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Functional assay to guide precision radiotherapy by assessing individual patient radiosensitivity

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Approximately half of all patients with cancer receive radiation therapy (RT) during the course of their treatment, often with curative intent [1]. Radiation therapy is a highly effective modality for treating cancers, but despite advances in treatment planning and delivery, some patients will experience acute toxicity or long-term side effects after RT. Radiation treatments are designed to deliver the prescribed dose of radiation to the tumor while minimizing the risk of a clinically significant toxicity to surrounding normal tissue. The radiation oncologist identifies the optimal RT plan for each patient by comparing dose volume histograms (DVH) for different plans to determine how much radiation dose will be delivered to different volumes of the tumor target and each adjacent normal organ. Utilizing the DVH, the risk of radiation toxicity to a given tissue type can be estimated based on population-level data [2], and for many clinical scenarios a 5% risk for toxicity is applied as a threshold. However, individual patient responses are heterogeneous. Therefore, biomarkers are needed to determine radiosensitivity before treatment and individualize risk assessment. Biomarkers to predict which patients will develop complications after radiation therapy could be used to customize treatment planning by allowing clinicians to prescribe higher doses of radiation - which could lead to better tumor control - for patients at low risk for developing complications. Moreover, a biomarker that identifies radiosensitivity of a specific patient prior to therapy could guide the selection of a lower radiation dose or even an alternate therapeutic approach omitting RT to minimize radiation dose to normal tissue in high-risk patients.

Potential biomarkers of radiation-associated toxicities include genomic sequencing of germline DNA [3], measurement of serum factors [4], and cellular and functional assays following radiation exposure. Previously, levels of radiation-induced CD8 T-lymphocyte apoptosis (RILA) in peripheral blood exposed to radiation *ex vivo* were shown to predict the risk of fibrosis, a late complication of radiation therapy [5]. In irradiated peripheral blood samples from patients with breast cancer, lower levels of RILA were associated with increased risk for developing breast fibrosis after radiation treatment.

The development of a radiation-induced sarcoma (RIS) is a rare but severe complication of radiation therapy, occurring in less than 1% of all cancer patients receiving radiation therapy, but comprising up to 3% of all soft tissue sarcomas [6]. Some studies suggest poorer outcomes for RIS compared to sporadic soft tissue sarcomas [7], and RIS are particularly challenging to treat in part because of previous radiation treatment to the tumor site [8]. Although patients with a familial genetic predisposition to cancer such as Neurofibromatosis Type I may carry a higher risk of RIS [9], no functional biomarkers are currently available to identify patients at high risk for developing RIS. In *EBioMedicine*, Mirjolet et al. present data showing that RILA is associated with the development of radiation-induced sarcomas [10]. Specifically, the authors compared RILA in peripheral blood CD8 lymphocytes exposed to radiation *ex vivo* from 120 patients with radiation-induced sarcomas and 240 patients with cancers other than sarcoma, matched by age, sex, and primary tumor location. The authors found that median RILA values were significantly lower in patients with RIS (18.5%, 5.5–55.7) than in patients with other cancers (22.3%, 3.8–52.2). These data suggest that RILA could be used to predict risk for developing radiation-induced sarcomas, but there is significant overlap of RILA between patients that develop RIS and those with other cancers at the individual patient level. Nevertheless, this information about individual radiosensitivity has the potential to be incorporated with other biomarkers to stratify patients for RT and for long-term follow up for RIS.

Furthermore, these findings have implications for understanding mechanisms of radiation sarcomagenesis and raise concerns about the use of treatments that protect normal tissue from radiation-induced apoptosis. The findings by Mirjolet et al. [10] are consistent with a model where, in patients with cells that are more resistant to radiation-induced apoptosis, sarcoma-initiating cells may be damaged by radiation and survive to cause a sarcoma years later. Recent studies in genetically engineered mice in which p53 levels can be reversibly downregulated by *in vivo* shRNA have shown that blocking radiation-induced apoptosis in hematopoietic cells during fractionated total body irradiation decreases the subsequent development of radiation-induced lymphomas [11]. However, whether this finding extends to radiation-induced sarcomas following high-dose focal irradiation is not clear. The results by Mirjolet et al. [10] instead suggest that blocking radiation-induced apoptosis of sarcoma-initiating cells could increase the risk of sarcoma development. In this scenario, therapies designed to prevent radiation-induced cell death to ameliorate normal tissue

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toxicity from RT might have the unintended consequence of increasing radiation-induced sarcomagenesis. Therefore, these findings have implications beyond individual patient risk for radiation complications and may extend to the use of radiation protectors during RT.

Disclosures

DGK is a cofounder of and stockholder in XRAD Therapeutics, which is developing radiosensitizers. DGK is a member of the scientific advisory board for and owns stock in Lumicell Inc., a company commercializing intraoperative imaging technology. He is an inventor of the handheld imaging device under U.S. patent 20,140,301,950-A1 and is a co-inventor on a submitted patent on radiosensitizers. XRAD Therapeutics, Merck, Bristol Myers Squibb, and Eli Lilly provide research support to DGK.

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References

[1] Moding EJ, Kastan MB, Kirsch DG. Strategies for optimizing the response of cancer and normal tissues to radiation. Nat Rev Drug Discov 2013;12:526–42.
[2] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10–9.
[3] Broeks A, Braaf LM, Huseinovic A, Nooijen A, Urbanus J, Hogervorst FBL, et al. Identification of women with an increased risk of developing radiation-induced breast cancer: a case only study. Breast Cancer Res 2007;9:R26.
[4] Stenmark MH, Cai X-W, Shedden K, Hayman JA, Yuan S, Ritter T, et al. Combining physical and biologic parameters to predict radiation-induced lung toxicity in patients with non-small-cell lung cancer treated with definitive radiation therapy. Int J Radiat Oncol Biol Phys 2012;84:e217–22.
[5] Azria D, Riou O, Castan F, Nguyen TD, Peignaux K, Lemanski C, et al. Radiation-induced CD8 T-lymphocyte apoptosis as a predictor of breast fibrosis after radiotherapy: results of the prospective multicenter french trial. EBioMedicine 2015;2:1965–73.
[6] Penel N, Grosjean J, Robin YM, Vanseymortier L, Clisant S, Adenis A. Frequency of certain established risk factors in soft tissue sarcomas in adults: a prospective descriptive study of 658 cases. Sarcoma 2008;2008:459386.
[7] Gladdy RA, Qin L-X, Moraco N, Edgar MA, Antonescu CR, Alektiar KM, et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? J Clin Oncol 2010;28:2064–9.
[8] Mito JK, Mitra D, Barysauskas CM, Mariño-Enriquez A, Morgan EA, Fletcher CDM, et al. A comparison of outcomes and prognostic features for radiation-associated angiosarcoma of the breast and other radiation-associated sarcomas. Int J Radiat Oncol Biol Phys 2019. https://doi.org/10.1016/j.ijrobp.2019.01.082.
[9] Sharif S, Ferner R, Birch JM, Gillespie JE, Gattamaneni HR, Baser ME, et al. Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. J Clin Oncol 2006;24:2570–5.
[10] Mirjolet C, Merlin JL, Truc G, et al. RILA blood biomarker as a predictor of radiation-induced sarcoma in a matched cohort study. EBioMedicine 2019, https://www.ebiomedicine.com/article/S2352-3964(19)30109-4/fulltext. (in press).
[11] Lee C-L, Castle KD, Moding EJ, Blum JM, Williams N, Luo L, et al. Acute DNA damage activates the tumour suppressor p53 to promote radiation-induced lymphoma. Nat Commun 2015;6:8477.