Predictive Model for Assessment of Pathological Response of Colorectal Liver Metastases to Chemotherapy from CT Images

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Abstract

In this work, we propose a predictive deep learning model for assessment of pathological response of colorectal liver metastases to chemotherapy from CT images. We conducted a retrospective analysis of a prospectively maintained database of patients who underwent partial hepatectomy or biopsy of colorectal liver metastases. We introduce a novel variant of the Inception module that includes instance normalization layers to accommodate for various contrast agent timing and baseline examinations. The clinical Rubbia-Brandt tumor regression grade (TRG) obtained from histopathology images of the resected lesions was used as ground truth. For the most common TRG dichotomization, our model achieves an AUC of 0.87 ± 0.03. The results show that the model is able to establish a link between CT images and the pathological assessment.

1 Introduction

Colorectal cancer (CC) is the second most common cancer in women and third in men with an estimate of 1.3 million cases per year according to the World Health Organization\textsuperscript{[1]}. At a population level, early screening is challenging which partially explains why more than 50% of the patients develop colorectal liver metastases (CLM). Surgical resection is the most commonly accepted curative therapy for CLM, offering a five-year survival rate up to 58% in selected cases\textsuperscript{[2]}. When tumors are unresectable, the conventional approach is “conversion treatment”, which consist in reducing the tumor size trough chemotherapy. This technique allows up to 38% of patients initially deemed ineligible to become eligible for hepatic resection\textsuperscript{[3]}.

Response Evaluation Criteria In Solid Tumors (RECIST)\textsuperscript{[4]} is a set of published rules for objective assessment of treatment response with CT or MRI patients with cancer. The results are based on whether tumors volume disappear, regress, remain stable, or increase in diameter. Despite being widely used, this method is known for having limitations since lesion size does not adequately describe treatment response\textsuperscript{[5]}. After surgical resection of CLM, the tumor regression grade (TRG)\textsuperscript{[6]} is used to assess the response to chemotherapy. The TRG is an accepted ground truth based on histopathological assessment and encoded in a 5-point ordinal system ranging from 1 = absence of residual cancer to 5 = residual cancer.

The use of deep learning techniques in several medical imaging applications has exploded following the success of AlexNet\textsuperscript{[7]} in the ImageNet competition\textsuperscript{[8]}. A recent survey presented by G. Litjens...
et al. [9] emphasizes the vast use of deep learning techniques applied to different fields in medical imaging, but also stressed the need to properly validate these models with respect to specific medical needs.

In this work, we propose a deep learning model inspired from InceptionNet to learn the relationship between immediate post-treatment follow-up CT images and pathological response by the use of TRG as labels during training. An appropriate assessment of chemotherapy response is critical for treatment planning as it helps oncologists decide patients must undergo a second round of chemotherapy or even change the chemotherapy regimen.

2 Materials and Methods

2.1 Clinical Dataset

In this work, we used a private dataset from a prospectively maintained hepatobiliary biobank consisting of CT volumes, histology images and clinical information from 514 consenting patients treated at the Centre Hospitalier de l’Université de Montréal. The dataset contains 984 colorectal liver metastases. For our experiments from the aforementioned initial dataset, we selected a subset of data points that contains post-treatment CT volumes. The clinical Rubbia-Brandt TRG [6] on resected CLM was used as the ground truth. For our experiments, we selected lesions with an axial slide area greater than 100 mm$^2$. According to several authors, small lesions are difficult to assess because they are close to the physical limits of CT resolution [4]. The final number of lesions for our experiments was 112 belonging to 111 different patients. Since the size of the dataset is limited, we chose the axial slice with the largest area for a given lesion and up to 8 adjacent slides when lesion size would allow it. This strategy increased the number of data points up to 1310. For each lesion, a segmentation was performed and validated by a radiologist. We used these segmentation masks to create the images of the axial slices, but instead of applying the mask we created bounding boxes including at least 10 mm of surrounding lesion tissue. Since the CT volumes were acquired using different equipment and spatial resolution, we performed a spatial re-sampling to 1 mm × 1 mm × 1 mm.

2.2 Predictive Outcome Network (PONet)

Our network is based on a GoogleLeNet [10] model, where we used Inception blocks interspersed with Maxpool layers for features extraction at hierarchical levels. Following the feature extraction layers, three fully connected layers (FC) are used for classification. The first and second FC layers consisted of 256 neurons, followed by a dropout layer (drop rate = 0.4). Dropout was used to reduce over-fitting and to improve model generalization. For more details about model architecture, see Figure 1.

![Figure 1: Model architecture.](image)

The blocks from the Inception architecture address the common problem of large variations in the spatial location of targets. In medical images, the same object can be observed at different scales. Choosing the appropriate kernel size for convolutions is challenging since metastases can vary widely in volume. Moreover, the computational cost increases with the kernel size. To solve this problem, a concatenation of multiple feature extraction filters were used. Extraction with different kernel sizes
and pooling steps are processed in parallel, and all extracted features are concatenated at the end of the Inception module. The best feature extraction filters were chosen through back-propagation. Since lesions have different size batch size must be 1, then the use of batch normalization technique \textsuperscript{[11]} is not possible. Here we introduce an Inception module variant that performs contrast normalization by including Instance normalization layers (INL) \textsuperscript{[12]} after each convolutional filter on the Inception module. This normalization is performed element-wise and does not require the batch size to be > 1. That characteristic makes INL perfect for radiology applications. The use of the proposed Inception variant speeds up the training process and improves the model performance compared to the original Inception module.

3 Experiments and Results

For the conducted experiments, the dataset split was 60\% of images for training, 20\% for validation, and 20\% for testing. In order to compensate for dataset imbalance in the training process, oversampling was performed. The testing dataset remained unbalanced to maintain the original distribution between responsive and un-responsive patients. We report mean metrics and standard deviation based on five-fold cross-validation. We selected balanced accuracy and f1-score metrics. Also, we report sensitivity and specificity as shown in Table 1. Figure 2 presents the performance of our classifier from the classification experiments, yielding an overall AUC of 0.87 ± 0.03 for the dichotomization of TRG 1-2 vs. 3-4-5, compared to an AUC of 0.76 ± 0.03 for the dichotomization of TRG 1-2-3 vs. 4-5.

Table 1: Results table.

| Experiment | Balanced Accuracy | f1-score | Sensitivity | Specificity |
|------------|-------------------|----------|-------------|-------------|
| TRG 1 vs. 2-3-4-5 | 0.81 (0.09) | 0.92 (0.02) | 0.92 (0.04) | 0.70 (0.21) |
| TRG 1-2 vs. 3-4-5 | 0.78 (0.03) | 0.81 (0.03) | 0.81 (0.04) | 0.75 (0.05) |
| TRG 1-2-3 vs. 4-5 | 0.68 (0.01) | 0.67 (0.01) | 0.79 (0.10) | 0.60 (0.02) |
| TRG 1-2-3-4 vs. 5 | 0.85 (0.08) | 0.93 (0.03) | 0.79 (0.20) | 0.91 (0.05) |

Figure 2: ROC curve for different experiments.

4 Discussion and Conclusion

Based on the generated ROC curves, presenting the classification performance to predict the clinical TRG, the model seems to be able to generalize well across the different response groups and identify early stage features related to tumor reaction to drug regiments. The green and red lines represent the extreme dichotomizations where the most antagonistic classes are faced, making it easier for the model to accomplish the task, yielding promising results. The yellow curve represents the most natural dichotomization but is more challenging for the model to determine a well-defined threshold.
between TRG classes 2 and 3. Finally, the orange line represents a counter-intuitive split since TRG 3 is closest to non-pathological response and similar in appearance to TRG 4. The results reflect what is expected in clinical practice since we are forcing the model to learn a mislabeled data. All these demonstrate that our model is able to establish a relationship in learned features between CT data and pathological response determined from histopathology. Future work will consist of using Siamese Networks trained in a few-shot learning scheme in order to obtain better results on a small dataset like ours.

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