

Highlight: PET scans for Non-Hodgkin’s Lymphoma: Answering the Critical Questions to Assess Utility.

Robert Hayashi¹

¹Washington University in St Louis School of Medicine

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Abstract

Standard management of pediatric Non-Hodgkin’s Lymphoma (NHL) patients have included an initial assessment of the disease at presentation to establish it’s extent. This “staging” process has historically assigned patients using traditional classifications which were established decades ago when, like other pediatric malignancies, the more extensive involvement of the cancer for a patient directly correlated with the patient’s long term survival[[1]](#ref-0001). Advances in radiologic technology have evolved in the way the disease extent was evaluated, moving from conventional radiographs, to computerized tomography (CT) to magnetic resonance imaging (MRI) to most recently positron emission tomography (PET)[[2]](#ref-0002). Despite the development and use of PET scans for decades for various cancer diagnoses, the role of PET scans for NHL remains unclear[[3]](#ref-0003). Indeed, its value for many conditions is its ability to assess the response to initial therapy and establish the patient’s risk stratification guiding the remaining treatment plan[[4]](#ref-0004). Such efforts have not occurred in clinical trials of NHL and thus we are left to examine case series and try to discern its value for this disease.

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Robert J. Hayashi, MD, Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine, Siteman Cancer Center, St. Louis Children’s Hospital, St. Louis, MO.

Standard management of pediatric Non-Hodgkin’s Lymphoma (NHL) patients have included an initial assessment of the disease at presentation to establish it’s extent. This “staging” process has historically assigned patients using traditional classifications which were established decades ago when, like other pediatric malignancies, the more extensive involvement of the cancer for a patient directly correlated with the patient’s long term survival[1]. Advances in radiologic technology have evolved in the way the disease extent was evaluated, moving from conventional radiographs, to computerized tomography (CT) to magnetic resonance imaging (MRI) to most recently positron emission tomography (PET)[2]. Despite the development and use of PET scans for decades for various cancer diagnoses, the role of PET scans for NHL remains unclear[3]. Indeed, its value for many conditions is its ability to assess the response to initial therapy and establish the patient’s risk stratification guiding the remaining treatment plan[4]. Such efforts have not occurred in clinical trials of NHL and thus we are left to examine case series and try to discern its value for this disease.

Advances in the management of NHL have resulted in tremendous improvements in long-term, overall survival for all disease groups. As the outcomes continue to improve, with the event free survival (EFS) of some subgroups of NHL approaching or even exceeding 90%, the power of traditional prognostic factors have waned in their significance[5-7]. In this issue, *Kroeze, et al*[8]describes their experience with PET scans in a relatively large cohort of B cell lymphoblastic lymphoma patients. Their retrospective review reveals that several patients had findings which led to a different clinical stage than what was derived using other

imaging modalities. Some patients had a higher stage using PET compared to conventional CT's or MRI's while others would have been assigned a lower stage if PET were used as the primary imaging modality. Given that discrepancies in the clinical stage between PET scans and other imaging modalities have been observed by others, the authors advocate for the use of PET scans in staging NHL patients. Although this seems very reasonable, given the current state of the management of NHL in children, one must first reflect on the current success of up front therapy, the salvage rate for patients of recurrent disease, and the state of our understanding of how PET scans may assist in the risk stratification of patients.

The original Ann Arbor and Murphy staging classifications have struggled to maintain their relevance with the advancements of modern day therapy for NHL. Indeed, staging for mature B cell lymphoma has relied more on other staging classifications (FAB/LMB, BFM) which incorporates the ability to resect limited disease and serum LDH values to assign the final stage of the patient. The validity of such staging has been established by a series of trials both in the US and internationally adhering to a consistent backbone of therapy (FAB/LMB) which allows us to discern how clinical stage holds up with the stepwise modifications of treatment with each subsequent multi-center trial[9]. However, even in this case, as the EFS for mature B cell lymphoma is well over 90%, we are left to reflect upon how different stages correlate to outcomes using modern therapy[6].

NHL continues to struggle in defining the role of PET scan in establishing risk categories. There are many reasons for this. Firstly, NHL is a relatively rare condition and many trials have taken years to design and execute and are thus often ill equipped to answer ancillary study questions such as the role of PET scans in staging disease or the its role in assessing response to therapy. Secondly, studies which require national participation to accrue sufficient numbers of patients may not have the radiology resources to answer the clinical question making such imaging studies “optional” virtually eliminating the possibility that the data generated could be evaluated with any scientific rigor. Finally, NHL often presents abruptly, with rapidly growing tumors in compromising locations (i.e. mediastinal masses), so that baseline imaging is often not feasible and thus not practical for a patient in a tenuous clinical situation. Thus, with the absence of a baseline exam to use to assess responses to therapy short of a complete metabolic response, designing studies to examine the use of PET scans remain challenging.

Moving forward, we need to assess the value of refining staging assessments with the current state of treatment in NHL. Current clinical trials have often merged stages together (Low stage; I-II verses high stage III-IV) making distinctions between stages less critical. Recently completed trials in NHL have failed to demonstrate that clinical stage has prognostic importance[5, 7]. Modern therapies often result in vigorous responses, often leading to complete remission in a short period of time, making rapidity of response a variable that fails to segregate patients into meaningful groups that can be used to assess prognosis. Thus, even though if PET imaging may change the clinical stage relative to conventional imaging, its use may not impact clinical trial design or patient outcome.

Finally, in most clinical scenarios, despite the successes of upfront therapy, the ability to salvage relapsed disease remains a major clinical challenge, with the majority of patients failing to achieve long term survival once relapse occurs[10]. Thus, there is currently little utility to refine the means of identifying low stage disease with more sensitive imaging techniques as deescalating therapy for perceived favorable prognostic patients may not be practical until better salvage regimens become available.

Thus, the future of the use of PET scan in NHL remains to be determined. Proposals to investigate its use should probably be restricted to large scale clinical trials where a critical mass of patients receiving uniform imaging in the face of rigorous protocol driven therapy can generate data to assess whether more refined disease evaluations or the extent of initial response to therapy can identify patients for risk stratification for future prospective trials. Hopefully such efforts will come to fruition to clarify the role of PET scans in this disease.

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Correspondence to: Robert J. Hayashi, MD, Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine, 660 S. Euclid Ave. St. Louis, MO 63110, E-mail: hayashi_r@wustl.edu