There is a fundamental need for comprehensive patient characterization and treatment response assessment in clinical oncology. Molecular imaging allows for survey of functional and biological characteristics of a patient's disease throughout treatment. Traditional integration of imaging in clinical care has relied on qualitative evaluation. The overall objective of this dissertation was to evaluate the utility of quantitative molecular imaging in two oncologic malignancies, non-small cell lung cancer (NSCLC) and metastatic castration-resistant prostate cancer (mCRPC).

In lung cancer, there is an urgent need to identify early-stage NSCLC patients at risk of postsurgical disease recurrence. We evaluated quantitative metrics from pre-surgical $^{18}$F-FDG PET/CT in early-stage NSCLC patients, correlating uptake patterns with outcome intervals. We found metrics describing uptake heterogeneity, including Entropy-GLCM, showed significant, independent associations with 5-year disease-free survival. We also reported significant differences in imaging metrics across squamous cell carcinoma (SCC) and adenocarcinoma (AC) histologies. Our work highlights this phenomenon influences population-level correlation to outcome, with enhanced characterization and predictive ability when accounting for histological differences.

Typically characterized by qualitative assessment, i.e. counting of lesions, quantitative biomarkers of mCRPC are in their infancy. We investigated quantitative $^{18}$F-NaF PET/CT metrics by evaluating individual lesions throughout treatment for complete disease assessment. Total function burden ($SUV_{\text{total}}$) of metastatic bone lesions determined by NaF PET/CT was the strongest correlate of progression-related events in a population of mCRPC patients. Response in $SUV_{\text{total}}$ assessed within 12 weeks of starting therapy could serve as a surrogate endpoint of progression-related events. mCRPC patients are largely evaluated on appearance of new or worsening lesions, our strong correlation to progression-related events indicates the bias of clinical decisions mediated by a small population of lesions could undersample patient benefit.

Finally, we have outlined the development and testing of a novel algorithm to guide clinical biopsies for patients with multiple tumors. Typical workflow of clinical biopsies in these cases are based on physician discretion. By combining quantitative imaging information with physician feasibility requirements, robust biopsy site selection in was achieved. This novel algorithm can serve as a basis for automatic site selection in any case of patients with multiple lesions.