Iowa Initiative for Artificial Intelligence

Final Report

Project title:	Radiomic features of CT images of malignant melanoma tumors predict responses to checkpoint inhibition and immune activation
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Were specific aims fulfilled:	Y
Readiness for extramural proposal?	Y
If yes … Planned submission date	12/2020 – 3/2021
Funding agency	NIH
Grant mechanism	R01
If no … Why not? What went wrong?	

Brief summary of accomplished results:

The driving hypothesis of this research that

> *artificial intelligence (AI) utilizing a large cohort of labeled dataset produced by semi-automated segmentation and radiomic features could provide detailed insights into the tumor characteristics of tumor response under therapy and further predict the clinical outcomes of the therapy at its early stages*

was proven and feasibility of such predictions was demonstrated.

The main goal of the project was therefore to identify – from baseline and visit-1 CT imaging – which tumor will and which tumor will not respond to treatment (CMP-001, SD-101, TVEC, or Biovex), using only the two imaging sessions at 0 and 6 weeks.

The CMP-001 prediction accuracies on responding and non-responding lesions are 91% and 73% with an overall accuracy of 85%. The SD-101 prediction accuracies on responding and non-responding lesions are 100% and 40% with an overall accuracy of 80%. On the 3 lesions from 3 patients treated by TVEC or Biovex, the prediction accuracy is 100%.

The developed highly-automated approach to accurate 3D tumor segmentation followed by determination of CT-image-based radiomic features and RF machine learning offered a promising treatment-outcome performance level. A future prospective study is warranted to support further development of our approach in larger cohorts.

Research report:

Aims (provided by PI):

Aim 1: Authenticate computer segmentation of the CT images of tumors in patients with malignant melanoma

Aim 2: Correlate the radiomic features of pixel annotated images to patient response to novel immunotherapies

Aim 3: Curate larger image data sets (up to1000, or more) for artificial intelligence/machine learning training sets

Aims 1-2 fulfilled as planned, Aim 3 was overly optimistic and is being pursued as part of the follow-up grant submission.

Data:

A total of 90 scans were analyzed by two Board-Certified Body Imaging Radiologists using our LOGISMOS-JEI tool. Up to 3 visible lesions in the baseline scans were analyzed.

30 patients with metastatic melanoma undergoing IRB approved clinical trials were retrospectively identified and our retrospective IRB approved study. These patients either had TVEC viral intratumoral injections, CMP-00 or SD-101CpG oligodeoxynucleotide (ODN) intratumoral injections along with the checkpoint inhibitor therapy of pembrolizumab or nivolumab. The patients were imaged with a pre-defined follow-up set of 2 CT scans of chest, abdomen and pelvis after an initial baseline at the time of enrollment of the clinical trial.

AI/ML Approach:

The treatment outcome prediction was based on radiomics CT-image-based features computed on the segmented tumor tissue from baseline and the first follow-up scans. Supervised machine learning algorithm was implemented for classification using Python *sklearn* package. As many extracted features may be noise, or highly correlated with each other, Random Forest (RF) algorithm was selected to predict treatment response. Training RF to distinguish between different classes of objects is based on their features. This can be done using training samples in which objects are already (manually or using a different method) labelled. In our case, each lesion was treated as an independent object and labelled based on its volume change between baseline and the last follow-up (1: volume change >20%; 0: volume change<=20%).

Experimental methods, validation approach:

The analysis of each follow-up scan was performed with the results of baseline analysis visible to the radiologists to establish lesion correspondences at different time points and ensure consistent quality of the analysis. Lesions that only exist in the follow-up scans were excluded from the analysis. Among 79 lesions identified on baseline scans, 52 appeared in soft tissue or lymph nodes and have similar image appearances, the other 27 appeared in lung, liver, spleen and bone with larger appearance variations. The capability of treatment outcome prediction was assessed using the data of 52 lesions on soft tissue and lymph nodes. The outcomes of the treatment were derived from the percent volume change at the second follow-up comparing to the baseline on a per lesion basis. If the volume of a lesion decreased more than 20% at the

second follow-up, it was considered as responding to the treatment. 3-fold cross validation with complete training/testing set separation at the patient level was used to assess pilot approach performance.

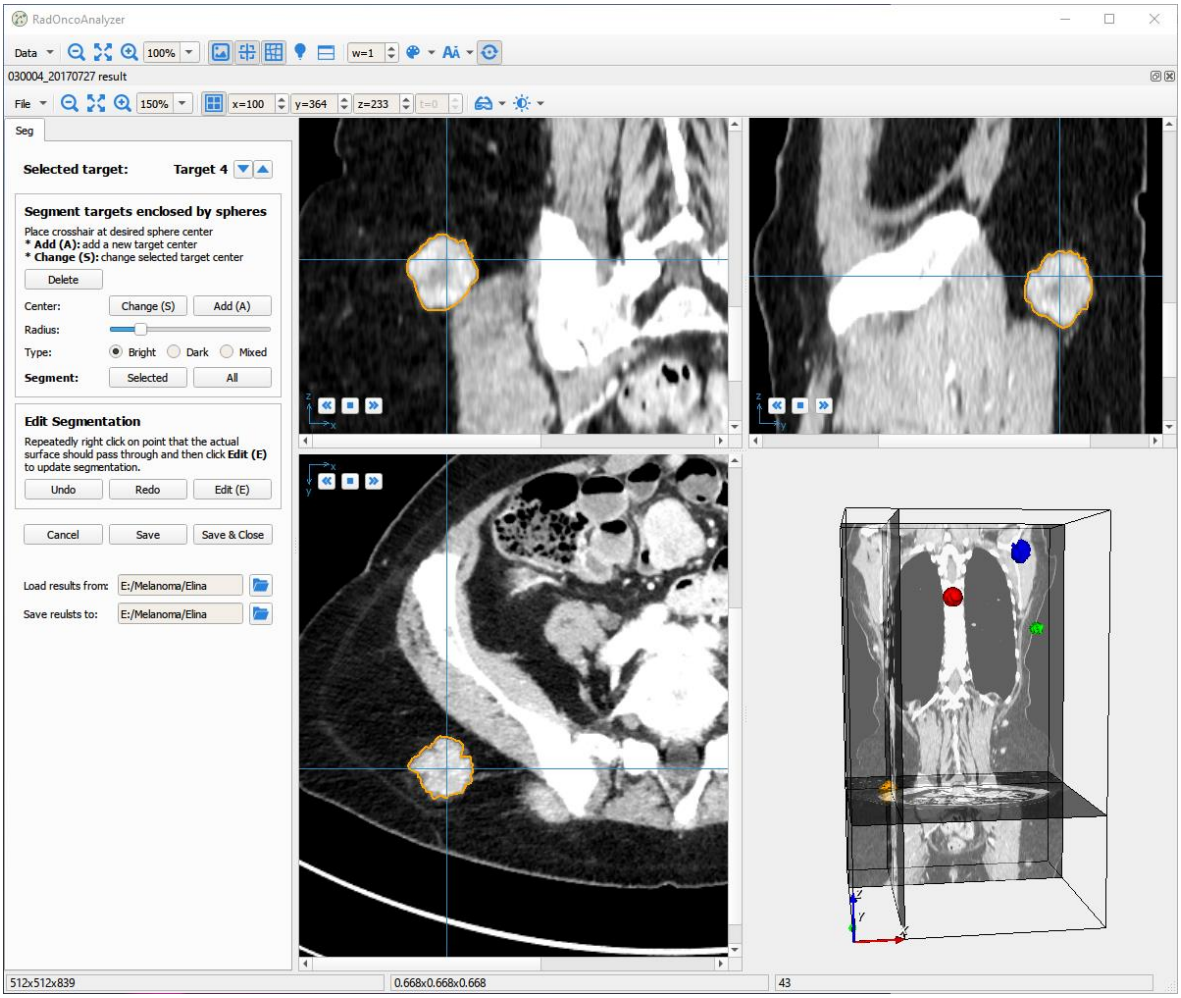

Figure 1. Screenshot of LOGISMOS-JEI segmentation of melanoma lesions.

Results:

The main goal of the project was to identify – from baseline and visit-1 CT imaging – which tumor will and which tumor will not respond to treatment, using only the two imaging sessions at 0 and 6 weeks.

Out of all 52 lesions tested, 34 responded to the treatment and 18 did not. The trained prediction models produced 94% and 67% accuracies on responding and non-responding lesions, respectively, and an overall accuracy of 85%. On 34 lesions from 18 patients treated by CMP-001 injection, 23 lesions responded to the treatment and 11 did not. **The CMP-001 prediction accuracies on responding and non-responding lesions are 91% and 73% with an overall accuracy of 85%**. On 15 lesions from 9 patients treated by SD-101 injection, 10 lesions responded to the treatment and 5 did not. **The SD-101 prediction accuracies on responding and non-responding lesions are 100% and 40% with an overall accuracy of 80%.** On the 3 lesions from **3 patients treated by TVEC or Biovex, the prediction accuracy is 100%.** Furthermore, on

13 responding lesions treated by CMP-001 that exhibited increased volumes at the first follow-up, the trained models predicted the final outcome with 100% accuracy. On 3 non-responding lesions treated by CMP001 that exhibited decreased volumes at the first follow-up, the trained models predicted the final outcome with 67% accuracy.

Ideas/aims for future extramural project:

The envisioned R01 grant proposal (Kuehn, Park PIs) will be written with the following ideas driving the proposal:

Hypothesis

Radiomic features of metastatic melanoma derived from sequential MR imaging can be used to predict the response to therapy using checkpoint inhibitors and directed immune activation.

Aims

Aim 1: Form a large retrospective cohort of at least 500 patients with metastatic melanoma for which sequential MR imaging data are available as follows:

- immediately preceding treatment with checkpoint inhibitors and directed immune activation
- 6 weeks (???) after starting treatment
- 6 months after starting treatment

Aim 2: Develop and assess performance of an AI approach that learns from past data how to predict the response to checkpoint inhibitors and directed immune activation therapies separately in soft tissue/nodal metastases and in liver lesions

- Part of this aim may be to determine whether soft/node and liver metastases require two separate or one combined AI tool
- Also, some rudimentary data from EMR should be also available – sex, age, BMI, etc.
- Also, demonstrate that 500 is enough to train (show that performance is not increasing from 450→500 while it is improving from 200→300→400→450 …)

Aim 3: Apply the developed method in a prospective (???) multi-center study assessing the method's performance in a cohort of at least 200 (???) patients from 5-10 clinical centers

- Explain why a prospective character is actually different from the retrospective one used for training
- Maybe show that the prediction can lead to a change in therapy sufficiently early (after 6 weeks?) so that the progression at 6(?) months is less frequent than when staying the course

OR

Aim 3 or 4 – not sure this is realistic – use the developed approaches to identify the best treatment from time 1 – and show that this approach is better than what is used now.

Publications resulting from project:

- Jinha M. Park, Honghai Zhang, Andreas Wahle, Yanan Liu, David Kuehn and Milan Sonka: Radiomic features in CT images of malignant melanoma tumors predict responses to checkpoint inhibition and directed immune activation. To be submitted to Radiology Imaging Cancer (RSNA journal – in preparation).