

Evaluation of the Prognostic Value of FDG PET/CT Parameters for Patients With Surgically Treated Head and Neck Cancer

A Systematic Review

Gwenaelle Creff, MSc; Anne Devillers, MD; Adrien Depeursinge, PhD; Xavier Palard-Novello, MD, PhD; Oscar Acosta, PhD; Franck Jegoux, MD, PhD; Joel Castelli, MD, PhD

Supplemental content

IMPORTANCE Head and neck squamous cell cancer (HNSCC) represents the seventh most frequent cancer worldwide. More than half of the patients diagnosed with HNSCC are treated with primary surgery.

OBJECTIVE To report the available evidence on the value of quantitative parameters of fluorodeoxyglucose F 18-labeled positron emission tomography and computed tomography (FDG-PET/CT) performed before surgical treatment of HNSCC to estimate overall survival (OS), disease-free survival (DFS), and distant metastasis (DM) and to discuss their limitations.

EVIDENCE REVIEW A systematic review of the English-language literature in PubMed/MEDLINE and ScienceDirect published between January 2003 and February 15, 2019, was performed between March 1 and July 27, 2019, to identify articles addressing the association between preoperative FDG-PET/CT parameters and oncological outcomes among patients with HNSCC. Articles included those that addressed the following: (1) cancer of the oral cavity, oropharynx, hypopharynx, or larynx; (2) surgically treated (primary or for salvage); (3) pretreatment FDG-PET/CT; (4) quantitative or semiquantitative evaluation of the FDG-PET/CT parameters; and (5) the association between the value of FDG-PET/CT parameters and clinical outcomes. Quality assessment was performed using the Oxford Centre for Evidence-Based Medicine level of evidence.

FINDINGS A total of 128 studies were retrieved from the databases, and 36 studies met the inclusion criteria; these studies comprised 3585 unique patients with a median follow-up of 30.6 months (range, 16-53 months). Of these 36 studies, 32 showed an association between at least 1 FDG-PET/CT parameter and oncological outcomes (OS, DFS, and DM). The FDG-PET/CT volumetric parameters (metabolic tumor volume [MTV] and total lesion glycolysis [TLG]) were independent prognostic factors in most of the data, with a higher prognostic value than the maximum standard uptake value (SUVmax). For example, in univariate analysis of OS, the SUVmax was correlated with OS in 5 of 11 studies, MTV in 11 of 12 studies, and TLG in 6 of 9 studies. The spatial distribution of metabolism via textural indices seemed promising, although that factor is currently poorly evaluated: only 3 studies analyzed data from radiomics indices.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that the prognostic effectiveness of FDG-PET/CT parameters as biomarkers of OS, DFS, and DM among patients with HNSCC treated with surgery may be valuable. The volumetric parameters (MTV and TLG) seemed relevant for identifying patients with a higher risk of postsurgical disease progression who could receive early therapeutic intervention to improve their prognosis. However, further large-scale studies including exclusively surgery-treated patients stratified according to localization and further analysis of the textural indices are required to define a reliable FDG-PET/CT-based prognostic model of mortality and recurrence risk for these patients.

Author Affiliations: Department of Otolaryngology-Head and Neck Surgery, Rennes University Hospital, Rennes, France (Creff, Jegoux); Department of Nuclear Medicine, Centre Eugène Marquis, Rennes, France (Devillers, Palard-Novello); University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland (Depeursinge); LTSI (Image and Signal Processing Laboratory), INSERM, U1099, Rennes, France (Acosta); Department of Radiation Oncology, Cancer Institute Eugène Marquis, Rennes, France (Castelli).

Corresponding Author: Gwenaelle Creff, MSc, Department of Otolaryngology-Head and Neck Surgery, Rennes University Hospital, 2 rue Henri Le Guilloux, F-35000 Rennes, France (gwenaelle.creff@chu-rennes.fr).

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Head and neck squamous cell cancer (HNSCC) represents the seventh most frequent cancer worldwide.¹ The American Joint Committee on Cancer (AJCC) staging is generally used to estimate prognosis and to guide therapy.

Treatment of HNSCC requires a multidisciplinary approach and involves either surgery alone or surgery followed by radiotherapy, with or without chemotherapy, or curative radiotherapy with concomitant chemotherapy or anti-epidermal growth factor receptor agents (eg, cetuximab). The percentage of patients treated with surgical resection varies according to the HNSCC anatomic site. Cancer of the oral cavity has the highest percentage of primary surgical resections (71.4%), whereas hypopharyngeal cancer has the lowest proportion (42.1%).²

Despite the therapeutic progress (robotic-assisted surgery, new molecular targeted therapies, and improvement in the radiotherapy fields), the prognosis remains poor and is related to a high recurrence rate of 30% to 40%.^{3,4} Thus, there is a real need to identify patients at high risk of recurrence to improve their therapeutic strategy.

Fluorodeoxyglucose F 18-labeled positron emission tomography and computed tomography (FDG-PET/CT) allows us to reveal the metabolic activity of a tumor (glycolysis) in addition to anatomic information. This examination is now commonly used to assess the extent of HNSCC⁵ and for the posttreatment follow-up⁶ based on a visual analysis.

Visual analysis is sufficient for diagnosis, staging, and the detection of recurrence; however, quantification appears necessary to estimate patient outcome. The commonly studied parameters are the standardized uptake value⁷ (SUVmax, SUVmean, or SUVpeak), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)⁸ (Table 1). In addition, owing to the emerging development of radiomics, which aims to decode the tumor phenotype and heterogeneity from imaging data,^{9,10} texture and shape analyses have started to be evaluated in terms of prognostic value.

Although the role of FDG-PET/CT in estimating survival of patients with HNSCC treated with radiochemotherapy has been examined in several studies,¹¹⁻¹³ fewer data are available for patients treated with surgery who present with different clinical and histological profiles. To our knowledge, there has been no review in the scientific literature focusing on the prognostic value of FDG-PET/CT in patients with HNSCC who have been treated surgically.

Thus, the aims of this review were to report the available evidence on the value of quantitative parameters of FDG-PET/CT performed before surgical treatment of HNSCC to estimate overall survival (OS), disease-free survival (DFS), and distant metastasis (DM) and to discuss their limitations.

Methods

Search Strategy

A systematic review was conducted between March 1 and July 27, 2019, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.¹⁴

We performed a systematic electronic search of English-language articles reporting data obtained on humans and published between January 2003 and February 15, 2019, in the MEDLINE/PubMed database and ScienceDirect without any tem-

Key Points

Question Is there an association between parameters of fluorodeoxyglucose F 18-labeled positron emission tomography and computed tomography (FDG-PET/CT) and prognosis among patients with surgically treated head and neck cancer?

Findings This systematic review of 36 studies that included 3585 unique patients highlights the prognostic value of FDG-PET/CT parameters, especially volumetric parameters, as biomarkers of overall survival, disease-free survival, and distant metastasis among patients with surgically treated head and neck cancer.

Meaning The findings of this review suggest that FDG-PET/CT parameters may be used to identify patients with a higher risk of postsurgical disease progression who could then receive early therapeutic intensification to improve their prognosis without increasing iatrogenic toxic effects; however, further research is required to define a reproducible, reliable FDG-PET/CT-based prognostic model of patients' mortality and recurrence risks.

Table 1. Most Frequently Used Quantitative Parameters in FDG Positron Emission Tomography and Computed Tomography

Parameter	Significance	Definition and method to measure
SUVmax	Maximum standard uptake value	Maximal voxel value in the tumor
SUVpeak	Peak standard uptake value	Mean SUV within a small, fixed-size ROI (ROIpeak) of 1.2-cm diameter centered on a high-uptake part of the tumor
SUVmean	Mean standard uptake value	Mean SUV in the ROI (defined by applying a threshold or by visual assessment)
MTV	Metabolic tumor volume	Sum of the volume of voxels with SUV exceeding a certain threshold value in a tumor, reflecting the volume of FDG activity in a tumor assessed by automated volume of interest delineation
TLG	Total lesion glycolysis	Obtained by multiplying MTV and the mean SUV of the MTV

Abbreviations: FDG, fluorodeoxyglucose F 18; ROI, region of interest; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

poral restriction and using the terms *positron emission tomography* or *PET* or *PET/CT* and *surgery* or *surgical treatment* or *tonsillectomy* or *salvage surgery* or *preoperative* or *laryngectomy* and *prognostic* or *prognosis* or *survival* and *head and neck cancer*.

We excluded studies selecting patients receiving a form of radiochemotherapy as a unique treatment or studies including patients treated with surgery and patients treated with radiochemotherapy in which the treatment appeared as a prognostic factor in univariate analysis or if an analysis in the surgical treatment subgroup had not been performed. We also excluded meta-analyses, systematic reviews, letters to the editor, and data obtained only from visual analyses of the FDG-PET/CT images because this review focuses on the prognostic value of parameters obtained from quantitative or semiquantitative analyses. Studies that included fewer than 15 patients were also excluded. References from review articles were checked for cross-reference. Identical studies were identified to avoid duplications.

PICO Criteria

The PICO criteria (patients, intervention, comparison, and outcome) for the review are given in Table 2.

Table 2. Description of the PICO Strategy

PICO criterion	Description
Patients	Patients with HNSCC treated with surgery (primary or for salvage), with at least 6 mo of follow-up, who underwent FDG-PET/CT before treatment
Intervention	Quantitative or semiquantitative analysis of preoperative FDG-PET/CT parameters
Comparison	Predictive value of FDG-PET/CT parameters
Outcome	Prognosis: overall survival, disease-free survival, distant metastasis

Abbreviations: FDG-PET/CT, fluorodeoxyglucose F 18-labeled positron emission tomography and computed tomography; HNSCC, head and neck squamous cell carcinoma.

Quality Assessment

The selected studies were assessed for risk of bias on the basis of the following 5 variables:

- Retrospective vs prospective study design
- Sufficient description of the modality to obtain the FDG-PET/CT parameters
- Uniform inclusion criteria
- Incomplete outcome data
- Number of patients included (studies with <15 patients were automatically excluded)

The risk of bias was classified as high if no was given for 3 or more criteria.

The level of evidence was scored according to the Oxford Centre for Evidence-Based Medicine level of evidence guide,¹⁵ as follows:

1. Systematic review of inception cohort studies
2. Inception cohort studies
3. Cohort study or control arm of randomized trial
4. Case series or case-control studies or poor-quality prognostic cohort study

Results

Among the 128 articles initially identified, 36 relevant studies published between January 2003 and February 15, 2019, with exploitable data were retained for analysis after exclusion of duplicates ($n = 11$) and inappropriate articles ($n = 81$) (eFigure in the [Supplement](#)). No randomized clinical trial on this topic was found in the literature; most were retrospective series (27 studies). In total, 3585 unique patients were included in the analysis from these 36 studies,¹⁶⁻⁵¹ with a median follow-up of 30.6 months (range, 16-53 months) (Table 3).

Overall Survival

Fourteen studies^{17-19,21,22,24,26-28,31,32,35,41,51} (826 unique patients) investigated the prognostic value of quantitative PET parameters on OS. Owing to its simplicity and interpretability, SUVmax was the first parameter analyzed. It was correlated with OS in 5 of 11 studies.^{18,19,22,24,27,28,31,32,35,41,51} In a prospective study including 53 patients with hypopharyngeal cancer,⁴¹ an SUVmax of 28.5 or higher (cutoff defined using the log-rank test) was associated with OS according to multivariate analysis (hazard ratio [HR], 3.94; 95% CI, 1.13-12.71) with adjustment for clinical T category and treatment group.

Recently, to take into account not only the value of 1 voxel but also the tumor volume, especially the heterogeneity, 2 other parameters were investigated: the MTV and TLG. In univariate analysis, the MTV was correlated with OS in 11 of 12 studies,^{17-19,22,26-28,31,32,35,41,51} and TLG was associated with OS in 6 of 9 studies.^{18,26-28,31,32,35,41,51} For instance, Kikuchi et al²⁷ reported data from 47 patients with oropharyngeal cancer, of whom 38% were treated with surgery; the authors showed that MTV and TLG were associated with OS (MTV: HR, 4.8; TLG: HR, 3.9), whereas SUVmax was not associated with OS (HR, 1.1). Ten studies performed multivariate analysis.^{17,18,22,26-28,31,32,41,51} Both MTV and TLG remained correlated with OS in 6 studies^{17,18,22,26,27,31} and 3 studies,^{18,32,41} respectively. All of these studies showed that MTV and/or TLG had a prognostic effect, most of them with a higher predictive value than SUVmax^{18,19,22,27,28,31,32,35,41} and even than the clinical parameters (TNM and AJCC stages).²²

Two studies analyzed the prognostic value of radiomic parameters in OS.^{21,26} In addition to histogram-based parameters (SUVmean, MTV, and TLG), 4 textural indices computed from gray-level co-occurrence matrices (correlation, entropy, energy, and coarseness) were evaluated among 284 patients.²⁶ According to multivariate analysis, MTV (HR, 1.012; 95% CI, 1.003-1.021) and correlation (HR, 4.506; 95% CI, 1.178-17.239) remained independently correlated with OS. Based on the data from 52 patients,²¹ only the shape matrix defined by asphericity, which measures the deviation of the tumor's shape from the shape of a sphere with the same volume, was associated with OS (HR, 6.4), whereas SUVmax (HR, 5.6), MTV or tumor stage (HR, 1.51; 95% CI, 0.33-6.99) were not correlated with OS in multivariate analysis.

Disease-Free Survival

Nineteen studies (1679 unique patients) specifically analyzed the FDG-PET/CT prognostic value in locoregional control, recurrence, and DFS.^{16-24,26-30,33-36,41}

The SUVmax was the most commonly studied parameter (18 studies^{16,18-24,26-30,33-36,41}), although only 6 of those studies found a correlation between SUVmax and DFS. Total lesion glycolysis was associated with locoregional control in approximately half of the studies (7 of 11 studies^{18,21,22,26-29,33-35,41}). In contrast, the MTV was associated with DFS in 12 of 14 studies.^{17-19,21-23,26-29,33-35,41}

For instance, the FDG-PET/CT data of 70 patients with HNSCC, half of whom were treated with surgery, were prospectively analyzed.²³ According to multivariate analysis, only the MTV and the retention index (a variation of SUVmax between FDG-PET/CT performed 1 hour and 2 hours after injection) were prognostic factors (MTV: HR, 0.247; 95% CI, 0.075-0.817; retention index: HR, 0.331; 95% CI, 0.152-0.721). In the specific population of 70 patients with human papillomavirus-positive oropharyngeal carcinoma, an MTV greater than 41 mL was also correlated with a poor DFS (HR, 1.02; 95% CI, 1.01-1.03).³⁴ Only 1 study (with 53 patients)⁴¹ did not show a correlation between the FDG-PET/CT parameters and DFS (SUVmax ≥ 28.5 : HR, 1.88; 95% CI, 0.51-12.10; MTV ≥ 12.00 cm³: HR, 1.27; 95% CI, 0.14-27.40; and TLG ≥ 12.00 g, HR, 1.14, 95% CI, 0.37-3.33).

Three studies^{21,26,29} analyzed the prognostic value of textural indices in DFS, and 2 studies^{21,29} found a correlation. Among 108 patients, a special uptake pattern, ring shape, was associated with DFS (HR, 12.47; 95% CI, 4.59-33.91) in multivariate analysis after corrections for TNM and definitive therapy.²⁹ The asphericity was also analyzed among 52 patients²¹ and was associated with DFS (HR, 7.70;

Table 3. Summary of Results of the 36 Studies That Analyzed the Prognostic Value of FDG-PET/CT Before Surgical Treatment

Source	No. of participants	Follow-up, mo	Localization	Treatment	End point	Quantitative PET/CT parameter ^a	Results	OCEBM score
Joo et al, ¹⁶ 2013	120	33	HNC NO	Primary surgery	DSS5	SUVmax	SUVmax >8.5: decreased DSS5 ^b	3
Choi et al, ¹⁷ 2011	56	33	HNC + CUP syndrome	Primary surgery	DFS, OS	SUVpeak, MTV 2.5	MTV >20.7 cm ³ : decreased OS and DFS ^b	3
Ryu et al, ¹⁸ 2014	105	44	Oral cavity	Primary surgery	OS, DFS, NM	SUVmax, MTV, TLG	MTV and TLG: independent predictive factor for OS (HR, 3.07; 95% CI, 1.54-6.13; HR, 3.50; 95% CI, 1.59-7.70); DFS (HR, 2.81; 95% CI, 1.53-5.18; HR, 2.97; 95% CI, 1.37-6.41); NM (HR, 4.75; 95% CI, 1.30-17.33; HR, 5.36; 95% CI, 1.46-19.60) ^b	3
Zhang et al, ¹⁹ 2014	80	21	Oral cavity	Primary surgery	DFS, OS	SUVmax, MTV 2.5	MTV >17.5 mL decreased DFS/OS	3
Joo et al, ²⁰ 2014	157	28	HNC	Neck dissection	DSS5	SUVmax	SUVmax N contralateral ≥ 2.5 : decreased DSS5 (HR, 1.05)	3
Apostolova et al, ²¹ 2014	52	26	HNC + nasopharynx	16.7% Primary surgery	OS, DFS	SUVmax, SUVmean, MTV, TLG, ASP	OS: high ASP (HR, 6.4); DFS: MTV (HR, 5.1); and ASP (HR, 11.6) ^b	3
Abgral et al, ²² 2014 ^c	80	51	HNC	45% Primary surgery	DFS, OS	SUVmax, SUVpeak, MTV 2-7 (0.5), 30%-40%-50%	MTV 5.0: predictive factor for DFS (HR, 6.18; 95% CI, 1.517-25.169) and OS (HR, 17.285; 95% CI, 1.957-152.642) ^b	2
Abgral et al, ²³ 2016 ^c	70	22	HNC	44% Primary surgery	DFS	SUVmax, RI, MTV 40%, %AMTV, TLG, % Δ TLG	RI (HR, 0.331; 95% CI, 0.152-0.721) and MTV (HR, 0.247; 95% CI, 0.075-0.817): prognostic factors for DFS ^b	2
Cacicido et al, ²⁴ 2017 ^c	58	31	HNC + nasopharynx + CUP syndrome	36.2% Primary surgery	OS, DFS, LRC, DM	SUVmax	SUVmax N >5.4: increased risk for DM (HR, 3.3; 95% CI, 1.17-9.25) ^b	2
Chung et al, ²⁵ 2016	85	48	Oropharynx	Primary surgery	DM	SUVmax	SUVmax >9.7: increased risk for DM (HR, 57.713; 95% CI, 2.243-1484.920)	3
Guezennec et al, ²⁶ 2019	284	24	HNC + nasopharynx	22% Primary surgery	RFS, OS	SUVmax, SUVmean, MTV 40%, TLG, correlation, entropy, energy, coarseness	MTV (HR, 1.012; 95% CI, 1.003-1.021) and correlation (HR, 4.506; 95% CI, 1.178-17.239): associated with OS ^b	3
Kikuchi et al, ²⁷ 2015	47	30	Oropharynx	38% Primary surgery	DFS, DSS, OS	SUVmax, MTV 2 SDs, TLG	MTV total >65 cm ³ : associated with DFS, DSS, and OS ^b	3
Kim et al, ²⁸ 2016	86	48	Oropharynx	Primary surgery	DFS, OS, LRC, DM	SUVmax, MTV 40%, TLG	MTV T >21.3/MTV N >10.8/TLG T > 133.9: prognostic factors for DFS/DM ^b	3
Koyasu et al, ²⁹ 2014	108	36	HNC	30.6% Primary surgery	DFS, DSS	Uptake pattern, SUVmax, MTV 2 SDs, TLG	MTV >20 cm ³ (HR, 5.55; 95% CI, 1.26-24.43) and uptake pattern (ring shape, HR, 12.47; 95% CI, 4.59-33.91): associated with DSS ^b	3
Allal et al, ³⁰ 2004 ^c	120	48	HNC + CUP syndrome	39% Primary surgery	LC, DFS	SUVmax	SUVmax >3.5: associated with LC (RR, 0.16; 95% CI, 0.03-0.69) and DFS (RR, 0.39; 95% CI, 0.17-0.85) ^b	2
Lee et al, ³¹ 2012	57	45	Tongue NO	Primary surgery	OS	SUVmax; SUVmean; MTV 2.5/3/3.5/4; TLG	MTV >7.78 cm ³ (HR, 2.698; 95% CI, 1.083-6.721): prognostic factor for OS ^b	3
Moon et al, ³² 2013	69	26	Tonsil	39.1% Primary surgery	OS	SUVmax, SUVmean, MTV 2 SDs, TLG	TLG (HR, 1.020; 95% CI, 1.003-1.037): predictive factor associated with OS ^b	3
Abd El-Hafez et al, ³³ 2013 ^c	126	31	Oral cavity	Primary surgery	DFS, DSS2	SUVmax; MTV 2.5/3/3.5/4; MTV 30%/40%/50%/60%/70%; TLG	TLG T 3.0 \geq 71.4 and SUVmax N \geq 7.5: prognostic factors for DSS2 (HR, 3.3; 95% CI, 1.5-6.9 and HR, 2.3; 95% CI, 1.1-4.6) ^b	2
Alluri et al, ³⁴ 2014	70	25	Oropharynx stage III/IV	18.6% Primary surgery	DFS	SUVmax, SUVmean, SUVpeak, MTV, TLG	MTV total and MTV T: associated with DFS ^b	3
Kim et al, ³⁵ 2011	100	29	HNC + nasopharynx + sinus	Primary surgery	LRC, DFS, OS	SUVmax, MTV 2.5, TLG	MTV >41 mL: negative prognostic factor for DFS (HR, 2.391; 95% CI, 1.037-5.511)	3
Joo et al, ³⁶ 2013	42	38	Larynx	Primary surgery	Paraglottic space invasion, LRC, DSS5	SUVmax	SUVmax T >7 and SUVmax N >2.2: associated with LRC and DSS5	3

(continued)

Table 3. Summary of Results of the 36 Studies That Analyzed the Prognostic Value of FDG-PET/CT Before Surgical Treatment (continued)

Source	No. of participants	Follow-up, mo	Localization	Treatment	End point	Quantitative PET/CT parameter ^a	Results	OCEBM score
Zhang et al, ³⁷ 2018	148	NA	Oral cavity	Neck dissection	NM	SUVmax	SUVmax >2.5: high NPV for occult NM (99.1% in patients with small volume OCSCC)	3
Lowe et al, ³⁸ 2019 ^c	287	NA	HNC	Neck dissection	NM	SUVmax	SUVmax >1.8: optimal cutoff to predict NM (0.942; 95% CI, 0.93-0.953)	2
Chaulhan et al, ³⁹ 2012 ^c	49	NA	HNC	Neck dissection	NM	SUVmax	SUVmax scores 3 and 4 on the 5-point scale FDG uptake: predict NM (PPV = 93.5%)	2
Ozer et al, ⁴⁰ 2012	243	NA	HNC + CUP syndrome	Neck dissection	NM	SUVmax	SUVmax >2.5 does not appear to offer an advantage in staging the clinically NO neck	3
Suzuki et al, ⁴¹ 2016 ^c	53	34	Hypopharynx	36% Primary surgery	OS, LRC, DM	SUVmax, SUVpeak, MTV 45%, TLG	SUVmax ≥28.5 and TLG ≥42 g: associated with OS time	2
Suzuki et al, ⁴² 2018	51	48	HNC	Salvage surgery	OS, DSS, DM, LM	SUVmax, SUVmean, MTV 45%, TLG	TLG ≥42 g: correlated with DM ^b	3
Choi et al, ⁴³ 2019	71	16	Oral cavity	Salvage surgery	OS, DFS	SUVmax, SUVmean, SUVpeak, MTV 2.5, TLG	TLG >5.4 g: correlated with shorter OS, DSS, DM, LM ^b	3
Kim et al, ⁴⁴ 2016	78	53	HNC	Salvage surgery	OS, DFS 3	SUVmax	MTV >8.8 and TLG >29.4: predictive of both DFS (HR, 4.37; 95% CI, 2.29-8.32; HR, 3.52; 95% CI, 1.86-6.68, respectively) and OS (HR, 5.71; 95% CI, 2.86-11.29; HR, 6.03; 95% CI, 3.03-11.99, respectively) ^b	3
Lee et al, ⁴⁵ 2018	100	36	Larynx + hypopharynx	Salvage surgery	OS, DFS 2	SUVmax, SUVmean, SUV peak, MTV 2.5, TLG	SUVmax ≥4.4: correlated with OS (HR, 4.25; 95% CI, 1.54-11.74) and DFS 3 (HR, 4.79; 95% CI, 2.02-11.32); there was no clinically relevant difference in OS with and without salvage surgery (60.0% vs 55.6%)	3
Yi et al, ⁴⁶ 2012 ^c	82	38	HNC	Salvage surgery	DM	SUVmax	MTV >6.5 mL and TLG >17.1 g: predictive of DFS 2; SUVmax >4.0 and TLG >17.1 g: prognostic factors for OS ^b	3
Fakhry et al, ⁴⁷ 2012	37	19	HNC + nasopharynx + sinus	Salvage surgery	DM	SUVmax	PET/CT may be useful in the detection of DMs prior to salvage surgery in the high-risk patients with recurrent HNSCC (NPV, 97%)	2
Morand et al, ⁴⁸ 2018	71	21	Oral cavity	Primary surgery	LRC, NM	SUVmax, MTV 42%, TLG	PET/CT does not appear to offer a first-choice technique for the detection of DM before salvage surgery (PPV, 74%, NPV, 97%)	3
Rosko et al, ⁴⁹ 2017	46	NA	Larynx	Salvage surgery	NM	SUVmax	SUVmax ≥9.5: predictor of occult NM disease for cNO patients ^b ; LC: SUVmax ≥2.5 and TLG ≥28.4 g: had a higher risk of local recurrence	3
Gilbert et al, ⁵⁰ 2012	269	NA	Larynx	Salvage surgery	NM	SUVmax	PET/CT is an imperfect predictor of NM in recurrent laryngeal cancer (PPV, 66.7%, NPV, 76.7%)	3
Suzuki et al, ⁵¹ 2018	28	45	Oral cavity	Primary surgery	OS, LRC, DFS, DM	Tumor and node: SUVmax, SUVpeak, MTV, TLG	PET/CT could not correctly predict occult NM before salvage laryngectomy (NPV, 62.5%)	3

Abbreviations: ASP, asphericity; CUP, carcinoma of unknown primary; DM, distant metastasis; DFS, disease-free survival; DSS, disease-specific survival; DSS2, DSS at 2 years; DSS5, DSS at 5 years; FDG-PET/CT, fluorodeoxyglucose F 18-labeled positron emission tomography and computed tomography; HNC, head and neck cancer; HR, hazard ratio; LC, local control; LM, lung metastasis; LRC, locoregional control; MTV, metabolic tumor volume; N, node; NA, not applicable; NM, nodal metastasis; NPV, negative predictive value; OCEBM, Oxford Centre for Evidence-Based Medicine; OCSCC, oral cavity squamous cell carcinoma; OS, overall survival; PPV, positive predictive value; RFS, recurrence-free survival; RI, retention index; RR, risk ratio; SUV, standard uptake value; T, tumor; TLG, total lesion glycolysis.

^a An entry of "MTV 2 SDs" indicates that the MTV was determined by using a delineation with an absolute threshold of SUV equal to the aortic arch SUV mean plus 2 SDs; MTV 2.5 indicates that MTV was measured using a delineation with an absolute threshold of SUV at 2.5; MTV2-7 (0.5) indicates that MTV was determined using a delineation with an absolute threshold of SUV ranging from 2 to 7 in steps of 0.5; MTV 30%-40%-50% indicates that MTV was determined using a delineation with a relative threshold of SUVmax at 30% of SUVmax, 40% of SUVmax and 50% of SUVmax; and %Δ (MTV or TLG) corresponds to the percentage variation of MTV and TLG between the measures taken at an early PET/CT (1 hour after injection) and at a delayed PET/CT (2 hours after injection).

^b Results from multivariate analysis.

^c Prospective study.

95% CI, 2.71-22.27), whereas tumor stage was not (HR, 1.37; 95% CI, 0.39-4.85).

Distant Metastasis

Four studies^{24,25,28,41} analyzed the association of prognostic FDG-PET/CT with DM. Two studies^{28,41} showed a higher prognostic value of DM for MTV and TLG compared with SUVmax.

Among 86 patients with p16-positive oropharyngeal cancer,²⁸ the MTV measured on the tumor site (MTV T) and on the lymph node (MTV N) as well as tumor TLG were associated with higher DM rates (MTV T: HR, 1.05; 95% CI, 1.00-1.10; MTV N: HR, 1.09; 95% CI, 1.03-1.16; and tumor TLG: HR, 1.01; 95% CI, 1.00-1.02). We did not find any study focused on the prognostic value of textural indices on the DM rate.

Anticipating Nodal Relapse

The value of FDG-PET/CT studies in forecasting occult nodal metastasis in clinically node-negative neck (cNO) HNSCC was evaluated in 9 articles involving 1294 unique patients.^{18,20,37-40,48-50}

In a prospective multicentric study of 287 patients with T2 to T4 HNSCC cNO, an optimal SUVmax cutoff of 1.8 was found to be associated with occult nodal metastasis (negative predictive value [NPV], 0.942; 95% CI, 0.930-0.953). The surgical treatment plan was then changed in 22% of patients (14% had additional nodal levels and 5% had fewer).³⁸ Similarly, an SUVmax of 9.5 or higher was the only independent risk factor for occult metastatic disease for cNO oral cavity cancer and was associated with a consequential higher risk of local recurrence.⁴⁸

The prognostic value of SUVmax was shown among 157 patients with HNSCC and unilateral node metastasis.²⁰ A contralateral lymph node SUVmax of 2.5 or higher was associated with contralateral lymph node metastasis (HR, 3.28; 95% CI, 0.85-5.71) and had a clinically meaningful adverse effect on the 5-year disease-specific survival rate (HR, 1.05).

The FDG-PET/CT volumetric parameters (MTV and TLG) were also associated with a higher risk of occult nodal metastasis (odds ratios [ORs], 4.75; 95% CI, 1.30-17.33 and 5.36; 95% CI, 1.46-19.6, respectively) among 105 patients with cNO oral cavity cancer.¹⁸

Before Salvage Surgery

The prognostic value of FDG-PET/CT before salvage surgery was analyzed in 6 studies.⁴²⁻⁴⁷ According to univariate analysis, 4 studies⁴²⁻⁴⁵ showed an association between SUVmax and OS and DFS, and 3 studies also found that they were associated with FDG-PET/CT volumetric parameters (MTV and TLG).^{42,43,45} According to multivariate analysis, SUVmax did not remain a prognostic factor, whereas the MTV persisted as one in 2 studies^{43,45}; TLG remained a prognostic factor in all of the studies. For instance, before 51 salvage surgeries in patients with laryngeal and pharyngeal cancer,⁴² after multivariate analysis with adjustment for clinical stage, only TLG of 5.4 or higher was found to be associated with shorter OS (HR, 3.14; 95% CI, 1.04-11.57), whereas an MTV of 2.4 or higher (HR, 1.92; 95% CI, 0.75-4.88) and SUVmax (HR, 3.4; 95% CI, 0.51-13.86) were not. The cutoff values of FDG uptake parameters were ascertained by the lowest-*P* value method. Although no clinically relevant difference was noted in locoregional recurrence-free survival, TLG was also associated with DFS, DM, and lung metastasis-free survival. The prognostic values of MTV and SUVmax were not investigated in terms of these 4 end points.

The prognostic value of FDG-PET/CT in DM before salvage surgery was also shown in 2 other studies.^{46,47} Among 82 patients with suspected recurrent HNSCC, an association between a high SUVmax and DM was found (NPV 0.97; 95% CI, 0.88-0.99).⁴⁶ Only the SUVmax was analyzed in these 2 studies.

Discussion

In the era of personalized medicine in oncological development, the lack of reliable and available prognostic molecular biomarkers limits the evolution of therapeutic strategies in HNSCC, except for human papillomavirus status with the new staging system.⁵² Owing to the technological progress and the recent increase in radiomics, the potential for imaging as a comprehensive tumor biomarker has begun to be highlighted.⁵³

The FDG-PET/CT prognostic value in patients with HNC treated with radiochemotherapy has been the subject of several recent publications. In the results of this review, it also appears to be relevant for those treated with surgery (32 of the 36 studies included found a correlation).

Nevertheless, 27 of the 36 studies included patients exclusively treated with surgery, and only 17 studies focused only on primary surgery without taking into account salvage surgical treatment. When these patients received different treatments, they showed different clinical and tumoral characteristics. Thus, we can legitimately wonder whether these prognostic value results are generalizable. This is why among the 128 studies initially identified and among those that included patients treated with surgery and radiochemotherapy, we only kept those for which the treatment did not appear as a prognostic factor in univariate analysis^{21-24,27,29,32,34} or for which an analysis in the surgical treatment subgroup had been performed.^{26,30,41} The others^{54,55} were systematically excluded.

Similarly, we excluded the studies including patients with non-mucosal HNSCC.^{56,57} However, we noticed that 19 studies included patients without distinction of the different localizations of HNC (oropharynx, hypopharynx, oral cavity, larynx), and this parameter was almost never taken into account for the statistical analysis.

These two points raise concerns about the value of the results, especially when the cutoff measurement of the analyzed FDG-PET/CT parameters is the median of the population included, which leads to major differences in the values found between studies. Moreover, we wonder if it would not be more relevant to assess the cutoff point by optimizing the correlation with clinical outcome (eg, Cox model).⁵⁸ In addition, according to survival analysis, dichotomizing the population into 2 groups of risk regarding a cutoff point could introduce measurement error and reduce the ability to detect a correlation.⁵⁹ Instead of categorizing continuous variables, keeping them continuous with linear regression is relevant.⁶⁰

Moreover, the way to define the volumetric PET parameters is discussed. Even though SUVmax is the most commonly used parameter, we showed that the volumetric parameters presented a higher prognostic value for OS, DFS, and DM (Table 3 and Table 4), probably because they take into account not only the value of 1 voxel but also the overall tumor uptake. Nevertheless, to be used, these volumetric parameters need a specific delineation that can be based on 4 techniques: a threshold of SUV (absolute [all voxels with an SUV value > *x*], relative [>*x*% of SUVmax], or adaptive), gradient-based, clustering, or statistical methods, and no consensus has currently been

Table 4. Association Between Positron Emission Tomography Parameters and Clinical Outcome in Univariate and Multivariate Analyses

Outcome	No. of positive studies/No. of total studies (%)			
	SUVmax	MTV	TLG	Texture
Univariate analysis				
OS	5/11 (45)	11/12 (92)	6/9 (67)	2/2 (100)
DFS	6/18 (34)	12/14 (86)	7/11 (64)	2/3 (67)
DM	2/4 (50)	2/2 (100)	2/2 (100)	0
Multivariate analysis				
OS	1/4 (25)	6/10 (60)	3/8 (38)	NA
DFS	2/10 (20)	10/10 (100)	3/7 (43)	NA
DM	0/2	2/2 (100)	2/2 (100)	NA

Abbreviations: DFS, disease-free survival; DM, distant metastasis; MTV, metabolic tumor volume; NA, not applicable; OS, overall survival; SUVmax, maximum standard uptake value; TLG, total lesion glycolysis.

found.⁶¹ Of the 26 studies analyzing the volumetric parameters, only 5 studies^{21,22,31,33,34} did not use an automatic threshold of SUV equal to 2.5 or approximately 40% for the value of the threshold.

Textural indices that take into account the relationships between voxels begin to be relevant for prognostic value and are perhaps even better than volumetric indices. In fact, among 470 patients with p16-negative oropharyngeal cancer treated with primary radiochemotherapy, the overall concordance index for DFS in the PET/CT textural indices model (heterogeneity, SUV entropy, irregularity, and asphericity) was higher than that for clinical stage, performance status, SUVmax, and MTV.⁶² Nevertheless, we found only 3 radiomics studies analyzing data from patients treated with surgery, and those studies also included patients treated with radiochemotherapy (accounting for 16.7%, 22%, and 30.6% of the patients who received surgical treatment).

The most common cause of therapy failure in patients with HNSCC is undetected DM.⁶³ The RTOG 9501 study⁶⁴ reported a DM rate of 19.3% to 21.2% in patients treated for locally advanced HNC. The chance of curing them is very low when DM occurs, and OS decreases dramatically.⁶⁵ Nevertheless, we found only 4 studies^{24,25,28,41} analyzing the prognostic value of FDG-PET/CT factors for DM, and none of those studies analyzed the association between textural indices and DM.

The management of clinically node-negative neck cancer is controversial. The presence of cervical lymph node metastasis is an important prognostic factor for HNC; as Mamelle et al⁶⁶ showed among 914 patients with HNSCC, the number of positive nodes was an independent prognostic factor for survival in multivariate analysis. Although neck dissection is an effective procedure to eradicate positive nodes, the morbidity rate of this procedure is not negligible (approximately 30%⁶⁷). Therefore, it would be interesting to better detect positive nodes to adapt therapeutic strategies. The use of FDG-PET/CT appears to be more accurate than CT alone or ultrasonography, with a sensitivity of 71.43% vs 23.8% and 4.76%, respectively; a specificity of 96.67%, 93.33%, and 93.33%, respectively; a positive predictive value of 93.5%, 71.0%, and 33.33%, respectively; and an NPV of 82.85%, 63.63%, and 58.33%, respectively, among 51 neck dissections.³⁹

Furthermore, the prognostic value of occult nodal metastasis in cNO seems to be found before salvage surgery. Kim et al⁶⁸ showed the superiority of FDG-PET/CT against CT and/or MRI in detecting residual nodal disease among 39 patients before salvage surgery for HNC, with a sensitivity of 89% (95% CI, 74%-96%) and specificity of 95% (95% CI, 73%-99%) for FDG-PET/CT vs a sensitivity of 76%

(95% CI, 58%-88%) and specificity of 74% (95% CI, 48%-90%) for CT and/or MRI. Nevertheless, this result is not highlighted before salvage surgery for recurrent laryngeal cancer.^{49,50} In fact, among 46 patients with recurrent laryngeal cancer cNO, FDG-PET/CT obtained a sensitivity of only 16.7% (95% CI, 3.5%-46.0%) and an NPV of 76.7% (95% CI, 62.1%-87.0%).⁴⁹

Surgical salvage is associated with high complication and morbidity rates.⁶⁹ Thus, it is interesting to select patients before undergoing such surgery, with the aim of improving the survival rate.⁷⁰ However, only 3 studies focused on the prognostic value of FDG-PET/CT volumetric parameters before salvage surgery.^{42,43,45}

In this review, PET coupled with CT appears to have an interesting prognostic value among patients with HNSCC treated with surgery. In addition, PET coupled with magnetic resonance imaging, even if it is a less commonly used technique, appears to be a promising research path. Among 72 patients who underwent PET/magnetic resonance imaging before surgery, MTV (HR, 3.06; 95% CI, 1.31-7.13), the ratio of MTV to the apparent diffusion coefficient (ADC) (HR, 3.12; 95% CI, 1.31-7.48), and the TLG:ADC ratio (HR, 4.33; 95% CI, 1.72-10.87) were independent prognostic factors of DFS.⁷¹

This FDG-PET/CT prognostic value should be further biologically interpreted. In fact, among 33 patients with HNSCC included prospectively to investigate the safety and activity of cetuximab during preoperative treatment, the FDG-PET/CT response was correlated with residual tumor cellularity in the surgical specimens ($r = 0.84$), and there was a trend toward downregulation of Ki67.⁷² In that study, the authors noted an important decrease in Ki67 expression and/or low tumor cellularity without any clinically meaningful modification of the tumor size; thus, FDG-PET/CT appeared to be more accurate than conventional imaging for detecting tumor evolution.

Conclusions

To our knowledge, this is the first systematic review focusing on the prognostic effectiveness of FDG-PET/CT parameters as biomarkers of OS, DFS, and DM among patients with HNSCC treated with surgery (primary or for salvage). We noted a promising role of the volumetric parameters (MTV and TLG) for identifying patients with a higher risk of postsurgical progression who could receive early therapeutic intervention to improve their prognosis. However, additional large-scale studies that include patients exclusively treated with surgery are stratified according to localization, and focus on the textural indices are necessary to obtain conclusive results.

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