USING RADIOMICS FOR PREDICTING THE HPV STATUS OF OROPHANARYNGEAL TUMORS

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USING RADIOMICS FOR PREDICTING THE HPV STATUS OF OROPHANARYNGEAL TUMORS

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ACADEMIC ETHICS AND INTEGRITY STATEMENT

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ABSTRACT

USING RADIOMICS FOR PREDICTING THE HPV STATUS OF OROPHANARYNGEAL TUMORS

Determining human papillomavirus (HPV) status is crucial for the appropriate treatment for oropharyngeal cancer, traditionally achieved through a biopsy. This paper aims to create a new noninvasive method using computed tomography (CT) radiomics for determining HPV status and to explore its potential viability and accuracy as an alternative in routine clinical practice. 238 patients' CT scans were normalized and resampled. From the segmented CT scans, 1142 radiomics features could be obtained.The number of radiomic variables was reduced by employing correlation coefficient analysis, and 25 out of 1142 features were chosen by using backward elimination and random forest feature importance analysis. The Random Over-Sampling (ROSE) algorithm was applied to the training set to balance the data, resulting in 161 samples for each HPV class. A Random Forest (RF) classification algorithm was employed as the prediction model, utilizing five-fold cross-validation (CV). Model accuracy was evaluated using the remaining 20% of the imbalanced data. The practical utility of the model was explored in light of previous research and error rates associated with biopsy procedures. The RF algorithm accurately identified HPV status with 91% accuracy (95% CI: 83-99) and an area under the curve (AUC) of 0.77 (95% CI: 65-89) in the testing dataset. HPV status could be accurately predicted non-invasively from CT images.The error rates were similar to those observed in biopsy procedures. Nevertheless, further efforts are required to enhance standardization, interpretability, robustness, and reproducibility in future work.

Keywords: Radiomics, HPV Status, Machine Learning, Computed Tomography, Oropharyngeal Cancer

ÖZET

OROFARİNGEAL TÜMÖRLERİN HPV DURUMUNU TAHMİN ETMEK İÇİN RADİYOMİK KULLANIMI

İnsan papillomavirüsü (HPV) durumunun, orofarengeal kanser tedavi seçimi üzerinde önemli sonuçlarÿ vardır. Altın standart, bir biyopsi yapmaktır. Bu makalenin amacı, HPV durumunun belirlenmesi için yeni bir bilgisayarlı tomografi (BT) radiomics tabanlı invaziv olmayan bir çözüm geliştirmek ve rutin klinik uygulamada uygun ve doğru bir alternatif olup olamayacağını araştırmaktır. 238 hastanın BT taramaları normalize edilmiş ve yeniden örnekleme yapılmıştır. Segmentli BT taramalarından, 1142 radiomics özelliği elde edilebilmiştir. Radiomik özelliklerin sayısı, korelasyon katsayısı analizi uygulanarak azaltılmış ve 1142 özellikten 25'i geriye doğru eleme ve rastgele orman özellik önem analizi kullanılarak seçilmiştir. Eğitim seti için veri dengesini sağlamak için Random Over-Sampling (ROSE) örnekleme algoritması uygulanmış ve sonuç olarak, eğitim setinin HPV sınıfları için her biri için 161 örnek elde edilmiştir. Bir Rastgele Orman (RF) sınıflandırma algoritması, beş kat çapraz doğrulama (CV) kullanılarak bir tahmin modeli olarak uygulanmıştır. Model etkinliği, kullanılmayan dengesiz verilerin %20'si üzerinde tek başına değerlendirilmiştir. Modelin rutin uygulanabilirliği, önceki araştırmalar ve biyopsi prosedürleri için bildirilen hata oranları göz önünde bulundurularak araştırılmıştır. HPV durumu, RF algoritması ile %91 doğruluk (95% CI: 83-99) ve test verilerinde 0.77 (95% CI: 65-89) AUC ile doğru bir şekilde tahmin edilebilmiştir. HPV durumu, BT görüntülerinden invaziv olmayan bir şekilde doğru bir şekilde tahmin edilebilir. Hata oranları bir biyopsiye kıyasla benzerdir. Ancak, standartlaşma, yorumlanabilirlik, sağlamlık ve tekrarlanabilirlik konularında gelecek çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Radiomics, HPV Durumu, Makine Öğrenimi, Bilgisayarlı Tomografi, Orofaringeal Kanser

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LIST OF ABBREVIATIONS

$3D$	Three Dimensional
$AJCC$	American Joint Commission on Cancer
AUC	Area Under the Curve
CCA	Correlation Coefficient Analysis
CT	Computed Tomography
CV	Cross Validation
FHR	Electronic Health Records
FNA	Fine Needle Aspiration
GLM	General Linear Model
GTV_p	Gross Primary Tumor Volume
HNC	Head and Neck Cancer
$HNSCC$	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
IHC	Immunohistochemistry
LR	Logistic Regression
Log	Laplacian of Gaussian
ML	Machine Learning
MRI	Magnetic Resonance Imaging
$NCCN$	National Comprehensive Cancer Network
OPC	Oropharyngeal Cancer
$PACS$	Picture Archiving and Communication Systems
PET	Positron Emission Tomography
PCR	Polymerase Chain Reaction
RF	Random Forest
ROC	Receiver Operating Characteristic Curve
ROI	Region of Interest
$ROSE$	Random Over-Sampling
$TCIA$	The Cancer Imaging Archive

VOI	Volume of Interest
$Xgboost$	Extreme Gradient Boosting

1. INTRODUCTION

The seventh most prevalent cancer worldwide and the ninth most common cancer in the United States, head and neck cancer (HNC) refers to a variety of upper aerodigestive tract tumors [1]. Approximately 644,000 new cases of head and neck cancer are projected to be detected annually worldwide, with two-thirds of these occurrences taking place in developing nations [2]. The American Joint Committee on Cancer determines HNC cancer medicine as including tumors originating from both major and minor salivary glands as well as malignancies coming from mucosal areas of the oral cavity, larynx, paranasal sinuses, and pharynx [3]. Even after curative therapy, the majority of HNCs are already in the last state when they are diagnosed, which drastically lowers the survival rate. Important risk factors for HNC include smoking or chewing tobacco, drinking too much alcohol, eating areca (betel) nuts, paan masala (Gutkha), being overexposed to sunlight, gamma, and ultraviolet radiation, having cancer in the family, and getting older [4]. Additionally, human papillomavirus (HPV) has been linked to oropharyngeal cancer (OPC), a subtype of HNC, and this type of cancer linked to HPV makes up approximately 25% of all HNCs [5]. The National Comprehensive Cancer Network (NCCN) recommends HPV testing for all oropharyngeal tumors in their guidelines [6]. In the United States, the percentage of head and neck cancers diagnosed as OPC that tested positive for HPV increased from 16.3% in the 1980s to more than 72.7% in the 2000s. This seems to be a result of increased awareness, the discovery of the link between HPV and cancers of the head and neck, and improved diagnostic HPV testing [7].

1.1 Importance of Knowing the HPV Status

Planning a prognosis and a course of treatment requires knowledge of the HPV status in OPC patients. HPV-positive OPC has a lower mortality rate than HPV-negative illness, with a 60% mortality rate with N3 or M1 sickness and an 80-90%

5-year survival rate even with lymph node involvement. Both overall mortality from all causes (10.4% vs. 33.3%) and mortality primarily from head and neck cancer (4.8% vs. 16.2%) were lower in HPV-positive patients. Despite having a poor 5-year survival rate of about 67%, OPSCC, which tests negative for HPV, has a poor prognosis [8, 9]. Therefore, knowing a patient's HPV status aids in identifying those who may have a better prognosis and may not need as aggressive a course of therapy. According to studies, radiation and chemotherapy treatments have a stronger tendency to decrease and control HPV-positive tumors' growth. Contrarily, HPV-negative cancers might be more resistant to conventional therapies, requiring more intensive or unconventional therapeutic modalities [10]. Additionally, there is significant interest in de- escalating treatment intensity for patients infected with HPV oropharyngeal cancer to mitigate the toxicities associated with treatment while preserving outstanding results due to the favorable prognosis of this kind of disease [11]. Identifying patients who may be candidates for treatment de-escalation methods, such as lowering radiation dosage or chemotherapy intensity, is made easier with the use of HPV status information. This strategy aims to achieve the best possible compromise between reducing adverse effects from the treatment and controlling the tumor effectively [12]. Eligibility for particular clinical trials and targeted therapy is influenced by HPV status in oropharyngeal cancer. For individuals who are HPV-positive, several studies and cutting-edge treatments explicitly targeting HPV-related biological pathways may be beneficial. Clinicians can find suitable clinical trial choices and possibly investigate targeted treatments based on the underlying genetic features of the tumor by determining the HPV status [13]. The presence of HPV may also affect post-treatment surveillance plans. A more targeted and unique approach to post-treatment monitoring is made possible by modifying the surveillance procedures based on HPV status and concentrating on regions with a higher risk of recurrence [14]. In the end, determining HPV status enhances the accuracy of therapy selection and helps to improve patient outcomes in oropharyngeal cancer. Typically, radiotherapy and drug therapy are used in conjunction to treat oropharyngeal cancer. The particular strategy is determined by the cancer's stage, the patient's general condition, and HPV status [15].

1.2 Diagnostic and Characterization Methods

For oropharyngeal cancer, a variety of diagnostic and characterization techniques are currently available and in use [16]. Rapid diagnosis and treatment increase a patient's likelihood of recovering from an illness [17]. Oropharyngeal tumors are routinely diagnosed and characterized using a variety of traditional techniques, such as physical examination, imaging studies, and tissue samples [18]. For instance, the medical professional may do a medical history assessment, during which they will look through the patient's medical background and discuss any symptoms, risk factors, or existing disorders that may be related to oropharyngeal tumors. This aids in the diagnostic process and aids in understanding the patient's general health [19]. A physical examination will also be performed, during which a medical practitioner will carefully inspect the head, neck, and oropharynx. Any abnormal growths or other symptoms that might point to the presence of a tumor will be examined by medical professionals [20]. The oropharyngeal region can be seen, and tumors can be detected using a variety of imaging modalities [21]. One of these is a computed tomography (CT) scan which produces cross-sectional images of the head and neck that reveal the size, position, and extent of the tumor [22]. Additionally, magnetic resonance imaging (MRI) creates precise images of soft tissues [23]. The morphology of the tumor and the involvement of neighboring tissues can both be learned via an MRI [24]. Using a radioactive tracer, positron emission tomography (PET) scans look for areas with elevated metabolic activity, which may be a sign of the presence of malignant cells [25]. Another technique is endoscopy, which involves using a small, flexible tube with a light and camera (an endoscope) to look at the oropharynx and other structures. Endoscopy enables direct visualization and can aid in locating spots for additional analysis [26]. For establishing the existence of a tumor and identifying its features, biopsy tissue sampling is essential. An oropharynx biopsy entails the removal of a tiny sample of tissue, which is then sent to a lab for examination. HPV molecular testing is possible on this tissue [27]. Conventional laboratory techniques like p16 immunohistochemistry (IHC) and polymerase chain reaction (PCR) can be utilized to determine the HPV status of a patient. The 8th edition of the American Joint Commission on Cancer (AJCC) recommended P16 IHC as a diagnostic test for oropharyngeal cancer staging [28]. How-

ever, this may increase the effort and cause a delay in clinical applications. The biopsy can be done either as part of the endoscopy or separately. One of these is fine needle aspiration (FNA), in which a tiny needle is occasionally used to remove cells or a small sample of tissue from the tumor for microscopic analysis. Excisional or incisional biopsy is a different type of biopsy that is used to remove the entire tumor or a piece of it for study in larger tumors [29]. Additional investigations, including genetic analyses or staging techniques, may be carried out after the tumor is discovered to better describe it and choose the best course of treatment [30]. It's crucial to remember that the diagnostic procedure can change based on the particular instance, the preferences of the healthcare professional, and the accessibility of resources. To guarantee a precise diagnosis and thorough understanding of oropharyngeal tumors, a multidisciplinary strategy comprising numerous specialists, such as otolaryngologists, radiologists, and pathologists, is frequently used.

1.3 A New Alternative: Radiomics

In addition to all of the classic diagnostic techniques listed above, a brand- new technique known as radiomics has recently attracted interest. The field of radiomics has advanced swiftly toward practical application in the hopes of improving cancer treatment and accurate detection. Radiomics is a quantitative approach to medical imaging that makes use of sophisticated mathematical analysis to enhance the data already available to doctors [31]. Radiomics quantifies textural information by mathematically extracting the spatial distribution of signal intensities and pixel interrelationships using analysis methods from the field of artificial intelligence [32]. Due to their potential prognostic value for treatment outcomes and cancer genomes, radiomic features have recently gained a lot of attention and may be useful in personalized medicine. Radiomics may hold great promise for the collection of critical phenotypic information, such as intra-tumor heterogeneity, which would then provide key information for individualized treatment [33]. The application of radiomics in oropharyngeal malignancy diagnosis and precision medicine has shown promise. For instance, it enhances characterization and diagnosis. Radiomics can extract a wide array of quantitative attributes

from imaging data, enabling a more thorough characterization of oropharyngeal cancers. These characteristics can be examined by radiomics to reveal details regarding tumor size, shape, heterogeneity, and spatial patterns that might not be visible from eye inspection alone. This improved characterization can help in making the distinction between benign and malignant tumors, determining how aggressive the tumor is, and guiding treatment choices. The tumor's response to various treatment modalities, such as radiation therapy or chemotherapy, can be predicted using radiomics features collected from pre- treatment imaging. Researchers have discovered links between specific patterns, or biomarkers, and successful treatment outcomes by examining radiomic signatures. This data can be used to forecast treatment outcomes, identify individuals who would benefit from more aggressive treatment modalities, or choose patients who are most likely to respond well to less intrusive procedures [31]. Radiation oncologists can optimize radiation dose distribution and intensity modulation to target the tumor more precisely while preserving healthy tissues by incorporating radiomic characteristics into treatment planning algorithms. Radiation therapy that is guided by radiomics attempts to provide a more individualized kind of care that maximizes tumor control while minimizing adverse effects [34]. Additionally, radiomics can help with prognosis prediction and risk stratification for people with oropharyngeal cancer. Radiomics models can classify patient subgroups as high-risk or low-risk based on their tumor characteristics by assessing imaging features. These models can help in calculating the likelihood of metastasis, disease recurrence, or overall survival, which can inform treatment choices and follow-up plans [35]. Additionally, radiogenomics, or the combination of radiomics and genomics, can help us better understand the biology of oropharyngeal cancer by integrating it with genomic data. Radiogenomic techniques can help us understand tumor behavior and treatment response more thoroughly by pointing out correlations between radiomic characteristics and genomic abnormalities, such as certain gene mutations or molecular subtypes. The identification of possible imaging-based biomarkers that can direct targeted therapeutics may also be aided by this combination [36]. In some circumstances, radiology may be used in addition to or as a substitute for biopsy [37]. This non-invasive method can be useful in identifying and diagnosing a number of disorders, including cancer. In some instances, radiomics may include crucial information that helps in making the distinction be-

tween benign and malignant lesions or determining the aggressiveness of tumors. This might lessen the necessity for invasive procedures like biopsy in some circumstances. Radiomics can also be used to track a cancer patient's reaction to treatment. The success of treatment and tumor development or regression may be determined by tracking changes in radiomic characteristics over time [31]. Without submitting the patient to extra-invasive procedures, this non-invasive monitoring strategy could supplement conventional biopsy-based assessments and provide additional information on therapy response. As a result, the radiomics technique has the ability to capture complex tumor properties, such as shape, texture, and spatial correlations, which may provide extra information beyond what can be learned from a biopsy sample alone [37]. By identifying the most questionable or important locations for the sample, radiology can help direct the biopsy procedure. Radiomics can increase the precision and diagnostic yield of biopsies by examining radiomic characteristics, imaging-based biomarkers, or tumor heterogeneity patterns, ensuring that the most representative tissue samples are obtained [38]. Radiomics should be seen as an additional instrument that can offer more data to support clinical judgment. It may help target biopsies, track therapeutic efficacy, and offer non-invasive insights on tumor features [37]. It can be used with biopsy results and other clinical data to help create a more thorough knowledge of the illness and better personalize treatment plans for specific patients. Biopsy and radiomics are two different methods for identifying and diagnosing diseases, particularly cancer. Each of them has advantages and drawbacks. Radiomics' non-invasive nature is undoubtedly one of its advantages. Radiomics analysis is based on non-invasive medical imaging techniques like CT, MRI, or PET scans. Both geographically and temporally diverse tumors exist in solid tumors. As a result, the use of invasive biopsy-based molecular assays is constrained. However, radiomics, which may non-invasively detect intra-tumoral heterogeneity, now have a wide range of applications [39]. Radiomics can track alterations in tumor features over time, allowing for the monitoring of a treatment's effectiveness or the development of a disease [31]. In summary, radiomics provides a non-invasive whole-lesion assessment with the possibility of temporal monitoring and multi-dimensional analysis. It is deficient in tissue confirmation and thorough histological data, though.

1.4 Contribution

In the literature, a number of algorithms have been proposed for radiomics based HPV status determination [40]. This work is different in that the developed method is based on a not yet tried machine-learning algorithm combination. Additionally, a thorough comparison of our approach and results with the biopsy technique was conducted for the first time. Advantages and disadvantages of each approach and typical error rates encountered are given. Finally, the future work needed to translate the non- invasive radiomics approach to routine clinical practice is outlined. We expect that this analysis will lead us to take the steps needed to include this new promising approach to tumor characterization in the arsenal of the oncologist.

2. METHODS

2.1 Data Set

495 patients in the collection of data from The Cancer Imaging Archive (TCIA) [[41] were incorporated into the research. Since the images of the patients who were not involved in the work were not suitable for the study, the research only examined 238 individuals' contrast-enhanced CT scans, 204 of whom were HPV positive and had been given an OPC diagnosis. The gross primary tumor volume (GTVp), (Figure 2.1) which is divided by experts, is taken into account in radiomic researches [42]. In the employed data collection, GTVp-eligible segments were present because determination of HPV status is also the primary purpose of the algorithms used.

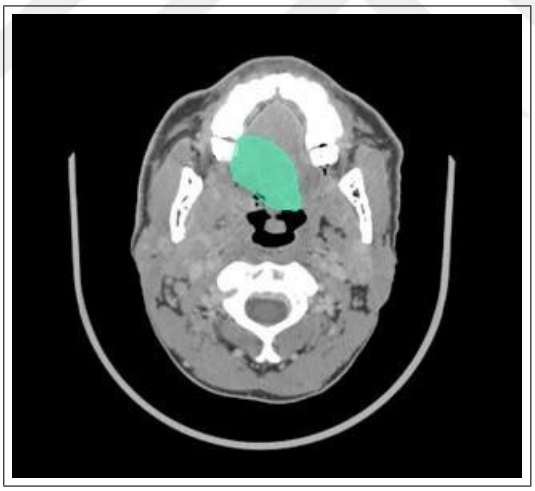


Figure 2.1 One slice of CT image of a patient with OPC. Green-colored segmentation represents the tumor area.

2.2 Image Pre-processing

Prior to the radiomic feature extraction protocol, all patients' CT scans were re-scaled and standardized. Resampling CT images produced 1 mm x 1 mm x 1 mm, which was used to remove varying voxel sizes [43]. The three- dimensional (3D) slicer

program (version 5.0.3) was used to do resampling and interpolation methods applying the Python tool Radiomics, riginating from the Pyradiomics library [44].

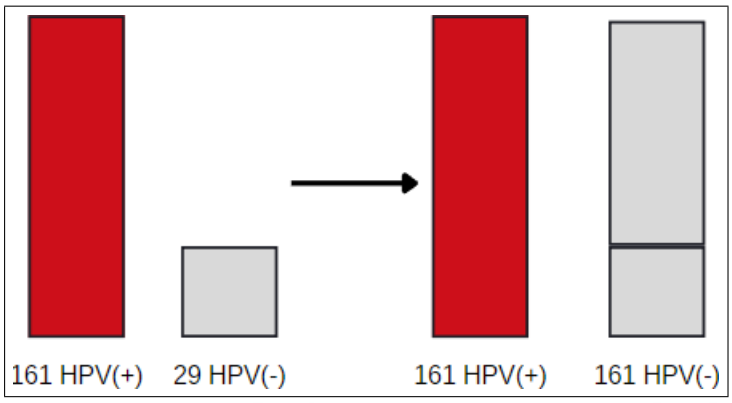


Figure 2.2 Random over-sampling application on training data.

2.3 Feature Extraction

After performing image preprocessing, the feature extraction process was carried out using 3D Slicer software (version 5.0.3) [45]. A standard bin width of 10 was set in order to implement gray-level discretization and reduce variability [46]. These included characteristics of the initial images, Wavelet transformed images, and Laplacian of Gaussian (Log) filtered images (Figure 2.3). Various region of interest (ROI) and volume of interest (VOI) elements are quantified throughout the feature extraction process, and phenotypic traits are given a numerical representation. After the images have been converted into features, the newly generated data are utilized to train and evaluate machine learning (ML) models. These characteristics are applied to quantitative image comparisons [47]. [48] has detailed explanations of the radiomics aspects.

2.4 Data Pre-processing and Resampling

Data on a large scale for 1142 features were applied to Z-score normalization. 20% of the data was designated for testing, while the remaining 80% was designated for

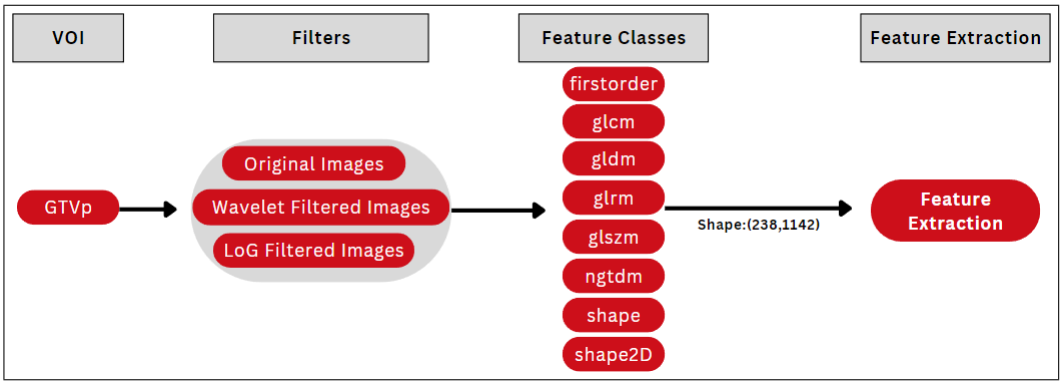


Figure 2.3 The process of extracting features and the procedures for distributing data in five-fold cross-validation.

training. The training set and the test set exhibited an unequal distribution of HPV classes. The test set contained 48 instances (43 HPV positive, 5 HPV negative), while the training data contained 190 instances (161 HPV infected, 29 HPV uninfected). Since the number of cases with HPV status is imbalanced, Random Over-Sampling (ROSE) [49] resampling method was chosen as a resampling algorithm. The only training set was subjected to a resampling technique because the dataset was so severely unbalanced. Following the application of data balancing, 161 samples for each positive and negative HPV class in the training set were obtained (Figure 2.2).

2.5 Feature Selection

Radiomics approaches typically produce high dimensional data, which increases the risk of over-fitting, worsens model confusion, and degrades prediction accuracy. The term "feature selection" refers to the process of extracting a subset from an initial feature set in accordance with a predetermined feature selection criterion, which chooses the dataset's pertinent features [50]. There are numerous techniques for choosing functional features [51]. In this research, correlation coefficient analysis (CCA), random forest (RF) feature importance analysis, and backward elimination methods were used in this work in that order. (Figure 2.4). CCA was initially employed as a filter-based technique to subtract unneeded characteristics that were extremely closely related (absolute correlation coefficient > 0.9). The Gini impurity metric, which offers a better

way to gauge feature importance, was used to run the random forest model [52]. The fifty most crucial traits were chosen using the sequential backward selection approach, with k-nearest neighbor serving as a forecaster. The feature selection techniques were carried out in Python (version 3.9) using the MLxtend and Scikit-learn libraries [53].

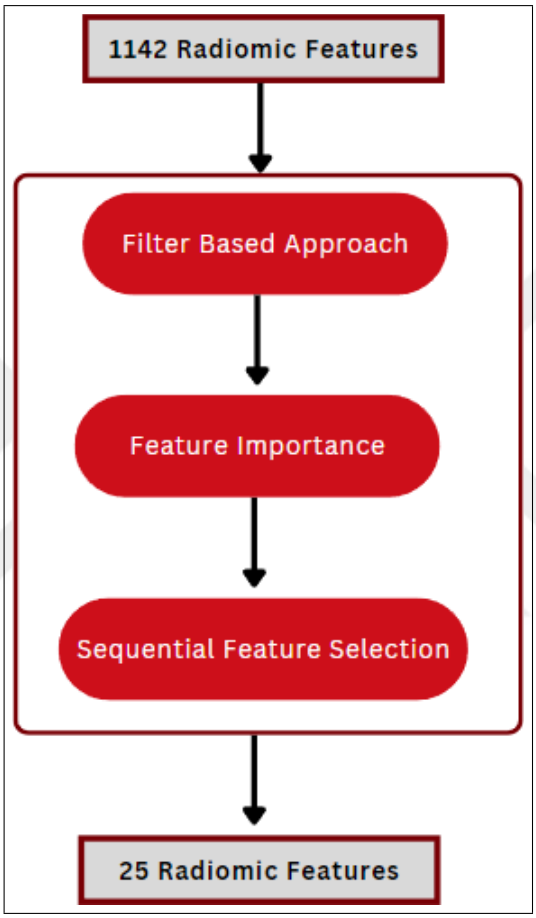


Figure 2.4 Flowchart for the feature selection process.

3. RESULTS

3.1 Model Training and Evaluation

The prediction machine learning model employed in this study was a random forest (RF) classification algorithm, which was evaluated using a five-fold cross-validation (CV) approach. The random forest (RF) model underwent 500 distinct combinations of hyperparameters during training, using the Randomized Search CV method on the feature sets to determine the best ones that maximize model efficiency. This operation (five folds nested cross-validation) was run five times for various training and testing sets. On the 20% of the initial unbalanced data that was not used, the model's performance was assessed separately. HPV status was predicted by an RF algorithm with an accuracy of 91% (95% CI: 83-99) and an area under the curve (AUC) of 0.77 (95% CI: 65-89) on the testing data. The confusion matrix and ROC curve (receiver operating characteristic curve) for the random forest model with ROSE resampling algorithm performance result on the test data are demonstrated in Figure 3.1 and Figure 3.2 respectively.

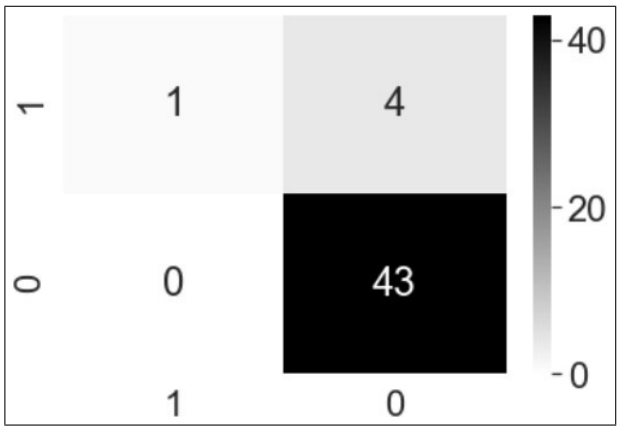


Figure 3.1 Confusion matrix of Random Forest model with the Rose re- sampling algorithm.

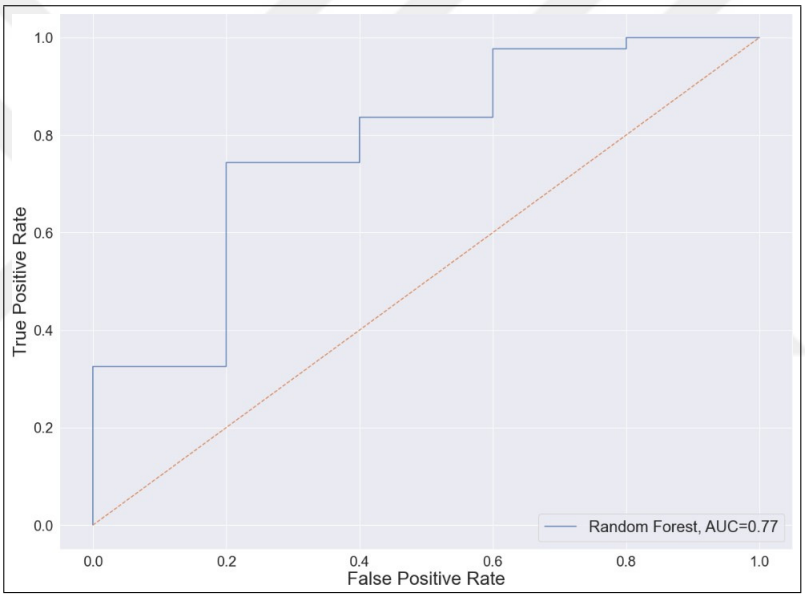


Figure 3.2 ROC Curve of Random Forest model with the ROSE re-sampling algorithm.

4. DISCUSSION

This paper aimed to create a novel radiomics-driven approach for determining HPV status in patients with oropharyngeal cancer (OPC) and make a thorough analysis of its applicability in routine clinical practice. We used data offered by The Cancer Imaging Archive (TCIA) to conduct the study. By the use of the RF algorithm in combination with resampling, we were able to identify the HPV situation with an accuracy of 91% (95% CI: 83-99) AUC of 0.77 (95% CI: 65-89) on the independent testing data. Other algorithms and different datasets have been investigated in several previous studies as discussed in the article [40]. The outcomes in this study were similar to previous findings although the collection of data utilized was small and highly imbalanced.

4.1 Limitations

The study was conducted with limited and unbalanced data. No testing has been done to determine how robust the radiomic characteristics are to segmentation alterations. The results have been obtained using an independent test dataset but not have been verified with data obtained from other institutions.

4.2 Comparison with Biopsy and Future Work for Widespread Application

Biopsy may miss the most aggressive or representative areas of the tumor, resulting in a false-negative result [54]. Moreover, biopsy samples may fail to detect cancer cells, because the tumor can be small or located in a challenging anatomical site, and primary and secondary tumors are situated in this region. In some cases, the biopsy may only capture normal or benign tissue, leading to a false-negative result [55].

Multiple biopsies or alternative diagnostic techniques may be required to increase the accuracy of diagnosis. Also, in certain cases, the obtained biopsy sample may not provide enough tissue for comprehensive analysis. This can limit the ability to perform additional tests, which are essential for personalized treatment decisions and prognostic evaluation. Furthermore, pathologists play a critical role in interpreting biopsy samples and providing a diagnosis. There can be interobserver variability, where different pathologists may interpret the same biopsy sample differently. This subjectivity can affect diagnostic accuracy and subsequent treatment decisions [56]. Biopsy samples may not fully capture the complexity of the tumor, including variations in genetic mutations, protein expression, or cellular characteristics. This can limit the accuracy of prognosis and treatment planning based on a single biopsy sample [67]. Besides, biopsies, especially those performed using invasive techniques such as surgical excision or fine needle aspiration, carry some risks and potential complications. These can include bleeding, infection, damage to nearby structures, and patient discomfort [57]. The risks and benefits should be carefully considered, particularly in patients with comorbidities or high surgical risk and biopsy alone may not provide complete staging information, as it primarily focuses on confirming the presence of cancer cells and determining the tumor type. Additional imaging research, for example CT scans are often necessitated to assess the extent of the tumor, involvement of nearby lymph nodes, and the presence of distant metastases [58]. Also, the diagnostic error rates in biopsies can vary depending on several factors, such as the sampling error, inadequate tissue for identification, the presence of inflammation making diagnosis challenging, artifact, and pathologist inconsistency [56]. Diagnostic errors can include false positives (incorrectly identifying a condition as present) or false negatives (missing the presence of a condition). For instance, in the study [56], sample error accounted for 60.0% of inconsistent findings, pathologist inconsistency accounted for 23.3%, inadequate tissue was provided for the biopsy, and inflammation masked the diagnosis by 3.4%. The error rates can change depending on the specific biopsy procedure and the condition being evaluated.

It is important to acknowledge these limitations when interpreting biopsy results in oropharyngeal cancer. Clinicians may want to consider a complementary approach such as radiomics in order to improve diagnostic accuracy and guide appropriate treat-

ment strategies.

Meanwhile, advancements in imaging techniques and the use of minimally invasive procedures have helped reduce the risks and improve the accuracy of biopsies in recent years.

While radiomics holds promise in the realm of medical imaging, there are also various reported issues and difficulties generally associated with its implementation and application [59]. Radiomics involves the extraction and analysis of a large number of quantitative features from medical images [31]. However, there is a lack of standardized protocols and guidelines for feature extraction, leading to variability in the methods used across different studies and institutions. This lack of standardization can impact the reproducibility and comparability of radiomic results, making it challenging to establish consistent and reliable radiomic models. Radiomics heavily relies on the quality and consistency of the medical images used for analysis. However, imaging techniques, acquisition parameters, and equipment can vary between institutions, scanners, and even individual radiologists. These variations in image acquisition can introduce variability and bias in the radiomic features, affecting the accuracy and generalizability of the results. Radiomics often requires extracting many characteristics from medical images, and not all of these characteristics may be relevant or informative for a specific clinical question. The selection of relevant features becomes crucial, but it can be challenging due to the high- dimensional nature of radiomic data. Improper feature selection techniques or overfitting (finding patterns that are specific to the training dataset but not representative of the general population) can lead to overly optimistic results and reduced generalizability of the radiomic models. Moreover, radiomics relies on the availability of large and diverse datasets for training and validation purposes . However, obtaining high-quality imaging data with corresponding clinical annotations can be challenging due to issues such as data privacy, limited sample sizes, and variations in data collection across institutions. Limited data availability and potential biases in the data can impact the development and validation of robust radiomic models [33]. Furthermore, while radiomics studies have shown promising results in research settings, there is a need for robust validation and clinical translation. The

performance of radiomic models in real-world clinical settings may differ from the initial research findings. Further validation studies, preferably in multi-institutional settings, are needed to establish the clinical usefulness and effectiveness of radiomics in various disease contexts. The radiomics results should also provide a probability for the likelihood of a correct result for a particular patient. Also, radiomic models often provide quantitative and statistical measures, but the interpretation of these measures and their integration into clinical decision-making can be challenging [38]. The clinical relevance and meaningfulness of radiomic features need to be further explored and validated to ensure their utility in guiding treatment decisions and patient management. Addressing these reported issues requires ongoing research and collaboration among radiomics researchers, imaging experts, and clinicians. Efforts towards standardization, data sharing, rigorous validation, and clinical integration are essential to overcome these challenges and maximize the potential of radiomics in healthcare. The Image Biomarker Standardization Initiative (IBSI), founded by study participants [59], was created to overcome these difficulties by creating the goals, which are: nomenclature and descriptions for frequently utilized radiomic characteristics; a common image processing using radiomics plan for the computation of imaging-based characteristics; data collection and related reference values for the calibration and testing of image processing software implementations.

For radiomics to achieve widespread clinical acceptance, several requirements must be fulfilled. For instance, there is a need for standardized methods and guidelines for radiomics feature extraction, analysis, and interpretation. Consensus on imaging acquisition protocols, feature definitions, and analytical approaches will ensure consistency and reproducibility across different institutions and studies. Also, validation and robust evidence is required for clinical acceptance. Radiomics models should undergo rigorous validation to demonstrate their clinical utility and performance. This includes internal validation on independent datasets and external validation on diverse patient populations. Prospective studies comparing radiomics with current standard-of-care methods are essential to establish its added value. Radiomics features and models should provide clinically relevant information that can impact patient management and treatment decision-making. The derived imaging biomarkers should correlate

with important clinical endpoints, such as prognosis, treatment response, or survival. Demonstrating improved patient outcomes through radiomics-based interventions will drive its acceptance. Radiomics tools and analyses should be also seamlessly integrated into existing clinical workflows and decision support systems. This requires user-friendly interfaces, efficient data handling, and integration with electronic health records (EHR) and picture archiving and communication systems (PACS). Radiomics should not disrupt the clinical workflow but rather enhance it. Patient privacy, data security, and ethical considerations should be considered when implementing radiomics in clinical practice. Compliance with regulations, and obtaining informed consent for data use and analysis are essential. Healthcare professionals, including radiologists, oncologists, and other specialists, need education and training to understand the principles, limitations, and interpretation of radiomics. Continuing education programs, workshops, and resources should be developed to ensure healthcare professionals are equipped with the necessary knowledge and skills to effectively utilize radiomics in clinical practice. Cost-effectiveness and reimbursement are other issues for the clinical usage of radiomics. Widespread clinical acceptance of radiomics requires consideration of its cost-effectiveness and reimbursement. Demonstrating its value in improving patient outcomes, optimizing treatment strategies, and reducing healthcare costs will enhance its chances of reimbursement by healthcare systems and insurance providers. Regulatory approval is another crucial issue in clinic. Regulatory bodies play a role in assessing the safety, efficacy, and quality of radiomics tools and algorithms. Obtaining regulatory approval or clearance for specific radiomics applications can enhance confidence and acceptance among clinicians and healthcare institutions.

By addressing these requirements, radiomics can overcome challenges and gain widespread acceptance in clinical practice, ultimately benefiting patients through improved diagnosis, treatment planning, and personalized medicine.

4.3 Future ML Work

In spite that our models are able to forecast HPV status with a good level of AUC and relative accuracy, more research ought to be done utilizing expanded clinical information to verify the effectiveness of the created ML model. All the above-mentioned concerns about radiomics should also be addressed (interpretability, standardization, reproducibility).

5. CONCLUSIONS

In conclusion, this work attempts to demonstrate that it is clinically important and possible to create a novel CT radiomic-based non-invasive technique for the identification of HPV status with accuracy rates that can challenge those obtained from biopsy. It also investigates whether and how radiomics could be a viable alternative technology. The algorithm developed in this study predicts the HPV status with promising accuracy. Further research studies are required to increase accuracy, safety, reproducibility, standardization, and interpretability for widespread clinical acceptance

5.1 List of publications produced from the thesis

1. Sarac, K., Guvenis, A. Using radiomics for predicting the HPV status of oropharyngeal tumors. J. Eng. Appl. Sci. 71, 11 (2024). https://doi.org/10.1186/s44147-023-00355-w

2. Sarac, K., Guvenis, A. (2023). Determining HPV Status in Patients with Oropharyngeal Cancer from 3D CT Images Using Radiomics: Effect of Sampling Methods. In: Rojas, I., Valenzuela, O., Rojas Ruiz, F., Herrera, L.J., Ortuno, F. (eds) Bioinformatics and Biomedical Engineering. IWBBIO 2023. Lecture Notes in Computer Science(), vol 13920. Springer, Cham. https://doi.org/10.1007/978-3-031-34960-7_3

3. Sarac, K., Guvenis, A. Predicting HPV Status From 3D CT Images of Oropharyngeal Cancer Patients Using ROSE and Random Forest Algorithms. International Multidisciplinary Symposium on Drug Research and Development (DRD 2023). May 4-6 2023, Izmir, Turkey.

APPENDIX A. DETERMINING HPV STATUS IN PATIENTS WITH OROPHARYNGEAL CANCER FROM 3D CT IMAGES USING RADIOMICS: EFFECT OF SAMPLING METHODS

A.1 Abstract

Non-invasive detection of human papillomavirus (HPV) status is important for the treatment planning of patients with oropharyngeal cancer (OPC). In this work, three-dimensional (3D) head and neck computed tomography (CT) scans are utilized to identify HPV infection status in patients with OPC by applying radiomics and several resampling methods to handle highly imbalanced data. 1142 radiomic features were obtained from the segmented CT images of 238 patients. The features used were selected through correlation coefficient analysis, feature importance analysis, and backward elimination. The fifty most important features were chosen. Six different sampling methods which are Synthetic Minority Oversampling Technique (SMOTE), Support Vector Machine Synthetic Minority Oversampling Technique (SVMSMOTE), Adaptive Synthetic Sampling Method (ADASYN), NearMiss, Condensed Nearest Neighbors (CNN), and Tomek's Link were performed on the training set for each of the positive and negative HPV classes. Two different machine learning (ML) algorithms a Light Gradient Boosting Machine (LightGBM) and Extreme Gradient Boosting (XGBoost) were applied as predictive classification models. Model performances were assessed separately on 20% of the data. Oversampling methods displayed better performance than undersampling methods. The best performance was seen in the combination of SMOTE and XGBoost algorithms which had an area under the curve (AUC) of 0.93 (95% CI: 82-99) and an accuracy of 90% (95% CI: 78- 96). Our work demonstrated a reasonable accuracy in the forecast of HPV status by using 3D imbalanced and small datasets by using resampling methods. Further work is needed to test the algorithms on larger, balanced, and multi-institutional data.

Keywords: HPV Status, Radiomics, Resampling, Machine Learning.

APPENDIX B. PREDICTING HPV STATUS FROM 3D CT IMAGES OF OROPHARYNGEAL CANCER PATIENTS USING ROSE AND RANDOM FOREST ALGORITHMS

B.1 Abstract

Head and neck malignancies, which include a variety of tumor types are the sixth most prevalent cancer in the world [1]. Human papillomavirus (HPV) has appeared as a novel risk element for this type of cancer, particularly for oropharyngeal cancer (OPC) [2]. Patients who test positive for HPV infection have significantly different clinical behaviors and outcomes in OPC than those who test negative [3]. Therefore, planning the course of treatment (pharmacological and radiation therapy) for patients with OPC is highly dependent on their HPV status. In this research, three-dimensional (3D) head and neck computed tomography (CT) images are used to identify HPV status in patients with OPC by utilizing radiomics and machine learning (ML) algorithms. 238 patient's CT images from The Cancer Imaging Archive (TCIA) were resampled and normalized. 1142 radiomic characteristics were obtained from the segmented CT scans. The number of features was decreased by applying correlation coefficient analysis [4], and 25 out of 1142 features were chosen by using backward elimination [5] and random forest feature importance analysis [5]. Random Over-Sampling (ROSE) [6] oversampling algorithm was performed on the training set since the dataset used was highly imbalanced. After data balancing was applied, 161 samples were obtained for each positive and negative HPV class of the training set. A random forest (RF) classification algorithm was performed as a prediction model using five-fold cross-validation. To decide the optimum hyperparameters, which maximize model performance, 500 different combinations of hyperparameters were tested on the RF model using the Randomized Search CV method on training feature sets. Five iterations of this operation were carried out for various training and testing partitions (five-fold nested cross-validation). Model efficiency was evaluated separately on the unused 20% of the initial imbalanced data. HPV status was determined by an RF al-

gorithm with an accuracy of 91% (95% CI: 83-99) and an area under the curve (AUC) of 0.78 (95% CI: 66-89) on the test data. In conclusion, radiomic features obtained from 3D CT scans can accurately predict HPV status noninvasively in OPC patients by using ROSE oversampling and Random Forest classification algorithms despite the small and imbalanced data. Further work is needed to check the methods for balance and larger data.

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