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REVIEW

Surveillance in Patients With Diffuse Large B Cell Lymphoma

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Abstract

With improvement in the cure rates for diffuse large B cell lymphoma, the question of surveillance imaging in patients who achieve complete remission after the initial therapy has become relevant. Some of the clinical practice guidelines recommend surveillance scanning. However, several studies have reported no benefit in overall survival with scans. Moreover, studies have highlighted an increased risk for developing secondary malignancies because of exposure to ionizing radiation from the scans. Different international societies have contrasting guidelines for the role of surveillance computerized tomography scans in patients who achieve complete remission after first-line therapy. Any benefit of surveillance imaging must be balanced by the costs, risk of radiation exposure, and lack of survival benefit. The PubMed platform was searched using relevant keywords for English-language articles with no date restrictions. Search terms were cross-referenced with review articles, and additional articles were identified by manually searching reference lists. Results were reviewed by the authors and selected for inclusion based on relevance. We present a review of this current data available for surveillance imaging in patients with diffuse large B cell lymphoma.

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INTRODUCTION

In an era when cure rates for malignancies are improving, particularly in lymphomas, the question of early surveillance and possibly early intervention has become more relevant. The role of surveillance imaging in lymphomas has been a subject of debate for several years. This assumes more importance in aggressive lymphomas, particularly diffuse large B cell lymphomas (DLBCL), where the cure at relapse is possible. Different international societies have contrasting guidelines for the role of surveillance computerized tomography (CT) scans in patients who achieve complete remission after first-line therapy.[1-3] Any benefit of surveillance imaging must be balanced by the costs, risk of radiation exposure, and lack of survival benefit.

There have been several studies conducted to determine the benefit of routine surveillance imaging in the above-mentioned patient population. We present a review of the current data available for surveillance imaging in patients with DLBCL.

The PubMed platform was searched using the keywords surveillance, non-Hodgkin's lymphoma, CT scans, computerized tomography, PET scans, positron-emission tomography, diffuse large B cell lymphoma, and DLBCL for English-language articles with no date restrictions. Search terms were cross-referenced with review articles, and additional articles were identified by manually searching reference lists. Results were reviewed by the authors and selected for inclusion based on relevance to the topic.

Historically, a diagnosis of relapse is usually made at the time of development of symptoms. The argument for surveillance is to detect early relapse and to initiate interventions that would ultimately improve survival. There can be a lag time between radiological development of disease and development of clinical symptoms. By use of routine surveillance imaging, the hope is to detect the disease during this window.[3] The length of this window varies, depending on the histology of the tumor. Indolent

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ARTICLE HIGHLIGHTS

- Surveillance scans in asymptomatic patients with diffuse large B cell lymphoma remains controversial.
- Different international societies have contrasting guidelines for the role of surveillance computerized tomography scans in patients who achieve complete remission after first line therapy.
- Surveillance scans in diffuse large B cell lymphoma have failed to show significant survival benefit.
- Benefits of surveillance imaging must be balanced against the costs, risk of radiation exposure, and lack of survival benefit.

lymphomas such as follicular lymphomas are likely to have a longer period of asymptomatic progression when compared with aggressive histologies such as DLBCL and Burkitt lymphoma, in which case the time to onset of symptoms would be fairly rapid.

To design an ideal screening test, the sensitivity and specificity of the test and the prevalence of the disease in the population which is being screened are relevant. Data from the Nebraska Lymphoma Group suggest that the chances of relapse in patients with DLBCL being detected in any incidental follow-up visit are approximately 1 in 40 or 50.[4] Based on the data available for the sensitivity of a CT scan, the positive predictive value of an abnormal scan to accurately detect a lymphoma would be only 20%. This translates to a high false-positive rate of 80%, which leads to unnecessary procedures and anxiety in patients with an abnormal scan.[4]

RATIONALE FOR SURVEILLANCE IMAGING

The rationale for surveillance imaging in lymphoma is based on the hope for improved clinical outcomes of patients with lower disease burden in the setting of relapsed disease.[5] Risk stratification of lymphoma is based on the age-adjusted international prognostic index (IPI), which takes into account the age of the patient, performance status, stage of the disease, and serum lactate dehydrogenase level. High IPI has been associated with higher rates of relapse and increased risk of death.[6] Hence, surveillance imaging has been recommended on the belief that, by earlier detection of disease, when the tumor burden is low and the patient is clinically asymptomatic, the outcomes may be better.

A prospective study performed by Maurer et al[7] found patients with DLBCL to have a low risk of recurrence once they reach 2 years in remission, with a subsequent risk of relapse of 8%, and an overall survival equivalent to age- and sex-matched controls. Thus surveillance, if warranted, would have the maximum benefit within the first 2 years of achieving a complete response.

There have been several retrospective studies evaluating the role of surveillance scans in lymphomas (Table 1).[8-13] However, no clear clinical benefit has been shown.

A study by Thompson et al[13] attempted to estimate the benefit of post-remission surveillance scans in a large retrospective analysis. The study evaluated 680 patients with DLBCL who achieved complete remission after standard chemo-immune therapy. CT scans were used in 80% for surveillance. Over a 7-year period of observation, 20% of patients experienced relapses. Seventy-four percent of the relapses occurred in within the first 2 years of surveillance and a majority of them were identified outside the routine clinic visit. Surveillance scans detected relapse before the development of symptoms in only 1.6% of the patients. There was no difference in overall survival of the patients whose relapse was detected through surveillance scans when compared with patients whose relapse was detected because of development of symptoms. The authors concluded that this data argued against the use of routine surveillance imaging in DLBCL.

In a retrospective analysis by Liedtke et al,[14] 108 patients with relapsed lymphoma who had undergone induction and autologous hematopoietic stem cell transplantation (auto-HST) were evaluated. Of the 108 patients, 22% had relapse diagnosed by surveillance imaging. A strong association was found between lower age-adjusted IPIs and relapses detected during surveillance imaging. A low-risk age-adjusted IPI was seen in 79% of the asymptomatic patients when

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TABLE 1. Recent Retrospective Studies Evaluating Surveillance Scans[a]

Author	Type of study	Type of lymphoma	Type of scan	Surveillance duration/frequency	No. of patients	Median overall survival	Conclusion
Kang et al, 2017[8]	Retrospective	DLBCL, BL, T cell lymphomas, pre-B ALL, NK/T cell, T-ALL	CT scans	3 months for the first 2 years, then every 6-12 months	644	20 months vs 19.6 months (P=.04)	No difference in outcomes with surveillance scans
Cohen et al, 2017[9]	Meta-analysis	DLBCL, HL	CT scans/PET scans	Variable	3099	Variable	No difference in overall survival
Tang et al, 2016[10]	Retrospective	PTCL	CT scans/PET scans	Every 3 months	338	n/a	Limited utility
Cheah et al, 2014[11]	Retrospective	Transformed DLBCL	PET/CT	6 months for 2 years, then annually 5 years	55	77% at 5 years	No clinical benefit
Epperla et al, 2016 [12]	Retrospective	DLBCL post-ASCT	PET/CT	3-6 months for 3 years	160	21 months vs 19.2 months	No difference in OS
Thompson et al, 2014[13]	Retrospective	DLBCL	CT scan/PET scan	3-6 months	680	19 months vs 12 months	No statistically significant difference in OS

[a]ASCT = autologous hematopoietic stem cell transplantation; BL= Burkitt lymphoma; CT = computerized tomography; DLBCL = diffuse large B cell lymphoma; HL=Hodgkin lymphoma; n/a = not available; NK/T cell = natural killer–T cell lymphoma; OS = overall survival; PET = positron-emission tomography; PET/CT = positron-emission tomography/computerized tomography; Pre-B ALL= pre-B acute lymphoblastic leukemia/lymphoma; PTCL = peripheral T cell lymphoma; T-ALL= T cell acute lymphoblastic leukemia.

compared with only 39% of the symptomatic patients. This study concluded that surveillance imaging after auto-HST was useful in detecting patients with low age-adjusted IPI. However, there was no statistically significant difference noted in the overall survival among the two groups (54% vs 43% surveillance and clinical groups, respectively; P=0.12).[14]

A population analysis was performed by El-Galaly et al[15] evaluating patients from the Danish and Swedish lymphoma registries. These two countries have different protocols for surveillance imaging for patients with DLBCL. Patients in both the cohorts had similar follow-up intervals; however, routine surveillance imaging was not performed in Sweden whereas CT scans (once every 6 months for the first 2 years) were performed in Denmark. The study did not show any difference in the overall survival with routine surveillance imaging. Risk factors for poor outcomes identified in the study were age older than 60 years, elevated lactate dehydrogenase levels, and Eastern Cooperative Oncology Group performance status of more than 2. However, surveillance imaging did not impact the outcomes in the high-risk groups. The authors recommended against surveillance imaging and commented that the money spent on surveillance imaging might be better used in addressing lymphoma survivorship.

Epperla et al[12] conducted a retrospective multicenter study evaluating the role of surveillance imaging on outcomes of patients with DLBCL after auto-HST. One hundred sixty patients with DLBCL who achieved complete remission after auto-HST were evaluated. Patients underwent PET-CT scans every 3 to 6 months for the first 3 years. The endpoint of the study was to compare the overall survival of patients who relapsed clinically versus those who had a relapse detected by imaging. Among the 45 patients who relapsed, 71% of the relapses were detected via surveillance scans. However, the study did not show a statistically significant difference in the overall survival (643 days vs 586; P=0.68). Most of the relapses occurred within the first 2 years. The authors concluded by noting that there is a limited utility for routine imaging in patients after an auto-HST.

Most of the studies regarding surveillance imaging in lymphoma have been retrospective. There have been very few prospective trials in this setting. A study by Zinzani et al[16] evaluated 160 patients with Hodgkin lymphomas and 183 patients with aggressive non-Hodgkin lymphomas. PET scans were performed every 6 months for the first years after achieving a complete remission and then annually. Among the non-Hodgkin lymphoma group, 51 relapses were detected, among whom 30 were symptomatic at the time of diagnosis. This study concluded that PET scan was able to detect asymptomatic relapses. This study, however, did not evaluate the survival benefit with early detection and is insufficient to support the use of surveillance imaging.

Another factor that could be contributing to lack of improvement in overall survival is that in DLBCL, relapses that are detected by surveillance imaging are more likely to be less aggressive and more likely to have a long indolent course where they are asymptomatic, when compared to patients with aggressive lymphomas. These patients are more likely to be symptomatic. This could lead to lead time bias and not necessarily impact the outcome.[11]

Cheah et al[11] conducted a study evaluating the role of surveillance PET-CT scans in patients with transformed lymphomas who had achieved remission. A majority of the patients in the study had undergone auto-HST following induction. Fifty-five patients were evaluated over a period of 3 years with PET-CT scans once every 6 months. The specificity of the scans for detecting relapse was 94%, sensitivity was 83%, the positive predictive value was 63%, and the negative predictive value was 98%. More importantly, all the PET-detected relapses were of low-grade histology. However, all the symptomatic relapses were DLBCL, necessitating treatment. This study indicates that the clinical outcomes may not necessarily be impacted by early detection of relapse via surveillance scans.

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Cohen et al[9] presented a meta-analysis evaluating the role of surveillance imaging among patients with both DLBCL and Hodgkin's lymphoma. Fifteen studies were analyzed and although the authors noted that the positive predictive value of for surveillance imaging is increased in patients with a higher likelihood of relapse such as patients with a high IPI, the early detection of relapse does not improve survival.

Moreover, the false-positive scans can lead to unnecessary procedures such as biopsies, untoward complications from the procedure, and may also negatively impact the emotional health of the patients. Studies have shown surveillance scans to increase the anxiety and stress in the patients undergoing them.[17] Exposure to ionizing radiation can also increase the risk of secondary cancers. Patients with lymphoma who had more than eight imaging studies performed were found to be at an increased risk of developing secondary malignancies when compared with patients who had fewer studies (hazard ratio, 2.25; $P<0.001$).[18] A recent study suggested a 3% increased risk of second primary malignancies for every additional CT scan in patients with lymphomas.[19] Additionally, side effects related to the use of contrast media such as acute kidney injury and allergic reactions should also be considered.

Use of surveillance imaging significantly increases the cost of health care as well. In a study from Huntington et al,[20] routine surveillance scans were associated with minimal survival benefit using the quality-adjusted life year (QALY) 0.020 QALYs with CT scans.[20] However, costs associated were substantially higher at $164,960/QALY. These costs are significant, particularly in the absence of significant clinical benefit.

CURRENT GUIDELINES FOR SCREENING

The guidelines for screening vary widely among the various international societies without a clear consensus (Table 2).[21-23] However, with an increasing body of evidence showing lack of survival benefit, there has been a declining trend of performing routine surveillance scans. A population-based analysis in Canada performed by Cheung et al[21] noted a decline in the number of surveillance scans in lymphoma patients since 2013.

The American Society of Hematology Choosing Wisely campaign guidelines recommend limiting surveillance CT scans in asymptomatic patients following treatment for aggressive lymphoma.[22]

The European Society of Medical Oncology guidelines acknowledge that there is no survival benefit with surveillance CT scans after achieving complete remission. They strongly recommend against PET-CT as surveillance measures; however, they refrain from making a statement regarding CT scans.[2] The National Comprehensive Cancer Network recommends against surveillance scans after 2 years unless clinically recommended.[1] They recommend CT scans no more frequently than 6 months in the first 2 years. In contrast, the British

TABLE 2. Guidelines for Surveillance Scans[a]

Organization	Recommendations
NCCN[1]	Scans no more frequently than 6 months in the first 2 years Scans after 2 years not recommended
ESMO[2]	No PET/CT for surveillance
BCCA[21]	No surveillance scans
American Society of Hematology "Choosing Wisely" campaign[22]	Limit surveillance CT scans in asymptomatic patients following treatment for aggressive lymphoma Scans after 2 years not recommended
Lugano classification recommendations[23]	No surveillance scans

[a]BCCA = British Columbia Cancer Agency; CT = computerized tomography; ESMO = European Society of Medical Oncology; NCCN = National Comprehensive Cancer Network; PET/CT = positron-emission tomography/computed tomography.

Columbia Cancer Agency in Canada and Lugano classification [21,23] both recommend against surveillance CT scans once complete remission is attained.

Surveillance scans can be considered in patients with high-risk disease such as high IPI, double hit lymphomas, and double expressors. However, adequate data to support survival benefit is lacking. In patients with a high risk of relapse, scans may be considered on a case-by-case basis, after discussion with the patient regarding the risk of surveillance scans and with the knowledge that detection may not necessarily change the outcomes.[8] These recommendations do not apply to clinical trials where surveillance scans are necessary to study the disease-free survival and outcomes of the patients.

PRIMARY CARE PERSPECTIVE

Current National Comprehensive Cancer Network guidelines recommend that a patient be followed by the hematologist/oncologist for up to 5 years after curative treatment.[1] Relapses are more common in the first 2 years after treatment. Primary care physicians need not perform any imaging studies or investigations for surveillance in asymptomatic patients. During the general medical evaluations, history and physical should be targeted towards uncovering any clinical features of relapse in the history and physical examination, at which point imaging and appropriate laboratory studies should be pursued in the form of CT scans, serum lactate dehydrogenase levels, complete blood counts, comprehensive metabolic panel, and referral back to the hematologist/oncologist.

Given the lack of proven benefit, routine surveillance imaging should not be pursued in an asymptomatic patient.

CONCLUSION

Surveillance imaging for DLBCL remains controversial to date, with lack of consensus among the various international societies. There has been increasing evidence showing lack of benefit in the survival with surveillance scans. Moreover, the psychological impact, economic burden, and risk of secondary malignancies with imaging studies is significant. Prospective randomized studies evaluating the benefit of overall survival with surveillance scans is warranted. Unless such studies identify a high-risk population that would benefit from surveillance, imaging studies should not be routinely performed in asymptomatic patients. Primary care physicians caring for survivors should not pursue investigations for surveillance in asymptomatic patients.

Abbreviations and Acronyms: **auto-HST** = autologous hematopoietic stem cell transplant; **CT** = computerized tomography; **DLBCL** = diffuse large B cell lymphoma; **IPI** = international prognostic index; **PET-CT** = positron-emission tomography–computed tomography

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