Integrating Vision and Language Models for Interpretable Resectability Prediction of Pancreatic Ductal Adenocarcinoma

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1 INTRODUCTION

Pancreatic Ductal Adenocarcinoma (PDAC), the predominant malignant form of pancreatic cancer, is the seventh leading cause of cancer death globally despite only being the 14th most common cancer [23]. The preoperative assessment of resectability for PDAC presents an ongoing challenge for healthcare professionals, mainly due to the risk of overestimating the tumor's resectability. Currently, surgical resection of the tumor combined with systemic therapy is the only potentially curative treatment option available for PDAC patients [28]. Despite advances in medical research and treatment methodologies, due to its aggressive nature, interobserver variability, and limited responsiveness to current treatment options, healthcare professionals are cautious about proceeding with high-risk surgeries [17, 20, 26].

As a highly heterogeneous disease, genetic mutations and diverse contributing factors make it difficult to pinpoint the potential origins of the tumor [11, 21]. However, the National Comprehensive Cancer Network (NCCN) guidelines recommend conducting a preoperative diagnostic from imaging through a multi-phase computed tomography (CT) to classify resectability [12]. Specifically, medical professionals are tasked with relying on their observations, as the determination of resectability depends on their capacity to identify factors such as the tumor's relationship with blood vessels, and the existence of metastatic disease [2]. Despite these potential limitations and risk of human error, the assessment of inter-observer agreement between healthcare professionals for both overall resectability status and specific vascular involvement has been positive as experience and personal interest in pancreatic cancer are more influential than the number of patients at a hospital or the hospital's specialty in ensuring assessment consistency [12].

Resectability is summarized into three classification categories: Resectable (RES), Borderline Resectable (BR), and Unresectable Locally Advanced (LA). Valuable noninvasive and informative information regarding the entire tumor is extracted using radiological imaging. RES PDAC is described as a tumor without contact with the superior mesenteric or common hepatic artery. In contrast, BR PDAC is a tumor that contacts less than 180 degrees of either the superior mesenteric artery or common hepatic artery. Meanwhile, LA PDAC is defined as a tumor that makes contact with more than 180 degrees of the superior mesenteric artery or common hepatic artery [12].

Hence, adopting a non-invasive, interpretable AI-powered model could serve as a transformative tool for the preoperative evaluation of PDAC while distancing itself from radiomic feature extraction. A novel standard in the accuracy and reliability of PDAC resectability predictions will be developed through the use of integrating visual data through Vision Transformers (ViT) and textual data through Large Language Models (LLM) transformer models may provide leverage in improving patient management and move away from radiomic feature extraction.

2 RELATED WORK

This section reviews existing literature on automated PDAC detection, deep learning models in PDAC research, and the emergence of transformer technology in cancer research. It highlights the novelty and necessity of the proposed approach compared to traditional methods and the potential of multimodal transformers in overcoming existing predictive limitations.

2.1 PDAC Research

2.1.1 Segmentation approach for PDAC Detection. In identifying PDAC, radiologists must evaluate various features that indicate the presence of the tumor, including a mass within the pancreas, dilated pancreatic ducts, and vascular involvement [4]. Thus, semi-supervised learning for accurate segmentation of tumors and vasculature from CT scans demonstrates the potential to enhance the observability precision of vascular involvement by leveraging radiomic features to provide a comprehensive analysis of tumor characteristics [5]. Segmentation is a process that involves dividing an image into multiple regions to simplify, providing a more meaningful representation for analysis. Therefore, the reliability of radiomic features is heavily influenced by the segmentation quality since they are quantitative measures extracted from medical images that describe tissue and lesion characteristics such as heterogeneity and shape [13]. For the model to learn effectively, it is essential that experienced radiologist refine and manually pre-segment the volume of interest in the CT scans [14]. Moreover, deep learning emerged as a promising approach for developing segmentation models in pancreatic research [8]. Following this advancement, implementing deep learning models and radiomics on automated detection of pancreatic tumors through contrast-enhanced

CT scans is possible. Subsequently, the success in segmentation created opportunities to develop additional features for PDAC detection [32].

2.1.2 *Machine learning approaches in PDAC Resectability.*

Throughout this section, the machine learning approaches demonstrate remarkable accuracy, offering the potential to deliver expert confidence in their decision. However, throughout the studies, model performances are heavily criticized due to validation availability. The study by Baecker et al. discusses potential limits in data such as the age group boundaries, reduced predictive capability of the model when excluding patient data from the last three months prior to pancreatic ductal adenocarcinoma (PDAC) diagnosis, and omission of predictive factors (eg. back pain). Nonetheless, the insights by Jia et al. show that various models, such as both a custom neural network (PrismNN) and a logistic regression (PrismLR), can sufficiently classify resectability through the use of only data from the Electronic Health Record (EHR). EHR data encompasses diverse textual and numerical information such as demographics, diagnoses, laboratory test results, medication orders, and procedural codes. On the other hand, attempts are being made to identify PDAC through only visual data. Alternatively, efficient visual deep learning networks such as ResNet and DenseNet combined with supervised learning algorithms have also shown promising results in validation studies [19]. Long Short-Term Memory network, CE-ConvLSTM proposed by Yao et al., has been utilized to address the limitations of current predictive models by predicting survival outcomes and resection margin status. AI-based models such as VasQnet and VasQNet with rule-based decision deferral (RBDD) could use AI-generated segmentations to classify tumor resectability. Additionally, the VasQNet extension can compare classification with ground-truth observations made by radiologists [6].

Moreover, the emergence of Transformers has provided insights into PDAC research. A dual approach by Dong et al. developing a texture-aware transformer that combines CNN and transformer modules demonstrates improved accuracy. The model integrates features from the CNN and transformer blocks to facilitate the fusion of cross-modality features. Thus, classifying the degree of vascular invasion and predicting overall survival times creates a possible prognosis for PDAC patients.

2.2 Transformer Research

Transformers are in contention to replace Recurrent Neural Networks (RNNs) and Convolutional Neural Networks (CNNs) due to their scalability and parallelizability [24]. Moreover, in cancer research, more comprehensive information about the tumor and its relationship with surrounding structures can be achieved due to transformers' inherent interpretability. Xia et al. discusses the increase with healthcare professionals seeking a second confirmation through an interpretable approach. Nonetheless, the evaluation of multimodal transformers remains an emerging area of medical research.

2.2.1 *Vision Transformers.*

The Vision Transformer (ViT), introduced by Dosovitskiy et al., is a model that is overtaking CNN in image recognition tasks after its success in natural language processing (NLP); the advantages include its key component of self-attention. Unlike CNNs, transformers can weigh the importance of different patches of images that are linearly embedded while attaching positional embeddings; this enables the model to capture contextual meaning. In PDAC research, a study utilizes an anatomy-guided transformer on non-contrast CT scans that accurately detects resectable pancreatic masses by distinguishing PDAC from other pancreatic abnormalities or normal pancreas [29]. The models surpass the diagnostic performance of human radiologists in the study's evaluations as enhancement of sensitivity and specificity is evident [29]. However, non-contrast CT scans may not provide as detailed information about the vascular structures, tissue differentiation, or organ perfusion as the standard contrast-enhanced scans.

2.2.2 *Large Language Model Transformers.*

LLMs can generate rich contextual embeddings for text that enable them to capture semantic information effectively. Prominent LLMs such as Generative Pre-trained Transformer (GPT) and Bidirectional Encoder Representations from Transformers (BERT) are emerging due to their adaptability and ability to handle multi-modal inputs and generalize across various domains. However, they have different applications. In medical applications, LLMs obtain the potential to be alternative expert systems when fine-tuned on domain-specific information. Therefore, LLMs have the potential to be trained with the newest medical research to facilitate improving access to medical knowledge and supporting clinical decision-making [18]. Given that the heterogeneity of the disease makes it difficult for experts to summarize the extent of the severity since LLMs can consider various variables such as EHR characteristics and medical history. Thus, LLMs are able to extract embeddings from these variables and those from EHRs [7].

2.2.3 *Multi-modal Transformers.*

Multi-modal transformers aim to leverage and integrate information from multiple data modalities, such as text and images. The findings from Xu et al. emphasize the self-attention mechanism, allowing the model to focus on relevant parts of the input from different modalities.

3 RESEARCH QUESTIONS AND OBJECTIVES

The primary research question is: How can integrating Vision and Language data enhance the interpretability and accuracy of resectability for Pancreatic Ductal Adenocarcinoma?

Sub-questions include:

- What are the optimal features that can be extracted from vision and language data?
- How does the accuracy of resectability prediction change when addressing predictive limitations in the context of scarce data?
- How can the choice of fusion strategies influence the importance of either modality?

- What are the challenges and opportunities in integrating Vision Transformer (ViT) with Language Model (LLM) Transformer for multimodal prediction?

4 HYPOTHESES AND CONTRIBUTIONS

The thesis hypothesizes that integrating ViT and LLM Transformers will significantly enhance the accuracy of PDAC resectability predictions, offering a scalable and explainable AI solution.

Explainable Artificial Intelligence (XAI) in medical research is essential as models have to be more transparent, interpretable, and understandable for experts. Thus, ViT and LLM's could excel in its explanatory abilities and provide insights into the model's decision-making process. By incorporating a wide range of information across different modalities, leveraging ViTs and LLMs in healthcare settings will allow medical professionals to benefit from improved diagnostic accuracy, personalized treatment plans, and efficient patient care. Alternative methods like deep learning can enable the acquisition of new patterns and offer alternate ways of utilizing data.

5 MATERIALS AND METHODS

The methodology involves training a ViT on imaging data, utilizing an LLM Transformer to process structured text data from health records, and combining both for multimodal prediction. This includes processing raw imaging and structured EHR data, fine-tuning pre-trained models, and employing a fusion approach for final classification.

5.1 Dataset

The study will utilize a dataset comprising 126 scans indicating locally advanced PDAC and 344 scans for resectable and borderline cases from the Amsterdam University Medical Center. Additionally, EHR Data for each patient is provided.

5.2 Software

The open-source machine learning framework used is PyTorch due to its ease of use. The libraries to test pre-trained models will be extracted from the Hugging Face library.

5.3 Vision Transformer

5.3.1 Data Augmentation. Since the data has been segmented, augmentation through rotation in the axial direction and selecting cropped regions to shift are viable options discussed in previous research. However, other augmentation techniques will be applied to maximize accuracy.

5.3.2 Data Balancing. A vital consideration throughout the vision transformer literature is the limitation on data validation. However, data handling methods such as the Difference Enhancement-Random Sampling (DERS) and nested N-fold Cross-Validation described by Jiang et al. and [9] are a viable option to overcome these limitations.

5.3.3 Model Selection. The model selection will be determined based on fine-tuning pre-trained ViT models on the medical images. The model will aim to extract relevant features that could indicate the resectability of PDAC, such as tumor size, location, and involvement of surrounding tissues or vessels. To do this, the model's final layer must be modified to output feature vectors instead of the classification labels. Popular transformer architectures are DEiT and BEiT with research shown that on medical classification, vision models pre-trained on ImageNet have seen to be effective, thus, other options such as COCO, JFT-300M, and OpenImages can be potentially used to pre-train the transformer.

Model complexity will be regulated by implementing intrinsic methods into the transformer architecture.

5.3.4 Norm regularization. L1 regularization in the transformer layers can be used to encourage sparsity in the model parameters by adding a penalty to the cost of the weight. The benefits include preventing overfitting and enhancing the model's data generalization.

5.3.5 Activation Functions. Replace traditional activation functions with laterally inhibiting activation functions such as the Softmax Linear Units (SoLUs).

5.3.6 Weight Regularization. Dropout is a regularization technique that affects the network's structure by randomly omitting the connections of a subset of neurons during training. Dropout can be applied to the transformer layers in various forms, this includes applying it in the embedding, attention, Feed-Forward Networks (FFN) or intermediate layers.

5.3.7 Loss function. Similarity in tumor cells contribute to the existence of noise, thus, the symmetric cross-entropy loss function can prevent overfitting [27]. Other potential insights and considerations during the research that could significantly benefit the model include adversarial robustness, continual learning, modularity, and compression [22].

5.4 Large Language Model

The choice of architecture will depend on the approach and the type of data that will be chosen. An encoder architecture will focus on extracting features from the EHR text. By extracting these features only, the integration with features extracted from CT scans will be feasible. Therefore, pre-trained models such as BERT are optimal for this scenario. An extension to the methodology would be to include decoders, as they efficiently generate descriptive captions for images and can transfer patient information into a comprehensive narrative. For example, GPT could generate explanations based on the trained images, which could also prove immensely beneficial for transparency. Therefore, after analysis of the EHR data, the approach can be judged based on the most optimal feature extraction for the input of the multimodal [1].

5.4.1 Data Pre-processing. Data Augmentation will be applied to encourage robustness and generalizability of the model due to the limited amount of data available.

5.5 Multimodal approach

The fusion mechanism is a core feature distinguishing multimodal transformers from unimodal models. Moreover, two multi-modal architectures differ based on the required results: the encoder and the encoder-decoder. The encoder architecture will be more significant in this research as the expected feature extraction from the ViT and LLM will be combined at the input level of the transformer. Pre-trained models such as CLIP and OWL-VIT successfully make a pair prediction of image and text [1].

5.5.1 Fusion methods. The fusion method will depend on which modality will be more influential in representation, the computational and complexity demands of each modality, and the importance of interpretability.

Sequential fusion would be a viable option as it is useful when one modality provides contextual information for another. Thus, processing one type of data first, most likely images, and then using the output to generate a caption could be significant for the final classification. On the other hand, early fusion can convert images into textual descriptions through image captioning while combining additional text inputs from the raw EHR data before processing them for classification.

6 EXPECTED OUTCOMES AND POTENTIAL CHALLENGES

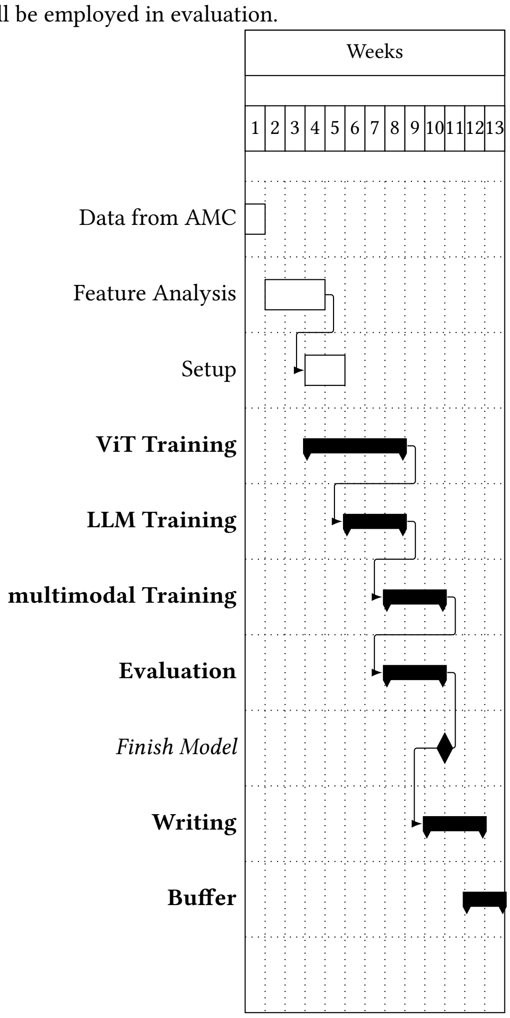
The project expects to develop a cutting-edge predictive model that leverages the integration of Vision Transformer (ViT) and Large Language Models (LLMs) for the early detection and accurate assessment of pancreatic ductal adenocarcinoma (PDAC) resectability. Additionally, the project will hope to advance in intrinsic transformer model interpretability, offering insights into decision-making processes, potentially through novel visualization techniques that map model focus areas against clinical significance. Hopefully, a substantial increase in the accuracy of PDAC resectability assessments can lead to more personalized and effective treatment plans, potentially reducing unnecessary surgeries. The main challenge is to effectively integrate visual and textual data and balancing the dataset to mitigate class sample bias.

7 RISK ASSESSMENT

The risk assessment will cover potential data and methodological challenges, with a contingency plan outlined for each identified risk. Firstly, computation and complexity of creating a vision transformer from scratch without a pre-trained model may require an abundance amount of time. Therefore to prevent time constraints, Fine-tuning a pre-trained model will be developed first. Secondly, the structure of the EHR data may result in insufficient features for the LLM to extract, therefore, open-source datasets will be considered to augment the data [25]. Alternatively, if the LLM proves to be inaccurate, the option of a Decision Tree or Reinforcement Learning to analyze the EHR data is viable. Ultimately, if the models do not fuse to make an accurate model, a pre-trained multi-modal model will be used.

8 PROJECT PLAN

A detailed project plan will include milestones for building prediction models, integrating multimodal learning, and intrinsic interpretability strategies. The overarching plan is to create a successful multimodal prediction model that can classify the resectability of PDAC through ViT and LLM. The first milestone will focus on building a vision-only pre-trained ViT, in the same time the second half will be dedicated to the non-pre-trained vision model. Once completed, the focus will shift to using a pre-trained LLM on EHR data. Alternatively, if the LLM proves to be inaccurate, the option of a Decision Tree or Reinforcement Learning to analyze the EHR data is viable. Ultimately, a fusion technique will be applied between the two models. A pre-trained multimodal will be dedicated during the weeks of "evaluation" and "finish model". The intrinsic interpretability strategies will be employed in evaluation.



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