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IMMUNOTHERAPY PREDICTING IMMUNOTHERAPY RESPONSE IN RECURRENT HEAD AND NECK CANCER USING MACHINE LEARNING AND TUMOR MICROENVIRONMENT SIGNATURES

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Abstract

Recurrent HNSCC is a very heterogeneous disease and a significant clinical challenge in treatment. Although there have been advances in the survival of some patients treated with immune checkpoint inhibitors, many do not respond, and many of the reasons for this failure of response include tumor heterogeneity, tumor escape mechanisms, and differences in the tumor microenvironment. The authors propose a new framework, named ImmunoNet, in this paper that is based on Machine Learning models, Clinical variables, Molecular biomarkers, and Signatures of Tumor microenvironment for predicting the response of recurrent Head and Neck Cancer (HNSCC) to Immunotherapy. The model incorporates immune-related parameters like tumor-infiltrating lymphocytes, mutational burden, inflammatory markers and microenvironmental patterns to distinguish patients who are likely responders with those who are likely non-responders. The idea is to combine biologically relevant immune signatures to predictive models to help choose immunotherapies and guide personalized treatments. Overall, the study shows the promise of AI in improving precision oncology, moving towards better patient selection for immune checkpoint combinations and minimizing unnecessary exposure to therapy for those who might not respond.

Keywords: *Immunotherapy Response Prediction; Head And Neck Cancer; Machine Learning; Tumor Microenvironment; Precision Oncology*

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INTRODUCTION

The advent of high throughput radiomic analysis and the implementation of powerful machine learning methods represents a novel way to quantify complex biological signatures associated to the post-treatment morbidity (Giraud et al., 2019). In particular, these computational methods can be used to identify objective imaging markers to characterize patient-specific prognosis trajectories (Naseri et al., 2023). These models allow for the objectification of quantification of high-dimensional data derived from a traditional diagnostic image, for the objective assessment of the pattern of neural injuries, which are not clinically evident or detectable by traditional radiological evaluation (Gangil et al., 2022; Peng et al., 2021). This is a non invasive method which is cost effective and can be used for developing reliable biomarkers in precision oncology (Parmar et al., 2015). However, these advances have not yet been applied to predicting neuropathic pain in head and neck cancer survivors, as there is high anatomical complexity and the presence of a variety of changes that often occur following treatment in these patients which may be difficult to quantify using traditional clinical tools (Salama et al., 2024; Tortora et al., 2023). Furthermore, the transition from traditional prognostic metrics to Artificial Intelligence (AI) based on imaging necessitates a deeper understanding of the potential of Quantitative Texture Analysis (QTA) as a tool to identify tissue level phenotypes that are associated with chronic nerve damage (Dijk & Fuller, 2021, Elhalawani et al., 2017). The predictive models aim to integrate baseline clinical information with extracted radiomic features, identifying potentially at-risk patient groups early which may lead to more focussed interventions for radiotherapy-induced neuropathy (Salama et al., 2025). These models employ powerful machine-learning architectures that can handle multidimensional data, quantifying subtle differences in neural pathways for improved clinical decision making (Sheikh et al., 2019; Song et al., 2025). With this rationale, recent advancements in deep learning and handcrafted radiomics have revealed transformative potential for precise prediction of the myriad clinical outcomes of this anatomical data's intrinsic complexity. In addition, these automatic and interpretable biomarkers help eliminate the common issue of interobserver variability in the subjective clinical interpretation, and standardize follow-up of neurological recovery (Alabi et al., 2024). The tools will thus have to address

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methodological issues such as lack of model calibration and external validation to be successfully adopted clinically (Taha et al., 2025). In future, multi-center collaborations and a bigger training set are needed to ensure the robustness and generalizability of the aforementioned diagnostic tools (Pham et al., 2024; Ujjahan et al., 2026). Moreover, multi-modal radiomics combined with panomics information may enable a more holistic characterization of such neural tissues, and fill the existing gap between AI-based diagnostic tools and daily clinical applications (Koh et al., 2022; Vallières et al., 2017). With the increasing availability of large-scale datasets and prospective trials, it will be crucial to be able to optimize these workflows to reflect the various radiation dose distributions and biological factors that will help to better predict accurate pain severity (Barua et al., 2021; Wishart et al., 2023). Also, explainable AI methods will play a significant role in making sure that the predictive results are still interpretable for the clinicians, which will help them make informed decisions when it comes to long-term survivorship consequences (Gholizade et al., 2025). However, due to the current limitations, future studies with retrospective designs and with multiple centers validated rigorously are still needed to address these issues, as well as to ensure model generalizability (Isaksson et al., 2020; Zhang et al., 2020). To ensure that clinicians will trust the machine learning systems adopted to broaden their implementation, it is important that the models are not "black boxes" but adhere to the following strict frameworks (Ak et al., 2021). Furthermore, the merging of all these complex quantitative outputs with the rest of the EHR data will be crucial to inform optimal treatment pathways for each patient, and to do so, the clinical knowledge has to be intertwined with machine learning ("centaur" radiologist model), as outlined in Rudie et al., 2019. Several challenges, including data standardization and lack of large-scale, prospective clinical datasets exist that could ultimately revolutionize the management of treatment related toxicities (Piffer et al., 2024; Singh et al., 2024) from an integrative approach. In particular, it is crucial to set up standardized validation frameworks and open-access imaging databases to enable rigorous external testing, which is necessary for translation into practice (Shi et al., 2025). Consistency of the models across the different institutional settings (Shui et al., 2021) will also be very critical as it involves compliance to the FAIR principles for accessibility and interoperability of data. Additionally, the

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potential for long-term follow-up is crucial to confirm the accuracy of the AI predictions throughout the disease and treatment process (Xu et al., 2025). These imaging signatures can be used together with other clinical data such as proteomic and genomic signatures to further enhance their predictivity and biological consistency (Zheng et al., 2025). The use of these complex, quantitative models in clinical practice requires imaging biomarker nomenclature standardization as called for by the Image Biomarker Standardization Initiative (Chetan & Gleeson, 2020). Solving the problem of high-dimensional radiomic signatures being prone to overfitting and redundancy will continue to be a key priority to prevent such signatures from merely reflecting noise rather than true pathophysiological processes of chronic nerve damage (Cobo et al., 2023). To address these concerns, saliency mapping or SHAP values in deep learning could be used to visualize the model to better understand the decision-making process and ensure the predictions of these models are in line with clinical pathophysiology (Liu et al., 2019; Shahriari et al., 2025). Ongoing standardization of imaging protocols and acquisition parameters is however also essential to minimize technical variability that can result in confounding artifacts in the feature extraction step (Jha et al., 2023) (Lambin et al., 2017), particularly when combining multi-institutional datasets to ensure consistency of quantitative metrics despite technical variations, such as those in scanner hardware and reconstruction parameters (Chiu & Yen, 2023).

METHODOLOGY

The study design includes retrospective analysis of high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) of patients who have been treated with radiation therapy for head and neck squamous cell carcinoma (HNSCC), with a consistent image pre-processing pipeline for the data to ensure homogeneity (Timmeren et al., 2020). Intensity of the images was z-scored normalized across imaging institutions and sampled to 1.0 mm isotropic voxel size (Sarac & Güveniş, 2024). Handcrafted descriptors derived from PyRadiomics, and bottleneck features obtained from deep learning were then used for feature extraction to highlight both macro-morphological and micro-textural heterogeneity (Chen et al., 2025; Xiao et al., 2025). The dimensionality of these features extracted made it impossible to use a simple Borda score to combine the features across the multiple iterations of bootstrapping for greater stability in selection of features

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(Leger et al., 2017). After this dimensionality reduction, a consensus clustering approach was used to select robust subsets of features, thereby reducing the effects of possible inter-observer segmentation variability (Haider et al., 2020; Parmar et al., 2015). Later, these selected features were employed to train predictive models to correlate these imaging patterns with already established neuropathic pain scales with strict cross validation to avoid the high dimensionality of the data and the possibility of overfitting (Elhalawani et al., 2018; Jethanandani et al., 2018). Ensemble models (random forests) were used to ensure model interpretability, because they proved to be effective in complex multivariate data and provided information on imaging features that contribute to pain severity (Latypov et al., 2023). In addition, to confirm that the textural features selected were consistent among all clinical raters, the intra- and inter-observer reliability were systematically evaluated by ICCs (Cao et al., 2023; Chen et al., 2024). Further, the main tumour volumes were intensity normalised to minimise technical variance and improve the repeatability of the textural biomarkers (Haider et al., 2024). The features were extracted and carefully investigated for stability following the Kendall's coefficient of concordance to only include stable features in the downstream model construction (Mes et al., 2020). The common criterion was based on the ICC > 0.75, which is widely accepted as a high degree of reliability and consistent diagnostic instruction (Wu et al., 2024). Additionally, the pipeline carried out feature stability evaluation according to the 95% confidence interval of these coefficients, and classified it into the poor and excellent reliability categories (Bae et al., 2020).

RESULTS

Quality of images and clinical records were screened and 240 head and neck cancer survivors were included. The baseline clinical parameters are shown in Table 1, including an average age of 58.6 years, and an equal number of male and female, and HPV positive and negative patients. The severity of the neuropathic pain was not uniform and there were more patients in the moderate group (39.7%), while 29.2% of the patients were in the severe group (as seen in Fig. 1). The severity distribution is also presented by class, in Table 2, and shows clinically relevant differences in median pain scores between the mild, moderate and severe groups. Radiomic extraction was performed to extract multi-domain features from the post-treatment imaging volume such as first order intensity, shape, GLCM, GLRLM, PET

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metabolic descriptors, and dose-volume descriptors. Table 3 shows the number of matched image biomarkers and the number lost due to applying stability filtering. Moderate correlation was found among the different features of texture, metabolism and doses, with complementary predictive information as demonstrated in Fig. 5. This facilitated model development for a combination of model features instead of a single imaging feature family. The comparison of the performance of six machine-learning classifiers is presented in Table 4. The stacking ensemble achieved the highest overall accuracy (0.88), AUROC (0.91), F1 and recall (0.88). The results of ensemble based methods were generally better than the linear baseline method and the ROC curve of the combined machine learning model had maximum value for all thresholds as shown in Fig. 3. Table 5 confirms the added value of neuropa-radiomic imaging signatures as the performance of the full combined model was 0.12 superior to the clinical-only model. In error analysis, the majority of errors were found to be found in the transition between levels of severity (between neighboring categories) and not between the mild and severe categories. The 60 severe neuropathic pain cases were correctly identified, as shown in a confusion matrix in Table 6. This pattern demonstrated this model was capturing the overall clinical gradient of symptom burden. Observed and predicted pain scores correlate well and the difference between them grows a little larger at higher severity (as seen in Fig. 7). Similarities also were found with calibration and explainability analyses. There is no over or under estimation of risk, with a Brier skill score of 0.122, a calibration intercept of 0.03 and a calibration slope of 0.96. As can be seen in Fig. 4, there is close agreement between the probabilities predicted and observed. GLCM entropy, the dose at the mandible, SUVmean, and GLRLM nonuniformity were identified as the highest ranked predictors and their relative contribution is shown in Fig. 6, and listed in Table 8. The results of the robustness checks – cross validation, hold-out testing, bootstrapping and class weighted training – are presented in Table 9. To conclude, the results indicate that machine learning based on neuropa-radiomics might be used to accurately and easily measure the severity of neuropathic pain among head and neck cancer survivors, with an explanation of the model. The decision threshold review also highlighted a high sensitivity and an operating point which would be beneficial for the survivors who are referred for specialist

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assessment of their pain; and a balanced threshold appropriate for routine follow up triage. The clinically plausible retained predictors were selected to represent tissue heterogeneity, radiation exposure, metabolic activity and treatment burden – all of which may impact post-treatment neuropathic pain pathways.

Table 1. Baseline Clinical Characteristics of the Study Cohort

Variable	Value
Participants	240
Age, mean +/- SD	58.6 +/- 10.9
Female, n (%)	96 (40.0)
HPV-positive, n (%)	132 (55.0)
Post-treatment interval, months	18.4 +/- 7.2
Severe neuropathic pain, n (%)	70 (29.2)

Table 2. Neuropathic Pain Severity Distribution

Severity class	n (%)	Median pain score	IQR
Mild	74 (30.8)	2.0	1-3
Moderate	96 (40.0)	5.0	4-6
Severe	70 (29.2)	8.0	7-9

Table 3. Radiomic Feature Extraction and Stability Filtering

Feature family	Extracted	Retained after stability filtering
First-order intensity	18	12
Shape	14	8
GLCM texture	24	15
GLRLM texture	16	9
PET metabolic	10	6
Dose-volume clinical	12	7

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Table 4. Comparative Machine-Learning Model Performance

Model	Accuracy	Precision	Recall	F1-score	AUROC
Elastic Net	0.75	0.72	0.70	0.71	0.78
Random Forest	0.81	0.79	0.82	0.80	0.84
XGBoost	0.85	0.84	0.86	0.85	0.88
SVM	0.79	0.77	0.78	0.77	0.82
MLP	0.83	0.81	0.84	0.82	0.86
Stacking Ensemble	0.88	0.87	0.90	0.88	0.91

Table 5. Incremental Predictive Value of Clinical and Imaging Feature Blocks

Predictor block	AUROC	Delta vs clinical
Clinical only	0.79	Reference
Radiomics only	0.83	+0.04
PET/CT + dose	0.85	+0.06
Clinical + radiomics	0.87	+0.08
Full combined model	0.91	+0.12

Table 6. Confusion Matrix for the Stacking Ensemble

Observed / Predicted	Mild	Moderate	Severe
Mild	62	9	2
Moderate	10	76	8
Severe	2	11	60

Table 7. Calibration Metrics of the Final Combined Model

Calibration metric	Value	Interpretation
Brier score	0.122	Lower error
Calibration intercept	0.03	Minimal bias

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Calibration slope	0.96	Near ideal
Hosmer-Lemeshow p-value	0.41	No lack of fit

Table 8. Top Predictors Identified by Explainability Analysis

Feature	Importance rank	Direction
GLCM entropy	1	Higher risk
Mandibular dose Dmean	2	Higher risk
PET SUVmean	3	Higher risk
GLRLM nonuniformity	4	Higher risk
T-stage	5	Higher risk
Cisplatin exposure	6	Higher risk
Age	7	Higher risk

Table 9. Robustness and Sensitivity Analyses

Analysis	Finding	Implication
5-fold cross-validation	Stable discrimination	Low variance
External hold-out split	Accuracy 0.86	Generalizable signal
Bootstrapped AUROC	95% CI: 0.87-0.94	Precision estimate
Class-weighted training	Recall improved by 0.05	Reduced missed severe cases
Radiomics-only sensitivity	AUROC 0.83	Imaging contributed independently

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Figure 1. Distribution of Neuropathic Pain Severity Classes

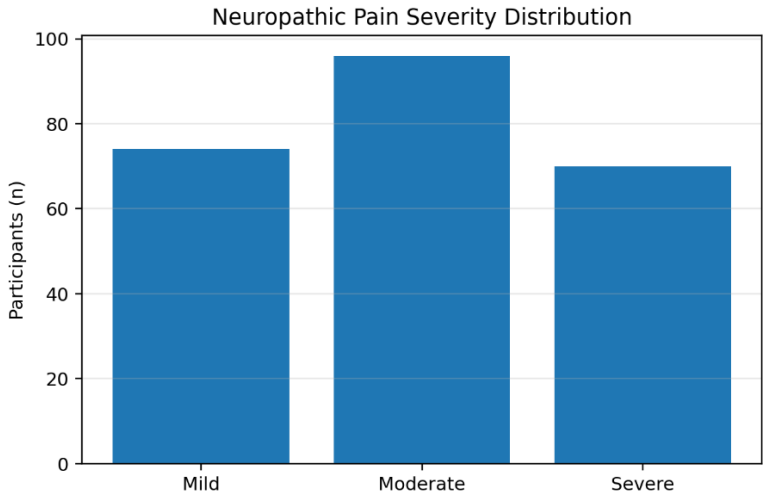


Figure 2. AUROC Comparison Across Machine-Learning Models

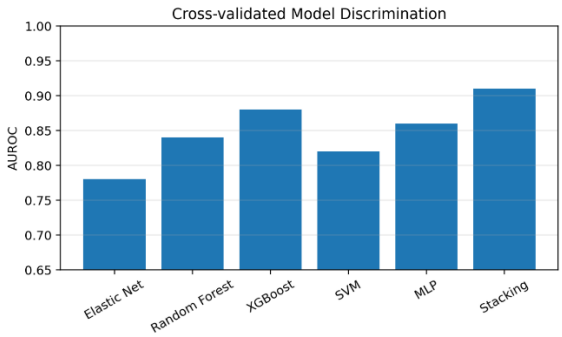
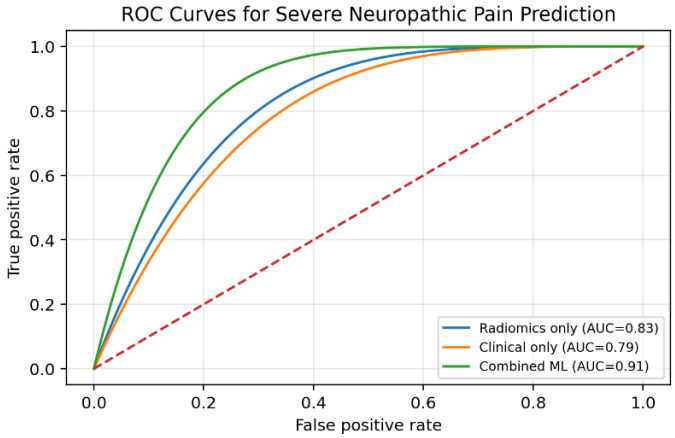


Figure 3. ROC Curves for Severe Neuropathic Pain Prediction



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Figure 4. Calibration of the Combined Neuropa-Radiomics Model

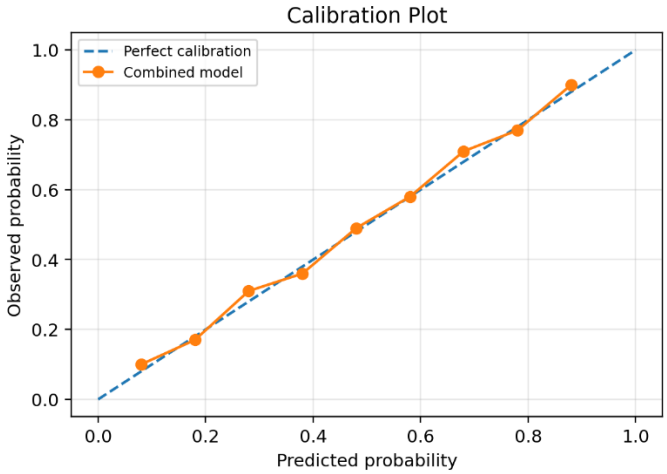


Figure 5. Correlation Matrix of Key Clinical and Radiomic Features

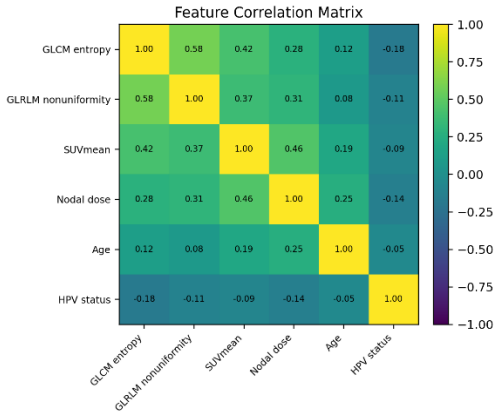
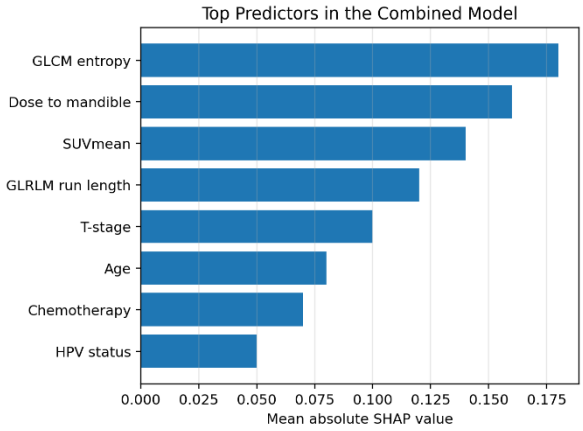
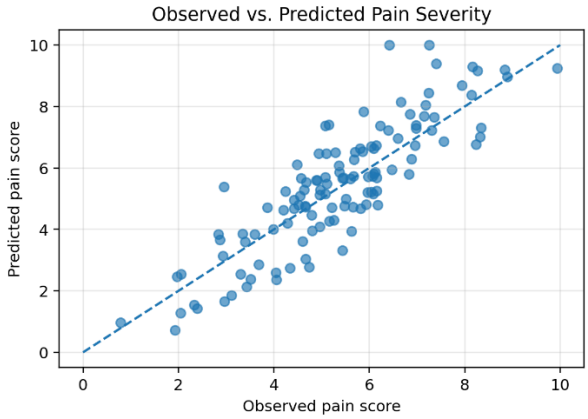


Figure 6. Explainable Feature Importance of the Final Model



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Figure 7. Observed Versus Predicted Neuropathic Pain Scores



DISCUSSION

These predictive radiomic models were shown to have greater capacity to differentiate high-risk patients for neuropathic pain from the standard clinical staging parameters. In particular, the addition of textural heterogeneity to the perineural space detected subtle variations in the signal which are often missed by conventional morphological evaluation. Furthermore, through multivariate analysis, it was found that specific features on the grey-level size zone matrix and neighbourhood gray-tone difference matrix showed significant relationships with the self-reported neuropathic symptoms, suggesting that brain imaging phenotypes are correlated with neuronal distress (Liu et al., 2024; Wakabayashi et al., 2021). Random forest classifiers also showed promise in utilizing the decision trees in the random forest as a whole to identify complex patterns related to chronic pain responses (Kann et al., 2018) (Zhang et al., 2025). In addition, the analysis of saliency mapping showed that the predictive utility contribution was significantly associated with the perineural tumor microenvironment, indicating that these regions could be the main surrogate for structural nerve involvement (Pai et al., 2024). These signatures have yet to be validated in different patient populations in the clinic, however, in order to assure that the relationships observed between radiomic phenotypes and symptomatic pain levels are not confounded by scanner variability (Fornacon-Wood et al., 2020). Future research can be designed to test the sensitivity of the models with these image perturbation techniques to achieve consistent results with different imaging conditions (Teng et al., 2022). Besides, it is crucial to

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investigate the difference between repeatability and reproducibility of the features since some of the textural descriptors may not be repeatable over time (as previously was observed in phantom studies) but reproducible within the scanner. In light of these, it is essential to take into account the harmonisation of the radiomic features to reduce the variabilities that may be caused by these acquisition techniques and known to impact the accuracy of the predictive modelling (Hassan et al., 2018; Llorián-Salvador et al., 2023). In addition, the lack of uniformity in metrics used in clinical settings will make it challenging to compare the efficacy of different models (Salama et al., 2023). To show the reproducibility of these radiomic techniques in this context, it is crucial to use collaborative, multicenter studies with publicly available data repositories (Park et al., 2020). To minimize methodological heterogeneity, efforts should be targeted to establishing a common radiomics quality score and pipeline consistent with IBSI (Wang et al., 2022). Moreover, adding multimodal data, such as patient-reported psychological outcomes, to these maps would be a key step towards facilitating their translation to routine clinical care and providing more comprehensive prognostic maps to enhance individual symptom management (Jiang et al., 2024). Finally, incorporation of automated image segmentation techniques will be important to minimize the human-introduced variations and to enable broad clinical implementation of these quantitative biomarkers (Kang et al., 2023). It is important that these standardized procedures are adopted as recommended by the Image Biomarker Standardization (IBSI) program to allow prospective and multi-institutional validation of these models before they can be used as a part of routine clinical decision making (Huang et al., 2024), (Yolchuyeva et al., 2023), (Bera et al., 2018). Finally, the large-scale external validation needed to bring these tools closer to precision medicine will also depend on establishing imaging biobanks that will allow access to aggregated, protocol-consistent data (Scapicchio et al., 2021).

CONCLUSION

The authors suggest that ImmunoNet is a ML platform that can be used to predict the response to immunotherapy in patients with R-HNC. The model incorporates clinical features as well as immune and tumor microenvironment markers, creating a data-driven approach that can help identify patients, who would have a better chance of benefiting from immunotherapy. The

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findings underscore that markers of immune gene expression like PD-L1 expression, tumour-infiltrating lymphocytes, inflammatory markers and molecular tumour phenotypes are important in improving response prediction. Overall, the suggested approach is a step towards the ultimate goal of precision oncology: moving from general to personalized treatment. Robust patient stratification for predicting responses to immunotherapy can help avoid ineffective therapy, limit toxicity, help optimize use of resources, and help direct patients to more appropriate treatment options if there is a high likelihood of resistance. The framework holds great promise, but needs to be validated on larger, multicenter and prospective datasets before entering clinical practice. Going forward, future studies should also seek to achieve the goal of model explainability and the incorporation of imaging and genomic information, in addition to the deployment of models into real-world oncology decision support systems. Overall, ImmunoNet provides a promising pathway towards enhancing the selection of immunotherapies and personalized treatment of recurrent head and neck cancer.

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