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PRECISION MEDICINE-COMMENTARY

Current Opportunities and Future Vision of Precision Medicine in Radiation Oncology

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At the 2016 American Society for Radiation Oncology annual meeting, Dr Thomas Lynch delivered a keynote address in which he presented the remarkable development of targeted therapy for non-small cell lung cancer with activating mutations in the epidermal growth factor receptor (EGFR) (1). He described the care of 1 patient, whose lung cancer had had an exceptional response to a first-generation EGFR inhibitor but that ultimately progressed, with tumor cells harboring a resistant EGFR mutation. The patient subsequently derived benefit from a next-generation EGFR inhibitor. The use of small molecule inhibitors to treat EGFR mutant lung adenocarcinoma was the culmination of years of basic science and translational research (2, 3). It was also an example of precision medicine in oncology, in which therapy is tailored to a specific gene mutation in an individual patient's cancer. After the plenary session, a somewhat deflated colleague asked me when this kind of precision medicine would come to radiation oncology.

From one perspective, the current practice of radiation oncology already encompasses the central tenets of precision medicine. During treatment planning, radiation oncologists contour patient-specific tumor and normal tissue anatomy. Beam angles, shapes, and energies are designed to maximize the therapeutic ratio. Radiation oncologists select optimal treatment plans according to patient-specific dose-volume histograms of normal tissues and target volume coverage. Furthermore, the individual patient and tumor characteristics factor into determining which patients are offered radiation therapy. For example, the treatment approach for a 75-year-old woman with a stage T1, estrogen receptor-positive, progesterone receptor-positive, invasive ductal adenocarcinoma might include lumpectomy and an aromatase inhibitor without adjuvant radiation therapy (4). In contrast, adjuvant radiation therapy and trastuzumab would routinely be recommended to a 40-year-old woman with *Her2*-amplified T1 invasive ductal adenocarcinoma after lumpectomy. Similarly, in prostate cancer, the treatment for individual patients can vary from active surveillance to radiation therapy alone to radiation therapy plus hormonal therapy, depending on a number of clinical (age, comorbidities, and so forth) and tumor-specific (prostate-specific antigen, Gleason score, stage) parameters.

However, from another perspective, it could seem as if radiation oncology is failing to incorporate the tremendous advances in cancer genomics and cancer biology into individual patient treatment. Instead, when a patient is offered radiation therapy, the same radiation dose is typically delivered, regardless of the molecular features of the individual cancer.

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Others have recently highlighted the opportunity to widen the therapeutic window of radiation therapy in the era of precision medicine by combining technology-driven improvement of treatment conformality with biology-driven approaches (5). In this issue of the Red Journal, investigators discuss how advances in genomics (6), imaging (7), and "big data" (8) can be leveraged to tailor radiation therapy to individual patients in an effort to improve outcomes. Although these and other approaches to precision medicine should be tested to try to improve radiation therapy, the limits to personalized cancer medicine that arise from tumor heterogeneity (9) must be appreciated to avoid what some have recently concluded is a state of irrational exuberance in precision medicine for cancer (10).

Although the concept of performing genomic sequencing to identify an "actionable mutation" that can then be paired with a molecularly targeted drug remains appealing, thus far, DNA-guided precision medicine has benefited only a small subset of cancers (10). Most responders to date have had tumors with a gain-of-function oncogenic mutation or an overexpressed protein driving tumor growth and maintenance. In addition to EGFR mutant lung adenocarcinoma and *Her2*-amplified breast cancer, successful applications of DNA-guided targeted therapy include EML4-ALK^{+} lung adenocarcinoma, BRAF^{V600E} mutant melanoma, and *c-kit* mutant gastrointestinal stromal tumors, which have shown dramatic responses to crizotinib, vemurafenib, and imatinib, respectively. However, in this subgroup of cancers, most patients with macroscopic metastases develop resistance to targeted therapy because of intratumor heterogeneity and the selection of pre-existing resistant subclones (9). Remarkably, the presence of a gain-of-function mutation does not always cause sensitivity to a molecularly targeted drug. For example, the presence of the identical BRAF^{V600E} mutation in colorectal cancer does not lead to the same sensitivity to vemurafenib as in melanoma (11), apparently because of EGFR signaling (12). Furthermore, a randomized controlled trial of patients with metastatic cancer harboring a targetable mutation showed no difference in progression-free survival with matched molecularly targeted therapy compared with the physician's choice of treatment (13). Therefore, although the success of DNA-guided targeted therapy for certain cancers with specific driver mutations should be celebrated, the value of genomic sequencing for identifying targeted therapies cannot necessarily be extrapolated to other cancers. The implication for precision medicine in radiation oncology is that specific gene mutations, gene expression patterns (14), or imaging biomarkers (5) should be studied to try to identify radiation-sensitive and radiation-resistant tumors. However, the identification of a useful biomarker for one type of cancer might not necessarily translate to other cancers. Moreover, tumor heterogeneity has the potential to limit our ability to tailor radiation therapy to individual patients.

Opportunities for Precision Medicine in Radiation Oncology: Selecting Individual Patients for Adjuvant Radiation Therapy

Many patients with nonmetastatic cancer undergo surgery and adjuvant radiation therapy. Randomized clinical trials have established the value of adjuvant radiation therapy for specific populations of cancer patients by increasing local control and, in some scenarios, overall survival. However, in these trials, more than one half of the patients randomized to surgery alone achieve local control (15-17). For these patients, radiation therapy adds toxicity and cost without any benefit. Therefore, an opportunity exists to personalize the decision to deliver adjuvant radiation therapy to those patients at greatest risk of local recurrence. For example, intraoperative imaging of microscopic residual cancer in the tumor bed has the potential to be used to stratify patients for adjuvant radiation therapy (18). Such intraoperative imaging technology is now being tested in early-phase clinical trials (19, 20) and could be combined with clinical and/or pathologic features to help guide the decision regarding postoperative radiation therapy. Just as patients with localized breast cancer are now selected for adjuvant chemotherapy based in part on a gene expression score, similar tests of resected breast cancer (21) and prostate cancer (22) specimens could be used to tailor adjuvant radiation therapy to those patients most likely to benefit. Although these approaches for precision radiation oncology have the potential to refine the selection of individual patients for adjuvant radiation therapy, prospective testing and validation in well-designed clinical trials will be required before they can be broadly implemented in the future.

Opportunities for Precision Medicine in Radiation Oncology: Prescribing Radiation Dose Based on Genetic Drivers of Individual Cancers

Genetic drivers of individual cancers also have the potential to be used for prescribing the radiation dose. For example, the discovery that oropharyngeal squamous cell carcinomas associated with human papillomavirus (HPV) infection show significantly better rates of progression-free survival after chemoradiation therapy than other oropharyngeal squamous cell carcinomas (23) provided the rationale for ongoing clinical trials of treatment de-escalation for patients with HPV-associated head and neck cancer. HPV infection leads to the expression of several viral genes, including *E6*. The E6 protein binds to the tumor suppressor p53, which causes p53 degradation, which, in turn, leads to p16 overexpression. Therefore, detecting the expression of p16 in oropharyngeal cancer by immunohistochemistry is a surrogate for a tumor associated with HPV infection and