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Editorial

The course forward: next generation sequencing as part of the next generation management of patients with locally advanced cervical cancer

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▸ See the article "A novel gene signature associated with poor response to chemoradiotherapy in patients with locally advanced cervical cancer" in volume 33, e7.

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In the era of increasingly personalized oncology and molecularly-driven treatment approaches, Kim et al. [1] address the relative lack of predictive biomarkers for response to definitive radiation therapy (RT) in patients with locally advanced cervical cancer (LACC). Of 528 such patients with available formalin-fixed paraffin-embedded tumor specimens, the authors identified 26 patients who experienced recurrence within 36 months of completing therapy—the so-called no durable benefit (NDB) group, and propensity matched those for tumor features to patients who remained alive and disease free for at least 5 years—termed the durable clinical benefit (DCB) group – before processing the tumor specimens for transcriptomics analysis. After RNA extraction and quality control, they were unfortunately left with only a small cohort of 4 NDB and 5 DCB patients on which to perform their analysis.

Though small and inherently heterogeneous, the groups were still well-matched for tumor stage (including lymph node status), and all patients received concurrent platinum-based chemoradiation therapy (CCRT). The authors identified 185 differentially expressed genes, which clustered into gene expression pathways that are familiar amongst previous studies of recurrence and death in patients treated with definitive RT for LACC [2-5]. Namely, signatures representing extracellular matrix organization, epithelial to mesenchymal transition (EMT) and wound healing signatures, and activation of the PI3K-Akt signaling pathway were among the most highly enriched in the NDB tumors. Further, the authors found increased predicted representation of cancer associated fibroblasts in the NDB tumors, signaling not only a local microenvironment restructuring, but an immunosuppressive phenotype as well.

Based on this small cohort, they proposed an "NDB score" calculated from the differentially enriched pathways in NDB versus DCB patients, and applied the dichotomized score to publically available datasets including the The Cancer Genome Atlas (TCGA)-CESC and 2 small cohorts of patients treated with definitive CCRT. After confirming that the score did stratify patients for overall survival in the whole TCGA cohort, they showed that it was specifically predictive for patients treated with definitive RT and not for patients treated with primary surgery, suggesting that this score is either specific to radiation response or perhaps a surrogate for more advanced disease. From the TCGA cohort, the authors were able to evaluate other previously described signatures, including the potential response to programmed cell death protein 1 (PD-1) blockade was estimated from tumor immune dysfunction and exclusion score

and T-cell-inflamed gene expression profile, and the radiosensitivity index defined on a panel of human tumor cell lines that did not include cervical cancer.

Based on these sub-analyses, the authors concluded (with appropriate reference to the study's limitations) that a predictive gene signature of recurrence after definitive radiation could be applied to patients with LACC, and that future therapeutic strategies might focus on targeting of the non-immune component of the tumor microenvironment as well as the immune compartment.

Indeed, recent efforts to simply add on further cytotoxic therapy for this disease, either in the form of neoadjuvant or adjuvant chemotherapy does not appear to budge the needle. Rather some success, albeit modest, is recently realized in targeting the microenvironment with anti-VEGF therapy and anti-PD-1 therapy in the recurrent and metastatic setting [6,7].

Recurrence of the themes in aggressive, therapeutic resistant cervical cancers of mutations/alterations along the PI3K-Akt pathway and hallmarks of the EMT suggests we are on the right track with ongoing pre-clinical and clinical research, including development of therapeutic strategies to thwart tumor metabolism [8], and the myeloid cell targeting therapy plerixafor [9]. With these and other elegant studies, cervical cancer will soon enter the realm of personalized, molecular oncology.

Nevertheless, one absolutely cannot discuss improving outcomes for cervical cancer without acknowledging that the vast global burden of this disease, particularly of LACC, occurs in low and middle income countries with limited relevant resources, namely a terrible lack of radiotherapy equipment. Without sufficient resources to deliver even the standard of care therapy to many women, oncologists in these settings are sometimes forced to ration treatments, minimize curative but resource-intense brachytherapy, and trial staying therapeutic approaches such as neoadjuvant chemotherapy prior to definitive RT or hysterectomy [10]. This stark global inequity is as true an enemy of improved outcomes as are the intricate molecular mechanisms underlying radioresistance. Thus, a concerted effort to improve access to the current standard of care alongside these translational studies is imperative to improve outcomes for cervical cancer [11]. Though the TME and Akt pathway signatures are great clues to follow, it is also the time to act on global oncologic inequity.

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