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Integrating tumor and nodal imaging characteristics at baseline and mid-treatment CT scans to predict distant metastasis in oropharyngeal cancer treated with concurrent chemoradiotherapy

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Abstract

Purpose: Prognostic biomarkers of disease relapse are needed for risk-adaptive therapy of oropharyngeal cancer (OPC). This work aims to identify an imaging signature to predict distant metastasis in OPC.

Materials/Methods: This single-institution retrospective study included 140 patients treated with definitive concurrent chemoradiotherapy, for whom both pre and mid-treatment contrast-enhanced CT scans were available. Patients were divided into separate training and testing cohorts. Forty-five quantitative image features were extracted to characterize tumor and involved lymph nodes at both time points. By incorporating both imaging and clinicopathological features, a random survival forest (RSF) model was built to predict distant metastasis-free survival (DMFS). The model was optimized via repeated cross-validation in the training cohort, and then independently validated in the testing cohort.

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Statistical Analysis

Drs. Jia Wu and Ruijiang Li were responsible for statistical analyses.

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Results: The most important features for predicting DMFS were the maximum distance among nodes, maximum distance between tumor and nodes at mid-treatment, and pre-treatment tumor sphericity. In the testing cohort, the RSF model achieved good discriminability for DMFS (C-index=0.73, $P=0.008$), and further divided patients into two risk groups with different 2-year DMFS rates: 96.7% vs. 67.6%. Similar trends were observed for patients with p16+ tumors and smoking 10 pack-years. The RSF model based on pre-treatment CT features alone achieved lower performance (C-index=0.68, $P=0.03$).

Conclusion: Integrating tumor and nodal imaging characteristics at baseline and mid-treatment CT allows prediction of distant metastasis in OPC. The proposed imaging signature requires prospective validation, and if successful, may help identify high-risk HPV-positive patients who should not be considered for de-intensification therapy.

Keywords

Nodal spread; mid-treatment imaging; HPV; oropharyngeal cancer; prognostic marker

INTRODUCTION

The prevalence of oropharyngeal cancer (OPC) has been increasing in recent years, which is largely attributable to the epidemic of oral human papillomaviruses (HPV) infection in the US(1). Patients with HPV-positive OPC are highly responsive to standard treatment of radiation and chemotherapy, and generally have a better prognosis than HPV-negative patients(2). However, chemoradiotherapy is associated with significant morbidity with both acute and long-term toxicity(3). Current treatment for HPV-associated OPC patients likely represents over-treatment for many individuals. There is significant interest to develop rational de-intensification treatment strategies that preserve the high cure rate while reducing late toxicity in this population(4–6).

Current de-intensification strategies usually stratify patients based on traditionally identified prognostic factors such as stage and smoking history, which are closely related to overall survival(2). However, de-intensification or omission of systemic chemotherapy may be better informed by the risk of specific relapse, i.e., distant metastasis, which remains the major cause of death among OPC patients(7). RTOG 1016 is a phase III randomized trial designed to test the non-inferiority of a less toxic systemic drug cetuximab vs. high dose cisplatin, which is the current standard systemic treatment for HPV-positive OPC. Unfortunately, with 987 patients enrolled based on clinical stage, the trial failed to meet its primary objective(8). This highlights the need for improved prognostic biomarkers to refine risk stratification and inform the optimal treatment.

CT imaging plays a critical role in the diagnosis, staging, response evaluation, and follow up of patients with OPC(9). For patients receiving definitive radiation therapy with or without chemotherapy or targeted therapy, contrast-enhanced CT is routinely acquired for every patient for radiation treatment planning purposes. In addition, it is also often acquired for radiation replanning during the treatment course to address tumor shrinkage or patient anatomic changes; this is known as the mid-treatment scan. Because of their universal use in radiation treatment planning and their relatively low cost, contrast-enhanced CTs are ideal

for radiomic studies. There have been a plethora of studies using a quantitative radiomic approach to search for new imaging markers beyond tumor size(10–18). To date, almost all studies have focused on analysis of the primary tumor and ignored the lymph nodes, which are a frequent site for regional metastasis in OPC(19). Another potential limitation is that most previous studies apply the radiomic approach to imaging at baseline prior to initiation of therapy. Mid-treatment imaging, on the other hand, offers the unique opportunity to assess early treatment response, which may be better correlated with disease outcome(20). Mid-treatment imaging also allows the potential to modify therapy compared with post-treatment imaging.

In this work, we investigate the ability of baseline and mid-treatment imaging characteristics to predict distant metastasis in OPC patients treated with concurrent chemoradiotherapy. We hypothesize that integrating quantitative image features of the tumor and lymph nodes extracted from both baseline and mid-treatment CT can provide a more complete evaluation of disease burden and thus may allow better prediction of clinical outcomes.

MATERIALS AND METHODS

Overview of study design

This study was carried out in three phases, as laid out in Figure 1. First, we preprocessed the preand mid-treatment CT scans, and tested stability of the quantitative imaging features against variations in tumor and lymph node contours. Second, we employed a machine learning technique to build a random survival forest (RSF) model for predicting distant metastasis-free survival (DMFS) based on the training cohort. Third, we assessed the prognostic value of the RSF model in an independent testing cohort. We followed the instructions in (21,22) to report details of each step.

Patients

In this institutional review board-approved, Health Insurance Portability and Accountability Act-compliant study, we retrospectively collected data for 174 oropharyngeal patients who were continuously treated at our institution from February 2009 to March 2017. The inclusion criteria were: 1) patients underwent definitive concurrent chemoradiotherapy for oropharyngeal squamous cell carcinoma, and 2) contrast-enhanced CT scans and radiation treatment plans for both pre- and mid-treatment are available. The exclusion criteria were: 1) patients without biopsy confirmed squamous cell carcinoma; 2) patients who had previously received definitive surgery, radiotherapy, or induction chemotherapy, 3) patients with metastatic disease at presentation; 4) patients with no primary tumor or involved lymph nodes (T0 or N0). A total of 140 patients were eligible and included in this study (Supplement Fig. 1). By balancing the clinicopathological risk factors (stage, smoking history, etc), all study patients were splitted roughly with a 1:1 ratio into separate training and testing cohorts. The clinical characteristics and treatment information are summarized in Table 1.

HPV status was assessed by tumor p16 immunohistochemistry staining, with >70% nuclear staining considered as positive. Patients were closely followed with post-treatment physical

examination at 4, 8, and 12 weeks and PET/CT or MRI at 3 to 4 months after treatment completion. Subsequent follow-up typically included imaging evaluation every 2–3 months for the first 2 years, every 3–4 months for the third year etc. Median follow-up time for all patients was 24 months.

CT image acquisition

All patients underwent an initial contrast-enhanced CT scan for radiation therapy planning. After receiving ~30–36 Gy radiation dose, patients went through a second contrast-enhanced CT scan for radiation re-planning, to account for potential anatomic change due to tumor regression, node shrinkage, or weight loss. Two types of CT scanners were used including General Electric Discovery ST (n=52) and Siemens Biograph (n=88). CT scans were acquired at a tube potential of 120 kV and a tube current of 190–600 mA. CT images were reconstructed at a slice thickness of 1.5–2.5 mm, and in-plane spatial resolution of $0.98 \times 0.98 - 1.17 \times 1.17 \text{ mm}^2$.

Delineation of primary tumor and involved lymph nodes

The primary tumor and involved lymph nodes were separately contoured on pre- and mid-treatment CT scans for radiation treatment planning purposes by attending radiation oncologists who specialize in the treatment of head and neck cancer. For identifying involved lymph nodes on mid-treatment scans, the pre and mid-treatment CT scans were co-registered and node contours were then automatically propagated to the mid-treatment scans. The involved nodes were visually inspected by a radiation oncologist and manually edited if there were significant changes. These image-based contours were directly imported into Matlab for analysis.

Extraction of quantitative image features of tumor and lymph nodes

A total of 45 quantitative image features were extracted for each patient to characterize the tumor and lymph node phenotypes at baseline and mid-treatment CT scans as well as the changes between the two scans, as shown in Fig. 2. The number of image features in our study is relatively small compared with many other radiomic studies. The rationale is that many radiomic features have been shown to be redundant and may be non-reproducible(23). Considering this, we focused on a relatively compact set of image features with clear interpretation and clinical relevance, in order to minimize the risk of false discovery and maximize the chance of reproducible findings.

For the primary tumor, we calculated its volume, shape, margin, intensity, and Gray-Level Co-occurrence Matrix (GLCM) texture features to measure intra-tumor heterogeneity. A similar set of features has been used in breast cancer(24). For GLCM texture analysis, the CT image was first resized isotropically to a spatial resolution of 1 mm^3 , and then pixel values outside the range of –50 to 200 Hounsfield Unit (HU) were excluded. After that, a quantization scheme with a fixed bin width of 5 HU was applied to the image pixel values. The co-occurrence matrix was obtained using 3D analysis and 26-voxel connectivity at one voxel distance in the resized CT image. In computing these features, we followed the Image Biomarkers Standardization Initiative (ISBI) guideline. Please see their detailed formulas in (25).

For involved lymph nodes, in addition to volume, margin and intensity features, we proposed three additional features to measure locoregional disease spread: 1) number of distinct involved lymph nodes contoured on CT, 2) nodal spread which indicates the maximum distance among the involved nodes, and 3) node-tumor spread which measures the maximum distance from the tumor's edge to the furthest involved node in the neck.

Finally, in order to explicitly measure treatment response during chemoradiotherapy, we computed five features to account for changes in tumor and nodal disease burden, including tumor volume, nodal volume, number of nodes, nodal spread, and node-tumor spread which measure physical quantities with SI units. All the image features were computed in a 3D manner. The feature calculation was implemented with Matlab (MathWorks, Natick, MA).

Evaluation of feature stability against scanner differences, contour variations, and dental artifacts

First, we assessed the variability of image features across different CT scanners. Second, we evaluated stability of the proposed image features against uncertainty in target contouring. To do so, 40 patients were randomly selected in the training cohort, and the primary tumor and involved nodes were independently contoured by a second radiation oncologist. We then computed the intraclass correlation coefficient (ICC) of image features based on the original contour and new contour. Finally, since dental fillings or other metal implants may introduce significant image artifact for some patients, the affected CT slices were manually inspected and marked by a radiation oncologist. The CT slices with dental artifacts were excluded for computing intensity and texture features. We assessed the impact of dental artifact on the proposed features, by randomly excluding a similar amount of CT slices in patients without dental artifacts. We then computed the ICC of derived features and compared with those computed from the complete image.

Training a machine learning model to predict distant metastasis

We proposed a machine learning pipeline to construct the model for predicting distant metastasis based on the training cohort. We implemented the random survival forest (RSF) model(26) based on the extracted imaging features as well as clinicopathologic factors including T, N stage, p16 status, and smoking history. To address the issue of unbalanced survival data, we adopted the synthetic minority over-sampling technique (27). During model fitting, repeated cross validation scheme was applied to optimize the hyper-parameters, which can mitigate potential risk of overfitting. In brief, we performed cross validation of the RSF model by randomly splitting patients into three folds stratifying for distant metastasis, and obtained the predicted risk scores on the holdout set. This process was repeated for 100 times. We then aggregated the predicted risk scores for all training patients from 100 repetitions of three-fold cross validation. Based on these results, we can select the optimal hyper-parameters of RSF model, including node size, maximum number of nodes, and tree number. Moreover, the feature importance associated with optimized RSF model was reported, which allowed us to evaluate the relative contribution of individual features to the overall prediction. In brief, the feature importance is computed by comparing prediction performance for the permuted feature to the original feature(26). Positive values

of feature importance indicate a beneficial effect on prediction, while negative values indicate a detrimental effect on prediction.

Evaluation of the random survival forest (RSF) model

We evaluated the RSF model regarding its prognostic value for predicting DMFS in the testing cohort. We further evaluated the model's ability to stratify within subgroups of patients who had p16+ disease, a smoking history less than 10 pack-years, or those who are considered candidates for treatment de-intensification (p16+, T1–2, N0–2b, smoking 10 pack-years). In addition, we performed a multivariate analysis to adjust the proposed model with clinical and pathological factors such as age, gender, as well as presence of level IV node involvement(28). Patients with any nodal involvement of levels IV or Vc were considered to have low neck nodal involvement, which is referred to level IV node involvement(29).

Statistical analysis

We fitted the Cox proportional hazard model between different predictors and DMFS. The concordance index (c-index) or the Harrell C statistic was used to assess prognostic accuracy. Kaplan-Meier analysis and logrank test were used to evaluate patient stratification into different risk groups. The hazard ratio (HR) was used to measure the degree of survival differences, and 95% confidence interval (CI) were also reported. We assessed correlation between nodal spread (continuous variable) and presence of level IV node involvement (dichotomous variable) using the point-biserial correlation coefficient. All statistical tests were two-sided, with a p-value less than 0.05 considered significant. The model's ability to predict 2-year DMFS was evaluated with ROC analysis. All statistical analyses were performed in R.

RESULTS

Image features and the effects of CT scanners, target contours, dental artifacts

The proposed image features for all patients are shown in a heat map (Supplement Fig. 2). These features were largely independent of each other (Supplement Fig. 3). We did not observe statistically significant differences in imaging features between two types of CT scanners (Supplement Fig. 4 and 5). Regarding inter-observer differences in contouring, the two sets of target contours generated by two different physicians showed a good degree of overlap assessed by dice coefficients (Supplement Fig. 6), and the corresponding image features showed a high reproducibility with ICC mostly above 90% (Supplement Fig. 7). Finally, we confirmed the robustness of proposed imaging features against dental artifacts (Supplement Fig. 8).

Image features of the lymph nodes were most important for predicting DMFS

In the final RSF model, 4 of the 5 most important features are related to lymph nodes (Fig. 3A). The top-ranked feature was the nodal spread measured at mid-treatment, following by the node to tumor spread measured at mid-treatment, the tumor sphericity measured at baseline, and involved lymph node number measured at mid-treatment. The change-related

features evaluated in this study did not appear to be useful for predicting distant metastasis. By contrast, the most important clinicopathologic feature was T stage ranked at 8th.

The random survival forest model for predicting DMFS was independently validated

The trained random survival forest model was significantly associated with DMFS (C-index=0.73, Wald $P=0.008$), when evaluating on the testing set. At a cutoff value of 0.96 (tertile of the training cohort), patients can be stratified into high- vs. low-risk groups for developing distant metastasis, with HR = 11.6, log-rank $P=0.004$, as shown in Fig. 4B. The two patient groups had significantly different prognoses, with the 2-year DMFS rate of 96.7% and 67.6% for low and high-risk group. Using the same cutoff value, similar patterns were observed for subgroups of patients with p16+ tumors (Fig. 4D), smoking 10 pack-years (Supplement Fig. 10B). The RFS model achieved an AUC of 0.788 to predict 2-year DMFS status in the testing set (Supplement Fig. 11A). In multivariable analysis, the imaging model remained a strong independent prognostic factor after adjusting for other variables (Table 2). Of note, among 31 patients (p16+, T1–2, N0–2b, smoking 10 pack-years) who are considered candidates for treatment de-intensification, our proposed model could identify 8 patients (25.8%) with a higher risk for developing distant metastasis (Supplement Fig. 12A).

The random survival forest model with pre-treatment CT features alone had lower performance

We repeated the entire analysis pipeline to predict DMFS using 20 pre-treatment CT features (Fig. 2). The top ranked features were tumor sphericity, nodal spread, and node to tumor spread (Fig. 3B). When validating on the testing cohort, the model was prognostic of DMFS (C-index=0.68, Wald $P=0.048$). However, the stratification of the testing cohort and subgroups was not significant (log-rank $P>0.05$, Supplement Fig. 13). During testing, this model achieved an AUC of 0.721 to predict 2-year DMFS status (Supplement Fig. 11B). The model could identify 5 patients (16.1%) among candidates for treatment de-intensification (Supplement Fig. 12B).

DISCUSSION

We developed and validated a random survival forest model for predicting the risk of distant metastasis in oropharyngeal cancer. The model provided independent prognostic information beyond established clinical factors including stage, smoking history, and HPV status. It further stratified patients within the subgroup of patients with HPV-positive OPC. This suggests that our model has the potential to identify HPV-positive OPC patients who have a higher risk of distant relapse such as those in the high-risk groups and should not be considered for treatment de-intensification. Moreover, since all of these patients received radiation and concomitant systemic therapy, the proposed imaging signature could be used to help select high-risk patients who might benefit from adjuvant immunotherapy(30,31). On the other hand, the prognosis of HPV-negative disease remains poor with conventional chemoradiotherapy and novel treatment strategies are needed for these patients.

To our knowledge, this is the first study that assessed both tumor and nodal imaging characteristics at baseline and mid-treatment for predicting prognosis in head and neck cancer using a quantitative radiomic approach. We showed that mid-treatment imaging appeared to provide more useful information than pre-treatment imaging for predicting distant metastasis. Kabarriti et al. found that the change in primary tumor volume measured at mid-treatment CT compared with baseline was predictive of locoregional recurrence in OPC patients treated with definitive radiation therapy(20). However, the change in tumor volume was not associated with the risk of distant metastasis in our cohort.

To provide a more complete evaluation of the disease, we analyzed imaging phenotypes of the primary tumor and involved lymph nodes as well as their spatial relation. In our study, we found that specific imaging characteristics of the nodes could play a more important role in predicting distant metastasis than tumor features. Among the most important features were nodal spread, node to tumor spread, and number of involved nodes. These image features are related, but not identical, to the most recent AJCC 8th edition pathological nodal staging criteria(32), which include size, laterality, and number of metastatic nodes. Interestingly, a recent study showed that the extent of nodal disease (major axis length) was prognostic of overall survival in head and neck cancer as well as nasopharyngeal cancer(33), which is consistent with our findings specifically for oropharyngeal cancer. In this sense, our study differs from the vast majority of previous radiomic studies that have focused on the primary tumor only(10–14,16,17). By contrast, our imaging signature includes features of the involved lymph nodes, which may be a more direct reflection of the metastatic potential, adding new information not contained in the primary tumor.

Previous radiomic studies have largely used overall survival as the endpoint for developing prognostic imaging markers(10–13). However, endpoints that reflect specific pattern of relapse (e.g., locoregional recurrence or distant metastasis) may provide more valuable information to guide intensification of local vs systemic therapy. In this regard, several recent studies have proposed radiomic signatures of local control based on primary tumor characteristics(14,17,18,20). By contrast, few studies have specifically investigated predictors of distant metastasis. In a recent study 1600 texture features were extracted for developing a radiomic signature to predict distant metastasis in head and neck cancer including OPC(15). In our cohort we did not find an association between distant metastasis and any tumor texture. This can be due to differences in patient population and number of texture features used. Another study found that 4 CT image features in a previously proposed radiomic signature were associated with distant metastasis in p16+ OPC(16). However, it is unclear whether any of these tumor-derived features was truly independent of tumor volume, which is an established prognostic factor. Our imaging model for distant metastasis is shown to have prognostic value independent of tumor volume and clinicopathologic factors including p16 status.

In this work, we proposed the farthest distance between edges to quantify the nodal spread and tumor-to-node spread. Alternatively, one may use the center-to-center distance. Intuitively, the farthest distance may better capture the full extent of disease spread. Indeed, we found that the farthest distance demonstrated superior prediction power over center-based metrics for predicting distant metastasis (Supplement Fig 14). The definition of image

features in our model relies on delineation of gross tumor and involved lymph nodes. Because they are routinely delineated by experienced radiation oncologists for treatment planning purposes, the contours of these structures are expected to be reasonably accurate. While the exact contours may vary across radiation oncologists, detailed consensus guidelines exist that attempt to minimize the inter-observer differences (29,34).

One important advantage of our imaging model is that it uses geometry-based features and thus may be less dependent on the exact value of image intensity. By contrast, many features used in previous radiomic studies such as histogram and texture are sensitive to variations in image intensity, which can be caused by a variety of technical factors such as inconsistent use of contrast agents in CT scans and image acquisition parameters, e.g., kVp, mAs, reconstruction kernels(23). By relying on clinically used contours, our imaging model is anticipated to be less affected by these technical factors, and this will likely enhance the reproducibility in future multi-center validation studies. We found that feature redundancy had no impact on the prediction performance of the RSF model (Supplement Fig 15).

The main limitation of our study is its retrospective nature with a relatively small single-institutional cohort. Although a repeated cross validation scheme was adopted, the final decision tree-based imaging model is hypothesis-generating and should be tested in independent and ideally prospective studies with larger cohorts. Another limitation is that the RSF model does not explicitly perform feature selection, although ranking of feature importance is given. We included patients with both p16-positive and negative tumors. When we controlled for p16 status as a co-variate in multivariable analysis, the imaging signature remained independently prognostic. Future work can analyze patients separately according to HPV status given the different biology between the diseases.

Cone-beam CT (CBCT) is usually acquired daily during treatment, and may allow earlier evaluation of treatment response. However, CBCT is acquired without contrast enhancement and the image quality is much lower than contrast-enhanced CT. In future work, it may be worth exploring the utility of CBCT for early response evaluation. Beyond CT imaging, MR imaging and FDG-PET have also shown prognostic value in head and neck cancer(35–41). It may be beneficial to combine CT with PET imaging to further improve the accuracy of prediction in future.

In summary, based on quantitative analysis of baseline and mid-treatment imaging, we developed a random survival forest model for predicting distant metastasis in oropharyngeal cancer. Therefore, integrating tumor and nodal imaging characteristics may allow better prediction of distant metastasis and potentially aid in patient stratification for risk-adaptive therapy in oropharyngeal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HPV	Human papillomavirus
OPC	Oropharyngeal cancer
DMFS	Distant metastasis free survival
RSF	Random survival forest
CT	Computed tomography

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Summary Statement

We analyzed baseline and mid-treatment imaging characteristics of oropharyngeal cancer. Among 45 quantitative image features of tumor and involved lymph nodes, the maximum distance among nodes and maximum distance between tumor and nodes at mid-treatment were the most important features for predicting distant metastasis, while pre-treatment tumor sphericity was also useful. Integrating tumor and nodal imaging characteristics may allow better prediction of distant metastasis in oropharyngeal cancer.

Figure 1.
 Overview of the proposed study design

Figure 2.

Schematic illustration of 45 quantitative CT image features proposed in this study. There were 20 pre-treatment features (11 tumor, 9 involved lymph nodes), 20 mid-treatment features (11 tumor, 9 involved lymph nodes), and 5 change-related features between pre and mid-treatment time points.

Figure 3. Feature importance for predicting the risk of distant metastasis obtained from 3-fold cross validation of random survival forest model with 100 repeats. All features are ordered by the feature importance value and the top 10 most important features are presented for models using: A) both pre- and mid-treatment scans and B) pre-treatment scan alone. Imaging features are color-coded by time point and type (see their definition in Fig. 2).

Figure 4.

Kaplan-Meier curves of distant metastasis free survival (DMFS). Patients are stratified according to the risk scores of random survival forest model trained by pre- and mid-treatment CT features. Plots are for: A) training set, B) testing set, C) p16-positive subgroup from the training set, and D) p16-positive subgroup from the testing set. HR = hazard ratio.

Table 1.

Demographic and Clinical Characteristics of the Study Cohort.

Parameter	Whole Cohort (n=140)	Training Cohort (n=73)	Testing Cohort (n=67)
Age (y)			
Median (range)	62.4 (36.7–84.2)	63.9 (36.7–83.1)	62.0 (38.5–84.2)
Gender			
Male	130 (92.9%)	66 (90.4%)	64 (95.5%)
Female	10 (7.1%)	7 (9.6%)	3 (4.5%)
T category (AJCC 7 th edition)			
T1	20 (14.3%)	10 (13.7%)	10 (14.9%)
T2	54 (38.5%)	28 (38.4%)	26 (38.8%)
T3	40 (28.5%)	20 (27.4%)	20 (29.9%)
T4a	24 (17.1%)	13 (17.8%)	11 (16.4%)
T4b	2 (1.4%)	2 (2.7%)	0 (0)
N category (AJCC 7 th edition)			
N1	14 (10%)	6 (8.2%)	8 (11.9%)
N2a	8 (5.7%)	3 (4.1%)	5 (7.5%)
N2b	76 (54.3%)	40 (54.8%)	36 (53.7%)
N2c	33 (23.6%)	18 (24.7%)	15 (22.4%)
N3	9 (6.4%)	6 (8.2%)	3 (4.5%)
AJCC stage (7 th edition)			
III	10 (7.1%)	6 (8.2%)	4 (6.0%)
IVA	119 (85.0%)	60 (82.2%)	59 (88.1%)
IVB	11 (7.9%)	8 (11.0%)	3 (4.5%)
p16 status			
Positive	124 (88.6%)	64 (87.7%)	60 (89.6%)
Negative	16 (11.4%)	9 (12.3%)	7 (10.4%)
Systemic therapy			
Cetuximab	66 (47.1%)	36 (49.3%)	30 (44.8%)
Cisplatin	65 (46.4%)	33 (45.2%)	32 (47.8%)
Carboplatin or other	9 (6.4%)	4 (5.5%)	5 (7.5%)
Smoking history			
> 10 pack-years	55 (39.3%)	29 (39.7%)	26 (38.8%)
10 pack-years	85 (60.7%)	44 (60.3%)	41 (61.2%)
Distant metastasis			
Yes	18 (12.9%)	10 (13.7%)	8 (11.9%)
No	122 (87.1%)	63 (86.3%)	59 (88.1%)

Table 2.

Univariate and Multivariable Analyses of the Proposed Imaging Model and Clinicopathologic Factors for Predicting DMFS in Testing Cohort.

Predictors	Univariate			Multivariable		
	HR	95% CI	P Value	HR	95% CI	P Value
Image-based decision tree model	1.98	1.20 – 3.27	0.008	2.10	1.10 – 4.02	0.024
Tumor volume [#]	1.02	0.99 – 1.04	0.264	-	-	-
Number of involved lymph nodes [#]	1.13	0.97 – 1.31	0.116	-	-	-
Presence of level IV node involvement [#]	1.72	0.41 – 7.20	0.459	1.52	0.22 – 10.40	0.668
Age	1.04	0.97 – 1.11	0.313	1.08	0.99 – 1.19	0.095
Gender ¹	1.71	0.43 – 7.76	0.798	1.37	0.05 – 6.38	0.899
T ²	1.02	0.50 – 2.05	0.966	-	-	-
N ³	1.11	0.54 – 2.32	0.774	-	-	-
Stage ⁴	1.46	0.62 – 3.42	0.384	-	-	-
p16 ⁵	0.39	0.08 – 1.95	0.253	-	-	-
Smoking ⁶	0.58	0.12 – 2.85	0.499	-	-	-

¹ male as 1, female as 0;

² T1/T2/T3/T4a/T4b was coded as 1,2,3,4,5

³ N1/N2a/N2b/N2c/N3 was coded as 1,2,3,4,5

⁴ II/III/IVA/TVB was coded as 1,2,3,4

⁵ p16+ as 1, p16- as 0

⁶ smoking <=10 pack-years as 0, otherwise 1

[#] Baseline values