Longitudinal MRI based radiomics: Estimating rectal cancer response to chemoradiation

A. Rationale

Colorectal cancer is the most prevalent gastrointestinal cancer in the West; it is the fourth most commonly diagnosed cancer in the United States. Approximately a third of colorectal cancer cases are rectal cancer [1-2]. The current standard of care for rectal cancer involves neoadjuvant chemoradiation (NAC) followed by total mesorectal excision (TME) [3-4]. This technique has been employed since the 1980s when Heald et al. found it reduce recurrence rates to 2.7% percent in 1986. Since then, many studies have corroborated these low recurrence rates; however, TME is a highly invasive procedure, sometimes involving the removal of the entire rectum, with many possible surgical complications and adverse effects on quality of life, including the struggles of a colostomy [3, 5-6]. Additionally, the necessity of TME has been disputed, as up to 27% of patients have achieved a pathological complete response on NAC alone. [3, 7-8] Therefore, there has been an increased demand for the estimation of rectal cancer response to NAC during treatment in order to spare highly-responsive patients from the risks of TME. The apparent diffusion coefficient (ADC) is an established oncologic biomarker due to its ability to reflect tumor cellularity by measuring extracellular water diffusion, but its correlation with rectal cancer response to NAC remains unclear [7-10]. Radiomics features, or quantitative features extracted from medical images, provide potential solutions, as they have been correlated with rectal cancer response to NAC in the past [11-14]. However, radiomics features extracted from true fast imaging with steady-state precession (TrueFISP), an MRI commonly used for

rectal treatment planning, have yet been analyzed [15]. Additionally, previous studies fail to compare anatomical and functional MRI-based radiomics features while analyzing longitudinal changes in features. This study will aim to compare the estimative abilities of mean ADC values and longitudinal MRI-based radiomics features, while characterizing the most estimative radiomics features in terms of base image, feature category, time throughout NAC, and delta versus single time features.

B. Research Questions, Hypotheses, and Expected Outcomes

- Research Questions
    - How do the estimative abilities of mean ADC values, longitudinal ADC map-based radiomics features, and longitudinal TrueFISP-based radiomics features compare?
    - How do the following affect the classifying ability of radiomics features: 1) radiomics feature category, 2) time of image acquisition during NAC, and 3) delta versus single time features?
- Hypotheses
    - The extracted radiomics features will have superior estimative abilities due to the additional information provided by radiomics features when compared to the ADC.
    - Delta features and times toward the end of NAC will provide the highest estimative ability due to the information it provides regarding the tumor after several doses of treatment.

- Engineering goals
    - To identify and characterize the radiomics features with the strongest classifying ability for radiomics based prediction of rectal cancer response to chemoradiation.
- Expected Outcomes
    - Expected that longitudinal TrueFISP-based features will have superior estimative ability compared to mean ADC and ADC map-based features.
    - Expected that gray level co-occurrence matrix features, radiomics features from the middle and end of NAC, and delta radiomics features will have the strongest estimative ability [4, 7, 13].

C.

Procedure

Part I: Registering MRIs and extracting radiomics features

- TrueFISP MRI and ADC map data previously acquired from 10 UCLA rectal cancer patients will be handled and de-identified by PhD student, Yu Gao, and gifted for analysis, resulting in 10 MRI sets of each image type.
- Of the total imaging times available per MRI set, identify five times that are evenly distributed throughout the NAC course.
- For each MRI set, use the rigid registration function on MIM ver. 6.6.5 to register each of the MRIs from the four later times to the first. Adjust the alignment of the MRIs as necessary, and copy the gross tumor volume contour from the first MRI onto each of the later MRIs.

- Use PyRadiomics ver. 2.2.0 to extract 92 radiomics features from the TrueFISP MRI and ADC maps acquired at each time [16].
    - Download the parameter file from the PyRadiomics website and edit to only include the 18 first order, 23 gray level co-occurrence matrix, 16 gray level run length matrix, 16 gray level size zone matrix, 14 gray level dependence matrix, and 5 neighboring gray tone difference matrix features [16].
    - Save the TrueFISP-based and ADC map-based features into separate excel files.
- In preparation for feature evaluation, separate the features by MRI set into individual sheets within the excel file for each image type.
- For each MRI set, identify the first order mean feature from the first and last time among the ADC map-based features and save in a separate excel sheet. These are the mean ADC values to be evaluated.

Part II: Evaluating mean ADC values' estimative abilities

- Import the excel file containing the mean ADC values of the tumor contours per MRI set per time and each MRI set's Dworak grades.
- Open the mean ADC from the first and fifth time, the difference between the two, and the Dworak grade for each MRI set in a matrix.
- Identify the responders and non-responders as MRI sets with Dworak grades of 2, 3, or 4, and 0 or 1, respectively.
    - Open the responder and non-responder mean ADCs in separate matrices.

- Create a for loop that calculates the AUCs between responders' and non-responders': 1) mean ADC from time one, 2) mean ADC from time five, and 3) delta mean ADC between times five and one [7]. Record AUCs in a matrix.
- Graph boxplots of the mean ADCs from times one and five and the delta mean ADC comparing the values in responders versus non-responders.

Part III: Evaluating radiomics features' estimative abilities

- Write a program in Matlab R2015a to calculate delta features for later feature evaluation:
    - Import excel files containing TrueFISP-based and ADC map-based feature data.
    - Open the feature data into separate matrices, one for TrueFISP, one for ADC.
    - Separate features into five matrices, one for each time during NAC, and use the subsequent matrices to calculate delta features as differences in features between two times in NAC.
    - Open delta features into a separate matrix to be tested through the "leave-one-out" method.
- Write a program in Matlab R2015a to calculate the AUCs and testing and training accuracies of each radiomics feature with a "leave-one-out" logistic regression method:
    - Create a nested for loop such that for each feature, the feature for one MRI set will be left out once. For each time it loops:
        - Use the other nine MRI sets' feature and response data to construct a generalized linear regression with a logit link.
        - Use the regression line on the tenth MRI set and record the accuracy of the guess into a vector that will be used to calculate testing accuracy.

        - Use the regression line to estimate the responses of the other nine MRI sets. Store the accuracies of the guesses into a matrix to be used to calculate training accuracy.
    - Calculate the testing accuracy of each feature as a percentage out of 10. Record the testing accuracy in a matrix for all testing accuracies.
    - Calculate the average training accuracy of each feature by averaging each column of the matrix of training accuracies. Record the training accuracy in a matrix with all training accuracies.
    - Calculate the AUC between the feature values in responders versus nonresponders and record in a matrix containing the AUCs of all features.
- Graph the three features for ADC map- and TrueFISP-based single time, and ADC map- and TrueFISP-based delta features with the top testing accuracies as boxplots comparing feature values in responders versus non-responders.
- Concatenate the testing accuracies, average training accuracies, and AUCs of single time and delta features and use a threshold of 0.8 on both accuracies to identify the high-accuracy features.
    - Write the names, times, AUCs, and training and testing accuracies into an excel file.
- Identify the superior base MRI, and among these high-accuracy features, analyze the frequencies and relative frequencies of: 1) different feature categories, 2) times during NAC, and 3) single time versus delta features.

Risk and Safety

All procedures will be conducted computationally, therefore involving no risks and posing no risk to the other members of the lab.

1. Human participants research

Not applicable to this project.

2. Vertebrate animal research

Not applicable to this project.

3. Potentially hazardous biological agents research

Not applicable to this project.

4. Hazardous chemicals, activities & devices

Not applicable to this project.

Data analysis

Once the radiomics features have been extracted, mean ADC values are identified, and delta features are calculated, the AUC will be used to analyze the significance in the differences in mean ADCs and feature values between responders and non-responders [7].

Addendums

1. In addition, write a program in Matlab R2015a to calculate testing accuracies for each radiomics feature with a "leave-one-out" support-vector machine (SVM) method:
    a. Create a nested for loop such that for each feature, each MRI set is left out once. For each time it loops:
        i. Identify the ideal box-constraint for the SVM by:
            1. Running a second "leave-one-out" method with the nine MRI sets
            2. Using fitcsvm to with a variety of box-constraints with each of the nine combinations of eight MRI sets
            3. Averaging the testing accuracies of each box-constraint to identify the maximum accuracy box-constraint
        ii. Use the ideal box-constraint to generate an SVM from the nine MRI sets feature and response data
        iii. Use the SVM to predict the response of the tenth MRI set
    b. Record the correct or incorrect guesses on each run in order to calculate the overall testing accuracy of each of the features at the end of the loop.
2. Write a program in Matlab R2015a to identify the most highly selected features
    a. Read the names of the high-accuracy features selected by both the LR and SVM "leave-one-out" methods into a single cell array
    b. Create a nested for loop to identify and count the frequency of each of the 92 radiomics features among the cell array of all selected features
    c. Save the frequencies into an excel sheet

D. Bibliography

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