Prognostic value of $^{18}$F-FDG PET/CT before and after radiotherapy for locally advanced nasopharyngeal carcinoma

P. Xie, J.-B. Yue, Z. Fu, R. Feng & J.-M. Yu

Department of Radiation Oncology, Shandong Tumor Hospital and Institute, Jinan, China

Received 5 February 2009; revised 6 June 2009 & 28 July 2009; accepted 3 August 2009

Background: The purpose of this study was to evaluate the prognostic value of maximal standard uptake values (SUV$_{\text{max}}$) from serial fluor-18-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) in patients with locally advanced nasopharyngeal carcinoma (NPC).

Materials and methods: From October 2002 to January 2004, 62 patients with locally advanced NPC who underwent $^{18}$F-FDG PET/CT scan before and after radiotherapy were reviewed retrospectively. We examined the association of SUV$_{\text{max}}$ and the results of long-term follow-up of the patients.

Results: Patients having tumors with a lower SUV$_{\text{max}}$ had significantly better 5-year overall survival (OS) ($P = 0.0187$) and disease-free survival (DFS) ($P = 0.0163$) than patients with a greater SUV$_{\text{max}}$. The patients who showed with metabolic complete response had a significantly higher 5-year OS ($P = 0.0237$) and DFS ($P = 0.0186$) than patients with metabolic partial response. Poor prognosis was found in patients with the SUV$_{\text{max}}$ of neck nodes larger than that at the primary tumor site (SUV$_{\text{max-N}} >$ SUV$_{\text{max-P}}$) ($P = 0.0440$).

Conclusions: $^{18}$F-FDG uptake, as measured by the SUV$_{\text{max}}$ before radiotherapy and metabolic response after radiotherapy, may predict the prognosis in locally advanced NPC. High $^{18}$F-FDG uptake before and after radiotherapy may be useful for identifying patients requiring more aggressive treatment.

Key words: $^{18}$F-FDG, nasopharyngeal neoplasms, PET/CT, prognosis, radiotherapy

introduction

The mainstay treatment of nasopharyngeal carcinoma (NPC) has been radiotherapy. Early-stage NPC is usually curable by radiotherapy. However, in locally advanced disease, despite good initial local control after radiotherapy, there is a significant rate of local failures and distant metastases [1]. The identification of prognostic factors that accurately correlate with treatment outcome would help in determining patients with NPC who might benefit from more aggressive multimodality treatment combinations and consequently improve treatment outcomes. Although traditional prognostic factors may provide some useful clinical information, they cannot predict treatment outcome reliably. Therefore, identification of novel prognostic factors that potentially predict outcome is of great interest.

In many kinds of cancer patients, fluor-18-fluorodeoxyglucose positron emission tomography with computed tomography ($^{18}$F-FDG PET/CT) has been used in the initial diagnosis, staging work-up, and early detection of recurrence [2, 3]. Furthermore, some studies have shown that tumor FDG uptake may have prognostic significance, in that patients with high FDG uptake generally have less favorable outcomes [4–6]. Additionally, it has been indicated that $^{18}$F-FDG PET or PET/CT can effectively detect subclinical and clinical therapeutic responses at earlier stages than is possible using conventional approaches [7]. Though many studies about the usefulness of FDG uptake have been conducted, the prognostic value of post-treatment maximal standardized uptake value (SUV$_{\text{max}}$) in patients with NPC is still under investigation.

In the present study, we used $^{18}$F-FDG PET/CT scan SUV$_{\text{max}}$ to determine whether serial $^{18}$F-FDG uptake could be used as a prognostic marker of overall survival (OS) and disease-free survival (DFS) in patients with locally advanced NPC. The objective of this study was to evaluate the utility of whole-body $^{18}$F-FDG PET/CT in predicting prognosis in patients with locoregionally advanced NPC who received definitive radiotherapy combined with platinum-based chemotherapy. This study was undertaken to evaluate the value of $^{18}$F-FDG PET/CT in predicting prognosis in patients with locally advanced NPC.

patients and methods

patients

We retrospectively analyzed the medical records of 62 patients with stage 3 and 4a-b NPC who underwent $^{18}$F-FDG PET/CT before and after radiotherapy and were referred for definitive radiotherapy to the
Department of Radiation Oncology, Shandong Tumor Hospital and Institute, Jinan, China, between October 2002 and January 2004. Eligible patients were those with biopsy-proven carcinoma, including those with differentiated nonkeratinizing carcinomas and undifferentiated carcinomas, who had received definitive radiotherapy combined with concurrent chemotherapy and adjuvant chemotherapy. Patients in a poor condition (Karnofsky index ≤ 70%) were excluded. All patients were initially evaluated with a complete medical history and physical examination, complete blood count, baseline serum biochemistry, fiberoptic nasopharyngoscopy with nasopharyngeal biopsy, and pretreatment whole-body 18F-FDG PET/CT scan. Other routine imaging modalities included chest radiography, CT scan or magnetic resonance imaging of the head and neck, abdominal ultrasonography, and whole-body bone scan. Tumors were staged according to the American Joint Committee on Cancer staging system.

PET imaging
All patients fasted for at least 8 h before 18F-FDG PET/CT scanning, and their blood glucose level was measured. In patients with diabetes mellitus, blood glucose concentration had to be under the control level before the PET/CT scan. All patients were rest for at least 1 h before PET/CT scan. 18F-FDG (5.55–7.40 MBq/kg), of radiopharmaceutical purity >95%, was injected i.v. After 1 h, images were acquired in 2D mode on a Discovery LS PET/CT, GE. The SUVmax in each region of interest was determined using the whole-body attenuation corrected image and the formula, tissue concentration of 18F-FDG measured by PET/the injected dose/body weight. All the 62 patients underwent the pretreatment whole-body 18F-FDG PET/CT scan, and 58 underwent post-treatment whole-body 18F-FDG PET/CT scan as part of routine follow-up of 1–5 months (median 2.1 months) after treatment completion [8].

treatment
All patients received definitive intensity-modulated radiotherapy combined with concomitant and adjuvant platinum-based chemotherapy. During treatment planning and radiotherapy, each patient was immobilized in the supine position, using a custom-made thermoplastic mask encompassing the entire head and neck. The CT simulation was carried out with administration of i.v. contrast in all patients, and images were acquired at intervals of 3–5 mm from the skull base to the level of the carina using a Philips Brilliance CT simulator (Philips Medical Systems) and transferred to Varian Eclipse 3D Treatment Planning System (Varian Medical Systems). The target volume was defined according to International Commission on Radiation Units publications 50 and 62. The adjacent critical organs were delineated on the same CT slices. In the planning procedure, five to nine coplanar or noncoplanar fields were usually selected for adequate coverage of the target volume. Radiotherapy was administered as 1.8–2.0-Gy daily fractions using 6-MV photon beams (CLINAC 2100C, Varian), 5 days per week, for a total dose of 70–72 Gy for gross target volume, 60–66 Gy for clinical target volume of high risk, and elective nodal irradiation involved radiation doses of 50–60 Gy. All patients were treated with adjuvant chemotherapy using cisplatin and 5-fluorouracil after completion of radiotherapy. For concomitant chemotherapy, fluorouracil (500 mg/m2/day, days 1–14) and cisplatin (12–15 mg/m2/day, days 1–7) were given every 4 weeks on days 1 and 29. For adjuvant chemotherapy, fluorouracil (600 mg/m2/day, days 1–14) and cisplatin (80 mg/m2/day) were given every 3 weeks. For those patients with persistent abnormal FDG uptake, additional one to three cycles of chemotherapy were given.

study design and statistical analysis
Recurrence was histologically confirmed when patients developed clinically symptomatic recurrent disease. To evaluate the prognostic value of PET/CT, OS and DFS were chosen as end points and were measured from the date of radiotherapy initiation to the date of death or recurrence. We used SPSS statistical software, version 11.5, for statistical analysis. The survival function was estimated using the Kaplan–Meier method. The difference in survival rates among groups was tested for significance using the log-rank test. Multivariate analysis was carried to identify the prognostic factors influencing OS and DFS using Cox proportional hazards regression model. All statistical tests were conducted at a two-sided level of significance of 0.05.

results
Patient characteristics are shown in Table 1. Median follow-up for surviving patients was 61 months (range 9–69 months). Thirty-nine patients were alive at last follow-up and 23 had died. All 62 patients had abnormal FDG uptake before treatment. The median of pretreatment SUVmax was 8.55, and the values ranged from 2.8 to 24.6. Thirty-six patients had a pretreatment SUVmax higher than 8.0, and 26 patients lower than 8.0. Fifty-three patients presented with lymph nodes metastasis. Of these patients, the median of lymph nodes SUVmax was 6.7, and the values ranged from 2.5 to 16.7, and 12 patients presented with SUVmax of neck nodes larger than that at the primary tumor site. Of the 62 patients, 23 had local recurrence during the observation period, seven showed distant metastases, and the rest displayed no recurrence or metastases. Fifty-eight of the 62 patients’ treatment responses were evaluated by 18F-FDG PET/CT scan. The post-treatment PET/CT scan did not show any abnormal FDG uptake (SUVmax < 2.5, metabolic complete response, MCR) in 35 patients. Persistent abnormal FDG uptake (SUVmax ≥ 2.5, metabolic partial response, MPR) was found in 23 patients.

Five-year OS rate and DFS rate of all patients were 62.9% and 51.6%, respectively. As shown in Figure 1, the ability of SUVmax to predict prognosis was depicted by an Receiver Operating Characteristic (ROC) curve. Area under the curve is 0.564, and the best cut-off value is 8.0. Furthermore, patients with an SUV below 8.0 had a significantly better OS (X2 = 5.53, P = 0.0187) and DFS (X2 = 5.77, P = 0.0163) than patients with an SUV of ≥ 8.0. The patients who showed with MPR had a significantly lower 5-year OS (X2 = 5.12, P = 0.0237) and DFS (X2 = 5.54, P = 0.0186) than patients with MCR, as shown in

Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>Constituent ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>18–67</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Pathology classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonkeratinizing</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>32</td>
<td>52</td>
</tr>
<tr>
<td>American Joint Committee on Cancer stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>39</td>
<td>63</td>
</tr>
<tr>
<td>Stage 4a</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Stage 5b</td>
<td>8</td>
<td>13</td>
</tr>
</tbody>
</table>
Table 2. The DFS rates stratified by the results of pre and post-treatment FDG uptakes are shown in Figures 2 and 3. The median SUVmax at which there was no evidence of recurrence or metastasis in 5 years was 7.92 (range 2.8–15.3), compared with the median SUVmax of the recurrent or metastatic patients, which was 10.58 (range 3.0–24.6) ($U = 319.5$, $P = 0.024$).

There was a weak correlation between SUVmax at the primary site and neck nodes ($r = 0.399$). Poor prognosis was associated with an SUVmax of neck nodes larger than that at the primary tumor site ($X^2 = 4.05$, $P = 0.0440$).

A multivariate Cox proportional hazards model of OS or DFS outcome was constructed to evaluate the pretreatment tumor stage, tumor size, nodal status, SUVmax (as dichotomized with 8.0 threshold), and post-treatment metabolic response as predictors of disease progression and survival. The multivariate analysis indicated that only metabolic response and tumor stage were the significant predictors of OS and DFS in our patient population, as shown in Table 3. The results of regression models showed that the standardized regression coefficient of MR and stage were 0.497 and 0.450, respectively.
indicates the intimate correlation between the primary SUV_max. SUV_max has been reported to be correlated with glucose delay after 18F-FDG injection, the partial volume effect, and the calculation of SUV is semiquantitative because of the imaging become one of the potential prognostic factors. Although [6]. Therefore, the SUV that represents the FDG uptake may expression of various biologic markers of tumor aggressiveness [9–12]. Functional imaging, such as 18F-FDG PET or PET/CT, may provide metabolic information on the entire tumor. Additionally, accumulating data indicated that FDG PET may serve as a noninvasive method, which can indirectly measure the expression of various biologic markers of tumor aggressiveness [6]. Therefore, the SUV that represents the FDG uptake may become one of the potential prognostic factors. Although calculation of SUV is semiquantitative because of the imaging delay after 18F-FDG injection, the partial volume effect, and the applied normalization scheme [13–15], 18F-FDG uptake using SUV_max has been reported to be correlated with glucose metabolism, as well as with the concentration of tumor cells and glucose metabolic rate. Patients with high concentrations of tumor cells or highly metabolic tumor cells would be expected to have a poorer prognosis [16]. At present, besides providing useful diagnostic information regarding pretreatment staging and post-treatment follow-up [17–19], intensity of FDG uptake is emerging as a valuable predictive factor regarding treatment outcome.

Sasaki et al. [20] found that it was five to be the best cut-off SUV to predict prognosis in patients with non-small-cell lung cancer (NSCLC). However, Lee et al. [21] found that the best cut-off SUV_max to predict prognosis in NPC was 8.0. In our long-term follow-up analysis with 62 locally advanced NPC, we have confirmed that 8.0 is the most discriminative cut-off. Furthermore, patients with tumors of a lower SUV_max had a higher 5-year OS rate and DFS than patients with a higher SUV_max, although there is no statistical significance in multivariate analysis. We also confirmed that patients with local recurrence or distant metastasis within 5 years had a significantly higher SUV_max than other patients. This indicates the intimate correlation between the primary SUV_max and tumor recurrence or metastasis. Our results are generally in agreement with Chan et al.’s study [22].

Quite a number of malignant tumors can receive clinical complete response via appropriate treatment, but it does not mean that the treatments destroyed all tumor cells. FDG uptake value was suggested as a predictor of pathologic response. Song et al. [23] reported that 32 patients with esophageal carcinoma received 18F-FDG PET before and after treatment. They demonstrated that FDG PET is an effective modality for noninvasive assessments of tumor pathologic response in patients with highly metabolic tumors. The metabolic response to therapy as determined by FDG PET has been shown to be predictive of survival outcome in lymphoma, NSCLC, and anal cancer [24–27]. In this study, we have found that metabolic response is an effective prognostic factor in locally advanced NPC patients. In our opinion, tumor MCR of post-treatment represents its high sensitivity to radiotherapy, as a result of high response and favorable prognosis.

Although tumor cells are regarded as coming from single clones, their microenvironment varies, as does their 18F-FDG uptake. In addition, blood supply can also affect 18F-FDG uptake. Therefore, the SUVs of primary tumor and lymph nodes in the same patients are not completely coherent. In our study, a weak correlation was discovered between the SUV_max of the primary and nodes. Patients with a node SUV_max higher than that of the primary site had a poorer prognosis. We think it is probably because these tumors are more aggressive in metastasizing or because of relative growth conditions. Lee et al. [21] acquired a similar result with the study of 41 patients.

In conclusion, we have shown here that 18F-FDG PET/CT uptake before and after treatment, as determined by SUV_max, maybe a valuable tool to evaluate prognosis in locally advanced NPC patients. Patients with a high FDG uptake of pre or post-treatment may be considered at increased risk of failure and may benefit from more effective approaches, for instance, higher radiation dose or combined more aggressive chemotherapy, and consequently improve treatment efficiency.

**discussion**

Although NPC is highly sensitive to radiotherapy or chemotherapy, the long-term survival is unsatisfactory, especially for those patients with locally advanced disease. The 5-year OS rate for patients with locally advanced NPC was found to be 50%–70%. Therefore, to identify the factors that can predict better prognosis, especially those with noninvasive methods, is a matter of urgency for improving treatment outcome.

It has been reported that prognostic factors can be identified by immunohistochemical staining of tumor tissue. However, biopsy samples do not represent the genetic information or protein expression of the entire tumor [9–12]. Functional imaging, such as 18F-FDG PET or PET/CT, may provide metabolic information on the entire tumor. Additionally, accumulating data indicated that FDG PET may serve as a noninvasive method, which can indirectly measure the expression of various biologic markers of tumor aggressiveness [6]. Therefore, the SUV that represents the FDG uptake may become one of the potential prognostic factors. Although calculation of SUV is semiquantitative because of the imaging delay after 18F-FDG injection, the partial volume effect, and the applied normalization scheme [13–15], 18F-FDG uptake using SUV_max has been reported to be correlated with glucose metabolism, as well as with the concentration of tumor cells and glucose metabolic rate. Patients with high concentrations of tumor cells or highly metabolic tumor cells would be expected to have a poorer prognosis [16]. At present, besides providing useful diagnostic information regarding pretreatment staging and post-treatment follow-up [17–19], intensity of FDG uptake is emerging as a valuable predictive factor regarding treatment outcome.

Sasaki et al. [20] found that it was five to be the best cut-off SUV to predict prognosis in patients with non-small-cell lung cancer (NSCLC). However, Lee et al. [21] found that the best cut-off SUV_max to predict prognosis in NPC was 8.0. In our long-term follow-up analysis with 62 locally advanced NPC, we have confirmed that 8.0 is the most discriminative cut-off. Furthermore, patients with tumors of a lower SUV_max had a higher 5-year OS rate and DFS than patients with a higher SUV_max, although there is no statistical significance in multivariate analysis. We also confirmed that patients with local recurrence or distant metastasis within 5 years had a significantly higher SUV_max than other patients. This indicates the intimate correlation between the primary SUV_max and tumor recurrence or metastasis. Our results are generally in agreement with Chan et al.’s study [22].

Quite a number of malignant tumors can receive clinical complete response via appropriate treatment, but it does not mean that the treatments destroyed all tumor cells. FDG uptake value was suggested as a predictor of pathologic response. Song et al. [23] reported that 32 patients with esophageal carcinoma received 18F-FDG PET before and after treatment. They demonstrated that FDG PET is an effective modality for noninvasive assessments of tumor pathologic response in patients with highly metabolic tumors. The metabolic response to therapy as determined by FDG PET has been shown to be predictive of survival outcome in lymphoma, NSCLC, and anal cancer [24–27]. In this study, we have found that metabolic response is an effective prognostic factor in locally advanced NPC patients. In our opinion, tumor MCR of post-treatment represents its high sensitivity to radiotherapy, as a result of high response and favorable prognosis.

Although tumor cells are regarded as coming from single clones, their microenvironment varies, as does their 18F-FDG uptake. In addition, blood supply can also affect 18F-FDG uptake. Therefore, the SUVs of primary tumor and lymph nodes in the same patients are not completely coherent. In our study, a weak correlation was discovered between the SUV_max of the primary and nodes. Patients with a node SUV_max higher than that of the primary site had a poorer prognosis. We think it is probably because these tumors are more aggressive in metastasizing or because of relative growth conditions. Lee et al. [21] acquired a similar result with the study of 41 patients.

In conclusion, we have shown here that 18F-FDG PET/CT uptake before and after treatment, as determined by SUV_max, maybe a valuable tool to evaluate prognosis in locally advanced NPC patients. Patients with a high FDG uptake of pre or post-treatment may be considered at increased risk of failure and may benefit from more effective approaches, for instance, higher radiation dose or combined more aggressive chemotherapy, and consequently improve treatment efficiency.

**funding**

There is no funding source in this study.

**acknowledgements**

The authors thank Dr Huiqing Li and Jinsong Zheng for their assistance with this paper.

**references**


