Identifying Molecular Determinants of Local Control After Radiation Therapy to Spinal Metastases from Non-Small Cell Lung Cancer (NSCLC)
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Purpose
Local failure is a common problem after conventional external beam radiation therapy (cEBRT) for spinal metastases from non-small cell lung cancer (NSCLC). Molecular determinants of this observed radioresistance to cEBRT are unknown. Determination of predictive biomarkers for cEBRT resistance could help identify patients who will benefit from upfront stereotactic body radiation therapy (SBRT) for spinal metastases from NSCLC.

Hypothesis
Specific genetic driver mutations and gene expression patterns in NSCLC confer resistance to conventional radiation therapy for spinal metastases, indicating that these patients may benefit from intensified upfront radiation treatment with SBRT.

Method of Research
Preliminary data indicates that subsets of common mutations in NSCLC are more frequent in patients who suffer progression after spinal radiation therapy. Here, we propose to sequence high confidence candidate genes for mutation rate in patients who do and do not experience progression after spine radiation therapy. We plan to perform targeted gene sequencing of 50 candidate genes from patients who underwent spine RT including a cohort that ultimately required surgical intervention due to progression. We will identify those mutations that are most closely associated with risk of progression after radiation therapy. These genes will represent a biomarker panel that can be investigated for predictive ability in future studies. Finally, we plan to modulate the identified genes in an in vitro cell culture system to determine their contribution to radioresistance. Through analysis of the molecular consequences of alterations in these genes, we will identify specific gene expression and cell signaling changes that promote radioresistance, and potentially represent therapeutic targets.

Expected Results
After completion of these proposed studies, we expect to develop a biomarker panel for NSCLC that predicts local control outcomes after spine RT and will guide personalized radiation therapy treatments. Identification of disrupted signaling pathways will motivate further molecular analysis of the tumor biology that drives metastatic NSCLC in the spine.