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Prognostic utility of ^{18}F-FDG PET-CT performed prior to and during primary radiotherapy for nasopharyngeal carcinoma: Index node is a useful prognostic imaging biomarker site

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ABSTRACT

Purpose: To evaluate the prognostic value of ^{18}F-FDG-PET-CT performed prior to (prePET) and during the third week (iPET) of radiation therapy (RT) in nasopharyngeal carcinoma (NPC).

Materials and methods: Thirty-patients with newly diagnosed loco-regionally advanced NPC treated with radical RT underwent prePET and iPET. The median follow-up was 26 months (8–66.9). The maximum-standardised-uptake-value (SUVmax), metabolic-tumour-volume (MTV) and total-lesional-glycolysis (TLG) of the primary tumour (PT), index-node (IN) (lymph node with highest TLG), total-lymph-nodes (TN) and combined primary-tumour and nodal (PTN), and their % reductions in iPET were analysed, and results were correlated with 2-year Kaplan–Meier loco-recurrence-free-survival (LRFS), regional-failure-free-survival (RFFS), distant-metastatic-failure-free-survival (DMFFS), disease-free-survival (DFS), and overall-survival (OS). Optimal-cutoffs (OC) were derived from Receiver-Operating-Characteri stic curves.

Results: For LRFS, the only predictor was reduction in PT MTV by >50%: 95.2% vs. 75.0%, $p = 0.024$.

Results: For other treatment outcomes, only nodal or PTN predicted outcomes. The IN SUVmax (pre-PET-OC = 10.45 g/mL and iPET-OC = 8.15) and TLG (prePET-OC = 90 g and iPET-OC = 33.4) were the best predictors of outcome: RFFS (iPET SUVmax/TLG): 100% vs. 50%, $p < 0.001$ and 100% vs. 44%, $p = 0.032$; DMFFS (prePET SUVmax/TLG); 100% vs. 51.9%, $p = 0.004$ and 100% vs. 47.6%, $p = 0.002$; DFS (prePET TLG and iPET SUVmax): 87.5% vs. 33%, $p = 0.045$ and 78.7% vs. 20%, $p = 0.01$; and OS (prePET TLG): 100% vs 66.3%, $p = 0.036$.

Conclusions: We have demonstrated IN of prePET and iPET to be a feasible and potentially useful novel imaging biomarker to predict for patients with NPC who have a high risk of regional or distant metastatic failure. Future work is required to validate our findings in a well-powered, prospective study with a standardised treatment protocol, and their potential use to guide individualised therapy for NPC.

The advent of intensity-modulated radiation therapy (IMRT) and incorporation of magnetic resonance imaging (MRI) and ^{18}F-Flurorodeoxyglucose (FDG) positron emission tomography (PET) into radiotherapy planning and staging has significantly improved loco-regional control of nasopharyngeal carcinoma (NPC), with decreased toxicity [1–3].

Cisplatin based concurrent chemo-radiotherapy (CRT) is now the standard treatment for stage II–IVa NPC following the initial Intergroup 0099 Trial [4]. The role of adjuvant chemotherapy has received continuing debate despite being included as part of this trial with conflicting results in subsequent randomised trials and there is ongoing concern regarding poor patient tolerance and increased toxicities [5–8].

To improve compliance and decrease toxicities, induction chemotherapy has been investigated and has shown positive results in improving distant metastatic failure free survival in phase II trials [9,10]. The selection of patients who may best benefit from this or other CRT approach still needs to be refined using better prognostic indicators [11–14]. The use of imaging biomarkers may improve individualised treatment strategies for combined chemotherapy and radiotherapy. There is limited published data on the prognostic value of pre-treatment FDG PET-CT tumour

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volume parameters for treatment outcome in NPC [15–20]. No studies to date have evaluated the role of FDG PET-CT during treatment or the additional benefit of assessing volumetric nodal metabolic burden to predict treatment outcome. Use of functional imaging with FDG PET-CT may allow better prognostication of patients at high risk of distant metastatic or regional failures and may hence benefit from additional adjuvant systemic therapy. There is limited data on the use of CT or MRI for adaptive radiotherapy during RT for NPC [21–23].

The primary aim of this study is to evaluate the prognostic value of FDG PET-CT performed prior to RT (prePET) and during the third week of RT (iPET) in patients with newly diagnosed NPC. The secondary aim is to assess the feasibility of measuring volumetric nodal tumour metabolic burden and determine if this improves the prediction of treatment outcome including risk of distant metastatic failure.

Materials and methods

Study population

Patients with biopsy-proven, nasopharyngeal cancer without distant metastatic disease treated by primary RT with curative intent were retrospectively reviewed as part of a study approved by the local research ethics committee. Only patients with both staging and mid treatment FDG PET-CT performed during the 3rd week of RT were included for analysis (average from commencement of RT: 17 ± 3.4 days).

Imaging technique, image interpretation and metabolic parameter measurement

Details of the image acquisition and reconstruction technique, and the methodology for image interpretation are provided in our previous publication [24].

In addition to the methodology of the previous paper, this paper also measures the maximum standardised-uptake-value (SUVmax), metabolic-tumour-volume (MTV) and total-lesional-glycolysis (TLG) of primary tumour (PT), the index-node (IN), total lymph nodes (TN) and combined primary tumour and nodal (PTN), and their % reductions in iPET. We defined IN as the lymph node or confluent nodal group with the highest TLG reflecting highest metabolic burden. The fixed SUV threshold of 2.5 was chosen as the segmentation algorithm for the generation of the MTV and TLG, consistent with our previous result, other studies on NPC and meta-analysis [25].

Treatment

All patients were treated with step and shoot IMRT or helical TomoTherapy®: total treatment dose to the GTV was 69.96–70 Gy (2.0–2.12 Gy/fraction, total fractions 33–35); high risk regions received 59.4–63 Gy (1.8 Gy/fraction); and the low risk regions received 54–56 Gy (1.6–1.64 Gy/fraction). Concurrent weekly Cisplatin (40 mg/m^2) was administered in 28 patients. Induction chemotherapy was administered in 13 patients, consisting of Cisplatin (70 mg/m^2) 3 weekly and Gemcitabine (1000 mg/m^2) weekly for 8 weeks for eight patients, and two cycles of Cisplatin (75 mg/m^2) and Docetaxel (75 mg/m^2) for five patients. Adjuvant chemotherapy was administered in three patients consisting of three cycles of Cisplatin (100 mg/m^2) and 5FU (1000 mg/m^2), in accordance with published protocols [5,8]. Management of all cases were reviewed and consensus reached in our Head and Neck multidisciplinary team meetings prior to commencing treatment. The patients were followed up weekly during treatment, and at least 3 monthly in the first 2 years and 6 monthly afterwards.

Statistical analysis

The predictive accuracy of all three metabolic parameters (SUVmax, MTV and TLG), including absolute values and percentage reductions, of primary tumour (PT), index nodes (IN), total nodes (TN) and combined primary tumour and nodes (PTN) for oncological outcomes were evaluated using receiver operating characteristic (ROC) analysis with the area under the curve (AUC) as an index of accuracy. Optimal cutoffs (OC) were derived from the ROC curves aiming for the best sensitivity and specificity. Time of local, regional and distant relapse and death were calculated from the date of the staging prePET. Local recurrence free survival (LRFS), regional failure free survival (RFFS), distant metastatic failure free survival (DMFFS), disease-free survival (DFS), and overall survival (OS) curves were estimated using Kaplan–Meier (KM) analysis and compared using the log-rank (Mantel-Cox) test. The Cox proportional hazards models with 95% confidence interval and multivariate analysis were performed using clinical confounders (T stage: T1/2 vs. T3/T4, N stage: N0/1/2 vs. N3 and overall AJCC stages: I/II vs. III/IVa). Statistical significance was considered established when the p value was <0.05 and all levels of significance were two sided. Statistical analysis was performed using the IBM SPSS Statistics, version 22.0.

Results

Study population

Thirty consecutive patients from February 2009 to January 2015 were included in this analysis: median age 54 (range 29–75). AJCC 7th edition staging comprised of: II = 12, III = 8 and IV = 10 patients, and nodal staging comprised of: N0 = 4, N1 = 10, N2 = 12, N3 = 4 patients. Histology grade (WHO) included: grade 1 = 3, grade 2 = 7 and grade 3 = 20 patients. The median follow up was 26 months (range 8–66.9). At the time of analysis, 26 patients (87%) were alive and 20 (67%) were disease free while 10 (33%) had treatment failure. Six patients had loco-regional failures (local failure: 2, regional failure: 2 and combined: 2), and six patients has distant failure, of which 4 had distant failure only and 2 had concurrent loco-regional failure.

Correlation of prePET and iPET primary tumour and nodal metabolic parameters with treatment outcome

The optimal cutoffs and predictive values of prePET and iPET metabolic parameters for treatment outcomes (the 2-year Kaplan–Meier survivals) are summarised in Table 1.

Different prePET and iPET parameters predict specific oncologic outcomes.

For LRFS, the only statistically significant predictor was reduction in the primary tumour between prePET and iPET MTV by >50% (95.2% vs 75.0%, p = 0.024). There was no significant association of primary tumour metabolic parameters or % reduction between prePET and iPET of considered parameters with other treatment outcomes.

For other treatment outcomes, only nodal or combined PTN predicted treatment outcomes. The IN SUVmax (pre-PET OC = 10.45 g/mL and iPET OC = 8.15 g/mL) and TLG (pre-PET OC = 90 g and iPET OC = 33.4 g) provided the overall best predictor of treatment outcome, with significant associations with RFFS (iPET), DMFFS (pre-PET), DFS (prePET and iPET) and OS (prePET). Fig. 1 (Supplementary material): (a)–(d) refer to Kaplan–Meier estimates of survival rates stratified according to optimum cutoffs of prePET