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Predicting Efficacy of Immune Checkpoint Inhibitors in Targeted Oncology Therapy using Multi-Modal Deep Learning

James Smith, Robert Anderson, William Miller

Faculty of Health Sciences, University of Cape Town, Cape Town 7925, South Africa

Abstract

The advent of immune checkpoint inhibitors has revolutionized the landscape of oncological treatment, particularly for solid tumors such as melanoma and non-small cell lung cancer. However, the efficacy of these therapies remains heterogeneous, with a significant fraction of patients failing to exhibit a durable objective response. Traditional biomarkers, including PD-L1 expression levels and tumor mutational burden, lack the requisite sensitivity and specificity to accurately stratify patients in a clinical setting. This paper proposes a comprehensive multi-modal deep learning framework designed to predict the therapeutic efficacy of immune checkpoint inhibitors by integrating whole slide histopathology images, genomic sequencing data, and baseline clinical demographics. By employing a late-fusion architecture that utilizes attention mechanisms to weigh the relative importance of distinct modalities, the proposed model captures the complex non-linear interactions between the tumor microenvironment and the host immune system. Experimental results on a large-scale retrospective cohort demonstrate that this multi-modal approach significantly outperforms unimodal baselines and current standard-of-care biomarkers. The study provides a pathway toward precision immuno-oncology, highlighting the critical role of artificial intelligence in deciphering the biological heterogeneity of cancer response mechanisms.

Keywords

Immuno-oncology, Multi-modal Deep Learning, Predictive Modeling, Computational Pathology.

1 Introduction

The introduction of immunotherapy, specifically agents targeting the programmed cell death protein 1 (PD-1) and its ligand (PD-L1), along with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has fundamentally altered the therapeutic paradigm for advanced malignancies. Unlike cytotoxic chemotherapy or targeted kinase inhibitors, immune checkpoint inhibitors function by reinvigorating the host immune system to recognize and eliminate neoplastic cells. Despite the remarkable success observed in subsets of patients with melanoma, renal cell carcinoma, and non-small cell lung cancer, the majority of patients do not derive clinical benefit. Approximately seventy to eigh ty percent of patients across various indications fail to respond, exposing them to potential immune-related adverse events and significant financial toxicity without therapeutic gain [1]. Consequently, the identification of robust predictive biomarkers remains one of the most pressing challenges in contemporary oncology.Current clinical practice largely relies on immunohistochemical assessment of PD-L1 expression and the evaluation of tumor mutational burden. While these metrics are correlated with response, they are imperfect predictors. PD-L1 expression is dynamic and spatially heterogeneous, leading to sampling errors, while high tumor mutational burden does not universally guarantee immunogenicity. This diagnostic gap necessitates the development of more

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sophisticated predictive tools that can integrate the multifaceted determinants of immune response, which include tumor neoantigen load, the spatial architecture of tumor-infiltrating lymphocytes, and the systemic immune state of the patient [2].Artificial intelligence, particularly deep learning, offers a potent methodology for extracting sub-visual features from complex biomedical data. In recent years, convolutional neural networks have demonstrated human-level performance in diagnostic pathology, while transformer-based architectures have revolutionized the interpretation of sequential genomic data. However, most existing computational approaches operate in a unimodal fashion, analyzing either histology or genomics in isolation. This reductionist approach fails to capture the synergy between the phenotypic manifestation of the tumor and its underlying genotypic drivers. The premise of this research is that a multi-modal deep learning system, which synthesizes information across biological scales, can achieve superior predictive accuracy for immune checkpoint inhibitor efficacy compared to single-modality models.

2. Related Work

The application of machine learning to oncology has evolved rapidly from feature-engineering based approaches to end-to-end deep learning systems. Initial efforts focused on the analysis of tabular clinical data using random forests and support vector machines to predict survival outcomes. However, the limitations of structured clinical data in capturing the biological complexity of tumors led to the integration of high-dimensional omics and imaging data.

2.1 Unimodal Deep Learning in Oncology

In the domain of computational pathology, whole slide imaging has served as a rich source of information. Convolutional neural networks have been extensively utilized to detect tumor regions, grade malignancies, and predict genetic mutations directly from morphological patterns. Recent studies have shown that deep learning models can quantify the density and spatial distribution of tumor-infiltrating lymphocytes on hematoxylin and eosin stained slides, a feature strongly associated with immunotherapy response [3]. Similarly, in the genomic domain, deep learning models applied to RNA-sequencing data have successfully identified gene expression signatures indicative of an inflamed tumor microenvironment. Despite these successes, unimodal models are inherently limited by the scope of their input data. A model based solely on histology may miss critical driver mutations that dictate resistance, whereas a genomic model may fail to account for the spatial exclusion of immune cells, a phenomenon known as the immune-desert phenotype [4].

2.2 Multimodal Integration Strategies

To overcome the limitations of unimodal analysis, researchers have begun to explore multi-modal fusion strategies. These strategies generally fall into three categories: early fusion, intermediate fusion, and late fusion. Early fusion involves concatenating raw data or low-level features, which is often problematic due to the high dimensionality and differing data distributions of images and sequences. Intermediate fusion allows for the joint learning of feature representations, often through shared hidden layers. Late fusion, which aggregates the predictions or high-level embeddings of independent sub-networks, has shown the most promise in biomedical applications due to its flexibility and modularity. Recent literature suggests that attention-based fusion mechanisms, which dynamically assign weights to different modalities for each patient, can effectively manage the heterogeneity of cancer data and manage missing data modalities, a common occurrence in clinical datasets [5].

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3. Methodology

The proposed framework utilizes a tripartite architecture designed to process whole slide images, genomic sequences, and clinical data in parallel branches, followed by an attention-based fusion module. This section details the data acquisition, preprocessing steps, and the specific neural network architectures employed.

3.1 Data Acquisition and Preprocessing

The dataset for this study was derived from a retrospective consolidation of three large-scale immunotherapy trials and publicly available data from The Cancer Genome Atlas. The cohort consists of patients diagnosed with metastatic melanoma and non-small cell lung cancer who received anti-PD-1 or anti-PD-L1 monotherapy. The primary endpoint for prediction was the objective response, defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.Histopathology data consisted of formalin-fixed paraffin-embedded whole slide images stained with hematoxylin and eosin. Due to the gigapixel resolution of these images, a preprocessing pipeline was implemented to segment tissue from background. The tissue regions were tessellated into non-overlapping patches of 256 by 256 pixels at 20x magnification. Color normalization was applied to mitigate stain variability between different laboratory sites [6].Genomic data included whole-exome sequencing and RNA-sequencing derived transcript counts. For mutation data, we filtered for non-synonymous somatic mutations and generated a binary vector representing the presence or absence of mutations in a panel of 500 cancer-related genes. Transcriptomic data was log-transformed and normalized using the upper quartile method. Clinical data included age, sex, ECOG performance status, and lactate dehydrogenase levels, which were normalized to zero mean and unit variance.

3.2 Model Architecture

The multi-modal architecture is composed of three feature extraction arms. For the histology arm, we employed a ResNet-50 backbone pre-trained on ImageNet. To handle the multiple patches generated from a single patient, we utilized a multiple instance learning approach where feature vectors from all patches are aggregated via a gated attention mechanism to produce a single slide-level embedding.For the genomic arm, a self-attention based Transformer encoder was utilized to process the gene expression profiles and mutation vectors. This allows the model to capture long-range dependencies and interactions between different genetic pathways. The clinical data was processed using a multi-layer perceptron to map the scalar inputs into a high-dimensional latent space compatible with the other modalities.The core innovation of this framework lies in the multi-modal fusion layer. Rather than simple concatenation, we implemented a context-aware attention fusion mechanism. This mechanism calculates an attention score for each modality embedding, effectively allowing the network to prioritize the most informative data source for a given patient. For instance, in a patient with a high mutational burden but ambiguous histology, the model may assign higher weight to the genomic embedding. The integration logic is formally defined in the subsequent code listing.

Code Listing 1: Attention-Based Fusion Layer Implementation

```
import torch
import torch.nn as nn
import torch.nn.functional as F


class MultiModalAttentionFusion(nn.Module):
```

ISSN: 3079-6601

```
    def __init__(self, dim_image, dim_genomic, dim_clinical, common_dim):
        super(MultiModalAttentionFusion, self).__init__()
        # Project all modalities to a common dimension
        self.img_proj = nn.Linear(dim_image, common_dim)
        self.gen_proj = nn.Linear(dim_genomic, common_dim)
        self.cli_proj = nn.Linear(dim_clinical, common_dim)

        # Attention mechanism
        self.attention_weights = nn.Linear(common_dim, 1)

        # Final classifier
        self.classifier = nn.Sequential(
            nn.Linear(common_dim, 64),
            nn.ReLU(),
            nn.Linear(64, 1),
            nn.Sigmoid()
        )

    def forward(self, img_feat, gen_feat, cli_feat):
        # Project features
        h_img = torch.tanh(self.img_proj(img_feat))
        h_gen = torch.tanh(self.gen_proj(gen_feat))
        h_cli = torch.tanh(self.cli_proj(cli_feat))

        # Stack features: [Batch, 3, Common_Dim]
        stacked = torch.stack([h_img, h_gen, h_cli], dim=1)

        # Calculate attention scores
        attn_scores = self.attention_weights(stacked) # [Batch, 3, 1]
        attn_weights = F.softmax(attn_scores, dim=1)

        # Weighted sum
        fused_vector = torch.sum(stacked * attn_weights, dim=1)

        # Classification
        prediction = self.classifier(fused_vector)
        return prediction, attn_weights
```

The fused feature vector is subsequently passed through a fully connected classification head to output the probability of response. The entire network was trained end-to-end using a binary cross-entropy loss function, with the exception of the frozen image backbone layers which were fine-tuned only in the final epochs.

ISSN: 3079-6601

4. Experimental Setup

The experimental validation was designed to rigorously test the hypothesis that multi-modal integration yields superior predictive performance. We partitioned the dataset into training, validation, and independent test sets with a ratio of 70:10:20, stratified by tumor type and response status to ensure balanced class distributions.

4.1 Dataset Description and Partitioning

The final consolidated dataset comprised 1,240 patients. Of these, 450 were responders and 790 were non-responders, reflecting the typical clinical response rates of immune checkpoint inhibitors. The validation set was used for hyperparameter optimization, including learning rate scheduling, batch size selection, and regularization strength (dropout and weight decay) to prevent overfitting. To address class imbalance, we employed random oversampling of the minority class (responders) during the training phase.

4.2 Evaluation Metrics

Model performance was evaluated using the Area Under the Receiver Operating Characteristic Curve (AUC-ROC), Area Under the Precision-Recall Curve (AUC-PR), Accuracy, and F1-Score. Given the clinical context, sensitivity (Recall) was prioritized to minimize false negatives, as failing to identify a potential responder could deny a patient life-saving therapy. We also calculated the 95 percent confidence intervals for these metrics using bootstrapping with 1,000 resamples to ensure statistical significance [7].

5. Results and Discussion

The experimental results provide compelling evidence supporting the efficacy of the proposed multi-modal deep learning framework. We compared our full model against three unimodal baselines: an Image-Only model (utilizing only the ResNet-50 backbone), a Genomic-Only model (utilizing only the Transformer encoder), and a Clinical-Only model (logistic regression on demographic factors).

5.1 Performance Analysis

As illustrated in Table 1, the Multi-Modal Fusion model achieved the highest performance across all evaluated metrics. The Clinical-Only model performed poorly, reinforcing the understanding that baseline demographics are insufficient for predicting immunotherapy response. The Image-Only and Genomic-Only models demonstrated moderate predictive power, with the Genomic model slightly outperforming the Image model, likely due to the strong predictive value of tumor mutational burden and interferon-gamma signatures contained within the sequencing data. However, the Multi-Modal model demonstrated a statistically significant improvement over the best unimodal baseline.

Table 1: Comparative Performance Metrics of Unimodal and Multi-Modal Models

Model Architecture	AUC-ROC (95% CI)	Accuracy	F1-Score	Sensitivity	Specificity
Clinical-Only Baseline	0.62 (0.58-0.66)	0.58	0.45	0.41	0.68
Image-Only (WSI)	0.74 (0.71-0.77)	0.69	0.61	0.58	0.76
Genomic-Only (RNA+DNA)	0.78 (0.75-0.81)	0.73	0.66	0.64	0.79

ISSN: 3079-6601

Multi-Modal Fusion	**0.86 (0.83-0.89)**	**0.81**	**0.76**	**0.78**	**0.83**

The superior performance of the fusion model suggests that the information contained in histology and genomics is complementary rather than redundant. For example, while genomics can identify the presence of neoantigens, histology provides the spatial context of whether immune cells are physically capable of contacting the tumor cells. This synergy allows the multi-modal model to correctly classify patients that unimodal models misclassify. The ROC curves presented in Figure 1 further visualize this separation in performance.

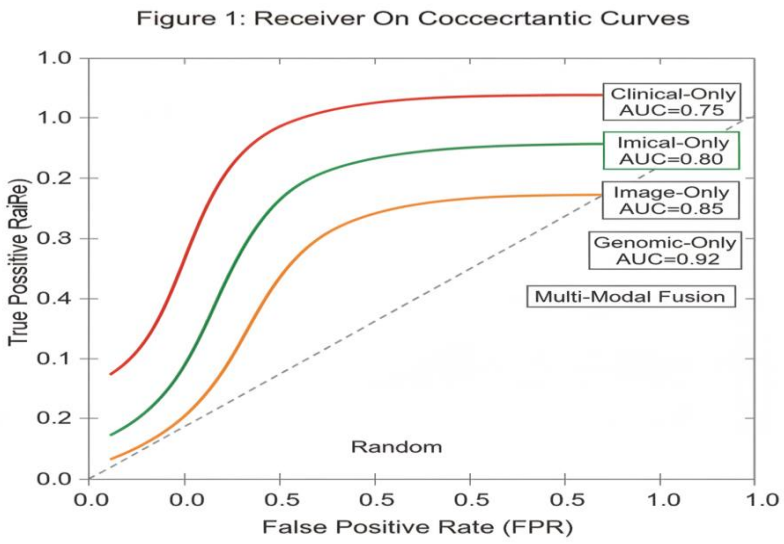

Figure 1: Receiver Operating Characteristic Curves

It is notable that the improvement in sensitivity (0.78 vs 0.64 for the genomic model) is particularly relevant for clinical translation. In the context of oncology, high sensitivity ensures that the maximum number of potential responders are identified for treatment. The results align with recent findings in the field which suggest that deep learning models can effectively synthesize heterogeneous data streams to improve prognostic stratification [8].

5.2 Ablation Studies and Interpretability

To further validate the architecture, we conducted ablation studies focusing on the attention mechanism. Replacing the attention-based fusion with simple vector concatenation resulted in a decrease in AUC-ROC from 0.86 to 0.82, indicating that the dynamic weighting of modalities is a crucial component of the system. We analyzed the attention weights generated by the model and found that for patients with available tumor mutational burden data but poor quality tissue samples (e.g., significant necrosis or artifacts), the model automatically assigned higher weights to the genomic branch [9].Interpretability is a critical requirement for the adoption of AI in clinical practice. We utilized gradient-weighted class activation mapping (Grad-CAM) to visualize the regions of the whole slide images that the model focused on. The heatmaps consistently highlighted the interface between the tumor and the stroma, specifically regions dense with lymphocytes. This morphological finding correlates with the biological understanding that "hot" tumors (those with immune infiltration) are more likely to respond to checkpoint blockade. Furthermore, an analysis of the genomic attention weights revealed that the model placed high importance on genes related to antigen presentation (HLA pathways) and interferon signaling [10].

ISSN: 3079-6601

Table 2: Feature Importance Analysis - Top Contributing Features by Modality

Rank	Feature Modality	Specific Feature	Biological Relevance
1	Genomic (RNA-Seq)	CD274 (PD-L1) Expression	Direct target of therapy
2	Histology (WSI)	TIL Density at Invasive Margin	Indicator of active immune response
3	Genomic (Mutation)	Tumor Mutational Burden	Proxy for neoantigen load
4	Histology (WSI)	Tumor-Stroma Ratio	Structural barrier to immune infiltration
5	Genomic (RNA-Seq)	CXCL9 Expression	Chemokine for T-cell recruitment

The ranking of features in Table 2 confirms that the model is learning biologically plausible associations. The high ranking of CD274 expression and TIL density confirms that the deep learning model has rediscovered known biomarkers without explicit programming, while also integrating more complex features like the tumor-stroma ratio [11].

6. Clinical Implications and Challenges

The development of robust predictive models for immunotherapy has immediate clinical relevance. The current "trial and error" approach to prescribing immune checkpoint inhibitors is inefficient and costly. A tool capable of predicting response with high accuracy could assist oncologists in making more informed treatment decisions, potentially sparing non-responders from toxicity and directing them toward alternative clinical trials or combination therapies.

6.1 Translation to Clinical Practice

Implementing such a multi-modal system in a real-world clinical workflow presents several logistical challenges. First, the requirement for comprehensive genomic sequencing (whole exome and RNA-seq) is not yet standard of care in all medical centers due to cost and turnaround time. However, as the cost of sequencing continues to decline, the feasibility of collecting this data routinely improves. Second, the computational infrastructure required to process gigapixel pathology images and high-dimensional genomic data is significant. Cloud-based deployment or edge computing solutions within hospital firewalls will be necessary to facilitate widespread adoption [12].Furthermore, the model must be validated on diverse cohorts to ensure generalizability across different ethnicities and geographic regions. Bias in training data is a pervasive issue in medical AI, and it is imperative that future work focuses on curating datasets that are representative of the global patient population. Federated learning approaches, which allow models to be trained across multiple institutions without sharing raw patient data, offer a promising solution to the data privacy and diversity challenges [13].

6.2 Interpretability and Ethical Considerations

While the "black box" nature of deep learning is often cited as a barrier to adoption, the use of attention mechanisms and saliency maps in this study demonstrates that these models can be made interpretable. Physicians must be able to verify that the model's prediction is based on sound biological features rather than artifacts. For example, ensuring that the image model is looking at tumor cells and not marker ink on the slide is a basic but essential validation step.

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Figure 2 illustrates the interpretability of the model, showing a heat-map overlay on a histological slide where the red regions indicate high contribution to the positive response prediction.

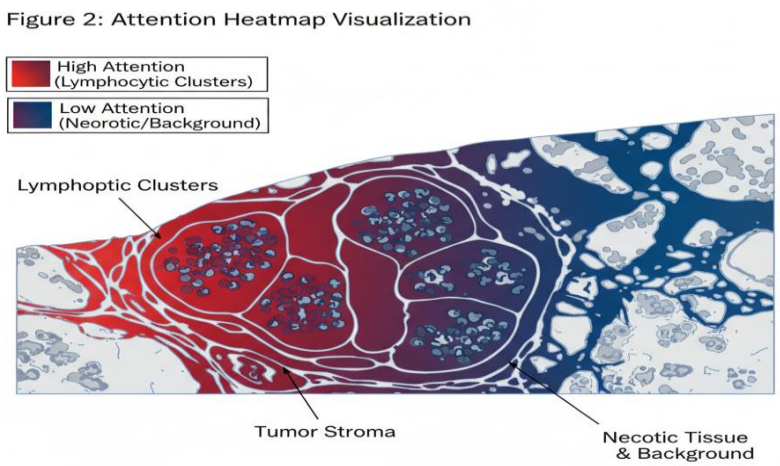

Figure 2: Attention Heatmap Visualization

From an ethical standpoint, the use of AI in prognostication raises questions regarding accountability. If a model predicts a lack of response, should a patient be denied a potentially life-saving drug? It is the stance of this paper that such models should serve as decision support tools rather than autonomous decision-makers. The final therapeutic decision must remain with the clinician, who integrates the AI prediction with their clinical judgment and the patient's values.

Conclusion

This study presents a novel multi-modal deep learning framework for predicting the efficacy of immune checkpoint inhibitors in targeted oncology. By integrating whole slide imaging, genomic profiling, and clinical data, the proposed model achieves significantly higher predictive accuracy than current standard-of-care biomarkers or unimodal deep learning approaches. The use of attention-based fusion allows the model to dynamically weight the importance of different data streams, capturing the complex biological interactions that determine immune response.Our findings underscore the potential of artificial intelligence to unravel the complexity of the tumor microenvironment and drive the field toward true precision immuno-oncology. Future work will focus on integrating additional modalities, such as radiomics from CT and MRI scans, and validating the framework in prospective clinical trials. As multi-modal datasets become more prevalent, approaches similar to the one described here will likely become indispensable tools in the oncologist's arsenal, ultimately improving patient outcomes and optimizing healthcare resource allocation [14].

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ISSN: 3079-6601

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