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Accuracy of FDG PET-CT response assessment following radiotherapy alone for head and neck squamous cell carcinoma: retrospective analysis of 45 patients

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Keypoints

- FDG PET-CT is an established tool for response assessment following definitive concurrent chemoradiotherapy for head and neck squamous cell carcinoma with a high negative predictive value guiding treatment decisions.
- Little data is available regarding the accuracy of FDG PET-CT for response assessment following definitive radiotherapy without chemotherapy.
- We retrospectively analysed the accuracy of FDG PET-CT for response assessment following radiotherapy alone without planned neck dissection in 45 patients.
- PET-CT had a high negative predictive value of 93% and positive predictive value of 88%.
- Based upon the high negative predictive value, PET-CT can be used to avoid surgical intervention following radiotherapy alone.

Introduction

Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography – computed tomography (PET-CT) is established as an accurate tool for response assessment following concurrent chemo-radiotherapy for head and neck squamous cell carcinoma , with a high negative predictive value (NPV), guiding selective surgical intervention [1-3]. The phase III PET neck surveillance trial demonstrated that PET-CT guided imaging surveillance following concurrent chemo-radiotherapy compared with a planned neck dissection achieved similar survival with far fewer neck dissections and was cost effective [2]. However, the addition of concurrent chemotherapy to radiotherapy is often contra-indicated due to comorbidity, and has not been found to be beneficial for patients with stage I/II disease, age ≥70 years old, WHO performance status ≥2 [4]. There is a paucity of data to determine whether response assessment PET-CT after radiotherapy alone is sufficiently accurate to influence management.

In our centre we have adopted a policy of observation if a complete metabolic response on PET-CT is achieved following radiotherapy ± chemotherapy [3, 5]. The aim of this report is to analyse the accuracy of FDG PET-CT response assessment following radiotherapy alone without a planned neck dissection.

Methods

Ethical considerations

The study was registered with the Institutional Quality Improvement Board.

Study design

45 consecutive patients with head and neck squamous cell carcinoma who underwent FDG PET-CT for response assessment following curative-intent radiotherapy (without chemotherapy) between 2009-2014 were retrospectively identified. Inclusion criteria were i) squamous cell carcinoma of the oropharynx, larynx, hypopharynx or unknown primary ii) radiotherapy with curative intent, iii) FDG PET-CT as a baseline prior to treatment. Patients with prior therapeutic resection of primary and/or lymph node disease were excluded.

Response assessment

Tumour response was routinely assessed 4 months after the completion of radiotherapy by clinical examination and FDG PET-CT (according to previously described imaging protocols [3, 5]). Planned neck dissections were not performed.

Categorisation of FDG PET-CT response assessment

Categorisation of FDG PET-CT response was based upon radiology reports as previously described [3, 5]. Results of post-treatment FDG PET-CT were qualitatively categorised into 'complete', 'equivocal' or 'incomplete' for the primary site and nodal sites separately. A complete response was defined as the absence of any abnormal focal FDG uptake or diffuse FDG uptake in the absence of corresponding anatomical abnormality on the CT which was considered to be radiotherapy related. An incomplete response was defined as focal uptake, corresponding to a structural abnormality and of greater intensity than background liver activity. Scans were classed as equivocal if focal FDG uptake was below liver background but above that of surrounding normal tissues.

Analysis and statistics

Duration of follow up was defined from final day of radiotherapy. Sensitivity, specificity, positive predictive value (PPV) and NPV were calculated using 2x2 tables constructed using clinico-pathological outcomes.

Results

Median follow up for living patients was 32 months (range 8-65). Median age was 68 years (range 40-83). 32/45 (71%) were male. Disease and treatment characteristics are shown in Table 1. Reasons for not delivering chemotherapy concurrently with radiotherapy were: age ≥70 years old in 19 patients, early stage disease (stage I/II) in 10 patients (including 1 patient ≥70 years old), comorbidity/limited performance status in 15, social situation in 1, patient choice in 1.

On pre-treatment PET-CT 37 patients had an FDG-avid primary lesion and the median primary tumour maximum SUV was 11.9 (range 2.9-53). 31 patients had FDG-avid lymph node disease on baseline PET-CT and the median lymph node maximum SUV was 9 (range 3-14.5). Median time to response assessment FDG PET-CT following radiotherapy was 17.6 weeks (range 13-22 weeks). Overall, 29 of 45 (64%) patients had a locoregional complete metabolic response. Overall, treatment failure at the primary site and lymph nodes occurred in 10/45 (22%) and 11/45 (24%) patients respectively (including combined primary and nodal treatment failure in 4 patients). Table 2 demonstrates the sensitivity, specificity, PPV and NPV for the response assessment FDG PET-CT outcomes. Where primary tumour or lymph nodes were not assessable on the baseline FDG PET-CT these were omitted from the analysis of the respective response assessments.

With regard to the primary site, a complete metabolic response was demonstrated in 27 of 36 (75%) of patients with an FDG-avid primary site at baseline assessment; NPV was 92%. FDG uptake suggestive of persistent disease was present in 8 of 36 patients (22%), and an equivocal response in 2 of 36 (6%) patients. Median SUV in the incomplete and equivocal FDG PET-CT group for primary site was 5.6 (range 3.9-10.9). For the primary tumour site demonstrating an incomplete (n=8) or equivocal response (n=2), status was determined for analysis on the basis of biopsy, surgery and subsequent clinical progression/ follow up in 5, 2 and 3 patients respectively. PPV combining incomplete and equivocal scans was 80%, PPV for incomplete response scans alone was 75%. Both patients with equivocal uptake in the primary site has subsequently proven residual disease.

With regard to lymph node disease, a complete metabolic response was demonstrated in 20 of 31 (65%) of patients with FDG-avid nodal disease at baseline; NPV was 95%. FDG uptake suggestive of persistent disease was present in 9 of 31 (29%), and equivocal response in 2 of 31 (6%). Median SUV in the incomplete and equivocal FDG PET-CT group for lymph nodes was 4.7 (range 2.8-9.6). For lymph nodes demonstrating an incomplete (n=9) or equivocal response (n=2), status was determined for the analysis on the basis of subsequent clinical progression/ follow up, biopsy and

neck dissection in 7, 3 and 1 patients respectively. PPV combining incomplete and equivocal scans was 91%; PPV for incomplete response scans alone was 78%. Both patients with equivocal lymph node uptake had evidence of persistent disease (neck dissection in one, and clinical regional progression with distant disease in the other).

8 of 45 (18%) of patients had new distant metastatic disease detected on response assessment FDG PET-CT (4 with complete locoregional response): 5 developed lung metastases, 2 lung and bone metastases, and one liver metastases.

Discussion

The accuracy of a test depends upon the population to which it is applied and the accuracy of PET-CT for response assessment may vary depending upon treatment strategy. To guide a surveillance strategy following radiotherapy alone, which is a less intensive treatment than chemo-radiotherapy, it is essential to determine whether the NPV of FDG PET-CT is high with regard to both primary and nodal disease.

Synopsis of key findings

In this series of 45 patients, the NPV of a complete metabolic response of PET-CT was high, 92%, 95% and 93% for the primary site, lymph nodes and overall. The PET-CT response scan was false negative in 2/45 (4%) patients. The PPV of incomplete response or equivocal FDG uptake grouped together was high, 80%, 91% and 88% for primary site, lymph nodes and overall. Overall sensitivity and specificity were high (88% and 93% respectively). Despite the use of PET-CT for staging pre-treatment, 18% of patients were found to have developed distant metastatic disease on response assessment PET-CT.

Study limitations

Limitations include the retrospective nature of the analysis, along with the limited size of study population. Few patients had an equivocal response, precluding conclusions regarding optimal management of this subgroup. Human papilloma virus testing was not routinely available for patients treated in this era.

Comparison with other studies

To the best of our knowledge there are no other reports of FDG PET-CT for response assessment exclusively following radiotherapy alone. Multiple studies have examined PET-CT following patients

treated exclusively with chemo-radiotherapy [6, 7] or including a majority of patients receiving chemotherapy [3, 8]. Within these single centre studies the NPVs for the primary lesion and lymph nodes are consistently high (98-100% and 91-99% respectively). By contrast, PPVs are more limited (33-81% and 61-83% respectively). In a meta-analysis [1] including predominantly studies of PET-CT post-chemoradiotherapy, the PPV and NPV for primary site and lymph nodes of PET was found to be 58.6%, 95.1% and 52.1% and 94.5% respectively. By comparison with these studies, the NPV for primary and lymph nodes in the current series after radiotherapy alone is in a similar range, whilst the PPVs of primary and lymph nodes is higher than might have been anticipated. Consistent with our data on NPV is a prior study of early PET-CT 6 weeks post-treatment [9] which reported on a series of patients with human papilloma virus-positive oropharyngeal carcinoma of whom 92% received radiotherapy alone; NPV was 94% and a PPV of 56%. The cause of the high PPV in our series is unclear and may be related to small sample size. PET-CT performed at differing timepoints may have differing accuracy and the delayed timing of PET-CT may have led to an improved PPV. Meta-analysis has shown that PET-CT performed ≥12 weeks post treatment improves diagnostic accuracy [1]. Along with others [10], we have previously adopted a policy of performing response assessment 4 months post-treatment.

Summary

FDG PET-CT response assessment following radiotherapy alone has a high NPV for both primary site and lymph nodes and can be used to guide treatment decisions to avoid the need for further investigation and neck dissection respectively.

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Table 1: Disease site, TNM stage, AJCC stage, histology and treatment

Characteristic	**Number (%)**
Primary tumour site:	
Oropharynx	27 (60%)
Oral cavity	1 (2%)
Hypopharynx	5 (11%)
Larynx	6 (13%)
Unknown primary	6 (13%)
T stage	
T0	5 (11%)
T1	5 (11%)
T2	15 (33%)
T3	11 (24%)
T4	9 (20%)
Nodal (N) stage	
N0	14 (31%)
N1	5 (11%)
N2a	2 (4%)
N2b	18 (40%)
N2c	6 (13%)
N3	0 (0%)
Metastases (M) stage	

M0	45 (100%)
Stage II III IV	 10 (22%) 8 (18%) 27 (60%)
Histology SCC	 45 (100%)
Radiotherapy dose schedule 70Gy in 35 fractions 65Gy in 30 fractions	 43 (96%) 2 (4%)

Table 2: Diagnostic performance of response assessment FDG PET-CT in patients with head and neck cancer after radiotherapy (incomplete or equivocal responses grouped together for analysis)

	Primary site (n=36)	Neck nodes (n=26)	Overall (primary and neck (excluding distant metastases) (n=45)
FDG PET-CT incomplete or equivocal response	10	11	16
FDG PET-CT complete response	26	20	29
True positive	8	10	14
True negative	24	19	27
False positive	2	1	2
False negative	2	1	2
Sensitivity	80%	91%	88%
Specificity	92%	95%	93%
Positive predictive value	80%	91%	88%
Negative predictive value	92%	95%	93%