

# **Multimodal Machine Learning for mCRC: Designing a Radiopathomics Pipeline for Therapy Response Prediction**

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## **Abstract**

In the contemporary medical landscape, artificial intelligence (AI) has emerged as a powerful tool for automating complex tasks with reliability and precision. AI-driven biomarkers extracted from medical images, including radiological and histopathological data, have gained significant interest for their ability to provide valuable insights into clinical diseases. Notably, AI has demonstrated success in oncology, supporting diagnosis, prognosis, and outcome prediction, enhancing clinical decision-making and patient management.

This doctoral dissertation addresses a critical unmet clinical need in metastatic colorectal cancer (mCRC), one of the most common and lethal cancers worldwide. A high proportion of patients are diagnosed with metastases or develop them within a short timeframe. Currently, the standard therapeutic approach follows a "one-fits-all" strategy, where all metastatic patients undergo chemotherapy, despite only a small percentage responding to treatment. Consequently, non-responders suffer unnecessary toxicity without therapeutic benefit. To address this challenge, this dissertation aims to design and develop an AI pipeline to predict chemotherapy resistance of mCRC patients, enabling more personalized and effective treatment strategies while minimizing toxic side effects.

A comprehensive review of the state of the art was conducted to assess existing approaches for mCRC patients. AI studies based on both radiological and histopathological images, i.e., radiomics and pathomics studies, have demonstrated the potential of AI in addressing various clinical tasks related to mCRC. However, there is a lack of robust and validated AI systems specifically designed to predict chemotherapy response. Studies exploiting a combined radiopathomics approach have shown superior performance over single-modality models in several applications. Nevertheless, no radiopathomics study has yet addressed this particular clinical question.

Therefore, histopathological and radiological images were processed to develop a robust pipeline to predict mCRC therapy response. Given the small number of patients with both modalities, two different pipelines were designed and developed, one for each imaging modality. Then, the best radiomics and pathomics models were integrated into a final radiopathomics model to predict mCRC therapy response. Several technical aspects were addressed during the development of the two pipelines.

In the radiomics pipeline, an unsupervised dataset analysis was performed to better understand the dataset's characteristics and identify potential biases affecting the radiomics features. This analysis helped us detect outlier pixel values and image acquisition parameters that were skewing the feature values. Within the pathomics

pipeline, we investigated the unresolved technical question of target patch selection for stain normalization. Our findings revealed that this choice not only influenced the colorimetric appearance of normalized patches but also altered their structural content, potentially affecting the extracted features. Then, we implemented the Bag of Words (BoW) method to aggregate patch-level features at the patient-level. In this context, we explored the challenge of determining the optimal number of clusters in unsupervised analysis, demonstrating how different cluster validity indices can provide diverse insights into the obtained clusters.

After addressing biases, normalization, and patch aggregation, feature selection and classifiers were evaluated for generalization robustness within both pipelines. The most stable models were then assessed on the final dataset division, demonstrating moderately high performances on the test set. Finally, the best-performing radiomics and pathomics classifiers were combined and evaluated using leave-one-out cross-validation to assess their predictive performance. This multimodal approach achieved overall higher performances compared to unimodal models and enhanced prediction confidence, highlighting the potential of radiopathomics in improving chemotherapy response prediction.

In conclusion, this dissertation highlights the critical importance of carefully supervising each stage of the design and development of a multimodal pipeline that integrates radiological and histopathological images, particularly when working with small datasets. This multimodal approach mirrors the medical decision-making process, where specialists from different disciplines collaborate to evaluate the same patient. Similarly, by combining routinely collected radiological and histopathological images, AI has the potential to autonomously uncover novel predictive biomarkers, ultimately supporting clinicians in making more informed therapy decisions for mCRC patients.