Original Study

Limited Utility of Surveillance Imaging for Detecting Disease Relapse in Patients With Non-Hodgkin Lymphoma in First Complete Remission

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Abstract

Surveillance imaging with computed tomography (CT) or positron emission tomography (PET) with CT (PET/CT) is commonly used in practice in patients with non-Hodgkin lymphoma (NHL) who are in remission after front-line therapies. In the current study, we demonstrated that despite routine imaging, the majority of relapses in patients with NHL are detected by patient-reported symptoms or physical examination, or both.

Introduction: Surveillance imaging with computed tomography (CT) or positron emission tomography with CT (PET/CT) is commonly used in practice in patients with non-Hodgkin lymphoma (NHL) who are in remission after front-line therapies. We aimed to determine the utility of routine imaging for detecting first relapse in patients with NHL in complete remission (CR) after first-line therapies. **Patients and Methods:** We retrospectively analyzed patients with NHL who achieved CR after first-line therapies and then subsequently had disease relapse. We evaluated whether the relapse was detected solely by surveillance CT or PET/CT or by patient-reported symptoms or physical examination findings, or both. Subgroup analysis was performed on baseline histologic type (indolent vs. aggressive NHL). Data were also collected to determine the cost of surveillance PET/CT and the number of additional diagnostic imaging procedures, invasive procedures, and iatrogenic complications directly resulting from an abnormality detected on a surveillance scan. **Results:** One hundred sixty-three patients with first relapse of NHL between January 1, 2000 and December 31, 2010 were included. The majority of the relapses were detected by patient-reported symptoms or physical examination, or both, as opposed to surveillance imaging (77.9% [n = 127] vs. 22.1% [n = 36]; $P < .0001$). There was no overall survival difference between the 2 groups ($P = .66$). Patient-reported symptoms led to the detection of the majority of relapses in aggressive (85.7% [n = 72] vs. 14.3% [n = 12]; $P < .0001$) as well as indolent NHL (69.6% [n = 55] vs. 30.4% [n = 24]; $P = .0007$). Surveillance PET/CT contributed to more than 75% of follow-up health care costs in the first 2 years of monitoring for relapse. The surveillance imaging group had 1 reported case of iatrogenic pneumothorax. **Conclusion:** Our retrospective analysis suggests that there is a limited role for surveillance imaging by CT or PET/CT in detecting first relapse in NHL. There was no difference in survival outcomes between the 2 groups in our study.

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Introduction

The majority of patients diagnosed with non-Hodgkin lymphoma (NHL) respond to first-line combination chemotherapies or chemoimmunotherapies, but some patients eventually have a relapse of disease, despite having achieved a complete response (CR) with initial therapy.[1] Owing to the risk of disease relapse, all patients with NHL in first remission routinely undergo posttherapy monitoring with regular outpatient visits aimed at early detection of relapse through patient-reported symptoms, abnormal physical examination, laboratory findings, or a combination of these

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findings. In addition, routine surveillance imaging at scheduled intervals among asymptomatic patients with NHL in first CR is standard practice in most of the United States[2]; however, this practice remains controversial without a general consensus. Moreover the timing (ie, every 3-6 months vs. longer intervals), the duration (1-3 years vs. longer intervals), and the type of imaging modality (plain radiographs vs. computed tomography [CT] vs. positron emission tomography [PET]) vary among clinicians.[2]

Previous studies, mainly including patients with either Hodgkin lymphoma[3,4] or aggressive NHL[1,5,6] do not lend convincing evidence in favor of routine surveillance imaging because the majority of relapses are diagnosed on clinical grounds. Limited data are available to define the role of surveillance imaging in indolent NHL,[7] and to our knowledge, no studies in the contemporary era have assessed the role of this strategy across aggressive and indolent NHL histologic subtypes. National Comprehensive Cancer Network guidelines for patients with NHL in remission suggest CT no more often than every 6 months for 2 years after completion of treatment in patients with indolent NHL, with no ongoing routine surveillance imaging after that time unless prompted by clinical signs or symptoms.[8] The European Society of Medical Oncology guidelines recommend minimal adequate radiologic examinations at 6, 12, and 24 months after the end of treatment in aggressive NHL.[9] Both organizations do not recommend PET or PET/CT for routine surveillance once patients have achieved a CR. Although PET/CT has demonstrated utility in staging of newly diagnosed patients with NHL and for interim/end-of-therapy response assessment,[10-17] it has never been shown that surveillance with PET/CT in NHL improves survival[6,16,18], but it does contribute to significant follow-up health care costs.[1,16]

At our institution, the follow-up strategy during the first 3 years for patients with NHL in CR after first-line therapies include quarterly outpatient visits with history and physical examinations as well as laboratory analysis. Routine surveillance imaging with CT or PET/CT was done every 4 months in the first year after remission induction therapy and every 6 months in the second year. The purpose of this study was to determine the value of routine imaging for detecting *first relapse* in patients with aggressive and indolent NHL in CR after first-line therapies, evaluate whether surveillance imaging influenced survival in patients with relapsed NHL, and explore the incremental cost of routine PET/CT as a follow-up strategy for early detection of relapsed NHL.

Patient and Methods

Patient Population

We reviewed medical records of all patients with NHL at our institution between January 1, 2000 and December 31, 2010. Patients were included in the retrospective analysis according to the following criteria: previously untreated patients with NHL 18 years of age or older who achieved CR after first-line chemotherapy according to standard criteria[19] and then subsequently had a relapse of disease. Patients with NHL achieving a CR after second or subsequent lines of therapy or after hematopoietic cell transplantation were excluded. The medical records of eligible patients were evaluated for information on initial disease characteristics (age, sex, Eastern Cooperative Oncology Group performance score, histologic type, Ann Arbor stage, B symptoms, extranodal involvement, previous radiotherapy, and initial therapy) and patient characteristics at the time of relapse (site, B symptoms, stage, lactate dehydrogenase levels, and diagnostic modality that determined relapse). We established prognostic scores for each histologic type using the International Prognostic Index (IPI) score for diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL), the Follicular Lymphoma International Prognostic Index (FLIPI) score for follicular lymphoma and marginal zone lymphoma, the Mantle Cell Lymphoma International Prognostic Index (MIPI) score for mantle cell lymphoma, and the Prognostic Index for Peripheral T-Cell Lymphoma for peripheral T-cell lymphoma.[20-23] Routine follow-up after first CR consisted of clinician visits and laboratory analysis performed every 3 to 4 months in the first 2 years, every 6 months in the next 3 years, and yearly thereafter. Surveillance imaging was routinely performed every 4 months in the first year, every 6 months in year 2, and annually in years 3 to 5. Detection of disease relapse for all patients with NHL included in the study was dichotomized into 2 groups. The first group included patients in whom relapse was detected by patient-reported symptoms or physical examination findings, or both (during intervals between scheduled imaging) (symptoms group). The second group included patients in whom surveillance imaging led to the detection of disease relapse (imaging group).

Subgroup analysis was performed on baseline histologic type, categorized as indolent vs. aggressive NHL. Data were also collected to determine the number of additional invasive procedures and iatrogenic complications directly resulting from an abnormality detected on surveillance imaging. Cost analysis was restricted to patients diagnosed at our institution between 2006 and 2010 with follow-up for at least 2 years after CR. The study was approved by the institutional review board and the protocol review and monitoring committee at our cancer center.

Statistical Analysis

Categorical variables in the baseline clinical characteristics of the patient population were presented by the counts and percentages for the symptoms group vs. the imaging group and compared by the χ^2 goodness-of-fit test. If the expected counts in 1 category of a group were > 4, the P value was computed from the asymptotic χ^2 distribution of the test statistic; otherwise, a resampling method was used to compute the P value. Continuous variables were presented by their means, and the 2-sample t test was used to determine significant differences between their means values in the 2 groups. The proportion test was used to determine significant differences between the methods of detecting relapse among the patients with NHL. Overall survival between the symptoms group and the imaging group was estimated using the Kaplan-Meier method and log-rank test using the "survival" package of R (www.r-project.org; R statistical software, Foundation for Statistical Computing, Vienna, Austria). All comparisons were considered significant if the $P \leq .05$.

Follow-up health care costs were based on 2010 Ambulatory Payment Classification under Medicare's Hospital Outpatient Department Prospective Payment System for PET/CT and physician office visits; laboratory costs were determined by the 2010 Clinical Diagnostic Laboratory Fee Schedule.