Abstract

Inter-lesion heterogeneity, or differences between lesions in a patient, is known to exist in metastatic cancer patients. While inter-patient (between patient) heterogeneity is being accounted for through precision medicine approaches, these treatments are traditionally based on the information gathered from the biopsy of a single lesion, failing to account for inter-lesion heterogeneity. By failing to account for inter-lesion heterogeneity, treatment may be prescribed that is appropriate to treat one lesion, but not necessarily the rest of the disease. This work will take place in metastatic prostate cancer patients due to the disease burden (patients can have hundreds of bone lesions) which complicates the study of inter-lesion heterogeneity using traditional methods. As metastases are located primarily in bone, traditional biopsy is too invasive and acquires too little tumor content to study heterogeneity and its evolution. Molecular imaging, such as positron emission tomography (PET), offers a way to measure whole-body disease non-invasively. Due to its non-invasive nature, it is possible to not only study inter-lesion heterogeneity at a single timepoint, but also to acquire longitudinal imaging to study response heterogeneity. The overall goal of this thesis was to characterize, investigate, and integrate inter-lesion spatial heterogeneity into metastatic prostate cancer patient's treatment.

To this end, three questions were posited and answered in this work. The first question was, "How does heterogeneity evolve?" Two aspects of this evolution were studied: anatomic spread and response. The evolution of anatomic metastatic spread was studied in a composite cohort of three patient populations representing early-, mid-, and late-stage metastatic disease. Differences in anatomic distribution of disease burden between the early-, mid-, and late-stage populations were evaluated for 11 skeletal regions. While there were significant increases in the number of lesions in the appendicular skeleton from the early- to mid- and late-stage populations, the disease burden did not change significantly.

Next, evolution of response was assessed in the early patient cohort of metastatic castration-sensitive prostate cancer (mCSPC) patients receiving GM-CSF with or without a DNA vaccine (pTVG-HP) and scanned with ^{18}F-NaF PET at baseline, month 3, and month 6. Disease response from pre-treatment to month 3, and from month 3 to month 6 was evaluated to study the temporal evolution of response heterogeneity. Very few lesions evolved from responding to non-responding, or vice versa. Despite this, a significant decrease in the proportion of non-responding lesion was observed in the patients treated with the vaccine. Patients treated with the vaccine also had a significantly greater proportion of responding disease compared to those treated with GM-CSF alone. While no differences were found in the proposed measure of response heterogeneity, significant differences in disease dynamics were observed and demonstrates the potential of these response metrics.

The next question was, “How can heterogeneity act as a biomarker?” In parallel with the first question, biomarkers were also studied in terms of anatomic heterogeneity biomarkers and response heterogeneity biomarkers. To assess anatomic heterogeneity biomarkers, region-specific SUV metrics were extracted from 11 skeletal regions and the two composite regions. Several region-specific metrics from regions of the axial skeleton correlated to progression-free survival and several were more predictive of progression-free survival than their whole-body counterparts. Including metrics from anatomic regions increases the prognostic capabilities of quantitative NaF PET/CT when assessing disease in patients with metastatic prostate cancer. Substantial inter-lesion response heterogeneity was quantified and present in the late disease patient population. Quantitative measures of non-responding disease burden (number of lesions, SUV_{total}) were prognostic of progression-free survival, demonstrating the value of lesion-wise quantification of response.

The third question was, “How can heterogeneity be used to guide interventions?” Two interventions were considered: directing bone biopsies based on molecular imaging response, and prescribing radiation therapy to resistant disease sites. In our biopsy work, biopsies of two

lesions per patient were performed based on quantified lesion imaging response, sampling one partially responding and one progressing lesion per patient. This study confirmed inter-lesion response heterogeneity in two ways. The first was that biopsying progressing lesions obtained tumor in more cases than biopsying partially responding or stable lesions. Secondly, biologic validation was performed by looking for AR-V7, a known escape mechanism to enzalutamide treatment. AR-V7 was found only in biopsy samples from progressing lesions, suggesting that progressing lesions are resistant to therapy. The second intervention was a newly proposed method to select patients with oligo-resistant or oligo-progressive prostate cancer for metastasis-directed radiation therapy. This workflow utilized quantitative molecular imaging response to target resistant lesions with radiation therapy and will be tested for clinical feasibility in an upcoming clinical trial.

This work makes a case for incorporating considerations of disease heterogeneity as measured by quantitative molecular imaging into metastatic prostate cancer patient care. Not only does imaging enable the study of disease heterogeneity evolution, but heterogeneity biomarkers may be predictive of progression-free survival. Finally, two specific interventions are detailed to incorporate this heterogeneity into patient care.