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Original Article

Accuracy of Response Assessment Positron Emission Tomography-Computed Tomography Following Definitive Radiotherapy Without Chemotherapy for Head and Neck Squamous Cell Carcinoma

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Abstract

Aim: There are few data to inform on the use of response assessment 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) following radical radiotherapy without chemotherapy for head and neck squamous cell carcinoma (HNSCC). This retrospective study evaluated the accuracy of PET-CT in HNSCC following radical radiotherapy.

Materials and methods: In total, 138 patients with HNSCC treated with radical radiotherapy without chemotherapy who underwent a baseline and response assessment FDG PET-CT were identified. FDG PET-CT outcomes were analysed with reference to clinicopathological outcomes.

Results: The median follow-up was 26 months. FDG-avid disease at baseline was present for the primary site and lymph nodes in 118 and 86 patients, respectively. With regard to the primary tumour, the negative predictive value (NPV) of a complete metabolic response (CMR) was 95%; the positive predictive value (PPV) of equivocal uptake and a positive scan were 6% and 82%, respectively. The likelihood ratios for a CMR, equivocal and positive scans of the primary site were 0.19, 0.22, 14.8, respectively. With regard to lymph node disease, the NPV of a CMR was 91%, the PPV of equivocal uptake and a positive scan were 33% and 88%, respectively. Likelihood ratios for lymph node disease for CMR, equivocal and positive scans were 0.19, 0.97 and 15.1, respectively.

Conclusion: Compared with the accuracy reported in the literature following chemoradiotherapy, response assessment FDG PET-CT following radical radiotherapy without chemotherapy had a similarly high NPV, whereas the PPV following a positive scan was higher.

Key words: Head and neck cancer; PET-CT; radiotherapy; response assessment

Introduction

Concurrent chemoradiotherapy is a standard of care for the management of locally advanced head and neck squamous cell carcinoma (HNSCC) for organ preservation [1] and unresectable disease [2]. Historically, a planned neck dissection was widely used following chemoradiotherapy based upon histopathological data from neck dissection series showing evidence of persistent disease in up to 40% of samples [3]. Cross-sectional imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI) is inherently limited in ability to distinguish persistent disease from post-treatment residuum [4,5]. However, combined functional and anatomical imaging with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) offers the promise of improved accuracy of response assessment. The PET-NECK randomised controlled trial compared PET-CT-guided surveillance (PET-CT 12 weeks post-treatment) with planned neck dissection following chemoradiotherapy; survival outcomes were similar, with only 20% of patients undergoing neck dissections in the PET-CT arm with reduced complications and superior cost-effectiveness [6]. These data are supported by a recent

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systematic review and meta-analysis of 20 studies [7] and show a very high negative predictive value (NPV) facilitating the avoidance of further intervention. Response assessment with PET-CT following chemoradiotherapy is now recommended in intercollegiate PET-CT imaging guidelines published in 2016 by the Royal College of Radiologists [8] and Head and Neck Cancer: UK National Multidisciplinary Guidelines in 2016 [9,10].

The use of chemotherapy for patients undergoing non-surgical treatment with radiotherapy is only appropriate for a limited proportion of patients. The addition of chemotherapy has not been shown to be beneficial for patients ≥70 years old, stage I/II disease, World Health Organization (WHO) performance status ≥2 [11] and is often not appropriate with significant comorbidity. Radiotherapy alone is a considerably less intensive treatment than chemoradiotherapy, expected to have a higher rate of locoregional treatment failure [1]. The accuracy of a test is dependent upon the population to which it is applied. Therefore, the accuracy of PET-CT for response assessment may differ following alternative treatment strategies. There are few data available to inform on the accuracy of PET-CT for response assessment following radical radiotherapy without chemotherapy, and the appropriateness or otherwise of PET-CT in this scenario is not addressed in guidelines recommending PET-CT following chemoradiotherapy [8–10]. It is particularly important to establish whether the NPV of PET-CT following radiotherapy alone is high enough to guide a PET-CT-guided surveillance strategy.

In our centre we have routinely used response assessment PET-CT following chemoradiotherapy and radiotherapy alone for a decade [12,13]. We reported our initial experience of PET-CT following radiotherapy alone in a small series of 45 patients suggesting a high NPV, but limited by sample size [14]. To the best of our knowledge there are no other reports of PET-CT exclusively following radiotherapy alone. The aim of this report is to update our experience of the accuracy of PET-CT following radiotherapy alone in a large series, determining the NPV and positive predictive value (PPV) for primary site and nodal disease.

Materials and Methods

The study involved retrospective analysis of a prospective database carried out under a waiver of informed consent and ethics approval by the Institutional Review Board. Consecutive patients who underwent a response assessment FDG PET-CT for HNSCC following radiotherapy between August 2008 and May 2017 were identified from an institutional database. Electronic case notes were used to confirm patients who fulfilled the eligibility criteria for the analysis.

Eligible patients fulfilled all of the following criteria: (i) histologically confirmed squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, larynx, paranasal sinuses or unknown site (presumed mucosal origin), (ii) definitive radiotherapy with curative intent, (iii) FDG PET-CT as a baseline prior to treatment, (iv) FDG PET-CT as response assessment. Patients were excluded with a history of prior therapeutic resection of primary and/or lymph node disease, use of chemotherapy, FDG PET-CT carried out only following response assessment after CT and/or MRI.

Data Collection

Demographic, clinical and imaging data, including PET-CT findings, maximum standardised uptake value (SUV_{max}) at the primary site and lymph nodes at presentation, SUV_{max} at the primary site and lymph nodes at response assessment, were obtained from a review of institutional electronic case note records and an imaging review.

Staging

Staging was routinely carried out by physical examination, fiberoptic endoscopy, examination under anaesthetic with biopsy where indicated, MRI or contrast-enhanced CT of the head and neck region and CT of the thorax. FDG PET-CT was carried out primarily to provide a baseline for future response assessment for patients with either bulky stage II or stage III/IV disease. Results were routinely reviewed in a specialist head and neck multidisciplinary meeting and a TNM classification, based on all available clinical and radiological data, according to the American Joint Committee on Cancer TNM staging seventh edition [15], was assigned.

Radiotherapy

Radiotherapy techniques changed several times between the study period of 2008–2017. A conformal three-dimensional CT-planned technique was used in the early part of this period, as previously described [16]. Intensity-modulated radiotherapy (IMRT) was subsequently implemented into routine clinical practice. During the initial period of IMRT use, a compartmental approach to target delineation was adopted [17]. A primary tumour clinical target volume (CTV) was created to include at least the gross tumour volume + 10 mm, modified to anatomical boundaries and including the whole involved anatomical compartment, e.g. the whole oropharynx or larynx/hypopharynx; the high dose nodal CTV was constructed to include the whole involved nodal level. Since 2016 a volumetric approach to outlining has been used, based on primary tumour and involved lymph nodes +10 mm to the high dose CTV and lymph node levels within elective dose CTVs. The planning target volume was created by auto-expansion of the CTV by 4 mm [16]. Institutional protocols were followed, with a radical treatment dose of 70 Gy in 35 fractions over 7 weeks or 65 Gy in 30 fractions over 6 weeks, with lower doses to prophylactic dose regions (54–63 Gy in 30–35 fractions over 6–7 weeks). IMRT was delivered with a 5–7 angle step and shoot IMRT technique or in the latter period of the study with a volumetric arc therapy technique.

Response Assessment and Follow-Up

Tumour response was routinely assessed 4 months after the completion of treatment by clinical examination, nasoendoscopy and FDG PET-CT; examination under anaesthetic and biopsies were carried out at clinical discretion following a response assessment. Patients with less than a complete response were evaluated for salvage surgery. Subsequently, patients were routinely followed up for a total of 5 years prior to discharge.

FDG PET-CT Protocol

FDG PET-CT examinations prior to June 2010 were carried out on a 16-slice Discovery STE PET-CT scanner (GE Healthcare, Amersham, UK), from June 2010 to October 2014 on a 64-slice Philips Gemini TF64 scanner (Philips Healthcare, the Netherlands) and after October 2014 on a 64-slice Discovery 710 scanner (GE Healthcare). Serum blood glucose was routinely checked and if blood glucose was >10 mmol/l scanning was not carried out. Patients fasted for 6 h prior to intravenous fluorine-18 FDG injection (dose varied according to patient body weight). PET acquisition from skull vertex to upper thighs was carried out 60 min after tracer injection. A silence protocol was used in the uptake period after tracer injection to minimise physiological tracer activity within the head and neck region. The CT component was carried out according to a standardised protocol (without the use of iodinated contrast medium) with the following settings: 140 kV; 80 mAs; tube rotation time 0.5 s per rotation; pitch 6; section thickness 3.75 mm (to match the PET section thickness). Patients maintained normal shallow respiration during the CT acquisition. Images were reconstructed using a standard ordered subset expectation maximisation algorithm with CT for attenuation correction. Both non-attenuation-corrected and attenuation-corrected datasets were reconstructed.

Categorisation of FDG PET-CT Response Assessment

The categorisation of FDG PET-CT response for the purposes of this analysis was based upon formal PET-CT reports. All FDG PET-CT scans were reported by a team of experienced radiologists dual certified in radiology and nuclear medicine. FDG PET-CT images were assessed qualitatively (by comparison of tumour or nodal tracer activity with background physiological uptake). Semi-quantitative assessment (SUV_{max}) of residual tumour or nodal uptake was also documented but this was not fundamental to the qualitative interpretation of response. Primary tumour and nodal SUV_{max} values were documented. The results of post-treatment FDG PET-CT were categorised into positive, equivocal or complete metabolic response (CMR) for the primary site and nodal sites separately, as previously described [12,13]. Areas of FDG uptake were classified as positive if uptake was focal, corresponding to a structural abnormality and of greater intensity than background liver activity. Scans were classed as equivocal if focal FDG uptake was reduced from baseline, was below liver background but above that of surrounding normal tissues. Scans were classed as negative in the absence of any abnormal focal FDG uptake or diffuse FDG uptake in the absence of corresponding anatomical abnormality on the CT that was considered to be radiotherapy related. The presence or absence of residual tissue on the CT component of the post-treatment FDG PET-CT was recorded.

Analysis and Statistics

Follow-up duration was defined as from the last day of radiotherapy treatment. Disease status post-treatment was determined from pathology and/or radiology correlation with a notes review of outcomes. In patients who did not receive a biopsy/surgical intervention, serial negative physical examinations over the follow-up period and any relevant imaging investigations were used as confirmation of disease-free status. Sensitivity, specificity, PPV and NPV were calculated using 2 × 2 tables constructed using clinicopathological outcomes. For analysis of positive, equivocal or CMR for primary site and lymph nodes separately, likelihood ratios were calculated together with post-test probability.

Results

In total, 138 patients were identified who had undergone baseline and response assessment PET-CT following radiotherapy (without concurrent chemotherapy). Patient, tumour and treatment characteristics are summarised in Table 1. The median age was 71 years (range 27–84); 85/138 (62%) patients had stage IV disease (TNM 7) and 77/138 (56%) of patients had oropharyngeal carcinoma. Reasons for not delivering chemotherapy were: age >70 years in 76/138 (55%), comorbidity in 40/138 (29%), early stage disease in 22/138 (16%). The median follow-up for all patients was 26 months (range 6–120) months.

Based on clinical/radiological ± pathological data on follow-up, 57/138 (41%) patients had disease progression. Primary tumour progressed in 27/138 (20%) patients; of these 27 patients, progression was biopsy proven in 14 patients and based on radiology without biopsy in 13 patients. Primary progression in the absence of developing lymph node or distant progression occurred in 13 patients. Lymph node progression occurred in 29/138 (21%) patients; in 16 of these 29 patients, lymph node progression was biopsy proven and based on radiology in the remaining patients. Lymph node progression occurred without progression of the primary tumour or development of distant metastases in 15 patients; 23/138 (17%) patients were found to have developed distant metastatic disease on follow-up (based on radiology without biopsy in 19 patients and biopsy proven in four patients).

The median time to response assessment FDG PET-CT following (chemo)radiotherapy was 17 weeks (range 8–22 weeks; interquartile range 16–18 weeks); 80/138 (58%) patients had a CMR on PET-CT. On response assessment PET-CT, 16/138 (12%) patients were found to have new

Table 1
Demographics, tumour and treatment details ($n = 138$)

Characteristics	$n = 138$	%
Gender		
Male	97	70
Female	41	30
Smoking		
Current	58	42
Ex	48	35
Never	21	15
Not recorded	11	8
Tumour site (subsite)		
Oropharynx	77	41
Base of tongue	30	
Tonsil	44	
Soft palate	2	
Posterior pharyngeal wall	1	
Larynx	22	16
Supraglottis	15	
Glottis	6	
Subglottis	1	
Hypopharynx	16	12
Pyriform fossa	11	
Post-cricoid	3	
Posterior pharyngeal wall	2	
Oral cavity	2	1
Buccal mucosa	1	
Floor of mouth	1	
Paranasal sinus	6	4
Maxillary sinus	3	
Nasal cavity	2	
Sphenoid sinus	1	
Unknown primary	15	11
T stage		
T0	15	11
T1	20	14
T2	37	27
T3	41	30
T4	25	18
N stage		
N0	46	33
N1	16	12
N2	75	54
N2a	5	
N2b	52	
N2c	18	
N3	1	1
Stage group (AJCC)		
I	4	3
II	16	12
III	33	24
IV	85	62
Histopathology		
Well differentiated	1	1
Moderately differentiated	35	25
Poorly differentiated/basaloid	83	60
Not recorded	19	14
HPV status (in oropharynx and unknown primary only, $n = 88$)		
Positive	33	38
Negative	16	18
Not tested	43	49
Radiotherapy dose		
70 Gy in 35 fractions	118	86
65 Gy in 30 fractions	20	14

(*continued on next page*)

Table 1 (*continued*)

HPV, human papillomavirus.

distant metastases. Two of these 16 patients had a complete locoregional response with the detection of distant metastases.

Assessment of Primary Tumour Response by FDG PET-CT and Correlation with Outcome

The primary tumour was FDG avid in 118 patients, with a mean SUV of 13 (range 2–58). The primary was non-FDG avid in five patients with a biopsy-proven primary tumour (two after diagnostic tonsillectomy) and 15 patients had an unknown primary tumour. On response assessment PET-CT, a CMR was reported in 75/118 (64%), an equivocal response in 16/118 (14%) and positive in 27/118 (23%). Table 2 summarises the accuracy of PET-CT, comparing complete versus equivocal and positive scans grouped together for the primary site in addition to lymph nodes and overall. Table 3 details primary site outcomes, likelihood ratios and post-test probability for CMR, equivocal and positive categories separately. The NPV of a primary tumour site CMR was 95%. The mean SUV_{max} for patients with equivocal primary site uptake was 5.3 (range 3.8–7.8). The PPV of equivocal uptake was 6%. The mean SUV_{max} for patients reported as a positive scan at the primary site was 7.1 (range 3.7–13.4). The PPV of a positive scan was 82%.

Assessment of Lymph Node Response by FDG PET-CT and Correlation with Outcome

With regard to lymph node disease, 86/138 (62%) patients had FDG-avid lymph node disease at baseline, the mean SUV was 9.7 (range 2.8–27.4); 46 patients had N0 disease, two patients had undergone excision biopsies of the only sites of lymph node disease and four patients had non-avid lymph node disease.

On response assessment PET, 57/86 (66%) patients with FDG-avid nodal disease at baseline had a CMR. Eighteen of these 57 patients were noted to have residual lymph node visible on the low-dose non-contrast CT component of the PET-CT scan. Equivocal and positive scans were reported in 3/86 (3%) and 26/86 (30%) patients, respectively. Table 2 summarises the accuracy of PET-CT, comparing complete versus equivocal and positive scans together for analysis. Lymph node outcomes, likelihood ratios and post-test probability for CMR, equivocal and positive response categories are summarised in Table 4. The NPV of a lymph node CMR was 91%. For the three patients with an equivocal PET-CT response in the lymph nodes, the mean SUV_{max} was 2.9 (range 2.8–3.1); the PPV of an equivocal scan was 33%. The mean SUV_{max} for patients reported as a positive scan in lymph nodes was 5.2 (range 3.0–9.6). The PPV of a positive scan was 88%.

Table 2
Details of accuracy of positron emission tomography-computed tomography (PET-CT) response scans comparing complete metabolic response versus equivocal and positive scans grouped together

	Primary site ($n = 118$)	Neck nodes ($n = 93$)	Overall (primary, neck and distant) ($n = 138$)
PET-CT positive	43	29	58
PET-CT negative	75	57	80
True positive	23	24	42
True negative	71	52	68
False positive	20	5	16
False negative	4	5	12
Sensitivity	85%	83%	78%
Specificity	77%	91%	81%
Positive predictive value	53%	83%	72%
Negative predictive value	95%	91%	85%
Accuracy	80%	88%	80%

years, stage I/II disease, WHO performance status ≥2) [11] and may not be advisable due to comorbidity. Many patients are therefore treated with radical radiotherapy alone; this is an increasingly common scenario with an aging population. Although FDG PET-CT-guided surveillance has been shown to be an effective strategy following chemoradiotherapy [6,7], there is a lack of data to establish if PET-CT is as accurate following radiotherapy alone. To the best of our knowledge this is the largest reported series of patients treated with radiotherapy without chemotherapy undergoing a response assessment PET-CT; other reports have not analysed this group of patients separately to those treated with chemoradiotherapy [13,18–20]. Most series include either very few patients treated with radiotherapy alone [13,18,19] or none [21,22]. By contrast, Sjovall *et al.* [20] presented a series of 105 patients that included 98 treated with radiotherapy alone; the high proportion of patients not receiving chemotherapy reflects their institutional guidelines to avoid chemotherapy in the absence of 'heavy tumour burden'. A recent meta-analysis [7] on the use of response assessment PET-CT in HNSCC included patients treated with radiotherapy ± chemotherapy but did not report how many patients had radiotherapy only or analyse this subgroup separately.

Table 3
Positron emission tomography-computed tomography (PET-CT) response assessment for patients with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG)-avid primary site disease at baseline ($n = 118$), analysing negative, equivocal and positive scans as separate categories

PET-CT response scan outcome for FDG-avid primary site		Primary site disease status on follow-up		Likelihood ratios	Post-test probability
Category	Number	Disease	No disease		
Negative	75	4	71	0.19	0.05
Equivocal	16	1	15	0.22	0.06
Positive	27	22	5	14.8	0.82
Total	118	27	91		

Table 4
Positron emission tomography-computed tomography (PET-CT) response assessment for patients with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG)-avid lymph node disease at baseline ($n = 86$) analysing negative, equivocal and positive scans as separate categories

PET-CT response scan outcome for FDG-avid lymph node disease		Primary site disease status on follow-up		Likelihood ratios	Post-test probability
Category	Number	Disease	No disease		
Negative	57	5	52	0.19	0.09
Equivocal	3	1	2	0.97	0.33
Positive	26	23	3	15.1	0.89
Total	86	29	57		

Discussion

We report here our experience in a large retrospective series of using FDG PET-CT for response assessment following radiotherapy alone in HNSCC. The use of concurrent chemotherapy has not been shown to improve treatment outcomes for several groups of patients (age ≥70

A high NPV is critical to the use of PET-CT as a tool to safely avoid the necessity for a planned neck dissection and to avoid unnecessary investigation/biopsy of the primary site [18]. Prior series have shown high NPVs (Slevin *et al.* [13] 99% for nodes, 99% for the primary site; Bird *et al.* [19] 98% for nodes, 100% for the primary site; Vainshtein *et al.* [22] 91% for nodes, 98% in the primary site; Ng *et al.* [23]

overall 92%; Nelissen *et al.* [21] 93% for nodes, 95% for the primary site; Sjovall *et al.* [20] overall NPV 94%) with the meta-analysis [7] reporting an NPV of 98% (based on a prevalence set at 10%). In the current series, the NPV for lymph nodes was 91% and for the primary tumour site was 95%. The NPV for both the primary tumour and lymph nodes in our series seem to be in a similar range to other predominantly chemoradiotherapy series; although the NPV for lymph nodes of 91% is at the lower end of the spectrum across studies, it remains similar to other large chemoradiotherapy series [21,22]. The overall NPV was lower at 85%; this is due to the development of distant metastases in some patients.

The PPV of response assessment PET-CT has been widely reported to be limited (Slevin *et al.* [13] 53% for nodes, 47% for the primary; Nelissen *et al.* [21] 66% for nodes, 44% for the primary site; Bird *et al.* [19] 61% for nodes, 53% for the primary site; Sjovall *et al.* [20] 56% overall) and 58% overall in the meta-analysis [7]. In the current study, the PPV for lymph nodes and the primary site was high compared with these studies (83% for nodes, 82% for primary sites). This may reflect the higher prevalence of residual disease in a group of patients judged not appropriate to receive chemotherapy and therefore having a less efficacious approach to treatment. In addition, there is considerable heterogeneity in the methods by which equivocal scans are analysed, and this can have a large impact on PPV. This is demonstrated in the current study, in which the PPV for uptake at the primary site was 82% if positive scans were analysed alone and 53% if positive and equivocal scans were grouped together for the purposes of analysis. The analysis of these categories separately as opposed to grouped together is directly relevant to clinical decision making. These data regarding the impact of including equivocal scans in calculating PPV are consistent with the finding of Nelissen *et al.* [21] of increasing PPV with increasing SUV cut-off (e.g. for primary site an $SUV_{max} > 3$ had a PPV of 45% compared with 65% for SUV >6). In our centre we have adopted a policy of response assessment PET-CT at about 4 months post treatment. A recent analysis [24] has suggested that diagnostic performance of PET-CT improves up to 11 weeks post-treatment and then plateaus. Similarly, Nelissen *et al.* [21] found higher rates of false-positive and false-negative scans when PET-CT was carried out prior to 12 weeks post-treatment. It is possible that later scanning timepoints may contribute to the relatively low rate of false-positive scans by allowing post-radiotherapy changes in inflammation and vascularity [25]. The limited number of series scanning significantly beyond 12 weeks post-treatment precludes a clear determination as to whether this later timepoint is advantageous [7,13,26]. Therefore, it seems likely that the higher PPVs in the current study compared with many in the literature reflect residual disease prevalence, method of analysis and possibly scan timing rather than differences in test accuracy depending on the use or otherwise of chemotherapy.

The classification of PET-CT response scans into positive, equivocal and negative was qualitative, as previously reported [12,13] and as used by other groups [18]. Others have advocated a quantitative approach [27]. The optimal approach has yet to be established, although it does limit comparison between series.

Limitations of this series include the heterogenous nature of the patient group, including 16% with early stage (stage I/II disease) and the variable reasons for the omission of chemotherapy, including age and comorbidity. Human papillomavirus (HPV) data (using p16 as a surrogate) is only available for a limited proportion of patients; p16 testing was not routinely carried out during the initial period of this study. The meta-analysis [7] has suggested that the diagnostic performance of PET-CT is slightly lower for HPV-positive patients, although importantly in the PET-NECK study [6] there was no difference in survival in the surveillance and neck dissection arms when stratified for HPV status.

In summary, this is the largest reported series of response assessment PET-CT following radiotherapy without chemotherapy. The NPV for primary site and lymph nodes was high; the NPV seems to be similar to results of chemoradiotherapy series, suggesting that PET-CT can be used to guide a surveillance strategy following radical radiotherapy alone. The PPV for positive scans following radiotherapy was higher than that generally reported for PET-CT following chemoradiotherapy.

Conflict of Interest

The authors declare no conflict of interest.

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