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Next-generation surveillance strategies for patients with lymphoma

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Abstract

While remission and cure rates for Hodgkin and non-Hodgkin lymphoma continue to improve, surveillance approaches remain controversial, especially in light of recent reports suggesting limited benefit for routine radiologic assessment. Routine cross-sectional imaging results in considerable patient expense and anxiety, and this approach does not clearly improve patient outcomes. Next-generation approaches including minimal residual disease detection may provide an opportunity to identify relapse early and intervene prior to progression of clinical disease. This review discusses the role of surveillance imaging in Hodgkin and non-Hodgkin lymphoma and provides an introduction to serologic assessment of minimal residual disease. Future studies will need to focus on the clinical application of minimal residual disease surveillance and its ability to predict relapse, treatment response and survival.

Keywords

computed tomography; Hodgkin lymphoma; lymphoma; minimal residual disease; non-Hodgkin lymphoma; PET; surveillance

The American Cancer Society projected that 80,900 new cases of lymphoma would be diagnosed in 2015 (9050 cases of Hodgkin lymphoma [HL], 71,850 cases of non-Hodgkin lymphoma [NHL]) [1]. Among these cancer patients the most common subtypes of aggressive lymphomas are commonly curable with standard therapies, and patients with indolent lymphoma subtypes often have prolonged survival, but all subtypes are plagued by risk of relapse. Because the biologic and clinical behavior of HL and NHL vary dramatically across subtypes, the approach for surveillance of patients achieving a remission after induction therapy should be tailored to the individual patient's risk for relapse. Despite the lack of compelling data to support a particular surveillance strategy, historic approaches to

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surveillance have relied upon serial radiographic imaging assessments, including computed tomography (CT) and PET or fusion PET/CT, which can be expensive, associated with considerable patient anxiety, and have not been demonstrated to improve survival. In this review, we will first discuss the clinical behavior and relapse patterns for several subtypes of HL and NHL, review the current guidelines and evidence for surveillance approaches, consider novel nonimaging-based surveillance strategies and finally review the role of surveillance for other long-term complications in lymphoma survivors.

Clinical behavior & relapse patterns by lymphoma subtype

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma, with an average age at diagnosis in the late 60s [2]. DLBCL outcomes can vary markedly and the international prognostic index (IPI) has been used to stratify patients into risk groups with differences in expected relapse rates, progression-free survival (PFS) and overall survival (OS). A landmark study identified clinical variables: stage III/IV disease, lactate dehydrogenase (LDH) level above the upper limit of normal, age >60 years, ECOG performance status 2 and involvement of >1 extranodal site as poor prognostic factors for DLBCL with each contributing one point to the IPI score [3]. In a follow-up observational cohort study involving DLBCL patients treated with modern chemoimmunotherapy in the province of British Columbia, a revised version of the IPI recategorized scores using the same clinical components and identified three distinct prognostic groups [4]. Patients with a revised version of the IPI score of 0 were classified as very good with a 4-year PFS of 94% and OS of 94%, patients with a score of 1–2 were classified as good (4-year PFS 80%, OS 79%), and patients with a score of 3, 4 or 5 were classified as poor risk (4-year PFS 53%, OS 55%; $p < 0.001$ comparing risk groups). Other studies indicate that the IPI model and other models developed among patients of European ancestry do not predict OS well for other demographic subgroups [5].

While DLBCL has traditionally been managed as a single disease, it is increasingly evident that biologically unique and prognostically important molecular subgroups exist. Through gene expression profiling, two prominent subtypes have been identified, including germinal center B-cell-like (GCB) and activated B-cell-like (ABC) DLBCL [6]. In one representative series, there was a significantly better 3-year OS with standard cyclophosphamide, doxorubicin, vincristine and prednisone with rituximab (R-CHOP) use in the GCB subtype when compared with the non-GCB (predominantly ABC) subtype (75 vs 69%) [7]. Less intensive novel approaches, integrating agents such as bortezomib, lenalidomide and ibrutinib may improve outcomes for patients with ABC-like DLBCL [8–10], thus surveillance strategies that identify relapse in these patients might augment the benefits of these agents.

Almost a third of patients with DLBCL fail or relapse after receiving first-line treatments. [11] Most relapses occur within the first 2 years following therapy, and patients who receive rituximab (R) and relapse within a year are at highest risk for early mortality and failure of salvage therapy [12, 13]. Complete response duration is therefore an important prognostic factor in patients who relapse. Additional factors, including interim PET/CT scans, have been evaluated as a possible predictor for achievement of response and time to relapse. In

one retrospective series from China, the results of an interim PET/CT performed after two cycles of R-CHOP were prognostic for 3-year PFS as those patients who were PET negative had a 3-year PFS of 75.8% compared with 38.2% for PET-positive patients. However, Pregno and colleagues performed a similar analysis and found that up to 40% of patients with an interim PET/CT while receiving R-CHOP that was positive achieved a negative PET/CT by the conclusion of therapy [14]. In addition, a positive interim PET/CT had a positive predictive value of only 36% when predicting subsequent relapse. Recently published criteria have attempted to rate the degree of PET avidity when assessing interim and post-treatment PET/CTs, assigning a score based on the relation of the lesion to the mediastinum or liver [15,16]. This graded approach to PET/CT interpretation may be more clinically useful in the care of patients and may identify patients who are truly responding versus those who need alternative therapies.

When feasible, autologous stem cell transplant (ASCT) provides the best chance of long-term OS based on the landmark PARMA study [17]. The optimal pretransplant salvage regimen remains a topic of debate; however, most regimens are centered around platinum-containing chemotherapy. Individuals with relapsed DLBCL treated with either rituximab, ifosfamide, carboplatin, etoposide or rituximab, dexamethasone, cytarabine, cisplatin followed by autologous transplant had a 3-year OS of 49% in the CORAL study. [12] In addition, gemcitabine, dexamethasone and cisplatin appear to be noninferior when compared with dexamethasone, cytarabine, cisplatin, with no differences in post-transplant outcomes and the opportunity to receive salvage therapy as an outpatient [18]. There is currently no standard therapy in the third-line setting or for patients with relapsed disease who are unfit for stem-cell transplantation, and patients are often best managed in the context of a clinical trial.

Follicular lymphoma (FL) is the most common indolent subtype of NHL. While standard therapies are not considered curative, there are multiple first-line approaches that result in a 5-year OS of greater than 75% [19]. Chemoimmunotherapy has emerged as the standard first-line approach to patients with FL, but debate remains regarding the optimal initial therapy and sequence of regimens [19, 20]. Maintenance therapy with R has also been demonstrated to prolong PFS (but not OS) in randomized controlled trials and large cohort studies [20,21]. The randomized PRIMA study demonstrated the benefit of 2-year maintenance rituximab after first-line treatment in patients with FL [20]. PFS was 74.9% in the rituximab arm and 57.6% in the observation group. Similar to the IPI for DLBCL, the follicular lymphoma IPI combines five clinical and laboratory variables at diagnosis to identify patients as low-, intermediate- or high-risk for early death [22]. In patients with a good prognosis (0–1 adverse factors) on the follicular lymphoma IPI scale, the 10-year OS is 71%, but high-risk patients have a markedly decreased 10-year OS of 36% [22]. Although FL responds well to first-line therapy of combined R plus chemotherapy, this disease is characterized by repeated relapses with disease progression 3–5 years after initial treatment and progressively shorter remissions thereafter [19].

Mantle cell lymphoma (MCL), accounts for 5% of NHL, most often affecting men between the ages of 50 and 70 years and is typically stage IV at diagnosis with bone marrow involvement [23]. Fit patients are often managed with an aggressive induction regimen

consolidated with an autologous stem cell transplant, which has historically resulted in prolonged PFS in the front-line setting [24–26]. MCL is considered to be incurable with standard therapies, although the median OS has improved significantly. [26] The MCL IPI (MIPI) combines age, performance status, lactate dehydrogenase and leukocyte count at diagnosis to determine a risk group for untreated patients with MCL [23,27]. The 5-year OS rates in MIPI low, intermediate and high-risk groups were 85, 63 and 34% respectively in a recently updated analysis using contemporary therapeutic approaches. High-risk patients continue to have poor OS despite currently available therapies. In addition to MIPI, several additional variables appear to predict the duration of response to therapy in patients with MCL, including Ki67 proliferative index, pre-transplant PET/CT and pretreatment cytogenetics [23,28–32]. Identification of minimal amounts of residual lymphoma also has been associated with early relapse in patients completing induction therapy for MCL [33].

Unlike DLBCL and other NHL subtypes, the outcomes for HL patients are quite good, with a long-term PFS of 75% in advanced HL [34]. The International Prognostic Score has been developed to assess 5-year rates of freedom from progression for patients with advanced HL and includes assessment of albumin, hemoglobin, gender, age, stage, leukocyte count and lymphocyte count [35]. Each additional factor identified in the patient reduces the predicted PFS by about 8% [35]. Despite the prognostic value of International Prognostic Score, an early interim FDG-PET scan appears to be among the most useful prognostic factors in advanced HL. Interim PET accurately predicts the treatment outcome in patients treated with standard doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and has been used for choosing risk-adapted treatment in advanced HL in clinical trials. In one series, interim PET/CT after two cycles of ABVD demonstrated a 3-year PFS of 28% for patients with a positive interim scan and 95% for patients with a negative interim scan ($p < 0.0001$) [36].

Treatment failure occurs in 10% of localized HL and 20% of advanced stage HL due to either therapy-resistant or relapsing disease [37]. The use of more intensive regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) has yielded initial superior disease control, with a 7-year failure-free survival of 85% [36]. Treatment with BEACOPP, when compared with standard of care ABVD, resulted in better initial tumor control, but a study that randomized patients to ABVD or BEACOPP and then performed ASCT for all patients who relapsed following initial therapy revealed that although the 7-year rate of freedom from first progression was 85% among patients who received initial BEACOPP and 73% among patients who received initial ABVD ($p = 0.004$), the 7-year freedom from second progression was 88% for BEACOPP and 82% for ABVD ($p = 0.12$), and the 7-year OS was 89 and 84%, respectively ($p = 0.39$) [38]. While BEACOPP has improved PFS in a subgroup of patients with HL, it has a toxicity profile associated with severe acute hematologic effects, infertility and produced secondary neoplasm in 9% of patients [39]. Thus, the potential early and late adverse events associated with BEACOPP are generally believed to outweigh the potential early-term benefits. This is accentuated by the fact that eligible patients with relapsed HL can proceed to receive salvage therapy followed by autologous transplant, which results in long-term remission in 40–50% of patients, largely influenced by pretransplant response to salvage therapy [40]. It is advantageous to achieve complete response before transplantation, since suboptimal response to salvage therapy is a major determinant of ASCT failure [41].

Strategies & recommendations for surveillance imaging in HL & NHL

Screening for relapse in asymptomatic patients is an area of intense research and there is considerable variability among providers and centers. A successful screening approach would identify patients with relapsed disease prior to the development of symptoms, with the theory that early identification of relapse could lead to improved outcomes. Although it would stand to reason that earlier detection of cancer results in improved outcomes, this has often not been the case when reviewed systematically, resulting in considerable disagreement regarding the most appropriate surveillance approach for lymphomas [42].

Patients with lymphoma can generally be divided into two groups: those who are treated with curative intent and those who are not treated with curative intent. Patients treated with curative intent include fit patients who receive aggressive induction regimens for aggressive NHL and HL. Patients who are not treated with curative intent generally include patients with advanced indolent NHL and MCL as well as patients who are unable to tolerate aggressive induction regimens. Patients treated with curative intent have a reasonable likelihood of never relapsing while those patients who are not treated with curative intent will likely relapse at some point. Current guidelines for routine surveillance imaging for several subtypes of NHL and HL are reviewed in Table 1, and selected reports of the incidence of imaging-only detection of relapsed NHL and HL are detailed in Table 2.

Aggressive NHL

Aggressive NHL, especially DLBCL, comprises the most frequently evaluated group of patients with regard to the role of surveillance imaging, and currently available guidelines provide differing recommendations. The recently reported Lugano classification discourages the use of routine surveillance scans in the absence of a clinical indication (i.e., laboratory abnormalities, symptoms or exam findings), and this recommendation has been incorporated into the most recent version of the National Comprehensive Cancer Network (NCCN) guidelines for management of DLBCL for patients with early-stage DLBCL while the guidelines continue to allow CT's every 6 months for the first 2 years after treatment for patients in complete remission (CR) [16, 57]. The European Society of Medical Oncology guidelines, most recently updated in 2011, recommend against the use of PET/CT in routine surveillance but do not address CTs [58]. The 2013 ASH Choosing Wisely Campaign also included limiting surveillance CTs in a symptomatic patients with aggressive NHL [59].

Several series have reviewed outcomes for patients undergoing routine surveillance screening. Thompson *et al.* described a series of 552 patients with DLBCL identified through the University of Iowa/Mayo Molecular Epidemiology Resource [46]. Roughly 20% of patients experienced a relapse after achieving remission to induction therapy, and 64% of these relapses were identified prior to a scheduled follow-up visit due to development of symptoms or other clinical signs that prompted a radiographic evaluation. Only nine of 552 patients (1.6%) experienced relapse that was identified based on routine surveillance imaging in asymptomatic patients. The authors reported a similar cohort from France, in which only four of 222 (1.8%) followed patients experienced a relapse of DLBCL identified in routine imaging without accompanying clinical signs or symptoms suggesting relapsed disease.

A prospective evaluation of the role of PET/CT in patients with aggressive NHL evaluated 183 patients who underwent routine surveillance PET/CT every 6 months for the first 2 years after achieving a remission and then annually [47]. This series confirmed the sensitivity of routine PET/CT, as several patients had an inconclusive positive PET/CT that led to a biopsy confirming relapse that would have otherwise had no evidence of relapse on a CT scan. In this report, 12 out of 1184 surveillance scans performed for NHL proved to be false positives (i.e., their PET was considered positive for relapse but upon biopsy there was no confirmed disease). Seventy-nine scans for patients with NHL were considered inconclusive and required further evaluation, including 25 patients whose clinical evaluation merited a biopsy where 12 patients were confirmed to have relapsed disease.

Additional retrospective studies have questioned the utility of surveillance imaging. Abel *et al.* reported outcomes from seven NCCN institutions, in which patients received either CT-only, PET-only or PET and CT surveillance imaging after completing a course of induction therapy for DLBCL [48]. Among 625 patients, 50 experienced a relapse during a surveillance period of 5 years, and roughly 26% of relapses were identified through routine imaging without presence of symptoms, representing 2.1% of all included patients. Cheah *et al.* reported outcomes of 116 patients in Australia who were followed with PET/CT surveillance imaging [49]. A minority of these patients relapsed, and only six of 13 relapses were detected on routine imaging, including four patients where it was felt that a routine CT would not have identified the relapsed disease. However, as only six out of 116 patients (5%) experienced a relapse that was identified solely by surveillance imaging, the overwhelming majority of patients would have completed a series of PET/CT's that had no impact on their clinical care. Hong *et al.* presented a series of 106 patients with DLBCL, of whom 15 patients experienced a relapse [50]. While both CT and PET/CT were able to reliably exclude relapse (negative predictive value of 100% for both modalities), the positive predictive value for CT was only 30% and for PET/CT was 11.5%. Among the 26 PET/CT's felt to be abnormal, only three resulted in a confirmed relapse. The false positive rate was also elevated in an Israeli series of 119 patients with DLBCL who underwent screening PET/CT's in first remission [51]. In this cohort, 20% of PET/CT's were considered positive, and only 37% of the positive PET/CT's resulted in the confirmation of relapse while 63% were ultimately found to be a false positive.

El-Galaly and colleagues recently reported outcomes for 258 patients, including 173 with DLBCL, who had relapsed lymphoma and assessed their method of relapse detection and clinical outcomes [52]. Twenty-six percent of patients with relapsed DLBCL had relapse detected by routine imaging compared with 41% with abnormal symptoms and 24% with abnormal symptoms plus abnormal laboratories/physical exam. Although detection by imaging was associated with improved OS, this difference was no longer significant when patients who relapsed prior to their first scheduled scan were excluded.

Hodgkin lymphoma

Interestingly, despite having an improved prognosis and decreased risk of relapse, the most recent version of the NCCN guidelines continue to recommend routine chest x-ray or CT scan every 6–12 months for up to 2 years after completing therapy for patients achieving a

remission after induction therapy [60]. However, the Lugano classification recommends against routine surveillance scans [16]. The American College of Radiology has also developed Appropriateness Criteria to address the role of surveillance imaging in Hodgkin lymphoma, in which CTs performed every 6 months for the first 2 years, followed by yearly for years 3–5 is considered ‘usually appropriate’ in most clinical scenarios [45]. The role of surveillance PET/CT in this setting is not considered appropriate, and the committee recommended that CT be used in most cases for surveillance. However, the American College of Radiology guidelines were developed prior to the widespread availability of observational results discussed below.

Several recent series have evaluated the role of surveillance imaging in Hodgkin lymphoma, providing additional insight into its role. A review of 241 patients at three centers in the USA included 174 patients who received routine imaging surveillance while 67 patients were followed clinically without scheduled scans [53]. There was no difference in 5-year OS between the two groups ($p = 0.41$). There was a shorter time to relapse in the routine surveillance group (18 months) compared with the clinical surveillance group (33 months). However, all 11 patients who relapsed were able to achieve a CR after salvage therapy and all but one completed autologous transplant, suggesting that the earlier detection of relapse did not result in more resistant disease or inability to tolerate salvage therapy.

An additional series from New Zealand and Israel evaluated 368 patients, including 63 patients who had only clinical follow-up and 305 patients with routine imaging [54]. In this series, there was no significant difference in the number of relapse or time to relapse among the 36 patients who experienced relapse. There was no significant difference in 5-year PFS between the two groups.

El-Galaly *et al.* reported a European series of 161 patients who received either routine or clinically indicated PET/CTs as surveillance in first remission [55]. The positive predictive value of a routine PET/CT was only 22% as most positive routine PET/CTs were ultimately not found to be associated with true relapse.

The same group also reported outcomes for 43 patients with relapsed HL, in which 37% of relapses were identified solely by imaging while the remaining were due to patient symptoms, laboratory findings or exam findings [52]. A Canadian series of 258 patients with relapsed HL again found that a minority of patients (22%) with relapsed HL had the relapse detected by surveillance imaging during a period when the patients were asymptomatic [56]. In this series, the postrelapse PFS and OS were not significantly different based on method of detection.

Follicular lymphoma, mantle cell lymphoma & other indolent NHL

The surveillance strategy for patients with indolent NHL is typically different as these patients have not been treated with curative intent and will likely relapse during the period of follow-up, often after several years of surveillance. For follicular lymphoma, the NCCN recommends CT scans every 6 months for 2 years, followed by no more than yearly scans, while the recommendations for other indolent forms of NHL and mantle cell lymphoma do not specifically address the role of scans due to limited data. While the rate of detection of

relapse in asymptomatic patients is higher in patients with indolent NHL compared with aggressive, it remains unclear that earlier detection of relapsed disease (i.e., prior to symptom development) results in significant improvement of survival [47, 61].

Risks & costs associated with routine surveillance scans

Although generally considered safe, serial surveillance scans can be associated with possible risks of additional malignancies, significant financial hardship due to the costs of the scan as well as costs of missed work and transportation, anxiety and stress related to awaiting results, and additional physical risks that are associated with invasive procedures to evaluate benign processes that are prompted by incidental findings. Brenner and Hall have estimated that up to 2% of all cancers can be attributable to radiation from CT scans in an analysis relying on organ-specific cancer incidence and mortality in atomic bomb survivors [62]. Another analysis estimated the risks for development of cancer and cancer-related mortality for patients with lymphoma who complete routine surveillance and found that for patients with NHL completing a 5-year course of CT surveillance, the lifetime cancer incidence attributable to the radiation exposure was 0.0066 for males and 0.0089 for females [63]. A population-based report from Taiwan has also found that patients receiving >8 CT scans in follow-up for NHL had a significantly greater risk for developing a secondary malignancy (HR: 2.25; 95% CI: 1.61–3.13; $p < 0.001$) including breast and liver/biliary cancers [64]. In addition, the cost of surveillance imaging is quite high and can place significant financial stress on patients and the healthcare system in general. Based on 2010 SEER data for expected relapses and the costs of imaging based on Health Care Procedure Coding System codes and/or Current Procedure Terminology codes, the cost of CT surveillance imaging per death avoided has been estimated [65,66]. This model compared 2- and 5-year surveillance strategies and predicted outcomes based on assumptions regarding reduced likelihood of lymphoma-related death from 5 to 25% for patients completing a surveillance program [42]. It is unclear if even a 5% reduction in lymphoma-related deaths is actually observed based on surveillance alone (given that rates of disease detection for aggressive lymphomas are often <10%), resulting in a very high cost per lymphoma-related death prevented.

Considerations for appropriate use of radiographic surveillance in HL & NHL

Alternative uses of radiologic resources could result in the development of improved strategies for surveillance that improve disease detection, support treatment strategies that improve survival, and provide more cost-effective means for surveillance. It is becoming increasingly evident that indiscriminant surveillance of patients with lymphoma with serial CTs and PET/CTs is no longer appropriate. While many series identify a significant proportion of relapses that are identified by routine surveillance, the positive predictive value of a positive scan is comparatively low, resulting in a significant number of false positives and needless anxiety and procedures for patients. In addition, it remains unclear that surveillance results in any survival benefit.

As surveillance imaging is simply a screening tool for relapsed disease, we can draw comparisons to screening programs in other diseases, such as lung cancer. Although routine

CT for all people is not a cost-effective manner to screen for lung cancer, the National Lung Screening Trial identified a high-risk group of patients as those aged between 55 and 74 who had a 30 pack-year history of cigarette smoking and who were either still smoking or had quit within the past 15 years [67]. Through annual low dose CT, the investigators reported a 20% decrease in lung cancer-related mortality by employing the screening system. In addition, computer-aided, risk-adapted screening approaches have been forwarded that may provide means to perform selective surveillance on patients based on both the baseline likelihood of experiencing relapse after treatment and results of surveillance studies during prior time periods [68].

Such a process in HL or NHL is feasible but would require identification of a high-risk subset of patients and the potential to improve survival through early detection of relapsed disease. In many cases where patients are eligible for aggressive salvage regimens, the timing of relapse detection is not essential. However, for elderly patients who may not be fit for a transplant or other aggressive salvage, a focused screening program designed to evaluate difficult to examine sites such as the abdomen/pelvis would potentially identify sites of relapse early enough to benefit from local therapy and/or less aggressive palliative options. Identification of the ideal population for screening and conduct of a large randomized study comparing screening to no screening would be challenging but represents the best way to identify the most appropriate use of post-treatment surveillance in HL and NHL. However, given the low rate of detection of asymptomatic relapse, the number of events would be very low in such a study. As a result, population-based assessments through currently available national and international databases could potentially answer this question using a series of thousands of patients treated at different centers and in different regions. Modeling approaches could be also used to determine the characteristics of an ideal surveillance imaging modality and imaging approaches could be tailored to meet those criteria.

Nonradiographic & novel approaches to surveillance strategies

Absolute lymphocyte count & lactate dehydrogenase

Based on the questionable benefit of routine imaging surveillance in HL and NHL, recent recommendations have departed from routine surveillance imaging, particularly for DLBCL [16]. Alternative methods are therefore needed and include peripheral blood-based assessments.

Both absolute lymphocyte count (ALC) and LDH have been explored as indicators of disease relapse. For example, a lower ALC 3 months after completing therapy was predictive of early relapse in a series of 59 patients with DLBCL who received combination chemoimmunotherapy, and in another series, a decrease in ALC at any time predicted relapse [69,70]. The ALC/absolute monocyte count ratio may also predict relapse [71].

In a landmark paper describing surveillance methods in NHL, Weeks *et al.* identified LDH as a sensitive predictor of relapse in asymptomatic patients, although the risk of relapse for patients who presented with an elevated LDH at diagnosis and achieved a CR was quite low even if the LDH remained elevated after therapy [72]. However, the positive predictive

value of an elevated LDH in otherwise asymptomatic patients remained modest in subsequent series [73–75]. As a result, an increase in LDH in an otherwise asymptomatic patient should be analyzed in the context of a thorough history and physical exam and consideration of additional methods to assess for possible relapse.

Minimal residual disease evaluation

While a sensitive serologic assessment that avoids repeated radiation exposure is appealing to both patients and practicing clinicians, currently available laboratory assessments are not adequate. This has sparked the development of alternative methods, including minimal residual disease (MRD) measurement. MRD refers to a small number of malignant cells that remain after therapy in patients who are otherwise in a clinical remission, without detectable disease by alternative methods. These residual cells are thought to account for a large fraction of eventual relapses, and therefore their detection has become an important goal in a number of hematologic malignancies, most notably acute lymphoblastic leukemia and chronic myelogenous leukemia [76,77].

A number of methods for MRD detection have been explored for lymphoma patients, including multicolor flow cytometry, end point PCR, quantitative PCR and most recently, next-generation sequencing. End point PCR and quantitative PCR have been applied most frequently in NHL. These PCR-based methods rely on detection of tumor-specific DNA sequences, the most common of which are outlined below.

PCR for recurrent translocations

In the case of mature lymphoid neoplasms such as NHLs, certain translocations are commonly used for PCR-based MRD assays. These included the *IGH-BCL2* translocation in FL and the *IGH-CCND1* translocation in MCL (t[14;18] and t[11;14] respectively; see Table 3). These tumor-specific gene translocations benefit from their presence in many patients – that is, one assay can detect MRD across many patients. For example, almost 90% of patients with FL have a *BCL2* translocation [78], although these are spread across several common breakpoints.

The experience with MRD by PCR in lymphoma dates back to the early 1990s. Studying patients with FL receiving ASCT, Gribben and colleagues demonstrated that patients with MRD-negative bone marrow grafts had superior outcomes compared with those patients who received MRD-positive bone marrow grafts [79,80]. Since that time, the improved survival of patients who achieve bone marrow MRD negativity as assessed by *BCL2* PCR has been demonstrated in a number of studies [81,82], with additional information gained by the introduction of quantitative PCR [83].

PCR for patient-specific immunoglobulin genes

While PCR for recurrent translocations has proven useful in both FL and MCL [84], this assay is only suitable for patients who have common breakpoints. In FL, for example, currently only the major breakpoint region and minor clustering region of the *BCL2* gene are used for MRD detection, limiting its application to between 50 and 65% of patients. In cases where consensus PCR assays are not suitable, methods using patient-specific gene

rearrangements can be used. Because NHLs are mature lymphoid neoplasms, their DNA has undergone rearrangement of either the B-cell receptor loci (*IGHV* and *IGK*) in the case of B-cell lymphomas, or the T-cell receptor loci in the case of T-cell lymphomas. These rearranged sequences have been used to make patient-specific MRD assays based on the specific sequence from the tumor (allele-specific oligonucleotide PCR). This has been used in addition to the *IGH-CCND1* translocation (or the *IGHV* locus) in MCL [84,85]. The major advantage of this assay is its broad applicability – any patient with a rearranged *IGHV* locus is a potential candidate, which encompasses most, if not all, B-cell NHLs. However, the major disadvantage of this assay remains the need to define a set of patient-specific primers or probes for the assay.

Next-generation sequencing of immunoglobulin & TCR genes

Recently, an alternative assay targeting the immunoglobulin loci based on high-throughput sequencing (Ig-HTS) was reported [86]. This assay (also named Clonosight, from Sequentia, Inc.) relies on amplicon sequencing using consensus PCR primers to capture all known *IGH-VDJ*, *IGH-DJ* and *IGK* rearranged loci. Once amplified, this PCR product is then sequenced using a next-generation sequencing (NGS) platform. When performed on a primary tumor sample, this allows clonotypic tumor sequences to be identified as the most common sequence seen. After identification of tumor-specific sequences, their presence can be detected in either peripheral blood mononuclear cells or bone marrow samples. When applied to cellular peripheral blood samples in acute lymphoblastic leukemia, Ig-HTS had a sensitivity of at least one in 1 million leukocytes ($1:1 \times 10^6$), as opposed to allele-specific oligonucleotide PCR-based techniques, which have a sensitivity of $1:1 \times 10^{4-5}$ according to most reports [86].

One of the most exciting applications of Ig-HTS is in detection of DLBCL. Unlike leukemias, very few patients with DLBCL have detectable circulating tumor cells in their peripheral blood or bone marrow [87]. This has previously limited the applications of MRD detection in DLBCL, as these assays have traditionally been performed on either cellular peripheral blood or bone marrow samples. To avoid this problem, the first application of Ig-HTS in DLBCL focused on the detection of circulating tumor DNA [88]. Circulating tumor DNA (ctDNA) is defined as tumor-specific DNA sequences found in either the plasma or serum of the blood, outside of the cellular compartment [89]. Recent studies in solid tumors including breast, colon and lung cancer have suggested ctDNA detection as a useful tool for disease monitoring [90–92].

In DLBCL, initial reports suggest that detection of ctDNA is more sensitive than detection of circulating tumor cells for measurement of disease burden [88,93]. In the largest series to date, directly comparing ctDNA to circulating tumor cells with Ig-HTS, a 150-fold increase in allele fraction of tumor DNA was seen in the ctDNA or plasma fraction [93]. Due to the low abundance of cell-free DNA, this difference was lower in terms of absolute tumor molecules per milliliter of blood, but increased overall detection of tumor DNA was still seen in the plasma fraction. The clinical utility of ctDNA detection by IgHTS is being established currently as well. In one series, ten out of 11 patients with relapsed DLBCL had detectable ctDNA by Ig-HTS at a median of 7.4 months prior to the date of progression [94].

This early detection of relapsed or progressive DLBCL could offer patients the possibility of earlier curative consolidative therapy such as salvage chemotherapy or autologous bone marrow transplantation.

Similar to Ig-HTS for B-cell lymphomas, sequencing of the rearranged *TCRB* locus can be used for MRD monitoring in mature T-cell lymphomas. In one proof of principle study on ten patients with mycosis fungoides or Sezary syndrome, NGS of *TCRB* was used to measure disease prior to bone marrow transplantation [95]. While flow cytometry only identified circulating lymphoma cells in four out of ten patients, *TCRB* sequencing revealed disease before transplant in 10/10 patients, demonstrating the increased sensitivity of this assay compared with traditional measures of disease.

Methods for detection of ctDNA with nonimmunoglobulin genes

The methods for detection of ctDNA – and cellular MRD – outlined above rely on detection of either patient-specific immunoglobulin rearrangements or shared common translocations. However, novel methods for detection of ctDNA in solid tumors have recently been reported. These typically involve detection of known somatic alterations, particularly single nucleotide variants, and use methods ranging from digital PCR [90,91], amplicon sequencing [90] or targeted NGS [92]. One of the major limitations of these methods remains identifying somatic alterations that are shared between patients, limiting the applicability of any single reporter to a subset of patients. The broad applicability of Ig-HTS and *TCRB* sequencing to most, if not all, patients, remains the major advantage over current alternative assays for MRD monitoring.

Additional indicated surveillance for survivors of HL & NHL

Although a detailed review of long-term complications is beyond the scope of this article, it is important to recognize that patients completing therapy for HL and NHL remain at risk for numerous secondary complications later in life and require ongoing surveillance, which is in part guided by the type of therapy received and the patient's underlying nonlymphoma-related risk factors. While patients would ideally be managed continuously in an oncology clinic with a focus on survivorship, many patients are not followed longitudinally by their oncologist and require an astute primary care physician for ongoing surveillance. A complete review of survivorship recommendations for patients with HL was recently compiled by Ng [96].

Radiation-associated complications & recommended surveillance

Radiation is most frequently employed in the management of HL and NHL involving the neck and chest. Importantly, many initial reports of complications related to radiation therapy were described in patients experienced to mantle-field radiation at high doses while current radiation exposure is more limited with involved-field and involved-site protocols.

Breast cancer has been a well-described long-term complication in patients treated for HL with radiation therapy and typically occurs after a long latency period [45]. Travis *et al.* have described an international series of >3000 women treated for HL and described a relative risk of 10.5 compared with the general population for women treated with at least 40

Gy and who did not receive alkylators [97]. As a result of this described risk, methods of surveillance have been investigated, including the use of breast MRI. In a prospective study of 148 patients who received irradiation for HL to the chest and who were >8 years beyond treatment, yearly breast MRI and mammogram were performed for 3 consecutive years [98]. The sensitivity of MRI to detect a new breast cancer was not improved compared with mammogram, but when used together, the sensitivity increased to 94%. As a result, the NCCN currently recommends utilizing both screening modalities beginning at age 25 years or 8 years after receipt of radiation therapy, whichever occurs last [99].

Additional radiation-related long-term toxicities include hypothyroidism and early onset of cardiovascular disease. Radiation-induced cardiac disease has been estimated in 10–30% of patients by 5–10 years post-treatment, and thyroid dysfunction may complicate up to 50% of patients who receive radiation to the upper mediastinum or low neck [45,100–101]. As a result, screening for thyroid disease with yearly thyroid-stimulating hormone and assessment of modifiable cardiac risk factors including blood pressure and lipids is indicated for patients who have completed radiation therapy to the chest and/ or neck [96].

Chemotherapy-associated myelodysplastic syndrome & acute myeloid leukemia

While radiation therapy has been associated with increased risks of secondary malignancies, cardiovascular disease, thyroid dysfunction and other late toxicities, combination chemotherapy also increases risks for patients treated for NHL and HL. Among the most serious late complications is secondary MDS or AML. The Stanford group recently reported outcomes for 754 patients treated for HL from 1974 to 2003. With modern therapies that decreased exposure to alkylating agents, the rate of secondary myeloid diseases decreased to 1%, while it was 13% in patients treated predominantly with alkylator-based therapy and subtotal lymphoid irradiation [102]. While less is known regarding the risk for secondary myeloid disorders in NHL, Armitage *et al.* summarized outcomes for patients receiving conventional therapy and high-dose therapy for NHL and found variable incidence of secondary disorders, including some rates >10% [103]. As NHL is a disease of older patients, a baseline number of patients will likely develop MDS regardless of prior therapy. As a result, patients presenting with unexplained cytopenias or other findings concerning for MDS or AML should be evaluated with a peripheral blood smear and bone marrow biopsy.

Conclusion & future perspective

Lymphoma survivors continue to require post-treatment surveillance for disease relapse and treatment-related complications. Despite continued improvement in front-line therapies, a significant portion of patients continues to relapse. However, the approach to surveillance of the last generation, in which asymptomatic patients were subjected to repeated cross-sectional imaging, is unlikely to result in improved outcomes and is increasingly obsolete. We recommend a program of targeted scans for patients with clinical signs/symptoms, or for whom early radiographic detection is essential. In a well-selected population of patients, the positive predictive value of a positive scan may be more acceptable and the risk/benefit ratio of surveillance scans may be more appropriate. Improved early detection through assessment of peripheral blood for MRD represents a clinically feasible tool to identify

subclinical relapse in asymptomatic patients and potentially intervene and may emerge as a standard approach to surveillance in the future.

It is feasible that management of patients with NHL and HL who are in remission will routinely include MRD assessment with the potential incorporation of less intensive therapy for patients who have subclinical relapse. Additionally, patients with evidence of MRD postinduction would be eligible for appropriate consolidation regimens. This may provide an opportunity to avoid intensive salvage therapy for many patients while improving survival. We look forward to the continued development of these and other technologies that will improve our ability to care for survivors of HL and NHL and implement a screening program that decreases disease-related deaths.

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References

Papers of special note have been highlighted as:

• of interest;

•• of considerable interest

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J. Clin.* 2015; 65(1):5–29. [PubMed: 25559415]
2. Shenoy PJ, Malik N, Nooka A, et al. Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. *Cancer.* 2011; 117(11):2530–2540. [PubMed: 24048801]
3. A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project. *N. Engl. J. Med.* 1993; 329(14):987–994. [PubMed: 8141877]
•• Describes the International Prognostic Index which has been relied upon to determine prognosis in aggressive non-Hodgkin lymphoma.
4. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007; 109(5):1857–1861. [PubMed: 17105812]
5. Flowers CR, Shenoy PJ, Borate U, et al. Examining racial differences in diffuse large B-cell lymphoma presentation and survival. *Leuk. Lymphoma.* 2013; 54(2):268–276. [PubMed: 22800091]
6. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature.* 2000; 403(6769):503–511. [PubMed: 10676951]
7. Sinha R, Dejoubner N, Flowers C. Novel agents for diffuse large B-cell lymphoma. *Expert Opin. Investig. Drugs.* 2011; 20(5):669–680.
8. Nowakowski GS, Laplant B, Macon WR, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large b-cell lymphoma: a Phase II study. *J. Clin. Oncol.* 2015; 33(3):251–257. [PubMed: 25135992]
9. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large b-cell lymphoma. *Blood.* 2009; 113(24):6069–6076. [PubMed: 19380866]
10. Wilson WH, Gerecitano JF, Goy A, et al. The Bruton's tyrosine kinase (BTK) inhibitor, Ibrutinib (PCI-32765), has preferential activity in the ABC subtype of relapsed/refractory *de novo* diffuse

large B-cell lymphoma (DLBCL): interim results of a multicenter, open-label, Phase 2 study. *Blood*. 2012; 120 Abstract 686.

11. Mondello P, Younes A. Emerging drugs for diffuse large B-cell lymphoma. *Expert Rev. Anticancer Ther*. 2015; 15(4):439–451. [PubMed: 25652253]
12. 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. [PubMed: 20660832]
13. Lerch K, Meyer AH, Stroux A, et al. Impact of prior treatment on outcome of transformed follicular lymphoma and relapsed *de novo* diffuse large B cell lymphoma: a retrospective multicentre analysis. *Ann. Hematol*. 2015; 94(6):981–988. [PubMed: 25645656]
14. Pregno P, Chiappella A, Bello M, et al. Interim 18-FDG-PET/CT failed to predict the outcome in diffuse large B-cell lymphoma patients treated at the diagnosis with rituximab-CHOP. *Blood*. 2012; 119(9):2066–2073. [PubMed: 22234681]
15. Meignan M, Gallamini A, Haioun C, Polliack A. Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8–9 April 2010. *Leuk. Lymphoma*. 2010; 51(12):2171–2180. [PubMed: 21077737]
16. Cheson BD, Fisher RI, Barrington SF, et al. 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. [PubMed: 25113753] ••This is the most recent ‘Lugano’ classification detailing updated staging, response assessment and surveillance recommendations for Hodgkin and non-Hodgkin lymphoma.
17. 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. [PubMed: 7477169]
18. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J. Clin. Oncol*. 2014; 32(31):3490–3496. [PubMed: 25267740]
19. Nastoupil LJ, Sinha R, Byrtek M, et al. Comparison of the effectiveness of frontline chemoimmunotherapy regimens for follicular lymphoma used in the United States. *Leuk. Lymphoma*. 2015; 56(5):1295–1302. [PubMed: 25263322]
20. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a Phase 3, randomised controlled trial. *Lancet*. 2011; 377(9759):42–51. [PubMed: 21176949]
21. Nastoupil LJ, Sinha R, Byrtek M, et al. The use and effectiveness of rituximab maintenance in patients with follicular lymphoma diagnosed between 2004 and 2007 in the United States. *Cancer*. 2014; 120(12):1830–1837. [PubMed: 24668580]
22. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma International Prognostic Index. *Blood*. 2004; 104(5):1258–1265. [PubMed: 15126323]
23. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. 2008; 111(2):558–565. [PubMed: 17962512]
24. Nastoupil LJ, Shenoy PJ, Ambinder A, et al. Intensive chemotherapy and consolidation with high dose therapy and autologous stem cell transplant in patients with mantle cell lymphoma. *Leuk. Lymphoma*. 2015; 56(2):383–389. [PubMed: 24828864]
25. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL network. *Blood*. 2005; 105(7):2677–2684. [PubMed: 15591112]
26. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a Phase 2 study from the Groupe d’Etude des Lymphomes de L’Adulte. *Blood*. 2013; 121(1):48–53. [PubMed: 22718839]
27. Hoster E, Klapper W, Hermine O, et al. Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European mantle-cell lymphoma network. *J. Clin. Oncol*. 2014; 32(13):1338–1346. [PubMed: 24687837]

28. Cohen JB, Hall NC, Ruppert AS, et al. Association of pre-transplantation positron emission tomography/computed tomography and outcome in mantle cell lymphoma. *Bone Marrow Transplant.* 2013; 48(9):1212–1217. [PubMed: 23584442]
29. Magnusson E, Cao Q, Linden MA, et al. Hematopoietic cell transplantation for mantle cell lymphoma: predictive value of pretransplant positron emission tomography/ computed tomography and bone marrow evaluations for outcomes. *Clin. Lymphoma Myeloma Leuk.* 2014; 4(2):114–121. [PubMed: 24388482]
30. Sarkozy C, Terre C, Jardin F, et al. Complex karyotype in mantle cell lymphoma is a strong prognostic factor for the time to treatment and overall survival, independent of the MCL International Prognostic Index. *Genes Chromosomes Cancer.* 2014; 53(1):106–116. [PubMed: 24249260]
31. Katzenberger T, Petzoldt C, Holler S, et al. The Ki67 proliferation index is a quantitative indicator of clinical risk in mantle cell lymphoma. *Blood.* 2006; 107(8):3407. [PubMed: 16597597]
32. Cohen JB, Ruppert AS, Heerema NA, et al. Complex karyotype is associated with aggressive disease and shortened progression-free survival in patients with newly diagnosed mantle cell lymphoma. *Clin. Lymphoma Myeloma Leuk.* 2015; 15(5):278–285. e1. [PubMed: 25660723]
33. Campo E, Rule S. Mantle cell lymphoma: evolving management strategies. *Blood.* 2015; 125(1): 48–55. [PubMed: 25499451]
34. Gordon LI, Hong F, Fisher RI, et al. Randomized Phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (e2496). *J. Clin. Oncol.* 2013; 31(6):684–691. [PubMed: 23182987]
35. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced Hodgkin's disease. *N. Engl. J. Med.* 1998; 339(21):1506–1514. [PubMed: 9819449] ••This details the International Prognostic Score that is used to inform prognosis in advanced stage Hodgkin lymphoma.
36. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian–Danish study. *J. Clin. Oncol.* 2007; 25(24):3746–3752. [PubMed: 17646666]
37. Nicolas M, Christian G. Decision-making in the management of adult classical Hodgkin's lymphoma: determining the optimal treatment. *Expert Rev. Hematol.* 2015; 8(2):205–216. [PubMed: 25634543]
38. Viviani S, Zinzani PL, Rambaldi A, et al. ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned. *N. Engl. J. Med.* 2011; 365(3):203–212. [PubMed: 21774708]
39. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N. Engl. J. Med.* 2010; 363(7):640–652. [PubMed: 20818855]
40. Sirohi B, Cunningham D, Powles R, et al. Long-term outcome of autologous stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma. *Ann. Oncol.* 2008; 19(7):1312–1319. [PubMed: 18356139]
41. Moskowitz CH, Matasar MJ, Zelenetz AD, et al. Normalization of pre-asct, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood.* 2012; 119(7):1665–1670. [PubMed: 22184409]
42. Cohen JB, Flowers CR. Optimal disease surveillance strategies in non-Hodgkin lymphoma. *Hematology.* 2014; 2014:481–487. [PubMed: 25696898] ••This is a reference to a recently published manuscript from the ASH Education Book which presents a more detailed assessment of post-treatment surveillance in non-Hodgkin lymphoma.
43. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas. 2014. www.nccn.org
44. NCCN clinical practice guidelines in oncology: Hodgkin's lymphoma. 2014. www.nccn.org
45. Ha CS, Hodgson DC, Advani R, et al. ACR appropriateness criteria follow-up of Hodgkin lymphoma. *J. Am. Coll. Radiol.* 2014; 11(11):1026–1033. e1023. [PubMed: 25278496]
46. 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. [PubMed: 25267745] ••This is a large review of the role of surveillance in a series of patients treated and

followed at the Mayo/Iowa Molecular Epidemiology Resource and is one of the papers outlining the case against routine screening.

47. Zinzani PL, Stefoni V, Tani M, et al. Role of [18F]fluorodeoxyglucose positron emission tomography scan in the follow-up of lymphoma. *J. Clin. Oncol.* 2009; 27(11):1781–1787. [PubMed: 19273712] •The only prospective assessment of the role of postremission surveillance imaging.
48. Abel GA, Vanderplas A, Rodriguez MA, et al. High rates of surveillance imaging for treated diffuse large B-cell lymphoma: findings from a large national database. *Leuk. Lymphoma.* 2012; 53(6):1113–1116. [PubMed: 22098406]
49. Cheah CY, Hofman MS, Dickinson M, et al. Limited role for surveillance PET-CT scanning in patients with diffuse large B-cell lymphoma in complete metabolic remission following primary therapy. *Br. J. Cancer.* 2013; 109(2):312–317. [PubMed: 23807169]
50. 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. [PubMed: 24428199]
51. 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. [PubMed: 23423884]
52. El-Galaly TC, Mylam KJ, Bogsted 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. [PubMed: 24493389]
53. Pingali SR, Jewell SW, Havlat L, et al. Limited utility of routine surveillance imaging for classical Hodgkin lymphoma patients in first complete remission. *Cancer.* 2014; 120(14):2122–2129. [PubMed: 24711253]
54. 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. [PubMed: 24313286]
55. 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. [PubMed: 22207683]
56. Bestawros A, Foltz L, Srour N, Savage KJ, Connors JM. Patients' and physicians' roles in detecting recurrent Hodgkin lymphoma following complete remission. *Ann. Oncol.* 2013; 24(5):1359–1363. [PubMed: 23230136]
57. Zelenetz AD, Gordon LI, Wierda WG, et al. Non-Hodgkin's lymphomas, version 4.2014. *J. Natl Compr. Canc. Netw.* 2014; 12(9):1282–1303. [PubMed: 25190696]
58. Ghielmini M, Vitolo U, Kimby E, et al. ESMO Guidelines Consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). *Ann. Oncol.* 2013; 24(3):561–576. [PubMed: 23175624]
59. Hicks LK, Bering H, Carson KR, et al. The ASH Choosing Wisely® campaign: five hematologic tests and treatments to question. *Blood.* 2013; 122(24):3879–3883. [PubMed: 24307720] •Details the ASH Choosing Wisely Campaign which has been instrumental in focusing efforts on limiting post-treatment scans.
60. Hoppe RT, Advani RH, Ai WZ, et al. Hodgkin lymphoma, version 2.2012 featured updates to the NCCN guidelines. *J. Natl Compr. Canc. Netw.* 2012; 10(5):589–597. [PubMed: 22570290]
61. Truong Q, Shah N, Knestrick M, et al. Limited utility of surveillance imaging for detecting disease relapse in patients with non-Hodgkin lymphoma in first complete remission. *Clin. Lymphoma Myeloma Leuk.* 2014; 14(1):50–55. [PubMed: 24119465]
62. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N. Engl. J. Med.* 2007; 357(22):2277–2284. [PubMed: 18046031]
63. Shenoy P, Sinha R, Tumeh JW, Lechowicz MJ, Flowers CR. Surveillance computed tomography scans for patients with lymphoma: is the risk worth the benefits? *Clin. Lymphoma Myeloma Leuk.* 2010; 10(4):270–277. [PubMed: 20709663]

64. 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
65. Tumeh JW, Moore SG, Shapiro R, Flowers CR. Practical approach for using medicare data to estimate costs for cost-effectiveness analysis. *Expert Rev. Pharmacoecon. Outcomes Res*. 2005; 5(2):153–162. [PubMed: 19807571]
66. Surveillance, Epidemiology, and End Results Program (SEER). Seer*Stat Database: Incidence - Seer 9 Regs Research Data, Sub (1973–2011) - Linked to County Attributes - Total U.S., 1969–2012 Counties, National Cancer Institute, Dccps, Surveillance Research Program, Surveillance Systems Branch, Released April 2014, Based on the November 2013 Submission. www.seer.cancer.gov
67. Aberle DR, Adams AM, et al. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med*. 2011; 365(5): 395–409. [PubMed: 21714641]
68. Ayer T, Alagoz O, Stout NK. OR Forum - a POMDP approach to personalize mammography screening decisions. *Operations Research*. 2012; 60(5):1019–1034.
69. Aoki T, Nishiyama T, Imahashi N, Kitamura K. Lymphopenia following the completion of first-line therapy predicts early relapse in patients with diffuse large B cell lymphoma. *Ann. Hematol*. 2012; 91(3):375–382. [PubMed: 21811783]
70. Porrata LF, Rsitow K, Inwards DJ, et al. Lymphopenia assessed during routine follow-up after immunochemotherapy (R-CHOP) is a risk factor for predicting relapse in patients with diffuse large B-cell lymphoma. *Leukemia*. 2010; 24(7):1343–1349. [PubMed: 20485372]
71. Yan-Li L, Kang-Sheng G, Yue-Yin P, Yang J, Zhi-Min Z. The lower peripheral blood lymphocyte/monocyte ratio assessed during routine follow-up after standard first-line chemotherapy is a risk factor for predicting relapse in patients with diffuse large B-cell lymphoma. *Leuk. Res*. 2014; 38(3):323–328. [PubMed: 24439567]
72. Weeks JC, Yeap BY, Canellos GP, Shipp MA. Value of follow-up procedures in patients with large-cell lymphoma who achieve a complete remission. *J. Clin. Oncol*. 1991; 9(7):1196–1203. [PubMed: 1710656]
73. Hong J, Yoon HH, Ahn HK, et al. Prognostic role of serum lactate dehydrogenase beyond initial diagnosis: a retrospective analysis of patients with diffuse large b cell lymphoma. *Acta Haematol*. 2013; 130(4):305–311. [PubMed: 24008775]
74. El-Sharkawi D, Basu S, Ocampo C, et al. Elevated lactate dehydrogenase levels detected during routine follow-up do not predict relapse in patients with diffuse large B-cell lymphoma who achieve complete remission after primary treatment with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone-like immunochemotherapy. *Leuk. Lymphoma*. 2012; 53(10):1949–1952. [PubMed: 22462615]
75. William BM, Bongu NR, Bast M, et al. The utility of lactate dehydrogenase in the follow up of patients with diffuse large B-cell lymphoma. *Rev. Bras. Hematol. Hemoter*. 2013; 35(3):189–191. [PubMed: 23904809]
76. Hauwel M, Matthes T. Minimal residual disease monitoring: the new standard for treatment evaluation of haematological malignancies? *Swiss Med. Wkly*. 2014; 144:w13907. [PubMed: 24452390]
77. Schrappe M. Minimal residual disease: optimal methods, timing, and clinical relevance for an individual patient. *Hematology Am. Soc. Hematol. Educ. Program*. 2012:137–142. [PubMed: 23233572]
78. Weinberg OK, Ai WZ, Mariappan MR, Shum C, Levy R, Arber DA. “Minor” BCL2 breakpoints in follicular lymphoma: frequency and correlation with grade and disease presentation in 236 cases. *J. Mol. Diagn*. 2007; 9(4):530–537. [PubMed: 17652637]
79. Gribben JG, Freedman AS, Neuberger D, et al. Immunologic purging of marrow assessed by PCR before autologous bone marrow transplantation for B-cell lymphoma. *N. Engl. J. Med*. 1991; 325(22):1525–1533. [PubMed: 1944436]
80. Gribben JG, Neuberger D, Freedman AS, et al. Detection by polymerase chain reaction of residual cells with the BCL-2 translocation is associated with increased risk of relapse after autologous

- bone marrow transplantation for B-cell lymphoma. *Blood*. 1993; 81(12):3449–3457. [PubMed: 8507880]
81. Freedman AS, Neuberg D, Mauch P, et al. Long-term follow-up of autologous bone marrow transplantation in patients with relapsed follicular lymphoma. *Blood*. 1999; 94(10):3325–3333. [PubMed: 10552941]
 82. Hardingham JE, Kotasek D, Sage RE, et al. Significance of molecular marker-positive cells after autologous peripheral-blood stem-cell transplantation for non-Hodgkin's lymphoma. *J. Clin. Oncol.* 1995; 13(5):1073–1079. [PubMed: 7738613]
 83. Rambaldi A, Carlotti E, Oldani E, et al. Quantitative PCR of bone marrow BCL2/ IGH+ cells at diagnosis predicts treatment response and long-term outcome in follicular non-Hodgkin lymphoma. *Blood*. 2005; 105(9):3428–3433. [PubMed: 15637137]
 84. Pott C, Hoster E, Delfau-Larue MH, et al. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL Intergroup Study. *Blood*. 2010; 115(16):3215–3223. [PubMed: 20032498]
 85. Pott C, Schrader C, Gesk S, et al. Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma. *Blood*. 2006; 107(6):2271–2278. [PubMed: 16332971]
 86. Faham M, Zheng J, Moorhead M, et al. Deep-sequencing approach for minimal residual disease detection in acute lymphoblastic leukemia. *Blood*. 2012; 120(26):5173–5180. [PubMed: 23074282]
 87. Mancuso P, Calleri A, Antoniotti P, Quarna J, Pruneri G, Bertolini F. If it is in the marrow, is it also in the blood? An analysis of 1,000 paired samples from patients with B-cell non-Hodgkin lymphoma. *BMC Cancer*. 2010; 10:644. [PubMed: 21106070]
 88. Armand P, Oki Y, Neuberg DS, et al. Detection of circulating tumour DNA in patients with aggressive B-cell non-Hodgkin lymphoma. *Br. J. Haematol.* 2013; 163(1):123–126. [PubMed: 23795711]
 89. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer*. 2011; 11(6):426–437. [PubMed: 21562580]
 90. Dawson SJ, Tsui DW, Murtaza M, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N. Engl. J. Med.* 2013; 368(13):1199–1209. [PubMed: 23484797]
 91. Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. *Nat. Med.* 2008; 14(9):985–990. [PubMed: 18670422]
 92. Newman AM, Bratman SV, To J, et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat. Med.* 2014; 20(5):548–554. [PubMed: 24705333]
 93. Kurtz DM, Green MR, Bratman SV, et al. Noninvasive monitoring of cellular versus acellular tumor DNA from immunoglobulin genes for DLBCL. *ASCO Meeting Abstracts*. 2014; 32(15 Suppl.):8504.
 94. Roschewski M, Dunleavy K, Pittaluga S, et al. Monitoring of circulating tumor DNA as minimal residual disease in diffuse large B-cell lymphoma. *Blood*. 2014; 124(21):139–139.
 95. Weng WK, Armstrong R, Arai S, Desmarais C, Hoppe R, Kim YH. Minimal residual disease monitoring with high-throughput sequencing of T cell receptors in cutaneous T cell lymphoma. *Sci. Transl. Med.* 2013; 5(214) 214ra171.
 96. Ng AK. Current survivorship recommendations for patients with Hodgkin lymphoma: focus on late effects. *Blood*. 2014; 124(23):3373–3379. [PubMed: 25428219] •Depicts a concise recommendation for surveillance of long-term toxicities in lymphoma survivors.
 97. Travis LB, Hill D, Dores GM, et al. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J. Natl Cancer Inst.* 2005; 97(19):1428–1437. [PubMed: 16204692]
 98. Ng AK, Garber JE, Diller LR, et al. Prospective study of the efficacy of breast magnetic resonance imaging and mammographic screening in survivors of Hodgkin lymphoma. *J. Clin. Oncol.* 2013; 31(18):2282–2288. [PubMed: 23610104]
 99. Coccia PF, Pappo AS, Altman J, et al. Adolescent and young adult oncology, version. 2.2014. *J. Natl Compr. Canc. Netw.* 2014; 12(1):21–32. quiz 32. [PubMed: 24453290]

100. Carver JR, Shapiro CL, Ng A, et al. American society of clinical oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J. Clin. Oncol.* 2007; 25(25):3991–4008. [PubMed: 17577017]
101. Hancock SL, Cox RS, Mcdougall IR. Thyroid diseases after treatment of Hodgkin's disease. *N. Engl. J. Med.* 1991; 325(9):599–605. [PubMed: 1861693]
102. Koontz MZ, Horning SJ, Balise R, et al. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. *J. Clin. Oncol.* 2013; 31(5):592–598. [PubMed: 23295809]
103. Armitage JO, Carbone PP, Connors JM, Levine A, Bennett JM, Kroll S. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. *J. Clin. Oncol.* 2003; 21(5):897–906. [PubMed: 12610191]

EXECUTIVE SUMMARY

Clinical behavior & relapse patterns by lymphoma subtype

- Hodgkin and non-Hodgkin lymphoma represent a diverse group of hematologic malignancies.
- Current approaches to induction therapy are curative in large subsets of patients with Hodgkin and aggressive non-Hodgkin lymphoma.
- Despite improvements in therapy, many patients with all subtypes relapse and require additional therapy.

Strategies & recommendations for surveillance imaging in Hodgkin & non-Hodgkin lymphoma

- Historic approach to surveillance included routine cross-sectional imaging for up to 5 years for patients in remission.
- Current recommendations are transitioning away from routine scans as the rate of detection of an asymptomatic relapse is low.

Risks & costs associated with routine surveillance scans

- Surveillance CT scans carry a small increased lifetime risk for cancer.
- Expenses associated with completing a surveillance program are high.

Considerations for appropriate use of radiographic surveillance in Hodgkin & non-Hodgkin lymphoma

- Surveillance should only be used in patients with clinical signs or symptoms of disease, or who are at high risk for relapse in a particular site that is not easily examined and which would require rapid implementation of therapy

Nonradiographic & novel approaches to surveillance strategies

- Laboratory-based assessments including lactate dehydrogenase and absolute lymphocyte count are not reliable indicators of relapse.
- Minimal residual disease represents a novel approach to identification of subclinical relapse and is evaluable using peripheral blood.

Additional indicated surveillance for survivors of Hodgkin & non-Hodgkin lymphoma

- Lymphoma survivors are at risk for several additional complications, including secondary organ dysfunction, endocrinopathies and secondary malignancies.
- Oncologists and primary care physicians should be familiar with treatment-related late toxicities and screen patients appropriately.

Table 1

Selected guidelines for routine imaging surveillance for patients with Hodgkin or non-Hodgkin lymphoma who achieve remission after induction chemotherapy.

Lymphoma histology	Guideline recommendation		
	<i>Lugano</i> [16]	<i>NCCN</i> [†] [43,44]	<i>ACR</i> [45]
Follicular lymphoma	CT	CT every 6 months x 2 years, then yearly	–
Diffuse large B-cell lymphoma	Only as clinically indicated	Stage I/II: as clinically indicated Stage III/IV: no more frequently than every 6 months for 2 years	–
Burkitt lymphoma	–	Not specified [‡]	–
Peripheral T-cell lymphoma	–	Not specified [‡]	–
Classical Hodgkin lymphoma	Only as clinically indicated	CT every 6–12 months × 2 years	CT every 6 months × 2 years, then annually until year 5

All patients should receive appropriate radiologic evaluation at any time in follow-up if there is clinical suspicion of relapsed disease and identification of relapse would result in a change in management approach.

[†] NCCN Guidelines Version 1.2015 for non-Hodgkin lymphoma and 2.2014 for Hodgkin lymphoma.

[‡] NCCN guidelines for Burkitt lymphoma do not specify a specific imaging modality for surveillance but do recommend follow-up every 2–3 months for 1 year, then every 6 months. Follow-up for peripheral T-cell lymphoma is not specified.

ACR: American College of Radiology; CT: Computed tomography; NCCN: National Comprehensive Cancer Network.

Table 2

Selected references detailing outcomes for patients with lymphoma based on method of relapse detection.

Study (year)	Disease	Monitored patients (n)	Relapses (n)	Relapses detected by scans only (%)	Positive predictive value of surveillance scan (%)	Ref.
Thompson <i>et al.</i> (2014)	NHL (Mayo)	552	112	8	–	[46]
Thompson <i>et al.</i> (2014)	NHL (Lyon)	222	55	7	–	[46]
Zinzani <i>et al.</i> (2009)	NHL	183	54	–	–	[47]
Abel <i>et al.</i> (2012)	NHL	625	50	26		[48]
Cheah <i>et al.</i> (2013)	NHL	11 6	13	46	60	[49]
Hong <i>et al.</i> (2014)	NHL	106	15	–	–	[50]
Avivi <i>et al.</i> (2013)	NHL	11 9	31	29	37	[51]
El-Galaly <i>et al.</i> (2014)	NHL	–	17 3	26	–	[52]
Pingali <i>et al.</i> (2014)	HL	241	11	55 [†]	–	[53]
Dann <i>et al.</i> (2014)	HL	366	36	47 [†]		[54]
El-Galaly <i>et al.</i> (2012)	HL	161	22	45	28	[55]
El-Galaly <i>et al.</i> (2014)	HL	–	43	37	–	[52]
Bestawros <i>et al.</i> (2013)	HL	–	258	22	–	[56]

[†]These articles included reviews for patients who received routine surveillance and who did not receive routine surveillance. The percentage reported is of the entire group of patients followed.

HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma.

Table 3

DNA markers used for monitoring minimal residual disease in non-Hodgkin lymphomas.

Marker	Chromosome	Source of DNA	Method of detection	Disease
<i>IGH-BCL2</i>	t (14 ;18)	PBMC; bone marrow	End point PCR; qPCR	FL
<i>IGHV</i>	14	PBMC; bone marrow; plasma [†]	End point PCR; qPCR; NGS	DLBCL [†] , FL, MCL
<i>IGH-CCND1</i>	t (11 ;14)	PBMC; bone marrow	End point PCR; qPCR	MCL
<i>TCRB</i>	7	PBMC; bone marrow	NGS	T-cell lymphomas

[†]Data for IGHV use for MRD monitoring in DLBCL uses cell free DNA from plasma.

DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; NGS: Next-generation sequencing; PBMC: Peripheral blood mononuclear cell; qPCR: Quantitative PCR.