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Evidence Summary 26-5

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Follow-up Care for Survivors of Lymphoma who have Received Curative-Intent Treatment

J. Sussman, N. Varela, M. Cheung, L. Hicks, D. Kraftcheck, J. Mandel, G. Fraser, L. Jimenez-Juan, A. Boudreau, S. Sajkowski, R. McQuillan.

Report Date: April 12, 2016

An assessment conducted in March 2025 deferred the review of Evidence Summary (ES) 26-5. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access ES 26-5 here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/471

For information about this document, please contact Dr. J. Sussman, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Sussman J, Varela N, Cheung M, Hicks L, Kraftcheck D, Mandel J, et al. Follow-up care for survivors of lymphoma who have received curative-intent treatment. Toronto (ON): Cancer Care Ontario; 2016 April 12. Program in Evidence-Based Care Evidence Summary No.: 26-5.

Journal Citation (Vancouver Style): Sussman J, Varela NP, Cheung M, Hicks L, Kraftcheck D, Mandel J, Fraser G, Jimenez-Juan L, Boudreau A, Sajkowski S, McQuillan R. Follow-up care for survivors of lymphoma who have received curative-intent treatment. Curr Oncol. 2016 Oct;23(5):e499-e513.

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Evidence Summary 26-5

Follow-up Care for Survivors of Lymphoma who have Received Curative-Intent Treatment: Evidence Summary

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

INTRODUCTION

The lymphomas are made up of a large group of neoplasms that arise from the lymphatic system. In 2014, the Leukemia & Lymphoma Society of Canada estimated that there would be 9000 new cases of lymphoma diagnosed in Canada (1000 Hodgkin lymphomas and 8000 non-Hodgkin lymphomas), making lymphoma the sixth most common malignancy in Canada (1). There are many types and subtypes of non-Hodgkin lymphoma. Worldwide, diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin lymphoma, accounting for 30 to 40 per cent of all newly diagnosed cases (2). DLBCL and Hodgkin lymphoma (HL) are considered curable with therapies that include chemotherapy, immunotherapy and radiation.

A significant proportion of patients will relapse, typically within the first two years after primary treatment, and many can be treated successfully for cure with salvage chemotherapy and stem cell transplantation. For this reason, surveillance is considered important in this group to detect relapse as early as possible based on the assumption that earlier detection will lead to better outcomes by detecting subclinical disease with a lower tumour burden.

Surveillance testing, which includes physical examination, blood testing and imaging, is currently used to follow patients with DLBCL and HL who are considered to be in remission after treatment to detect recurrence. There is known to be a wide variation in practice, especially in the frequency of imaging, and recent population studies have suggested significant over testing in asymptomatic patients may occur, and not result in improved outcomes. Currently there are no Canadian guidelines which summarize the evidence regarding the type and timing of surveillance testing for asymptomatic patients with DLBCL and HL who have been treated for cure. The intent of this evidence summary is to assess the available evidence on the follow-up of asymptomatic survivors of lymphoma who have received curative-intent treatment.

RESEARCH QUESTIONS

Three research questions were developed to direct the search for available evidence on the follow-up of asymptomatic survivors of lymphoma who have received curative-intent treatment.

1. What clinical activities have been shown to be effective at detecting clinical recurrence or further hematological neoplasm?
2. What is the appropriate frequency and timing for the clinical activities that have been shown to be effective at detecting clinical recurrence or further hematological neoplasm (malignancy)?

3. What surveillance procedures have been shown to be effective at detecting therapy-related secondary malignancies following treatment for lymphoma?

TARGET POPULATION

All asymptomatic adolescent (≥15 years) and adult survivors of lymphoma who have completed curative-intent treatment and undergo routine follow-up for lymphoma; these patients may or may not be followed by an oncologist.

INTENDED PURPOSE

The purpose of this evidence summary is to report the available data regarding the posttreatment follow-up and surveillance of patients with lymphoma treated with curative intent.

INTENDED USERS

This evidence summary is targeted for all people involved in clinical follow-up of asymptomatic survivors of lymphoma who have received curative-intent treatment including:

- Hematologists
- Medical and radiation oncologists
- Radiologists
- Family physicians
- Nurses
- Administrators and policy makers

METHODS

This evidence summary was developed by a Working Group consisting of one radiation oncologist, two hematologists, one regional primary care lead, two radiologists, one registered nurse, two patient representatives, and a health research methodologist at the request of the Cancer Care Ontario Survivorship programs, from the Clinical Programs and Quality Initiatives, due to the absence of evidence-based practice documents in Ontario for the follow-up and surveillance of asymptomatic patients with lymphoma treated with curative intent. The Working Group was responsible for reviewing the identified evidence and drafting the summary. Information regarding members of the Working Group can be found in Appendix 1.

Conflict-of-interest declarations for all authors and reviewers are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

This evidence review was conducted in two planned stages; a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

The Cochrane Database of Systematic Reviews was searched from January 2000 to August 2015 using the word "lymphoma". Likewise, the MEDLINE and EMBASE databases were searched using Ovid to identify existing systematic reviews that addressed one or more of the research questions above. Systematic reviews older than five years were considered not relevant, because the main goal of a search for systematic reviews is to identify recent secondary sources covering the primary relevant literature on the topic of interest, the follow-up care for survivors of lymphoma who have received curative-intent treatment. Medical Subject Heading (MeSH) terms related to lymphoma follow-up were combined with text words as a search filter. The full literature strategy used to retrieve potential relevant studies is presented in Appendix 3.

Systematic reviews were included if they met the following criteria:

1. The existing systematic reviews searched for studies evaluating the follow-up care for adult and/or adolescent survivors of lymphoma who have received curative-intent treatment.
2. The literature search strategy for the existing review was reproducible and appropriate.
3. The existing systematic review reported the sources searched as well as the dates that were searched.

Identified systematic reviews that met the eligibility criteria would be assessed using A Measurement Tool to Assess Systematic review (AMSTAR) (3) to determine whether or not an existing review could be incorporated as part of the evidentiary base. Any identified reviews that did not meet the criteria above, whose AMSTAR assessments indicated important deficiencies in reporting completeness, or that were otherwise not incorporated as part of the evidence base would be reported in the reference list, but not further described or discussed.

Search for Primary Literature

If no existing systematic review or evidence-based practice guideline was identified, or if identified reviews were incomplete or out-of-date, a systematic review of the primary literature was also planned.

Literature Search Strategy

The MEDLINE (Ovid) (1946 through August 31, 2015) and EMBASE (Ovid) (1996 through Week 35, 2015) databases were searched for evidence in August 2015. The search strategy included the MeSH "exp lymphoma" combined with additional terms and text words for the intervention (follow-up) and the population (survivors). The results were limited to English language articles and articles published from 2000 to 2015. The full literature strategy used to retrieve potential relevant studies is presented in Appendix 3.

Study Selection Criteria and Process

Inclusion Criteria:

Articles identified in this literature search were eligible for inclusion if they met the following criteria:

1. Primary studies evaluating the the follow-up care for adult and/or adolescent survivors of lymphoma who have received curative-intent treatment.
2. Published full-report articles of randomized or nonrandomized studies with an appropriate control group, decision model studies, and single-arm studies with a sample size of at least 100 patients.
3. Studies reporting the outcomes of interest such as recurrence/relapse rate, overall survival rate, and relapse-free survival rate.

Exclusion Criteria:

Studies were excluded if they were:

1. Abstracts, letters, case reports, comments, books, notes, or editorial-type publications.
2. Articles published in a language other than English because resources were not available for translation services.
3. Single-arm studies with a sample size <100 patients.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (NV). For those items that warranted full text review, one reviewer (NV) assessed each item independently and consulted with other members of the Working Group whenever there was uncertainty.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one reviewer (NV). All extracted data and information was assessed by a second reviewer (JS), and audited by an independent auditor to verify the accuracy of the information obtained from the studies included in this report. For primary studies, key characteristics, including author, year of publication, study design, study population, sample size, posttreatment follow-up protocol, and median follow-up time were recorded. Outcomes of interest including relapse rate, time to relapse, method of relapse detection and detection rate by follow-up activity, overall survival rate, and relapse-free survival rate were extracted when available.

Any randomized clinical trial would be assessed for quality by examining the following seven criteria: method of randomization, reporting of blinding, power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, nonrandomized, and single-arm evidence would be assessed according to full reporting of the patient selection criteria, the follow-up each patient received, all relevant outcomes, and the source of funding. All authors reviewed and discussed a draft of this report with the aim of assessing the quality of the evidence as a whole, without the use of a scoring system or cut-offs, according to the policy of the PEBC

RESULTS

Search for Existing Systematic Reviews

The search for systematic reviews identified one citation which was retrieved for full text review (4), but the outcomes of interest were not reported on. No other relevant systematic reviews were identified.

Search for Primary Literature

Literature Search Results

As presented in Figure 1, out of 1950 titles and abstracts identified in the search of the MEDLINE and EMBASE databases, 1841 appeared potentially eligible on initial review, and 124 of these were verified to be eligible for full-text review. From these, 11 full-report studies were identified that addressed the the follow-up care for adult and/or adolescent survivors of lymphoma who have received curative-intent treatment and reported the outcome of interest. The remaining 113 studies were excluded because they failed to pass the inclusion criteria. Table 1 summarizes the number and types of studies included per research question.

Figure 1. Literature search flow diagram of included studies addressing the follow-up care for adult and/or adolescent survivors of lymphoma who have received curative-intent treatment

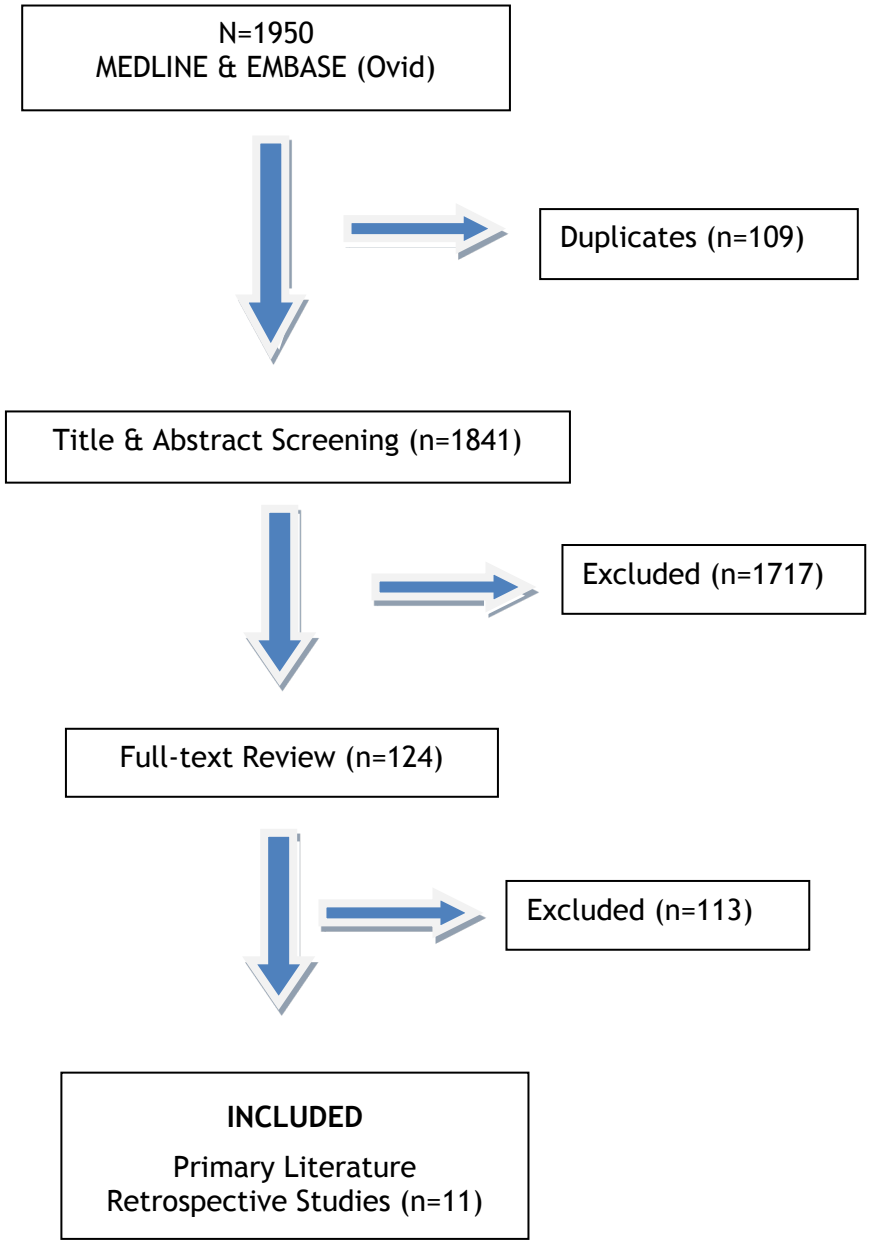

Table 1. Research questions and included studies addressing the follow-up care for adult and/or adolescent survivors of lymphoma who have received curative-intent treatment

Question	Included Studies

1. Clinical activities to detect recurrence or further hematological neoplasm in survivors of lymphoma	11 retrospective studies (5-15)
2. Frequency and timing for clinical activities to detect recurrence or further hematological neoplasm in survivors of lymphoma	9 retrospective studies (5-10,12, 14,15)
3. Activities to detect therapy-related secondary malignancies in survivors of lymphoma	None

Study and Patient Characteristics

The primary literature search identified 11 nonrandomized retrospective studies assessing the follow-up of asymptomatic survivors of lymphoma who have received curative-intent treatment, and reporting the outcomes of interest: overall survival rate and relapse-related outcomes (relapse detected by different follow-up schedules, symptomatic versus asymptomatic relapses, relapse-free survival rate, median time to relapse, number of imaging tests per relapse detected). The included studies involved patients with diffuse large B-cell lymphoma, classical Hodgkin lymphoma, lymphoid malignancies, and aggressive Hodgkin lymphoma. See Table 2.

Study Design and Quality

The primary literature returned 11 nonrandomized retrospective studies that met the inclusion and exclusion criteria. A description of the study designs and quality of the studies is presented in Appendix 4. Overall, the body of the evidence is limited mainly by its design based on retrospective analysis of electronic medical records, and the relatively small sample size with low number of relapses. The sample size of the included studies ranged from a low of 109 (7) to a high of 1221 in a population-based study comparing the survival rate of patients with lymphoma undergoing different clinical follow-up policies (8). The majority of the studies encompassed patients with non-Hodgkin lymphoma (5,8,10-12,14,15); three studies focused on the follow-up of patients with Hodgkin lymphoma (6,7,13), and one study reported on both types of lymphoma (9). The number of relapses ranged from a low of 15 (10) to a high of 163 (15) in patients with non-Hodgkin lymphoma, and from a low of 11 (13) to a high of 42 (9) in patients with Hodgkin lymphoma.

Table 2. Summary of the studies assessing the follow-up care for asymptomatic survivors of lymphoma who have received curative-intent treatment

Study [country]	Aim	Population and Posttreatment Follow-up	Intervention	Number of Patients Included	Outcome Reported
Hong et al. 2014 (10) [South Korea]	To assess the role of routine imaging vs symptom-directed unplanned early OPD visits in patients with DLBCL.	Adult patients with DLBCL (≥20 years) in CR as demonstrated by FDG-PET/CT and who had at least one OPD visit for relapse monitoring. **Follow-up*** OPD visits	Planned Visits vs Unplanned Visits	106 (856 visits) with DLBCL in complete remission	Relapse detection rate Overall Survival rate- from initial therapy, and from relapse
Pingali et al. 2014 (13) [USA]	To compare the outcomes of patients with cHL who underwent routine surveillance imaging vs clinical surveillance.	Adult patients newly diagnosed with cHL at three participating academic tertiary care medical centres, and who have achieved complete remission confirmed by CT and/or PET at the end of the first-line therapy. **Follow-up** <u>Arm 1: Imaging Surveillance</u> ○ History, physical examination, laboratory studies ○ Surveillance CT and/or PET scans before the follow-up visit <u>Arm 2: Clinical Surveillance</u> ○ History, physical examination, and laboratory studies ○ Scans were only obtained to evaluate concerning signs or symptoms of relapse.	Clinical surveillance vs Imaging surveillance	241 patients with cHL in complete remission.	5-year overall survival 5 year-incidence of relapse Median time to detect relapse Number of scans/relapse detected Scan rate

Study [country]	Aim	Population and Posttreatment Follow-up	Intervention	Number of Patients Included	Outcome Reported
Dann et al. 2013 (6) [Israel, New Zealand]	To evaluate the effectiveness of follow-up imaging in HL using PET/CT or CT as a routine mode of surveillance in addition to dedicated imaging if relapse is suspected compared with clinical follow-up and dedicated imaging performed upon suspicion of relapse.	Adult patients (>18 years of age at diagnosis) treated with curative intent treatment and who have achieved CR. **Follow-up*** ○ Arm1: Clinical Surveillance ○ Arm 2: Imaging Surveillance Arm	Clinical surveillance vs Imaging surveillance	International multicentre study 368 patients ○ 291 treated in two Israeli centres (Rambam Health Care Campus in Haifa, and Hadassah-Hebrew University Medical Centre in Jerusalem) ○ 77 treated in one New Zealand academic centre (Auckland Medical Centre in Auckland)	Median time to relapse HR follow-up mode Relapse detection rate Number of scans//relapse Number of imaging tests per patient to detect relapse Progression-free survival rate
Truong et al. 2014 (15) [USA]	To determine the value of routine imaging for detecting relapse in patients with NHL in CR after first-line therapy	Patients with NHL in CR **Follow-up*** ○ Clinician Visits, Laboratory Analysis ○ Imaging Surveillance	Clinical surveillance vs Imaging surveillance	1086 patients with lymphoid malignancies	Proportion of relapse detection Overall survival rate

Study [country]	Aim	Population and Posttreatment Follow-up	Intervention	Number of Patients Included	Outcome Reported
Cheah et al. (5) [Australia]	To assess the role of PET-CT scans in the surveillance of patients achieving complete response after primary therapy for DLBCL	Patients with DLBCL in complete remission after primary therapy and who underwent PET-CT scanning. **Follow-up*** Surveillance Imaging	Surveillance imaging: symptomatic vs Surveillance imaging asymptomatic	450 surveillance PET-CT scans from 116 patients	Overall survival rate Postrelapse
Lin et al. 2012 (12) [Taiwan]	To describe the value of surveillance CT in the detection of disease relapse in patients with DLBCL and FL3 and to evaluate whether relapse detected by different methods influences outcome	Patients with DLBCL and FL3 in CR or CRu† **Follow-up*** ○ Physical examination & laboratory evaluation ○ Surveillance CT	Clinically detected vs Surveillance CT detected	341 patients (314 DLBCL and 27 FL3)	Proportion of relapse detection Mean time from latest normal CT to relapse Number of scans/relapse detected Mean interval of surveillance CT Mean number of CT/year

Study [country]	Aim	Population and Posttreatment Follow-up	Intervention	Number of Patients Included	Outcome Reported
Goldschmidt et al. 2011 (9) [Israel]	To describe the diagnostic modality by which relapse was detected and to evaluate whether the use of PET/CT influenced survival rate in patients with relapsed HL or aNHL	Patients >18 years at diagnosis of HL or aNHL (DLBCL, peripheral T-cell lymphoma, Burkitt's lymphoma, lymphoblastic lymphoma) who relapsed at least one month after achieving first complete remission **Post Treatment Follow-up*** ○ Clinical evaluation ○ Imaging	Clinical detection vs Imaging detection	125 patients (42 HL and 83 aNHL)	Proportion of relapse detection Overall survival rate
Liedtke et al. 2006(11) [USA]	To evaluate the role of surveillance imaging in detection of relapse disease and its impact on outcomes of salvage treatment	Patients with biopsy confirmed relapse aNHL **Follow-up:** Surveillance Imaging. No further details were reported	Unscheduled imaging/clinical symptoms vs Routine imaging <u>Unscheduled imaging due to</u>: Self-reported symptoms or new physical examination, and/or abnormal findings on routine exam	108 patients <u>Routine imaging</u>: 24 <u>Unscheduled imaging</u>: 84	Relapse detection (proportion) Number of scans/relapse detected Progression-free survival Overall survival rate

Study [country]	Aim	Population and Posttreatment Follow-up	Intervention	Number of Patients Included	Outcome Reported
Dryver et al. (7) 2003 [Canada]	To evaluate the utility of the clinical assessments, radiological tests, and laboratory tests to detect Hodgkin's relapse	Patients with Hodgkin's lymphoma relapse following initial curative therapy **Follow-up*** ○ Clinical evaluation ○ Imaging	Clinical symptoms vs Imaging detection vs Lab testing	109 suspected relapses from 68 patients	Relapse Detection (proportion) according to modality detection: ○ Patient ○ Physician ○ Imaging ○ Lab test
El-Galaly et al. (8) [Denmark, Sweden]	To compare the survival rates of Danish and Swedish patients with DLBCL; two countries with similar healthcare systems but completely different standards for routine imaging	Patients from the Danish Lymphoma Group Registry (LYFO) and Swedish Lymphoma Registry (SLR) population-based lymphoma registries which cover ≥90% of adult patients with lymphoma in Denmark and Sweden **Standard Follow-up*** **SWEDEN** ○ Clinical Visits ○ Imaging only if relapse is clinically suspected **DENMARK** ○ Clinical Visits ○ Routine Imaging	Sweden and Denmark's national follow-up Policies for patients with DLBCL in CR	1221 patients with DLBCL in CR LYFO: 525 SLR: 696	Overall survival rate

Study [country]	Aim	Population and Posttreatment Follow-up	Intervention	Number of Patients Included	Outcome Reported
Thompson et al (14). 2015 [USA, France]	To assess the utility of posttherapy surveillance imaging in a cohort of patients with DLBCL from the United States and to confirm the results in an independent cohort of patients from France <u>Population</u>: two cohorts of patients with DLBCL in CR.	Patients with newly diagnosed DLBCL who have received anthracycline-based immunochemotherapy as their initial therapy **Post Treatment Follow-up*** **<u>MER COHORT</u>** ○ Clinical Visits ○ No details reported on imaging **<u>LYON COHORT</u>** ○ Clinical Visits ○ Surveillance CT Scans	Before scheduled visits vs Scheduled Visits	Data were collected from two cohorts of patients with DLBCL, one from the United States and the second one from France. ○ <u>MER Cohort</u>: patients identified from the Molecular Epidemiology Resource (MER) from the United States. ○ <u>Lyon Cohort</u>: patients identified from the León Bérard cancer centre, Lyon, France.	Overall survival rate Median time to relapse (in patients diagnosed with asymptomatic DLBCL relapse by imaging)

aNHL (aggressive non-Hodgkin lymphoma); cHL (classical Hodgkin lymphoma); CR (complete remission); CRu (complete remission unconfirmed); CT (computed tomography); DLBCL (diffuse large B-cell lymphoma); FDG-PET/CT (fluorodeoxyglucose-positron emission tomography/computed tomography); FL (follicular lymphoma); FL3 (follicular lymphoma grade 3); HL (Hodgkin lymphoma); HR (hazard ratio); MER (Molecular Epidemiology Resource); NHL (non-Hodgkin lymphoma); OPD (outpatient department); PET (positron emission tomography).

* See Table 3 for detailed follow-up schedule

† Complete remission unconfirmed

Outcomes

Question 1: What clinical activities have been shown to be effective at detecting clinical recurrence or further hematological neoplasm in asymptomatic survivors of lymphoma who have received curative-intent treatment? (Table 3)

Detection of Relapse

Nine studies reported on the follow-up care of asymptomatic survivors of lymphoma who have received curative-intent treatment (5-7,9-13,15). Two studies involving patients with non-Hodgkin lymphoma in complete remission detected a statistically significant difference in number of relapses initially suspected by clinical manifestations (patient-reported symptoms or physical examination) as compared with those initially suspected by imaging before clinical manifestation (10,15). The study reported by Hong et al. (10) assessed the role of routine imaging versus symptom-directed unplanned early outpatient department visits in patients with DLBCL and reported that early visits due to any symptoms or signs have a strong association with the detection of relapse compared with planned visits with or without clinical symptoms or signs (rate: 33% versus 0.5%; $p<0.001$). Similarly, the study reported by Truong et al. (15) found that patient-reported symptoms led to the detection of the majority of relapses in aggressive non-Hodgkin lymphoma (86% versus 14%; $p<0.0001$).

Two additional studies in patients with non-Hodgkin lymphoma detected that the proportion of relapses initially suspected by clinical manifestations ranged from a low of 54% (5) to a high of 78% (11,12), and the proportion of those initially suspected by surveillance imaging ranged from a low of 22% (11,12) to a high of 46% (5).

Three studies involved patients with Hodgkin lymphoma (6,7,13). The study reported by Pingali et al. (13) compared the incidence of relapse between patients managed with clinical surveillance alone versus those who underwent routine surveillance imaging, and reported that differences between groups were not statistically significant (7.4% versus 3.4%; $p=0.39$). The two remaining studies reported that the proportion of relapses in patients initially suspected by clinical manifestations ranged from a low of 13% (6) to a high of 64% (7), and the proportion of those initially suspected by surveillance imaging ranged from a low of 8% (6) to a high of 27% (7).

Overall Survival

Seven studies reported on overall survival outcomes (5,8,10,11,13-15). Six of these studies reported comparable survival rates for relapses initially detected by clinical manifestations and those initially detected by surveillance imaging (5,8,11,13-15).

The study reported by Hong et al. (10) found a median times from relapse to death and overall survival times for 11 patients with relapse initially detected by early unplanned visits (clinical manifestations) of 6.7 and 38.3 months, respectively; but determining whether routine imaging can prolong the survival of relapsed patients was not possible due to the small number (n=4) of patients with relapse initially detected by planned visits with or without routine imaging (3 and 1, respectively). Three of these relapses, detected on planned visits with imaging, had times from relapse to death of 5.7, 7.9, and 9.0 months, and overall survival times of 17.1, 18.9, and 50.2 months; the time from relapse to death and overall survival time of the other patient with relapse detected on a planned visit without routine imaging were 7.6 and 51.9 months, respectively.

Time to Relapse

Four of the studies reported on this outcome (6,12-14). Only the study reported by Lin et al. (12) detected a significant benefit for patients with first presentation of relapse found by

clinical manifestations compared with patients with asymptomatic relapse found by surveillance imaging (mean: 4.5 versus 6.0 months; *p*=0.042). The study conducted by Thompson et al. (14), reported the median times from diagnosis to relapse in asymptomatic patients to be 19 and 11 months in a cohort of patients from the United States and France, respectively; the median time from diagnosis to relapse in patients with clinical manifestations of relapse was not reported. The study conducted by Dann et al. (6) reported median time to relapse of 8.6 months for both patients undergoing routine clinical follow-up and patients undergoing routine clinical follow-up with routine imaging. Pingali et al (13) reported median times to relapse in patients with Hodgkin lymphoma as 33 and 18 months for relapses initially suspected by clinical manifestations and those initially suspected by imaging, respectively.

Frequency of Imaging

Three of the studies reported on frequency of imaging (6,12,13). Two of these studies found that in patients with Hodgkin lymphoma, routine surveillance imaging was statistically significantly associated with a higher number of scans when compared with clinical surveillance. Dan et al. (6), reported that routine imaging required 47.5 imaging studies to detect a single relapse, compared with 4.7 imaging studies in the clinical follow-up arm. The number of imaging studies required per patient in the routine imaging follow-up arm was 3.9 compared with 0.6 in the clinical follow-up arm ($p<0.001$). Similarly, the study conducted by Pingali et al. (13) reported a scan rate in the routine surveillance imaging group to be 4.5 times greater than the rate in the clinical surveillance group (0.89 versus 0.21, respectively; $p<0.0001$); the number of scans performed per relapse detected was 127 in the routine surveillance imaging arm compared with 14.6 scans in the clinical surveillance group.

No statistically significant differences were reported in a study of patients with non-Hodgkin lymphoma conducted by Lin et al. (12). The average number of scans per patient was 3.2 in both groups, the routine surveillance imaging arm and in the arms where relapse was detected by clinical manifestations (*p*=0.749); the mean number of scans per year was reported to be 2.3 and 2.4 for routine surveillance imaging and clinical manifestation, respectively (p=0.423).

Table 3. Clinical activities for detecting clinical recurrence or further hematological neoplasm in asymptomatic survivors of lymphoma who have received curative-intent treatment.

Study [Period]	Study Population and Median Follow-up[Range]	Sample Size Pts in CR	Relapses (n) Method of Relapse Detection	Outcomes [95% CI]
Hong et al. 2014 (10). [May 2004-Feb. 2012]	Patients with DLBCL in CR Follow-up: 30 mo.	856 OPD visits from 106 patients in CR (median 6, range 1-25 visits) Planned Routine Visits: 823 o Imaging: 501 o Without imaging: 322 Unplanned early visits: 33 due to abnormal symptoms	n=15 Planned Visits: 4 Unplanned Visits: 11	**Relapse detection rate** Planned Visits: 0.5% Unplanned Visits: 33% p<0.001 **Overall survival - from Initial therapy** Planned Visits: not calculated (small number of relapses) Unplanned Visits: 38.3 [31.1-45.5] mo. **Overall survival - from relapse** Planned Visits: not calculated (small number of relapses) Unplanned Visits: 6.7 [3.0-10.3]mo.
Pingali et al. 2014 (13) [Jan. 2000-Dec. 2010]	Adult patients with cHL in CR after first-line therapy Follow-up Imaging: 4.1 [0.3-10.7] years Clinical: 4.5 [0.4-10.6] years p=*0.12*	Clinical Surveillance: 67 Imaging Surveillance: 174	n=11 Clinical Surveillance: 5 Imaging Surveillance: 6	**5-year OS** Clinical: 96% [86-99%] Imaging: 97% [92-99%] p=0.41 **5-year Incidence of Relapse** Clinical: 7.4% Imaging: 3.4% p=0.39 **Median time to relapse** Clinical: 33 months Imaging: 18 months p=NR **Number of scans /relapses detected** Clinical: 14.6 scans Imaging: 127 scans p=NR **Scan rate: 4.5 [3.1-5.5]** Clinical: 0.21 scans/year Imaging: 0.98 scans/year p<0.0001

Study [Period]	Study Population and Median Follow-up[Range]	Sample Size Pts in CR	Relapses (n) Method of Relapse Detection	Outcomes [95% CI]
Dann et al. 2013 (6) [2001-2010]	Patients with HL in CR Follow-up: Clinical: 43 mo. Clinical/Imaging: 63 mo.	368 patients Clinical follow-up: 63 treated in NZ. Imaging performed only if suspicions for relapse Routine Imaging (PET/CT or CT): 305 ○ 292 from the Israeli centres ○ 13 from the New Zealand academic centre due to the presence of a residual mass at the end of treatment (CRu)	n=33 Clinical surveillance: 8 Imaging surveillance: 25 ○ Routine Imaging: 17 ○ Dedicated Imaging due to clinical suspicion or inconclusive PET/CT: 8	**Median time to relapse** Clinical: 8.6 [1.3-15.8] mo. Imaging: 8.6 [7-10]mo. **HR** Follow-Up Mode**:** 0.6 [0.3-1.5] *p=0.32* **3-year relapse detection rate** Clinical surveillance: 13% Imaging surveillance: 8% ○ Routine imaging: 6% ○ Imaging due to clinical suspicion of relapse: 6% p=NR **Number of scans/relapse detected** Clinical: 4.75 Scans Imaging: 47.5 Scans p=NR **Number of iImaging tests per patients to detect relapse** Clinical: 0.6 Imaging: 3.9 p<0.001 **3-year PFS** Clinical: 86% Imaging: 93% p=NS
Truong et al. 2014 (15) [2000-2010]	Patients with lymphoid malignancies Follow-up 24 [1-157] mo.	1086 patients	n=84 Clinically: 72 Through patient-reported symptoms or physical examination Imaging Surveillance: 12	**Proportion of relapse detection** Clinical: 86% Imaging: 14% *p<0.0001* **Overall survival** The method of detecting relapse had no effect on overall survival (*p*=0.77)

Study [Period]	Study Population and Median Follow-up[Range]	Sample Size Pts in CR	Relapses (n) Method of Relapse Detection	Outcomes [95% CI]
Cheah et al. 2013 (5) [2002-2009]	Patients with DLBCL - PET-CT scanning Follow-up: 53 [8-133] mo.	116 patients, 450 surveillance PET-CT scans	n=13 Symptomatic: 7 (54%) Asymptomatic: 6 (46%)	**OS postrelapse:** p=0.76
Lin et al. 2012 (12) [2003-2009]	Patients with DLBCL or FL3	341 patients	n=113 DLBCL: 314 FL3: 27 Clinical diagnosis: 88 DLBCL: NR FL3: NR Routine imaging: 25 DLBCL: 22 FL3: 3	**Proportion of relapse detection** Clinical Diagnosis: 78% Routine Imaging: 22% p=NR **Mean time from latest normal CT to relapse** Clinical Diagnosis: 4.5 Routine Imaging: 6.0 p=0.042 **Number of scans/relapse detected** Clinical Diagnosis: 3.2 Routine Imaging: 3.2 p=0.749 **Mean interval of surveillance CT** Clinical Diagnosis: 4.8 Routine Imaging: 4.4 p=0.473 **Mean number of CT/Year** Clinical Diagnosis: 2.3 Routine Imaging: 2.4 p=0.423
Goldschmidt et al. 2011 (9)	Patients with HL or aNHL in CR HL: 42 aNHL: 83 DLBCL: 81 PeripheralT-cell:1 Lymphoblastic: 1	NR	n=125 Clinical diagnosis: 78 HL: 20 aNHL: 58 Routine imaging: 47 HL: 22 aNHL: 25	**Proportion of Relapse detection** Overall Clinical: 62% Imaging: 38% HL: Clinical: 16%, Imaging: 17.6% aNHL: Clinical: 46.4%, Imaging: 20%

Study [Period]	Study Population and Median Follow-up[Range]	Sample Size Pts in CR	Relapses (n) Method of Relapse Detection	Outcomes [95% CI]
Liedtke et al. 2006 (11) [1993-2000]	Patients with biopsy confirmed relapse aNHL Follow-up: 5-years	NR	n=108 Clinical symptoms: 84 ○ Self-reported: 78 ○ Routine Exam: 6 Routine imaging: 24 Note: 73 out of 84 relapses were detected by unscheduled imaging due to patient-reported symptoms or abnormal findings on exam. It is not clear how the other 11 relapses were detected or confirmed.	**Proportion of relapses detected** Routine Imaging: 22% Unscheduled Imaging: 78% p=NR **Number of scans/relapse detected** Routine imaging: 3.5 Unscheduled imaging: 2.0 p=NR **Progression free survival** Routine imaging: 34 mo. Unscheduled imaging: 11 mo p=0.12 **5-year oerall survival** Routine imaging: 54% Unscheduled imaging: 43% p=0.13
Dryver et al. (7) 2003 [1990-1999]	Patients with HL relapse Follow-up: 38 [1-120] mo.	109 suspected relapses from 68 patients Suspected by: Patient: 46 Physician: 28 Imaging: 31 Lab Test: 4	True n=22 Clinical Symptoms: 14 ○ Patient Concern: 10 ○ Physician Concern: 4 Routine Imaging: 6 ○ Chest X-ray: 4 ○ Routine CT: 2 Laboratory Test: 2	**Proportion of Relapses Detected** Clinical Symptoms: 64% ○ Patient Concern: 46% ○ Physician Concern: 18% Routine Imaging: 27% ○ Chest X-ray: 18% ○ Routine CT: 9% Laboratory Test: 9% p=NR
El-Galaly et al. 2015 (8) [2007-2012]	Patients with DLBCL in CR Follow-up: 51 mo.	1221 patients LYFO*: 525 SLR†: 696	N/A	**3-year Overall Survival** Danish: 92% Swedish: 91% p=0.7

Study [Period]	Study Population and Median Follow-up[Range]	Sample Size Pts in CR	Relapses (n) Method of Relapse Detection	Outcomes [95% CI]
Thompson et al. 2015 (14). [2002-2009]	Patients with DLBCL in CR Follow-up **MER:** 71 [6-129] mo. **LYON:** 77 [5-162] mo.	**MER Cohort**: 552 **LYON Cohort**: 222	**MER (n=85)** Before Scheduled Visit: 63 due to symptoms Scheduled Visits: 22 • Clinical Features: 13 • Routine Imaging: 9 **LYON (n=55)** Before Scheduled Visit: 28 due to symptoms Scheduled Visit: 18 • Clinical Features: 14 • Routine Imaging: 4	**MER** **Overall survival – DLBCL relapses** Before scheduled Visit: 15 [8-26] mo. Scheduled visits: 21 [11-57] mo. p=0.56 **Median time to DLBCL relapse detected by imaging** 19 [8-46] mo. **LYON** **Overall survival – DLCBL relapses** Before Scheduled visit: 12 [3-22] mo. Scheduled visits: 19 [3-82] months *p=0.25* **Median time to DLBCL relapse detected by imaging** 11 [7-16] mo.

AML (acute myeloid leukemia); aNHL (aggressive non-Hodgkin lymphoma); BCC (parotid basal cell carcinoma); cHL (classical Hodgkin Lymphoma); CI (confidence interval); CMR (complete metabolic response); CR (complete remission); CRu (complete remission unconfirmed); CT (computed tomography); DLBCL (diffuse large B-cell lymphoma); FFP (freedom from progression); FL3 (follicular lymphoma grade 3); FPR (false positive rate); HL (Hodgkin lymphoma); HR (hazard ratio); MER (Molecular Epidemiology Resource); mo (months); NPV (negative predicted value); NR (not reported); NS (not significant); NZ (New Zealand); OPD (outpatient department); OS (overall survival rate); PET (positron emission tomography); PFS (progression-free survival rate); PPV (positive predicted value); Pts (patients); R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone); SN (sensitivity); SP (specificity); SUV (standardized uptake values) TRD/TRM (time from relapse to death).

[*] Danish Lymphoma Group Registry
[†] Swedish Lymphoma Registry

Question 2: What is the appropriate frequency and timing for the clinical activities that have been shown to be effective at detecting clinical recurrence or further hematological neoplasm (malignancy) in asymptomatic survivors of lymphoma who have received curative-intent treatment?

The literature search did not return any study specifically designed to evaluate the effectiveness of different frequencies and timings of follow-up schedules on asymptomatic survivors of lymphoma who have received curative-intent treatment. However, the nine studies that were discussed while addressing the research question 1 listed the follow-up schedules used by the institutions from which each population was selected and their relationship with relapse detection. Eight of these studies described the follow-up schedules used by single institutions (5-7,9,10,12,14,15). The study reported by El-Galaly et al (8) described the follow-up schedule of two neighbouring Scandinavian countries with similar health care systems but completely different traditions for routine imaging: Denmark and Sweden. The majority of the studies reported a clinical follow-up every two to three months for the first two years, then every four to six months for the following three years (years 3-5), with annual visits afterwards. Surveillance imaging was mainly performed in cases where relapse was suspected. A full description of the follow-up schedules reported by each study is presented in Table 4.

Table 4. Frequency and timing of clinical activities for detecting clinical recurrence or further hematological neoplasm in asymptomatic survivors of lymphoma who have received curative-intent treatment.

Study [country]	Protocols / Follow-up Frequency
Hong et al. (10) [South Korea]	**Clinical visits:** history, physical, CBC • First 2 years: Every 2-3 months • Years 3-5: Every 4-6 months • Years 5+: Annually **Scans (CT or FDG-PET/CT)** – At discretion of the attending physician
Dann et al. (6) [Israel, New Zealand]	**Arm 1: Clinical surveillance** • First 3 years: Every 3-4 months • Year 3-5: Every 6 months • Imaging: Only when clinical findings suspicious for relapse **Arm 2: Imaging surveillance** Clinical surveillance and imaging as follows: • First 2 years: Every 6 months • Year 3: Once
Truong et al. (15)	**Clinical visits and laboratory analysis**

Study [country]	Protocols / Follow-up Frequency
[USA]	• First 2 years: Every 3-4 months • Years 3-5: Every 6 months • Years 5+: Annually **Surveillance scans (PET/CT or CT) – routinely performed** • First year: Every 4 months • Year 2: Every 6 months • Years 3-5: Annually
Cheah et al. (5) [Australia]	**Surveillance imaging (PET/CT)** • First 2 years: Every 6 months • Years 3-5: Annually
Lin et al. (12) [Taiwan]	**Clinical visits and laboratory analysis** (blood count with a differential, serum lactate dehydrogenase, and serum beta 2-microglobulin) • First 2 years: Every 1-3 months **Surveillance Imaging (CT) – Routinely Performed** (head, neck, chest, abdomen, and pelvis) • First 2 years: Every 3-6 months or when clinically indicated • Years 3-5: Annually or when clinically indicated
Goldschmidt et al. (9) [Israel]	**Clinical visits** • First 2 years: Every 3-4 months • Years 3-5: Every 6 months • Years 5+: Annually **Surveillance imaging (CT, PET, or PET/CT)** • First 2 years: Every 6 months • End of year 3**:** Once
Dryver et al. (7) [Canada]	**Clinical visits** – Clinical assessment (history and physical), a chest x-ray, CBC • First 2 years: Every 3 months • Years 3-5: Every 6 months • Years 5+: Annually **Surveillance scans** – At the discretion of the treating physician • X-ray: Conducted during the clinical visits

Study [country]	Protocols / Follow-up Frequency	
El-Galaly et al. (8) [Denmark, Sweden]	**DENMARK**	**SWEDEN**
	Clinical visits – Symptom assessment, clinical examination, blood test	
	• First 2 years: Every 3 months • Years 3-5: Every 6 month	• First 2 years: Every 3-4 months • Year 3: Every 6 months • Years 4-5: Annually
	Surveillance Scans (CT) –Neck, thorax, abdomen	
	• First 2 years: Every 6 months According to a survey among attending lymphoma specialists from 6 large Danish hematology centres, all hematologists prescribed routine CT scans during the first 2 years of follow-up: • CT every 6 months for 2 years: 94% • CT annually for 1 or 2 years: 6% Prescribed CT after the second year of follow-up: 15%	• Only if relapse is clinically suspected In Sweden, routine imaging for DLBCL in CR is discouraged by the national guidelines, and in a survey of the 10 major hematology/oncology centres covering >90% of the total Swedish lymphoma population, all centres reported adherence to the guidelines
Thompson et al. (14) [USA, France]	**USA - MER Cohort**	**FRANCE - LYON Cohort**
	Clinical Visits	
	• First 3 years: Every 6 months • Years 3+: Annually	• First 2 years: Every 3 months • Years 3-5: Every 6 months • Years 5+: Annually
	Surveillance Scans (CT)	
	Not reported	• First year: At 6 and 12 months (frequency of CT scan adapted to the initial stage and prognostic score)

CBC (complete blood count); CR (complete remission); DLBCL (diffuse large B-cell lymphoma); FDG-PET/CT (fluorodeoxyglucose-positron emission tomography/computed tomography); CT (computed tomography); PET (positron emission tomography).

Question 3: What surveillance procedures have been shown to be effective at detecting therapy-related secondary malignancies in asymptomatic survivors of lymphoma who have received curative-intent treatment?

The literature search did not return any study specifically designed to evaluate follow-up schedules to detect therapy-related secondary malignancies in asymptomatic survivors of lymphoma who have received curative-intent treatment. Documentation of therapy-related

secondary malignancies may be more available in the radiation safety literature rather than in the lymphoma diagnosis and/or follow-up literature.

DISCUSSION

There is accumulating descriptive literature that suggests that patients with lymphoma treated with curative intent who achieve complete remission (CR) may not benefit from routine surveillance with diagnostic imaging. Currently, routine surveillance protocols, often informed by clinical trials protocols and local practice culture, include history, physical examination, blood tests, and imaging. Surveillance investigations are based on the presumption that early detection of recurrence may improve the outcomes of patients in CR because of a higher likelihood of successful response to salvage therapy due to lower clinical burden. It is also recognized that certain therapies may be associated with a predictable incidence of late organ adverse effects, such as heart disease or second cancers, and some routine testing is directed toward monitoring of the development of these complications. In this review, we sought to examine the evidence for surveillance and toxicity screening in this population.

Currently, no Canadian consensus document exists to set out the optimal follow-up care for asymptomatic survivors of lymphoma who have received curative-intent treatment. This evidence summary was framed by three areas of inquiry: clinical activities to detect relapse, the frequency and timing of clinical activities to detect relapse, and activities to detect therapy-related secondary malignancies in survivors of lymphoma.

Eleven retrospective studies were identified that specifically reported on surveillance activities to detect recurrence. Complete remission was mainly defined by CT scan criteria. In the majority of studies, a planned imaging approach, most often with computed tomography (CT) scans, was compared with imaging that was carried out in response to signs and symptoms. The study populations included aggressive histology NHL and Hodgkin lymphoma of stages I through III. There were no prospective comparisons found. In all studies, no significant differences were found between planned versus unplanned visit on survival, our key outcome of interest. Unfortunately, since all nonrandomized studies carry an unclear risk of bias, the quality of the evidence supporting this summary is low.

There is a lack of consistent evidence to support routine imaging surveillance in survivors of lymphoma who have been treated with curative intent, and who are considered to be in remission at the completion of all planned therapy. It was noted in many of the studies that even on the planned surveillance arms of the studies, the majority of relapses were detected in the interval between planned imaging appointments, most often initiated by signs and symptoms reported by the patients.

We also reviewed the clinical visit schedules reported in the trials. In nine studies, the timing of clinical visits was described. We were unable to find neither any studies that compared routine clinical visits with visits only in response to symptom, nor any comparison of the use of routine blood work versus blood work at the discretion of the treating oncology team, and therefore, no clinical visit schedule was described. The majority of the studies reported a clinical follow-up every two to three months for the first two years, then every four to six months for the following three years (years 3-5), with annual visits afterwards. Surveillance imaging was mainly performed in cases of suspected relapse. It is recognized that most relapses will occur in the first two to three years after completion of therapy and this is reflected in a clinical visit pattern that was fairly consistent between studies. This pattern is similar to the 2015 National Comprehensive Cancer Network (NCCN) guideline (16); the follow-up of patients with Hodgkin lymphoma should be mainly based on interim history and physical examination; CT scans are acceptable once during the first 12 months, and should be clinically prompted afterwards. Similarly, the 2015 NCCN guideline (17) for patients with non-Hodgkin lymphoma recommends mainly clinical follow-up with imaging only as clinically indicated for patients with

DLBCL stages I and II, and no more often than every six months for the first two years and as clinically indicated afterwards in patients with DLBCL stages III and IV. We cannot comment specifically on the added value of blood work in surveillance testing but there may be other reasons to monitor blood work, particularly after chemotherapy to assess for adverse effects; this continues to be at the discretion of the treating oncology team.

Finally, we are unable to comment on the surveillance for second malignancies in survivors of treated lymphoma as no studies were found to specifically address this issue. We recognize that there are population studies that describe risks of second malignancies such as breast cancer in young women treated with chest radiation that can be considered in the development of follow-up guidelines.

CONCLUSION

The evidence does not support that routine diagnostic imaging result in improved outcomes in asymptomatic survivors of lymphoma who were treated for cure and were in a complete response at the completion of planned treatment.

Prospective studies are required to first characterize the nature of follow-up visits as they are currently practiced. Subsequently they could evaluate the multiple aspects of follow-up for this patient population. Such studies should address what components of a follow-up visit are of value from the perspective of both the health care system and the patients.

INTERNAL REVIEW

The evidence summary was reviewed by the Director of the PEBC. This evidence summary was also reviewed by Dr. Tom Kouroukis, Provincial Hematology Disease Site Lead at Cancer Care Ontario; Dr. Julian Dobranowski, Provincial Head of CCO's Cancer Imaging Program; Dr. Blair Macdonald, Gastrointestinal and Genitourinary Radiologist at the Ottawa Hospital; and the members of the Hematology Cancer Disease Site Group. Information regarding members of the Hematology Cancer Disease Site Group can be found in Appendix 5. The Working Group is responsible for ensuring the necessary changes are made.

Approval by Cancer Survivorship Program

After internal review, the report was presented to the Cancer Survivorship Program. Members of the Cancer Survivorship Program previously reviewed the document, and formally approved the document (March 17th, 2016).

ACKNOWLEDGEMENTS

The Cancer Survivorship Program and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Sheila McNair, Hans Messersmith, Caroline Zwaal for providing feedback on draft versions.
- Julian Dobranowski, Tom Kouroukis, Blair Macdonald and members of the Hematology Cancer Disease Site Group for reviewing the document.
- Elizabeth Chan for conducting a data audit.
- Janet Rowe for copy editing.

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Appendix 1: Members of the lymphoma follow-up working group

Name	Affiliation
Jonathan Sussman Working Group Chair Radiation Oncologist	Division of Radiation Oncology Juravinski Cancer Centre Hamilton, Ontario
Matthew Cheung Hematologist	Odette Cancer Centre Sunnybrook Health Sciences Centre Toronto, Ontario
Lisa Hicks Hematologist	Division of Hematology/Oncology St. Michael's Hospital Toronto, Ontario
Laura Jimenez-Juan Radiologist	Department of Medical Imaging Sunnybrook Health Sciences Centre Toronto, Ontario
Danny Kraftcheck Regional Primary Care	Provincial Primary Care and Cancer Network Hamilton Niagara Haldimand Brant Hamilton, Ontario
Angela Boudreau Registered Nurse	Odette Cancer Centre Sunnybrook Health Sciences Centre Toronto, Ontario
Jonathan Mandel Radiologist	Department of Diagnostic Imaging and Nuclear Medicine Oakville Trafalgar Memorial Hospital Oakville, Ontario
Graeme Fraser Hematologist	Division of Malignant Hematology Juravinski Cancer centre Hamilton, Ontario
Robin McQuillan Patient Representative	Cancer Care Ontario Patient and Family Advisor Toronto, Ontario
Shawn Sajkowski Patient Representative	Cancer Care Ontario Patient and Family Advisor Toronto, Ontario
Norma Varela Health Research Methodologist	Program in Evidence-Based Care, McMaster University Hamilton, Ontario

Appendix 2: Conflict of interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors and internal reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest. Nine authors declared no conflicts of interest, and two (JM, LH) declared conflicts. JM reported a potential conflict because if lymphoma imaging indications were to become more liberal, his income as radiologist could potentially increase by more than $10,000. JM also declared that he had received $5,000 or more in a single year, plus other research support from SIEMENS, and he had been principal investigator for a clinical trial involving PET/MR studies. LH declared that she had been a co-principal investigator on a CIHR-industry grant from Gilead Sciences.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this evidence summary, in accordance with the PEBC COI policy. To obtain a copy of the policy, please contact the PEBC office by e-mail at ccopgi@mcmaster.ca.

Appendix 3: Literature Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 exp Lymphoma/ (152067)
2 (malignan$ adj5 lymphoma$).tw. (18875)
3 1 or 2 (156723)
4 second* primary tumo?r*.mp. (1100)
5 (detect* adj2 relapse*).ti,ab. (985)
6 (early adj2 detect*).ti,ab. (57377)
7 exp Neoplasms, Radiation-Induced/ (17848)
8 exp disease-free survival/ (49447)
9 recurrence-free survival.mp. (6348)
10 exp lymphatic metastasis/ or exp neoplasm recurrence, local/ or exp neoplasm regression, spontaneous/ or exp neoplasm, residual/ (162901)
11 follow-up.ti. (76832)
12 surveillance.ti. (30124)
13 aftercare.ti. (688)
14 evaluation.mp. and follow-up.ti. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9360)
15 long term care.ti. (7935)
16 exp Neoplasms, Second Primary/ (11094)
17 survivors.ab,ti. (61837)
18 or/4-17 (449523)
19 exp clinical chemistry tests/ or exp hematologic tests/ (352956)
20 diagnostic imaging/ or exp tomography, x-ray computed/ or tomography/ (366060)
21 or/19-20 (716528)
22 3 and 18 and 21 (1046)
23 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1986428)
24 22 not 23 (1002)
25 limit 24 to english (817)
26 animals/ (5564286)
27 humans/ (14304076)
28 26 not 27 (4001326)
29 25 not 28 (798)
30 limit 29 to yr="2000 -Current" (512)
31 remove duplicates from 30 (496)

Database: Embase <1996 to 2015 Week 35>
Search Strategy:
---

1 exp lymphoma/ (156567)
2 (malignan$ adj5 lymphoma$).tw. (12734)
3 or/1-2 (158354)
4 second* primary tumo?r*.mp. (1076)
5 (detect* adj2 relapse*).ti,ab. (1327)
6 (early adj2 detect*).ti,ab. (62554)
7 exp radiation induced neoplasm/ or exp disease free survival/ or exp recurrence free survival/ or exp lymph node metastasis/ or exp tumor recurrence/ or exp tumor regression/ or exp minimal residual disease/ or exp second cancer/ (189706)
8 follow-up.ti. (70226)
9 surveillance.ti. (29572)
10 aftercare.ti. (547)
11 evaluation.mp. and follow-up.ti. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (9788)
12 long term care.ti. (5744)
13 survivors.ti. (16502)
14 or/4-13 (367701)
15 exp clinical chemistry/ or exp blood examination/ (160148)
16 diagnostic imaging/ or exp computer assisted tomography/ (646633)
17 or/15-16 (794270)
18 3 and 14 and 17 (1772)
19 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1890233)
20 18 not 19 (1637)
21 limit 20 to english (1506)
22 animals/ (735436)
23 humans/ (11060548)
24 22 not 23 (506080)
25 21 not 24 (1504)
26 limit 25 to yr="2000 -Current" (1454)

Appendix 4: Quality assessment for included studies

Reference [Country]	Lymphoma Type & Sample Size (n)	Outcome Criteria	Recruitment Method	Comparison Type	Intervention	Source of Funding	Comments
Hong et al. 2014 (10) [South Korea]	n=856 OPD visits from 106 patients Planned: 823 Unplanned:33	Relapses suspected by routine imaging vs clinically suspected/ unplanned early visit	Single institution: the Gachon University Gil Medical Center	Between follow-up groups of survivors who relapse	Planned OPD visits vs Unplanned early visit due to abnormal symptoms or signs	Not reported	Seven patients received autologous SCT as consolidative therapy
Pingali et al. 2014 (13) [USA]	cHL n=241 Follow-up: Clinical: 67 Imaging: 174	Relapses suspected by routine imaging vs clinical surveillance	Three academic tertiary care medical centres: the Medical College of Wisconsin (Milwaukee, Wisconsin), the University of Nebraska Medical Center (Omaha, Nebraska), and the Washington University School of Medicine (St. Louis, Missouri)	Between follow-up groups of survivors who relapse	Imaging surveillance vs clinical surveillance	The Donald J. Schuenke Cancer Fe llowship	All but 1 relapsed patient underwent autologous SCT as part of the salvage therapy (2nd line therapy)

Reference [Country]	Lymphoma Type & Sample Size (n)	Outcome Criteria	Recruitment Method	Comparison Type	Intervention	Source of Funding	Comments
Dann et al., 2013 (6) [Israel, New Zealand]	cHL n=368 Follow-up: Clinical: 63 Imaging: 305	Relapses suspected by clinical follow-up vs imaging-based approach	Three medical centres: Rambam Health Care Campus (Haifa, Israel), Hadassah-Hebrew University Medical Centre (Jerusalem, Israel), and Auckland Medical Centre (Auckland, New Zealand)	Between follow-up groups of survivors who relapse	Imaging surveillance vs clinical surveillance	Not Reported	Study population include 14 patients with CRu in the imaging group
Truong et al. 2014 (15) [USA]	NHL n=1086	Relapses suspected by clinical follow-up vs surveillance Imaging	Single institution: Osborn Hematopoietic Malignancy and Transplantation Program, West Virginia University, United States	Between follow-up groups of survivors who relapse	Imaging surveillance vs clinical surveillance	Not Reported	
Cheah et al. 2013 (5) [Australia]	DLBCL n=116	Symptomatic vs asymptomatic relapses	Single institution: Peter MacCallum Cancer Centre, Melbourne, Australia	Between groups of symptomatic and asymptomatic patients who relapse	Imaging surveillance vs clinical symptoms	A grant from the Victoria Cancer Agency and a New Investigator Scholarship, awarded by the Haematology Society of Australia and New Zealand	Seven patients received SCT as part of the salvage therapy (2nd line therapy)

Reference [Country]	Lymphoma Type & Sample Size (n)	Outcome Criteria	Recruitment Method	Comparison Type	Intervention	Source of Funding	Comments
Lin et al. 2012 (12) [Taiwan}	DLBCL and FL3 n=341	Asymptomatic imaging-detected relapses vs symptomatic imaging-detected relapses	Single institution: The Chang Gung Memorial Hospital, Taipei, Taiwan	Between follow-up groups of survivors who relapse	Imaging surveillance vs clinical symptoms	Department of Health, Taiwan (grant number: DOH99-TD-C-111-006)	Study population included 21 patients with CRu (8 in the imaging group and 13 in the clinical/symptomatic group). Sixteen patients received SCT as part of the salvage therapy (2nd line therapy)
Goldschmidt et al. 2011 (9) [Israel]	HL, aNHL (DLBCL) n= NR	Clinically suspected vs imaging findings	Single institution: Hadassah-Hebrew University Medical Centre, Jerusalem, Israel	Between follow-up groups of survivors who relapse	Clinical surveillance vs imaging surveillance	Not Reported	Forty-seven patients received SCT as part of the salvage therapy (2nd line therapy)
Liedtke et al. 2006 (11) [USA]	aNHL n= NR	Clinically suspected by routine imaging vs unscheduled imaging	Single institution: Memorial Sloan-Kettering Cancer Centre, New York, USA	Between follow-up groups of survivors who relapse	Routine imaging vs clinical symptoms (patient-reported symptoms or findings on routine exam)	A fellowship from the Lymphoma Research Foundation	Eighty-eight patients received SCT as part of the salvage therapy (2nd line therapy)
Dryver et al. 2003 (7) [Canada]	HL	Clinically suspected vs	Single centre: Toronto Sunnybrook Regional Cancer	Between follow-up groups of	Clinical symptoms vs routine imaging vs	Not Reported	

Reference [Country]	Lymphoma Type & Sample Size (n)	Outcome Criteria	Recruitment Method	Comparison Type	Intervention	Source of Funding	Comments
	109 suspected relapses from 68 patients	imaging suspected	Centre, Toronto, ON, Canada	survivors who relapse	laboratory test		
El-Galaly et al. (8) [Denmark, Sweden]	DLBCL n=1221 LYFO*: 525 SLR†: 696	Routine follow-up with imaging vs routine follow-up without imaging: Denmark vs Sweden	Two population-based registries: The Danish Lymphoma Group Registry LYFO and the Swedish Lymphoma Registry SLR.	Between two national follow-up policies for survivors who relapse	Sweden vs Denmark follow-up practice for patients with DLBCL in CR	Not Reported	No validated the number of people who actually got imaging in each country; therefore, results from this study refers to differences in policies between Sweden & Denmark for the follow-up of patients with DLBCL in CR
Thompson et al. 2015 (14) [USA, France]	DLBCL MER=552 LYON=261	Relapses suspected due to symptoms vs those detected on scheduled visits	Two centres: The Molecular Epidemiology Resource of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of research Excellence, USA (MER); and the Léon Bérard Cancer Center, Lyon, France (LYON)	Between follow-up groups of survivors who relapse	Scheduled vs unscheduled visits	The Lymphoma SPORE [CA P50 CA97274], Predolin Foundation, Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, and the Arnold and Kit Palmer Benefactor Award	

aNHL (aggressive non-Hodgkin lymphoma); cHL (classical Hodgkin lymphoma); CRu (complete remission unconfirmed); DLBCL (diffuse large B-cell lymphoma); FL3 (follicular lymphoma grade 3); HL (Hodgkin lymphoma); MER (Molecular Epidemiology Resource); NHL (non-Hodgkin lymphoma); OPD (outpatient department);SCT (stem-cell transplantation).

* Danish Lymphoma Group Registry
† Swedish Lymphoma Registry

Appendix 5: Members of the Hematology Cancer Disease Site Group

Name	Affiliation
Michael Crump Working Group co-chair	Princess Margaret Hospital, Toronto, Ontario
Jordan Herst Working Group co-chair	Northeastern Ontario Regional Cancer Centre at Sudbury Regional Hospital, Sudbury, Ontario
Fulvia Baldassarre Health Research Methodologist	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario
Janet MacEachern Hematologist/oncologist	Grand River Regional Cancer Centre, Kitchener, Ontario
Jonathan Sussman Radiation Oncologist	Juravinski Cancer Centre, Hamilton, Ontario
David Hodgson Radiation Oncologist	Princess Margaret Hospital, Toronto, Ontario
Matthew Cheung Hematologist /oncologist Disease Site Group co-chair	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, Ontario
Patricia Disperati Hematologist/oncologist	Toronto East General Hospital, Toronto, Ontario
Graeme Fraser Hematologist / internist	Juravinski Cancer Centre, Hamilton, Ontario
David Robinson Patient Representative	Sudbury
Robert Stevens Hematologist/oncologist	Grand River Regional Cancer Centre, Kitchener
Nicole Laferriere Hematologist/ internist	Northwestern Ontario Regional Cancer Centre at Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario
Yael Zaretski Hematologist / internist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, Ontario
Jason Tay Hematologist	Ottawa Hospital-General Campus, Ottawa, Ontario
Leonard Minuk Hematologist	London Health Sciences, London Cancer Centre, London, Ontario
Mitchell Sabloff	Ottawa General Hospital, Ottawa
Irwin Walker Hematologist / internist	McMaster University Medical Centre, Hamilton, Ontario
Sindu Kanjeekal Hematologist/oncologist	Windsor Regional Cancer Centre at Windsor Regional Hospital, Windsor, Ontario

Andrea Lee Hematologist	1060 Speers Road, Suite 118, Oakville, Ontario
Ivan Tyono Pharmacist	Odette Cancer Centre at Sunnybrook Health Sciences Centre, Toronto, Ontario
Lisa Hicks Hematologist/internist	St. Michael's Hospital, Toronto, Ontario
Tom Kouroukis Hematologist/internist	Juravinski Cancer Centre, Hamilton, Ontario
André Schuh Hematologist/internist	Princess Margaret Hospital, Toronto, Ontario
Chris Bredeson Hematologist/internist	The Ottawa Hospital General Campus, Ottawa, Ontario
Melissa Brouwers	McMaster University, Hamilton, Ontario
Shailendra Verma	The Ottawa Hospital Cancer Centre, Ottawa, Ontario
Marko Simunovic	Juravinsky Cancer Centre, Hamilton, Ontario
David McDonald	Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia
Joseph Connors	BC Cancer Agency, Vancouver, British Columbia
Ur Metser	University Health Network, Toronto, Ontario