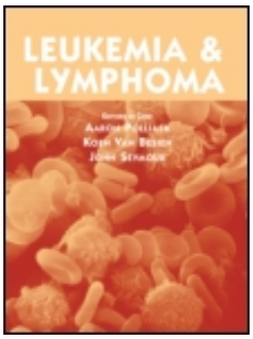

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COMMENTARY

Adding weight to a sinking ship: more reasons not to perform routine surveillance imaging in patients with diffuse large B-cell lymphoma in remission

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Despite improvements in the outcome of patients with diffuse large B-cell lymphoma (DLBCL), even with optimal treatment, failure occurs in approximately 40% of patients [1,2]. Some patients who suffer relapse with chemosensitive disease can still be cured using salvage therapy and high dose consolidation supported by stem-cell transplant (either autologous or allogeneic) – age, organ function, stem cell availability and performance status permitting [3,4]. One strategy frequently employed to maximize cure fraction has been routine surveillance imaging in first remission. The ideal characteristics of a screening (or in this case, surveillance) test are high sensitivity (so as not to miss disease relapse, even if low volume), high specificity and positive predictive value (PPV) (to avoid unnecessary biopsies or repeat scans), minimal test-related morbidity and low cost (given that many patients who will never relapse undergo testing). Furthermore, the population being tested should have a suitably high prevalence of detectable subclinical disease, and the test in question must detect disease prior to a "critical point" after which intervention is substantially less likely to be effective [5]. For screening to be effective, there should be a detectable preclinical phase of adequate length prior to the development of signs or symptoms. If the lead time between screen detected relapse and symptomatic relapse is too short (e.g. highly proliferative tumors such as Burkitt lymphoma or acute leukemias), surveillance is of little benefit.

Whether currently available surveillance imaging modalities in first remission of DLBCL satisfy these criteria is questionable. The study by Hong *et al.* in the current issue of ***Leukemia and Lymphoma*** emphasizes this point [6]. The authors conducted a retrospective analysis of 106 patients with DLBCL treated with chemo-immunotherapy who achieved complete metabolic remission on end-of-treatment positron emission tomgraphy (PET) scanning, followed with either routine imaging (using either contrast-enhanced computed tomography [CT] alone or PET [PET-CT]) or clinical review only. Imaging surveillance was performed at the discretion of the treating clinician. Fifteen (14%) patients suffered disease relapse, among whom 11 (73%) instances were detected by clinical findings on unscheduled outpatient visits and four (27%) by routine surveillance imaging. It required 501 routine scans to detect these four subclinical relapses. Both CT and PET-CT displayed excellent sensitivity; however, the moderate number of false positive PET-CT scans in particular (13.7%) resulted in a number of additional procedures, ranging from repeat scans after a time interval to lymph node biopsies under general anesthesia. Interestingly, the number of false positive CT scans was much lower (1.7%). Whilst it may be tempting to use these findings to argue in favor of CT surveillance, the existing literature does not support this. Studies of CT surveillance have consistently demonstrated that only 11–22% relapses are detected prior to clinical evidence of relapse [7–10]. Part of the reason for this is likely that CT alone has a low probability of detecting nodal relapse < 1 cm in diameter, and extranodal sites such as bone [11].

Surveillance scans are not completely without morbidity. In addition to the minority of patients exposed to the additional risks of unnecessary biopsy, other potential adverse consequences include generation of patient anxiety, which can be an unpleasant reminder for patients even years after achieving remission [12], and additional radiation exposure with risk of second malignancy, particularly relevant for younger patients already treated with chemotherapy [13,14]. In patients undergoing CT scans with iodinated contrast, nephrotoxicity occurs in 2–7% of the otherwise healthy population and a higher proportion if there is underlying renal impairment [15].

Also, surveillance imaging is expensive. The finding of Hong *et al.* that 125 scans needed to be performed on patients in remission to detect one subclinical relapse [6] is consistent with other recent studies of PET-CT in which estimates range from 22 to 137 scans per subclinical relapse [11,16–22]. Even conservatively estimating the cost of a PET-CT scan

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Table I. Assessment of CT and PET-CT with regard to desirable criteria for a surveillance test in the setting of diffuse large B-cell lymphoma in first remission.

Desirable criteria for a surveillance test	CT alone	PET-CT
Ability to detect subclinical disease	Poor: 11–22% of relapses [7–10]	Variable but higher than CT: 13–100% of relapses [11,16,17,19–23]
High sensitivity (few false negatives)	Yes, sensitivity close to 100% in most studies	Yes, sensitivity close to 100% in most studies
High PPV (few false positives and disease with moderately high prevalence in the population tested)	Probably not. Estimates scarce from published literature but 30% in Hong *et al.* [6]	Variable. PPV widely variable depending on reporting style and patient selection: 12–85% if unselected [17,20,23] and higher if confined to patients with IPI ≥ 3 [11]
Low morbidity	Risk of contrast-induced nephrotoxicity of 2–7%, higher if baseline renal impairment [15]; risk of cumulative radiation exposure; patient anxiety	Risk of cumulative radiation exposure; patient anxiety
Low cost	No; cost varies widely between healthcare settings but typically USD$500–1000 per scan	No; cost varies widely between healthcare settings but typically USD$1000 + per scan
Test must detect disease prior to a "critical point"	Uncertain	Uncertain
Treatment is more effective if initiated prior to development of symptoms	Unproven	Unproven

CT, computed tomography; PET-CT, positron emission tomography–computed tomography; PPV, positive predictive value.

at USD$1000 without factoring the health resource costs of consequential negative biopsies, it can be calculated that the cost of detecting a subclinical relapse can exceed USD$100 000. Unsurprisingly, economic analyses have found that surveillance imaging contributed 75–81% of the cost of follow-up, not including the cost of unnecessary procedures [21,23]. Costs may be lowered by confining the surveillance strategy to those patients with the greatest risk of relapse. Hong *et al.* found that the PPV of both modalities improved when only patients with International Prognostic Index (IPI) ≥ 3 were considered, a result mirrored in another study [11]. However, a prospective randomized study of surveillance imaging in patients with IPI ≥ 3 would be required to demonstrate clinical benefit before a selective surveillance strategy could be recommended.

Whether early detection of relapsed lymphoma truly leads to improved outcome from salvage chemotherapy with or without stem cell transplant remains unproven. Investigators from the Memorial Sloan-Kettering Cancer Center have shown that for patients with chemosensitive aggressive non-Hodgkin lymphoma (NHL), age-adjusted IPI at the time of initiation of second-line chemotherapy predicts both progression-free and overall survival after both autologous [24] and allogeneic [25] stem cell transplant. The same group, analyzing 108 patients with relapsed aggressive NHL treated with ifosfamide, carboplatin and etoposide, found that patients with relapse detected by imaging were more likely to have low second-line age-adjusted IPI (79% vs. 39%), and had a non-significant trend toward improved likelihood of 5-year progression-free survival (34% vs. 11%, $p = 0.12$) and overall survival (54% vs. 43%, $p = 0.13$) [26]. However, no studies to our knowledge, including that of Hong *et al.*, have demonstrated a survival benefit for patients in whom relapse was detected by imaging versus clinical findings.

So what is the current status of surveillance imaging in the follow-up of patients with DLCBL? Table I summarizes the performance of both CT and PET-CT against desirable criteria for a surveillance test. It appears that, with the exception of high sensitivity, neither modality adequately satisfies the criteria to justify routine use in an unselected population of patients with DLBCL in first remission. Due to the combination of high cost and numerous studies showing limited evidence of benefit, routine surveillance imaging appears ready to sink without trace. The importance of this message is epitomized by the inclusion of recommendations against routine surveillance imaging in both the 2013 American Society of Clinical Oncology "top five list in oncology" and the American Society of Hematology "Choosing Wisely" list [27,28]. Furthermore, the latest version of the National Comprehensive Cancer Network's NHL guidelines no longer recommends routine surveillance imaging in the follow-up of patients with DLBCL [29]. Many clinicians also serially monitor serum lactate dehydrogenase (LDH) in patients with DLBCL in remission. Although significantly cheaper than imaging, several recent studies have found elevated serum LDH to have limited sensitivity (44–69%) and PPV (9–38%) for detection of relapsed lymphoma [30–32]. Furthermore, most patients in whom relapse is immediately preceded by elevated LDH also have clinical manifestations [30]. Thus, routine monitoring of LDH appears to have little role. It is possible that the development of molecular monitoring using tumor-specific DNA [33] may allow even earlier detection of impending relapse, which could facilitate the opportunity to investigate novel therapies (such as lenalidomide, ibrutinib, idelalisib or pidilizumab) for molecular relapse. Until then, patients and physicians alike can take comfort that a thorough history and examination, with further investigation reserved for evaluation of any concerning symptoms or physical findings, remain the standard of care in the post-remission follow-up of patients with DLBCL.

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