

# Role of Pretreatment Fluorodeoxyglucose Positron Emission Tomography Quantitative Parameters in Prognostication of Head-and-Neck Squamous Cell Carcinoma

## Abstract

In spite of the good organ preservation strategies available for locally advanced head-and-neck squamous cell carcinoma (HNSCC), failure rates have been reported to be as high as 35%–50%. There has been an increasing interest in predicting response to treatment, to aid early intervention and better outcomes. Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) is a standard modality for posttreatment evaluation; however, it is still underutilized as a pretreatment investigative modality. Several articles have described quantitative parameters in pretreatment FDG-PET to prognosticate patients and determine the likelihood of response to treatment; however, they are still not used commonly. This article was a review of the literature available on pretreatment FDG-PET quantitative parameters and their value in predicting failure. A thorough review of literature from MEDLINE and EMBASE was performed on pretreatment quantitative parameters in HNSCC. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were reliable parameters to predict response to organ preservation therapy, disease-free survival, and overall survival. Maximum SUV ( $SUV_{max}$ ) was an inconsistent parameter. MTV and TLG may help predict poor response to organ preservation to initiate early surgical salvage or modify therapeutic decisions to optimize clinical outcomes. Routine use may provide additional information over  $SUV_{max}$  alone.

**Keywords:** Fluorodeoxyglucose-positron emission tomography, fluorodeoxyglucose-positron emission tomography quantitative markers, head-and-neck squamous cell carcinoma, organ preservation

## Introduction

Locally advanced head-and-neck squamous cell carcinoma (HNSCC) radical treatment options are most often either radiation therapy with concurrent chemotherapy or surgery, depending on subsite, patient's performance status, comorbidities, and choice. Particularly in larynx, hypopharynx, and oropharynx, organ preservation protocols have been popularized which use a combination of radiotherapy with chemotherapy and/or biological agents<sup>[1]</sup> because of improved clinical outcomes when compared to the use of radiotherapy alone;<sup>[2]</sup> however, locoregional failure rates have been reported to be as high as 30%–50%<sup>[3]</sup> and these multimodal approaches are also associated with significant short- and long-term morbidity.<sup>[4]</sup> As a result, there has been an increasing interest in predicting response to treatment – factors that predict a poor response to treatment – and early identification of a

suboptimal therapeutic response would be valuable in ceasing or intensifying ineffective treatment early on, reducing the associated morbidity and, if possible, increasing the chance of cure. In organ preservation protocols, studies reflect that posttherapy fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) scans performed before 12 weeks have lower negative predictive value for detecting residual disease;<sup>[5]</sup> hence, to avoid this delay in detecting nonresponders, there has been an interest in predicting therapeutic response from pretreatment or early-treatment FDG-PET scans.<sup>[6,7]</sup>

## Clinical and Research Consequences

### Factors determining prognosis in advanced head-and-neck squamous cell carcinoma

The important clinical factors that determine the prognosis of HNSCC

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**Narayana Subramaniam, Deepak Balasubramanian, P Shanmuga Sundaram<sup>1</sup>, Samskruthi Murthy, Krishnakumar Thankappan, Subramania Iyer**

*Department of Head and Neck Oncology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, <sup>1</sup>Department of Nuclear Medicine, Amrita Institute of Medical Sciences, Amrita Vidyapeetham, Kochi, Kerala, India*

**Address for correspondence:**  
Dr. Deepak Balasubramanian,  
Department of Head and Neck Oncology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.  
E-mail: deepakbala@live.com

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include age and performance status, subsite, and tumor stage.<sup>[8]</sup> For laryngohypopharyngeal cancers, the major determinants for staging the tumor are vocal cord fixity, extralaryngeal spread, and cartilage invasion;<sup>[9]</sup> computed tomography (CT) may have difficulties in determining these in advanced tumors and magnetic resonance imaging (MRI) tends to overstage the tumor in the presence of inflammation, leading to poor specificity.<sup>[10-13]</sup> FDG-PET scans provide direct information on tumor metabolism; malignant tissues have been demonstrated to selectively upregulate glucose transporters, glut-1 and glut-3, and hexokinase activity, leading to increased glycolysis, the degree of which may be linked directly to the clinical behavior of the tumor.<sup>[14,15]</sup> Analysis of the uptake of 2-(<sup>18</sup>F)-FDG yields several parameters that yield clinical information, such as standardized uptake value (SUV), metabolic rate, inverse coefficient of variation, and others.

### **Influence of factors determining prognosis on management**

The importance of pretreatment prognostic indices seems to be in the prediction of disease-free survival and/or locoregional control, depending on which index is used.<sup>[16-18]</sup> By identifying tumors that are less likely to be locoregionally controlled, early discontinuation of suboptimal treatment may confer better outcomes. In addition, postchemoradiation FDG-PET scans have a high negative predictive value (up to 95%) but considerably lower specificity and positive predictive value; hence, an unequivocal response to treatment can be a considerable challenge.<sup>[19]</sup> Identifying patients likely to have locoregional failure may also lower the threshold for salvage surgery in these patients.

### **Integrating positron emission tomography use into routine management of head-and-neck squamous cell carcinoma**

The role of FDG-PET in HNSCC has been established in organ preservation therapy,<sup>[20-22]</sup> in a post-treatment setting for locoregionally advanced disease,<sup>[23,24]</sup> metastasis of unknown origin,<sup>[25]</sup> and for the detection of second primary tumors or recurrent disease.<sup>[26]</sup> Although pretreatment FDG-PET has shown increased sensitivity and specificity in staging HNSCC compared to conventional cross-sectional imaging, the reasons for its limited utilization in this setting may be attributed to its cost, poor anatomical resolution, and availability.<sup>[27]</sup> However, additional prognostic information conveyed by the use of FDG-PET may favor its use in certain clinical settings.

### **Positron Emission Tomography Quantitative Parameters**

#### **Maximum standardized uptake value**

Maximum SUV ( $SUV_{max}$ ) is the most common parameter used to estimate metabolic activity in FDG-PET CT, based

on the principle that malignant cells have increased FDG uptake compared to the surrounding tissue;<sup>[28]</sup> it has been shown to correlate with metabolic activity, proliferation, and, in some instances, even prognosis.<sup>[29]</sup> SUV is calculated by the expression  $SUV = r/(a'/w)$ , where  $r$  is radioactivity concentration in kBq/ml measured by the PET scanner within the region of interest,  $a'$  is the decay-corrected quantity of intravenous radiolabeled FDG tracer, and  $w$  is the weight of the patient in grams, which acts as a surrogate for total volume of distribution for the tracer. Hence, it is assumed that if the <sup>18</sup>FDG is distributed evenly throughout the body the SUV will be 1. The  $SUV_{max}$  refers to the maximum SUV in the region of interest.

In head-and-neck cancers specifically, the role of  $SUV_{max}$  has been studied extensively. Schwartz *et al.*<sup>[30]</sup> showed that HNSCC patients undergoing definitive radiotherapy (including postoperative adjuvant radiation) with or without chemotherapy with a pretreatment  $SUV_{max}$  of >9 had poorer local control and disease-free survival. Torizuka *et al.*<sup>[31]</sup> showed that pretreatment  $SUV_{max}$  over 7 was associated with worse 2-year local control rates and disease-free survival. Similar data showed a general prognostic trend but were not potentially practice altering; subsequent studies were focused on identifying response to treatment to predict candidates whose treatment was likely to fail, in order to escalate or change the treatment modality. This was demonstrated by altering the timing of FDG-PET CT evaluation.

Brun *et al.*<sup>[6]</sup> performed 2 FDG-PET CTs: one pretreatment and the second on average after delivery of 24 Gy and compared the two. There was a statistically significant difference between complete remission, overall survival, and locoregional control rate between the low and high values of metabolic rate and  $SUV_{max}$ . They noted that metabolic rate was a superior index compared to  $SUV_{max}$ . These results, however, were not universal. Castaldi *et al.*<sup>[32]</sup> performed pretreatment, post 2-week treatment (early), and post 8 to 12-week treatment (late) PET CTs. They found no correlation with pretreatment or post 2-week treatment value, but post 8 to 12-week treatment ("late") scans with  $SUV_{max}$  over 8.7 were associated with lower rates of recurrence-free survival and disease-specific survival. Hentschel *et al.*<sup>[33]</sup> performed FDG-PET CT post 1 or 2 weeks' treatment, showing that a fall in  $SUV_{max}$  by 50% or more from the baseline was associated with improved locoregional control rates.

Cumulative data showed that  $SUV_{max}$  was a more complex parameter of tumor activity than initially thought; rather than an isolated prognostic factor, clinical implications were stronger when using it serially as a surrogate marker for an alteration in the metabolic activity of the tumor based on the response to treatment. Furthermore, these inconsistencies fueled the search for a more robust, reliable FDG-PET CT parameter to predict tumor response.

### Factors affecting standardized uptake value

The factors affecting SUV are broadly divided into biological, technological, and local factors.<sup>[34]</sup> Some of the biological factors include body weight and composition, body surface area, and respiratory movement; the first two may especially be relevant in patients on chemoradiation who may have significant weight loss. Technical factors have been eliminated to some extent by standardizing protocols, but it is recommended that serial PET evaluation is performed in the same center by the same machine, with the same dosage of FDG and the same interval between injection and imaging to minimize variability. Local factors may be especially relevant in a posttreatment setting – inflammation can mimic malignancy, especially in a postradiotherapy setting, producing an overestimation of tumor size or a false-positive result.

### Inconsistencies in using standardized uptake value as a parameter

The aforementioned factors may be the reason for the inconsistent performance of SUV. Hence, newer parameters were studied and several showed a more durable response when compared to  $SUV_{max}$ . Higgins *et al.*<sup>[35]</sup> showed in their study on 88 patients of primary oropharyngeal and laryngeal SCC that pretreatment FDG-PET CT-derived  $SUV_{mean}$  was associated with a decreased disease-free survival ( $P = 0.01$ ). They found no statistical significance between pretreatment  $SUV_{max}$  or total lesion glycolysis (TLG) and patient outcomes. A study by Schinagl *et al.*<sup>[36]</sup> reported  $PET_{vis}$  (a visual interpretation parameter from the PET) and  $GTV_{CT}$  (tumor volume as determined by CT) as the only parameters that could predict disease-free survival, distant metastasis-free survival, and overall survival, but  $SUV_{mean}$  and  $SUV_{max}$  could not. Their literature review further showed that out of a total of 15 studies that used  $SUV_{max}$  to predict treatment outcome, only 8 could establish a statistically significant relationship,<sup>[6,30,37-42]</sup> whereas 7 could not.<sup>[16,17,43-47]</sup> The reasons for this, besides those mentioned earlier, include considerable heterogeneity in treatment modalities, use of several varied end points, and the difference between  $SUV_{max}$  of the primary tumor and the lymph node metastases. Of the eight studies that showed statistical significance, 55% of the patients (227 patients) underwent primary surgery as treatment modality. From the existing data, the only definitive conclusion that can be drawn is that  $SUV_{max}$  is still unsubstantiated as a standalone parameter that can predict treatment response, either as a single value or even serially.

### Metabolic tumor volume

Metabolic tumor volume (MTV) is a fairly novel parameter, defined as the volume of tumor tissue that shows increased FDG uptake and represents both metabolic activity and three-dimensional volumetric data, unlike  $SUV_{max}$ . MTV is considered a more accurate marker of tumor metabolic

activity. MTV is defined as the hypermetabolic tissue within the region of interest that has an SUV of 2.5 or more. Although T-staging for larynx does not strictly include size of the tumor, there have been studies showing that tumor volume determined by imaging has a prognostic value,<sup>[48]</sup> making MTV an interesting tool to determine prognostication of HNSCC treated by chemoradiation. Hence, MTV was evaluated as a prognostic indicator by predicting locoregional control rates and recurrence rates and overall and disease-free survival in pre- and post-treatment settings.

Chung *et al.*<sup>[49]</sup> published one of the first studies on the role of MTV in predicting response to radiotherapy or chemoradiation in pharyngeal cancer. Their retrospective study was to determine the role of pretreatment FDG-PET-derived MTV values in 82 patients in predicting short outcome and disease-free survival. Their study demonstrated that, with an MTV of  $>40$  ml, there was a significantly lower chance of complete response (using RECIST criteria) or no recurrence. In a multivariate analysis, these patients also had a significantly lower disease-free survival. They found no correlation with outcomes and SUV. Interestingly, they were also able to derive a correlation between the range of MTV and each clinical T-stage and N-stage. The range of MTV for each clinical T-stage was wide (e.g.,  $cT_2$  ranged from 6.68 to 67.1 ml), possibly because of the third dimensional component of the tumor that cannot be assessed clinically. Furthermore, they found that with MTV, even if the tumor had a complete response to chemoradiation, patients tended to have a distant failure at a later date. They found that MTV did not have a correlation with SUV, and patients who had a high SUV but a low MTV had good clinical outcomes.

La *et al.*<sup>[43]</sup> studied the role of pretreatment MTV in predicting recurrence and/or death in locally advanced HNSCC. They showed that an increase of MTV by 17.4 ml was associated with a 1.9-fold increase in the likelihood of recurrence and a 2.1-fold increase in the likelihood of death. They also demonstrated a significant correlation between MTV and survival (both overall survival and disease-free survival). They found a significant correlation between MTV and GTV (gross tumor volume) but no relation between SUV and outcomes. Murphy *et al.*<sup>[50]</sup> studied 47 patients treated with radiotherapy or chemoradiation, who underwent pre- and posttreatment FDG-PET CT scans, and found that  $MTV_{2.0}$  (tumor volume having SUV threshold over 2.0) was a robust predictor of disease progression and death. Park *et al.*<sup>[51]</sup> in their study on 81 patients of advanced laryngohypopharyngeal tumors determined MTV and relation to 3-year locoregional and overall survival. They found that MTV was an independent prognostic factor for both. Nearly 58% of these patients, however, were treated with surgery. Their cutoff for MTV for risk stratification was also 18 ml.



**Table 1: Summary of studies showing positron emission tomography quantitative markers in prognostication of head-and-neck squamous cell carcinoma**

Parameter	Author	Cutoff	Number of patients	Subsite	Modality	Outcome parameter	
SUV <sub>max</sub>	Schwartz <i>et al.</i> <sup>[30]</sup>	9	63	OC, OP, L, HP	RT/CTRT	LC, DFS	
	Torizuka <i>et al.</i> <sup>[31]</sup>	7	50	OC, OP, L, HP	RT/CTRT/S	LC, DFS	
	Castaldi <i>et al.</i> <sup>[33]</sup>	8.7	26	OP, L, HP, NP	CTRT	RFS, DSS	
	Hentschel <i>et al.</i> <sup>[34]</sup>	Fall by 50%	37	OC, OP, L, HP	RT/CTRT	LRC, OS	
MR	Brun <i>et al.</i> <sup>[32]</sup>	16 ml	50	OC, OP, L, HP	RT+CT	CR, LRC, OS	
MTV	Chung <i>et al.</i> <sup>[49]</sup>	40 ml	82	OP	RT/CTRT	CR, OS	
	La <i>et al.</i> <sup>[43]</sup>	Increase in 17.4 ml	85	OP, NP	RT/CTRT	DFS, OS	
	Murphy <i>et al.</i> <sup>[50]</sup>	Increase in 18 ml	47	OP, NP	RT/CTRT	DFS, OS	
	Park <i>et al.</i> <sup>[51]</sup>	Increase in 17 ml	81	L, HP	RT/CTRT	LRC, OS	
	Tang <i>et al.</i> <sup>[52]</sup>	Increase in 17 ml	83	OC, OP, L, HP	RT	PFS, OS	
	Choi <i>et al.</i> <sup>[53]</sup>	Increase in 20.7 ml	56	OC, OP, L, HP	S	DFS, OS	
	TLG	Abd El-Hafez <i>et al.</i> <sup>[55]</sup>	71.4 ml	126	OC	S	DFS, OS
		Lim <i>et al.</i> <sup>[56]</sup>	Doubling	176	OC	CTRT	DFS, OS
Hanamoto <i>et al.</i> <sup>[57]</sup>		145	118	OP, NP, L, HP	CTRT	CR	

All of these studies show statistical significance. SUV<sub>max</sub> – Maximum standardized uptake volume; MR – Metabolic rate; MTV – Metabolic tumor volume; TLG – Total lesion glycolysis; OC – Oral cavity; OP – Oropharynx; L – Larynx, HP – Hypopharynx; NP – Nasopharynx; RT – Radiotherapy; CTRT – Chemoradiotherapy; S – Surgery; LC – Local control; DFS – Disease-free survival; RFS – Recurrence-free survival; DSS – Disease-specific survival; CR – Complete response; OS – Overall survival; LRC – Locoregional control; PFS – Progression-free survival; PET – Positron emission tomography

Tang *et al.*<sup>[52]</sup> studied 83 patients of HNSCC before definitive radiotherapy. Their study had a similar MTV cutoff of 17 ml, above which the risks of recurrence and death were 2.1 and 2 times more likely, respectively. They also found that prognostic significance was only based on the MTV of the primary tumor and not on the nodal metastases. Choi *et al.*<sup>[53]</sup> studied 56 patients with locally advanced HNSCC treated by surgery. Their cutoff for MTV was also 20.7 ml. This correlated with disease-free survival and overall survival. Romesser *et al.*<sup>[54]</sup> compared SUV and MTV/GTV in 41 advanced HNSCC patients undergoing intensity-modulated radiotherapy. They found that GTV of under 22.2 ml had good 2-year locoregional control rates and overall survival compared to those above this value. The corresponding MTV was 7.2 ml.

Overall, MTV has been shown to be a significant predictor of outcome, in spite of variation in treatment modality, both in pre- and post-treatment settings. It has a durable response and in a majority of studies correlates well with GTV but has no correlation with SUV. It has consistently been used to predict short- and long-term outcomes, but has yet to be used for early identification of those likely to fail on organ preservation therapy for treatment intensification or change in treatment modality – further studies are required.

### Total lesion glycolysis

TLG is derived from the product of SUV with MTV. This overcomes the limitation of some SUV measurements such as SUV<sub>max</sub>, a single pixel measurement, and is likely to be an aggregate estimation of activity in the entire tumor, incorporating both volumetric and metabolic activities into a single parameter, like MTV.

Abd *et al.*<sup>[55]</sup> measured the TLG in 126 oral cavity SCC patients who were undergoing surgery. They formulated a scoring system in multivariate analysis which included primary tumor TLG >71.4 ml, nodal positivity, and nodal SUV<sub>max</sub> >7.5, and patients were assigned scores between 0 and 3. The patients with a score of 3 had a 32-fold higher risk of cancer death than patients with a score of 0. Furthermore, in patients who had a score of 3, the mean TLG tended to be higher among those survived <9 months, compared to those who survived at least 9 months. Lim *et al.*<sup>[56]</sup> reported SUV<sub>max</sub>, MTV, and TLG from 176 patients treated with chemoradiation. They demonstrated that MTV and TLG were independent predictors of mortality. Hanamoto *et al.*<sup>[57]</sup> analyzed 118 patients of HNSCC who underwent chemoradiation. They noted that high MTV (>25 ml) and high TLG (>144.8 g) were independent, significant predictors of incomplete response compared to lower values. Table 1 shows a summary of the aforementioned data.

### Discussion

A major hurdle to acceptance of pretreatment FDG-PET as a prognostic tool in patients with HNSCC undergoing organ preservation protocols has been heterogeneity in the design of studies and their findings. As newer FDG-PET parameters such as MTV and TLG were developed, the results became more homogeneous. Pak *et al.*<sup>[58]</sup> in their meta-analysis of 13 studies including 1180 patients reported that MTV and TLG were independent indicators of progression and recurrence. High SUV was also shown to be associated with a higher risk of death, but could not robustly predict either recurrence or progression. This was also shown by the meta-analysis of prognostic impact of SUV on outcomes in 1415 patients by Xie *et al.*<sup>[59]</sup>

In the era of organ preservation protocols, the role of posttreatment FDG-PET is established, while that of pretreatment FDG-PET is controversial; however, early prediction of response to treatment and prognosis may be a valuable aid in predicting treatment failures. Incorporation of PET into radiation planning may also be more feasible than it was previously, given the better quality of CT imaging used for fusion and the availability of MRI for fusion.

No studies have directly compared the FDG-PET parameters with need for surgical salvage; however, reduced locoregional control rates may be considered a surrogate marker for this. In addition, given recommendations that postoperative FDG-PET for organ preservation protocols should be performed at 12 weeks after completion of therapy,<sup>[60]</sup> identifying individuals with a poor prognosis may be important to prevent disease progression during this period.

From a prognostic standpoint, recent studies correlating FDG-PET findings with molecular biomarkers have shown promising results. Rasmussen *et al.*<sup>[61]</sup> in 100 cases of HNSCC showed that  $SUV_{max}$  had a negative correlation with Bcl-2 and p16 expression and a positive correlation with  $\beta$ -tubulin-1 levels. Han *et al.*<sup>[62]</sup> in 32 patients of T2 tongue demonstrated that  $SUV_{max}$  correlated well with HIF-1 $\alpha$ , a hypoxia-associated factor associated with radiation resistance. This work has led to increased understanding of tumor biology; however, clinical applications are still under investigation.

## Conclusion

Given the durability and safety profile of FDG-PET, availability and cost are likely major inhibitory factors preventing more widespread use. With increased access to this technology and a fall in cost, its use in prognostication and predicting response to organ preservation protocols in HNSCC seems reasonable, as planning surgical salvage early may reduce the extent and morbidity associated with surgery. Technical improvements have made the use of FDG-PET in radiotherapy planning more reliable and feasible. Further studies, especially correlation between FDG-PET parameters and the need for surgical salvage, may be valuable in refining this as a tool for more routine clinical practice.

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## Conflicts of interest

There are no conflicts of interest.

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