Surveillance Scanning in Lymphoma

Sarah C. Rutherford, MD

Dr Rutherford is an assistant professor of medicine in the Weill Department of Medicine's Division of Hematology and Medical Oncology and the Meyer Cancer Center at New York-Presbyterian/Weill Cornell Medicine in New York, New York.

Correspondence:
Sarah C. Rutherford, MD
Weill Cornell Medicine
1305 York Avenue, Y-764
New York, NY 10021
Tel: (646) 962-2064
Fax: (646) 962-1617
E-mail: sar2014@med.cornell.edu

Abstract: Although the role of imaging in the management of most lymphomas is well established at baseline, during treatment, and following treatment, surveillance imaging after complete response remains controversial despite the numerous studies that have investigated follow-up computed tomography, positron emission tomography, and magnetic resonance imaging over the past 20 years. Although robust data do not support an impact of this strategy on survival in Hodgkin lymphoma, diffuse large B-cell lymphoma, or follicular lymphoma, many patients continue to undergo serial imaging studies. The role of imaging following treatment in peripheral T-cell lymphoma (PTCL) and mantle cell lymphoma (MCL) is poorly investigated, although the available literature questions the utility of scanning patients with PTCL or MCL in first remission. Of clear significance in all lymphoma subtypes is the effect of such imaging on patient anxiety, secondary cancers, and health care costs. Novel monitoring strategies, such as minimal residual disease detection with circulating tumor DNA, are being examined in lymphoma and may provide a more accurate method by which to survey patients. Here I review the current literature on follow-up imaging in lymphoma patients by subtype.

Keywords
CT, Hodgkin lymphoma, MRI, non-Hodgkin lymphoma, PET, surveillance imaging

Introduction

Despite the lack of evidence to support surveillance imaging in lymphomas, follow-up scans continue to be controversial and are still included as monitoring options in Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) by both the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology.[1-4] The impetus for these guidelines may be related to the potential curability of these 2 lymphoma subtypes, even in the relapsed setting.[5-8] In theory at least, patients may be in better condition and able to tolerate second-line therapy if the relapsed disease is detected earlier. However, studies that support such a strategy are subject to selection bias in favor of patients whose relapsed disease is discovered by planned imaging rather than on clinical grounds. These patients typically have less aggressive disease phenotypes than those presenting with symptoms, and therefore are more likely to have better outcomes regardless of the time of disease

detection. No studies have demonstrated a survival benefit in HL, and only one study suggests a survival advantage in DLBCL based on the results of follow-up imaging.[9]

Early studies typically reported on surveillance using computed tomography (CT), whereas more recent investigations have used positron emission tomography (PET)/CT. In the majority of lymphoma subtypes, imaging with PET/CT is a standard part of staging for a newly diagnosed patient. PET/CT was incorporated into the lymphoma response criteria in 2007.[10] The Lugano Classification established the 5-point Deauville criteria, which are used in the interpretation of interim and end-of-treatment PET scans with fluorodeoxyglucose (FDG) avidity in areas of lymphoma involvement. In the Deauville criteria, 1 means no abnormal FDG uptake, 2 means uptake less than mediastinum, 3 means uptake greater than mediastinum but less than liver, 4 means uptake moderately greater than liver, and 5 means uptake markedly greater than liver with new sites of disease. Deauville scores of 1 to 3 are compatible with complete metabolic response (CMR).[11]

Interim PET/CT scans are typically performed after a number of treatment cycles in many lymphomas. In particular, strong evidence supports escalation or de-escalation of therapy in HL based on PET results after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).[12] End-of-treatment PET/CT scans, often performed 4 to 8 weeks after completion of therapy, are part of consensus guidelines.[1,3,11] For those patients with HL or DLBCL who are in CMR at the end of treatment, the Lugano Classification recommends against routine surveillance screening. A key question to ask in this scenario is, "Which patients actually are in CMR?" Although the Deauville criteria appear to provide an objective scale, subjectivity in PET/CT scan results often occurs. Reviewing scans in-person with a radiologist is important to determine when a scan is truly positive, even if an area shows activity greater than the standardized uptake value (SUV) of the liver. For example, thymic rebound after completion of chemotherapy is a relatively common occurrence in young patients with HL or primary mediastinal large B-cell lymphoma and can result in SUVs mildly above the liver.[13] These patients and others with SUVs mildly greater than those for the liver and with radiologic patterns more consistent with nonmalignant findings, such as necrotic tissue, can be followed with a repeat PET/CT in 2 to 3 months to demonstrate resolution of FDG avidity.

Below, I review current data by lymphoma subtype on follow-up scanning for patients in complete response (CR) or CMR based on imaging after treatment.

Hodgkin Lymphoma

The majority of studies investigating surveillance imaging in lymphoma are retrospective, although 2 prospective trials in patients with HL have been published. Picardi and colleagues randomly assigned 300 patients with newly diagnosed HL to 1 of 2 arms: PET/CT vs ultrasound and chest radiography administered at intervals throughout the 9 years after completion of treatment.[14] All patients underwent surveillance imaging by 1 of the 2 methods. Eligibility criteria included high-risk disease (Ann Arbor or Cotswolds stage greater than or equal to IIB with bulky disease and/or extranodal lesions, or stages III-IV). PET/CT comprised images from the midbrain to upper thigh, whereas ultrasound included evaluation of superficial, anterosuperior mediastinal, abdominal, and pelvic nodes with chest radiography using frontal and lateral views. In the PET/CT group, 55 of 150 patients had positive findings; 40 were confirmed to have active lymphoma on biopsy and 15 were deemed to have false-positive PET/CT scans because biopsies were benign (including 5 with thymic hyperplasia). Of the 20 patients who underwent biopsy of a mediastinal mass, more than half were not found to have lymphoma (n=11). No patients relapsed in the absence of a positive PET/CT scan. In the ultrasound/chest radiography group, 43 of 150 patients were found to have abnormal results that were concerning for lymphoma progression; 39 had biopsy-proven lymphoma and 4 had negative results on biopsy (all in inguinal lymph nodes). One patient in this latter group relapsed who did not have abnormal findings on ultrasound/chest radiography. The authors concluded that patients with HL who have high-risk disease can be considered for monitoring by ultrasound/chest radiography rather than PET/CT. This has not become a widely accepted strategy.

The second prospective study in HL also enrolled patients with aggressive and indolent non-Hodgkin lymphoma (NHL).[15] A total of 421 patients in CR after first-line therapy underwent PET/CT at 6, 12, 18, and 24 months (160 HL, 183 aggressive NHL, and 78 indolent NHL). Some of the patients with HL who were included had positive PET scans after 2 cycles of frontline therapy (currently, these patients would likely be escalated or switched to a second-line therapy). Of the 160 patients with HL, relapse was detected based on PET/CT in 51 and on clinical presentation in 35. Eleven additional patients had inconclusive positive imaging findings. Although the study suggests that PET/CT is useful for relapse detection in lymphoma patients, a survival analysis was not included to support the impact of these findings.

Multiple retrospective studies have been published on follow-up imaging in HL (Table).[9,16-20] Although one early study concluded that imaging may be useful in

Table. Retrospective Studies of Follow-Up Imaging in Lymphoma

First Author, Year	Histology	No. of Pts	No. of Rel Pts	Imaging Type	Relapse Detected on Routine Imaging	Relapse Detected Based on Clinical Symptoms	OS Analysis
Goldschmidt, 2011[16]	HL Aggressive NHL DLBCL PTCL Lymphoblastic	125 42 81 1 1	125 42 81 1 1	CT or PET/CT	22 (52%) 25 (30%)	20 (48%) 58 (70%)	HR 1.2, 95% CI 0.69-2.08
El-Galaly, 2014[9]	HL Aggressive NHL DLBCL PTCL	258 43 173 42	258 43 173 42	CT, PET/CT, or MRI	70 (27%) 16 (37%) 62 (26%) 8 (19%)	188 (73%) 27 (63%) 128 (74%) 34 (80%)	Median OS 90 vs 38 mo, *P*=.00008
Jerusalem, 2003[17]	HL	36	5	PET	—	—	—
El-Galaly, 2012[18]	HL	161	22	PET/CT	10 (45%)	12 (55%)	—
Dann, 2014[19]	HL	368	33	PET/CT	17 (52%)	16 (48%)	5-y OS 94% vs 94%
Jakobsen, 2016[20]	HL	771	—	CT	—	—	3-y OS 96% vs 96%
Guppy, 2003[22]	DLBCL	117	35	CT	2 (6%)	30 (86%)	—
Liedtke, 2006[23]	DLBCL	108	108	Not included	24 (22%)	84 (78%)	5-y OS 54% vs 43%, *P*=.13
Petrausch, 2010[24]	DLBCL	75	23	PET/CT	3 (13%)	20 (87%)	—
Lin, 2012[25]	DLBCL	341	113	CT	25 (22%)	88 (78%)	Median OS not reached, *P*=.569
Avivi, 2013[26]	DLBCL	119	31	PET	9 (29%)	22 (71%)	—
Cheah, 2014[27]	DLBCL	116	13	PET/CT	6 (46%)	7 (54%)	No difference, *P*=.76
Hong, 2014[28]	DLBCL	106	15	CT or PET/CT	3 (20%)	12 (80%)	—
Thompson, 2014[29]	DLBCL	774 552 (MER) 222 (Lyon)	167 112 (MER) 55 (Lyon)	CT or PET/CT			MER: median OS 21 vs 15 mo, *P*=.56 Lyon: median OS 19 vs 12 mo, *P*=.25
El-Galaly, 2015[30]	DLBCL	1221	—	CT	—	—	3-y OS 92% vs 91%, *P*=.7
Fossard, 2017[32]	PCNSL	127	63	MRI or CT	12 (20%)	49 (80%)	1-y OS 41% vs 58%, *P*=.21
Mylam, 2017[33]	PCNSL	86	32	MRI	1	31	—
Guidot, 2018[41]	MCL	217	114	CT or PET/CT	38 (33%)	64 (56%)	HR 0.74, 95% CI 0.40-1.35
Tang, 2016[42]	PTCL	135	57	CT or PET/CT	9 (16%)	48 (84%)	—

(Table continued on following page)

Table. *(Continued)* Retrospective Studies of Follow-Up Imaging in Lymphoma

First Author, Year	Histology	No. of Pts	No. of Rel Pts	Imaging Type	Relapse Detected on Routine Imaging	Relapse Detected Based on Clinical Symptoms	OS Analysis
Cederleuf, 2017[43]	PTCL	232	60	CT	—	—	—
Oh, 1999[44]	FL	257	78	CT	11 (14%)	67 (84%)	—
Gerlinger, 2010[45]	FL	71	34	CT	16 (47%)	18 (53%)	OS 9 vs 8 y, *P*=.16

—, unknown or not reported; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio; MCL, marginal zone lymphoma; MER, Molecular Epidemiology Resource; mo, month(s); MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; No., number; OS, overall survival; PCNSL, primary central nervous system lymphoma; PET, positron emission tomography; PTCL, peripheral T-cell lymphoma; Pts, patients; Rel, relapsed; y, year(s).

follow-up of patients with HL,[17] the majority reported no survival benefit and therefore raised questions about the utility. Of particular interest is a study of 161 patients with HL who had achieved at least a partial response (PR) to frontline therapy.[18] The investigators assessed the positive predictive value of PET/CT scans. In this group of patients, only 21 of 76 PET/CT scans had true positive findings. Including all 211 PET/CT scans performed, the true positive rate was 5%. The positive predictive value of PET/CT results was 22% in routine scans and 37% in those done because of clinical symptoms. The authors estimated the cost of relapse diagnosed through routine PET/CT is more than $50,000.

The largest retrospective analysis of follow-up imaging in HL reviewed 368 patients at 3 centers.[19] The majority of the 305 enrolled patients underwent routine imaging with either CT or PET/CT every 6 months for 2 years and once in the third year. The remaining 63 patients did not undergo surveillance imaging. All were followed clinically every 3 to 4 months for the first 3 years after completing first-line treatment. The number with relapsed disease and time to relapse did not differ between groups. More of the patients in the group with clinical follow-up in the absence of scans were advanced stage at relapse (5/8, 63% vs 12/25, 48%); however, no difference in progression-free survival or overall survival (OS) existed between patients followed clinically and those who underwent routine scans.

Based on these studies, planned imaging in follow-up has not reliably shown a survival difference in HL. I recommend that patients with HL should be followed closely, with scans performed only if clinical symptoms prompt a concern for relapse. Abnormal imaging tests should be followed with a biopsy to confirm findings rather than with empiric treatment, given the high rate of false positives observed in some studies.

Diffuse Large B-Cell Lymphoma

As is the case in HL, PET/CT scans (baseline, interim, and end of treatment) are standard in the management of DLBCL (and are recommended by the Lugano Classification),[11] although no clear data exist to guide treatment based on interim PET results. A recent study correlating circulating tumor DNA with imaging results shows a promising novel strategy that may be used as an adjunct to imaging.[21] End-of-treatment PET/CT scans can sometimes show FDG avidity mildly greater than that of the liver in absence of persistent disease, as in HL, and these images should also be reviewed with radiology and repeated 2 to 3 months later to show resolution to less than liver SUV.

As noted above, the study by Zinzani and colleagues included 183 patients with aggressive DLBCL assessed prospectively, whereas all other studies looking at surveillance imaging in DLBCL were retrospective (Table).[9,15,16,22-30] In the prospective study, those patients who underwent surveillance imaging were found to relapse more frequently than those followed clinically, although the impact of this finding on survival is not known. A retrospective study by Liedtke and colleagues, which looked at 108 patients with relapsed aggressive NHL, concluded that routine imaging identifies patients with more favorable outcomes based on the age-adjusted International Prognostic Index.[23] Of the 108 patients, 24 (22%) had a relapse detected by surveillance imaging and 84 (78%) were found to have relapsed disease based on clinical presentation that prompted further assessment. Of interest, the 5-year OS was not statistically significant between the 2 groups (54% vs 43%; *P*=.13). Petrausch and colleagues assessed 75 patients with DLBCL.[24] This study pooled results for all patients with a positive PET/CT scan, including those scans

done because of symptoms that prompted concern for relapse. Of 27 patients with a positive PET/CT scan, 23 had a clinical presentation that prompted the scan and 4 did not. Relapse was confirmed by biopsy in 20 of 23 patients with symptoms and 3 of 4 patients without symptoms. Patients with relapsed disease were much more likely to be older than 60 years compared with those who remained in remission (16/20 with symptoms, positive PET/CT, and biopsy-proven relapse). The authors argue that patients older than 60 years should be considered for routine surveillance, whereas younger patients can be monitored in the absence of scanning.

The findings of the majority of other retrospective studies do not support routine surveillance. The study by Goldschmidt and colleagues included 81 patients with relapsed DLBCL, which occurred mostly in the first year after completion of therapy.[16] They found that stage, B symptoms, and prognostic score did not affect the way in which the relapse was detected (clinically vs by routine imaging), but extranodal involvement and timing of diagnosis did. OS was not affected by mode of relapse detection. Avivi and colleagues assessed follow-up PET/CT scans in patients with DLBCL treated with rituximab (Rituxan, Genentech/Biogen) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) vs CHOP.[26] They found that those who received rituximab were more likely to have false-positive scans, and therefore argued against surveillance with PET/CT in the modern era of DLBCL treatment. Cheah and colleagues reviewed 116 patients, 13 of whom relapsed, all within 18 months of completion of therapy (median follow-up was 53 months).[27] Six were diagnosed by routine PET/CT and 7 by clinical symptoms prompting PET/CT. Hong and colleagues followed 106 patients; 15 relapses occurred, including 3 detected by surveillance imaging.[28]

An analysis of 2 data sets, from the Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence and the Léon Bérard Cancer Center in Lyon, France, assessed a total of 902 patients with DLBCL.[29] Of these, 774 patients achieved a remission after therapy. Twenty-two percent of patients relapsed; in those with records available, 64% of these relapses occurred outside of a routine follow-up visit. Notably, there were no differences in outcome between the 2 groups. The largest published data included 525 Danish and 696 Swedish patients.[30] The Danish patients underwent surveillance imaging (typically CT scans every 6 months for 2 years), whereas the Swedish patients had clinical follow-up in the absence of imaging. Importantly, no difference in survival was observed between the 2 cohorts. Another study by El-Galaly and colleagues investigated a total of 258 patients with NHL or HL (including 173 with DLBCL) and unexpectedly found a median OS difference between relapses detected by imaging vs non-imaging (90 vs 38 months; P=.00008).[9] Multivariate analysis indicated that patients with DLBCL whose relapse was diagnosed after imaging had a reduced risk of death, although this reduction was not statistically significant when relapses with indolent histologies were excluded. Notably, transplant-eligible patients younger than 70 years whose relapses were detected on imaging were not more likely to complete stem cell transplant than their counterparts whose symptoms triggered the diagnosis of relapse. The authors cited a length of time bias in patients with aggressive DLBCL as a potential explanation for these findings and emphasized the need for prospective studies prior to making broad conclusions based on this report.

A systematic review of surveillance imaging in patients with DLBCL or HL pooled 3099 patients across 15 studies.[31] Twenty percent of these patients experienced relapse; 60% were identified by means other than surveillance imaging. No reports showed a survival advantage for those whose relapses were detected by imaging. These data, along with multiple studies cited above, indicate that there is insufficient support for routine surveillance scanning in patients with DLBCL.

Primary CNS Lymphoma

Follow-up imaging in primary central nervous system lymphoma (PCNSL), most often an aggressive lymphoma of DLBCL histology, has been minimally investigated. The largest study was conducted in 209 patients who were treated in Lyon, France, between 1985 and 2011.[32] The majority of patients received chemotherapy; about half underwent consolidation radiation. Of the 209, 127 had a CR and 63/127 (50%) eventually relapsed. Although 819 imaging studies were conducted (either MRI or CT) in patients undergoing surveillance, most of the relapses were found outside of the planned follow-up period. OS at 1 year was not significantly different between patients who were symptomatic vs asymptomatic at the time of relapse (41% vs 58%; P=.21). A second retrospective study reported on surveillance scanning in 86 patients with PCNSL (most of whom had DLBCL) in CR at the end of treatment.[33] Relapse was detected in 32 of 86 patients, the majority of whom had corresponding clinical symptoms (n=31). Thirty of 31 patients underwent MRI scans because of symptoms that developed outside of the planned visit times. Only 1 of 189 MRI scans done for surveillance purposes detected relapse. Both groups questioned the clinical utility of routine follow-up imaging in the diagnosis of relapse in PCNSL.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a heterogeneously managed disease. Some newly diagnosed patients can be monitored closely without initiation of treatment,[34] whereas others should be treated with chemotherapy followed by maintenance rituximab[35] or high-dose chemotherapy followed by autologous, or in some cases allogeneic, stem cell transplant.[36] Surveillance imaging of those in CR after first-line therapy is not well studied.[37-40] A recent publication reported on 217 patients with MCL who had achieved a response or stable disease after first-line therapy (166 CR, 41 PR, 10 stable disease).[41] Of the 114 patients who relapsed, 38 were diagnosed by routine imaging (25 by CT, 7 by PET/CT, 6 by other imaging), 61 were diagnosed based on clinical symptoms, and 3 were incidentally found to have relapsed disease. The median time to relapse was similar in both groups: 2.5 vs 2.8 years. There was no difference in OS based on method of relapse detection. These data support a strategy for clinical follow-up of patients with MCL after first-line therapy without surveillance imaging.

Peripheral T-Cell Lymphoma

Few studies have investigated follow-up scanning in peripheral T-cell lymphoma (PTCL), in part because additional therapy is frequently given after frontline treatment. For those in first CR, the NCCN recommends enrollment in a clinical trial, consideration of high-dose therapy with stem cell rescue, or observation.[2] Of the studies mentioned previously in this article that included patients with multiple lymphoma subtypes, only 2 enrolled patients with PTCL in addition to HL and DLBCL.[9,16] Conclusions were limited owing to the small numbers of patients with PTCL. Two studies specifically addressed surveillance scanning in PTCL.[42,43] Tang and colleagues reported on 338 patients with PTCL. One hundred thirty-five experienced a CR after first-line therapy, 61 of whom subsequently relapsed.[42] Relapse was detected in the majority of patients based on clinical presentation (48 patients, 84.2%), whereas relapse was found on surveillance scans in only 9 (15.8%). The information was not available for 4 patients. Most patients with relapsed disease were symptomatic (55 patients, 93.2%). A study by Cederleuf and colleagues included 109 Danish and 123 Swedish patients with nodal PTCL in CR following CHOP or therapy with cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP).[43] The Swedish patients underwent clinical follow-up and the Danish group was also followed with serial imaging, typically CT scans every 6 months for 2 years. Incidence of relapse was similar between the 2 groups (24% vs 28% in the Danish and Swedish patients, respectively; P=.32). OS after relapse did not differ between the groups, suggesting a minimal impact of surveillance scanning on outcome. Based on these data, the utility of follow-up imaging in PTCL is unproven.

Follicular Lymphoma and Marginal Zone Lymphoma

Given its often indolent nature, follicular lymphoma (FL) is an incurable disease that can be characterized by long periods without therapy. Frequent imaging in this subtype is particularly controversial given the amount of radiation that could be incurred over the course of the disease in a given patient. As a result, it has been more widely accepted to limit imaging in patients with FL compared with other lymphoma subtypes, and therefore few studies have been performed in this histology. A study of patients with stage I to III FL conducted between 1978 and 1994 followed 328 patients for a median of 101 months after first-line therapy.[44] Of these patients, 257 achieved a CR. In addition to clinical follow-up, patients underwent chest, abdominal, and pelvic radiography, and CT of the abdomen/pelvis. Imaging was typically done every 3 months for the first 5 years and then yearly. Relapse was detected in 78 of 328 patients in the follow-up period (based on clinical presentation in 55 patients, radiography in 19, and CT in 48). Only 11 of 78 relapses were found on CT in the absence of symptoms. Although a survival analysis was not conducted, the authors concluded that the yield of CT imaging was low in patients with stage I to III FL.

A second study was performed in 99 patients with FL who had undergone high-dose therapy and autologous stem cell transplant (ASCT) for recurrent disease.[45] Seventy-one of the 99 had sufficient clinical responses to this treatment and underwent surveillance after transplant. Of these, 34 were found to have relapsed disease. Eighteen (53%) of the relapses were found by clinical symptoms and 16 (47%) on monitoring studies, including CT-based imaging and/or bone marrow biopsy. OS was not statistically significant between the 2 groups (8 vs 9 years).

No study to my knowledge has investigated surveillance scanning specifically in marginal zone lymphoma. I advocate for a similar management strategy as in FL, particularly given the often-indolent course of disease: regular clinical follow-up and imaging tests based on symptoms.

Negative Impact of Surveillance Imaging

As outlined above, frequent scanning in the follow-up period is not well supported as clinically beneficial in

the majority of patients with lymphoma. A number of studies have investigated the negative impacts of this strategy. Thompson and colleagues assessed the psychological effects of routine scans in 70 patients with curable aggressive lymphomas.[46] They reported that 37% of patients met the criteria for clinically significant anxiety, typically related to a concern for relapse. The anxiety was not present at baseline and worsened around the time of planned imaging studies. These findings suggest that removing surveillance scans would lessen anxiety in lymphoma survivors. Secondary cancers as a result of radiation exposure are also of concern. A study using a risk model estimated that 29,000 future cancers could occur as a result of CT scans performed in the United States in 2007.[47] A second study investigating radiation exposure in whole-body PET/CT showed substantial increased lifetime attributable risk of secondary cancers.[48] An investigation of patients with NHL undergoing CT scans from 1997 to 2010 found that those patients who had more than 8 CT scans had a much higher risk of second primary malignancy compared with those who had 8 or fewer scans (hazard ratio, 2.25; 95% CI, 1.61-1.31; $P<.001$).[49] The researchers estimated that the risk of second primary malignancy in the more-frequently scanned group increased by 3% per CT scan performed. Finally, routine scanning is not a cost-effective strategy. In a 2015 publication, Huntington and colleagues assessed patients with DLBCL in first remission and concluded that surveillance imaging offers limited clinical utility and significant costs.[50] A study in 2014 reported that cost in US dollars for CT-detected relapse in patients with HL or NHL ranged from $21,725 to $157,605.[9] In an era of increased attention to cost savings in health care, as well as initiatives such as Choosing Wisely from the American Board of Internal Medicine's ABIM Foundation, these amounts are not well justified, particularly given the questionable lack of benefit of frequent scanning.

Conclusion

Increasing evidence supports monitoring without surveillance imaging in the majority of lymphoma patients following completion of treatment. Although frequent scanning may identify relapses earlier than close clinical follow-up of patients, no OS benefit has been reported in most studies. Novel methods of disease detection may prove to be useful in the surveillance setting and eventually spare patients from the negative aspects of frequent imaging tests, including psychological impact, secondary cancers, and added financial burden.

Disclosure

Dr Rutherford has served as a consultant for AstraZeneca, Celgene, Heron, Janssen Scientific Affairs, Juno Therapeutics, Karyopharm, Seattle Genetics, and Verastem.

References

1. Hoppe RT, Advani RH, Ai WZ, et al. NCCN Guidelines Insights: Hodgkin Lymphoma, Version 1.2018. *J Natl Compr Canc Netw*. 2018;16(3):245-254.
2. Horwitz SM, Zelenetz AD, Gordon LI, et al. NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016. *J Natl Compr Canc Netw*. 2016;14(9):1067-1079.
3. Eichenauer DA, Aleman BMP, Andre M, et al. Hodgkin lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv19-iv29.
4. Tilly H, Gomes da Silva M, Vitolo U, et al; ESMO Guidelines Committee. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v116-v125.
5. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051-1054.
6. Schmitz N, Pfistner B, Sextro M, et al; German Hodgkin's Lymphoma Study Group; Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065-2071.
7. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med*. 1995;333(23):1540-1545.
8. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28(27):4184-4190.
9. El-Galaly TC, Mylam KJ, Bøgsted M, et al. Role of routine imaging in detecting recurrent lymphoma: A review of 258 patients with relapsed aggressive non-Hodgkin and Hodgkin lymphoma. *Am J Hematol*. 2014;89(6):575-580.
10. Cheson BD, Pfistner B, Juweid ME, et al; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.
11. Cheson BD, Fisher RI, Barrington SF, et al; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphorra Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.
12. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374(25):2419-2429.
13. Brink I, Reinhardt MJ, Hoegerle S, Altehoefer C, Moser E, Nitzsche EU. Increased metabolic activity in the thymus gland studied with 18F-FDG PET: age dependency and frequency after chemotherapy. *J Nucl Med*. 2001;42(4):591-595.
14. Picardi M, Pugliese N, Cirillo M, et al. Advanced-stage Hodgkin lymphoma: US/chest radiography for detection of relapse in patients in first complete remission—a randomized trial of routine surveillance imaging procedures. *Radiology*. 2014;272(1):262-274.
15. Zinzani PL, Gandolfi L, Broccoli A, et al. Midtreatment 18F-fluorodeoxyglucose positron-emission tomography in aggressive non-Hodgkin lymphoma. *Cancer*. 2011;117(5):1010-1018.
16. Goldschmidt N, Or O, Klein M, Savitsky B, Paltiel O. The role of routine imaging procedures in the detection of relapse of patients with Hodgkin lymphoma and aggressive non-Hodgkin lymphoma. *Ann Hematol*. 2011;90(2):165-171.
17. Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography in the follow-up of patients with Hodgkin's disease. *Ann Oncol*. 2003;14(1):123-130.
18. El-Galaly TC, Mylam KJ, Brown P, et al. Positron emission tomography/computed tomography surveillance in patients with Hodgkin lymphoma in

first remission has a low positive predictive value and high costs. *Haematologica*. 2012;97(6):931-936.
19. Dann EJ, Berkahn L, Mashiach T, et al. Hodgkin lymphoma patients in first remission: routine positron emission tomography/computerized tomography imaging is not superior to clinical follow-up for patients with no residual mass. *Br J Haematol*. 2014;164(5):694-700.
20. Jakobsen LH, Hutchings M, de Nully Brown P, et al. No survival benefit associated with routine surveillance imaging for Hodgkin lymphoma in first remission: a Danish-Swedish population-based observational study. *Br J Haematol*. 2016;173(2):236-244.
21. Kurtz DM, Scherer F, Jin MC, et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. *J Clin Oncol*. 2018;36(28):2845-2853.
22. Guppy AE, Tebbutt NC, Norman A, Cunningham D. The role of surveillance CT scans in patients with diffuse large B-cell non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2003;44(1):123-125.
23. Liedtke M, Hamlin PA, Moskowitz CH, Zelenetz AD. Surveillance imaging during remission identifies a group of patients with more favorable aggressive NHL at time of relapse: a retrospective analysis of a uniformly-treated patient population. *Ann Oncol*. 2006;17(6):909-913.
24. Petrausch U, Samaras P, Haile SR, et al. Risk-adapted FDG-PET/CT-based follow-up in patients with diffuse large B-cell lymphoma after first-line therapy. *Ann Oncol*. 2010;21(8):1694-1698.
25. Lin TL, Kuo MC, Shih LY, et al. Value of surveillance computed tomography in the follow-up of diffuse large B-cell and follicular lymphomas. *Ann Hematol*. 2012;91(11):1741-1745.
26. Avivi I, Zilberlicht A, Dann EJ, et al. Strikingly high false positivity of surveillance FDG-PET/CT scanning among patients with diffuse large cell lymphoma in the rituximab era. *Am J Hematol*. 2013;88(5):400-405.
27. Cheah CY, Dickinson M, Hofman MS, et al. Limited clinical benefit for surveillance PET-CT scanning in patients with histologically transformed lymphoma in complete metabolic remission following primary therapy. *Ann Hematol*. 2014;93(7):1193-1200.
28. Hong J, Kim JH, Lee KH, et al. Symptom-oriented clinical detection versus routine imaging as a monitoring policy of relapse in patients with diffuse large B-cell lymphoma. *Leuk Lymphoma*. 2014;55(10):2312-2318.
29. Thompson CA, Ghesquieres H, Maurer MJ, et al. Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *J Clin Oncol*. 2014;32(31):3506-3512.
30. El-Galaly TC, Jakobsen LH, Hutchings M, et al. Routine imaging for diffuse large B-cell lymphoma in first complete remission does not improve post-treatment survival: a Danish-Swedish population-based study. *J Clin Oncol*. 2015;33(34):3993-3998.
31. Cohen JB, Behera M, Thompson CA, Flowers CR. Evaluating surveillance imaging for diffuse large B-cell lymphoma and Hodgkin lymphoma. *Blood*. 2017;129(5):561-564.
32. Fossard G, Ferlay C, Nicolas-Virelizier E, et al. Utility of post-therapy brain surveillance imaging in the detection of primary central nervous system lymphoma relapse. *Eur J Cancer*. 2017;72:12-19.
33. Mylam KJ, Michaelsen TY, Hutchings M, et al. Little value of surveillance magnetic resonance imaging for primary CNS lymphomas in first remission: results from a Danish multicentre study. *Br J Haematol*. 2017;176(4):671-673.
34. Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. *J Clin Oncol*. 2009;27(8):1209-1213.
35. Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med*. 2012;367(6):520-531.
36. Romaguera JE, Fayad L, Rodriguez MA, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. *J Clin Oncol*. 2005;23(28):7013-7023.
37. Hosein PJ, Pastorini VH, Paes FM, et al. Utility of positron emission tomography scans in mantle cell lymphoma. *Am J Hematol*. 2011;86(10):841-845.
38. Brepoels L, Stroobants S, De Wever W, et al. Positron emission tomography in mantle cell lymphoma. *Leuk Lymphoma*. 2008;49(9):1693-1701.
39. Gill S, Wolf M, Prince HM, et al. [18F]fluorodeoxyglucose positron emission tomography scanning for staging, response assessment, and disease surveillance in patients with mantle cell lymphoma. *Clin Lymphoma Myeloma*. 2008;8(3):159-165.
40. Karam M, Ata A, Irish K, et al. FDG positron emission tomography/computed tomography scan may identify mantle cell lymphoma patients with unusually favorable outcome. *Nucl Med Commun*. 2009;30(10):770-778.
41. Guidot DM, Switchenko JM, Nastoupil LJ, et al. Surveillance imaging in mantle cell lymphoma in first remission lacks clinical utility. *Leuk Lymphoma*. 2018;59(4):888-895.
42. Tang T, Chen Z, Praditsuktavorn P, et al. Role of surveillance imaging in patients with peripheral T-cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2016;16(3):117-121.
43. Cederleuf H, Hjort Jakobsen L, Ellin F, et al. Outcome of peripheral T-cell lymphoma in first complete remission: a Danish-Swedish population-based study. *Leuk Lymphoma*. 2017;58(12):2815-2823.
44. Oh YK, Ha CS, Samuels BI, Cabanillas F, Hess MA, Cox JD. Stages I-III follicular lymphoma: role of CT of the abdomen and pelvis in follow-up studies. *Radiology*. 1999;210(2):483-486.
45. Gerlinger M, Rohatiner AZ, Matthews J, Davies A, Lister TA, Montoto S. Surveillance investigations after high-dose therapy with stem cell rescue for recurrent follicular lymphoma have no impact on management. *Haematologica*. 2010;95(7):1130-1135.
46. Thompson CA, Charlson ME, Schenkein E, et al. Surveillance CT scans are a source of anxiety and fear of recurrence in long-term lymphoma survivors. *Ann Oncol*. 2010;21(11):2262-2266.
47. Berrington de González A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med*. 2009;169(22):2071-2077.
48. Huang B, Law MW, Khong PL. Whole-body PET/CT scanning: estimation of radiation dose and cancer risk. *Radiology*. 2009;251(1):166-174.
49. Chien SH, Liu CJ, Hu YW, et al. Frequency of surveillance computed tomography in non-Hodgkin lymphoma and the risk of secondary primary malignancies: A nationwide population-based study. *Int J Cancer*. 2015;137(3):658-665.
50. Huntington SF, Svoboda J, Doshi JA. Cost-effectiveness analysis of routine surveillance imaging of patients with diffuse large B-cell lymphoma in first remission. *J Clin Oncol*. 2015;33(13):1467-1474.