Importance of Histologic Verification of Positive Positron Emission Tomography/Computed Tomography Findings in the Follow-Up of Patients With Malignant Lymphoma

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Abstract

We evaluated histologically verified after therapy positron emission tomography/computed tomography (PET/CT)-positive lesions in the follow-up of 190 patients with malignant lymphoma in first complete remission. Among 32 patients with histologically verified disease, 10 exhibited relapse of lymphoma, 11 had second primary malignancies, and 11 had benign/normal lesions. The symptomatic PET/CT-positive patients had a significantly shorter overall survival than the asymptomatic PET/CT-positive patients. The histologic diagnosis should be considered in posttherapy PET/CT-positive lymphoma patients.

Introduction: Posttherapy positron emission tomography/computed tomography (PET/CT) scanning in patients with malignant lymphoma remains controversial. We aimed to evaluate the utility of achieving histologic verification of positive PET/CT findings in the follow-up of patients with malignant lymphoma. **Patients and Methods:** A total of 771 PET/CT scans were performed as posttherapy follow-up in 190 lymphoma patients who had experienced a complete remission at our institution. Fifty-two patients (27.3%) had ^{18}F-fludeoxyglucose-positive lesions on posttherapy PET/CT, and a histologic diagnosis was carried out in 32 cases (16.8%). Ten patients (5.2%) exhibited relapse of lymphoma. Twelve lesions in 11 patients (5.8%) were proven to be second primary malignancies (SPM). Eleven patients (5.8%) were proven to have benign or normal tissue lesions. **Results:** Among the 32 histologically verified PET/CT-positive patients, the symptomatic PET/CT-positive patients (n = 10; 4 SPM, 6 lymphoma relapse) had a significantly shorter overall survival rate than the asymptomatic PET/CT-positive patients (n = 22; 7 SPM, 4 lymphoma relapse, 11 benign/normal tissue lesions) (2-year overall survival, 48.2% vs. 100%, respectively; $P < .001$). **Conclusion:** This study emphasizes that the histologic diagnosis should be confirmed in posttherapy PET/CT-positive patients via biopsy before adjusting the treatment regimen as a result of the high false-positive rate, including unexpected SPM or benign/normal tissue lesions.

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Introduction

The disease of the majority of patients diagnosed with malignant lymphoma (ML) responds to first-line combination chemotherapy, although some patients subsequently experience disease relapse. Early detection of disease relapse is important for providing successful second-line treatment before the tumor burden becomes too large. Therefore, all patients with ML in first remission routinely undergo posttherapy follow-up with regular outpatient visits. Consensus-based guidelines recommend frequent follow-up visits with evaluations of new symptoms, a physical examination, and routine blood tests for patients in remission.[1,2] Routine surveillance imaging is often obtained at scheduled intervals during the initial years of follow-up, even in asymptomatic patients, in order to confirm the clinical conclusions. Surveillance imaging offers the theoretical benefit of detecting asymptomatic relapse, which may allow for earlier implementation of second-line therapy and consequently improved outcomes. However, it has not been previously

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shown whether the preclinical detection of asymptomatic lymphoma relapse using surveillance imaging improves survival, and previous studies have stressed the role of clinical symptoms and signs as the primary modes of detecting disease recurrence.[3-5] On the other hand, some reports have suggested that surveillance imaging-detected asymptomatic relapse is associated with a lower disease burden and possible survival advantage in patients with relapsed lymphoma.[6,7]

Whole-body positron emission tomography (PET) using ^{18}F-fludeoxyglucose (FDG) is recommended for use in pretreatment staging as well as response assessments for ML.[8] However, the follow-up strategy for identifying relapse has not been clarified and routine surveillance imaging is not recommended in most written guidelines.[2,9] The main limitation of posttherapy follow-up PET/computed tomography (CT) in lymphoma patients is its relatively low specificity and high false-positive rate.[10] In particular, recent studies suggest that rituximab administration in addition to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) may increase the incidence of false-positive PET findings, performed either during induction or at the end of therapy, as a result of immune-mediated inflammation.[11,12] Several previous studies demonstrated that high false-positive rates in rituximab-treated patients and consequently very low-positive predictive values of 21% to 23%.[7,12] In addition, routine surveillance PET/CT has several potential risks. Radiation exposure from surveillance scans may increase the risk of secondary malignancies.[13,14] Routine surveillance imaging can lead to false-positive findings, unnecessary invasive biopsies, significant patient anxiety, and a considerable increase in health care charges.[15-18]

In clinical practice, positive PET/CT results are among the main findings on which the decision to diagnose lymphoma relapse and start salvage chemotherapy is made; however, few studies conducted to date have verified the reliability of positive PET/CT by comparing it with histologic findings. In most of the previous studies, however, histologic verification was not always obtained in all cases to distinguish true relapse from false-positive lesions. The aim of this study was to evaluate the utility of achieving histologic verification of positive PET/CT findings in the follow-up of patients with ML in the first complete remission (CR) after first-line treatment.

Methods

Patients

We retrospectively reviewed 1057 consecutive PET/CT scans performed in 362 patients with ML at our institution between 2008 and 2013. The inclusion criteria for this study were as follows: (1) all patients were diagnosed with ML as primary malignancy; (2) all patients were treated according to National Comprehensive Cancer Network (NCCN) guidelines, and a first CR was experienced as the final response assessment in all cases; (3) all patients received at least 1 FDG-PET/CT scan during their follow-up after experiencing their first CR; and (4) individuals who had developed second primary malignancy (SPM) at the time of staging of the primary ML were excluded. From 362 patients initially indexed, 70 patients had to be excluded from analysis because of incomplete follow-up data or administration of salvage therapy before PET/CT was carried out. One hundred two patients who did not experience first CR were also excluded. A total of 190 patients (92 men and 98 women; median age, 61.5 years) were eligible for this retrospective study. The duration of ML was calculated from the date on which the patient was histologically diagnosed to the date of death or the end of the study in March 2013. Posttherapy PET/CT was categorized according to the indication as routine PET/CT when the patient was asymptomatic and considered to be in remission at the time of referral, and as clinically indicated PET/CT when the referring physician suspected relapse from patient-reported symptoms. There was no specific institutional policy for routine imaging, and each attending physician decided whether to perform routine PET/CT or clinically indicated PET/CT. FDG-positive, but not histologically verified, lesions were excluded because the aim of this study was to evaluate the utility of histologic verification of positive PET/CT findings. This study was approved by the institutional review board of Yokohama Municipal Citizen's Hospital.

PET/CT Imaging

All patients fasted for at least 6 hours before the PET/CT examination. Each subject intravenously received 2 to 5 MBq/kg of FDG, after which whole-body ^{18}FDG-PET/CT (Biograph6; Siemens) was performed. The total imaging time was approximately 30 minutes. Attenuation-corrected PET images were iteratively reconstructed with an ordered-subset expectation maximization algorithm and interpreted on a color monitor with the simultaneous display of nonattenuated and attenuated images in the transaxial, coronal, and sagittal planes.

Interpretation of PET/CT Examinations

All records of the whole-body PET/CT scans, comprising a total of 771 scans, were reviewed, and patients found to have the accumulation of FDG for the first time after experiencing a CR were identified. All PET images were analyzed by 2 independent radiologists. Any focus of increased FDG uptake over the background not located in areas of physiologic FDG uptake (central nervous system, heart, gastrointestinal tract, thyroid gland, muscle), the thymus (posttreatment reactive thymic hyperplasia), or the urinary tract was considered to be an abnormal finding. In cases of an abnormal FDG uptake, we correlated the findings with the clinical information. Actually, a strong FDG uptake is observed in malignant tissue as well as in inflammatory lesions. Therefore, we considered an abnormal FDG uptake to be related to tumor relapse, except when the clinical data clearly indicated uptake in nonmalignant lesions. The final diagnosis was obtained based on histopathology reports in all cases.

Truly positive PET/CT scans were defined by biopsy-verified lymphoma relapse or by clinical symptoms suggestive of lymphoma relapse. Positive PET/CT scans, but disproved by biopsy or by repeated imaging or follow-up, were considered falsely positive. Truly negative and falsely negative PET/CT were defined as continuous remission 2 months after a negative PET/CT and relapse within 2 months after a negative PET/CT, respectively.

Histologic Evaluations

According to our institutional policy, patients with suspicious findings on PET/CT were referred for biopsy when biopsy was technically feasible. Patients who had abnormal systemic symptoms suspicious of lymphoma relapse such as lymphadenopathy or