This is a thrilling time to be an oncologist. Recent breakthrough advances on a number of translational fronts have given renewed hope for cancers that have long been regarded as terminal disease. The Department of Radiation Oncology at Penn Medicine has spearheaded and received attention for several advances that have now reached standard-of-care or clinical trials, including for precision radiation/proton therapy, radio-immunotherapy, and circulating tumor cell (CTC) assays. Here we focus on non-small cell lung cancer (NSCLC) to describe recent exciting results that illuminate how circulating tumor cell and material assays may guide patient’s treatment and follow-up care. We found CTC assays give advanced lead time notice of tumor progression or recurrence for early stage (clinical stage 1) NSCLC undergoing stereotactic body precision radiation therapy (SBRT) as well as for locally advanced NSCLC undergoing chemo-radiation therapy. We will also touch on metastatic disease and potential ways CTC or circulating DNA assays may be guide salvage treatment and immunotherapy.