Towards a risk-benefit optimized clinical decision support framework for immune-checkpoint inhibitor-treated metastatic melanoma

Daniel T Huff

Abstract:

Choices about the treatment of cancer require patients and their physicians to face a fundamental risk-benefit tradeoff between treatment efficacy and treatment-related toxicities. This trade-off is especially pertinent in the specific disease setting of metastatic melanoma (MM) where, over the past decade, a new class of immunotherapy drug called immune-checkpoint inhibitors (ICI) have drastically improved outcomes for MM patients while also being characterized by high rates of immune-related adverse events (irAE). The overall objective of this thesis is to describe a clinical decision support framework which considers the risk-benefit trade-off of treatment efficacy versus treatment-related toxicity using molecular imaging with ^{18}F-FDG PET/CT.

To achieve this, we retrospectively analyzed ^{18}F-FDG PET/CT images of MM patients treated with ICI. We had three specific areas of interest: (1) assessment of disease response, and (2) assessment of immune-related adverse events (irAE) and (3) combine disease response and irAE into a novel risk-benefit strategy to support clinical decision making. We made use of multiple retrospective datasets to develop and validate the software tools and decision support framework described in this thesis.

To assess the ability of quantitative ^{18}F-FDG PET/CT imaging metrics to predict disease response to ICI, ^{18}F-FDG PET/CT images of MM patients receiving anti-PD1 ICI were collected before treatment (baseline), after 3-4 months of ICI, and at treatment end. The performance of lesion autocontouring methods was characterized, and imaging predictors were evaluated for their association with patient outcome. Patients who demonstrated a high increase in disease volume, or who had one or more lesion increasing in ^{18}F-FDG uptake at the month 3 scan had significantly shorter progression-free survival than

patients who did not. This assessment was made possible by the analysis of lesion-level longitudinal changes in ^{18}F-FDG uptake.

To assess irAE, a convolutional neural network (CNN) was trained to segment eight organs relevant to irAE detection. CNN performance was benchmarked against interobserver variability in organ segmentation as assessed by a multi-reader study. In our study, ^{18}F-FDG uptake in the thyroid, lung, and bowel was significantly higher in patients who experienced immune-related thyroiditis, pneumonitis, and colitis, respectively. In some cases, organ inflammation seen on ^{18}F-FDG PET/CT and quantified with the CNN preceded clinical symptoms and diagnosis of irAE, suggesting that ^{18}F-FDG PET may have a role to play in the early detection of irAE. Whole-organ segmentation via CNN was a critical aspect of our approach, as the optimal imaging metrics for irAE detection were derived from the histogram of ^{18}F-FDG SUV from within the whole organ.

Finally, balancing the risk of irAE against the benefit of ICI treatment is a serious consideration for managing ICI patients. To this end, preliminary work combining quantitative assessment of disease response and irAE risk into a decision support framework aimed to optimize the risk-benefit tradeoff of ICI treatment is described. The framework's use is demonstrated in two example cases of selecting between multiple treatment options with differing probabilities of response and irAE, and longitudinal monitoring patient response to ICI during treatment. In treatment selection, we demonstrate why MM patients with lower risk tolerance may opt for anti-PD-1 monotherapy, while patients with higher risk tolerance may prefer combination ICI with anti-CTLA4 and anti-PD-1 ICI. For longitudinal monitoring, we examine a case report of an MM patient who achieves a complete response, but experiences immune-related colitis as a side-effect of ICI treatment. Evidence of response and toxicity is quantified on ^{18}F-FDG PET/CT and used to track the risk-benefit status of the patient in time.

The thesis concludes with a discussion of this work in wider clinical context and how the results presented here may improve clinical management of ICI patients and be further built upon in the future.