Towards Precision Oncology: Predicting Mortality and Relapse-Free Survival in Head and Neck Cancer Using Clinical Data

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***Abstract*—Head and neck squamous cell carcinoma (HNSCC) presents significant challenges in clinical oncology due to its heterogeneity and high mortality rates. This study aims to leverage clinical data and machine learning (ML) principles to predict key outcomes for HNSCC patients: mortality, relapse-free survival, and freedom from distant metastasis. Utilizing data sourced from the Cancer Imaging Archive, an extensive pipeline was implemented to ensure robust model training and evaluation. Ensemble and individual classifiers, including XGBoost, Random Forest, and Logistic Regression, were employed to develop predictive models. The study identified key clinical features influencing HNSCC outcomes and achieved predictive accuracy and ROC-AUC values exceeding 90% across tasks. Logistic Regression demonstrated strong generalization for distant metastasis predictions, while XGBoost excelled in relapse-free survival, with an ROC-AUC of 94%. Key clinical features, including tumor stage, nodal status, and treatment type, were identified as critical predictors of patient outcomes. This study underscores the medical impact of using ML-driven insights to refine prognostic accuracy and optimize personalized treatment strategies in HNSCC.**

***Index Terms*—HNSCC, Precision Oncology, Machine Learning, Clinical Outcomes, Relapse-Free Survival, Mortality Prediction, Distant Metastasis, Personalized Medicine.**

I. Introduction

Cancer comprises a collection of diseases marked by the unchecked proliferation and division of abnormal cells, arising from disruptions in cellular regulatory systems. These disruptions, frequently driven by genetic mutations or environmental influences, result in the activation of oncogenes and the suppression of tumor-suppressor genes. Unlike benign growths, cancer possesses the ability to invade neighboring tissues and spread to distant sites through metastasis, significantly complicating treatment and leading to poorer prognoses [1].

Head and neck cancers encompass a variety of malignancies originating in the tissues of the head and neck, primarily affecting the mucosal surfaces of the mouth, throat, and voice box. These cancers, often classified as head and neck squamous cell carcinomas (HNSCC), can also arise in the salivary glands, thyroid, or sinuses, depending on the site of origin [2].

Major risk factors for head and neck cancers include tobacco use, alcohol consumption, and infection with human papillomavirus (HPV). HPV-positive cases generally have a more favorable prognosis compared to HPV-negative ones. Due to their location, these cancers frequently affect essential functions such as speech and swallowing. Treatment typically combines surgery, radiation therapy, and systemic approaches, aiming to enhance survival while maintaining quality of life. Despite advancements in early detection, issues like recurrence and treatment resistance remain significant challenges [2, 3].

Mortality prediction in cancer estimates a patient's likelihood of death given his clinical factors, aiding in treatment planning, resource allocation, and providing prognostic insights. Machine learning (ML) enhances this process by analyzing large, complex datasets to uncover patterns and relationships among clinical, demographic, and molecular features [4].

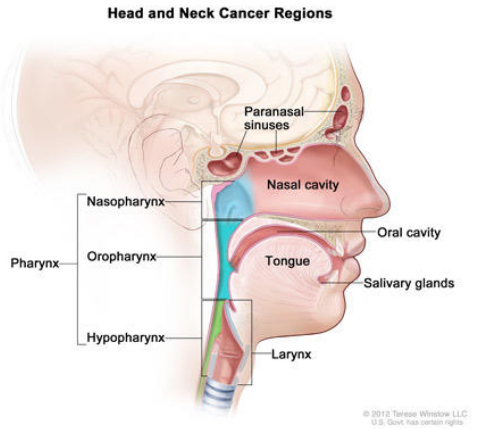

Fig. 1: Head and neck cancer regions.
Credit: © Terese Winslow

ML models, such as random forests, gradient boosting, and deep learning, can process structured data and unstructured

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data to deliver personalized predictions. These models also help identify key factors influencing mortality risk, supporting informed clinical decisions [4, 5].

In 2023, Dhariwal et al. presented a study on mortality predictions in HNSCC patients. This paper presents a novel approach to predicting mortality in head and neck cancers, focusing on the correlation between lifestyle factors like smoking, tobacco use, and key cancer attributes such as tumor-node-metastasis (TNM) staging and human papillomavirus (HPV) positivity. Using eight machine learning and four deep learning models, the study achieved a maximum accuracy of 98.8% with XGBoost. The duration of follow-up emerged as the most influential factor in mortality prediction, contributing 40.8% to the model's performance. The results, with a maximum area under the receiver operating characteristic (ROC) curve of 0.99. These studies further demonstrate the potential that ML models hold in predicting mortality in cancers, gradient boosting models predicting with high accuracies. [6, 7].

Kazmierski et al. [8] investigated prognostic modeling for head and neck cancer using deep learning and radiomics on data from 2552 patients. The multitask learning model provided the highest accuracy for predicting lifetime survival. Of the three models compared, the clinical data model performed best with an AUC of 0.74, emphasizing the importance of clinical features. The authors emphasized that while machine learning models show promise. They also suggested that ensemble learning techniques could enhance prediction accuracy.

Relapse-free survival (RFS) prediction estimates the likelihood that a cancer patient will remain free from recurrence after treatment. It is crucial for assessing treatment success and guiding long-term care decisions. Predictive models can help predict the relapse of cancer in patients based on their clinical and treatment data. this allows both doctors and patients to plan early for a possible relapse and prevent any fatalities.

HNSCC is a common cancer with a 5-year survival rate of about 50%. While radiotherapy is a key treatment, predicting outcomes is vital for selecting effective therapies. Attributes like TNM, HPV status, and radiology expression show promise in predicting treatment response. However, reliable predictions for improving treatment are still needed [9].

A predictive machine learning algorithm was developed to predict locoregional relapse at 18 months for oropharyngeal cancers with negative HPV status. The model, using clinical and Pyradiomics features from CT scans, was trained on the HN1 cohort (79 patients) and validated on the ART ORL cohort (45 patients). The XGBoost model achieved a precision of 0.92, recall of 0.42, AUC of 0.68, and accuracy of 0.64. Key features included voxel volume, grey level size zone matrix, and patient demographics (sex, age). This interpretable model shows potential for predicting relapse and guiding treatment decisions in clinical settings.

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Freedom from distant metastasis (FDM) refers to the absence of cancer spread to distant organs after treatment, serving as a key indicator of prognosis. Predicting FDM helps identify high-risk patients for more intensive treatment or monitoring [11**?**].

After careful study of literature, clinical features have proven to be highly effective in predicting mortality and chances of repalse on HNSCC patients. Further, it is also seen that most state-of-the-art models employ a highly trained XGBoost classifier due to being effective for prediction using clinical features because it efficiently handles complex, high-dimensional data, captures non-linear relationships, and offers high accuracy through feature importance ranking and regularization.

The aim for this study is to amalgamate clinical features and ML principles to present highly robust classifiers for precision oncology. The focused aims for the research are as follows:

1) Identify and train a ML model, for HNSCC patients, to predict:
   - Mortality;
   - Cancer relapse free survival;
   - Freedom from distant metastasis.
2) Identify the features that highly impact the predictions.
3) Evaluate the performance of the classifiers and substantiate results with mertices.

II. Methodology

A. Data Collection and Preprocessing

The dataset for this research was sourced from the Cancer Imaging Archive by the National Cancer Institute, NIH [13]. The dataset consists of imaging, radiation therapy, and clinical data from head and neck squamous cell carcinoma (HNSCC) patients at MD Anderson Cancer Center, used in two research projects. The second project, "Radiomics Outcome Prediction in Oropharyngeal Cancer," focuses on integrating quantitative imaging biomarkers into current risk stratification tools. It uses clinical data and contrast-enhanced CT scans from 495 oropharyngeal cancer (OPC) patients treated between 2005 and 2012. The project aims to correlate radiomics features, either alone or in combination with clinical factors, with tumor outcomes. Radiomics analysis was conducted using institution-developed software on the Matlab platform.

The clinical dataset comprises of both numerical and categorical values. The data also contains a few missing values, which needed to be handled properly. One-hot encoding is used to convert categorical variables into numerical format by creating binary columns for each category. In this dataset, variables like "cancer stage," "gender," or "treatment type" are categorical. One-hot encoding transforms these variables into separate columns, where each category is represented by a 1 (present) or 0 (absent). For instance, the "cancer stage" with

values ”Stage I”, ”Stage II”, ”Stage III” and ”Stage IV” would be transformed into 4 binary columns. This enables the model, such as XGBoost, to process categorical data without assuming any inherent order or numerical value, ensuring better model accuracy and interpretability.

Following this step, normalization and standardization were applied to the numerical features to further prepare the dataset for modeling. Normalization, which scales features to a range of 0 to 1, was used to ensure that all numerical values are on the same scale, preventing any single feature from dominating the model due to its magnitude. This is particularly useful when using algorithms like XGBoost [15], which can benefit from features having similar scales. This preprocessing pipeline helps enhance model performance, making it more robust and efficient in predicting the target variable.

K-Folds cross-validation was employed instead of a traditional 80-20 data split. This technique involves dividing the dataset into ’k’ subsets (or folds), and training the model on ’k-1’ folds while testing it on the remaining fold [14]. It provides a more reliable estimate of model performance, especially when working with smaller datasets, and is beneficial for assessing the generalizability of the model and reducing overfitting.

B. Model Configuration

1) Mortality Prediction: In this study, an ensemble model was developed to predict ”Vital status” based on clinical features using a soft voting strategy for class label aggregation. The target variable, ”Vital status,” was separated from the feature set, and the data was split into training and testing sets in an 80-20 ratio to ensure proper evaluation. The ensemble comprised three models: XGBoost, Logistic Regression, and Random Forest, chosen for their complementary strengths in handling tabular data. XGBoost was configured with 90 estimators and a learning rate of 0.3, Random Forest used 100 estimators, and Logistic Regression utilized the liblinear solver. A random state of 42 was applied across all models for reproducibility.

After training, the ensemble’s performance was evaluated using accuracy and Area Under the Curve (AUC) metrics on both training and testing datasets. While accuracy measures overall prediction performance, AUC provides a more nuanced assessment of the model’s ability to discriminate between positive and negative outcomes.

Receiver Operating Characteristic (ROC) curves were plotted to visualize the model’s classification performance and compare its discriminatory power. Additionally, a learning curve was generated to examine the model’s ability to generalize as the size of the training dataset increased, providing insights into its performance scalability.

This robust evaluation ensures a comprehensive understanding of the ensemble model’s predictive capabilities in the context of mortality prediction, leveraging the combined strengths of gradient boosting, logistic regression, and bagging-based decision trees to handle the complexity of clinical data effectively.

2) Relapse Prediction: In this study, the XGBoost model was configured to predict ”Relapse-free survival” based on clinical features. The target variable, ”Relapse-free survival,” was separated from the feature set, and the data was split into training and testing sets using an 80-20 ratio, followed by K-folds corss validation. The XGBoost model used for classification was configured with 100 estimators (trees) and a learning rate of 0.1, chosen to balance model complexity and training speed. The random state was set to 42 to ensure reproducibility of the results.

After fitting the model to the training data, performance metrics were computed, including accuracy and Area Under the Curve (AUC) for both the training and testing datasets. The AUC scores were calculated using the model’s predicted probabilities, which provide a more nuanced evaluation of the model’s ability to discriminate between positive and negative outcomes.

Feature importance was extracted from the trained model, which provides insights into which features contribute most significantly to the prediction of relapse-free survival. The importance scores were used to rank the features in descending order, highlighting the most influential variables.

Additionally, model evaluation was conducted using Receiver Operating Characteristic (ROC) curves to visualize the model’s classification performance. The learning curve was also plotted to assess how the model’s performance evolves with increasing training data, providing an indication of the model’s capacity to generalize across different dataset sizes.

This configuration ensures robust evaluation and understanding of the model’s predictive capabilities in the context of relapse-free survival, leveraging the power of XGBoost’s gradient-boosting approach to handle complex relationships within the clinical data.

The Random Forest model is used as a baseline for the XGBoost model to provide a comparative foundation for evaluating performance. Random Forest, an ensemble learning method based on multiple decision trees, offers a strong baseline due to its simplicity, robustness, and ability to handle complex datasets. By comparing the performance of the Random Forest model with the more advanced XGBoost model, the study can assess whether the latter, with its gradient-boosting capabilities, provides significant improvements in predictive accuracy and feature importance.

3) Freedom from Distant Metastasis Prediction: The approach for predicting ”Freedom from distant metastasis” using XGBoost follows a similar methodology as the one used for ”Relapse-free survival.” The target variable, ”Freedom from distant metastasis,” was separated from the feature set, and the data was split into training and testing subsets. XGBoost was configured with 100 estimators and a learning rate of 0.1 to balance model complexity and performance.

The model was trained and evaluated using accuracy and AUC scores, both for training and testing datasets. Feature importance was derived to identify the most influential clinical variables, and ROC curves were plotted to visualize the model’s discriminatory power. Additionally, a learning curve

TABLE I: Model Performance Comparison for Mortality Prediction

Model	Train Accuracy	Test Accuracy	Train ROC-AUC	Test ROC-AUC
Soft Voting Ensemble	0.9974	0.9091	1.0000	0.8920
XGBoost	1.0000	0.8990	1.0000	0.8808
Logistic Regression	0.9133	0.8990	0.9425	0.8695

was used to assess the model's performance across varying training set sizes.

This approach is useful as it ensures robust model evaluation and provides insights into the key factors influencing the prediction of distant metastasis. By applying consistent methodologies, the study enhances the reliability and interpretability of the predictive models for both target variables.

III. Results and Discussions

A. Mortality Prediction

The comparative analysis of the models for predicting "Vital status" highlights the effectiveness of the soft voting ensemble classifier and its individual components. The soft voting ensemble, combining XGBoost, Logistic Regression, and Random Forest classifiers, achieved a training accuracy of 99.74% and a test accuracy of 90.91%, with corresponding ROC-AUC scores of 1.0000 and 0.8920, respectively. These results demonstrate that the ensemble effectively integrates the strengths of its constituent models, yielding high discrimination power and robust generalization to unseen data.

Among the individual models, XGBoost stood out with a perfect training accuracy and ROC-AUC of 1.0000, reflecting its capacity to fully capture patterns in the training data. However, its test accuracy of 89.90% and ROC-AUC of 0.8808 indicate a slight tendency toward overfitting, a known risk when using highly expressive models like gradient boosting. Logistic Regression, in contrast, displayed a more restrained approach with a training accuracy of 91.33% and test accuracy of 89.90%. Its ROC-AUC scores of 0.9425 (training) and 0.8695 (test) highlight its robustness and ability to maintain stable performance without overfitting, making it particularly effective in generalizing across data splits.

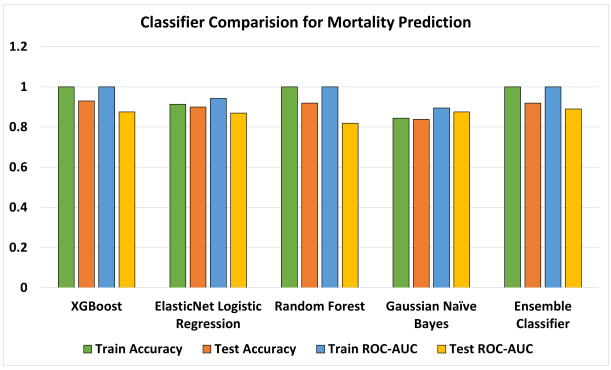

Fig. 2: Classifier comparison for predicting mortality.

The ensemble's superior test performance can be attributed to its soft voting mechanism, which combines class predictions from all three models to reduce individual biases and capitalize on complementary decision boundaries. This integration led to an improvement in generalization compared to the individual models, as reflected by the higher test ROC-AUC score of 0.8920, compared to the next best-performing XGBoost model at 0.8808. A visual comparison of the models and their performances is shown in figure 2. Further, figure 3 visualized and summarizes the most influential feature for predicting the mortality in HNSCC patients.

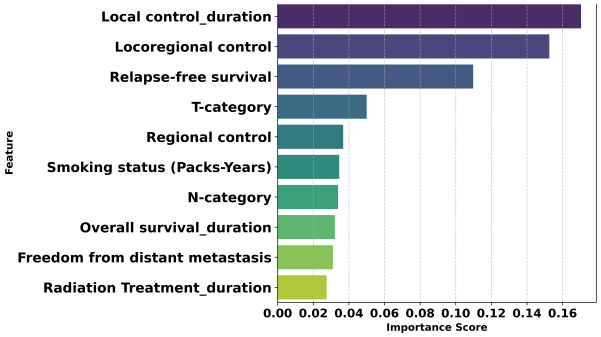

Fig. 3: Most influential features for the prediction of mortality in patients.

B. Relapse Prediction

Both XGBoost and Random Forest achieve perfect training accuracy of 1.0, indicating successful learning from the training data. On the test set, both models perform similarly with an accuracy of 0.9697. However, XGBoost outperforms Random Forest in ROC-AUC, achieving a score of 0.9988 compared to 0.9979 for Random Forest. The models' performance is summarized in Table II.

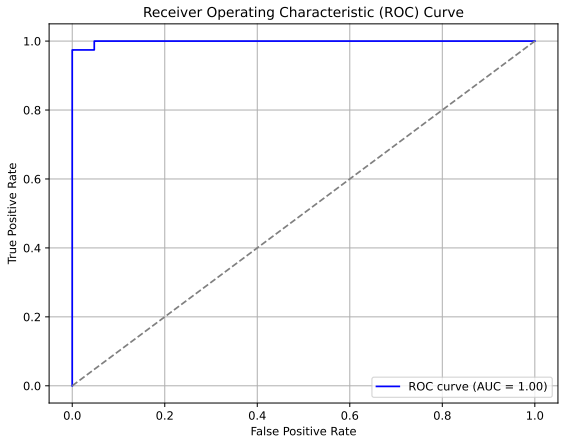

Fig. 4: ROC Curve for XGBoost for predicting relapse free survival.

TABLE II: Model Performance Comparison for Relapse Prediction

Model	Train Accuracy	Test Accuracy	Train ROC-AUC	Test ROC-AUC
XGBoost	1.0000	0.9697	1.0000	0.9988
Random Forest	1.0000	0.9697	1.0000	0.9979

This difference is significant as ROC-AUC measures the model's ability to distinguish between positive and negative cases. XGBoost's superior ROC-AUC indicates its better performance in predicting relapse-free survival, likely due to its gradient boosting approach, which refines predictions by iteratively correcting errors. In contrast, Random Forest uses a bagging technique that constructs independent decision trees without the same iterative refinement. The ROC curves for the XGBoost model and Random Forest Model are visualized in

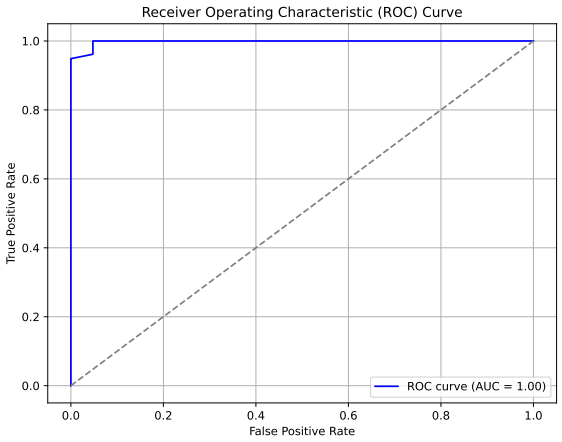

Fig. 5: ROC Curve for Random Forest for predicting relapse free survival.

Overall, while both models perform well, XGBoost's higher ROC-AUC demonstrates its superior ability to generalize and make more precise predictions for relapse-free survival.

The XGBoost model reveals that locoregional control is the most influential feature, with an importance score of 0.387, indicating its strong association with relapse-free survival. Freedom from distant metastasis also plays a significant role with an importance of 0.286. Other notable features include vital status, HPV status, and smoking history, which contribute to understanding patient prognosis and survival outcomes. The top 10 most influencial feature for the XGBoost classifier are visualized with their impact score in figure 6.

In the real-world context, these results highlight the importance of monitoring locoregional control and distant metastasis in clinical settings, as these factors are strongly linked to patient survival and relapse-free periods. Furthermore, factors such as HPV status and smoking history emphasize the need for personalized treatment strategies, focusing on these key risk factors to optimize patient care.

C. Freedom from Distant Metastasis Prediction

The comparative performance of the models for predicting "Freedom from distant metastasis" indicates that Logistic

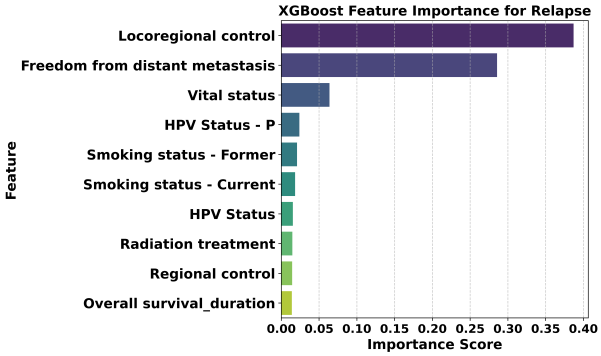

Fig. 6: Feature Importance from XGBoost for predicting relapse free survival.

Regression (LR) achieves superior results, with a test accuracy of 98.99% and a test ROC-AUC of 1.0. These metrics surpass those of XGBoost, which achieved a test accuracy of 96.97% and a test ROC-AUC of 0.9988, and Random Forest, which attained a test accuracy of 94.95% and a test ROC-AUC of 0.9758. Although all three models demonstrated perfect training accuracy and ROC-AUC, LR's ability to maintain excellent generalization to the test set highlights its robustness and suitability for this dataset. Figure 7 plots the classifiers' performance for predicting freedom form distant metastasis. Further, figure 8 visualizes the learning curve for the logistic regression model, showing close to 1 convergence for the training and validation curves.

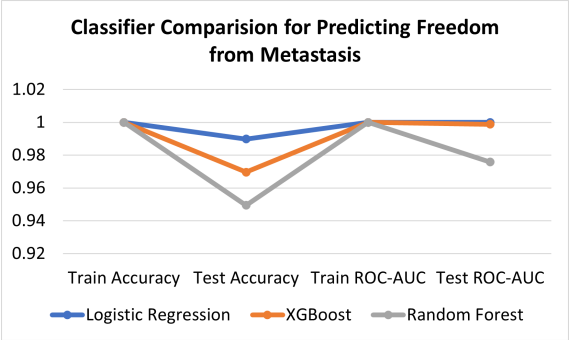

Fig. 7: Classifier comparison for predicting freedom from distant metastasis.

The success of LR in this context can be attributed to the nature of the dataset, where the relationships between features and the target variable are likely linear or approximately linear. This aligns with LR's strengths in efficiently modeling such relationships without overfitting, which is a potential issue for more complex models like XGBoost and Random Forest,

particularly when the dataset size is limited or when the data does not necessitate advanced non-linear interactions.

Furthermore, LR's simplicity and ease of interpretation provide significant advantages in clinical applications, where understanding the impact of each feature on the outcome is often critical. In contrast, while XGBoost and Random Forest excel in handling complex non-linear patterns and interactions, their marginally reduced generalization performance in this study suggests that their complexity was unnecessary for this dataset, potentially leading to overfitting.

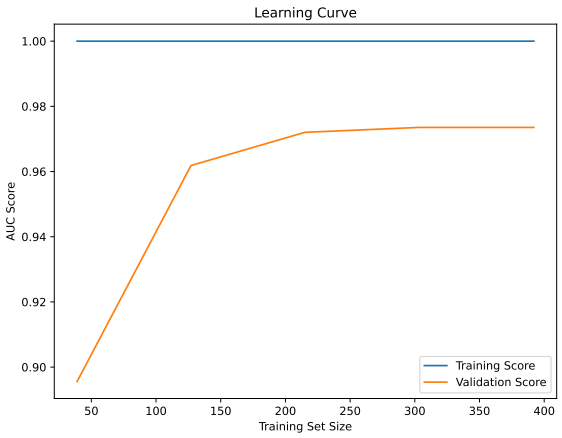

Fig. 8: Learning Curve for Logistic Regression predicting freedom from distant metastasis.

Overall, this analysis underscores the importance of aligning model selection with dataset characteristics. While advanced ensemble methods have their strengths, the linear nature of this dataset makes LR the most appropriate choice, offering not only higher predictive accuracy but also clinical interpretability and reliability.

The feature importance analysis for the Logistic Regression model in predicting "Freedom from distant metastasis" reveals key factors influencing the outcome. Among the top contributors, radiation treatment (number of fractions) had the highest coefficient (0.307), highlighting its critical role in determining metastasis risk. This was followed by T-category (0.155), age at diagnosis (0.154), and relapse-free survival (0.129), emphasizing the importance of tumor characteristics and patient-specific factors in prediction.

Other significant features included regional control duration (0.121), the use of concurrent chemoradiotherapy (0.114), and the cancer subsite (e.g., base of tongue; 0.097). Additionally, demographic and clinical variables such as gender (0.076), HPV-negative status (0.071), and smoking history (0.036) were also moderately predictive.

These findings highlight a mix of treatment-related, tumor-specific, and demographic factors that collectively influence metastasis prediction, underscoring the utility of logistic regression for feature interpretability in clinical decision-making.

IV. Conclusion

The findings of this study underscore the transformative potential of machine learning (ML) in predicting clinical outcomes for patients with head and neck squamous cell carcinoma (HNSCC). By leveraging advanced ML techniques on clinical data, the study achieved high predictive accuracies across key prognostic tasks, including mortality, relapse-free survival, and distant metastasis freedom. The ensemble soft-voting strategy demonstrated the advantage of combining diverse models for robust mortality predictions, while XGBoost outperformed other models in capturing the nuances of relapse-free survival. Additionally, Logistic Regression excelled in distant metastasis predictions, highlighting the importance of selecting model complexity tailored to the dataset.

Through feature importance analysis, this research identified critical clinical factors, such as locoregional control, distant metastasis freedom, tumor stage, and HPV status. These insights provide actionable value for patient stratification, aiding clinicians in optimizing treatment plans and improving care outcomes. The study establishes a framework for integrating ML-driven insights into precision oncology, facilitating early interventions and more effective, personalized care pathways for HNSCC patients.

Future research should aim to build on these promising results by incorporating multimodal data, such as genomic and radiomic features, to enhance predictive robustness and clinical applicability. Expanding the dataset to include larger, multi-institutional cohorts will further validate the findings and support broader adoption in clinical settings. By bridging the gap between computational advances and medical practice, this work represents a critical step towards enhancing prognostic precision and improving the quality of life for cancer patients.

Code - GitHub Repository

This repository contains extended code of the machine learning models implemented in our research.
GitHub - Naman Dhariwal & Abeyankar Giridharan

References

[1] Siegel, Rebecca L., Angela N. Giaquinto, and Ahmedin Jemal. "Cancer statistics, 2024." CA: a cancer journal for clinicians 74.1 (2024): 12-49.
[2] Chow, Laura QM. "Head and neck cancer." New England Journal of Medicine 382.1 (2020): 60-72.
[3] Mody, Mayur D., et al. "Head and neck cancer." The Lancet 398.10318 (2021): 2289-2299.
[4] Gormley, Mark, et al. "Reviewing the epidemiology of head and neck cancer: definitions, trends and risk factors." British Dental Journal 233.9 (2022): 780-786.
[5] Patterson, Rolvix H., et al. "Global burden of head and neck cancer: economic consequences, health, and the role of surgery." Otolaryngology–Head and Neck Surgery 162.3 (2020): 296-303.

[6] Dhariwal, Naman, Rithvik Hariprasad, and L. Mohana Sundari. "An artificial intelligence based approach toward predicting mortality in head and neck cancer patients with relation to smoking and clinical data." IEEE Access 11 (2023): 126927-126937.

[7] Dhariwal, Naman. "Brain Metastasis Origin and Patient Mortality Predictions Using MRI with Clinical and Imaging Feature Information by Deep Learning Architectures." 2024 3rd International Conference for Innovation in Technology (INOCON). IEEE, 2024.

[8] Kazmierski, Michal, et al. "Multi-institutional prognostic modeling in head and neck cancer: evaluating impact and generalizability of deep learning and radiomics." Cancer Research Communications 3.6 (2023): 1140-1151.

[9] Begg, Adrian C. "Predicting recurrence after radiotherapy in head and neck cancer." Seminars in radiation oncology. Vol. 22. No. 2. WB Saunders, 2012.

[10] Giraud, Paul, et al. "Interpretable machine learning model for locoregional relapse prediction in oropharyngeal cancers." Cancers 13.1 (2020): 57.

[11] Duprez, Fréderic, et al. "Distant metastases in head and neck cancer." Head & neck 39.9 (2017): 1733-1743.

[12] Ferlito, Alfio, et al. "Incidence and sites of distant metastases from head and neck cancer." ORL 63.4 (2001): 202-207.

[13] Grossberg A, Elhalawani H, Mohamed A, Mulder S, Williams B, White AL, Zafereo J, Wong AJ, Berends JE, AboHashem S, Aymard JM, Kanwar A, Perni S, Rock CD, Chamchod S, Kantor M, Browne T, Hutcheson K, Gunn GB, Frank SJ, Rosenthal DI, Garden AS, Fuller CD, M.D. Anderson Cancer Center Head and Neck Quantitative Imaging Working Group. (2020) HNSCC Version 4 [Dataset]. The Cancer Imaging Archive. DOI: https://doi.org/10.7937/k9/tcia.2020.a8sh-7363

[14] Anguita, Davide, et al. "The'K'in K-fold Cross Validation." ESANN. Vol. 102. 2012.

[15] Chen, Tianqi, and Carlos Guestrin. "Xgboost: A scalable tree boosting system." Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining. 2016.