Combining technology and biology to conquer cancer

Given the rapid advancements in technology and biology over the past decade, it has never been so exciting to be an oncologist now, particularly a radiation oncologist. In the early 2000s, the revolution in computer-driven radiotherapy technology enabled exquisitely precise direction of radiation beams to tumor targets. The advent of 4-dimensional computed tomography (CT) and on-board image-guided intensity-modulated radiotherapy, stereotactic ablative radiotherapy, intracranial gamma knife, particle therapy and other sophisticated imaging and treatment techniques have equipped radiation oncologists with novel tools to tightly conform ablative or definitive radiation doses to targets while avoiding inadvertent irradiation of surrounding critical normal structures. As a result, local control—and in some patients even survival—has been improved and treatment-related toxicity has been minimized.

However, cancer is a biological disease, not just a technologic challenge. As our ability to control local tumors improves with the use of new technology, the importance of systemic disease control grows in parallel—after all, in most cases it is metastatic disease that kills the patient. During the past decade, the development of genomic profile–based targeted therapy, immune checkpoint pathway–based immunotherapy, and chimeric antigen receptor (CAR)-T cell–mediated cancer killing has revolutionized the management of stage IV cancer of many types, particularly lung cancer, melanoma, head & neck cancer, lymphoma, leukemia, and myeloma, among others. We are now starting to think about the potential to "cure" stage IV disease, which historically has been considered incurable. Indeed, at this time we know considerably more about the biology of cancer, how it starts and how it progresses, than in the past.

In the past, we established the stage of cancer based on tumor histology, tumor location, and the degree of spread as detected by imaging such as CT, positron emission (PET)/CT, and magnetic resonance imaging. However, imaging can detect and classify cancer only when the cancer reaches a certain size, typically >5 mm. Biologically, however, "localized" disease, "advanced" disease, "metastatic" disease, and "recurrent" disease all represent ongoing biological processes, all involving a dynamic balance between the human defense system and cancer cells, that is always ongoing both before and after detection of a cancer by imaging. Circulating tumor cells (or circulating DNA or RNA) could already be present in a case judged to be "early stage" by imaging; conversely, some patients with systemically and locally controlled "stage IV" disease may survive for years, or even decades. We know now that the various stages of cancer involve different patterns of gene mutations and different levels of immunosuppression, among other biological processes. As such, recent developments in targeted therapy and immunotherapy have opened a new window for radiotherapy. For early-stage disease, immunotherapy given with a local treatment such as radiotherapy may lead to less tumor recurrence or metastasis. For metastatic disease, adding radiotherapy may overcome the resistance to targeted therapy that typically develops in most patients within 2 years after beginning targeted therapy, or could convert tumors that do not respond to immunotherapy ("cold" tumors, typically present in about 80% of common tumor types) into "hot" (responding) tumors. Moreover, cancer cells killed by radiation release tumor-associated antigens and immunoregulatory cytokines, thereby functioning as a kind of cancer-specific vaccine in situ; they further activate tumor-specific systemic immune responses to eradicate tumors even outside the radiation field (the abscopal effect). Radiation can also damage epithelial cells lining tumor blood vessels and improve the ability of immune cells, cytokines, targeted therapy agents, and chemotherapy to penetrate the tumor. These effects seem to be more prominent when the radiation used with immunotherapy involves giving high (ablative) doses, a type of therapy for which we coined the term "I-SABR" (immunotherapy and stereotactic ablative radiotherapy). I-SABR protocols are underway for both early-stage disease and locally advanced cancer worldwide.

This book provides a timely review of the details of the mechanisms underlying radiation- and immunotherapy-evoked effects, and provides updated information on clinical trials that combine biology (immunotherapy and targeted therapy) with technology (radiotherapy). Most importantly, it helps us to prepare for what comes next. Now is the era of both technology

and biology—better technology leads to better outcomes, and better biology needs better technology. By combining biology and technology, we can conquer cancer by providing both systemic and local control of disease. This is truly "precision medicine."

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