quite effective as anti-angiogenic therapy.

The cell cycle, the relative extent of cell birth and cell death, terminal differentiation as well as angiogenesis all affect tumor growth. Tumors appear to become more malignant as they progress. This malignant progression may affect not only the likelihood of metastastic spread but may well also affect radiation response. For example, p53 abnormalities increase as a function of the size of a breast cancer. It is well known that p53 is important for the cell cycle checkpoints and for preservation of the apoptotic pathway. We have found that other specific abnormalities associated with growth, invasion, metastasis and angiogenesis all increase with increasing tumor size or nodal involvement in breast cancer.

In order for radiation or any therapy to be effective, there must be a differential effect on the tumor as compared with the normal tissues. Understanding normal tissue radiation biology is essential to improving the therapeutic efficacy of any treatment. This affects planning the dose distribution both within and outside the target volume. Early-responding and late-responding tissues have different characteristics which should inform biologically optimized treatment planning. This is especially important with the increasing ability to dose paint as well to develop appropriate dose-dumping strategies. Permanent implantation of Auger-emitting isotopes should also be considered in this light. These isotopes create problems in homogeneity of dose and dose rate as well as gradual decrease in dose rate associated with the protracted radioactive decay.

TRAFFIC

I have chosen to use the term 'traffic' to consider the complexity associated with the establishment of a cancer, its growth and the response by the normal tissues. I use the term 'traffic' because of a comment made by Sir James Gowans, the Oxford immunologist, suggesting that there was little to be learned about automobile traffic from extensive study of the internal combustion engine. He meant, as do I, that while reductionism provides great insights into mechanism, complex systems have to be studied at many levels in order to have an appropriate understanding. The nature of local tumor invasion, preferred pathways of spread and how these are affected by treatment are all part of such traffic studies.

The traffic considerations associated with the immune system are a special case. The kinetics of tumor cells entering the lymphatic system and how this is affected by radiation should be quite important. The growth of tumor in lymph nodes, the kinetics of immune recognition, antibody-dependent cytotoxicity and cellular immunity are also likely to be affected in complex ways. Using the increasingly accurate and precise radiation treatment techniques, how much of the regional lymph nodes should be treated? What should the strategy of dose dumping be with regard to irradiating regional lymph nodes? Since these regional nodes are the initial site of the immune response, should they be restricted from the irradiated volume or is this irrelevant or compensated for by the destruction of nodal metastases? Irradiation of the tumor likely has many effects on the immune response. While tumor-infiltrating lymphocytes will be destroyed, radiation will cause an increase in availability and a modification of tumor antigens. Ionizing radiation is also associated with the production of chaperone proteins. These proteins appear to aid antigen-presenting cells in their function and increase the efficacy of the immune response. Finally, there is the 'adjuvant effect' of irradiated tumor cells. How much of it is due to any of these mechanisms is unclear. But what is clear is that there is a great difference between surgical excision of the tumor with little or no antigen remaining compared with destroying tumors with ionizing radiation.

The most obvious traffic important in cancer is that required for the development of systemic metastases. This process requires access to the blood vessels, egress from the blood vessels and host organ receptivity. Radiation is likely to have an effect on all of these phenomena in addition to the effects of radiation on the seeding ability of surviving tumor cells. The complexity of the multiple sites and effects of radiation are staggering but they need to be understood in order to craft the appropriate local-regional treatment plan.

Technological capacity and biological knowledge offer an opportunity to individualize treatment to each host-tumor circumstance. Standard treatment methods will be replaced by such individualization. But in order for this to occur, we must accept and embrace complexity.