Received: 8 May 2018 | Accepted: 16 August 2018

DOI: 10.1002/hed.25505

WILEY

ORIGINAL ARTICLE

Volumetric ^{18}F-FDG-PET parameters as predictors of locoregional failure in low-risk HPV-related oropharyngeal cancer after definitive chemoradiation therapy

Thong Chotchutipan MD[1,2] | Benjamin S. Rosen PhD[1] | Peter G. Hawkins MD[1] | Jae Y. Lee MD, PhD[1,3] | Anjali L. Saripalli MSE[1] | Dharmesh Thakkar BS[1] | Avraham Eisbruch MD[1] | Issam El Naqa PhD[1] | Michelle L. Mierzwa MD[1]

[1]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan, US

[2]Department of Radiation Oncology, Chulabhorn Hospital, HRH Princess Chulabhorn, College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

[3]Princeton Radiation Oncology, Princeton, New Jersey, US

Correspondence
Benjamin S. Rosen, PhD, Department of Radiation Oncology, University of Michigan, 1500 E Medical Center Dr., Ann Arbor, MI 48109.
Email: rosenbs@med.umich.edu

Funding information
This work was partially supported by NIH Grant R01-CA184153-04.

Abstract

Background: We sought to investigate the prognostic value of volumetric positron emission tomography (PET) parameters in patients with human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) and a ≤10 pack-year smoking history treated with chemoradiation.

Methods: A total of 142 patients were included. Maximum standardized uptake value, metabolic tumor volume, and total lesion glycolysis (TLG) of the primary tumor, involved regional lymph nodes, and total lesion were calculated. Cox proportional hazard modeling was used to evaluate associations of clinical and PET parameters with locoregional failure-free survival (LRFFS), distant metastasis-free survival (DMFS), and overall survival (OS).

Results: On univariate analysis, volumetric PET parameters were significantly associated with all endpoints, and 8th edition American Joint Committee on Cancer/Union Internationale Contre le Cancer staging was significantly associated with DMFS and OS. On multivariate analysis, total lesion TLG was significantly associated with LRFFS, while staging was most significantly prognostic for DMFS and OS.

Conclusion: Volumetric PET parameters are uniquely prognostic of LRFFS in low-risk HPV-related OPSCC and may be useful for directing de-intensification strategies.

KEYWORDS

FDG-PET, local control, OPSCC, radiation oncology, TNM staging

1 | INTRODUCTION

Human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) has increased in incidence in recent years[1] and is associated with a better prognosis than tobacco-related OPSCC.[2] Despite its better prognosis, standard treatment of HPV-related OPSCC is the same as for tobacco-related OPSCC, and may produce substantial complications that reduce the quality of life in cancer survivors.[3] To reduce these complications, several reported and ongoing studies have attempted to de-intensify treatments in HPV-related OPSCC.[4] However, appropriate patient selection for treatment de-intensification is vital in order to not jeopardize

Benjamin S. Rosen and Thong Chotchutipan contributed equally to this work.

the chance for cure. While de-intensification strategies uniformly stipulate HPV-positivity for inclusion, there is variability in the consideration of other factors such as smoking history and TNM classifications.[5] Reanalysis of RTOG 0129 established HPV-related OPSCC patients with smoking history ≤10 pack-years to have the most favorable prognosis, thus potentially making them good candidates for treatment de-intensification.[2] Recent prospective trials investigating de-intensified concurrent chemoradiation in HPV-related OPSCC patients have demonstrated high rates of tumor control and survival in patients with minimal smoking history.[6–9] Further disease classification within this group could lead to more precise individualized treatment.

The recently updated 8th Edition (Ed.) of the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual* has incorporated a novel staging system for HPV-related OPSCC.[10] This staging system was based on 2 landmark studies that demonstrated improved prognostication of overall survival (OS) compared to the previous 7th Ed. criteria.[11,12] However, when considering selection criteria for de-intensification of a locoregional treatment such as radiotherapy (RT), it is important to understand factors prognostic for locoregional failure (LRF), in addition to OS. Although the AJCC 8th Ed. staging system has shown prognostic utility regarding OS and distant failure, it is less well-defined for predicting risk of LRF.[11] This is likely related to the observation that the predominant pattern of failure in these patients following traditional therapies may be distant.[2,13,14] As such, the identification of effective tools for prognostication of LRF in HPV-related OPSCC is critical for appropriate implementation of treatment de-intensification in this population.

The role of ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) parameters as prognostic factors in head and neck cancer has been extensively investigated.[15] Maximum standardized uptake value (SUV_{max}), which represents maximal FDG SUV in the tumor, is the earliest parameter that has been explored. However, the use of SUV_{max} is limited by an inability to illustrate whole tumor metabolic activity. As such, the prognostic value of SUV_{max} in head and neck cancer is controversial.[16–22]

Recently, volumetric PET parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have been heavily studied.[23] MTV is the volume of tumor that shows FDG avidity and TLG is a product of MTV and mean SUV. Several studies have demonstrated the ability of MTV and TLG to predict treatment outcomes in OPSCC.[16–20,22,24–29] However, literature testing of its prognostic value specifically in patients with HPV-related OPSCC patients and a ≤10 pack-year smoking history is scarce. Given the need for and lack of effective prognostic biomarkers for LRF in HPV-related OPSCC, we sought to investigate the prognostic value of MTV and TLG in this patient group.

2 | MATERIALS AND METHODS

2.1 | Patient population

We retrospectively reviewed electronic medical records of 539 OPSCC patients who received radiation therapy with or without systemic therapy in the department of radiation oncology at University of Michigan between 2005 and 2016. A total of 299 HPV-related OPSCC patients with smoking history ≤10 pack-years were included. HPV-status was determined by detection of oncogenic HPV DNA or p16 protein in tumor samples. Patients were excluded if they (1) had undergone surgery and/or chemotherapy before radiation, (2) had been previously irradiated in the head or neck, (3) had distant metastasis at the time of diagnosis, (4) did not have an analyzable pretreatment PET/CT scan, or (5) had a follow up time of <6 months. After exclusion, 142 patients remained for analysis. This study was conducted under an Institutional Review Board-approved protocol (HUM00105976).

2.2 | Treatment regimen

At the time of diagnosis, staging procedures comprised history and physical examination, fiberoptic laryngoscopy, CT scan of the neck, and ^{18}F-FDG PET/CT scan. Some patients underwent MRI of the neck if clinically indicated. In this study, all patients were restaged according to the 8th Ed. AJCC/Union Internationale Contre le Cancer (UICC) TNM staging.

All patients received intensity-modulated radiation therapy (IMRT), as previously described.[30] IMRT dose prescriptions were 70 Gy to gross disease and 56-64 Gy to other at-risk areas, all in 35 fractions.

Concurrent systemic therapy consisted of weekly carboplatin (AUC1) and paclitaxel (30 mg/m^2) in 93 patients (65.5%), cetuximab in 30 patients (21.1%), and high-dose cisplatin (100 mg/m^2) every 3 weeks in 14 patients (9.9%). Other regimens were weekly carboplatin (AUC2) in 2 patients and weekly paclitaxel (30 mg/m^2) in 1 patients. Two patients received definitive radiation alone because of early stage and poor renal function.

After treatment, patients were routinely followed with clinical examination every 2-3 months in the first 2 years, every 4-6 months in the third to fifth year, then annually. Post-treatment PET/CT scan was done at approximately 7-16 weeks after treatment for response evaluation. If there was a suspicious residual disease in neck, neck dissection was conducted according to our institutional protocol. Regional failure was defined as disease recurrence in neck >90 days after completion of RT.

2.3 | PET/CT scan

Attenuation-corrected pretreatment combined ^{18}F-FDG PET/CT scans of each patient were analyzed. Using information from the image headers, acquisition parameters were

TABLE 1 Patient characteristics

Characteristic	Mean (range)
Age (y)	58.9 (33-79)
Smoking history (pack-years)	1 (0-10)
Characteristic	**Number of patients (%)**
Sex	
Men	126 (88.7%)
Women	16 (11.3%)
Smoking status	
Non-smoker	107 (75.4%)
Previous smoker	28 (19.7%)
Current smoker	7 (4.9%)
Tumor site	
Base of tongue	91 (64.1%)
Tonsil	51 (35.9%)
T classification	
1	31 (21.8%)
2	55 (38.7%)
3	23 (16.2%)
4	33 (23.2%)
N classification	
0	10 (7.1%)
1	80 (56.3%)
2	29 (20.4%)
3	23 (16.2%)
8th edition group classification	
I	57 (40.2%)
II	34 (23.9%)
III	51 (35.9%)
Concurrent systemic therapy	
Carbo/taxol	93 (65.5%)
Cetuximab	30 (21.1%)
Cisplatin	14 (9.9%)
Carboplatin	2 (1.4%)
Taxol	1 (0.7%)
None	2 (1.4%)

determined. The majority of PET scans (82%) were acquired on one of our institutional Siemens PET scanners (models: 1024, 1062, 1080, 1094 [TruePoint], Biograph 20, or Biograph 40). The remaining PET scans were acquired on a GE Medical Systems Discovery ST/STE (14%) or Phillips Gemini/Guardian (4%) system outside our institution. The heterogeneity of the PET systems used is likely due to 12-year time span of the retrospective study. Mean (±SD) prescan blood glucose level was 103 g/mL (±23 g/mL) and time interval between FDG and scan was 63 minutes (±10 minutes).

2.4 | PET parameter analysis

Pretreatment PET/CT scans were retrospectively reviewed by 2 radiation oncologists (T.C. and A.E. and/or M.M.) and consensus volumes of interest (VOI) were manually contoured. The primary tumor and each metastatic lymph node were contoured separately within the Contouring workspace of our Eclipse radiation treatment planning system (Varian Medical Systems, Palo Alto, California). Within this workspace, raw intensity values were converted into SUV using the injected activity, image acquisition time, and patient body weight. SUVs within the VOIs were then exported and analyzed using in-house software (Matlab, The Mathworks, Inc., Natick, Massachusetts). SUV_{max}, MTV, and TLG were calculated as follows: SUV_{max} was the maximum voxel intensity uptake in each VOI, MTV was defined as the volume with intensity uptake greater than 50% of SUV_{max}, and TLG was calculated by multiplying MTV with the mean value of intensity uptake within the MTV. For each patient, all PET parameters derived from the primary tumor, combined metastatic lymph nodes (if node positive), and total lesion were recorded.

2.5 | Statistical analysis

Treatment outcomes recorded in this study included failure-free survival (FFS) and OS, measured from the end of RT. Failures included LRF and distant metastasis, and survival times were censored at the time of first failure or date of last follow-up. Associations between primary tumor and nodal SUV_{max}, MTV, and TLG were explored using Pearson correlation. For each clinical variable (age, T classification, N classification, AJCC 8th Ed. group classification) and PET parameter, association with the clinical outcomes was explored using univariate Cox proportional hazards regression. Multivariate Cox proportional hazards models were built using stepwise regression. For each step, significance levels for both entry and stay were conservatively set at 0.10. To compare relative hazards among variables with different absolute units, the analysis was repeated using normalized z scoring of input variables. Harrell's concordance

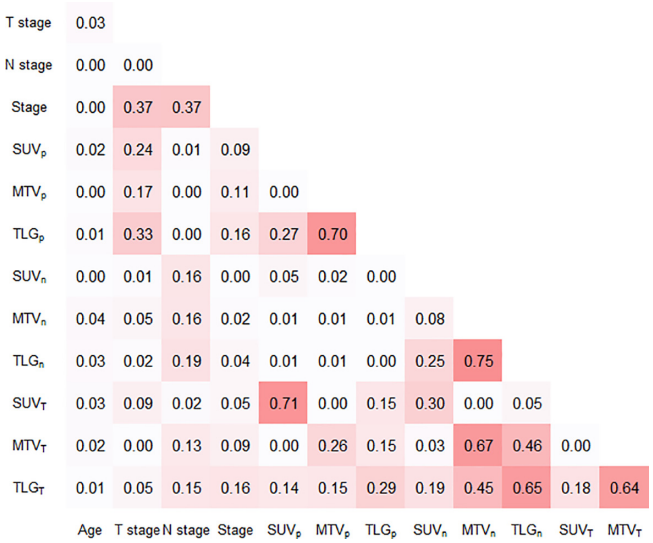

FIGURE 1 Squared Pearson correlation (R^2) and colorized heat map depicting intercorrelation between all tested variables [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Univariate analysis

	LRFFS				DMFS				OS			
	HR* (95% CI)		*P*	c-index	HR* (95% CI)		*P*	c-index	HR* (95% CI)		*P*	c-index
Age	1.50	(0.79-2.88)	.21	0.598	0.82	(0.50-1.35)	.43	0.569	0.96	(0.58-1.58)	.87	0.513
T classification	1.46	(0.77-2.76)	.24	0.590	2.07	(1.21-3.54)	.008	0.651	1.64	(1.02-2.64)	.04	0.580
N classification	1.24	(0.65-2.33)	.51	0.528	2.14	(1.30-3.51)	.003	0.739	1.86	(1.11-3.13)	.01	0.696
Group classification	1.20	(0.63-2.27)	.58	0.541	4.33	(1.73-10.86)	.002	0.764	4.71	(1.85-11.99)	.001	0.753
SUV_p	1.03	(0.56-1.90)	.93	0.539	1.50	(0.97-2.30)	.06	0.669	1.23	(0.78-1.93)	.37	0.583
MTV_p	1.70	(1.23-2.35)	.001	0.509	1.24	(0.82-1.89)	.30	0.569	1.33	(0.94-1.87)	.10	0.558
TLG_p	1.61	(1.16-2.23)	.004	0.495	1.37	(0.96-1.95)	.08	0.630	1.32	(0.94-1.85)	.11	0.591
SUV_n	1.61	(0.91-2.85)	.10	0.683	1.25	(0.78-2.00)	.35	0.618	1.13	(0.73-1.76)	.58	0.580
MTV_n	1.33	(0.80-2.19)	.27	0.644	1.53	(1.08-2.15)	.01	0.554	1.65	(1.20-2.26)	.002	0.622
TLG_n	1.47	(1.00-2.15)	.05	0.686	1.61	(1.23-2.11)	.001	0.589	1.52	(1.17-1.98)	.002	0.624
SUV_t	1.21	(0.67-2.16)	.52	0.600	1.38	(0.89-2.15)	.15	0.643	1.14	(0.73-1.78)	.56	0.570
MTV_t	1.79	(1.19-2.68)	.005	0.707	1.61	(1.12-2.30)	.01	0.683	1.80	(1.29-2.51)	.001	0.728
TLG_t	1.86	(1.29-2.70)	.001	0.756	1.84	(1.35-2.50)	<.001	0.745	1.68	(1.25-2.25)	.001	0.711

Abbreviations: CI, confidence interval; c-index, concordance index; DMFS, distant metastasis-free survival; Group classification, 8th Edition American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) staging; HR*, Cox proportional hazard ratio per normalized unit (*z* score); LRFFS, locoregional failure-free survival; MTV, metabolic tumor volume; OS, overall survival; SUV, standardized uptake value; TLG, total lesion glycolysis. Subscripts: n, nodal tumor; p, primary tumor; t, total lesion volume.

index (c-index) was calculated for each fitted Cox model to assess model performance.[31] For the significant PET parameters, tertile cutoff points (ie, 33rd and 66th percentile) were calculated and used to stratify patients into 3 groups. Kaplan-Meier survival curves were then generated to illustrate risk stratification of univariate and multivariate models, and log-rank *P* values were calculated. To investigate any heterogeneity caused by different image acquisition devices, measured PET parameters were stratified by machine manufacturer, and 2 sample *t* tests were calculated among groups. Two-sided *P* values under .05 were considered significant. All analyses were performed in R 3.4.1 (The R Foundation for Statistical Computing) and MATLAB R2017a (The MathWorks, Inc.). The stepwise selection procedure was implemented using the *My.stepwise* R package Ver. 0.1.0 and Kaplan-Meier curves were generated using the *survminer* R package Ver. 0.4.2.

3 | RESULTS

3.1 | Patients and PET parameter characteristics

In total, 142 patients were available for analysis (Table 1). The mean patient age (±SD) was 58.9 (±8.9) years. Most of the population was men (88.7%). Nonsmoker patients comprised 75% of the population, with the remainder <10 pack-years. In accordance with the 8th Ed. TNM staging, the percentages of patients with stages I–III were 40.2, 23.9, and 35.9, respectively.

Median follow up time was 36 months. Ten of 142 patients suffered LRF. Two patients had a local recurrence as the first failure, 7 patients had a regional recurrence as the first failure, and 1 patient had both local and regional recurrence as the first failure. Distant recurrence as first failure occurred in 16 patients. At the time of analysis, there were 17 deaths.

Median (interquartile range [IQR]) SUV_{max} of the primary tumor, metastatic lymph nodes, and total lesion were 11.7 g/mL (8-15.6), 10.2 g/mL (6.4-13.3), and 13.3 g/mL (9.7-17), respectively. Median (IQR) MTV of the primary tumor, metastatic lymph nodes, and total lesion were 8.7 cc (4.9-13.8), 6.6 cc (3.4-11.1), and 16.1 cc (11.2-22.5), respectively. Median (IQR) TLG of the primary tumor, metastatic lymph nodes, and total lesion were 51 g (29.6-114.4), 35 g (16.6-89.3), and 115.8 g (68.1-190.2), respectively. No significant difference by PET scanner manufacturer was found.

3.2 | Autocorrelation

The autocorrelations of PET and clinical variables are illustrated in Figure 1. In general, TLG and MTV were highly correlated (Pearson R = 0.836, 0.865, 0.802 for primary, nodal, and total lesion volumes, respectively). Primary tumor SUV_{max} had a higher correlation with total lesion SUV_{max}

TABLE 3 Optimal cox models from stepwise multivariate analysis

	HR* (95% CI)		*P*	c-index
Locoregional failure-free survival				
TLG_t	1.86	(1.29-2.70)	.001	0.756
Distant metastasis free survival				
Group classification	3.55	(1.39-9.07)	.008	0.812
TLG_t	1.45	(1.01-2.08)	.04	
Overall survival				
Group classification	4.00	(1.56-10.27)	.004	0.799
MTV_t	1.51	(1.01-2.27)	.04	

Abbreviations: CI, confidence interval; HR*, Cox proportional hazard ratio per *z*-score normalized unit; MTV, metabolic tumor volume, TLG = total lesion glycolysis. Subscript: t, total lesion (primary tumor + nodes).

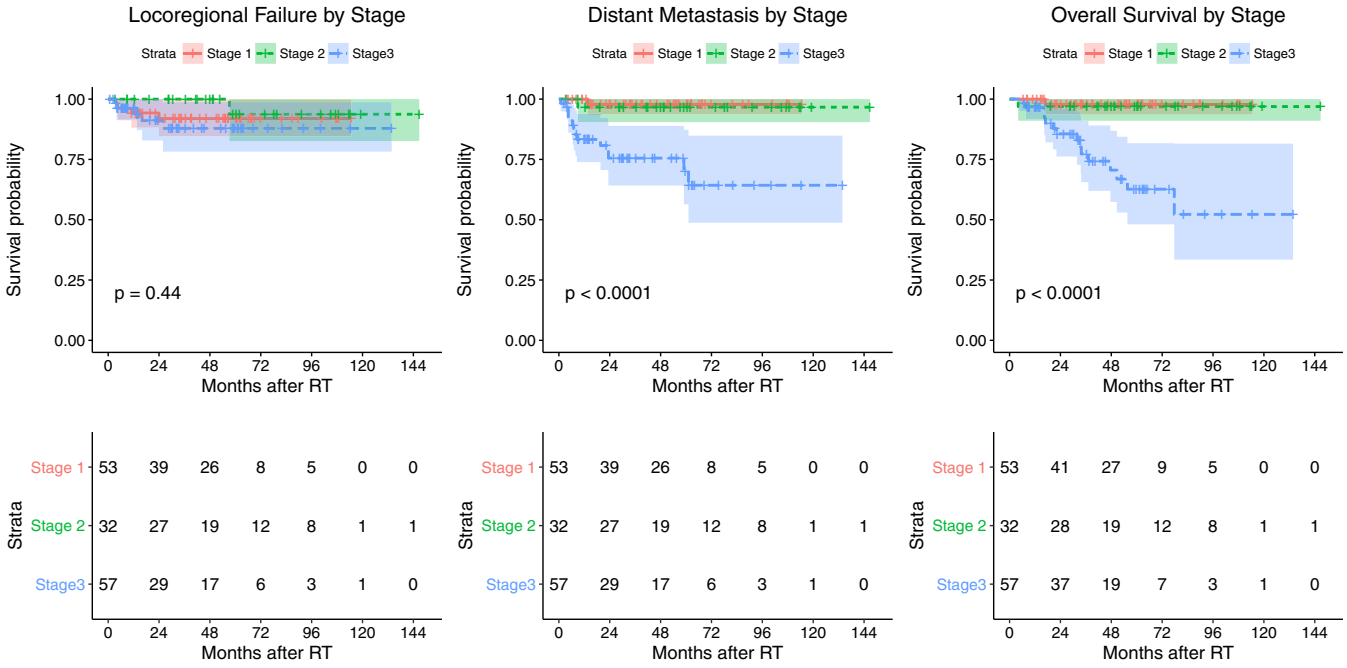

FIGURE 2 Kaplan-Meier plots for each endpoint by stage [Color figure can be viewed at wileyonlinelibrary.com]

than did nodal SUV_{max} (Pearson R = 0.845 vs 0.548, respectively). Primary tumor TLG was moderately correlated with T classification (Pearson R = 0.575). The parameter most correlated with overall classification was total lesion TLG, but the correlation was weak (Pearson R = 0.406).

3.3 | Univariate analysis

Associations of clinical and PET parameters with LRF, DM, and death were studied using univariate Cox analysis, with results listed in Table 2. Total lesion MTV and TLG were found to be associated with increased hazard for all 3 endpoints (LRF, DM, and death). The clinical T classification, N classification, and overall group classification, in addition to PET nodal MTV and nodal TLG, were associated with increased hazard for DM and death. Neither SUV_{max} nor age was associated with any of the clinical endpoints.

Total lesion TLG was the strongest predictor of LRF (HR of 1.86 per SD increase and c-index of 0.756). Group classification was the strongest predictor of DM and death (HR of 4.33 and 4.71 per SD increase and c-index of 0.764 and 0.753, respectively). Notably, none of the clinical factors were associated with LRF.

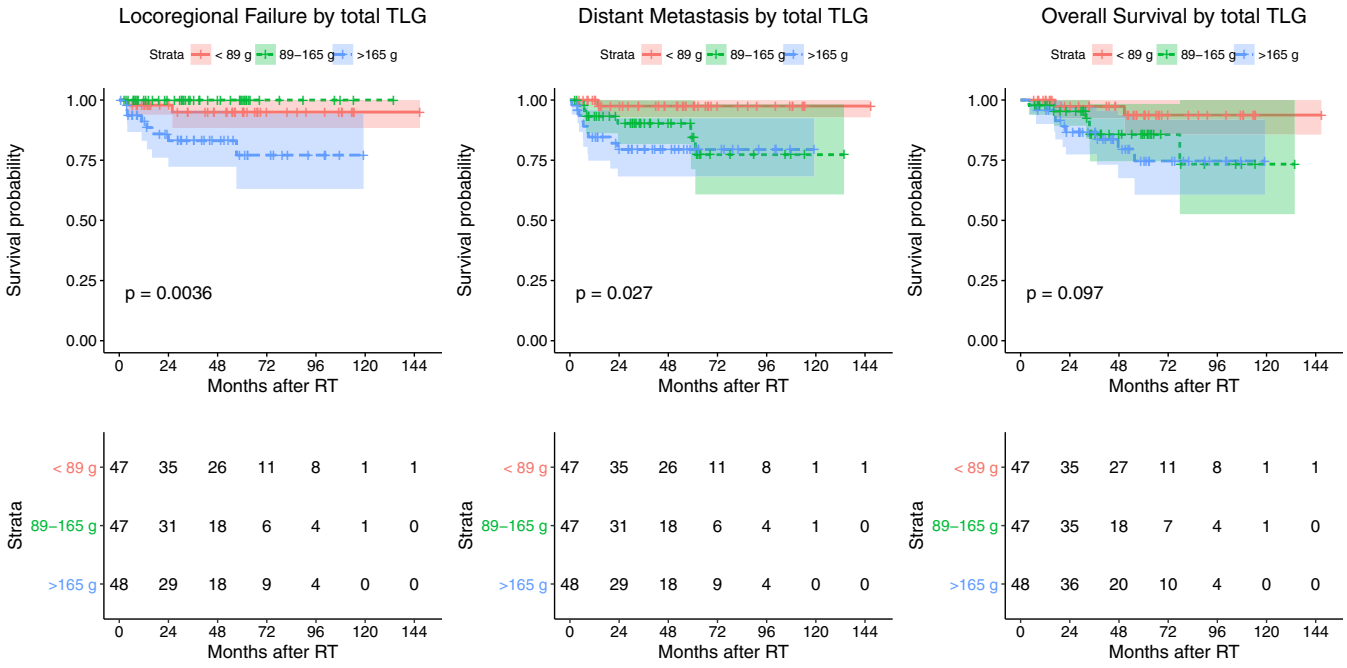

FIGURE 3 Kaplan-Meier plots for each endpoint by total lesion total lesion glycolysis (TLG) [Color figure can be viewed at wileyonlinelibrary.com]

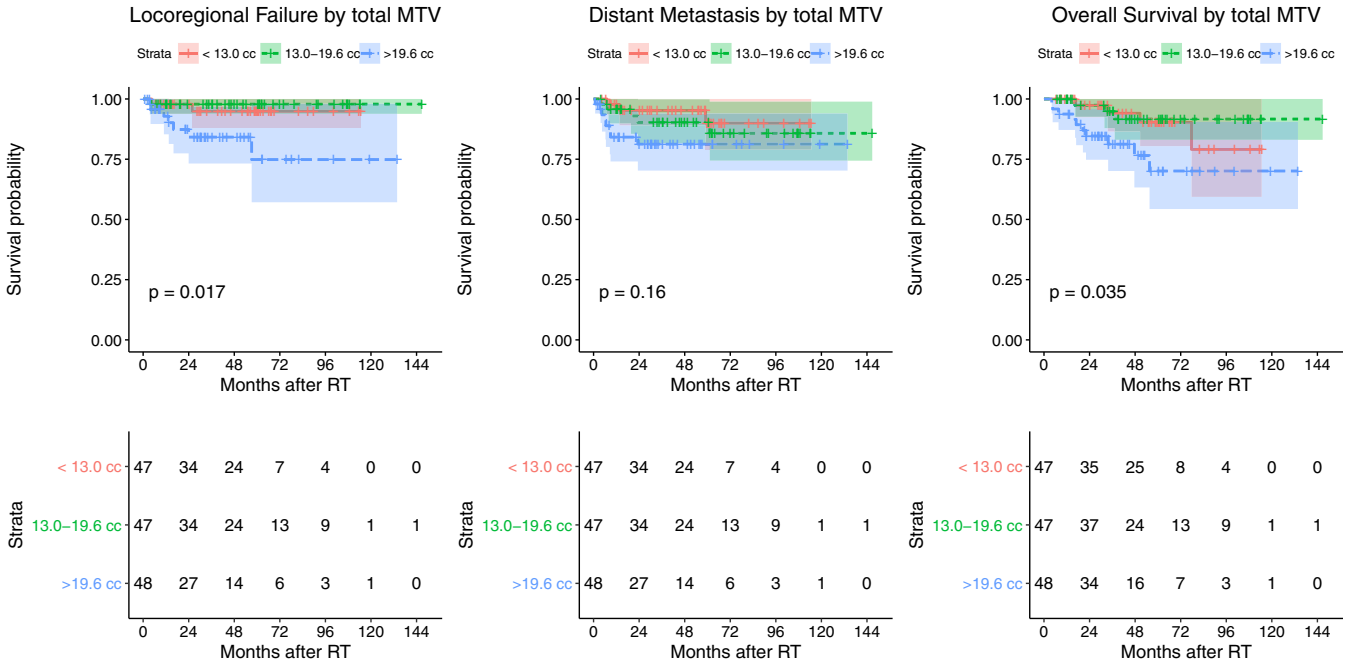

FIGURE 4 Kaplan-Meier plots for each endpoint by total lesion metabolic tumor volume (MTV) [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Multivariate analysis

In stepwise Cox regression for LRF, only total lesion TLG was retained, generating equivalent univariate and optimal multivariate LRF model. For DM and death, total lesion TLG and total lesion MTV were individually selected and remained statistically significant in 2-parameter models adjusted for group classification (Table 3). Normalized proportional hazard for DM and death, adjusting for classification were 1.45 and 1.51 for total lesion TLG and MTV, respectively.

3.5 | Kaplan-Meier analysis and tertile cutoffs

Figure 2 shows survival curves for all endpoints stratified by the 8th Ed. AJCC/UICC TNM staging. Tertile thresholds (33rd and 66th percentile values) for total lesion MTV and total lesion TLG were 13.0/19.6 cc and 89/165 g, respectively. In Kaplan-Meier analysis, stratification based on total lesion TLG was statistically significant in log-rank analysis for LRF ($P < .01$) and DM ($P = .03$) but not for OS ($P = .10$) (Figure 3). Stratification based on total lesion MTV was significant for LRF ($P = .02$) and OS ($P = .04$) but not for DM ($P = .16$) (Figure 4).

4 | DISCUSSION

In the work described here, we found that total lesion TLG and MTV correlated with LRF in patients with HPV-related OPSCC and a ≤10 pack-year smoking history who received definitive concurrent radiation and systemic therapy. This is compared to the 8th Ed. AJCC/UICC TNM staging, which showed no statistically significant association with LRF. In contrast, TNM staging was the strongest predictor of DM and OS, with total lesion volumetric PET parameters adding only marginally significant prognostic information to staging.

Several studies have demonstrated prognostic value of volumetric PET parameters in OPSCC.[16–20,22,24–27] Mena et al. retrospectively reviewed 105 HPV-related OPSCC and found a statistically significant association between total lesion TLG and event-free survival.[18] Our results are concordant with this observation. In comparison, the present work reviewed the largest homogeneous patient population of HPV-related OPSCC patients with ≤10 pack-year smoking history and was the first to include the 8th Ed. AJCC/UICC TNM staging for HPV-related OPSCC as a variable in multivariate analysis.

Our results showed total lesion TLG to be the strongest predictor of LRF. Primary tumor volumetric PET parameter was also significantly associated with LRF, although it demonstrated poorer prediction performance than total lesion PET parameters as reflected by a lower c-index. One meta-analysis of the prognostic value of MTV/TLG in head and neck cancer similarly showed that patients with high primary tumor volumetric PET parameters had lower HRs for failures and death than patients with high total lesion volumetric PET parameters.[23] This is possible because the total lesion represents the whole disease and provides more prognostic information beyond primary tumor alone. In our study, there was no statistically significant association between the 8th Ed. AJCC/UICC TNM staging and LRF, and the addition of volumetric PET parameters to the TNM staging appears to improve prognostication of LRF beyond staging. Prospective studies are warranted to further investigate this finding.

Treatment de-intensification in patients with HPV-related OPSCC and a minimal smoking history has been associated with good treatment outcomes.[6–9] The Eastern Cooperative

Oncology Group (ECOG) conducted a phase II trial that used complete clinical response to induction chemotherapy as selection criteria for reduction of radiation dose to 54 Gy in HPV-related OPSCC patients.[8] The study yielded excellent treatment results in patients with a smoking history ≤10 pack-years with 2-year PFS and OS of 92% and 93%, respectively. A different phase II study by Chera et al. investigated de-intensification of concurrent chemoradiation in 44 patients with HPV-related OPSCC, 95% of whom had ≤10 pack-year smoking history.[6,7] The protocol consisted of reduced dose radiation therapy (60 Gy) given concurrently with weekly low dose cisplatin (30 mg/m^2). Early results showed a high percentage (86%) of pathological complete response evaluated at 9 weeks after CCRT.[6] More recently updated follow up demonstrated excellent outcomes with 3-year local control, regional control, and OS of 100%, 100%, and 95%, respectively.[7]

The de-intensification strategies described above have relied on HPV-status, TNM stage, and smoking history to determine eligibility. However, while these factors are prognostic for OS, the utility of TMN stage and smoking history in prognosticating LRF is less well defined.[9,10] Given the importance of LRF risk when considering patients for de-intensification, tools for the accurate prognostication of LRF in these patients are vital. Our study showed that total lesion TLG/MTV could predict LRF and might help optimize treatment intensity in these patients. For example, patients with a very low predicted risk of LRF, based on these PET parameters, may be appropriate for further radiation dose reduction, which could further lower the probability of long-term complications. Conversely, patients with a high predicted risk of LRF may be poor candidates for de-intensification, despite the presence of other favorable factors.

Significant associations between volumetric PET parameters and DM/OS have been demonstrated in literature.[19,20] Our study similarly showed significant correlations between nodal and total lesion TLG /MTV, and DM and OS in univariate analysis. However, the prognostic value of these parameters was highly influenced by the 8th Ed. AJCC/UICC TNM staging, as total lesion TLG and MTV were barely statistically significantly associated with DM and OS in multivariate analysis, and added little prognostic information to the staging.

The prognostic value of SUV_{max} in head and neck cancer is controversial.[16–22] One prospective study in 98 patients with head and neck cancer showed no significant correlation between pretreatment SUV_{max} and response to radiation therapy.[21] Our result also did not find significant correlation between SUV_{max} and treatment outcomes.

There are several limitations to this study that require consideration. First, the retrospective nature of this study possibly contributed bias and confounding effects to relative risk estimates. In addition, while the tertile thresholds used here were convenient for dividing patients into 3 equal sized groups, the absolute values of these are dependent on the specific patient cohort. Alternative methods for selecting stratification thresholds exist, such as maximum log-rank statistic and minimally selected *P*-value. However, due to the low event rate and high propensity for false discovery due to multiple comparisons, these were not applicable in this work. Prospective studies for determining optimal stratification thresholds based on imaging parameters are warranted. Further, confounding effects such as the evolution of treatment and imaging parameters over the wide time-course of this study may have affected our results. Second, although a majority of our scans came from a single manufacturer, differences in absolute output across imaging devices was not fully characterized. Lastly, there is some uncertainty associated with manual delineation of tumors on ^{18}FDG-PET scans. Although each contour was reviewed by 2 radiation oncologists, it is possible that slight inter-observer contour deviations could lead to different characterization and thus different PET parameters. We believe that MTV and TLG may be more robust to these changes in comparison to SUV_{max}.

5 | CONCLUSIONS

Volumetric PET parameters are uniquely prognostic of locoregional failure-free survival in low-risk HPV-related OPSCC and may be useful for directing de-intensification strategies.

ORCID

Benjamin S. Rosen https://orcid.org/0000-0002-7827-4197
Peter G. Hawkins https://orcid.org/0000-0003-1100-9388

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How to cite this article: Chotchutipan T, Rosen BS, Hawkins PG, et al. Volumetric ^{18}F-FDG-PET parameters as predictors of locoregional failure in low-risk HPV-related oropharyngeal cancer after definitive chemoradiation therapy. *Head & Neck*. 2019;41: 366–373. https://doi.org/10.1002/hed.25505