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

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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
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 rested for at least 1 h before PET/CT scan. 18F-FDG (5.55–7.40 MBq/kg), of radiopharmaceutical purity >99%, 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 correction 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/m^2/day, days1–4, and cisplatin (12–15 mg/m^2/day, days1–5) were given every 4 weeks on days 1 and 29. For adjuvant chemotherapy, fluorouracil (600 mg/m^2/day, days1–4) and cisplatin (80 mg/m^2/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 SUV_{max} was 8.55, and the values ranged from 2.8 to 24.6. Thirty-six patients had a pretreatment SUV_{max} 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 SUV_{max} was 6.7, and the values ranged from 2.5 to 16.7, and 12 patients presented with SUV_{max} 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 (SUV_{max} < 2.5, metabolic complete response, MCR) in 35 patients. Persistent abnormal FDG uptake (SUV_{max} ≥ 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 SUV_{max} 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 (X^2 = 5.53, P = 0.0187) and DFS (X^2 = 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 (X^2 = 5.12, P = 0.0237) and DFS (X^2 = 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>
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<tbody>
<tr>
<td>Age Median</td>
<td>43</td>
<td>18–67</td>
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<tr>
<td>Gender Male</td>
<td>47</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>24</td>
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<tr>
<td>Pathology classification Nonkeratinizing</td>
<td>30</td>
<td>48</td>
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<tr>
<td>Undifferentiated</td>
<td>32</td>
<td>52</td>
</tr>
<tr>
<td>American Joint Committee on Cancer stage 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. Log-rank test for 5-year OS and DFS according to SUVmax

<table>
<thead>
<tr>
<th>Patients</th>
<th>5-Year OS (%)</th>
<th>5-Year DFS (%)</th>
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</thead>
<tbody>
<tr>
<td>Pre-SUVmax-P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 8.00</td>
<td>36</td>
<td>50.0</td>
</tr>
<tr>
<td>&lt; 8.00</td>
<td>26</td>
<td>80.8</td>
</tr>
<tr>
<td>Post-SUVmax-P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic partial response</td>
<td>24</td>
<td>45.8</td>
</tr>
<tr>
<td>Metabolic complete response</td>
<td>34</td>
<td>73.5</td>
</tr>
</tbody>
</table>

SUVmax, maximal standard uptake values; OS, overall survival; and DFS, disease-free survival.

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.
Annals of Oncology

The results of Cox multivariate analysis are presented in Table 3. The analysis was performed to determine the factors associated with overall survival (OS) and disease-free survival (DFS). The table shows the hazard ratio (HR) and 95% confidence interval (CI) for each factor, along with the corresponding P-values. The table indicates that the metabolic response (MR) is a significant predictor of both OS and DFS. The authors have concluded that FDG PET/CT can serve as an effective prognostic tool for patients with NPC.

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References


