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Original Research Article

Improving outcome prediction in oropharyngeal carcinoma through the integration of diffusion-weighted magnetic resonance imaging radiomics

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ABSTRACT

Background and purpose: Locoregional recurrence (LRR) is the primary pattern of failure in head and neck cancer (HNC) following radiation treatment (RT). Predicting an individual patient's LRR risk is crucial for pre-treatment risk stratification and treatment adaptation during RT. This study aimed to evaluate the feasibility of integrating pre-treatment and mid-treatment diffusion-weighted (DW)-MRI radiomic parameters into multivariable prognostic models for HNC.

Materials and methods: A total of 178 oropharyngeal cancer (OPC) patients undergoing (chemo)radiotherapy (CRT) were analyzed on DW-MRI scans. 105 radiomic features were extracted from ADC maps. Cox regression models incorporating clinical and radiomic parameters were developed for pre-treatment and mid-treatment phases. The models' discriminative ability was assessed with the Harrel C-index after 5-fold cross-validation.

Results: Gray Level Co-occurrence Matrix (GLCM)-correlation emerged as a significant pre-treatment radiomic predictor of locoregional control (LRC) with a C-index (95 % CI) of 0.66 (0.57–0.75). Significant clinical predictors included HPV status, stage, and alcohol use, yielding a C-index of 0.70 (0.62–0.78). Combining clinical and radiomic data resulted in a C-index of 0.72 (0.65–0.80), with GLCM-correlation, disease stage and alcohol use as significant predictors. The mid-treatment model, which included delta (Δ) mean ADC, stage, and additional chemotherapy, achieved a C-index of 0.74 (0.65–0.82). Internal cross-validation yielded C-indices of 0.60 (0.51–0.69), 0.56 (0.44–0.66), and 0.63 (0.54–0.73) for the clinical, combined, and mid-treatment models, respectively.

Conclusion: The addition of Δ ADC improves the clinical model, highlighting the potential complementary value of radiomic features in prognostic modeling.

1. Introduction

Thirty percent of head and neck cancer (HNC) patients will experience locoregional recurrence (LRR) within the first five years post-treatment, most commonly within two to three years [1,2]. The prognosis for patients with LRR is poor, with a median overall survival (OS) of less than one year following the failure of first-line therapy [3]. Most LRRs occur within high-dose treatment volumes, indicating that they are primarily linked to the development of resistance to (chemo)radiotherapy (CRT) [4–6]. It is becoming increasingly clear that tumors with identical location and histology can exhibit significantly different responses to RT, likely due to variations in biological, molecular, and genetic factors [7]. Identifying these factors could enable prospective patient selection and treatment adaptation, potentially improving tumor control while minimizing therapy-related morbidity [8,9].

However, it remains uncertain which tumors are inherently

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predisposed to develop resistance to RT, making it challenging to tailor the treatment based on the patient's individual risk profile. Accurate prognostication is crucial for guiding clinical decisions and implementing personalized therapeutic strategies. Beyond standard clinical factors like T and N classification, imaging biomarkers have shown potential for improving prognostic accuracy [10]. Radiomics, which extracts detailed information about tumor heterogeneity through data analysis, could present a rapid, non-invasive, and cost-effective method for stratifying HNC patients for individualized treatment planning [11]. Numerous studies have demonstrated the potential of radiomics in tumor type determination, classification, and prognostication [12–17]. Given the routine clinical use of Magnetic Resonance Imaging (MRI) in the staging of OPC, diffusion-weighted (DW)-MRI radiomics could serve as a practical tool to identify patients with high risk for LRR and direct them to appropriate treatment adaptation strategies [18,19].

This study aimed to evaluate the prognostic significance of pre-treatment and mid-treatment DW-MRI parameters in a large patient cohort and integrate these findings into two comprehensive multivariable prognostic models.

2. Material and methods

2.1. Patients, treatment and outcome

This study was approved by the Ethics Committee of the University Hospitals of Leuven (NCT01829646) and included 178 patients with oropharyngeal carcinoma (OPC) treated between 2005 and 2018. Written informed consent was obtained from all participants.

Details on patient selection, treatment protocols, and outcome measures are provided in the Supplementary Materials.

2.2. MRI imaging protocol and image data analysis

Each patient underwent an MRI prior to RT, as well as during the 4th week of RT. ADC maps were used for segmentation and feature extraction (Fig. 1). Details on imaging protocol and image data analysis are provided in the Supplementary Materials.

2.3. Feature selection, model building and validation

The study design and model development adhered to PROBAST guidelines and TRIPOD statement (Supplementary Table S1A and SB) [20,21].

A forward stepwise selection process was used to construct a multivariable model for predicting locoregional control (LRC). Details on model building and validation are provided in the Supplementary Materials.

2.4. Statistical analysis

The significance threshold was established at a p-value of < 0.05. Model building, receiver operating characteristic (ROC) and survival curves were established using SAS software (version 9.4 for Windows). CompareC in R (version 4.3.1) was used for a statistical comparison of the internally validated C-indices of the different models.

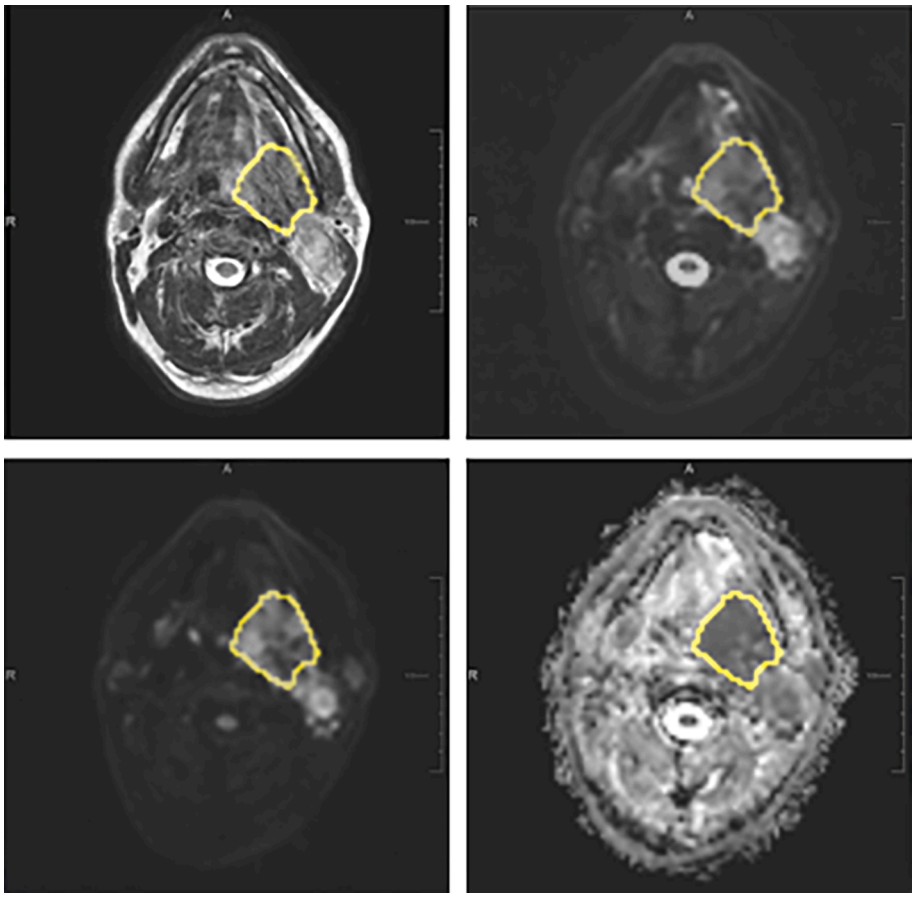

Fig. 1. Illustrative example of a region of interest (ROI) delineation of a patient included in the study. The delineations were made directly on the ADC map (bottom right) but also shown illustratively on other image contrasts. T2-weighted turbospin-echo (top left), DWI b = 0 s/mm^2 (top right), DWI b = 1000 s/mm^2 (bottom left).

3. Results

3.1. Patient characteristics

This study included a dataset of 178 OPC patients, whose detailed clinical characteristics are provided in Supplementary Table S2. Among these patients, 38 % (60 out of 158) tested positive for p16 and were classified as Human Papillomavirus (HPV) positive. The median patient age was 61 years (range: 53.67 to 66.91 years). The median follow-up period was 5 years, during which 74 % (131 out of 178) of the patients show LRC. 87 % of patients (52 out of 60) experienced a LRC in the HPV positive group, compared to 63 % (62 out of 98) in the HPV negative group. The 5-year survival estimates were 53 % for DM, and 55 % for OS. Kaplan-Meier curves for LRC, distant metastasis (DM), and overall survival (OS) are shown in Supplementary Fig. S1.

3.2. Clinical model for LRC

A forward stepwise selection approach was used to identify independent clinical prognostic factors for LRC. Univariate analysis results are presented in Table 1A. Multivariate analysis, shown in Table 1B and Supplementary Table S3, revealed that HPV status, disease stage, and alcohol use are significant predictors of LRC. Specifically, HPV positivity had a hazard ratio (HR) of 0.44 (95 % CI: 0.20–0.99), and advanced stage showed a HR of 2.16 (95 % CI: 1.30–3.60). Regarding alcohol use, significant differences were observed when comparing occasional drinkers to (past) heavy drinkers with a HR of 0.25 (0.09; 0.75). The model incorporating these factors achieved a C-index of 0.70 (95 % CI: 0.62–0.78).

3.3. Radiomic model for LRC

A total of 105 radiomic features were extracted from pre-treatment ADC maps of 178 OPC patients using PyRadiomics. The association between these radiomic features and LRC is provided in Supplementary Table S4. A radiomic model for LRC was developed via multivariate Cox regression analysis. Among the 105 features, 34 were significantly associated with LRC. High intercorrelation among these features led to the selection of five parameters with the least intercorrelation for further analysis (Table 2A and Fig. 2). These features were tested for independence in a multivariate analysis (Table 2B), with GLCM-correlation emerging as the only significant radiomic parameter, yielding a HR of 1.32 (1.12;1.54) for LRC and was subsequently used in model building. In a subgroup analysis, 30 out of 105 radiomic parameters significantly correlated with outcomes in HPV negative OPC patients, while no parameters showed a significant correlation in the HPV positive group (Supplementary Table S5).

Table 1
A. Univariable analysis of clinical predictors for LRC.

Variable	Test	Hazard Ratio (95 % CI)	P-value
Age	+1 year	1.02 (0.98;1.05)	0.34
AJCC stage	+1 level	1.73 (1.10;2.72)	0.02
Chemotherapy	Yes vs No	0.66 (0.35;1.25)	0.20
Tumor volume	+10 cc	1.11 (1.01;1.22)	0.04
Alcohol (Ref = Active heavy drinker)	Global test		<0.05
	Never/occasional	0.15 (0.02;1.07)	0.06
	Active heavy drinker	0.24 (0.09;0.61)	<0.05
	Past drinker	1.07 (0.55;2.11)	0.84
HPV	Positive vs Negative	0.29 (0.14;0.63)	<0.05
Smoking	Present/past vs Never	8.17 (1.13;59.29)	0.04

B. Multivariable model of independent predictors for LRC based on forward stepwise selection

Variable	Test	Hazard Ratio (95 % CI)	P-value
HPV	Positive vs negative	0.44 (0.20;0.99)	<0.05
AJCC stage	+1 level	2.16 (1.30;3.60)	<0.05
Alcohol	Global test		0.03
	Never/occasional vs. *Past drinker*	0.25 (0.09;0.75)	0.01
	Never/occasional vs. *Active heavy drinker*	0.26 (0.10;0.70)	<0.05

AJCC stage were included as ordinal variables. AJCC stage is based on 7th TNM edition. AJCC: American Joint Committee on Cancer. HR: hazard ratio, CI: confidence interval. n: 175 patients and 46 events.

3.4. Radiomic and clinical model for LRC

A stepwise approach was used to develop a mixed model for predicting LRC, incorporating all previously mentioned clinical and radiomic parameters. Multivariate analysis identified GLCM-correlation, alcohol use, and stage as significant predictors (Table 3 and Supplementary Table S6). The final model demonstrated a C-index of 0.72 (95 % CI: 0.65–0.80).

3.5. Mid-treatment model for LRC

A mid-treatment model was developed using the previously mentioned clinical parameters along with delta (Δ) mean ADC as a radiomic parameter of treatment response. Multivariate analysis (Table 4 and Supplementary Table S7) identified Δ mean ADC, stage, and concomitant chemotherapy as significant predictors, with the model achieving a C-index of 0.74 (95 % CI: 0.65–0.82). The Δ mean ADC values were significantly correlated with the percentage changes in tumor volume (Pearson correlation = 0.21, p = 0.02).

3.6. Model comparison and validation

The clinical prognostic model demonstrated superior performance compared to a model based solely on radiomic parameters. ROC curve analysis for 5-year LRC outcomes showed that the clinical model achieved a sensitivity of 0.74 and specificity of 0.62 at a chosen cutoff, whereas the radiomic model had a sensitivity of 0.74 and a lower specificity of 0.52 (Supplementary Fig. S2). The predictive model consisting out of radiomic and clinical parameters resulted in a sensitivity of 0.75 and specificity of 0.66. The mid-treatment model further enhanced predictive accuracy, with a sensitivity of 0.78 and specificity of 0.70, indicating better discrimination in predicting LRC compared to the other models (Supplementary Fig. S2).

Internal cross-validation revealed C-indices of 0.60 (95 % CI: 0.51–0.69) for the clinical model, 0.56 (95 % CI: 0.44–0.66) for the

Table 2
A. Univariable analysis of radiomic predictors for LRC.

Variable	Test	Hazard Ratio (95 % CI)	P-value
original_glcm_Correlation	+0.1 units	1.32 (1.12;1.54)	<0.05
original_glszm_ZoneEntropy	+1 unit	1.36 (1.03;1.80)	0.03
original_firstorder_Mean	x2 units	4.06 (1.49;11.07)	0.01
original_shape_LeastAxis	x2 units	2.26 (1.04;4.91)	0.04
original_glrlm_GrayLevelVariance	x2 units	1.83 (1.10;3.05)	0.02

B. Multivariable model of radiomic predictors for LRC based on forward stepwise selection

Variable	Test	Hazard Ratio (95 % CI)	P-value
original_glcm_Correlation	+0.1 units	1.32 (1.12;1.54)	<0.05

A log-transformation was applied for the variables original_firstorder_Mean, original_shape_LeastAxis, original_glrlm_GrayLevelVariance. HR: hazard ratio, CI: confidence interval. n: 161 patients and 42 events.

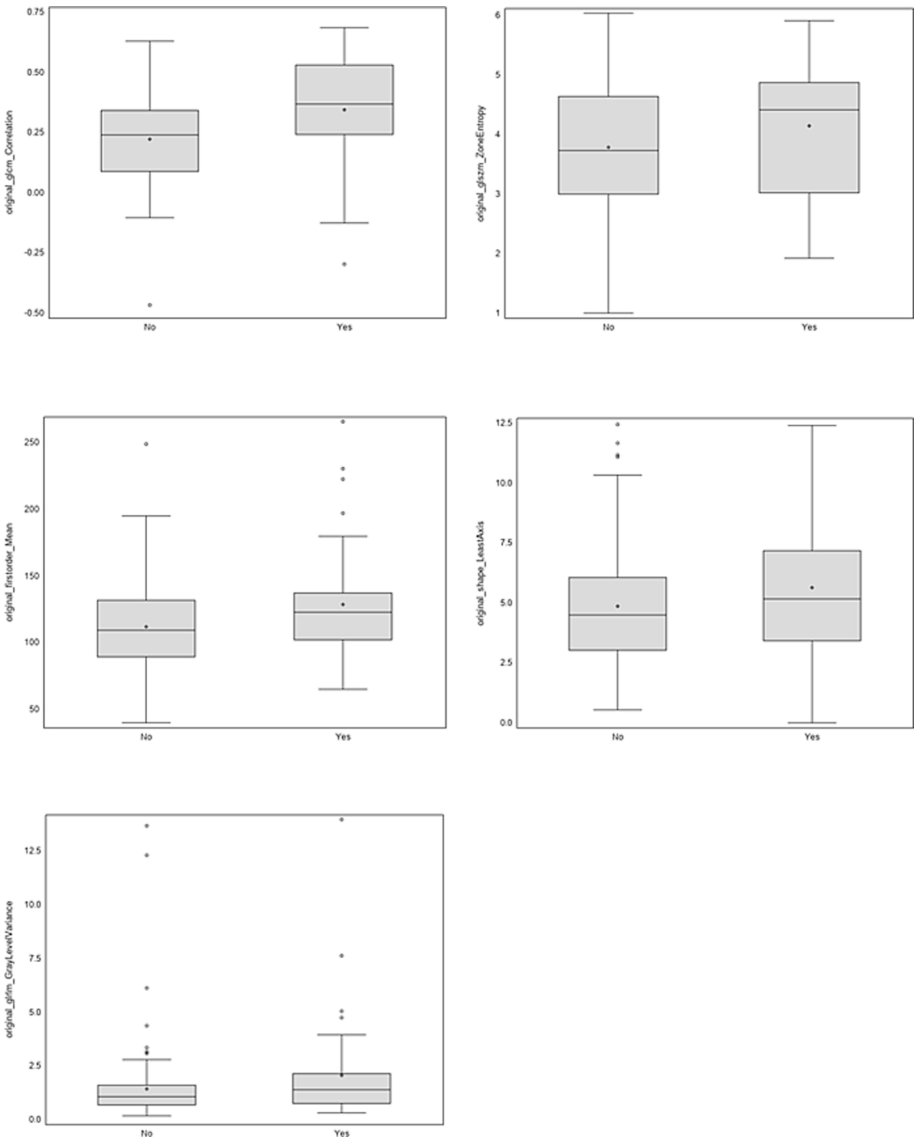

Fig. 2. Boxplots of the radiomic features selected for model building (see also Table 2A), categorized by locoregional control (LRC) status, where "yes" indicates the presence of LRC and "no" indicates its absence.

Table 3
Multivariable pre-treatment model of independent predictors for LRC based on forward stepwise selection.

Variable	Test	Hazard Ratio (95 % CI)	P-value
original_glcm_Correlation	+0.1 units	1.20 (1.02;1.42)	0.03
Alcohol	Global test		0.01
	Never/occasional vs *Past drinker*	0.18 (0.06;0.57)	<0.05
	Never/occasional vs *Active heavy drinker*	0.19 (0.06;0.54)	<0.05
AJCC stage	+1 level	2.03 (1.20;3.44)	0.01

AJCC stage is based on 7th TNM edition. AJCC: American Joint Committee on Cancer. HR: hazard ratio, CI: confidence interval. n: 158 patients and 41 events.

combined model, and 0.63 (95 % CI: 0.54–0.73) for the mid-treatment model (Supplementary Table S8). Comparison of the C-indices of the different models revealed no significant differences. The K-M curves for model stratification, using the median risk as the cutoff for classification across all models, were generated and are available in Supplementary Fig. S3.

Table 4
Multivariable mid- treatment model of independent predictors for LRC based on forward stepwise selection.

Variable	Test	Hazard Ratio (95 % CI)	P-value
Delta_mean_ADC	+10 units	0.87 (0.82;0.94)	<0.05
AJCC stage	+1 level	2.59 (1.49;4.51)	<0.05
chemo	Yes vs No	0.40 (0.18;0.89)	0.03

AJCC stage is based on 7th TNM edition. AJCC: American Joint Committee on Cancer. HR: hazard ratio, CI: confidence interval. n: 115 patients and 35 events.

4. Discussion

In this study, predictive models for LRC in OPC patients were developed by integrating pre- and mid-treatment DW-MRI radiomics with clinical data. Our results demonstrate the potential of using Δ ADC at mid-treatment for response prediction.

Understanding the factors associated with post-RT recurrence is essential for enhancing clinical decision-making in HNC. Previous studies have identified several clinical predictors of LRC in OPC, such as TNM stage, HPV status, primary tumor volume, age, N stage, and

smoking status [22–25]. In line with these results, our study identified AJCC stage, HPV status, and alcohol use as significant clinical pre-treatment predictors, with AJCC stage emerging as the strongest predictor. Additionally, GLCM-correlation – a radiomic feature that captures the spatial relationship between pixel intensities [26] – was established as a strong predictor of LRC. Incorporating GLCM-correlation into the clinical model resulted in a mixed model with improved discriminative accuracy, reaching a C-index of 0.72. However, after internal validation, the advantage of adding GLCM-correlation to the clinical model was no longer observed, resulting in a validated C-index of 0.56. It should be noted that HPV status was not included in the mixed model, possibly due to the sample size and the significant and strong correlation between GLCM-correlation and HPV status [27].

To our knowledge, this is the first prospective data collection study examining combined radiomic and clinical parameters from DW-MRI in OPC patients. Previous research has mainly focused on radiomics from CT or PET/CT scans, reporting AUC scores ranging from 0.45 to 0.85 [28–37]. MRI, currently the standard imaging modality for pre-treatment staging of OPC offers unique insights into tissue properties that CT cannot. However, fewer studies have explored MRI-based radiomics in HNC, with most focusing on nasopharyngeal carcinoma [26,38–42]. Comparing radiomics studies poses significant challenges due to variations in MRI modalities. However, two studies that developed and externally validated MRI-based radiomic models for pre-treatment prognostication in OPC reported performance outcomes comparable to those of our combined model [12,43]. Mes et al. achieved an AUC of 0.71 for OS and 0.74 for recurrence-free survival (RFS), which improved to 0.81 for OS and 0.78 for RFS when combined with clinical variables, while Bos et al. initially reporting an AUC of 0.74 with a sensitivity of 0.75 and specificity of 0.60, though performance declined in the validation cohort, with the AUC dropping to 0.64 and sensitivity to 0.68, while specificity remained 0.60 [12,43]. Both studies also identified GLCM-correlation as a predictor for LRC, although four other radiomics parameters were identified that were not withheld in our multivariate analysis. Nevertheless, GLCM-correlation has consistently been reported as a reliable predictive parameter across different imaging modalities, including FDG-PET/CT studies [22,40,43]. Pre-treatment ADC was not retained as a predictive factor in our multivariate analysis, which contrasts with some previous studies. This result can be attributed to the more significant impact of the remaining radiomics features, which overshadowed the effect of ADC [13,44–49].

Concerning our mid-treatment model, Δ mean ADC was demonstrated to be a strong predictor of LRC, with patients showing a significant increase in ADC having better recurrence rates compared to those with minimal Δ mean ADC, which aligns with previous studies [13,44–49]. Although mid-treatment MRI is not yet routine in a clinical setting, its use as part of adaptive treatment strategies represents a logical extension of its established role in staging. In fact, our mid-treatment model, which integrates Δ mean ADC, disease stage and addition of chemotherapy, achieved a C-index of 0.74 However, after internal validation, the C-index decreased to 0.63. Prior research indicates that mid-treatment hypo-perfused or FDG-avid areas are reliable predictors of poor outcomes, often exceeding the predictive value of pre-treatment analyses. In line with this concept, the University of Michigan reported that dynamic contrast-enhanced MRI (DCE-MRI) was able to detect tumor regions with consistently low blood volume after two weeks of treatment, which was proven to be indicative of an increased risk for LRR [50]. The development of a mid-treatment predictive model is based on the idea that targeting biologically aggressive tumor subvolumes during CRT may improve the therapeutic ratio of RT. This approach aims to provide personalized RT dosing by adapting treatment in real-time to balance increased doses to persistently aggressive areas while minimizing unnecessary toxicity to responding regions. DW-MRI has shown promise for this strategy, as evaluated by Mierzwa et al., who used ADC maps from pre-treatment and mid-treatment to define a boost volume [51]. Their phase II trial found that an MRI-based RT boost significantly reduced LRR but did not improve disease-free or overall survival. In line with this, our mid-treatment predictive model could help identify high-risk patients for similar approaches, though its external validation is necessary. Moreover, while other studies investigating the concept of dose escalation have shown acceptable toxicity, their benefit for LRR remains unproven [52,53]. Further phase II or III trials are needed to validate these concepts in larger patient cohorts.

It is important to note that Δ mean ADC values were significantly correlated with the percentage changes in tumor volume. Although the percentage changes in tumor volume were not significantly associated with LRC, these findings emphasize the complementary role of ADC changes in conjunction with tumor volume dynamics.

Models that combine clinical and radiomic data have shown increased predictive potential compared to those relying solely on clinical variables [12,17,31,35,43]. Despite promising results from multiple retrospective radiomics studies, integrating these models into clinical practice remains challenging due to issues like small datasets, lack of validation, and reproducibility concerns [8,54]. Our study design has attempted to overcome those limitations by utilizing a large, prospective cohort and using PyRadiomics software. The latter adheres to Image Biomarker Standardization Initiative (IBSI) standards, ensuring consistent and reproducible analysis [55]. Moreover, the entire ADC map volume was delineated by the radiologist, enabling more detailed texture analysis compared to studies with smaller or less detailed tumor sections. This allowed us to use the original pixel sizes without resampling. However, the reliance on manual delineation of MRI scans, even with thorough review by experienced radiologists, may introduce variability and potential inaccuracies. Additionally, as advised by Aly et al., we have adhered to PROBAST guidelines, which allowed us to effectively evaluate and mitigate potential biases [20,56]. The simplicity of our pre-treatment model, which incorporated up to five radiomic features selected through cluster analysis, according to Corti et al., minimized overfitting and enhanced its clinical utility [57].

Our study has several limitations. Given the limited number of events in the dataset, the feature selection process was designed to maximize the use of available information, utilizing all data for model construction. Since the primary focus was on identifying independent prognostic factors, discrimination metrics were the most suitable for directly evaluating model performance. Cross-validation was employed to mitigate optimism and provide a more reliable estimate of performance on an independent sample. However, external validation using independent datasets remains necessary for broader applicability. Models trained on internal data may not generalize well due to variations in image acquisition and processing methods, which can affect radiomic features [58,59].

Furthermore, the discriminative performance of our pre- and mid-treatment models decreased when applied to the internal validation cohort, which aligns with findings from previous studies. In addition, the radiomic features in this study were exclusively extracted from ADC maps. An advantage of using ADC maps is their inherent quantitative nature, which increases the reproducibility and limited inter-scanner and inter-vendor variability. Another limitation of our study is the use of different MRI field strength on model prediction particularly since the majority of HPV-positive cases was scanned with 3 T MRI, which reflects the increasing incidence of HPV-positive OPC over the past decade [60]. To address the latter, it is important to note that the scan protocol was adjusted to account for differences between 1.5 T and 3 T MRI scanners, minimizing any impact on the outcomes. Moreover, an exploratory subgroup analysis further confirmed no significant disparity in ADC mean values or texture parameters between the 1.5 T and 3 T subgroups. This is in concordance with study of Lavdas et al., reporting the variation in ADC values between different 1.5 T scanners or between different 3 T scanners to be comparable to or even larger than the differences observed between 1.5 T and 3 T scanners [61]. These findings suggest that the impact of using different field strengths on radiomic outcomes is minimal, ensuring that the results remain robust despite the use of

varying MRI machines.

Due to the absence of radiomics analysis during RT, the construction of our mid-treatment model was limited to first-order parameters and did not include the full set of 105 texture parameters that were considered in the pre-treatment model. The selection of these 105 features was a deliberate decision to balance capturing a wide range of radiomic information with maintaining statistical feasibility. While advanced wavelet transformations were not applied in this analysis to limit dimensionality and reduce the risk of overfitting, we recognize that incorporating additional transformations and feature selection techniques and regularization methods could further expand the feature space and enhance the clinical translation of our findings.

Patients with local relapse frequently develop regional relapse, highlighting the possible importance of additional imaging information on the initially affected lymph nodes. However, to simplify our analysis and improve feasibility, we focused on recurrences within the radiation field of the primary tumor, as evaluating lymph nodes would have required standardization of segmentation methods, introducing complexity and potentially affecting reproducibility and statistical power.

Another limitation is the use of p16 immunostaining as a surrogate for HPV, and the inability to confirm our findings in the HPV-positive subgroup, likely due to the small number of events. Lastly, it is important to note that the differences in performance between clinical and mixed models were modest, consistent with previous research across various imaging modalities [23,38,40,62].

The incorporation of clinically and biologically meaningful data in predictive modeling is essential and performance of radiomic models will likely improve with larger datasets. Furthermore, AI-based unsupervised clustering methods may enhance the role of DWI-MRI-based radiomic features in response prediction.

5. Conclusion

DW-MRI-based radiomics offers valuable potential for personalized risk stratification and treatment adaptation in OPC. Our findings highlight the potential of using a mid-treatment model for LRC prediction in OPC patients. The proposed models are attractive from a clinical standpoint, as a risk stratification, treatment adaptation and monitoring tool.

6. Data sharing statement

The authors do not own these data and hence are not permitted to share them in the original form (only in aggregate form, e.g., publications). Applications are reviewed and approvals granted subject to meeting all ethical and research conditions set forth by the Ethics Committee Research UZ/KU Leuven.

CRediT authorship contribution statement

Heleen Bollen: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Rüveyda Dok:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Frederik De Keyzer:** Conceptualization, Methodology, Software, Validation. **Sarah Deschuymer:** Conceptualization, Methodology, Writing – review & editing. **Annouschka Laenen:** Formal analysis, Writing – review & editing. **Johannes Devos:** Writing – review & editing. **Vincent Vandecaveye:** Conceptualization, Methodology, Software, Validation, Writing – review & editing. **Sandra Nuyts:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Ethics approval

This study was approved by the Ethics Committee Research UZ/KU Leuven (S54731).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2025.100759.

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