COMMENTARY

Personalized Medicine in Radiation Oncology—A Work in Progress

CrossMark

Christopher J. Anker, MD,* and Jennifer Y. Wo, MD†

*Division of Radiation Oncology, University of Vermont Cancer Center, Burlington, Vermont; and
†Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts

Personalized medicine holds immense promise in cancer care. With increasing understanding of the complexity of tumor heterogeneity, we are realizing that one size does not fit all, and perhaps, cancer therapy should be tailored to patients and their individualized tumor molecular signatures. Within medical oncology the search for personalized medicine has yielded numerous targeted agents. Novel medications have demonstrated significant activity within subsets of tumors which harbor specific targetable mutations. Trastuzumab is well established for *Her2*-positive breast cancer, and more recently, newer targeted agents, including crizotinib and vemurafenib, have been found effective in improving survival in *ALK*-rearranged lung cancers and *BRAF* V600E mutation—positive melanomas, respectively. Importantly, however, this search has highlighted the importance of understanding underlying tumor biology and driver mutations, which allows for appropriate patient and tumor selection. Another forefront in personalized medicine is the development of genetic assays that seek to predict tumor sensitivity to various chemotherapy agents, and there is increasing clinical validation of these models. The Oncotype DX 21 gene assay has been validated to predict both the recurrence risk and the magnitude of adjuvant chemotherapy benefit for breast cancer (1). However, an Oncotype DX score for stage II colon cancer has been found to be prognostic but not predictive of an adjuvant chemotherapeutic benefit (2).

The fundamental issues regarding the personalization of radiation therapy (RT) are those of dose, fractionation and target volumes. A form of personalized medicine is currently underway in the way of de-escalating radiation dose for human papillomavirus—positive oropharyngeal cancers. Moreover, despite negative phase 3 dose-escalation trials for numerous malignancies, for many of those same malignancies, significant research efforts in dose escalation continue. The chance of success in such trials could be increased with better selection of the target population, such as through genetic analysis.

Ahmed et al, authors of the accompanying article in this issue of the journal, should be commended for their previously published and ongoing efforts to personalize RT with the development of their radiation sensitivity index (RSI), a multigene expression model proposed to predict radiation responsiveness (lower RSI = more radiation sensitivity) (3-6). Understanding the basis for their model is the first step in evaluating the study's strengths and weaknesses. The surviving fraction following 2 Gy (SF2) was determined in breast, central nervous system, colon, melanoma, non-small cell lung cancer, ovarian, prostate, renal, and leukemia cell lines (4). Linear regression analysis correlated 10 hub genes with SF2, and the relative expression of these genes forms the basis of the RSI. Of note, because SF2 experiments all occurred under normally oxygenated conditions, differences in local environments of metastatic sites might cause differences in radiation sensitivity not detected by the current assay. The authors previously presented data supporting clinical validation of the RSI model within 14 rectal and 12 esophageal cancer patients following neoadjuvant chemoradiation and 92 head and neck cancer patients treated with definitive

chemoradiation (5). Potential caveats to accepting this as RSI substantiation include small cohort sizes and the contribution of concurrent chemotherapy.

Subsequently, the authors validated the RSI model using 2 previously published breast cancer databases of 503 patients, reporting that radiation-sensitive patients had improved 5-year relapse-free survival and distant metastasis−free survival rates when treated with RT compared to radiation-resistant patients (6). Differences in outcome disappeared for patients not receiving RT, suggesting the score only affects outcomes in the presence of RT, therefore arguing for its role as an RT biomarker.

In the accompanying paper by Ahmed et al (3), the authors further explore personalized radiation oncology by using RSI to evaluate differences in radiation sensitivity between colon primaries and sites of metastases. They propose that, in the treatment of oligometastatic disease, different doses may be required depending on the metastatic site, with liver being more radiation resistant than lung. RSI analyses were performed among 704 metastatic and 1362 primary colon lesions, and the authors reported large differences in RSI by anatomic site. In descending order of radiation resistance, RSI were ovary (0.48), abdomen (0.47), liver (0.43), brain (0.42), lung (0.32), and lymph nodes (0.31); $P<.001$. These findings were upheld when analyses were restricted to lesions from the same patient. Based on these findings, the authors hypothesized that liver metastases from a colon cancer primary were more radiation resistant than pulmonary metastases. It is important to note, however, that patient and treatment information and clinical outcomes were not available for this analysis. Last, in an effort to provide indirect clinical validation for their findings, the authors then compared clinical outcomes among a separate cohort of 9 and 14 patients with lung and liver metastases, respectively, all of whom were treated with stereotactic body RT (SBRT) to 60 Gy in 5 fractions. The rate of 2-year local control (LC) was noted to be significantly higher for lung than for liver metastases (100% vs 73%, respectively, $P=.026$). For this last analysis, RSI data were unavailable.

Although these hypothesis-generating findings are certainly provocative, clinical applicability of the results is hampered by several limitations. First, it is essential that the reader note there are 2 unrelated patient cohorts in this study: a tissue cohort without clinical data correlates and a limited clinical cohort without RSI correlation. Additionally, across studies, RSI dichotimization appears to differ by validation sets (in the current study, minimum density between RSI peaks, rectal and esophageal, receiver-operator curve, head and neck/breast, 25th percentile). Although each of these methods appears appropriate given differences in the data, the validity of RSI definitions of radiation resistance versus radiation sensitivity for each analysis should be assessed critically to adequately account for multiple testing.

The idea that some sites of metastasis are treatment-resistant has been previously described. Similar to this current study, ovarian metastases have also been proposed to be chemoresistant (7), with some studies suggesting a role for prophylactic oophorectomy (8). However, the authors aptly acknowledge, and we concur, that the critical limitations of their analyses are both the lack of clinical and treatment characteristics and the treatment-related outcomes available to correlate with their RSI analysis and the small patient subsets. Within their second analysis, restricted to primary and metastatic lesions from the same patient, only 2 patients comprised the lung cohort. Additionally, their clinical analysis involved only 23 patients.

The site of metastases as a predictor of radiation sensitivity, as proposed by the authors, is intriguing and has some biological plausibility. To our knowledge, this is the first study suggesting significantly worse LC for liver metastases treated with SBRT than that for lung. The study the authors refer to by Rule et al (9) did not show worse liver metastases LC on univariate analysis, and the study by Fumagalli et al (10) found that disease-free survival, not LC, was worse for liver metastases. Comito et al (11) found no difference in LC between lung and liver metastases from a colorectal primary, and found significantly worse LC for lung lesions treated to <60 Gy. Perhaps the differences in LC in the present study will change with longer follow-up.

A more fundamental question is how colon metastasis RSI will affect treatment plans and patient outcomes. With proven long-term survival in well-selected colon cancer patients with oligometastatic disease (12), radiation sensitivity assays may optimize RT treatment plans to allow for improved LC, chemotherapy-free interval, and potentially, a cure. The optimal RT dose-fractionation scheme for liver metastases has not been established; however, the regimen of 60 Gy in 5 fractions is supported by published data (13). Given concerns for potential gastrointestinal mucosal and biliary toxicity (14), whether further dose escalation would be feasible and effective as a strategy to overcome radiation resistance is still unclear. Alternative strategies including addition of radiation sensitizers or, in the case of ovarian metastases, oophorectomy, could also be considered. If validated, RSI may guide appropriate patient selection for dose escalation.

Regardless of whether the results of this study will be subsequently validated, this analysis makes one imagine the possibilities of how RSI or other potential radiation sensitivity indices may benefit patient care. Future important directions might involve radiation sensitivity assays in conjunction with genomic assays tasked with predicting patterns of failure (15), so that both dose-fractionation and treatment fields could be best individualized. Moreover, future studies should evaluate incorporation of ongoing efforts to identify other important factors of radiation resistance, including DNA repair. New integrative biomarkers such as telomeres may have a role as well, as they may provide insight toward individualized RT toxicity risk

as well as tumor response (16). Genetic profiling studies must be held to a high standard of validation before they are used routinely in clinical practice. The costs of these tests should be considered, with testing focused on those patients most likely to have a practice-changing result.

Ultimately, despite the limitations in this current study, RSI is important progress towards personalizing radiation therapy. The results generate important hypotheses that could dramatically influence patient care. However, the role of RSI appears in its nascent stages, and, although RSI is very provocative, future studies should further provide clinical validation of RSI in larger prospective clinical databases across all disease sites. Additionally, because RSI is based on SF2 data, as noted by the authors, future studies should evaluate the clinical applicability of the RSI model to hypofractionated RT and SBRT. To our knowledge RSI is the first published multigene assay attempting to personalize dose in radiation oncology, although genomics and proteomics are active areas of research. Whether or not RSI remains the best tool to determine radiosensitivity, it is definitely a step in the right direction.

References

1. Andre F, Delaloge S. First-generation genomic tests for breast cancer treatment. *Lancet Oncol* 2010;11:6-7.
2. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. *J Clin Oncol* 2011;29:4611-4619.
3. Ahmed KA, Fulp WJ, Berglund AE, et al. Differences between colon cancer primaries and metastases using a molecular assay for tumor radiation sensitivity suggest implications for potential oligometastatic SBRT patient selection. *Int J Radiat Oncol Biol Phys* 2015;92:837-842.
4. Eschrich S, Zhang H, Zhao H, et al. Systems biology modeling of the radiation sensitivity network: A biomarker discovery platform. *Int J Radiat Oncol Biol Phys* 2009;75:497-505.
5. Eschrich SA, Pramana J, Zhang H, et al. A gene expression model of intrinsic tumor radiosensitivity: Prediction of response and prognosis after chemoradiation. *Int J Radiat Oncol Biol Phys* 2009;75:489-496.
6. Eschrich SA, Fulp WJ, Pawitan Y, et al. Validation of a radiosensitivity molecular signature in breast cancer. *Clin Cancer Res* 2012;18:5134-5143.
7. Goere D, Daveau C, Elias D, et al. The differential response to chemotherapy of ovarian metastases from colorectal carcinoma. *Eur J Surg Oncol* 2008;34:1335-1339.
8. Lee S, Lee J, Ahn H, et al. The role of oophorectomy for colon cancer with ovarian metastasis (abstract). *J Clin Oncol* 2009;27:e15113.
9. Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. *Ann Surg Oncol* 2011;18:1081-1087.
10. Fumagalli I, Bibault JE, Dewas S, et al. A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases. *Radiat Oncol* 2012;7:164.
11. Comito T, Cozzi L, Clerici E, et al. Stereotactic ablative radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: A safe and effective approach. *BMC Cancer* 2014;14:619.
12. Aloia TA, Vauthey JN, Loyer EM, et al. Solitary colorectal liver metastasis: Resection determines outcome. *Arch Surg* 2006;141:460-467. discussion 466-467.
13. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. *Cancer* 2011;117:4060-4069.
14. Osmundson EC, Wu Y, Luxton G, et al. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. *Int J Radiat Oncol Biol Phys* 2015;91:986-994.
15. Macartney-Coxson DP, Hood KA, Shi HJ, et al. Metastatic susceptibility locus, an 8p hot-spot for tumour progression disrupted in colorectal liver metastases: 13 candidate genes examined at the DNA, mRNA and protein level. *BMC Cancer* 2008;8:187.
16. Mirjolet C, Boidot R, Saliques S, et al. The role of telomeres in predicting individual radiosensitivity of patients with cancer in the era of personalized radiotherapy. *Cancer Treat Rev* 2015;41:354-360.