Utility of Routine Post-Therapy Surveillance Imaging in Diffuse Large B-Cell Lymphoma

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A B S T R A C T

Purpose

We examined the utility of post-therapy surveillance imaging in a large, prospectively enrolled cohort of patients with diffuse large B-cell lymphoma (DLBCL) from the United States and confirmed our results in an independent cohort of patients from France.

Methods

Patients with newly diagnosed DLBCL and treated with anthracycline-based immunochemotherapy were identified from the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence and the Léon Bérard Cancer Center, Lyon, France. In those with relapse, details at relapse and outcomes were abstracted from records.

Results

680 individuals with DLBCL were identified from the MER, 552 (81%) of whom achieved remission after induction. 112 of the 552 patients (20%) suffered a relapse. The majority (64%) of relapses were identified before a scheduled follow-up visit. Surveillance imaging detected DLBCL relapse before clinical manifestations in nine out of 552 patients (1.6%) observed after therapy. In the Lyon cohort, imaging identified asymptomatic DLBCL relapse in four out of 222 patients (1.8%). There was no difference in survival after DLBCL relapse in patients detected at scheduled follow-up versus before scheduled follow-up in both the MER ($P = .56$) and Lyon cohorts ($P = .25$).

Conclusion

The majority of DLBCL relapses are detected outside of planned follow-up, with no difference in outcome in patients with DLBCL detected at a scheduled visit compared with patients with relapse detected outside of planned follow-up. These data do not support the use of routine surveillance imaging for follow-up of DLBCL.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for approximately 30% of all lymphomas. In the United States, approximately 15,000 new cases of DLBCL are diagnosed each year.^{1,2} Standard-of-care treatment is anthracycline-based immunochemotherapy (most commonly, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Approximately 80% to 85% of patients achieve a complete remission (CR), but a significant minority (20% to 25%) of these patients will relapse during observation. Second-line

chemotherapy followed by autologous stem-cell transplantation provides the possibility of cure in a subset of these patients.³ Therefore, surveillance for relapse is important.

The optimal frequency of surveillance scans after DLBCL is not clear⁶⁻¹⁴; the current National Comprehensive Cancer Network (NCCN) guidelines recommend computed tomography (CT) scan no more than every 6 months for 2 years after completion of treatment, and then only as clinically indicated.¹⁵ However, there is wide variation in the frequency and type of surveillance imaging, and many patients receive more scans than recommended by the NCCN.⁶

The rationale for surveillance imaging is the theoretical improvement in survival if relapses are detected at the preclinical stage, as responses to second-line therapy may be improved when tumor burden is low.^{16,17} Multiple studies have demonstrated that most DLBCL relapses occur outside the timeframe of a scheduled visit and therefore only a minority of relapses are actually detected at a preclinical state via imaging studies.^{6-14,18-20} Furthermore, relapses detected solely via imaging have not been associated with superior survival in multiple studies, despite being detected at earlier stages.¹⁰⁻¹² One recent study from El-Galaly et al²¹ reported a reduced risk of death in patients with DLBCL detected solely via imaging, however, this association was no longer significant after excluding those who relapsed with an indolent lymphoma histology and those with relapse before first surveillance imaging. Furthermore, scans have potential downsides—patient anxiety,²² radiation exposure,^{23,24} false-positive results leading to more testing,^{9,20,25} and cost. In this study, we examined the utility of post-therapy surveillance imaging in a large, prospectively enrolled cohort of patients with DLBCL predominantly from the upper Midwest of the United States and confirmed our results in an independent cohort of patients from France.

METHODS

Patients

Molecular Epidemiology Resource cohort. Following approval by the human subject institutional review board at the Mayo Clinic and University of Iowa, we identified patients from the Molecular Epidemiology Resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence,^{26,27} which prospectively enrolls patients within 9 months of a lymphoma diagnosis. Patients eligible for this analysis were those with newly diagnosed DLBCL enrolled from 2002 to 2009 and who received anthracycline-based immunochemotherapy as their initial therapy. All diagnoses were confirmed by study hematopathologists. Patients with primary mediastinal large B-cell lymphoma were included while patients with transformation of previous lymphoma, primary CNS lymphoma, gray-zone lymphoma, post-transplantation lymphoproliferative disorder, and HIV were excluded. Baseline clinical, laboratory, and treatment data were abstracted from medical records using a standard protocol. Patient management, including treatment and post-treatment surveillance strategy, was performed according to their treating hematologist/oncologist. Patients were systematically contacted every 6 months for the first 3 years and then annually for events including relapse, re-treatment, and death. Medical records were reviewed in patients with events to abstract clinical details at relapse and the relationship of any event to planned follow-up visits and imaging. Relapses were defined as “asymptomatic” if there were no reported symptoms and a normal examination was recorded.

Lyon cohort. We identified patients from the database of lymphoid malignancies from Léon Bérard Cancer Center, Lyon, France, which was approved by the French authority for the protection of privacy and personal data in clinical research (CNIL, approval No.1388403). This study was performed according to the principles of the Declaration of Helsinki. Patients eligible for this study were those with newly diagnosed DLBCL consecutively treated with anthracycline-based immunochemotherapy as their initial therapy from 1998 to 2009. Patient management was performed according to each treating physician. The institutional guideline for post-treatment strategy (derived from the French National Cancer Institute) is a physical examination every 3 months during the first 2 years, then every 6 months until 5 years, and then annually; and a CT scan at 6 months and at 1 year, with the frequency of CT scans adapted to the initial stage and prognostic score.²⁸ We applied the same inclusion/exclusion and medical record abstraction protocol as the MER.

Statistical Methodology

Event decomposition was defined as time from entering surveillance until progression, re-treatment of lymphoma, or death. If the surveillance date was unknown, 6 months from diagnosis was used as the estimated surveillance date. Overall survival (OS) after relapse was defined as time from relapse until death due to any cause. Cause of death was determined via medical record review using a standard protocol.²⁹ Event cumulative incidence curves were performed using a competing risk approach.³⁰ All analyses were performed using SASv9.2 and Rv2.13.0.

RESULTS

MER Cohort

Patient characteristics. Six hundred eighty newly-diagnosed patients with DLBCL treated with anthracycline-based immunochemotherapy were enrolled on the MER between 2002 and 2009. Patient characteristics can be found in [Table 1](#).

Treatment outcome details. Of the 680 individuals who entered the study at diagnosis, 13 (2%) died during induction, 72 (11%) had refractory disease, 16 (2%) received unplanned consolidative therapy, and 27 (4%) had an unknown status or timing of post-therapy assessment, leaving 552 (81%) patients who entered into post-treatment observation ([Fig 1A](#)). The characteristics at diagnosis of these 552 patients are listed in [Table 1](#). Of the 552 patients entering post-therapy observation, 112 (20%) suffered a relapse of lymphoma: 93 with DLBCL and 19 with another lymphoma subtype. 74% of observed relapses were within the first 24 months of surveillance; a cumulative incidence curve by event type by time from entering surveillance for the 552 patients can be found in [Appendix Figure A1A](#) (online only).

Post-therapy event details. Outside records were not available for eight of 112 patients with relapse, leaving 104 evaluable patients. Of the 104 evaluable relapses, 100 were biopsy-proven, three were re-treated based on imaging, and one data was not available. 67 of the 104 patients (64%) were evaluated for disease before their next scheduled follow-up visit; 63 had DLBCL at relapse and four had another lymphoma subtype. Of the 63 with DLBCL at relapse, the median (Q1, Q3) time from a previous scan was 4 months.^{2,9} The other 37 relapses (36%) were detected at a scheduled follow-up visit (22 DLBCL and 15 other lymphoma subtype); 22 were detected via CT, 13 were detected via PET, and two were detected by physical examination or clinical features which prompted a scan. 24 of the 37 patients had clinical features of relapse (symptoms or abnormal physical examination). Surveillance imaging identified 13 asymptomatic relapses; of which four were low-grade or other non-Hodgkin lymphoma subtype at relapse ([Fig 3A](#)). Therefore, surveillance imaging detected DLBCL relapse before clinical manifestations in nine of 552 patients (1.6%) observed post-DLBCL therapy. Across all 104 patients regardless of timing of visit, at the time of relapse, 67% had symptoms, 45% had an abnormal physical examination, and 46% had an elevated lactate dehydrogenase (LDH) level; 88% had at least one of these features ([Fig 4](#)).

Outcome after DLBCL relapse. We compared OS from relapse in the cases with DLBCL relapse. There was no difference in OS for the 22 patients with DLBCL relapse detected at a scheduled visit (median OS, 21 months; 95% CI, 11 to 57 months) compared with the 63 patients who presented before their next scheduled visit (median OS, 15 months; 95% CI, 8 to 26 months, $P = .56$, [Fig 2A](#)).

Table 1. Patient Characteristics

Characteristic	MER Cohort				Lyon Cohort			
	All (n = 680)		Entered Post-Treatment Observation (n = 552)		All (n = 261)		Entered Post-Treatment Observation (n = 222)	
	No.	%	No.	%	No.	%	No.	%
Age, years								
Median	63		61		66		65	
Range	18-92		18-92		19-90		19-90	
Age > 60 years	387	57	287	52	155	59	130	59
Male sex	359	53	283	51	125	48	109	49
LDH > ULN	342	55	262	51	192	74	158	71
Stage III/IV	412	61	314	58	168	64	137	62
≥ 2 Extranodal sites	127	19	97	18	70	27	54	24
PS ≥ 2	120	18	81	15	52	20	37	17
IPI								
0-1	242	36	222	40	72	27	65	29
2	186	27	153	28	65	25	60	27
3	168	25	126	23	61	24	52	23
4-5	84	12	51	9	63	24	45	20
Events	271	40	159	29	108	41	69	31
Deaths	198	29	110	20	82	31	49	22
Follow-up on living patients, months	()		()		()		()	
Median	71				77			
Range	6-129				5-162			
EFS24								
KM estimate, %	70				71			
95% CI, %	67 to 74				65 to 77			

LDH, lactate dehydrogenase; ULN, upper limit normal; PS, performance status; IPI, international prognostic index; EFS24, event-free survival at 24 months, KM, Kaplan-Meier estimate.

Features of relapse in nine asymptomatic DLBCL patients. The median time from diagnosis to relapse was 19 months (range, 8 to 46 months) in the nine patients diagnosed with asymptomatic DLBCL relapse by imaging. In five of these patients (56%), at the end of initial treatment, the post-treatment positron emission tomography (PET) scan reported [^{18}F]fluorodeoxyglucose uptake, but the provider made the clinical judgment to observe. In 1 patient (11%), the relapse was

not biopsy-proven. At the time of imaging that diagnosed the relapse, 2 of the 9 (22%) had an elevated LDH level.

Lyon Cohort

Patient characteristics. There were 261 patients with DLBCL in the Lyon cohort whose clinical characteristics are presented in Table 1.

Fig 1. (A) Molecular Epidemiology Resource (MER) cohort flowchart. (B) Lyon cohort flowchart. DLBCL, diffuse large B-cell lymphoma.

Fig 2. (A) Overall survival of 112 patients with relapsed diffuse large B-cell lymphoma (DLBCL) from Molecular Epidemiology Resource cohort. (B) Overall survival of 55 patients with relapsed DLBCL from Lyon cohort.

Treatment outcome details. Of the 261 patients, 11 (4%) died during induction, 24 (9%) had refractory disease, and four (2%) patients received unplanned consolidative therapy, leaving 222 patients (85%) who entered post-treatment observation (Table 1, Fig 1B). Of the 222 entering post-treatment observation, 55 (25%) had relapsed lymphoma (46 DLBCL and 9 other lymphoma subtype). Of

the 55 relapses, 46 were biopsy-proven and nine were re-treated based on imaging. A cumulative incidence curve by event-type for the 222 patients of the Lyon cohort entering observation is demonstrated in Appendix Figure A1B.

Post-therapy event details. Of the 55 patients with relapsed lymphoma, 34 (62%) were evaluated before the planned visit for

Fig 3. (A) Flowchart of 112 patients with relapsed diffuse large B-cell lymphoma (DLBCL) from Molecular Epidemiology Resource (MER) cohort. (B) Flowchart of 55 patients with relapsed DLBCL from Lyon cohort.

Fig 4. Clinical features at relapse detection in 104 Molecular Epidemiology Resource (MER) patients and 55 Lyon patients with diffuse large B-cell lymphoma with post-therapy relapse, regardless of timing of relapse. LDH, lactate dehydrogenase.

symptoms (28 DLBCL and 6 other subtype). The remaining 21 patients (38%) with relapse (18 DLBCL and 3 other subtype) were detected at a planned follow-up visit, and among them, 15 had clinical features of relapse. Surveillance imaging identified six asymptomatic relapses, two of which were low-grade or other lymphoma type at relapse (Fig 3B). Therefore, surveillance imaging detected DLBCL relapse before clinical manifestations in four out of 222 patients (1.8%) observed post-DLBCL therapy. Across all 55 patients with relapse regardless of timing of visit, 56% had symptoms, 56% had abnormal physical examination, and 53% had elevated LDH level; 91% had at least one of these features.

Outcome after DLBCL relapse. There was no significant difference in OS for patients with DLBCL relapse detected at a scheduled visit (median OS, 19 months, 95% CI, 3 to 82 months) compared with patients with DLBCL relapse who presented before their next scheduled visit (median OS, 12 months, 95% CI, 3 to 22 months, $P = .25$, Fig 2B).

Features of relapse in four asymptomatic DLBCL patients. The median time from diagnosis to relapse was 11 months (range, 7 to 16 months) in the four patients diagnosed with asymptomatic DLBCL relapse by surveillance imaging. At the end of initial treatment, two of these patients had persistent [^{18}F]fluorodeoxyglucose uptake on post-treatment PET scan, but the provider made the clinical judgment to observe. At the time of imaging that diagnosed the relapse, one of the four (25%) had an elevated LDH level.

Sensitivity Analyses

As a sensitivity analysis, we identified 276 of the 552 patients in post-treatment observation who received follow-up care at Mayo Clinic or the University of Iowa and abstracted the number, date, and type of imaging utilized for diagnosis, treatment, and surveillance of their DLBCL. Patients received a median of four scans during diagnosis and treatment evaluation (Appendix Table A1). Patients in post-treatment observation received a median of two scans per year during years 1 and 2 of observation, and one scan per year during years 3 to 6. About half the imaging performed (56%) during diagnosis and evaluation were PET compared with CT (44%), while the majority of imaging (80%) during surveillance were CT. The rates of relapse and

detection of relapse outside of planned visits were similar compared with the overall MER cohort (Appendix Fig A2, online only), though the number of asymptomatic relapses ($n = 7$) was slightly higher compared with patients who received follow-up elsewhere ($n = 2$).

We next examined for potential changes in imaging practice over time. There was no difference in the rate of relapse detection at a scheduled visit versus before a scheduled visit in patients diagnosed from 2002 to 2005 compared with 2006 to 2009 ($P = .98$). We also examined the subset of DLBCL patients presenting with an additional lymphoma subtype, predominantly low-grade B-cell lymphoma, at diagnosis. These patients were more likely to have a non-DLBCL relapse (37%) compared with others (12%, $P = .0068$). However, the frequency of detection of relapse at scheduled visit versus unscheduled visit and outcome after DLBCL relapse was similar between the two groups (data not shown).

DISCUSSION

This study of post-therapy surveillance imaging in a multi-institutional cohort of DLBCL patients found that routine imaging adds little to detection of relapse; asymptomatic relapses were detected in only 1.6% of patients who enter post-treatment surveillance. These results were confirmed in an independent cohort from Lyon, France, where asymptomatic DLBCL relapses were detected in 1.8% of patients in post-treatment surveillance. There were no differences in OS between patients with relapse detected outside of a scheduled follow-up visit and those whose relapse was detected at a planned visit. In addition, the majority of relapses were detected outside of a routine follow-up visit. In all patients with relapse, regardless of timing of relapse detection, 88% in the MER cohort and 91% in the Lyon cohort had symptoms, abnormal physical examination, and/or elevated LDH levels documented in the medical record. These results suggest an important role for educating patients regarding the signs and symptoms of relapse and the need for thorough history and physical examination during visits.

These data suggest little utility for performing routine imaging in the manner currently employed in follow-up of DLBCL patients in CR. Because relapsed DLBCL is potentially curable, there remains the theoretical benefit of better outcomes with earlier detection of relapse.¹¹ However, our results are in agreement with the five previous studies that have failed to show a survival benefit when relapses are detected before development of symptoms or physical examination abnormalities.^{11,12,14,25,31} Due to the small number of patients with asymptomatic relapse detected solely via surveillance scan in this cohort, we were unable to identify a subgroup of patients where surveillance may be useful. Determining the optimal follow-up strategy and potentially a group of patients where scans may be beneficial is difficult outside of a prospective, randomized trial. Given the infrequent detection of asymptomatic relapses via scan alone, this may not be feasible, and comparative effectiveness techniques utilizing large datasets may provide an alternative method to answer this question.

Our rate of asymptomatic DLBCL relapse detection via imaging is slightly lower than some of the previous literature. This may be due to several studies that examined the role of PET surveillance, which has improved sensitivity compared with CT scan, and therefore will likely identify more asymptomatic relapses,^{9,14,18,19,25} and the frequency of imaging differed across studies. The surveillance strategy in our cohort

was per the discretion of the treating physician. In addition, some authors report the percentage of asymptomatic relapses detected via scan out of the number of relapses, which is higher than the percentage of asymptomatic relapses detected via scan in the total number of patients who entered post-treatment surveillance.

It is important to remember that scans are not without risk. They expose patients to nephrotoxic contrast and ionizing radiation. Although the amount of radiation is small, this may be clinically significant in younger patients where repetitive scans may increase the risk of a secondary malignancy over their lifetime.³² Imaging studies, particularly PET scans, may have false-positive results and lead to further testing including unnecessary biopsies.^{20,25} Patients' quality of life may be negatively affected, as the anticipation of a scan is associated with increased anxiety levels for lymphoma survivors.²² Lastly, imaging costs money. This study was not designed to perform an economic analysis, but in the era of sky-rocketing health care costs, we must be certain that our practices are based on evidence and lead to improvement in patient outcomes. Routine surveillance imaging for patients with DLBCL is not based on evidence and does not improve outcomes.

Expert clinical guideline updates will need to carefully consider these findings. While this study was unable to demonstrate utility for routine surveillance imaging in DLBCL patients clinically felt to be in CR, we do not dismiss the importance of selected imaging in the post-therapy management of DLBCL. The finding that most relapses are detected in response to patient-reported symptoms suggests that improved early detection of relapse may result from enhanced surveillance of patient symptoms, with appropriate imaging to investigate concerns. Furthermore, our results do not directly apply to surveillance imaging in the conduct of clinical trials. Scheduled imaging at select validated time points to establish event-free or progression-free frequencies remains appropriate for trial designs, although the customary convention of considering such images standard of care will be scrutinized.

Strengths of this study include the inclusion of two independent, international, large cohorts of patients with DLBCL that included patients treated at academic and community centers. The French and Americans were likely treated with different regimens—adding strength to the generalizability of these findings. Limitations include that this is a retrospective analysis within a prospective cohort. Despite a standard systematic strategy to obtain patient and disease information, there is some missing data. In addition, the surveillance strategy was per the discretion of the treating physician and therefore nonuniform. There was no central review of imaging studies. Lastly, we acknowledge that imaging was frequently performed in conjunction with the planned follow-up visit, and therefore it is possible that the provider knew the results before seeing the patient, and if there was an abnormal result, they may have been more likely to elicit symptoms or report an abnormal physical

examination finding than if they did not have knowledge of the results. However, we attempted to mitigate this bias with comparing outcomes of patients with relapse detected outside of routine visit as compared with those detected at a scheduled visit, as opposed to comparing asymptomatic versus symptomatic patients.

In conclusion, the majority of DLBCL relapses are detected by patients outside of planned follow-up, there is no difference in survival of those with DLBCL relapse detected at planned visit versus outside of scheduled visit, and these data do not support the utility of surveillance imaging in detection of preclinical relapse as recommended by current guidelines. Nearly all relapses are accompanied by symptoms, physical examination findings, and/or laboratory abnormalities. Given the frequency of relapses detected by interim clinical symptoms, substantial opportunity exists to identify earlier relapses via enhanced symptom surveillance. At a minimum, patients in post-treatment observation should be educated on the signs and symptoms of lymphoma relapse, and providers should perform thorough history and physical examinations. Ideally, a randomized prospective trial or comparative effectiveness research is required to determine the optimal imaging strategy for surveillance of DLBCL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

Table A1. Sensitivity Analysis: Number of Imaging Studies for Patients Entering Post-Treatment Observation and Managed at Mayo Clinic and University of Iowa

Scans	Diagnosis and Treatment Evaluation	No. of Patients Evaluable					
		Post-Treatment Observation*					
		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+
Median number of any scans	276	276	246	209	166	118	78
Q1-Q3	4	2	2	1	1	1	1
Number of any scans	3-5	1-3	1-3	1-2	0-2	0-1	0-1
Mean	4.1	2.4	2.0	1.4	1.0	0.9	1.1
SD	1.7	1.3	1.2	1.0	0.8	0.8	1.5
Number of PET scans							
Mean	1.8	0.6	0.4	0.2	0.2	0.2	0.1
SD	1.1	0.9	0.8	0.6	0.5	0.5	0.5
Number of CT scans							
Mean	2.3	1.8	1.6	1.2	0.8	0.7	1.0
SD	1.6	1.3	1.3	1.0	0.8	0.8	1.3

Abbreviations: CT, computed tomography; PET, positron emission tomography; Q, quartile; SD, standard deviation.

*Denominator for year of follow-up is the number of patients with complete data (either had event or remained event-free during that year) for that time period. Example: 166 of the 276 patients either had an event during year 4 of surveillance or completed at least 4 years of follow-up after surveillance.

Fig A1. (A) Cumulative incidence of events in Molecular Epidemiology Resource cohort of 552 newly diagnosed patients with diffuse large B-cell lymphoma (DLBCL) entering surveillance. (B) Cumulative incidence of events in Lyon cohort of 222 newly diagnosed patients with DLBCL entering surveillance.

Fig A2. Flowchart in patients followed at Mayo Clinic or University of Iowa. DLBCL, diffuse large B-cell lymphoma.