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COMMENTARY

Why So Challenging to Personalize Radiation Dose?

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The primary treatment tool for radiation oncologists is of course, radiation. After many decades of clinical application, one would think the optimal radiation dose and fractionation for virtually every cancer would be beautifully defined according to clinical data for each tumor type. Not so in fact. For the majority of human cancers, radiation doses routinely prescribed in clinical practice largely reflect adjacent normal tissue tolerance and perceived patient safety (1, 2). We routinely limit radiation dose to bowel, brain, heart, lung, kidney, spinal cord, and many other normal organs according to the severity of clinical consequences from exceeding normal tissue tolerance. No wonder that for many tumor types we have not established rigorous dose-response profiles, but rather "clinical tolerance guidelines" that reflect combinations of safety, feasibility, and tumor response.

Over the years, key technological advances in radiation delivery have occasionally served to disrupt traditional clinical guidelines of radiation dose application. Brachytherapy for cervix and prostate cancer serve as prime historical examples in which the ability to safely deliver high-dose radiation within the tumor with rapid fall off allowed routine application of tumor equivalent doses exceeding 80 Gy, thereby providing exceptional local control rates. The advent of SBRT techniques in lung cancer similarly altered the landscape of "clinically acceptable" radiation dose delivery for small tumors in the thorax. Studies by Timmerman and colleagues (3) and others toppled the convention of delivering 2- or 3-Gy daily fractions for early-stage lung cancer by leveraging highly conformal delivery techniques that now routinely enable 4- to 12-Gy fraction delivery to early-stage lung cancer patients. This transformation allowed the safe and effective escalation of tumor equivalent doses to well above 80 Gy that provide exceptionally high local tumor control rates (4).

For most tumor types, however, normal tissue tolerance remains a significant restraint on total dose, and the report in this issue by Rosenthal et al (5) is a case in point. This article updates a study designed 35 years ago at MD Anderson Cancer Center to examine radiation dose in the postoperative setting for head and neck cancer patients, based primarily on pathology-based estimations of risk categories for recurrence. With long-term follow-up, the authors conclude that no dose-response relationship could be identified for improved tumor control in the study. However, the range of dose studied varied only modestly, from 57.6 Gy to 68.4 Gy. Twenty-eight percent of patients in the MD Anderson series experienced local or regional recurrence. Would this rate be significantly diminished by higher radiation dose if the opportunity for safe delivery paralleled that of brachytherapy or SBRT, in which effective doses over 80 Gy are routine? Unlike brachytherapy or SBRT, however, head and neck radiation generally requires broad field coverage of regions at risk, with a spectrum of critical surrounding normal tissues that cannot tolerate radiation doses of 80 Gy without significant toxicity risk.

Radiation dose is of course not the only meaningful parameter dictating ultimate tumor control after treatment. Rosenthal et al (5) highlight "treatment package time" to describe the elapsed days from initial head and neck surgery to the completion of radiation. Notwithstanding potential confounders reflecting disease severity and

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postsurgical delay, this theme of tumor cell repopulation has been well studied over several decades. There is compelling clinical data that prolongation of overall treatment time adversely impacts locoregional tumor control, particularly for rapidly proliferating tumors, such as head and neck squamous cell carcinomas, treated with radiation alone or in combination with chemotherapy (6-8). As the authors note, extending overall treatment time may offset the potential benefit of increased dose on local tumor control, and limiting the time interval between surgery and radiation may also be beneficial to limit tumor cell repopulation.

The Rosenthal et al article serves as a valuable stimulus for future studies in radiation oncology. This work represents a carefully conceived, prospective, controlled clinical study of radiation dose selection in a focused cohort of cancer patients. Although designed more than 35 years ago, before the era of concurrent chemotherapy, before we had knowledge of human papillomavirus association with outcome in head and neck cancer, and before we had access to intensity modulated radiation therapy, image-guided radiation therapy, and a variety of other techniques, this study asked an important question about radiation dose selection. We have a golden opportunity to perform rigorous and systematic investigation of radiation dose for a variety of tumors in the modern era. This query can be made with radiation alone, and in the setting of radiation combined with chemotherapy and molecular targeting and/or immunomodulatory agents (9).

To truly personalize radiation dose prescriptions for the future, the field of radiation oncology would ideally like to complement the use of tumor stage and pathology with the incorporation of molecular, genetic, and possibly imaging features to guide radiation dose selection. This approach would parallel the advent of precision medicine for cancer drug selection in oncology by focusing on individualization of radiation dose for each patient (10).

What dose of radiation should be delivered to each individual cancer patient? The question seems so simple, yet the answer has been confounding. The remarkably talented physician scientists entering the field of radiation oncology will no doubt answer this elusive question over the years to come. This will provide a landmark advance. With ever advancing precision in radiation delivery, the opportunity to safely deliver higher radiation doses continues to expand. The thoughtful application of radiation with targeted drugs will increase tumor control and survival rates for cancer patients. It is time to more rigorously personalize radiation dose prescriptions for the future.

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