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Editorial

Identifying the Radioresponsive Genome for Genomics-Guided Radiotherapy

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Nearly 20 years ago, sequencing of the human genome heralded 21st-century precision medicine that harnessed the power of genetic profiling to personalize cancer treatments. Although much effort is put into targeted sequencing to identify druggable targets for advanced cancers, consideration of predicting tumor benefit from radiation lags behind. A paper in this issue of the Journal provides the impetus to progress genetic profiling to guide the use of radiotherapy (1).

Pitter et al. (1) harnessed the power of the genomic revolution and an institutional study that carried out mutational profiling of actionable cancer target genes in patients with advanced disease. A sequencing assay tested all exons and select introns within 468 cancer-related genes in 20 107 patients. Of 1085 patients with somatic *ATM* mutations, 357 had radiotherapy as part of their treatment. Patients with loss of function (LOF) mutations vs variants of unknown significance were radiosensitive with a 2-year cumulative incidence of irradiated tumor progression (radiological or pathological) of 13.2% vs 27.5% (hazard ratio [HR] = 0.51, 95% confidence interval [CI] = 0.34 to 0.77; $P = .001$). Greater benefit was seen in patients with biallelic (HR = 0.19, 95% CI = 0.06 to 0.60; $P = .005$) vs mono-allelic (HR = 0.57, 95% CI = 0.35 to 0.90; $P = .02$) mutations.

ATM is the poster child of radiosensitivity genes. Individuals with ataxia telangiectasia who harbor homozygous germline mutations are hypersensitive to radiation, and radiotherapy is contraindicated. Over the past 40 years, the radiation oncology community pursued the hypothesis that individuals with heterozygous germline mutations will have a smaller but increased risk of radiation toxicity. Various assays were studied with mixed findings, and the sequencing of the *ATM* gene in 1995 (2) opened the door to looking at genetic variants. Findings were mixed because of past limitations of genetic testing and use of small cohorts. However, a 2016 meta-analysis of 5456 patients from 17 cohorts of breast or prostate cancer provided compelling evidence that common genetic variants in *ATM* predispose to radiotherapy side effects. A single nucleotide variant in *ATM* increased risk of acute (odds ratio [OR] = 1.5) and late (OR = 1.2) toxicity (3).

The impact of somatic changes in *ATM* in tumors is less studied, but there is evidence they impact on radiosensitivity. Because the first publication in 1975 highlighted extreme radiosensitivity in individuals with ataxia telangiectasia, radiotherapy is avoided. When unavoidable, a few reports of single patients showed efficacy of dose-reduced radiotherapy (one-third conventional dose) without toxicity (4). In 2017, targeted sequencing of tumors from 9 patients with exceptional clinical response to radiotherapy showed somatic truncating mutations in *ATM*, highlighting the need for sequencing larger cohorts (5).

Beyond the headline finding, the work raises hypotheses for future testing. Investigating LOF mutations in 11 other DNA damage response genes found no benefits in irradiated tumor control. However, the small patient numbers and large 95% confidence intervals large do not rule out the possibility, and further studies in large cohorts are warranted. It is also tempting to speculate there are actionable radiation target genes that might indicate an increased role of radiotherapy in the metastatic setting. In the Pitter et al. study (1), 75% of the 727 lesions were irradiated with palliative intent, and there was a low mean biological effective dose of 51 Gy. Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial showed patients with newly diagnosed metastatic prostate cancer, and a low metastatic burden improved overall survival when radiotherapy to the primary was added to the standard-of-care treatment (6). Pitter et al. (1) showed a trend that *ATM* LOF mutations associated with improved outside-field response and even a possible long-term benefit in 5-year overall survival that are worth further study. These hypothesis-generating trends also highlight the need for an agnostic approach to identifying actionable radiation target genes (eg, we must be open to identifying radiation target genes associated with radiation-induced immune responses).

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A 2019 report from a workshop convened by the American Society for Radiation Oncology produced a guide for radiation oncologists on the implications of genetic testing on radiotherapy decisions. The report concluded that "although genetic alterations can markedly influence tumor radiosensitivity preclinically, to date there are no validated gene mutations that are clinically actionable" (7). A year later, there is one, but challenges remain in generating the large-scale data required to identify more [eg, only 2.2% of patients in the Pitter et al. (1) advanced cancer cohort had actionable *ATM* LOF mutations].

The Pan-Cancer Analysis of Whole Genomes project published in February 2020 highlights the "promise of precision medicine to match patients to targeted therapies using genomics" (8). As always, there is emphasis on the druggable genome, but the paper published in this issue of the Journal shows opportunities for identifying the radioresponsive genome for genomics-guided radiotherapy.

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References

1. Pitter KL, Casey DL, Lu YC, et al. Pathogenic *ATM* mutations in cancer and a genetic basis for 2 radiotherapeutic efficacy. *J Natl Cancer Inst*. 2021;113(3):266–273.
2. Savitsky K, Bar-Shira A, Gilad S, Rotman G, et al. A single ataxia telangiectasia gene with a product similar to PI-3 kinase. *Science*. 1995;268(5218):1749–1753.
3. Andreassen CN, Rosenstein BS, Kerns SL, et al. International Radiogenomics Consortium (RgC). Individual patient data meta-analysis shows a significant association between the ATM rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients. *Radiother Oncol*. 2016;121(3):431–439.
4. DeWire MD, Beltran C, Boop FA, et al. Radiation therapy and adjuvant chemotherapy in a patient with a malignant glioneuronal tumor and underlying ataxia telangiectasia: a case report and review of the literature. *J Clin Oncol*. 2013;31(1):e12.
5. Ma J, Setton J, Morris L, et al. Genomic analysis of exceptional responders to radiotherapy reveals somatic mutations in ATM. *Oncotarget*. 2017;8(6):10312–10323.
6. Parker CC, James ND, Brawley CD, et al. Systemic therapy for advanced or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE) investigators. *Lancet*. 2018;392(10162):2353–2366.
7. Bergom C, West CM, Higginson DS, et al. The implications of genetic testing on radiation therapy decisions: a guide for radiation oncologists. *Int J Radiat Oncol Biol Phys*. 2019;105(4):698–712.
8. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Version 2. *Nature*. 2020;578(7793):82–93.