Evaluating surveillance imaging for diffuse large B-cell lymphoma and Hodgkin lymphoma

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Up to 50% of patients with Hodgkin lymphoma and diffuse large B-cell lymphoma will relapse, requiring additional therapy. Although surveillance imaging is commonly performed in clinical practice, its ability to identify asymptomatic relapses and improve survival for patients is not well defined. We evaluated the surveillance imaging role in relapse detection and reviewed its impact on survival for relapsed patients, and found that current imaging approaches do not detect most relapses prior to clinical signs and symptoms or improve survival. (*Blood*. 2017; 129(5):561-564)

Introduction

A 23-year-old woman with stage IIIA classical Hodgkin lymphoma (HL) achieves complete remission (CR) after standard treatment, and now asks about follow-up plans, including imaging. At the time of diagnosis, her International Prognostic Score was 1. A positron emission tomography (PET)/computed tomography (CT) scan after cycle 2 demonstrated a complete response with a Deauville score of 2. She is concerned about the risk of relapse, but wants to avoid any additional radiation exposure.

With current therapies, the majority of patients with HL and diffuse large B-cell lymphoma (DLBCL) will be cured with contemporary treatment approaches.[1,2] Most commonly, relapses for DLBCL and HL patients occur early in the posttreatment course, and relapses >5 years after completion of therapy are rare.[3] Because relapsed patients remain eligible for curative therapies and imaging with CT, PET, and PET/CT is widely available, routine surveillance imaging has traditionally been incorporated into patient management.

However, several groups have recently reviewed the appropriateness of routine surveillance in HL and DLBCL, including the American Society of Hematology (ASH) Choosing Wisely Campaign, which recommended against routine surveillance imaging for curable lymphomas due to concerns about a high rate of false-positive scans and an unclear survival benefit.[4] In addition, cumulative radiation doses from surveillance imaging are estimated to be 229 mSv in HL patients, and the projected lifetime cancer incidence is slightly increased in patients undergoing surveillance imaging after completing induction therapy for both HL and non-HL (NHL).[5,6] To address uncertainty surrounding the role of surveillance imaging in HL and DLBCL patients in remission after first-line therapy, we performed a systematic review to examine the sensitivity and specificity of surveillance imaging and its impact on survival to determine whether there is sufficient evidence to warrant use.

Methods

Search strategy

A comprehensive and methodical search of the literature of electronic databases (Medline, Embase, Cochrane) for studies published between 2000 and 2016 was conducted. A medical subject heading search strategy was constructed for Medline searches using criteria based on a defined population, intervention, comparison, outcomes, and timing (PICOT) question. The population included classical HL and DLBCL patients who completed first-line treatment. Surveillance CT and PET/CT imaging defined the intervention; the comparison was with patients who underwent observation without imaging; and the time period for evaluation was defined as following completion of first-line therapy until 5 years, relapse, or death. The medical subject heading search included combination of relevant search terms such as "Hodgkin disease," Lymphoma, Large B-Cell, Diffuse, "Positron-Emission Tomography," "Tomography, X-ray Computed." Additional relevant manuscripts were identified by reviewing reference lists from the identified papers and manual search of abstracts from annual meetings of ASH and the American Society of Clinical Oncology.

Study eligibility

All studies identified by the search were independently reviewed by 3 authors (M.B., J.B.C., and C.R.F.) and discussed in a consensus meeting to determine eligible studies, excluding studies where imaging was used for diagnosis or response evaluation without surveillance information.

Data extraction and statistical analysis

Standard data extraction templates were used to collect the number of patients, type of scans (PET/CT, PET, or CT), relapse frequency with and without surveillance imaging, frequency of asymptomatic relapses, sensitivity, specificity, positive predictive value (PPV) and negative predictive value, and number of false positives and negatives (if reported). The data extracted from the eligible studies were quantified and reported as weighted pooled proportions. All analyses were performed using Comprehensive Meta Analysis software (CMA version 2.2).

Results

Fifteen studies were identified that satisfied inclusion criteria, including 7 studies on DLBCL, 6 assessing HL, and 2 including HL and DLBCL (Table 1).[7-21] Thompson et al analyzed 2 separate DLBCL cohorts in 1 publication.[7] All of the included studies were retrospective except Zinzani et al and Picardi et al.[16,21] In total, 3099 patients were included in the summarized studies, among which 20% of patients experienced relapse. The frequency of relapse was 30% among patients who received CT only (n = 680), 28% among patients who underwent PET

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Table 1. Summarized findings of studies investigating the role of surveillance imaging in DLBCL and HL

Reference (study)	Disease	Modality	No. of patients	No. of relapses (%)	No. of relapses outside surveillance visit (% of relapses)	Asymptomatic relapses (% of relapses)
7 (Mayo)	DLBCL	CT or PET	552	112 (20)	69 (62)	13 (19)
7 (Lyon)	DLBCL	CT	222	55 (25)	34 (62)	6 (11)
8	DLBCL	CT	117	35 (30)	33 (94)	2 (6)
9	DLBCL	PET/CT	116	13 (12)	7 (54)	6 (46)
10	DLBCL	CT or PET	625	50 (8)	31 (62)	19 (38)
11	DLBCL	CT	341	113 (33)	88 (78)	25 (22)
12	DLBCL	PET	119	31 (26)	22 (71)	9 (29)
13	DLBCL	CT or PET	106	15 (14)	—	—
14	DLBCL	PET	75	23 (31)	20 (87)	3 (13)
15	HL/DLBCL	PET, CT, or gallium	—	125 (N/A)	78 (62)	47 (38)
16	HL/DLBCL	PET/CT				
17	HL	PET/CT	161	22 (14)	12 (55)	10 (45)
18	HL	CT or PET	305	28 (9)	8 (29)	17 (61)
19	HL	CT or PET	174	6 (3)	—	—
20	HL	CT or PET	36	5 (14)	—	—
21	HL	PET/CT	150	40 (27)	15 (38)	25 (63)

—, unknown/not reported; N/A, not applicable.

only (n = 194), and 19% among patients who underwent PET/CT (n = 427). Across all patients and all imaging modalities, 60% of relapses were identified by means other than surveillance imaging. Additional pooled analyses were not feasible due to the heterogeneous nature of previously reported studies. Selected studies are highlighted in the following sections.

DLBCL

Zinzani et al performed the largest prospective study of surveillance imaging for aggressive NHL to date (n = 183).[16] In this study, patients underwent serial PET at prespecified time points after achieving CR following first-line therapy. There were an increased number of relapses confirmed by PET (31%) compared with clinical signs alone (22%), but the impact of imaging on survival was not reported. The rate of true positive PET was highest in the first 18 months of follow-up.

Thompson et al reported outcomes for cohorts from Mayo Clinic and Lyon, France to describe use of surveillance PET/CT or CT in DLBCL patients who received an anthracycline-containing induction regimen, did not have refractory disease, and for whom surveillance-related follow-up was available.[7] Relapse occurred in 112 of 552 patients in the Mayo cohort undergoing surveillance, and 74% of relapses occurred within the first 24 months. Only 36% of patients experienced a relapse detected at a scheduled surveillance visit, and all but 13 of these patients had concurrent clinical signs of symptoms. In sum, relapsed DLBCL was detected by surveillance imaging prior to clinical manifestations in 9 of 552 Mayo patients (1.6%) and 4 of 222 Lyon patients (1.8%). In both cohorts, there were no significant differences in overall survival (OS) based on detection of relapse by surveillance imaging compared with other methods.

A combined analysis of lymphoma registries compared outcomes for 1221 patients aged 18 to 65 years with DLBCL who achieved a CR after treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) or R-CHOP with addition of etoposide (R-CHOEP) in Sweden (where posttreatment surveillance imaging is not standardly performed) or Denmark (where routine imaging is performed by either PET or CT),[22] demonstrating no difference in OS (hazard ratio, 0.91; $P = .6$ in multivariable analysis). Although patients with an International Prognostic Index (IPI) ≥2 had an increased pretest probability of identification of relapse by imaging, this did not contribute to a difference in OS.

Additional cohorts have evaluated the role of both PET/CT and CT in DLBCL. Cheah et al examined 116 patients who underwent 450 PET/CTs and found that only 13 patients in CR relapsed and only 6 had relapse identified by scan without other clinical symptoms (1.3%).[9] The PPV was 56% in patients with an IPI score <3, compared with 80% in patients with an IPI ≥3. Avivi et al reported outcomes for 119 patients with DLBCL who underwent PET/CT surveillance.[12] In a subset of patients who receive R-CHOP, the PPV was 23%, with a false-positive rate of 77%. In another study of CT surveillance, asymptomatic relapse occurred in 5.7% of patients, and 86% of relapses were associated with clinical signs/symptoms.[8]

HL

Similar to their NHL findings, Zinzani et al found that PET/CTs indicative of relapse in HL patients most commonly occurred within 12 to 18 months of treatment.[16] Fifty-one of 160 patients (32%) had relapse identified by PET/CT compared with 35 of 160 patients (22%) who had relapse identified by clinical signs and symptoms. An interim-positive PET/CT after 2 cycles of therapy was associated with an increased frequency of relapse detected by surveillance PET/CT. However, the authors did not report postrelapse survival results based on the method of detection.

Picardi et al randomized 300 patients with HL who achieved CR to receive surveillance imaging every 4 months for 2 years using abdominal ultrasound with chest radiography or PET/CT and found that 27% of patients in both groups relapsed.[21] Among all relapsed patients, 64% were identified by surveillance alone. The PPV for ultrasound/chest radiography was 91% and for PET/CT was 73% ($P = .01$). These were both markedly greater than the PPV of PET/CT reported in retrospective studies, which has been as low as 28% in 1 series.[17] However, Picardi et al did not report the OS for patients who had relapse detected by surveillance imaging alone.

Jakobsen et al also published a collaborative effort between the Swedish and Danish Lymphoma Registries evaluating the role of surveillance in 1230 patients with HL aged 18 to 65 years and who achieved a CR after receiving either doxorubicin, bleomycin, vinblastine, and darcarbacine (ABVD) or bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and

prednisone (BEACOPP). Similar to the DLBCL analysis, there was no difference in postremission survival based on the use of routine surveillance imaging ($P = .2$).[23]

Summary and recommendations

No retrospective or prospective study identified a survival advantage associated with the use of surveillance imaging for patients with DLBCL or HL who achieved remission after first-line therapy. Imaging also has disadvantages: although the test characteristics of PET/CT and CT varied between studies, a meaningful fraction of patients experience false-positive scan results producing additional anxiety and medical interventions.[24] In addition, surveillance imaging produces additional radiation exposure, although the risk of additional cancers and cancer-related death attributable to this exposure appears to be slight for most adults.[6] As a result, the Lugano Classification for evaluation, staging, and response assessment in lymphoma recommends against routine surveillance, especially with PET/CT.[25] However, it does appear that the PPV for surveillance imaging is improved in patients with a higher pretest likelihood of relapse such as DLBCL patients with high IPI and HL patients with a positive interim PET/CT. Despite the increased pretest likelihood of relapse in patients with high-risk features, Hapgood et al have recently described the outcomes for HL patients treated in British Columbia, in which the risk of relapse for patients with HL who are event-free at 2 years is only 5.6%, and this risk is not significantly impacted by pretreatment risk factors.[26] Future prospective studies are needed to determine whether surveillance imaging might provide benefits in highly selected populations.

In addition, novel approaches to disease surveillance are under development. Kurtz et al and Roschewski et al have both reported outcomes of surveillance by assessing for circulating tumor DNA in patients with DLBCL who have completed induction therapy.[27,28] Roschewski et al report a PPV of 88% for patients who have detectable circulating DNA, with relapse detected a median of 3.5 months prior to clinical relapse. These noninvasive monitoring approaches do not expose patients to radiation and may ultimately provide improved ability to detect relapse early in patients with CR after completing therapy. However, these surveillance approaches also require prospective evaluation to ascertain their value and impact on survival.

In summary, we recommend that patients with HL and DLBCL who achieve CR should not receive routine surveillance imaging, given the high number of scans that are required to identify 1 asymptomatic relapse and the lack of data demonstrating improved survival for asymptomatic patients who have relapse detected by surveillance imaging alone. Based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, we rate the strength of evidence for this recommendations as 1B (strong recommendation with decent evidence). We would recommend that the 23-year-old patient described in the case be observed without routine imaging and be reassured that her risk of relapse is low and that there is no evidence that her likelihood of survival in the setting of relapse would be changed by the method of relapse detection.

In patients with DLBCL with known high-risk features including an IPI of 3 to 5, it is reasonable to consider scans on an individual basis after a thorough discussion of the risks and benefits of surveillance imaging and with the understanding that early detection of relapse is not currently known to improve survival (GRADE 2C, weak recommendation with fair evidence). In these highly selected cases, surveillance should be limited to the first 2 years after induction therapy as the risk of relapse declines significantly at that time point and routine imaging is likely no longer appropriate. Additional high-risk patient subsets such as patients with double hit or double protein expressing NHL can be considered for surveillance imaging although data to support this approach are currently lacking and cannot be recommended in a standardized fashion. Scheduled surveillance imaging should be performed for patients enrolled on therapeutic clinical trials where scheduled imagining is required to reliably calculate progression-free survival as an end point, especially when progression-free survival is being compared between 2 or more regimens. However, investigators should also be cognizant of the costs associated with repeated scans as well as their clinical utility in the setting they are evaluating. In future years, it is our hope that more effective therapies, improved imaging modalities, and novel surveillance strategies will further decrease the need for routine surveillance imaging and the costs associated with such approaches.

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Authorship

Contribution: All authors designed research and contributed to the search terms; M.B., J.B.C., and C.R.F. performed search and refinements; and all authors analyzed the data and wrote the paper.

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