


Adding value to tumor staging in head and neck cancer: The role of metabolic parameters as prognostic factors

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Abstract

Background: Validated biomarkers in head and neck squamous cell carcinoma (HNSCC) are scarce.

Methods: We retrospectively analyzed 62 patients with HNSCC treated with radiotherapy +/- concurrent chemotherapy. Pretreatment metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were measured in a ¹⁸F-FDG positron emission tomography using a liver dependent standardized uptake value threshold. Cox regression analyses were performed to find associations with disease-free survival (DFS) and overall survival (OS).

Results: High values of MTV (>37 ml) were independently associated with a worse DFS (hazard ratio [HR] = 3.45; 95% confidence interval [CI], 1.52–7.84) and OS (HR = 3.27; 95% CI, 1.41–7.57). Similar results were found for high values of TLG (>247 g) for DFS (HR = 3.32; 95% CI, 1.44–7.65) and OS (HR = 3.42; 95% CI, 1.45–8.07).

Conclusions: MTV and TLG can be considered as independent prognostic factors for DFS and OS in patients with HNSCC. Considering how easily obtainable they are, they may be useful for predicting clinical outcomes in these patients.

KEYWORDS

cancer, head and neck, MTV, PET, TLG

1 | INTRODUCTION

Head and neck cancer (HNC) accounts for more than 330 000 deaths annually and it is newly diagnosed in approximately 650 000 patients every year, making it the sixth most common cancer worldwide.^{1,2} Nonetheless its relevance,

there are still many controversies and discrepancies among practitioners surrounding the therapeutic approaches for these patients, especially in locally advanced HNC.^{3–5} The two main tools to categorize patients with HNC and to assess treatment and prognosis are the Union Internationale Contre le Cancer (UICC) TNM classification and the American Joint

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Committee on Cancer (AJCC) staging system. Although practical, those strategies focus only on morphological criteria and do not consider characteristics inherent to each tumor.^{6,7} Up to this point, human papilloma virus (HPV) status and its surrogate marker P16 (CDKN2A) are the only two validated biomarkers in HNC, particularly in the oropharynx.⁸⁻¹⁰ Therefore, finding markers that could aid in predicting clinical outcomes and in treatment planning is of utter interest.

Ever since the introduction of fluorine-18-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) for staging, treatment planning, and monitoring patients with HNC, the relevance of this imaging technique has been exponentially increasing because of its ability to evaluate both tumor morphology and biological activity.¹¹⁻¹³ Furthermore, several quantitative PET parameters are being studied as prognostic factors in HNC. Among them, maximum standardized uptake value (SUV_{max}) is the parameter most widely used, primarily owing to how easily measured it is with current PET machines. Nonetheless, conflicting results on its prognostic value are being found in many studies.^{7,14-17} Other parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are showing good prognostic value with more homogeneous results than SUV_{max}.^{7,14,18-20} Even so, these parameters have several limitations to consider. In order to measure MTV and TLG, it is necessary to decide on one of the several segmentation methods available to define the volume of interest (VOI) as there is no consensus on which to use. Because of its practicality, a fixed threshold of a, in general, 40%–50% of SUV_{max} and an isocontour based on a fixed SUV threshold (usually SUV = 2.5) are the most widely used methods.²¹⁻²⁵ Both measurements are SUV dependent and therefore affected by its variations. The accuracy of the image reconstruction and correction algorithms, PET scanner's signal-to-noise properties, ¹⁸F-FDG uptake time, tumor size, patients' weight and blood glucose levels, among others factors, have a direct impact in SUV measurements, making it difficult to reproduce them properly.²⁵⁻²⁷ To minimize this variability, many authors recommend using the SUV of a reference region as threshold.^{24,26-29} Because of the stability over time of the SUV in the liver and mediastinum, those are the two main reference regions used for thresholding.^{26,27,30,31}

The aim of this study is to measure pretreatment MTV and TLG calculated using a liver SUV_{mean}-dependent parameter and analyze their association with disease-free survival (DFS) and overall survival (OS) in patients diagnosed with locally advanced head and neck squamous cell carcinoma (HNSCC) treated with radiotherapy +/- concomitant chemotherapy.

2 | MATERIALS AND METHODS

2.1 | Study population

We retrospectively reviewed biopsy-confirmed patients with HNSCC who were treated at Puerta de Hierro University Hospital between January 2012 and December 2018. The inclusion criteria were: adult patients (≥18 years of age) with the primary diagnosis of stage III/IV HNSCC without distant metastasis who had undergone pretreatment ¹⁸F-FDG PET-computed tomography (CT) for treatment planning and initial staging that had been treated with radiotherapy alone or with concurrent chemoradiotherapy. Patients with nasopharyngeal cancer, patients who had undergone previous treatments, and patients with coexisting malignancies were excluded. Patients with an interval between ¹⁸F-FDG PET-CT acquisition and treatment initiation longer than 6 weeks were also excluded. Approval for this study was granted by the Institutional Ethics Committee of our hospital. In consequence of the retrospective design of the review, informed consent from each patient was waived.

2.2 | Radiation therapy and follow-up

Patients were simulated in supine position and immobilization was carried out with a thermoplastic head-shoulders mask. Contrast-enhanced planning CT with 3 mm slice thickness was acquired. PET-CT was performed in all patients and was registered with planning CT to aid in the delineation of treatment volumes. For each patient, the following clinical target volumes (CTVs) were defined: CTV1 included the primary and pathological neck nodes gross tumor volumes (GTV); CTV2 included the CTV1 and the "high risk" first uninvolved lymph-node level; and CTV3 included elective bilateral lymph nodes regions according to published international guidelines.³² The corresponding planning target volumes (PTVs) were generated by adding 0.5 mm to the CTVs. Treatment was administered in 32 fractions using the simultaneous integrated boost up to doses of 69.12, 57.6, and 53.12 Gray (Gy) for PTV1, PTV2, and PTV3, respectively. Treatment with intensity modulated radiation therapy was administered in a TomoTherapy HiArt unit equipped with an image-guided radiation therapy system. Dose-limiting constraints for organs at risk were the following: Dmax of 45 Gy for spinal cord; V28 < 50% for parotid glands; V65 < 10% for mandible; Dmax of 55 Gy for brain stem; and Dmean < 50 Gy for constrictor muscles. Concomitant cisplatin-based chemotherapy was administered in most patients with two protocols: a regimen consisting of cisplatin plus oral tegafur described

elsewhere,³³ and a regimen of six cycles of weekly cisplatin (40 mg/m²). Cetuximab (400 mg/m² initial dose, followed by seven weekly doses at 250 mg/m²) was administered in patients who were not suitable for a cisplatin-based protocol. Radiotherapy alone was administered in the patients whose physical conditions were not optimal for chemotherapy.

To assess treatment response, ¹⁸F-FDG PET-CT was performed between 2 and 4 months after therapy completion. Head and neck imaging with CT or magnetic resonance imaging and physical examination were performed every 6 months for 3 years and once a year for two more years. In case of persistent disease or recurrence, salvage surgery or palliative treatment was indicated.

2.3 | ¹⁸F-FDG PET-CT imaging

Patients were asked to fast for at least 6 h until their serum glucose concentration was less than 180 mg/dl prior i.v. ¹⁸F-FDG (approximately 350–400 MBq) injection. CT scans were performed with a helical multidetector CT as follows: 110 kVp, a maximum modulated milliamperage of 85 mAs, six slices with a 5.0 mm thickness, and no i.v. or oral contrast, from the top of the skull to the mid-tight. CT data were used for attenuation correction and image fusion. PET-CT image acquisition was performed after 50–60 min of i.v. injection with a multimodality Siemens Biograph 6 scan (Biograph; Siemens, Erlangen, Germany) as follows: 4-min scan per bed position × 7–8 positions and ordered-subset expectation maximization reconstruction (four iterations, eight subsets).

2.4 | Image interpretation

¹⁸F-FDG findings were transferred into Siemens Leonardo reading station and analyzed by an experienced nuclear medicine physician (J. Mucientes) who was blinded to all patients' clinical outcomes, using the program Syngo@.via (Siemens Healthineers, Muenchen, Germany). Image voxels were converted into standardized uptake values. SUV is a decay-corrected measurement of activity per unit of mass of tissue adjusted for administered activity per unit of body weight.³⁴ For measuring the VOIs, we selected a background-level threshold method using the liver as the reference region. Liver SUV_{mean} was calculated by placing a 3 cm sphere on the center of its VIII segment.^{24,26–28} Targeted ¹⁸F-FDG-avid lesions were manually delimited in three imaging planes and all lesions (tumor and metastatic lymph nodes) with a SUV higher than liver SUV_{mean} + 2 standard deviations (SDs) isocontour were marked as the

VOIs. The software program automatically calculated the MTV of tumor and/or pathologic lymph nodes and both volumes were then combined. TLG was therefore obtained using the formula: MTV × Liver SUV_{mean}.

2.5 | Statistical analysis

Descriptive analysis for categorical variables was performed with means of absolute and relative frequencies; numerical variables were analyzed through means with standard deviation, medians with percentiles 25 and 75 (P25–P75), and minimum and maximum values. DFS was defined as the time between treatment initiation and relapse or death from any cause, whichever occurs first. Overall survival was defined as the time between treatment initiation and death from any cause. Patients who were followed-up until the end of the study with no events were considered as censored. Survival function was estimated through the Kaplan–Meier method. Differences between survival curves were compared through the log-rank test. We analyzed local control rate considering the death as a competing event; therefore, cumulative incidence function (CIF) was estimated instead of Kaplan–Meier curve.

The area under the curve (AUC) receiver operating characteristics (ROC) is a useful approach that represents the overall performance of a biomarker. In clinical practice, biomarkers with AUC–ROC curves >0.9 are considered very accurate; moderately accurate for AUCs between 0.7 and 0.9; slightly accurate for AUCs of 0.5–0.7 and no better than chance accuracy with an AUC <0.5. In order to obtain an optimal cutoff point for each one of the parameters (MTV and TLG) and the outcomes (OS and DFS), time-dependent ROC curves for survival data were developed.³⁵ Youden and Liu methods were used to define the optimal cut point. The Youden index method defines the optimal cut point as the point maximizing the difference between true positive rate and false positive rate over all possible cut-point values.³⁶ Liu's method defines the optimal cut point as the point maximizing the product of sensitivity and specificity.³⁷

Then, to measure the prognostic value for each one of the parameters, we executed two Cox proportional hazard models: a dichotomized one with the optimal cut points and a continuous one. Firstly, we developed a univariable approach, and secondly, a multivariable model adjusting by T classification, N classification, and age. Schoenfeld residuals were used to check the proportional hazards assumption. Univariable subanalyses per disease location were also developed and multivariable subanalyses were performed for the locations with a significant statistical association in their univariable analysis.

TABLE 1 Patient characteristics

Characteristic	Value (%)
Age, years	
Median	65
Range	38–87
Sex	
Male	49 (79)
Female	13 (21)
Smoking	
Yes	49 (79)
No	13 (21)
Disease location	
Oral cavity	7 (11)
Oropharynx	16 (26)
HPV positive	7
HPV negative	6
HPV not stated	3
Hypopharynx	6 (10)
Larynx	33 (53)
T-classification	
T1	2 (3)
T2	16 (26)
T3	29 (47)
T4	15 (24)
N-classification	
N0	14 (22)
N1	5 (8)
N2	37 (60)
N3	6 (10)
TNM overall stage	
III	22 (35)
IVa	29 (47)
IVb	11 (18)
Histologic differentiation	
ns	18 (29)
Grade 1	6 (10)
Grade 2	23 (37)
Grade 3	15 (24)
Treatment	
Radiotherapy alone	3 (5)
Chemoradiotherapy	59 (95)
Cisplatin + tegafur	31 (50)
Weekly cisplatin	17 (27)
Cetuximab	11 (18)

TABLE 1 (Continued)

Characteristic	Value (%)
Radiation dose, Gy	
Median	69
Range	45–70
<66 Gy	3 (5)
≥66 Gy	59 (95)
Chemotherapy percentage	
None or <80%	17 (27)
≥80%	45 (73)
Follow-up information	
Median follow-up, months	59.3 (48.6–68.5) ^a
Survival information	
Locoregional recurrences	21 (34)
Distant metastasis	13 (21)
4-year DFS	57 (43–69) ^a
4-year OS	63 (49–74) ^a

Abbreviations: DFS, disease-free survival; Gy, gray; HPV, human papilloma virus; N, lymph nodes; ns, not stated; OS, overall survival; T, tumor.

^a95% confidence interval.

To test the goodness of fit and performance of the models, Harrell's C index (C-index) and Akaike information criterion (AIC) were estimated, respectively. Values of C-index near 0.5 indicate that the risk score predictions are no better than flip a coin in determining which patient will make the event. Values near 1 indicate that the model is good at determining between two patients who will have an event first. AIC estimates the relative amount of information lost by a given model: the less information a model loses, the higher the quality of that model. Given a set of candidate models for the data, the preferred model is the one with the minimum AIC value. Significance level was set at 0.05. Software used was Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, Texas: StataCorp LLC).

3 | RESULTS

3.1 | Patient' characteristics

We retrieved the records of 79 patients diagnosed with stage III-IV HNSCC. We excluded 15 patients because pretreatment ¹⁸F-FDG PET-TC had been performed in a different center and two because of a longer than 6 weeks interval between PET acquisition and treatment initiation. Thus, 62 records were eligible for the analysis. Patients'

characteristics are summarized on Table 1. At the moment of the analysis, 25 deaths (40%) had occurred: 19 died with disease and 6 from other causes. Five patients were alive with disease. Twenty-one patients (34%) had locoregional recurrences and 13 (21%) developed distant metastasis. Local and locoregional control per disease location are shown in Table S1. Two patients died during treatment and, after a severe cervical radiodermatitis, another patient refused to complete the doses. Median follow-up was 59 months (95% confidence interval [CI], 48.6–68.5) with a 4-year DFS and OS for the whole cohort of 57% and 63%,

respectively. Four-year DFS and OS per disease location are presented in Table S2.

3.2 | PET parameters and cutoff values' determination

The median MTV, TLG, and SUVmax values were 16.09 ml (range, 0.08–132.04 ml), 104.75 g (range, 0.35–2412.89 g), and 12.74 (range, 3.0–30.57), respectively. Cutoff values acquired through the time-dependent

TABLE 2 Univariable Cox regression analysis for disease-free survival and overall survival

Variables	Overall survival		Disease-free survival	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age (years)	1.03 (0.99–1.07)	0.111	1.01 (0.99–1.05)	0.484
Sex				
Female	1		1	
Male	1.17 (0.44–3.14)	0.749	1.22 (0.46–3.26)	0.688
Smoking				
Yes	1		1	
No	0.76 (0.28–2.03)	0.587	1.14 (0.39–3.31)	0.815
T-classification				
T1–T2	1		1	
T3–T4	1.43 (0.57–3.59)	0.445	1.46 (0.58–3.67)	0.419
N-classification				
N0	1		1	
N+	1.08 (0.40–2.93)	0.874	1.23 (0.46–3.29)	0.677
Overall TNM stage				
III	1		1	
IVa	1.04 (0.42–2.58)	0.942	1.58 (0.60–4.17)	0.352
IVb	2.02 (0.70–5.86)	0.196	2.25 (0.72–7.00)	0.162
Histologic differentiation				
Grade 1–2				
Grade 3	1		1	
	1.48 (0.52–4.19)	0.459	1.06 (0.39–2.87)	0.909
Radiotherapy dose (Gy)				
<66	1		1	
≥66	0.77 (0.10–5.74)	0.799	1.0 (0.13–7.44)	0.997
Chemotherapy %				
<80%	1		1	
≥80%	0.51 (0.23–1.14)	0.102	0.70 (0.29–1.69)	0.432
SUVmax				
≤12.63	1		1	
>12.63	1.63 (0.73–3.62)	0.235	2.40 (1.05–5.44)	0.037

Abbreviations: CI, confidence interval; Gy, gray; HR, hazard ratio; N, lymph nodes; SUV_{max}, maximum standardized uptake value; T, tumor.

AUC-ROC were estimated at a 3-years' time point for MTV, TLG, and SUVmax. The cutoff points were 37 ml (AUC = 0.68), 247 g (AUC = 0.66), and 12.63 (AUC = 0.62), respectively. The same cutoff points were obtained with both Youden and Liu method. Thus, MTV, TLG, and SUVmax were dichotomized according to their corresponding cutoff values.

3.3 | Survival analysis

Univariable analyses for SUVmax (hazard ratio [HR] = 2.40, 95% CI = 1.05–5.44, $p = 0.037$), dichotomized MTV (HR = 3.62, 95% CI = 1.63–8.03, $p = 0.002$)

and TLG (HR = 3.28, 95% CI = 1.48–7.25, $p = 0.003$), as well as continuous MTV (HR = 1.25, 95% CI = 1.11–1.41, $p \leq 0.001$) and TLG (HR = 1.03, 95% CI = 1.01–1.05, $p \leq 0.001$) had a significant association with DFS (Tables 2 and 3). Both dichotomized (HR = 3.15, 95% CI = 1.41–7.04, $p = 0.005$) and continuous (HR = 1.19, 95% CI = 1.07–1.33, $p = 0.002$) measurements of MTV, as well as dichotomized (HR = 2.82, 95% CI = 1.23–6.21, $p = 0.010$) and continuous (HR = 1.04, 95% CI = 1.01–1.06, $p = 0.001$) measurements of TLG were associated with OS (Table 4). This trend was maintained for both OS and DFS in the patients with hypopharynx/larynx and oropharynx cancers, although the results for the later location were not statistically significant (Tables S3 and S4).

TABLE 3 Disease-free survival Cox regression analyses for MTV and TLG

	Univariable analysis		Multivariable analysis ^a			
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	C-index	AIC
Dichotomized MTV model						
≤37 ml	1		1			
>37 ml	3.62 (1.63–8.03)	0.002	3.45 (1.52–7.84)	0.003	0.673	185.065
Continuous MTV model						
Per 10-ml increment	1.25 (1.11–1.41)	<0.001	1.25 (1.09–1.42)	0.001	0.676	183.450
Dichotomized TLG model						
≤247 g	1		1			
>247 g	3.28 (1.48–7.25)	0.003	3.32 (1.44–7.65)	0.005	0.675	185.465
Continuous TLG model						
Per 25-g increment	1.03 (1.01–1.05)	<0.001	1.03 (1.01–1.05)	0.001	0.677	186.081

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; C-index, Harrell's C-index; g, gram; HR, hazard ratio; ml, milliliter; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

^aAdjusted by age, T-classification, and N-classification.

TABLE 4 Overall survival Cox regression analyses for MTV and TLG

	Univariable analysis		Multivariable analysis ^a			
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	C-index	AIC
Dichotomized MTV model						
≤37 ml	1		1			
>37 ml	3.15 (1.41–7.04)	0.005	3.27 (1.41–7.57)	0.006	0.673	183.609
Continuous MTV model						
Per 10-ml increment	1.19 (1.07–1.33)	0.002	1.21 (1.07–1.36)	0.002	0.676	182.434
Dichotomized TLG model						
≤247 g	1		1			
>247 g	2.82 (1.28–6.21)	0.010	3.42 (1.45–8.07)	0.005	0.696	182.984
Continuous TLG model						
Per 25-g increment	1.04 (1.01–1.06)	0.001	1.04 (1.02–1.06)	0.001	0.663	182.269

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; C-index, Harrell's C-index; g, gram; HR, hazard ratio; ml, milliliter; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

^aAdjusted by age, T-classification, and N-classification.

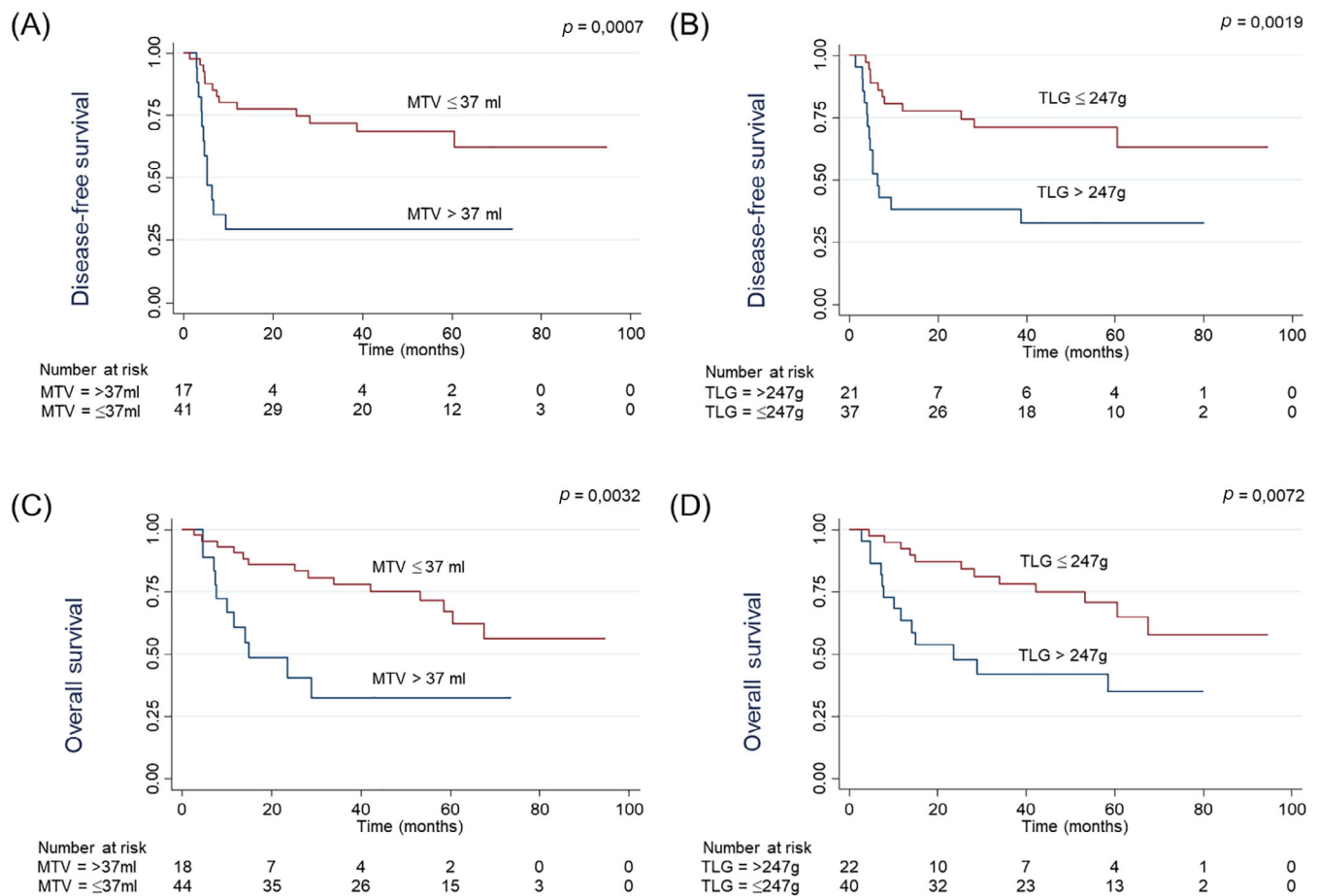


FIGURE 1 Kaplan–Meier’s curves for disease-free survival (DFS) and overall survival (OS) using the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) dichotomized models. A, Curves for DFS and a cutoff of 50 ml of MTV. B, Curves for DFS and a cutoff of 284 g of TLG. C, Curves for OS and a cutoff of 50 ml of MTV. D, Curves for OS and a cutoff of 284 g of TLG [Color figure can be viewed at wileyonlinelibrary.com]

Multivariable analyses for both models of MTV and TLG in the patients with hypopharynx/larynx cancer obtained a significant association with OS and DFS (Table S5). Oral cavity cancers and oropharynx subgroups analysis per HPV status were not estimable because of the small sample size in those analyses (Tables S3 and S4).

In the multivariable analyses for DFS, MTV and TLG measurements remained as independent prognostic factors. Patients with >37 ml MTV had higher hazard for recurrence (HR = 3.45, 95% CI = 1.52–7.84, $p = 0.003$) than patients with a ≤ 37 ml MTV. The same happened with patients with a >247 g TLG (HR = 3.32, 95% CI = 1.44–7.65, $p = 0.005$). HR for DFS was 1.25 (95% CI = 1.09–1.42, $p = 0.001$) for every 10-ml increment of MTV and 1.03 (95% CI = 1.01–1.05, $p = 0.001$) for every 25-g increment of TLG. AIC and C-index values are shown in Table 3.

Measurements for MTV and TLG also stayed as independent prognostic factors in the multivariable analyses for OS. Patients with >37 ml MTV had a higher hazard

for death (HR = 3.27, 95% CI = 1.41–7.57, $p = 0.006$) than patients with a ≤ 37 ml MTV. Equivalent results were found for patients with >247 g TLG (HR = 3.42 (95% CI = 1.45–8.07, $p = 0.005$). HR for death was 1.21 (95% CI = 1.07–1.36, $p = 0.002$) for every 10-ml increment of MTV and 1.04 (95% CI = 1.02–1.06, $p = 0.001$) for every 25-g increment of TLG. AIC and C-index are shown in Table 4.

Kaplan–Meier’s curves for DFS as well as OS using the MTV and TLG with the cutoff points of the dichotomized models are shown in Figure 1. CIF of local control for the same models are shown in Figure 2.

4 | DISCUSSION

We retrospectively found an independent association between pretreatment MTV and TLG with survival in HNSCC as higher values of these parameters predict a worse DFS and OS. According to C-index results, all

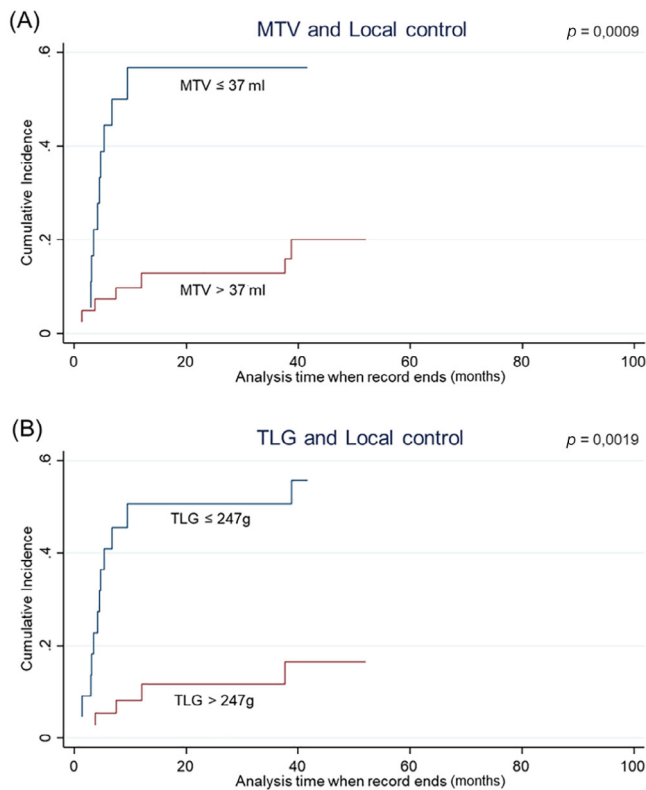


FIGURE 2 Cumulative incidence function of local control using the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) dichotomized models. A, Cumulative incidence for MTV and local control; B, cumulative incidence for TLG and local control [Color figure can be viewed at wileyonlinelibrary.com]

models created for MTV and TLG behaved as good models. Among them, continuous MTV model was superior for predicting DFS and continuous TLG model was superior for predicting OS, as per AICs results (Tables 3 and 4). This independent association was especially maintained in the subanalysis of patients with hypopharynx/larynx cancer, with good C-index results (Table S5).

In the last decades, the number of publications studying the prognostic value of MTV and TLG in HNSCC is increasing and the results are in general homogeneous, suggesting a good prognostic potential.^{7,14,18} Pak et al,⁷ Bonomo et al,¹⁴ and Xie et al¹⁸ have performed meta-analyses (MAAs) whose results indicate a significant association between MTV and survival in HNSCC. The MAA performed by Pak et al⁷ also suggest the same for TLG. Our previous MAA had similar results for both markers as well.³⁸

UICC TNM classification and AJCC staging system are the two standardized tools globally used for treatment evaluation and survival prediction in HNC. These systems describe the extension of the disease based on its morphological characteristics, presenting a descriptive

analysis in a short and precise code.⁶ Notwithstanding their practicality, these classification methods do not take into consideration biological features inherent to each tumor, thus limiting their prognostic capability.^{3,39,40} As the relevance of nonmorphologic factors within tumors is being recognized, it might be interesting to consider the possibility of including them in a comprehensive classification system.³

Although metabolic parameters have consistently shown a good prognostic value for HNC in many studies, these measurements have numerous limitations to consider. There are several segmentation methods to delineate VOIs: manual selection, based on a background-level threshold (e.g., relevant background SUV + 2–3 SDs), gradient based methods, a threshold based on a percentage of SUV_{max} (e.g., 40%–50%), an isocontour based on a fixed SUV threshold (e.g., SUV = 2.5), among others.^{21–24,26} The latter two are the most widespread methods used, particularly because they are easily obtainable with current PET machines. As mentioned earlier in this study, these methods are SUV-dependent and thus affected by the quality of the PET machine, image analysis, and patients' characteristics and preparation, limiting the possibility to reproduce and generalize those measurements.^{25,31,41–43}

In consequence and to minimize this variability, many authors recommend using a gradient-based segmentation method^{40,42,44} or to use the SUV of a reference region for thresholding,^{26,28–30} being the liver and the mediastinum the two regions more widely used.^{27,29,30} Taking all this into consideration, in order to obtain reproducible and generalizable cutoff values, there has to be a thorough and meticulous standardization in PET preparation. Among all 44 studies analyzing MTV in HNSCC included in the four MAAs published to this date,^{7,14,18,38} only two of them used the SUV of a reference region for segmentation, and both studies chose the mediastinum.^{45,46} During the manual search of our literature review,³⁸ we found one paper that used liver's SUV for thresholding.²⁴ However, as this last study was comparing several segmentation methods and they found no significant differences between them, their survival analysis was also made using the mediastinum as the reference region. To the best of our knowledge, this is the first study in HNSCC using the liver's SUV for thresholding MTV. Although this method is proposed in the PET Response Criteria in Solid Tumors 1.0 (PERCIST),²⁶ it is not commonly used in HNSCC papers.

This study has several limitations, primarily because of the limited number of patients with heterogeneous diseases, as well as its retrospective design with potential biases in data collection. Nevertheless, these variables seemed to offer important pretreatment information that could aid in monitoring recurrence and even in treatment planning.

We have found a significant and independent association between MTV and TLG with the survival of patients with hypopharynx/larynx cancer, agreeing with the results of other studies.⁴⁷⁻⁴⁹ The great morbidity, stigma, and decrease in quality of life associated with the treatment of cancer in these locations require a comprehensive analysis when deciding between an organ preservation strategy or primary surgery. Yabuki et al⁵⁰ performed a prospective study comparing the survival rate of patients with laryngeal cancer and high MTV according to the treatment strategy selected for each case (surgery-based vs. radiation-based). The study found a better survival rate for the patients who were treated with a surgery-based therapy. These results point to the possibility of MTV being able to help decide between treatments, and it might even throw some light into the existing controversies in HNC treatment strategy selection.^{4,5}

Many prospective and multicentric trials are still required to consider modifying the standardized protocols for managing patients with HNC. Nevertheless, and with all due limitations, pretreatment MTV and TLG offer valuable information that can aid in selecting patients who would benefit from a more thorough follow up for early recurrence detection and, perhaps in the future, may also aid in treatment strategy selection.⁵⁰

5 | CONCLUSIONS

The results of this study suggest an independent association of pretreatment MTV and TLG with DFS and OS in patients diagnosed with locally advanced HNSCC treated with radiotherapy +/- chemotherapy. Considering how easily obtainable they are with current technology, and despite their limitations, these parameters can be used to identify patients with a higher risk of recurrence.

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AUTHOR CONTRIBUTIONS

Jefferson Rijo-Cedeño: literature review, analysis and interpretation of data, drafting of the manuscript, final approval of the manuscript. Jorge Mucientes, Sara Seijas Marcos, and Sandra Carbonell: data collection, analysis and interpretation of data, final approval of the manuscript. Jesús Romero: literature review, study design, final approval of the manuscript. Ana Royuela: statistical analysis, final approval of the manuscript. Raquel Benlloch: literature review, final approval of the manuscript. José Ramón García-Berrocal: research coordinator, final approval of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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