The value of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography for staging of primary extranodal head and neck lymphomas.

Schrepfer, T; Haerle, S K; Strobel, K; Schaefer, N; Hälg, R A; Huber, G F

Abstract: OBJECTIVES/HYPOTHESIS: Using a retrospective approach, the aim of this study was to confirm the previously described value of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography ((18)F-FDG-PET/CT) in patients with primary extranodal lymphoma of the head and neck region. Additionally, the clinical significance of the semiquantitative analysis of the standardized uptake value (SUV), its predictive role in the follow-up setting, and its value in detection of synchronous primaries were studied. STUDY DESIGN: Retrospective chart review. METHODS: Twenty-six patients with a primary extranodal head and neck lymphoma (22 diffuse large B-cell lymphoma, one Hodgkin’s lymphoma, three malignant T-cell lymphomas) were included. We retrospectively evaluated the clinical outcomes according to the maximum standardized uptake values of the primary lesion (SUV(max)) and whether a positron emission tomography/computed tomography (PET/CT) was performed or not in the follow-up studies. The median SUV(max) was chosen as the cutoff value. The patients were then grouped as those with either low or high SUV(max), respective to the cutoff value. Event-free survival and cumulative survival were endpoints of interest. RESULTS: Nineteen patients (73%) were above the age of 60 years; the median age was 70 years (range, 28-87 years). Most primary sites were in the Waldeyer’s ring (15 patients, 60%), whereas in four patients (27%) only the palatine tonsil was affected. The SUV(max) ranged from 5.8 to 33.9. In one patient, relevant fluorodeoxyglucose (FDG) uptake within the intestine revealed a cecal adenocarcinoma as a secondary primary. Twenty of the 25 clinically followed patients (80%) achieved complete remission after treatment. Patients with high SUV(max) showed favorable survival (log-rank test, P = .044). A tendency for longer survival within the group with follow-up PET/CT studies could be noted but with no significant statistical difference (P = .349). CONCLUSIONS: (18)F-FDG-PET/CT imaging is a potent primary staging tool. It also has application as an instrument for evaluation of follow-up and response to therapy in patients suffering from primary extranodal lymphoma and for detection of secondary malignancies. Furthermore, (18)F-FDG uptake by the primary lesion may be related to better survival.

DOI: https://doi.org/10.1002/lary.20843

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-34194

Originally published at:
Schrepfer, T; Haerle, S K; Strobel, K; Schaefer, N; Hälg, R A; Huber, G F (2010). The value of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography for staging of primary extranodal head and neck lymphomas. The Laryngoscope, 120(5):937-44.

DOI: https://doi.org/10.1002/lary.20843
The Value of $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Staging of Primary Extranodal Head and Neck Lymphomas

Thomas Schrepfer, MD; Stephan K. Haerle, MD; Klaus Strobel, MD; Niklaus Schaefer, MD; Roger A. Hälg; Gerhard F. Huber, MD

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Study Design: Retrospective chart review.

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Results: Nineteen patients (73%) were above the age of 60 years; the median age was 70 years (range, 28–87 years). Most primary sites were in the Waldeyer's ring (15 patients, 60%), whereas in four patients (27%) only the palatine tonsil was affected. The SUV$_{\text{max}}$ ranged from 5.8 to 33.9. In one patient, relevant fluorodeoxyglucose (FDG) uptake within the intestine revealed a cecal adenocarcinoma as a secondary primary. Twenty of the 25 clinically followed patients (80%) achieved complete remission after treatment. Patients with high SUV$_{\text{max}}$ showed favorable survival (log-rank test, $P = 0.044$). A tendency for longer survival within the group with follow-up PET/CT studies could be noted but with no significant statistical difference ($P = 0.349$).

Conclusions: $^{18}$F-FDG-PET/CT imaging is a potent primary staging tool. It also has application as an instrument for evaluation of follow-up and response to therapy in patients suffering from primary extranodal lymphoma and for detection of secondary malignancies. Furthermore, $^{18}$F-FDG uptake by the primary lesion may be related to better survival.

Key Words: Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography, initial staging, lymphoma, head and neck.

Level of Evidence: 2b.

INTRODUCTION

The incidence of non-Hodgkin's lymphoma (NHL) strongly depends on geographical and ethnic differences and varies from 2/100,000 per year among the Asian population to about 10/100,000 in Caucasians in North America and Europe. It is the second most common neoplasm in the head and neck region and should always be considered in the differential diagnosis of a unilateral neck mass. Extranodal lymphoma is present in 25% to 40% of all NHL patients. Located within the head and neck region, the Waldeyer's ring (including nasopharynx, tonsils, and base of tongue) is the major site for malignant lymphoma. Within this anatomical location, the tonsils are involved in 80%, and diffuse...
large B-cell lymphoma (DLBCL) is the most common histological subtype.\textsuperscript{3–5} The peak incidence is in the sixth and seventh decade with a male predominance.\textsuperscript{6}

The standard treatment for patients with DLBCL is nonsurgical. It consists of immunochemotherapy using primarily cyclophosphamide, doxorubicin, vincristine, and prednisone; concomitant radiotherapy, or radiotherapy alone. The addition of rituximab, a monoclonal antibody, has significantly improved the overall outcome.\textsuperscript{7–10}

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (\textsuperscript{18}F-FDG-PET/CT) imaging is increasingly used in many centers for staging and assessment of the therapeutic response in patients diagnosed with lymphoma. Several studies have shown better performance of \textsuperscript{18}F-FDG-PET/CT for accurately staging lymphomas compared to computed tomography (CT) alone. Furthermore, for assessment of the response to therapy, positron emission tomography/computed tomography (PET/CT) has high prognostic value with respect to overall and event-free survival.\textsuperscript{11–14} The semi-quantitative measurement of the standardized uptake value (SUV), an easy-to-calculate and noninvasive index of the \textsuperscript{18}F-FDG metabolic rate, has been assessed for its prognostic value. The prognostic value of early \textsuperscript{18}F-FDG PET/CT compared with visual analysis in DLBCL\textsuperscript{15,16}

The outcomes of interest are the following: 1) confirm the previously described value of \textsuperscript{18}F-FDG-PET/CT in patients with primary extranodal lymphoma of the head and neck region and evaluate the clinical significance of the semiquantitative analysis of SUV values, and 2) determine the predictive role of \textsuperscript{18}F-FDG-PET/CT in the follow-up setting.

MATERIALS AND METHODS

In a retrospective chart review, 26 patients who presented with primary extranodal head and neck lymphoma between January 2002 and December 2008 at the Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Zurich, Switzerland, were analyzed. Inclusion criteria were: all patients with signs and symptoms only within the head and neck area, cyto- and/or histopathologically proven malignant lymphoma, \textsuperscript{18}F-FDG-PET/CT performed at initial staging, and no other diagnosis of head and neck cancer at the time of presentation.

Cyto- and histopathologic diagnosis was performed on the basis of morphology and immunohistochemistry by our clinical pathology department.

Especially in patients where both sites (nodal and extranodal) are involved, the exact definition of primary extranodal lymphoma is controversial.\textsuperscript{17} Diffuse large B-cell lymphoma and Hodgkin’s lymphoma arising within the parotid gland were considered to be a primary extranodal.

PET/CT Data Acquisition

All imaging and data acquisition was performed on a combined PET/CT in-line system (Discovery LS, STE or RX, General Electric Medical Systems, Waukesha, WI). This device integrates a PET scanner with a multislice helical CT and permits the acquisition of coregistered CT and PET images in the same session. First, an unenhanced CT scan (80 mA, 0.5 s/rotation, 140 kV, reconstructed slice thickness 4.25 mm) from the head to the pelvic floor was acquired for attenuation correction. Consecutively, the table position was moved axially to the initial position for the PET scan so that the first field of view covered the pelvic floor and the bladder. Seven cradle positions were scanned with a 2- to 4-minute emission scan per cradle position. PET images were acquired during tidal breathing, and CT scans were acquired during breath-hold. Before examination, patients stayed nil per os for at least 4 hours before the intravenous administration of an average of 10 mCi (370 MBq) of \textsuperscript{18}F-FDG. Additionally, an oral contrast agent (Micropaque Scanner; Guerbet AG, Aulnay-sous-bois, France) was given. Imaging started 60 minutes after the \textsuperscript{18}F-FDG injection. The patient was positioned on the table in a head-first supine position. The arms of the patients were placed in an elevated position above the abdomen to reduce beam hardening artifacts at the level of the liver. The PET images were reconstructed using a standard iterative algorithm (ordered subsets expectation maximization, two iterative steps) and reformatted into axial, coronal, and sagittal views.

The acquired images were viewed with software providing multiplanar reformatted images in all planes. Attenuation-corrected PET images were used for analysis. Lesions were interpreted as malignant if the uptake was higher than the uptake of the surrounding background tissue. Increased \textsuperscript{18}F-FDG uptake in well-known benign lesions or tissues such as brown fat were excluded from analysis. The intensity of \textsuperscript{18}F-FDG uptake was quantified by calculating the SUV max for every pathologic lesion. Furthermore, morphological findings of suspicious lesions provided by the low-dose CT component were also used for interpretation. The SUV was calculated using the formula: SUV = (activity/unit volume)/(injected dose/total body weight). The SUV of the primary extranodal site was denoted as the SUV max.

Statistical Analysis

To estimate the patients’ outcomes in association with follow-up PET/CT studies and its correlation to the SUV max, event-free survival (EFS) and cumulative survival (CS) were chosen as endpoints. EFS was defined as the date of enrollment to the time of progression, relapse, or death from any cause.

The impact of SUV max on EFS as a continuous variable was first evaluated using a Cox model. The reformulation of the proportional hazards regression of Andersen and Gill in combination with the Efron approximation for tie handling was used to explore survival differences. To predict EFS according to the SUV max value as a prognostic index, receiver operating characteristic (ROC) analysis was performed. Because no significant correlation could be shown in our series, no cutoff value could be determined by the ROC curve. Therefore, we decided to take the median SUV max as a cutoff value. The patients were then grouped as those with either low or high SUV max.

The Kaplan-Meier estimates for EFS were calculated for groups of patients with either high or low SUV max and patients with or without follow-up PET/CT. The survival functions of the different groups were compared using the log-rank test. The statistical analyses were performed using R\textsuperscript{18} version 2.8.1, and significance level was set at the .05 level.

RESULTS

Patients’ Characteristics

The patients’ clinical characteristics are summarized in Table I, and gender and age distribution are shown in Figure 1. Median age was 70 years (range, 28–87 years) with 73% of patients (19) aged above 60 years.
Six (86%) out of the seven patients below the age of 60 years were men.

**Types of Lymphomas**

In the majority of patients, histology revealed a DLBCL. One patient presented with a Hodgkin’s lymphoma within the parotid gland. Three patients were found to have a malignant T-cell lymphoma.

**Localization of Lymphomas**

Of the 25 patients with non-Hodgkin’s lymphoma, most presented within the Waldeyer’s ring (15 patients, 60%, respectively); in four patients (27%) only the palate tonsil was affected (stage I), and in one patient the hard palate along with lymph node metastases was involved (stage II). In two patients (8%), the thyroid gland without locoregional lymph node involvement was found to be the primary site (stage I and II, respectively). Overall, 12 patients (46%) presented with additional involved lymph nodes; the predominant location was supradiaphragmal (n = 9, stage II). One patient showed organ involvement (spleen, liver, stomach), whereas the bone marrow was disease free (stage IV). In one patient (3.8%) whole body $^{18}$F-FDG-PET/CT showed a relevant $^{18}$F-FDG-uptake within the intestine as shown in Figure 2. Further investigations, colonoscopy, and later hemicolectomy were performed and revealed cecal adenocarcinoma as a second primary. In all observed patients with malignant T-cell lymphoma, the primary site was the nasal or oral cavity (hard palate). In one case, the lymphoma showed destructive involvement of the facial skin, maxillary and ethmoid sinus, pterygoid muscle, and multiple locoregional lymph node metastases (no. 26, stage II).

Bone marrow aspiration was performed in 16 patients (62%), which was shown to be disease free. In a further six cases, the patient either refused or there was no need for any additional intervention. The results of the remaining four patients were not available or inconclusive.

**Stage of Lymphomas**

When $^{18}$F-FDG-PET/CT was used as a primary staging tool, one patient was found to have stage IV disease with multiple organ involvement (no. 17). Three patients were diagnosed as stage III (infradiaphragmal lymph nodes), whereas nine patients were in stage II (supradiaphragmal lymph nodes). Thirteen patients were found to have limited local disease (stage I). In cases where $^{18}$F-PET/CT was performed for further

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**Table I.** Characteristics of 26 Patients With PENHL

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
<th>No. of Patients</th>
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</tr>
<tr>
<td></td>
<td>Range</td>
<td>28–87</td>
</tr>
<tr>
<td>&gt;60</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Women</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>19</td>
</tr>
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<tr>
<td></td>
<td>II–III</td>
<td>4</td>
</tr>
<tr>
<td>Primary sites</td>
<td>Waldeyer’s ring</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Non-Waldeyer’s ring</td>
<td>7</td>
</tr>
<tr>
<td>SUV$_{\text{max}}$</td>
<td>Median</td>
<td>11.90</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5.80–33.90</td>
</tr>
</tbody>
</table>

PENHL = primary extranodal non-Hodgkin’s lymphoma; SUV = standardized uptake value.

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Fig. 1. Gender and age distribution.

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Laryngoscope 120: May 2010

Schrepfer et al.: $^{18}$F-FDG-PET/CT for Staging of HN Lymphoma

939
staging after a surgical intervention, that is, diagnostic tonsillectomy with palate excision biopsy (patients no. 1, 5, 8, 14, 15) and total parotidectomy (patient no. 25), no persistence of local metabolic active malignant lymphoid tissue was found. Due to these findings, two out of these six patients achieved complete elimination of disease by surgery alone, and no further treatment (chemotherapy, radiotherapy) was undertaken.

Clinical Outcome

The patients' details, along with the course of treatment, are listed in Table II. Treatment response and follow-up could not be evaluated in one patient because of noncompliance. Of the remaining 25 patients, 20 (80%) achieved complete remission after treatment. One patient (no. 20) is still undergoing induction therapy but showed complete clinical remission, whereas one patient (no. 25) developed locoregional relapse. Three patients (patients nos. 7, 24, 26) suffered from progressive disease and died within the observed time period. One patient (no. 12) died because of metastasizing intestinal adenocarcinoma, but showed complete remission of the DLBCL. Of the 25 patients with consistent follow-up data, five had died by December 2008. Of the three patients with T-cell lymphoma, only one achieved full recovery, whereas one died as a consequence of the disease, and one death was attributed to septic shock (no. 26).

Primary Outcomes

Clinical significance of the semiquantitative analysis of SUV values. The Cox proportional hazards regression showed no significant relation for SUV_{\text{max}} and EFS (21 observations, \( P = .069 \)). The hazard ratio of 0.703 even presents a trend toward lower survival times for a decreased SUV_{\text{max}}. Considering this result, the ROC curve for survival was not included to group the patients according to the SUV_{\text{max}} as a prognostic index. Therefore, the median was used as the cutoff value to separate the patients into two groups of either high or low SUV_{\text{max}} (median 11.90, minimum 5.80, maximum 33.90). The Kaplan-Meier estimates, showing the CS for the two SUV_{\text{max}} groups, are depicted in Figure 3. The log-rank test, which was used to investigate differences in the survival times between the groups of high and low SUV_{\text{max}} patients, disclosed a significant difference (21 observations, \( P = .044 \)). In contrast to previous results, the patients within the low SUV_{\text{max}} group were associated with reduced survival.

Predictive role in the follow-up setting. The cumulative survival, in relation to whether follow up PET/CT was performed or not, was evaluated using

Fig. 2. Positron emission tomography/computed tomography (PET/CT) findings in a selected study subject, a 71-year-old patient (patient no. 12) at initial staging performed by \( ^{18} \text{F} \)-fluorodeoxyglucose positron emission tomography/computed tomography. Increased fluorodeoxyglucose (FDG) uptake in the Waldeyer's ring (maximum standardized uptake value = 14, asterisk) and multiple left-sided cervical lymph nodes (arrowhead) caused by lymphoma involvement are shown. Biopsy of Waldeyer's ring showed diffuse large B-cell lymphoma. Focal pathologic FDG-uptake in the ileocecal area was investigated with colonoscopy and revealed an adenocarcinoma of the colon as a secondary malignancy (arrow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
<table>
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<th>Patient No.</th>
<th>Stage</th>
<th>Gender/Age (yr)</th>
<th>Type of Disease</th>
<th>Affected Subsite</th>
<th>Infradiaphragmal (No.)</th>
<th>Supradiaphragmal (No.)</th>
<th>Organ Involvement</th>
<th>SUV max</th>
<th>Treatment Response Status</th>
<th>Survival Follow-Up (mo)</th>
<th>Follow-Up ET/CT (yes = 1, no = 0)</th>
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<td>M/47</td>
<td>NK/TCL</td>
<td>Nasal cavity</td>
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<td>0</td>
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<td>14.1</td>
<td>CHOP + RT CR AIR</td>
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<td>I</td>
<td>M/74</td>
<td>NK/TCL</td>
<td>Hard palate</td>
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<td>RT PD DOD</td>
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<td>I</td>
<td>M/28</td>
<td>HL</td>
<td>Parotid gland</td>
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<td>CHOP PD D0sD</td>
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<td>26</td>
<td>II</td>
<td>M/59</td>
<td>PTCL, NOS</td>
<td>Nasal cavity</td>
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<td>Multiple</td>
<td>No</td>
<td>5.9</td>
<td>CHOP PD D0sD</td>
<td>1</td>
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*Remission of the local lymphoma (WR) but progression of cervical bulky disease.
†Cecal adenocarcinoma detected as a synchronous primary in fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography.
SUV = standardized uptake value; PET/CT = positron emission tomography/computed tomography; M = male; DLBCL = diffuse large B-cell lymphoma; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; CR = complete response; AIR = alive in remission; WR = Waldeyer’s ring; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; W = female; R-EPOCH = Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin; RT = radiation therapy; R-P = Rituximab, Prednisone; NA = not available; D0sD = dead of systemic disease; IM = incapable of measurement; TE = tonsillectomy; UT = undergoing treatment; NK/TCL = extranodal natural killer/T-cell lymphoma; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; PD = progressive disease; DOD = dead of disease; HL = Hodgkin’s lymphoma; PE = parotidectomy; LR = locoregional relapse; PTCL, NOS = peripheral T cell Lymphoma not otherwise specified.
Kaplan-Meier estimates. The corresponding survival functions are shown in Figure 4. The comparison of the two survival curves shows a tendency for longer survival within the group with follow-up PET/CT studies, but no statistically significant difference in survival time could be found as assessed by a log-rank test (25 observations, \( P = .349 \)).

DISCUSSION

\(^{18}\text{F-FDG-PET/CT}\) is valuable for initial staging and assessment of the patient’s response to treatment of primary head and neck lymphomas. It offers advantages over conventional imaging techniques by including the metabolic activity and the extension of the malignant disease because it can differentiate between malignant and nonmalignant lymph nodes smaller than 1 cm.

In a previously performed meta-analysis of 20 studies between 1997 and 2004, the sensitivity of \(^{18}\text{F-FDG-PET/CT}\) was found to be 91% and the false positive rate was 10% using a patient-based analysis. These rates appeared to be higher in patients with Hodgkin’s disease compared with those suffering from a non-Hodgkin’s lymphoma.\(^{20}\) \(^{18}\text{F-FDG-PET/CT}\) has not been considered to be reliable for the staging of low-grade NHL, because low metabolic activity correlates with low \(^{18}\text{F-FDG}\) uptake.\(^{21}\) The optimal management in patients suffering from a malignant lymphoma is strongly related to the histological subtype and correct assessment of the expansion of the disease (staging); patients with stage I or II disease (Ann Arbor/Cotswold) usually receive short
courses of chemotherapy, whereas patients with advanced-stage disease are treated by more extensive courses and radiotherapy. Due to its higher accuracy, 18F-FDG-PET/CT has been suggested as a routinely obtained modality in pretreatment staging of lymphoma, avoiding overly aggressive chemotherapy and extended field radiation (overtreatment).21 For diagnosing both nodal and extranodal disease, 18F-FDG-PET/CT was more accurate than CT alone and resulted in a change of staging in 8% with nodal disease and in 16% with extranodal disease.22,23

In our series, five patients out of 15 who presented with the Waldeyer's ring as the primary affected site underwent a diagnostic tonsillectomy. Four of these patients had only limited disease of the tonsils. Furthermore, one patient was treated with tonsillectomy alone and no adjuvant chemotherapeutic regimen was necessary due to the negative findings in the 18F-FDG-PET/CT imaging. This exemplifies the value of 18F-FDG-PET/CT and its implications to the extent of treatment. Here, the application of chemotherapeutics was reserved as a second-line treatment.

In our patient cohort, the overall outcome for patients with primary head and neck lymphomas was found to be independent of gender and age. Recent studies from Byun et al.15 showed a correlation between the SUVmax measured prior to any treatment and the clinical outcome of NHL patients. The results imply that high SUVmax is related to unfavorable survival. However, the usefulness of SUV in predicting outcome seems to be controversial. Results vary from one institution to another and are influenced by many factors, including the imaging delay after 18F-FDG injection or differences in individual uptake.15,24,25

Compared to the results from Byun et al., we found high SUVmax in correlation with better survival. This difference could be due to institutional variables for the SUV, ethnicity, gender, and age differences. In our series, the median age was 70 years, with 73% of the patients above 60 years; 73% were men. In the study by Byun et al., the median age of patients at 50 years, and an almost equal gender distribution was described. Our series shows an excellent overall outcome in every age group, especially for the DLBCL. Because high 18F-FDG uptake of malignant tissue is associated with a high proliferation rate, one can assume that metabolic imaging is an indicator of tumor aggressiveness, individual tumor chemo sensitivity, or tumor resistance to the planned treatment.

In our institution, 18F-FDG-PET/CT is used for patients with suspected advanced primaries and/or metastases. Its ability to detect a considerable number of synchronous primaries at the initial staging has been shown by Strobel et al. in patients with head and neck squamous cell carcinoma with 8.0% prevalence.26 In their series, focal 18F-FDG accumulations in the colon were found in 3% of all evaluated patients (8.9% malignant). Our study confirms this rate because we found one patient out of 26 (3.8%) to have invasive colon cancer incidentally detected by 18F-FDG-PET/CT and confirmed with endoscopy.

CONCLUSION

18F-FDG-PET/CT imaging is a valuable tool for staging and as a follow-up modality for assessing the therapeutic response of patients suffering from primary extranodal lymphoma and in detecting secondary malignancies. Furthermore, our results indicate that the initially measured SUV may be associated with the clinical outcome in patients with primary extranodal lymphoma, but further studies with larger groups are recommended.

BIBLIOGRAPHY