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Current Opportunities and Future Vision of Precision Medicine in Radiation Oncology

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At the 2016 ASTRO annual meeting, Dr. Thomas Lynch delivered a keynote address where 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 one patient, whose lung cancer had an exceptional response to a first-generation EGFR inhibitor, but 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, where 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 based on patient-specific dose-volume histograms of normal tissues and target volume coverage. Furthermore, 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 T1 ER+/PR+ invasive ductal adenocarcinoma may include lumpectomy and an aromatase inhibitor without adjuvant radiation therapy[4], while 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 radiotherapy plus hormonal therapy depending on a number of clinical (age, co-morbidities, etc.) and tumor-specific (PSA, Gleason score, stage) parameters.

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Conflicts of Interest: DGK is a member of the scientific advisory board and owns stock in Lumicell Diagnostics, a company commercializing intraoperative imaging systems. DGK is a founder and owns stock in XRAD Therapeutics, which is developing radiosensitizers. DGK has research support from XRAD Therapeutics and Merck and has received research support in the past from GlaxoSmithKline and Janssen.

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

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, authors 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. While 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 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 positive lung adenocarcinoma, $BRAF^{V600E}$ mutant melanoma, and *c-kit* mutant GI stromal tumors (GISTs), which show 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 to physician's choice of treatment[13]. Therefore, while the success of DNA-guided targeted therapy in 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 may 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 Radiotherapy

Many patients with non-metastatic cancer are treated with 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 over 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, there is an opportunity to personalize the decision to deliver adjuvant radiation therapy to those patients at highest risk for 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 pathological features to help guide the decision of 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 cancers[21] and prostate cancers[22] 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 are 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 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 chemo-radiotherapy than other oropharyngeal squamous cell carcinomas[23] provides 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 that in turn leads to p16 overexpression. Therefore, detecting expression of p16 in oropharyngeal cancer by immunohistochemistry is a surrogate for a tumor associated with HPV infection and identifies a subgroup of patients with better outcomes following chemo-radiotherapy[23]. While ongoing clinical investigations aim to identify which p16+ head and neck squamous cell carcinomas can safely be treated with less radiation therapy and/or chemotherapy[5], HPV-associated head and neck cancer serves as a paradigm for using the genetic drivers of tumor development to tailor radiation therapy to individual patients. Another example of a driver mutation that is correlated with radioresistance is oncogenic KRAS in lung adenocarcinoma[24] and in liver metastases[25]. Remarkably, the 1-year local control rate after stereotactic body radiation therapy (SBRT) for liver metastases with the combination of *KRAS* and *TP53* mutations was only 20% compared to 69% for all other metastases[25]. These findings suggest that tumor genotype can be a critical determinant of local control. Moreover, these results suggest that to achieve

optimal rates of local control in cancers with *KRAS* and *TP53* mutations, treatment intensification may be required. For example, future clinical trials for liver metastases with *KRAS* and *TP53* mutations could test increasing the radiation dose, utilizing alternative therapy such as surgery or radiofrequency ablation, or combining radiotherapy with concurrent chemotherapy or a drug that blocks the Ataxia Telangiectasia Mutated (ATM) kinase to increase radiosensitivity[26]. In addition to classifying tumor radiation resistance by genotype, gene expression can also be utilized to define a radiation sensitivity index that has the potential to be used to personalize radiotherapy dose prescription[27].

Challenges for Precision Medicine in Radiation Oncology

As radiation oncology moves toward a future of precision medicine based in part on genomic features of the tumor, it is important to recognize the challenge of tumor heterogeneity where one cancer is comprised of multiple subclones, each harboring different mutations. When a tumor is biopsied or resected, genomic analysis may reflect the mutations or gene expression present in the dominant clone. It is possible that targeting these pathways with molecularly targeted drugs and radiation therapy will increase local control and cure before additional heterogeneity develops at sties of metastasis. However, a recent study comparing paired medulloblastomas at diagnosis and recurrence after radiotherapy with or without chemotherapy demonstrated substantial genetic divergence of the dominant clone at recurrence[28]. This study showed that the dominant clone at recurrence arose through clonal selection of a pre-existing minor clone present at diagnosis[28]. Remarkably, only a minority of the mutations present in the tumor at diagnosis were retained at recurrence. Therefore, to optimize precision medicine in radiation oncology in the future, cancer therapy will not only need to be tailored to treat the dominant clone, but will also need to eradicate minor clones poised to seed local and distant recurrence. One approach to addressing the challenge of tumor heterogeneity is to combine radiation therapy with immunotherapy to try to activate an immune response against different subclones within a cancer. While appreciating the problem of tumor heterogeneity increases the challenge of applying precision medicine to our cancer patients, it will facilitate the development of strategies with the best chance of improving patient outcomes.

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