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Original Article

# Prognostic Value of 2-[$^{18}$F] Fluoro-2-deoxy-D-glucose Positron Emission Tomography-Computed Tomography Scan Carried out During and After Radiation Therapy for Head and Neck Cancer Using Visual Therapy Response Interpretation Criteria

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## Abstract

*Aims:* To evaluate the prognostic utility of 2-[$^{18}$F] fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (FDG PET-CT) carried out in the third week (iPET) and after completion (pPET) of definitive radiation therapy in patients with mucosal primary head and neck squamous cell carcinoma (MPHNSCC) and to investigate the optimal visual grading criteria for therapy response assessment.

*Materials and methods:* Sixty-nine consecutive patients with newly diagnosed MPHNSCC treated with radical radiation therapy with or without systemic therapy underwent staging. PET-CT, iPET and pPET were included. All PET-CT images were reviewed by using a visual grading system to assess metabolic response for primary tumour: 0 = similar to adjacent background blood pool activity; 1 = more than background but < mediastinal blood pool; 2 ≥ mediastinal blood pool and < liver; 3 ≥ liver; and 4 ≥ brain. The results were correlated with locoregional recurrence-free survival (LRFS), disease-free survival (DFS) and overall survival, using Kaplan-Meier analysis.

*Results:* The median follow-up was 28 months (range 6–62), the median age was 61 years (range 39–81) and AJCC 7th edition clinical stage II, III and IV were six, 18 and 45 patients, respectively. The optimal threshold for non-complete metabolic response (non-CMR) was defined as focal uptake ≥ liver (grade 3) for iPET and focal uptake ≥ mediastinum (grade 2) for pPET. The 2 year Kaplan-Meier LRFS, DFS and overall survival estimates for primary CMR and non-CMR in iPET were 89.8% versus 71.5% ($P = 0.062$), 80.1% versus 65.3% ($P = 0.132$), 79.1% versus 72.1% ($P = 0.328$) and in pPET 86.2% versus 44.6% ($P = 0.0005$), 77.6% versus 41.2% ($P = 0.006$), 81.2% versus 40.6% ($P = 0.01$), respectively. The negative predictive value (NPV) for LRFS for patients achieving both primary and nodal CMR in iPET was 100%. No locoregional failure was observed in patients with both primary and nodal iPET CMR ($P = 0.038$), whereas those with nodal iPET CMR had no regional failure ($P = 0.033$). However, the positive predictive values (PPV) for LRFS and DFS for iPET and pPET were found to be poor: 30% and 36% for iPET and 35% and 39% for pPET, respectively.

*Conclusion:* Standardised criteria using visual assessment are feasible. The metabolic response using visual assessment with standardised interpretation criteria of iPET and pPET can be useful predictors of tumour control. Dose de-escalation can be considered on the basis of a high NPV for iPET. However, the PPV of iPET is poor, indicating that additional discriminative tools are needed.



*Key words:* Adaptive radiotherapy; FDG PET; head and neck cancer; visual consensus reading

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## Introduction

Outcomes for the treatment of mucosal primary head and neck squamous cell carcinoma (MPHNSCC) have improved significantly using radiation therapy for organ preservation [1]. Most treatment failures still occur within the primary tumour volume or regional lymph nodes. However, intensification of treatment can result in long-term toxicities that impact poorly on patient function and quality of life.

2-[$^{18}$F] fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (FDG PET-CT) has been widely used to assess the treatment outcome after completion of chemoradiation therapy for locally advanced MPHNSCC. The role of post-treatment FDG PET-CT as a useful marker of prognosis is well established, with high negative predictive value (NPV) but low to moderate positive predictive value (PPV) for tumour recurrence [2]. The metabolic treatment response is usually based on qualitative assessment and there has been no established visual response assessment (VRA) criteria until very recently, with Marcus *et al.* [3] reporting on a five-point visual scoring system for the post-treatment setting.

Obtaining FDG PET-CT at an earlier time point can result in poorer specificity due to treatment-related inflammation. Research evaluating the role of FDG PET-CT in assessing the early treatment response during radiation therapy is limited to small studies with mixed results [4–9] and established qualitative assessment criteria are lacking. The VRA in mid-treatment PET-CT offers advantages over a semi-quantitative assessment, such as maximum standardised uptake value ($SUV_{max}$) in terms of standardisation and reproducibility. It is also less affected by confounding factors such as variations between scanners, patient's blood glucose level, reactive bone marrow or soft tissue uptake post-treatment and variability in uptake time post-FDG injection. The use of VRA criteria by measuring relative uptake to the mediastinum blood pool or liver has been validated for adaptive therapy in lymphoma, but its role for MPHNSCC during primary radiation therapy remains unproven.

Potentially the use of VRA with standardised criteria can predict for patients with good or poor outcomes early in the course of treatment and therefore identify potential candidates for de-escalation or escalation of treatment. The aim of this study was to investigate the utility of a five-point visual grading scale with FDG PET-CT, carried out in the third week of primary radiation therapy (iPET) and after the completion of radiotherapy (pPET), to detect residual disease and predict treatment outcome. The secondary objective was to establish the optimal visual threshold for the therapeutic response assessment during (iPET) and after radiation therapy (pPET).

## Materials and Methods

### *Study Population*

Eligibility criteria for this retrospective study, approved by the South Western Sydney Local Health District Human Research Ethics Committee, included biopsy-proven, newly diagnosed MPHNSCC, with no evidence of distant metastatic disease at the time of diagnosis, treated with radical intent radiotherapy (with or without chemotherapy) and received FDG-PET scans before, during (week 3) and after (3 months post-treatment, median 13 weeks, range 9–21) radiotherapy. Patients with cancers of the nasopharynx and nasal cavity were excluded from this study. The management plans for all patients were determined at our multidisciplinary team meeting.

We carried out the PET in the third week of radiation therapy, as we felt that this time point would be sufficient to assess the therapeutic response, but before significant inflammation occurs from treatment, which is clinically observed to start increasing from the second week of treatment [10]. This would also allow us time to adapt treatment in future trials.

### *Visual Consensus Reading*

A consensus reading was carried out by a review of the PET and CT images with two nuclear medicine physicians (NMP) and a radiation oncologist. All were blinded to clinical and other diagnostic data except the primary tumour site. The images were assessed on an Advantage Workstation (GE Healthcare). Serial FDG PET-CT images were viewed on three cross-sectional images (axial, coronal and sagittal), displayed and correlated using the PET-VCAR (Volume-Computer-Assisted-Reading) software to ensure accurate inclusion and comparison of primary tumour and nodal sites, and exclusion of adjacent normal structures. A five-point visual grading system was used to assess residual FDG uptake and metabolic response (for both primary tumour and nodal metastases) of both iPET and pPET: 0 = similar to adjacent background, e.g. blood pool activity in the ipsilateral/contralateral internal jugular vein or muscle if there were artefacts within the internal jugular vein; 1 = more than background but $<$ mediastinal blood pool; 2 $\geq$ mediastinal blood pool, and $<$ liver; 3 $\geq$ liver and 4 $\geq$ brain. Diffuse uptake thought to be treatment related was classified as a complete metabolic response (CMR). There was no patient with multi-focal primary disease, but in patients with nodal disease, only the most intense lymph node was used for assessment of FDG-PET parameters. For all studies, mean SUV uptakes of references sites – mediastinum (using thoracic aortic arch) and liver (using mid-liver at segment 5/8 and 4B junction) – were recorded and compared longitudinally between pre-PET, iPET and pPET to ensure standardisation. No significant differences were noted between the background mediastinal and liver uptake longitudinally across the three studies. For equivocal cases on visual assessment between the first two NMP, then a third NMP was used; and if necessary, semi-quantitative assessment using tumour to background ratios was used to reach a final agreement.

### *Imaging Technique*

The studies were acquired in the radiation therapy treatment position (for staging PET and iPET) on either a