Comparing the accuracy of quantitative versus qualitative analyses of interim PET to prognosticate Hodgkin lymphoma: a systematic review protocol of diagnostic test accuracy

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ABSTRACT
Introduction: Hodgkin lymphoma is an effectively treated malignancy, yet 20% of patients relapse or are refractory to front-line treatments with potentially fatal outcomes. Early detection of poor treatment responders is crucial for appropriate application of tailored treatment strategies. Tumour metabolic imaging of Hodgkin lymphoma using visual (qualitative) 18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a gold standard for staging and final outcome assessment, but results gathered during the interim period are less accurate. Analysis of continuous metabolic–morphological data (quantitative) FDG-PET may enhance the robustness of interim disease monitoring, and help to improve treatment decision-making processes. The objective of this review is to compare diagnostic test accuracy of quantitative versus qualitative interim FDG-PET in the prognostication of patients with Hodgkin lymphoma.

Methods: The literature on this topic will be reviewed in a 3-step strategy that follows methods described by the Joanna Briggs Institute (JBI). First, MEDLINE and EMBASE databases will be searched. Second, listed databases for published literature (MEDLINE, Tripdatabase, Pedro, EMBASE, the Cochrane Central Register of Controlled Trials and WoS) and unpublished literature (Open Grey, Current Controlled Trials, MedNar, ClinicalTrials.gov, Cos Conference Papers Index and International Clinical Trials Registry Platform of the WHO) will be queried. Third, 2 independent reviewers will analyse titles, abstracts and full texts, and perform hand search of relevant studies, and then perform critical appraisal and data extraction from selected studies using the DATARI tool (JBI). If possible, a statistical meta-analysis will be performed on pooled sensitivity and specificity data gathered from the selected studies. Statistical heterogeneity will be assessed. Funnel plots, Begg’s rank correlations and Egger’s regression tests will be used to detect and/or correct publication bias.

Ethics and dissemination: The results will be disseminated by publishing in a peer-reviewed journal. Ethical assessment will not be needed; only existing sources of literature will be searched.

Trial registration number: CRD42016027953.

INTRODUCTION
Background
Classical Hodgkin lymphoma (cHL) is the most common lymphoid malignancy affecting patients below the age of 30. Incidence rates of cHL in the USA and Central Europe are comparable, with 2.7 new cases per 100 000 men and women per year, and rates trending upwards.1,2 Despite high cure rates and effective treatments for cHL, 20% of patients relapse or are refractory to front-line therapies. About 15% of these patients die within 5 years of diagnosis.3 Overall outcomes are unsatisfactory for patients with relapsed/refractory Hodgkin lymphoma (HL) who proceed to high-dose therapies and autologous stem cell transplants (SCTs). About 40–50% of SCT recipients relapse and require additional treatments.4 Given our entry into the era of novel ‘targeted’ drugs and immune modulators, identification of poor front-line treatment responders is a growing concern.5

Implementations of modern imaging methods such as positron emission tomography (PET)/CT have provided the capability to precisely assess tumour metabolic activity concurrent with an exact measurement of tumour burden. HL has been described as ubiquitously 18-fluorodeoxyglucose (18FDG)-avid. Revised response criteria for malignant lymphoma have therefore included tumour metabolic activity as a key parameter for determining remission status. Historically, complete metabolic responses have been assessed visually using either binary (positive/negative) or semiquantitative (Deauville) scales.6,7 FGG-PET is an inherently quantitative method that generates large amounts of metabolic and morphological data. Visual binary and semiquantitative PET analyses do not
include quantitative and volumetric parameters (eg, total metabolic volume (TMV), total lesion glycolysis (TLG) or maximal standardised uptake volume (SUVmax)), and may be observer-biased. Recent studies have encouraged quantitative FDG-PET (QT PET) analyses to serve as novel biomarkers for staging and assessment of early (referred to as interim) and final malignant lymphoma tumour responses to treatments. For example, Rossi and colleagues demonstrated that gated QT PET parameters during the interim period. The systematic review will only include diagnostic cross-sectional studies that perform qualitative FDG-PET (QL PET) or visual evaluation of interim PET as a reference test.

Objective
The objective of this review will be to compare diagnostic test accuracies between quantitative and qualitative interim PET methods with the aim of improving cHL prognostication.

METHODS AND ANALYSIS
Methods
This systematic review protocol was developed according to: (1) the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P), and (2) the Joanna Briggs Institute (JBI) methodology for systematic reviews of diagnostic test accuracy. It has been enrolled with the PROSPERO prospective register of systematic reviews: CRD42016027953.

Study eligibility
Types of participants
The systematic review will consider all studies that investigated adult cHL (determined with the WHO diagnostic criteria), who were treated according to the current international guidelines. Studies that included adolescents (≤18 years old) will be excluded.

Index test
The systematic review will consider all studies that measure one or more of the following as an index test: QT PET, quantitative evaluation of interim FDG-PET by metabolic tumour volume, TLG or SUVmax. Only studies which used standardised international criteria for interim FDG-PET interpretation will be analysed.

Reference test
The systematic review will consider studies that perform qualitative FDG-PET (QL PET) or visual evaluation of interim PET as a reference test.

Diagnosis of interest
The systematic review will consider studies that evaluate prognostic accuracy of QT PET in patients with cHL as calculated by changes in negative and positive predictive values when compared with QL PET.

Types of studies
The systematic review will only include diagnostic cross-sectional study designs.
Search strategy

A search strategy will be developed using medical subject headings (eg, MeSH for MEDLINE) and then adopted to query each database. Keywords related to the overarching topic will also be identified. The search strategy seeks to identify and include both published and unpublished work, and will therefore use a three-step search strategy. First, limited searches of MEDLINE and EMBASE will be undertaken, followed by analyses of keywords contained in the title, abstract and the index terms used to describe an article. Second, all identified keywords and index terms will be searched across all relevant databases. Third, reference lists from the newly identified reports and articles will be searched for additional studies. All studies with title and abstract in English will be considered for inclusion, regardless of the language used in the body of the manuscript. Studies published with no time restriction will also be considered for inclusion.

The databases to be searched include:
- MedLine@Ovid, MEDLINE(R), Tripdatabase, Pedro, EMBASE, Cochrane Central Register of Controlled Trials, CINAHL and Web of Science.
- Searches for unpublished studies will be performed using:
  - Open Grey, Current Controlled Trials, MedNar, ClinicalTrials.gov, Cos Conference Papers Index and International Clinical Trials Registry Platform of the WHO.

Example search strategy (MedLine@Ovid interface):
1. Hodgkin*;
2. Quantitative PET OR Metabolic Tumour Volume OR Total Tumour Glycolysis OR Standardized Uptake Value;
3. Qualitative PET OR Visual evaluation PET OR Visual analysis PET;
4. Diag* OR sensitivity OR specificity OR predictive;
5. 1 AND 2 AND 3 AND 4.

Study records

Literature search results will be compiled and shared by the authorship team using EndNote VX7, enabling collaborative study selection. Two reviewers (VP and JK) will independently screen and select studies for possible inclusion in two phases. First, titles and abstracts will be assessed. Second, all relevant full texts will be analysed. Any disagreements will be resolved by discussion and consultation of a third reviewer (MK), as necessary.

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Data collection process

Data will be independently extracted by two reviewers (VP and MK) from studies included in the review using standardised data extraction tools from JBI-DATARI (see online supplementary appendix II). Extracted data will include characteristics of the populations, index tests, reference tests and the diagnoses relevant to the systematic review objectives. Disagreements will be resolved during team discussions, as necessary.

Data items/dealing with missing data

Both generic and trade names of the index tests will be extracted. Diagnostic accuracy of index versus reference tests will be compared using sensitivity, specificity and receiver operating characteristics (ROC) readouts, as well as patient characteristics (eg, age, gender, given disease). Study authors will be contacted, as necessary, to provide relevant information for comparative assessments.

Outcomes and prioritisation

The primary outcome of this systematic review will be to compare diagnostic and prognostic accuracy of quantitative and qualitative PET results in patients with cHL. We will seek data answering the following specific questions:
1. What was the rate of 5-year progression-free survival (PFS; followed from enrolment through the end of the study period)?
2. What is the predicted rate of treatment failure?

Data synthesis

All available diagnostic data will be pooled into a statistical meta-analysis using JBI-DATARI. Results from the included studies will be subjected to double data entry. Meta-analysis results will be presented with two graphical techniques. First, forest plots will illustrate sensitivity and specificity of each selected primary study by graphing the means and CIs. Means and CIs will also be in numeric form. Additionally, true-positive, false-positive, true-negative and false-negative values will be listed. Second, summary ROC curves will be created. The bivariate model for performing meta-analyses will be used.

Assessment of heterogeneity

Initially, clinical heterogeneity will be assessed by determining whether study inclusion criteria are sufficiently similar to the pooled results. If heterogeneity is found, characteristics of the differing studies will be carefully investigated. If it seems that heterogeneity is due to the existence of specific risks of bias in some studies, then the meta-analysis will be restricted to studies that do not contain those risks. To ensure sensitivity analysis, we will exclude all studies that are appraised as having a high risk of bias.
Subgroup analysis
Subgroup analysis will be used for different age and gender characteristics. Another subgroup analysis will be used for cHL and different comorbidities according to their type and severity. Another subgroup analysis will be used for initial disease stage and type of chemotherapy given. If the data are available in primary studies, we will perform subgroup analysis according to: PFS; standardised PET using Body Phantom experiments.

Metabias assessment
To show potential reporting bias, we will use funnel plots if more than 10 studies are available. Begg’s rank correlation and Egger’s regression tests will be used for detecting and correcting publication bias.

Confidence in cumulative evidence
On the basis of the results and quality of evidence, the ‘Grading of Recommendation Assessment, Development and Evaluation’ (GRADE) tool will be used. Quality of evidence will be assessed across the domains of: risk of bias, consistency, directness, precision and publication bias. Quality will be assessed as: high (further research is very unlikely to alter confidence in the accuracy estimate), moderate (further research will most likely impact confidence in the accuracy estimate, and may change the estimate), low (further research is very likely to impact confidence in the accuracy estimate, and will most likely change the estimate) or very low (the accuracy estimate is very uncertain).

ETHICS AND DISSEMINATION
This systematic review protocol was crafted in February 2016. Next, the systematic review development team will begin performing the protocol described herein. Dissemination of results will be targeted at patients and oncology practitioners through publication in a peer-reviewed journal. Ethical assessment is unnecessary as only existing sources of literature will be queried and evaluated.

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Contributors VP and MK conceptualised and designed the study. All authors contributed to selection criteria development, risk of bias assessment strategy and data extraction. MK, JK and DT were methodologists. VP, VB and TP were Hodgkin lymphoma content experts. All authors (VP, MK, VB, TP) read, provided feedback and approved the final manuscript.

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Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The only data which the authors will miss could be missing data from primary studies. In this case, the authors will contact authors of primary research to ask for sharing the additional data with them.

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