

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. While 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 *JNCI* provides the impetus to progress genetic profiling to guide the use of radiotherapy (1).

Pitter *et al* 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 (1). A sequencing assay tested all exons and select introns within 468 cancer-related genes in 20,107 patients. There were 1,085 patients with somatic *ATM* mutations of whom 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% (HR = 0.51, 95%CI = 0.34 to 0.77, p=0.001). Greater benefit was seen in patients with bi-allelic (HR = 0.19, 95%CI = 0.06 to 0.60, p=0.005) vs mono-allelic (HR = 0.57, 95%CI = A to B, p=0.02) 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 due to past limitations of genetic testing and use of small cohorts. However, a 2016 meta-analysis of 5,456 patients from 17 cohorts of breast or prostate cancer provided compelling evidence that common genetic variants in *ATM* pre-dispose to radiotherapy side-effects. A single nucleotide variant in *ATM* increased risk of acute (odds ratio 1.5) and late (odds ratio 1.2) toxicity (3).

The impact of somatic changes in *ATM* in tumors is less studied, but there is evidence they impact on radiosensitivity. Since 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 nine 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, as patient numbers were small and 95% confidence intervals large, they 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 which 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. The STAMPEDE trial showed patients with newly diagnosed metastatic prostate cancer and a low metastatic burden had improved overall survival when radiotherapy to the primary was added to the standard-of-care treatment (6). Pitter *et al* 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, e.g., we must be open to identifying radiation target genes associated with radiation-induced immune responses.

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, e.g., only 2.2% of patients in the Pitter *et al* advanced cancer cohort had actionable *ATM* LOF mutations.

The Pan-Cancer Analysis of Whole Genomes (PCAWG) 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 *JNCI* shows opportunities for identifying the radioresponsive genome for genomics-guided radiotherapy.

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