18 F-FDG PET/CT for response evaluation of regional lymph nodes in 97 head and neck squamous cell carcinoma patients

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CORRESPONDENCE: OUR EXPERIENCE

^{18}F-FDG PET/CT for response evaluation of regional lymph nodes in 97 head and neck squamous cell carcinoma patients: Differences in the predictive value of residual disease after radiotherapy and chemoradiotherapy

1 | BACKGROUND

Patients with unresectable locally advanced head and neck squamous cell carcinoma (HNSCC) are generally treated with chemoradiotherapy or radiotherapy alone.[1] After primary (chemo) radiotherapy, treatment response evaluation is performed around 12 weeks. Because salvage surgery in a previously irradiated neck is associated with a risk of complication and poor long-term outcome, salvage neck dissection is only performed in case of suspected residual lymph node metastasis.[2] However, treatment response evaluation after (chemo) radiotherapy is challenging because of the difficulties in differentiating residual disease from post-treatment tissue changes influencing CT and MRI imaging appearances.[3,4] Besides CT and MRI, ^{18}-fluorodeoxyglucose positron emission tomography combined with computed tomography (^{18}F-FDG PET/CT) has become an important modality for treatment response evaluation. The integration of ^{18}F-FDG PET/CT in the international NCCN guidelines has ensured patients with FDG PET negative lymph nodes, who otherwise might have undergone salvage neck dissection, to be monitored with clinical follow-up and periodic imaging instead.[5] Yet, for FDG PET positive lymph nodes smaller than 1 cm or FDG PET negative lymph nodes larger than 1 cm, there is insufficient evidence whether a salvage neck dissection should be performed; thereby leaving the difficult decision of a potentially unnecessary neck dissection to clinicians, the multidisciplinary team and the patient.[6] Moreover, patient characteristics, primary treatment and HPV status could influence the identification of residual disease and might impact the diagnostic performance of ^{18}F-FDG PET/CT.

We hypothesise that the predictive value of FDG PET positive lymph nodes for residual disease is lower after chemoradiotherapy compared with radiotherapy alone due to difference in therapy-induced changes. In addition, we hypothesise that p16 status, patient and tumour characteristics have influence on the diagnostic performance of ^{18}F-FDG PET/CT. Therefore the aim of our study was to assess the accuracy of ^{18}F-FDG PET/CT imaging in response evaluation of the neck in HNSCC patients, while differentiating between primary treatment, p16 status, patient and tumour characteristics.

2 | MATERIAL AND METHODS

2.1 | Data selection

Patients who received an ^{18}F-FDG PET/CT after primary treatment with (chemo)radiotherapy for HNSCC between February 2013 and November 2018 at the University Medical Center Groningen (UMCG) were included. Exclusion criteria were as follows: patients who underwent ^{18}F-FDG PET/CT scan for another reason than evaluation of treatment response, patients who were treated with surgery between initial treatment and ^{18}F-FDG PET/CT evaluation as well as patients with nasopharyngeal cancer. Patients with N0 disease were not excluded in order to resemble clinical practice and because previously undetectable regional metastasis can progress during treatment leading to regional detectable metastatic lymph nodes. However, a subgroup analysis omitting N0 disease was performed. Patients with less than 1 year follow-up after treatment or who were treated in a palliative setting were also excluded from analysis. As advised by the NCCN guidelines, response evaluation was undertaken by CT or MRI at 8 weeks. In case of suspected partial response, an ^{18}F-FDG PET/CT was performed 1 month after the initial treatment response. A total of 97 ^{18}F-FDG PET/CT scans were performed.

All included patients were treated with curatively intended intensity-modulated radiotherapy, using a simultaneous integrated boost technique. Most patients received bilateral elective irradiation of the neck to a total dose of 54.25 Gy, in fractions of 1.55 Gy. The primary tumour and pathological lymph node metastases were treated to a total dose of 70 Gy, in 2 Gy fractions. Patients treated with concomitant chemoradiotherapy were irradiated five times per week. Patients not eligible for chemoradiotherapy but <70 years old were treated with an accelerated schedule of six fractions per week up to a total dose of 70 Gy. Patients ≥70 years old were treated five times a week. Chemotherapy consisted of either weekly cisplatin 40 mg/m^2 for 7 weeks or three cycles carboplatin 300-350 mg/m^2 at day 1 in combination with 5-FU 600 mg/m^2 as continues infusion

on day 1-4 in 3-week cycles. Patient and clinical characteristics were retrospectively retrieved from electronic patient files and are presented in Table 1.

The presence of regional lymph node metastases was retrospectively assessed by analysis of the histopathology reports: lymph nodes were considered positive if viable tumour cells were detected on histological or cytological examination. Additionally, histopathological specimens of true positive, false positive and false negative ^{18}F-FDG PET/CT cases were revised without knowledge of the PET results by a head and neck pathologist. Negative lymph nodes were defined as the absence of malignant cells on histopathological examination or in the course of clinical follow-up. During follow-up, all patients underwent clinical consultation including physical examination of the neck every three months in the first 2 years. In case of detectable lymph nodes, an additional echo graphic evaluation was performed. The definition used for the absence of enlarged lymph nodes was undetectable lymph nodes during physical examination and/or imaging. P16 was used as surrogate marker for HPV status. P16 immunohistochemistry (clone E6H4, Roche Ventana, pre-diluted by supplier) was performed on oropharyngeal carcinomas.

Before ^{18}F-FDG PET/CT (Biograph mCT-64 PET/CT; Siemens, Knoxville, Tenn) scans patients were instructed to fast, except for the consumption of water, for at least 6 hours before administration of 3 MBq/kg -FDG. Serum glucose levels were evaluated before tracer injection. PET images were obtained with 2-3 minutes per bed position in three-dimensional setting. Images were reconstructed according to the European Association of Nuclear Medicine guidelines by using a time-of-flight iterative reconstruction method (three iterations; 21 subsets; and voxel size, 3.1819 × 3.1819 × 2 mm) with point-spread-function correction. Images were corrected for random coincidences, scatter and attenuation, and were smoothed with a Gaussian filter of 6.5 mm in full-width at half-maximum. The scintigraphic assessment of lymph nodes on the ^{18}F-FDG PET/CT was done visually in which the nodal FDG uptake was graded as positive or negative. For this assessment, the FDG avidity of the lymph node and of the primary tumour, as well as the site of uptake, was taken into account. No definite criteria were used based on SUVs. In case of doubt, consensus was achieved in a multidisciplinary meeting or additional echo graphic evaluation was performed. If this was unclear to the nuclear radiologist, the decision was made in a multidisciplinary meeting.

TABLE 1 Patient and tumour characteristics

	CRT	RT	Total
Patients N (%)	**42 (44%)**	**55 (56%)**	**97 (100%)**
Age at initial treatment[a]			
Median	59	67	63
Range	45-70	41-88	41-88
Time interval[b]			
Median	3.1	3.0	3.0
Range	2.5-3.9	2.4-3.8	2.4-3.9
Gender			
Male	29 (69.0)	43 (78.2)	72 (74.2)
Female	13 (31.0)	12 (21.8)	25 (25.8)
Tumour site			
Oropharynx	28 (66.7)	30 (54.5)	58 (59.8)
Larynx	9 (21.4)	14 (25.5)	23 (23.7)
Hypopharynx	3 (7.1)	7 (12.7)	10 (10.3)
Oral cavity	2 (4.8)	4 (1.8)	6 (6.2)
T classification[c]			
T1	7 (16.7)	6 (10.9)	13 (13.4)
T2	5 (11.9)	17 (30.9)	22 (22.7)
T3	13 (31.0)	18 (32.7)	31 (32.0)
T4	17 (40.5)	14 (25.5)	31 (32.0)
N classification[c]			
N0	4 (9.5)	19 (34.5)	23 (23.7)
N1	4 (9.5)	10 (18.2)	14 (14.4)
N2	32 (76.2)	22 (40.0)	54 (55.7)
N3	2 (4.8)	4 (7.3)	76 (6.2)
p16 status oropharyngeal carcinomas			
Positive	19 (67.9)	13 (44.8)	32 (55.1)
Negative	9 (32.1)	13 (44.8)	22 (37.9)
Unknown	0 (0.0)	3 (10.4)	3 (5.0)

Abreviations: CRT, chemoradiotherapy; RT, radiotherapy; Total, total study cohort.

[a] Age at last day of primary treatment.

[b] Time between last primary treatment and 18F-FDG PET/CT imaging, in months.

[c] Based on the 7th edition of the American Joint Committee on Cancer.

Key points

- The authors describe their experience in evaluating treatment response scans using ^{18}F-FDG PET/CT to detect residual lymph node metastases in a homogenous group of 97HNSCC patients while differentiating between radiotherapy and chemoradiotherapy as primary treatment modality and P16 status.
- A significantly higher rate of false positives (14.3%) and a lower sensitivity (66.7%) was observed after chemoradiotherapy compared with radiotherapy as primary treatment modality (respectively, 1.8% and 100%).
- A lower positive predictive value (25.0%) was observed after chemoradiotherapy compared with radiotherapy as initial treatment (87.5%).
- A lower positive predictive value (37.5%) was observed in p16 positive oropharyngeal cancers compared with p16 negative cancers (75.0%).
- Studies evaluating ^{18}F-FDG PET/CT for assessment of treatment response should stratify for primary treatment modality and HPV status.

2.2 | Statistical analysis

Statistical analysis was performed using SPSS (version 23 for Windows, Armonk, NY: IBM Corp.) to compute frequency tables, to calculate median, ranges and to perform the Pearson Chi-Square test. Univariate logistic regression analysis was used to analyse the association between false positives (FP), false negatives (FN), true positives (TP) and true negatives (TN) and other variables. Accordingly, the sensitivity, specificity, PPV, NPV, accuracy and p-values were derived. A *P*-value <.05 was considered statistically significant.

3 | RESULTS

A total of 97 patients were retrospectively included of which 55 patients were treated with radiotherapy and 42 with chemoradiotherapy. Patient and tumour characteristics are presented in Table 1. In the 58 oropharyngeal carcinomas tested for p16, there were 22 p16 negative tumours and 32 p16 positive tumours. HPV was confirmed in 25 (78.1%) of all p16 positive oropharyngeal carcinomas. In the remaining 7 (21.9%) p16 positive tumours, HPV status could not be assessed due to insufficient amount and/or quality of tumour tissue.

An ^{18}F-FDG PET/CT positive imaging scan was seen in 16 out of 97 patients (16.5%) at initial response evaluation. Negative imaging scans were seen in 81 out of 97 patients (83.5%). Using histopathological examination and a clinical follow-up of at least 1 year, seven out of sixteen (43.8%) positive scans were FP and one out of 81 (1.2%) negative scans was FN (Table 2). Examples of true and false positive lymph nodes on ^{18}F-FDG PET/CT scans are shown in Figure 1. Histopathological review of the FP lymph node specimens either showed reactive hyperplasia, fibrosis or necrosis. Sensitivity, specificity, PPV, NPV and accuracy were calculated accordingly and respectively 90% (95% CI, 55 - 99), 92% (95% CI, 84-96), 56% (95% CI, 38-72), 99% (95% CI, 92-99) and 92% (95% CI, 84-96).

Stratifying the group for primary treatment, a significantly higher percentage of FP ^{18}F-FDG PET/CT lymph nodes was observed in patients treated with chemoradiotherapy compared with radiotherapy alone, respectively 14.3% and 1.8% (*P* = .019). No significant differences between FN, TN and TP were observed between primary treatment regimens. Sensitivity, specificity, NPV, PPV and accuracy of ^{18}F-FDG PET/CT were all lower after primary treatment with chemoradiotherapy compared with radiotherapy alone (Table 2). Omitting patients with N0 disease from this analysis did not change the NPV of PPV, and comparable results were found for sensitivity, specificity and accuracy. More detailed information on this subgroup analysis can be found in supplementary Table S1.

Additionally, the group was stratified for p16 status; p16 positive oropharyngeal cancers and p16 negative cancers. A significantly higher percentage of FP ^{18}F-FDG PET/CT lymph nodes was seen in p16 positive oropharyngeal cancers compared with p16 negative cancers, respectively 3.1% and 1.6% (*P* = .025). Sensitivity, specificity, NPV, PPV and accuracy of ^{18}F-FDG PET/CT were all lower p16 positive oropharyngeal cancers compared with p16 negative cancers (Table 3).

Using univariate logistic regression analysis, FP was associated with chemoradiotherapy (HR 3.0, 95% CI 1.0-8.8) and positive p16 status (HR 5.8, 95% CI 1.07-32.0). No association was found between FP and patient or tumour characteristics; gender, age, tumour site and T-, N- or M-stage. No relation between TP, TN, FN and patient characteristics, tumour characteristics, primary treatment or p16 status was found.

4 | DISCUSSION

Our experience in a consecutive, homogenous group of 97 mucosal HNSCC patients shows that the percentage of FP and subsequently the PPV of ^{18}F-FDG PET/CT in treatment response evaluation of regional lymph nodes is influenced by the primary therapeutic treatment regimen, that is a PPV of 25.0% after chemoradiotherapy compared with 87.5% after radiotherapy without systemic treatment.

Additionally, p16 positivity is associated with a lower PPV compared with p16 negative tumour (37.5% versus 75.0%) and significantly higher percentage of false positives (5 vs 2, *P* = .025). The NPV of ^{18}F-FDG PET/CT evaluation for residual lymph node metastasis in response assessment is high regardless of primary treatment and/or p16 status. A possible explanation for the lower diagnostic performance after chemotherapy compared with radiotherapy alone

TABLE 2 True and false positive/negative ^{18}F-FDG PET/CT imaging scans with sensitivity, specificity, PPV, NPV and accuracy in relation to initial treatment

	Total scans	TP (%)	FP (%)	FN (%)	TN (%)
RT	55	7 (12.7)	1 (1.8)	0	47 (85.4)
CRT	42	2 (4.8)	6 (14.3)	1 (2.4)	33 (78.6)
Total	97	9 (9.3)	7 (7.2)	1 (1.0)	80 (82.5)
	Sensitivity (95% CI)	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Accuracy (95% CI)**
RT	100 (5.9-100)	97.9 (88.9-99.5)	87.5 (50.2-97.9)	100 (100-100)	98.1 (90.3-99.9)
CRT	66.7 (9.4-99.2)	84.6 (69.5-94.1)	25.0 (10.1-49.7)	97.1 (86.9-99.4)	83.3 (68.6-93.03)
Total	90.0 (55.5-99.75)	92.0 (84.1-96.7)	56.3 (38.0-72.9)	98.7 (92.6-99.8)	91.8 (84.4-96.4

Abbreviations: CRT, chemoradiotherapy; FN, false negatives; FP, false positives; NPV, negative predictive value; PPV, positive predictive value; RT, radiotherapy; TN, true negatives; Total, total study cohort; TP, true positives.

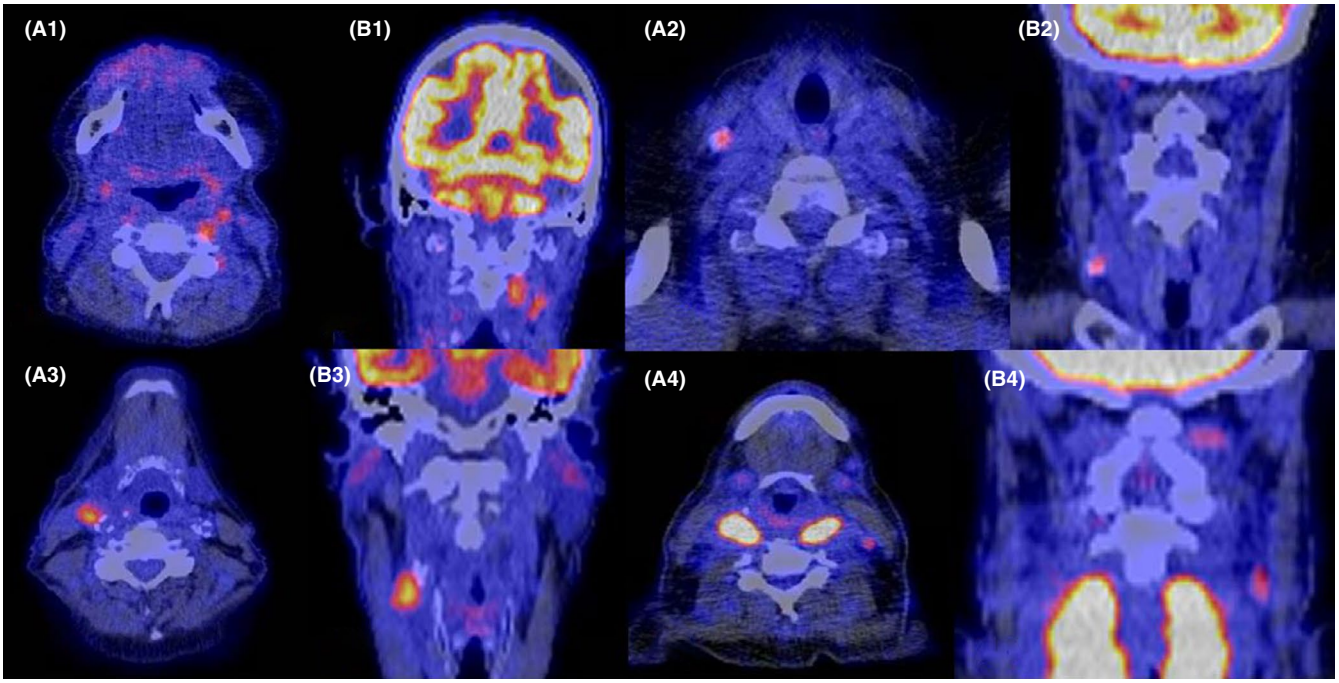

FIGURE 1 ^{18}F-FDG PET/CT images of true positive and false positive lymph nodes. Each number reflects a different case. Of all cases transversal images (A) and coronal images (B) are displayed. 1ab: response scan after chemoradiotherapy: false positive (no tumor) 2ab: response scan after chemoradiotherapy: true positive (tumor) 3ab: response scan after radiotherapy: true positive (tumor) 4ab: response scan after radiotherapy: false positive (no tumor); please note FDG-positive large goiter

TABLE 3 True and false positive/ negative ^{18}F-FDG PET/CT imaging scans with sensitivity, specificity, PPV, NPV and accuracy in relation to p16 status

	Total scans	TP (%)	FP (%)	FN (%)	TN (%)
All p16 -	65	6 (9.2)	2 (3.1)	0	57 (87.7)
p16 +	32	3 (9.4)	5 (1.6)	1 (3.1)	23 (71.8)
	Sensitivity (95% CI)	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**Accuracy (95% CI)**
All p16 -	100 (54-100)	96.6 (88.3-99.6)	75.0 (43.2-92.1)	100 (100-100)	96.9 (89.3-99.6)
p16 +	75 (19.4-99.4)	82.1 (63.1-93.9)	37.5 (18.5-61.4)	95.8 (80.7-99.2)	81.3 (63.6-92.8)

Abbreviations: FN, false negatives; FP, false positives; NPV, negative predictive value; PPV, positive predictive value; TN, true negatives; TP, true positives.

could be a higher and/or prolonged level of tissue inflammation after concomitant chemoradiotherapy. This could result in an increased FDG uptake which confounded the interpretation of the PET images resulting in a false-positive interpretations. Repeating the scan at 16 weeks could potentially diminish the false-positive interpretations in patient treated with chemoradiotherapy, as suggested by Liu.et al.[7]

The lower specificity in p16 positive tumours could be explained by the increased T-cell–based immune response reported in HPV positive tumours, resulting in the presence of inflammatory response in lymph nodes that takes longer to involute.[8]To our knowledge, this is the first study that investigated the effect of different treatment modalities on the diagnostic performance of ^{18}F-FDG PET/CT in treatment response evaluation. Also, most earlier studies investigating FDG PET did not distinguish between treatment response scans and scans made on clinical suspicion during follow-up.[9]

Yet, consideration should be given to some particular aspect of the study. First, although histopathological findings were used as gold standard for calculating the NPV, not all patients underwent a salvage neck dissection, and in some cases, a salvage neck dissection did not included a neck levels according to international guidelines. Therefore, clinical follow-up was additionally used as a reference for the absence of (developed) suspicious lymph nodes. A follow-up time of ≥1 year was used which is important because Van den Wyngaert et al demonstrated that residual disease can be detected up to one year after initial treatment.[10] Second, p16 was used as surrogate marker for HPV status, this includes the risk for misclassification of HPV negative tumours as HPV positive. Furthermore, daily clinical practice and following NCCN guidelines could result in pre-selection, in which a ^{18}F-FDG PET/CT is only made based on suspicion of residual primary, persistent disease or progression at CT or MRI imaging after 8 weeks.

4.1 | Comparison with other studies

The NPV in this study is comparable with that of a recent meta-analysis reporting 98%.[11] Likewise, our histopathogical re-assessment confirmed the earlier suggestion by Schröder et al, that reactive changes due to primary treatment with chemotherapy might cause false-positive lymph nodes on ^{18}F-FDG PET/CT.[9] Moreover, previous studies have shown a lower PPV for residual disease of ^{18}F-FDG PET/CT in p16 positive tumours compared with p16 negative tumours.[10,12]

Rulach et al compared PPV of PET in both p16 positive and p16 negative post-treatment tumours for tumours residual disease and found a lower PPV (30.0%) in p16 positive tumours compared with p16 negative tumours (81.8%).[12] In this study, we also observed a lower PPV for lymph node evaluation of p16 positive oropharyngeal cancers (37.5%) compared with (75.0%) in p16 negative tumours.

5 | CONCLUSION

The results of our institutional experience promote the use of ^{18}F-FDG PET/CT in treatment response evaluation. We suggest future studies analysing ^{18}F-FDG PET/CT for evaluation of treatment response should include initial treatment modality and HPV status as a potential confounder for predicting residual disease. Future research is necessary to assess whether a different approach in treatment response evaluation is required after chemoradiotherapy, especially in HPV positive tumours. This may lead to subsequent imaging surveillance strategies in the current algorithms and to an improvement of the accuracy of ^{18}F-FDG PET/CT imaging.

CONFLICT OF INTEREST

None to declare.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.