Systematic Review and Meta-Analysis

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Effectiveness of FDG-PET/CT for evaluating early response to induction chemotherapy in head and neck squamous cell carcinoma

A systematic review

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Abstract

Background: ^{18}F-Fluoro-Deoxy-Glucose Positron Emission Tomography with Computed Tomography (^{18}F-FDG PET/CT) may be a powerful tool to predict treatment outcome. We aimed to review the effectiveness of ^{18}F-FDG PET/CT in the assessment of early response to induction chemotherapy (IC) in patients with advanced Head and Neck Squamous Cell Cancer (HNSCC) without previous treatment.

Methods: PubMed, Cochrane Library, Science Direct and Web of Science were searched to May 2016. Reference lists of the included articles and additional studies identified by one nuclear medicine expert were screened for potential relevant studies that investigated the effectiveness of ^{18}F-FDG PET/CT performed before and after IC. Three authors independently screened all retrieved articles, selected studies that met inclusion criteria and extracted data. The methodology of the selected studies was evaluated by using the risk of bias checklist of the Agency for Healthcare Research and Quality (AHRQ).

Results: Seven out of 170 eligible studies met our inclusion criteria. A total of 207 advanced HNSCC patients were evaluated with ^{18}F-FDG PET/CT at baseline and after IC in the selected articles. Six from seven studies concluded that ^{18}F-FDG PET/CT allowed early evaluation response to IC and predicted survival outcomes.

Conclusion: The present systematic review confirms the potential value of ^{18}F-FDG PET/CT as a diagnostic tool for early IV response assessment in HNSCC patients. However, the lack of standard definitions for response criteria and heterogeneous IC protocols indicate the need to further studies in order to better define the role of ^{18}F-FDG PET/CT in these patients.

Abbreviations: ^{18}F-FDG PET/CT = ^{18}F-Fluoro-Deoxy-Glucose Positron Emission Tomography with Computed Tomography, AHRQ = Agency for Healthcare Research and Quality, AUC = Areas Under the Curves, CR = Complete Responde, CRT = Chemoradiotherapy, CT = Computed Tomography, EFS = Event-Free Survival, EORTC = European Organization for Research and Treatment of Cancer, GTV = Gross Tumoral Volume, HNSCCC = Head and Neck Squamous Cell Cancer, IC = Induction Chemotherapy, MRI = Magnetic Resonance Imaging (MRI), MTV = Metabolic Tumoral Volume, PR = Partial Response, PRISMA = Preferred Reporting Items for Systematic Reviews, RECIST = Response Evaluation Criteria in Solid Tumors, SUV_{max} = Maximum Standard Uptake Value, TLG = Total Lesion Glycolysis.

Keywords: FDG PET/CT, head and neck cancer, induction chemotherapy, systematic review

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1. Introduction

Head and neck cancers are a group of neoplasias that arise from the oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), and larynx. The most common histologic type is squamous cell carcinoma (HNSCC).[1] HNSCC is the sixth most common malignancy worldwide[2] and account for approximately 4% of all diagnosed malignancies.[3] The incidence is rapidly increasing due to tobacco and alcohol consumption, which are the most important risk factors. The human papillomavirus (HPV) in commonly related to oropharynx tumors, which shows a distinct response pattern to chemotherapy and radiotherapy.[3,4]

The assessment of the tumor extension is of paramount importance to provide cost-effective treatments.[5] The standard conventional imaging modalities for evaluating patients with HNSCC are computed tomography (CT) and magnetic resonance imaging (MRI). However, these methods are based on morphologic criteria and do not allow information of disease activity such as ^{18}F-fluoro-deoxy-glucose positron emission

tomography with CT (^{18}F-FDG PET/CT).[5] In this scenario, FDG PET/CT has been used for initial staging of head and neck cancer, restaging, detection of metastases, detection of unknown primary tumors presented with cervical metastases,[6] radiotherapy planning, and on the assessment of response to chemotherapy and radiotherapy.[7–9]

Treatment strategies for locally and advanced HNSCC have greatly changed in the past 20 years with an increase in the use of organ-preserving protocols, which combine radiotherapy with chemotherapy (chemoradiotherapy, CRT) and/or biological molecules in advanced stages. When compared with radiotherapy alone, the multimodality approach has shown higher tumor response rates and has significantly improved local control and outcome.[10]

HNSCC is a highly responsive malignancy at initial presentation[1] and induction chemotherapy (IC) before definitive CRT may reduce distant failure rates.[11] Several reports have revealed that HNSCC patients achieving a clinical complete response (CR) or partial response (PR) after IC had better survival rates than those with residual disease.[12] IC has been increasingly used, especially in cases in which a delay occurs between the definitive diagnosis and the beginning of CRT or surgery.[13] Furthermore, IC before CRT could lead to a better local control of advanced HNSCC stages (III and IV) but with an increased risk of acute toxicity. Early assessment of therapeutic efficacy is a key issue when considering the benefit of escalation in a nonresponder population or to avoid unnecessary toxicity and costs of ineffective treatment.[14]

Conventional diagnostic imaging modalities, such as CT and MRI, have been used for response evaluation of IC, and the RECIST Criteria (Response Evaluation Criteria in Solid Tumors) by anatomical parameters are widely accepted.[15] Some authors highlighted the limitations of anatomic imaging using RECIST and noted the benefits of metabolic tumor response assessment with ^{18}F-FDG PET/CT.[16–19] The early assessment of tumor response by ^{18}F-FDG PET/CT performed during therapy has been established for some tumors and has been recently proposed for others solid tumors. Several studies have shown that predictions of survival prognosis might be possible using the FDG PET/CT-based IC response evaluation in carcinoma of the esophagus,[20] stomach,[21] lung,[22] and ovarian.[23] The aim is to avoid overtreatment or ineffective treatment, to reduce acute and late side effects, and finally to improve the outcome.[24] Therefore, the evaluation of IC response by ^{18}F-FDG PET/CT has an important clinical use in predicting survival prognosis in HNSCC patients.[25]

Despite of the advances in multimodality therapy and technical delivery of radiotherapy for locally advanced HNSCC, outcomes remain suboptimal with survival rates of 50% to 60% in 5 years.[25] Despite aggressive combined modality treatment regimens (surgery, radiotherapy, and chemotherapy), HNSCC still shows high rates of recurrence, particularly because the majority of patients harbor advanced disease at presentation,[26] commonly involving regional lymph node metastasis.[1] Therefore, the purpose of this systematic review is to determine the locally advanced HNSCC patient's response to IC by ^{18}F-FDG PET/CT.

2. Methods

2.1. Protocol

This systematic review follows the Preferred Reporting Items for Systematic Reviews (PRISMA) checklist.[27] Approval of the ethics committee was not required, as the study is a systematic review, not involving human participants.

2.2. Study design

A systematic review that evaluated the value of ^{18}F-FDG PET/CT imaging at baseline and after IC in patients with locally advanced HNSCC was performed to answer the following question: "Is ^{18}F-FDG PET/CT effective the assessment of early response of IC in patients with HNSCC?"

2.3. Eligibility criteria

The aim of this study was to analyze studies that report the use of ^{18}F-FDG PET/CT to early IC response assessment concerning patients with HNSCC. No language or time restrictions were set. The study design included diagnostic tests, cohort, and cross-sectional studies.

Studies were excluded for the following reasons: studies in which ^{18}F-FDG PET/CT was used to evaluate other subtypes of head and neck cancer (not HNSCC); studies in which patients underwent previous CRT, radiotherapy, or surgery; reviews, letters, personal opinions, book chapters, conference abstracts, patents, case reports; studies in which FDG-PET was performed without integrated CT (not PET/CT) or studies in which FDG-PET/CT was not performed at baseline; studies in which patients had distant metastases; and studies with others radiopharmaceuticals (not ^{18}F-FDG).

2.4. Information sources and search strategy

The Cochrane Library, Science Direct, Web of Science, and PubMed electronic databases were comprehensively searched with the following keywords

(1) "PET-CT" OR "PET/CT" AND (2) "head and neck cancer" AND (3) "neoadjuvant chemotherapy" OR "induction chemotherapy" AND (4) "survival" OR "outcome response" OR "prognostic value." All databases were searched up to May 4, 2016. In addition, reference lists of selected articles were hand screened for potential relevant studies that could have been missed during the electronic database search. Field experts were also consulted during research process. Duplicate references were removed from reference manager software (EndNote® X7 Thomson Reuters, Philadelphia, PA).

2.5. Study selection

Eligibility of the selected articles was determined in 2 phases. In phase 1, both authors (RF and DLV) independently screened titles and abstracts identified in all electronic databases. The authors selected articles that appeared to meet the inclusion criteria on the basis of their abstracts. In phase 2, the same authors (RF and DLV) read the full text of all selected articles and excluded studies that did not meet the inclusion criteria. Disagreements between authors were solved by consensus and, when a consensus was not reached, a third author (NSM) was involved to make a final decision.

2.6. Data extraction

One of the authors (RF) collected all key information included in every article such as authors, year of publication, country, samples, median ages, study design, IC drugs and number of

cycles, time of ^{18}F-FDG PET/CT at the baseline and after IC, FDG dose, response criteria, PET/CT parameters and interpreters, time between FDG administration and scanning, reference standard, methods, results, and main conclusions. The second author (DLV) crosschecked all the collected data. Once again, disagreements between them were solved by consensus and the third author (NSM) became involved, when required, to make a final decision.

2.7. Risk of bias in individual studies

There is currently no validated tool clear indicated for risk of bias assessment among cross-sectional studies.[28] The Agency for Healthcare Research and Quality (AHRQ) elaborated and validated a checklist for general observational studies.[28–30] The AHRQ quality assessment was applied to all the selected articles. Two reviewers (RF and DLV) scored each item with "yes," "no," "unclear," and "not applicable" and assessed independently each included study. Disagreements between both reviewers were solved by consensus and the opinion of a third reviewer (NSM).

2.8. Summary measure

Maximum standard uptake value (SUV_{max}), metabolic tumoral volume (MTV), total lesion glycolysis (TLG), and gross tumoral volume (GTV) were the parameters analyzed to assess the response to IC by ^{18}F-FDG PET/CT imaging in patients with locally advanced HNSCC. For this purpose, all metabolic and volumetric parameters were compared at baseline and after IC.

2.9. Synthesis of results

A meta-analysis was planned if the data from the included studies were considered relatively homogeneous.

2.10. Risk of bias across studies

The risk has only to be applied if meta-analysis was possible.

3. Results

3.1. Literature search strategy

The literature search yielded 170 citations from The Cochrane Library, Science Direct, Web of Science, and PubMed. After discarding duplicates, 105 articles remained and were screened on title for eligibility. Afterward, 84 articles were discarded and the remaining 21 articles were considered for abstract screening. Reviewing titles and abstracts, 14 were excluded following the exclusion criteria. Thus, the 7 remaining studies added a total of 207 patients with advanced untreated HNSCC. While screening the references of these 7 articles, no new articles were found. A flow chart of the process of identification, screening, eligibility, and inclusion of studies is shown in Fig. 1.

3.2. Study characteristics

All the selected articles were published in medical journals.[12,13,31–35] Samples size ranged from 15 to 62 participants. Two studies were conducted in France,[31,32] 2 in Japan,[12,33] 1 in the United Kingdom,[13] 1 in Germany,[34] and 1 in the USA.[35] Three studies were prospective[12,13,31] and four retrospective.[32–35] The majority of patients were staged III or IV HNSCC and were male. The tumor location was distributed as follows: 74 from oral cavity/oropharynx, 69 hypopharynx, 3 nasopharynx, and 56 from larynx. One study included 4 tumors from sites that were not specified[35] and other study included 1 case of cervical esophagus carcinoma.[12] The characteristics of the included studies are summarized in Table 1.

All the included studies were evaluated by 2 ^{18}F-FDG PET/CT scans: at baseline and after IC. The characteristics of drug types, IC cycle duration, number of IC, reference standard, and endpoint were not randomized between the studies. Five from seven selected studies used SUV_{max} as the main parameter of FDG PET/CT to evaluate response of IC.[12,31–34] One study used MTV and TLG[35], and other study used GTV.[13] Two studies selected the same SUV_{max} thresholds.[12,33] The other selected studies have used different SUV_{max} thresholds.[31,32,34,35] The reference standards also varied among the selected studies. Four studies used patients' follow-up[12,13,31,35] and two used endoscopy as the reference standard.[32,34] Only 1 study selected histopathology response as the reference standard.[33] Regarding the interpretation of FDG PET/CT, in 4 studies, the observers were not described. Only 1 study evaluated HPV status.[13] A summary of the FDG PET/CT parameters, response criteria, endpoint, and main conclusion can be found in Table 2.

3.3. Methodological quality assessment

All studies, except one,[35] were evaluated as having moderate risk of bias based on the sum of the 9 applicable items of the AHRQ. The main methodological limitations representing potential risk of bias were related to the incomplete explanation of the confounding variables, the absence of follow-up in some studies,[32–34] and the source of information was not described.[12,33,34] Details about each one of the AHRQ items and the evaluation criteria are described in Table 3.

3.4. Synthesis of results

The heterogeneity of the selected studies concerning different SUV_{max} cut-offs, response criteria, and endpoints precluded a meta-analysis. Despite of the differences among the selected studies, almost all of them highlighted the effectiveness of FDG PET/CT for early prediction of IC response in advanced HNSCC patients.[12,31–35]

In 1 study[31], metabolic tumor response was assessed by the measurement criteria of the European Organization for Research and Treatment of Cancer (EORTC)[36] after the second cycle of docetaxel, cisplatin, and 5-fluouracil. The referred study divided the patients in 2 groups (Group 1 = responders; Group 0 = non-responders) and showed statistically significant differences between the 2 groups regarding the reference standard ($P = 0.0014$). From the group 1, composed by 10 responders on FDG PET/CT, none had relapsed after a median follow-up of 18.9 months.

In other study, 13 of 21 patients were considered as responders with ≥70% tumor reduction on control endoscopy after a single cycle of TPF.[32] From these 13 endoscopic responders, 9 patients were considered responders by ^{18}F-FDG PET/CT criteria (SUV_{max} decrease >30%). Among 8 nonresponders on endoscopy, 3 were responders by ^{18}F-FDG PET/CT criteria. Nine patients were considered nonresponders on ^{18}F-FDG PET/CT.

Some authors compared histopathologic response of 26 resected specimens (16 primary lesions and 11 lymph node) with ^{18}F-FDG PET/CT and MRI after 1 cycle of IC and divided into 2 groups: histopathology responders (n = 7; 3 grade 1a and 4

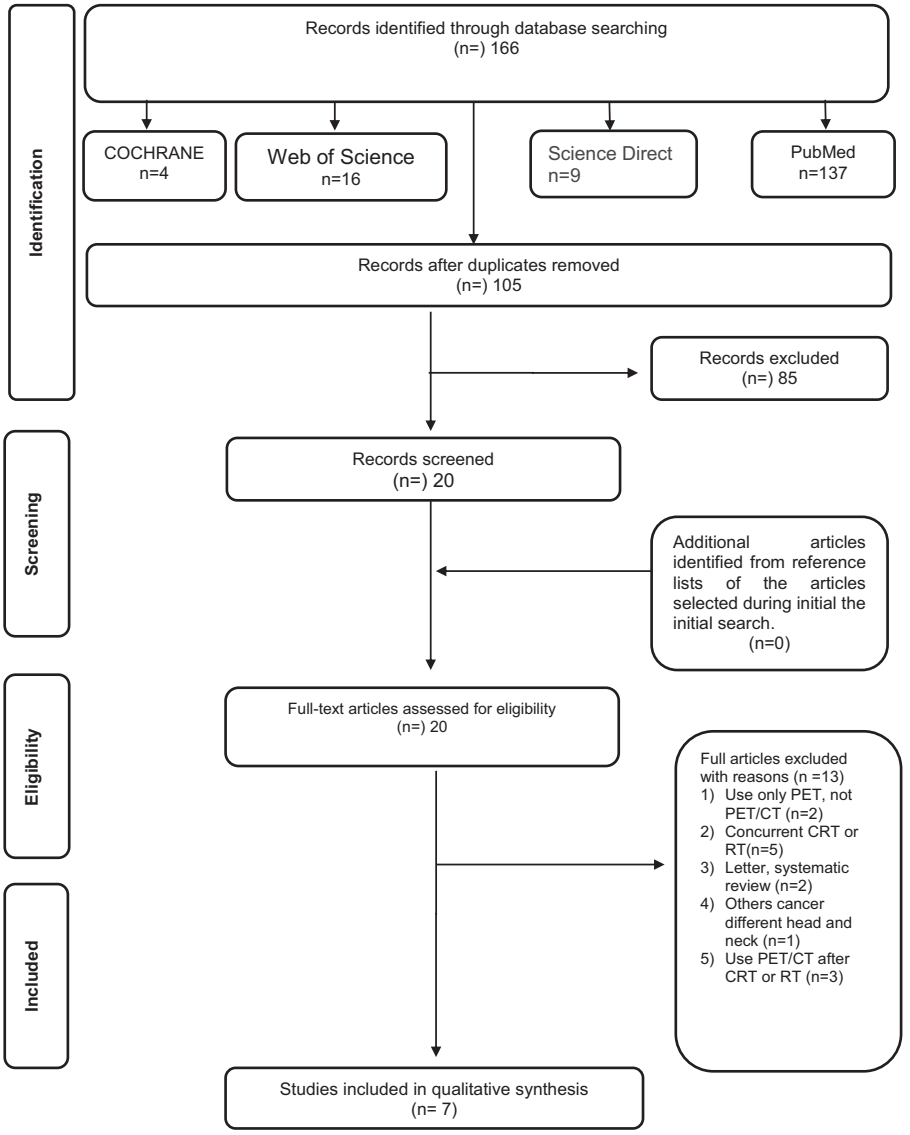

Figure 1. Flow diagram illustrating the literature search protocol and selection criteria adapted from PRISMA.

grade 1b) and nonresponders (n = 19; 3 grade 2 and 16 grade 3).[33] The grading of histopathologic regression in tumor beds was performed according to a previous study[37]: grade 1a, complete tumor regression; grade 1b, less than 10% vital tumor seen in tumor bed; grade 2, 10% to 50% residual tumor seen in tumor bed; grade 3, more than 50% remaining residual tumor seen in tumor bed. Specimens with grade 1a or grade 1b responses were regarded as histopathologic responders, while those with grade 2 or 3 were considered histopathologic nonresponders. This classification was made before data analysis. On the MRI parameters, no significant differences were found between the 2 groups. Between PET/CT parameters (pre-chemotherapy SUV_{max}, post-chemotherapy SUV_{max}, and % decrease SUV_{max}), only post-chemotherapy SUV_{max} and % decreased in SUV_{max} showed significant differences (3.6 ± 2.3 vs 11 ± 5.6, $P < 0.001$ and $61 \pm 15\%$ vs 18 ± 22, $P < 0.001$, respectively). The authors concluded that post-chemotherapy SUV_{max} and % decreased in SUV_{max} in FDG PET/CT could predict histopathology response to IC more accurately than MRI. Using a SUV_{max} decrease $\geq 55.5\%$ as cut-off, they achieved a sensibility of 86%, specificity of 95%, a positive predictive value of 86%, and a negative predictive value of 95%.

Another study has also used the SUV_{max} decrease $\geq 55.5\%$ as a threshold for responders on ^{18}F-FDG PET/CT and RECIST criteria on CT and MRI.[12]^{18}F-FDG PET/CT revealed 27 responders and 30 nonresponders. For 46 lymph node evaluations, 28 patients were considered responders and 18 nonresponders. These patients were also evaluated by RECIST criteria. Thirty patients were considered responders, while 27 patients were nonresponders. Of 57 patients, PET/CT and RECIST criteria matched in 42. Nonetheless, only the nonresponders revealed by ^{18}F-FDG PET/CT were significantly linked to a poor local control rate and the disease-specific survival rate at 2 years after the completion IC ($P = 0.03$ and $P = 0.02$, respectively). IC response evaluation of the primary lesion by ^{18}F-FDG PET/CT was the only independent prognostic factor in the disease-specific survival rate (nonresponder vs responder hazard ratio 4.9, 95% confidence interval: 1.4–17.1, $P = 0.01$).

Table 1

Main characteristics of the selected studies.

Reference	Year	Country	Study design	UICC stage (n)	Cases of HNSCC: total (Male/Female)	Age, y mean ± SD (range)	Induction chemotherapy (IC)		Time of FDG PET/CT, and the IC cycle-mean ± SD (range)	
							Drugs (mg/m^2)	Number of cycle	Baseline	After IC
Abgral et al[31]	2012	France	Prospective	III (4); IV (11)	15 (14/1)	57.5 ± 6.2	Docetaxel (75), cisplatin (75), 5-fluorouracil (750)	3	30 days	15.8 ± 4.9 after the 2nd cycle
Gavid et al[32]	2015	France	Retrospective	III (12); IV (9)	21 (18/2)	56.8 ± 7.1	Docetaxel (60),cisplatin (75), 5-fluorouracil (750)	2 or 3	*	15.6 ± 5.4 days after the 1st cycle
Kikuchi et al[33]	2011	Japan	Retrospective	II (2); III (2); IV (12)	16 (13/3)	61.6 ± 8.2 (50–74)	Nefaplatin-CDGP(80), TS-1 (S-1)(80)	1	(1–8 days)	20.5 (14–32 days)
Kikuchi et al[12]	2013	Japan	Prospective	III (14); IV (42)	56 (47/9)	65 (45–78)	Nefaplatin-CDGP (80), TS-1 (S-1) (80)	1	(1–12 days)	17 days (10–32 days)
Powell et al[13]	2013	United Kingdom	Prospective	III (2);IV (8)	9 (7/2)	55.8 ± 6.8 (42–63)	PF = cisplatin (75), 5-fluorouracil (1000)	2	*	After 2nd cycle
Semrau et al[34]	2015	Germany	Retrospective	II (3); III (16); IV (43)	62 (51/11)	(*)	Docetaxel (75), cisplatin (30), or carboplatin	1	*	(21–28 days)
Yu et al[35]	2014	USA	Retrospective	III (3); IV (25)	28 (20/8)	59 (29–82)	docetaxel*, cisplatin*, 5-fluorouracil (*)	3	*	(14–21 days)

*Not reported; TPF (docetaxel, cisplatin, and 5-fluorouracil).

Some authors compared endoscopic response and early metabolic response by FDG PET/CT with different parameters. The response parameters used on ^{18}F-FDG PET/CT were a decrease >20% in SUV_{max} (residual$SUV_{max} < 0.8$), a decrease >50% in SUV_{max} (residual$SUV_{max} < 0.5$), or a post$SUV_{max} \leq 10$ after IC. They concluded that these were the best predictors of long-term prognosis. These authors showed that post-IC SUV_{max} mean values were lower in endoscopic responders (6.0 ± 4.0: mean ± SD) than in nonresponders (14.5 ± 6.2). The residual SUV_{max} percentage was also lower in endoscopic responders than in nonresponders (34% ± 19% vs 81% ± 37%, respectively). Regarding the correlation with endoscopy, 98% of responders also had a metabolic response, while only 50% of nonresponders achieved metabolic response.[34]

Only 2 studies did not use SUV_{max} as the ^{18}F-FDG PET/CT parameter for evaluating early response to IC. The former study[13] compared changes in functional imaging parameters delineating the ROIs (regions of interest) containing the primary tumor or lymph node by using specific methods, previously related for PET/CT[38] and MRI[39] through GTV. GTV is commonly used in radiotherapy planning to determine radiation target. After IC, all patients had a greater reduction in ^{18}F-FDG-avid volume and 7 of the 9 included patients had a complete metabolic response on ^{18}F-FDG PET/CT (impossible to create a GTV using the threshold technique). The preliminary data of this study suggested that ^{18}F-FDG PET/CT has limited utility in guiding image-guided radiotherapy following IC. In this respect, functional MRI had an advantage over PET/CT by virtue of its higher resolution and specificity.[13]

In the second study that did not use SUV_{max} to assess the early response to IC by FDG PET/CT, the following parameters were analyzed: MTV and TLG.[35] The authors showed a reduction of 42% of MTV_G and 55% in TLG_G that could predict event-free survival (EFS). The values of sensitivities and specificities were 67% and 90%, respectively, for gradient MTV (MTV_G) and 62.5% and 90% for gradient TLG (TLG_G). The areas under the curve (AUC) for MTV_G, MTV with 38% threshold (MTV_{38}), and the MTV with 50% threshold (MTV_{50}) were 0.76, 0.77, and 0.76, respectively ($P = 0.03$). The AUC was 0.82 to TLG_G ($P = 0.009$) and 0.84 to both TLG_{38} and TLG_{50} ($P = 0.006$). Although these authors did not use SUV_{max} to evaluate outcomes, this parameter was measured and the median SUV_{max} decreases were 100% for patients who had no events and 51.88% for patients who had progressive disease or died. Still, these values were not statistically significant ($P > 0.05$).

4. Discussion

^{18}F-FDG PET/CT has dramatically changed the management of HNSCC patients in whom treatment is often expensive and associated with a significant morbidity.[40] A recent trial showed that PET/CT-guided surveillance may reduce the number of surgeries and it was more cost-effective than planned neck dissection, although the survival rates were similar in both approaches.[41] The high diagnostic performance of [18]F-FDG PET/CT in detecting recurrence in curatively treated patients with head and neck cancer has also been well established.[42] Nevertheless, the role of ^{18}F-FDG PET/CT concerning the early assessment of IC response deserves further investigation. Several authors have stated that the early assessment of IC response by means of ^{18}F-FDG PET/CT would be a powerful tool to predict treatment outcome.[12,31–35] However, some previous studies have found no survival benefit for HNSCC patients undergoing

Table 2

FDG PET/CT dose, parameters, interpreters, response criteria, reference standards, endpoints, and main conclusions of included studies.

Reference	FDG dose	Time between FDG administration and scanning (min)	PET/CT parameters used	Interpreters	Response criteria	Reference standard	Endpoint	Main Conclusion
Abgral et al[31]	370 MBq	60	SUVmax	Not reported	EORTC Criteria (Young 1999)	Follow-up	EFS	FDG PET/CT allowed early prediction of response to IC preceding curative CRT and allowed prediction of EFS. Needs further evaluation in larger prospective studies
Gavid et al[32]	4 MBq/kg	60	SUVmax	Dedicated post-treatment console	SUVmax reduction >30%	Endoscopy (after completion IC)	Response to IC	The present preliminary study demonstrated that the rate of early reduction in SUVmax exceeding 30% during IC differed significantly between responders and nonresponders.
Kikuchi et al[33]	200–250 MBq	50	SUVmax	Board radiologist/nuclear medicine physician	SUVmax reduction ≥55.5% or post-IC SUVmax ≤3.5	Pathology	Response to IC	FDG-PET/CT can predict histopathologic early response to IC in patients with HNSCC with higher accuracy than MRI. Further prospective studies should be performed.
Kikuchi et al[12]	200–250 MBq	50	SUVmax	Not reported	SUVmax reduction ≥55.5% or post-IC SUVmax ≤3.5	Follow-up	LC and DSS	Early evaluation of IC response in the primary lesion using FDG can predict LC and DSS prognosis. Further investigation into the optimal FDG-PET/CT method for PET-based IC response evaluation is required.
Powell et al[13]	400 MBq	60	GTV	Not reported	GTV 50%	Follow-up	Functional MRI	Functional MRI has an advantage over PET/CT by virtue of its higher resolution and specificity.
Semrau et al[34]	3 MBq/kg	60	SUVmax	Not reported	SUVmax reduction >30%; (resSUVmax <0.8)	Endoscopy (after completion IC)	LC, DMFS, DFS, CSS, OS	FDG-PET/CT parameters are at least as effective as endoscopic parameters at evaluating response to IC and may even provide a more differentiated assessment. There is no advantage of performing response assessment by RECIST. PET/CT should be included in future study protocols to further assess its value in organ preservation.
Yu et al[35]	average 418 MBq	65 (SD 7 min)	MTV and TLG	Board radiologist with nuclear medicine and neuroradiology experience	MTV reduction >42% or TLG reduction >55%	Follow-up	OS and PFS	Reduction in MTV or TLG of 42% and 55%, respectively, after NAC, predicts short-term EFS in patients with advanced HNSCC. It needs validation in a larger and prospective study, which would include other important clinical parameter such as HPV status.

DFS = disease-free survival, DMFS = distant metastasis-free survival, DSS = cancer-free survival, DSS = disease-specific survival, EFS = event-free survival, IC = induction chemotherapy, LC = local control, MRI = magnetic resonance imaging, MTV = metabolic tumor volume, OS = overall survival, PFS = progression-free survival, SUV = standardized uptake value, TLG = total lesion glycolysis.

Table 3

Quality assessment criteria for the included studies (AHRQ).

	Abgral et al[31]	Gavid et al[32]	Kikuchi et al[33]	Kikuchi et al[12]	Senrau et al[34]	Yu et al[35]	Powell et al[13]
Defined the source of information (survey, record review)	Y	Y	N	N	N	Y	Y
Listed inclusion and exclusion criteria for exposed and unexposed subjects or refer to previous publications.	Y	Y	Y	Y	Y	Y	N
Indicated time period used for identifying patients.	Y	Y	Y	Y	Y	Y	Y
Indicated whether or not subjects were consecutive if not population-based.	Y	Y	Y	Y	Y	Y	Y
Indicated if evaluators of subjective components of study were masked to other aspects of the status of the participants.	NA	NA	NA	NA	NA	NA	NA
Described any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements).	N	N	Y	N	N	Y	N
Explained any patient exclusions from analysis	N	N	Y	Y	Y	Y	Y
Described how confounding was assessed and/or controlled.	N	N	N	N	N	N	N
If applicable, explained how missing data were handled in the analysis.	NA	NA	NA	NA	NA	NA	NA
Summarized patient response rates and completeness of data collection.	Y	Y	Y	Y	Y	Y	Y
Clarified what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.	Y	N	N	Y	N	Y	Y
Total/applicable items [the Not Applicable (NA) items were excluded from the sum].	6/9	5/9	6/9	6/9	5/9	8/9	6/9

AHRQ: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
N = no, NA = not applicable, U = unclear, Y = yes.

IC.[25,43] To our knowledge, this is the first systematic review that assessed the effectiveness of ^{18}F-FDG PET/CT for evaluating early response of IC in HNSCC patients. The literature regarding this topic is scarce, as only 7 studies met the inclusion criteria.[12,13,31–35]

In our systematic review, the response to IC has been evaluated on ^{18}F-FDG PET/CT in 207 patients. From the 7 selected studies, 6 demonstrated that early therapeutic response can be evaluated by ^{18}F-FDG PET/CT after IC in patients with advanced staging HNSCC.[12,31–35] Unfortunately, the selected studies were heterogeneous concerning response criteria, reference standards, chemotherapy strategy, and endpoints. For this reason, a meta-analysis was not possible.

In the selected studies, the most used PET/CT parameter was SUV_{max}.[12,31–34] In addition, the aforementioned studies have used different SUV cut-offs. Therefore, the risk of bias related to the lack of standardization should be mentioned, providing different response measurements after therapy.[44] Only 1 study has verified limitations in ^{18}F-FDG PET/CT findings after IC and problems related to the specificity and spatial resolution of this imaging modality for early response of IC.[13] However, the authors have used GTV as the parameter for evaluating the response, which may have influenced the results. Some previous studies have demonstrated that GTV has not been incorporated into clinical algorithms due to difficulties in reproducibility and absence of prospective data validating the previous reports.[45] The aforementioned authors concluded that MTV is a parameter independently correlated with locoregional control and overall survival in oropharyngeal patients undergoing CRT.

The measurement of "response" is critical in cancer therapy. It is an important determinant of outcome, predicts survival, and guides treatment decisions.[18] For some imaging methods, such as CT and MRI, the RECIST can be considered as a currently available and reproducible method for measuring target lesions.[46] However, these response criteria are based only on

morphologic characteristics, such as tumor size, nodal size, and contrast-enhancement patterns.

Anatomical imaging biomarkers do not allow the evaluation of the disease activity and are of limited value for local restaging after IC and CRT due to difficulty in differentiating fibrotic or reactive tissue from viable tumor. Furthermore, these anatomical imaging methods, regardless of methodology, consider a reduction in tumor size as an early sign of clinical benefit.[19] Tumors may have irregular margins and show heterogeneous contrast enhancement, resulting in potential reader variability. It may take 2 or 3 months to detect any shrinkage, whereas functional imaging methods such as ^{18}F-FDG PET/CT can show changes as early as 8 days following the beginning of treatment, and these changes may have been predictive of a longer progression-free survival.[17,19] Early metabolism changes in ^{18}F-FDG in squamous-cell carcinoma during chemotherapy have been demonstrated in a previous experimental study.[47] This study showed a rapid decrease in ^{18}F-FDG uptake with subsequent tumor regression after an early transient increase in uptake. Glucose decreases after cytotoxic therapy may be an early sign of a response therapy following tissue necrotic changes before any decrease in tumor size. The authors concluded that all viable tumor cells areas such as hypermetabolic and that an early decrease in ^{18}F-FDG uptake after cisplatin therapy correspond to regressive changes and a reduction in the number of viable tumor cells.

Changes in tumor size do not necessarily reflect the killing of malignant cells. Traditional chemotherapeutic agents are cytotoxic in nature and act primarily by eliminating neoplastic cells. Some novel molecularly targeted therapies are predominantly cytostatic and act primarily by halting tumor growth rather than causing significant tumor cell death.[48] These agents may stabilize or potentially increase tumor size despite excellent clinical response. Therefore, for the targeted therapies, the size criteria based on anatomical imaging modalities are of limited value for evaluating treatment response. On the contrary, ^{18}F-FDG PET/CT may be a useful endpoint for assessing response to targeted therapies. The biologic basis of changes in ^{18}F-FDG uptake may be more complex than those for traditional cytoreductive therapies.[48] In the last version of RECIST, a section on detection of new lesions, including the interpretation of ^{18}F-FDG PET, was added.[15]

Due to the limitations of anatomic tumor response assessed on RECIST, the PERCIST (PET Tumor Response) has been proposed, aiming to serve as a starting point for use in clinical trial. However, PERCIST has not yet been well established, and so further revisions and enhancements would be necessary for the adequate validation method.[16] The European Organization for Research and Treatment of Cancer had proposed some useful and foresight response criteria on PET, available at that time, by using SUV_{max} as the main parameter.[36] In our systematic review, only 1 study considered the EORTC criteria.[31]

Our systematic review has also shown differences regarding chemotherapy strategy, the number of cycles of IC, and the time of performing ^{18}F-FDG PET/CT after this neoadjuvant therapy. All these differences may have influenced the results of our work, reinforcing the need of further standardized parameters. As images interpretation in the post-therapeutic setting with 18F-FDG PET/CT is challenging (due to anatomical distortions, inflammation, edema, fibrosis, asymmetry), an interval of 12 weeks has been recommended for performing this imaging modality after CRT and/or radiotherapy.[49] Nonetheless, the optimal timing of the first response assessment after IC or CRT is not yet known.

Regarding the reference standards, most of the selected studies have used patients' follow-up.[12,13,31,35] Follow-up requires a long time to serve as the reference standard and it may impair the early assessment of therapeutic efficacy using a metabolic response. Therefore, for this purpose, the histopathology response is the ideal reference standard. However, from the 7 selected studies, only 1 used the histopathology response as the reference standard.[33] If a more precise prediction of the histopathology response to IC could be achieved by a noninvasive modality (^{18}F-FDG PET/CT), the response to subsequent therapy may also be more precise, thus contributing to organ preservation. For this reason, further studies are required to evaluate the early IC response assessment by ^{18}F-FDG PET/CT using the histopathology response as the reference standard in order to reduce this source of bias. Some authors have developed a 5-point interpretation criteria for therapy response assessment (Hopkins Criteria) on PET/CT scans.[50] This subjective method has demonstrated a substantial interobserver agreement, a negative predictive value of 92%, and predicted overall survival and progression-free survival in HNSCC patients.[50] The method should be further investigated for evaluating early therapy response of IC.

The inclusion criteria can be considered as a limitation of our study, as we decided to only select studies that have used ^{18}F-FDG as the radiotracer on PET/CT. Other less studied radiopharmaceutical tracers have been tested for HNSCC patients.[51,52] Nowadays, the cost-effectiveness and availability of ^{18}F-FDG justify the current use, despite the lack of large and randomized studies. The main limitation refers to the heterogeneity of the selected studies concerning response criteria, reference standards, chemotherapy strategy, and endpoints. Nonetheless, all of the studies, [12,31–35] except one,[13] have demonstrated the effectiveness of ^{18}F-FDG PET/CT in advanced HNSCC patients.

In conclusion, our systematic review shows that ^{18}F-FDG PET/CT may assess early response of IC in HNSCC patients. However, as the 7 selected studies were heterogeneous regarding response criteria, reference standards, chemotherapy strategy, and the endpoints, further standardized studies would clarify the role of PET/CT in the context of predicting IC response in HNSCC patients. Moreover, the assessment of early response of IC by PET/CT may influence treatment outcome. The success of surgical salvage depends on early and accurate detection of IC response.

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