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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 3
METHODS 3
ACKNOWLEDGEMENTS 6
REFERENCES 6
APPENDICES 9
CONTRIBUTIONS OF AUTHORS 11
DECLARATIONS OF INTEREST 11
SOURCES OF SUPPORT 12

[Prognosis Protocol]

Interim PET for prognosis in adults with Hodgkin lymphoma: a prognostic factor exemplar review

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ABSTRACT

This is a protocol for a Cochrane Review (Prognosis). The objectives are as follows:

Primary objective

The objective of this systematic review is to identify all studies evaluating interim PET scan results as a prognostic factor, describe the characteristics and risk of bias of included studies and if possible, meta-analyse results on the association between PET scan results and overall or progression-free survival and adverse events.

BACKGROUND

Description of the condition

Hodgkin lymphoma (HL) is a cancer of the lymph nodes and lymphatic system with possible involvement of other organs such as the liver, lung, bone or bone marrow (Lister 1989). With an annual incidence of approximately two to three per 100,000 inhabitants in Western countries, HL is a comparatively rare disease, but it is one of the most common malignancies in young adults (Howlader 2015). In industrialised countries, the age distribution of HL shows a first peak in the third decade and a second peak after the age of 50 (Thomas 2002).

The World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues distinguishes between two types of HL: classic HL, representing about 95% of all HL, and lymphocyte-predominant HL, representing about 5% of all HL (Swerdlow 2008). Both types differ in morphology, phenotype and molecular features, and therefore in clinical behaviour and presentation (Re 2005).

The Ann Arbor Classification is used for staging and distinguishes between four different tumour stages. Stages one to three indicate the degree of lymph node and localised extranodal organ involvement or both, stage four includes disseminated organ involvement, which can be found in 20% of cases. Factors associated with a poor prognosis include a large mediastinal mass, three or more involved lymph node areas, a high erythrocyte sedimentation rate, extranodal lesions, B symptoms (weight loss > 10%, fever, drenching night sweats) and advanced age, but the factors considered significant vary slightly between different study groups ((German Study Hodgkin Lymphoma Study Group (GSHG), European Organization for Research and Treatment of Cancer (EORTC), and the National Cancer Institute of Canada (NCIC)). The Cotswold modification of the Ann Arbor Classification also takes into consideration the occurrence of bulky disease (largest tumour diameter greater than 10 cm) (Lister 1989). Hodgkin lymphoma is classified into early favourable, early unfavourable and advanced stage (Engert 2007; Klimm 2005). In Europe, the early favourable-stage group usually comprises Ann Arbor stages I and II without risk factors. The early unfavourable-stage group includes individuals with Ann Arbor stages I or II and one or more risk factors. Most individuals with stages IIB, III or IV disease are included in the advanced-stage risk group (Engert 2003).

With cure rates of up to 90%, HL is one of the most curable cancers worldwide (Engert 2010; Engert 2012; Rancea 2013a; von Tresckow 2012). A combination of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) is widely accepted as the standard chemotherapy regimen in early-stage HL (Canellos 1992; Engert 2010). Individuals in this stage usually receive a combination of chemotherapy and involved-field radiation therapy (IF-RT) (Engert 2010; von Tresckow 2012), whereas those with advanced-stage disease receive an intensified regimen, such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) (Bauer 2011; Borchmann 2011; Engert 2012; Skoetz 2013), or ABVD. A large randomised study showed that two cycles of ABVD followed by 20 Gy of IF-RT is sufficient for the treatment of early-favourable HL (Engert 2010), which is implemented into current standard treatment, whereas four cycles of chemotherapy followed by 30 Gy IF-RT is more suitable for individuals with early-unfavourable HL. Approximately 10% of people with HL will be refractory to initial treatment or will relapse; this is more common in those people with advanced stage or bulky disease. These individuals can be treated with high-dose chemotherapy and autologous stem cell transplantation (Rancea 2013).

The current treatment approach for HL is to maximise progression-free and overall survival and to minimise acute and long-term toxicities like cardiac and pulmonary damage, infertility and secondary cancers. Development of a secondary cancer is one of the major causes of morbidity and mortality once the risk of progression and relapse of HL is over, i.e. from about five years after first-line treatment onwards. In a large systematic review based on individual patient data in people with HL, Franklin and colleagues demonstrated that treatment de-intensification by avoiding additional radiotherapy reduces the risk of a secondary cancer (Franklin 2005).

Description of prognostic factor

This protocol for a systematic review of prognostic factors is an exemplar protocol of a new review type within the Cochrane Library. Methods have not been standardised by Cochrane, thus this protocol can serve as an exemplar protocol to be adapted for other research questions.

A prognostic factor is a characteristic of a patient or the disease that is likely to affect patient outcomes or health events, often related to overall survival and disease-free survival. Summaries of prognosis are particularly useful when associated with a treatment strategy, including helping to stratify patients for treatment. However, to arrive to an unbiased and meaningful assessment of prognosis, prognostic factors should be first evaluated in a cohort of patients treated in the same way (i.e. there should be no variation in their treatment based on a 'potential' prognostic factor), and at the same time point of their treatment. It is this differentiation that makes studies of prognosis a challenge to assess and include in a systematic review.

[18F]-fluorodeoxy-D-glucose (FDG)-positron emission tomography (PET, also called PET scanning) is an imaging tool that shows the tumour's metabolic activity, its stage and progression. The principle of FDG-PET is based on a radio-labelled glucose analogue being a good indicator of the glucose metabolism of a tissue. It comprises two parts: a vector (2-deoxy-D-glucose) being taken up by cells with a high metabolic rate, and 18F, a positron-emitting nuclide which is detected by scintigraphy. FDG-PET scanning provides the opportunity to identify the state and degree of progression of FDG-avid tumours and has therefore become a standard imaging tool for various cancers (Boellaard 2010). Hodgkin lymphoma is a FDG-avid tumour; in a study of 233 people with HL, 100% were FDG-avid (Weigler-Sagie 2010).

Over the last few decades FDG-PET has been used more and more for staging, potential prognosis, treatment planning and response evaluation in people with HL, and is a widely accepted procedure (Kobe 2010a; Markova 2009; Specht 2007). Interim FDG-PET scan identifies the state of disease after a few cycles of chemotherapy and it has been suggested to be a good predictor of prognosis, aiding the distinction between patients with poor prognosis from those with a better prognosis, while undergoing early treatment for HL (Gallamini 2007; Kobe 2010; Markova 2012). If we are able to establish the prognostic value of the interim PET, individuals at high risk of progression or relapse will potentially be identified by PET-positivity in interim PET-imaging and might benefit from an intensified therapy. At the same time, the majority of the individuals with a lower risk for relapse may be identified by interim PET-negativity status. This approach of therapy adap-

tation is a fairly new one, introduced after detailed exploration of the FDG-PET procedure (Engert 2012; Kobe 2008). The idea behind this approach is to achieve maximum efficacy in terms of overall survival and progression-free survival, by reducing the rate of long-term adverse events.

A recent Cochrane review on the role of PET-adapted treatment modification for people with HL found some evidence that progression-free survival was decreased in people with early-stage HL and a negative PET scan receiving chemotherapy only (PET-adapted therapy) compared to those receiving additional radiotherapy (standard therapy). However, it is still unclear whether individuals who are PET-positive could benefit from PET-adapted treatment and the effect of such an approach in those with advanced HL, as no randomised controlled trials (RCTs) on these research questions have been published (Sickinger 2015).

Why it is important to do this review

Guidelines by UK-based medical experts and patient representatives stated that interim PET is highly predictive of outcome in patients treated with ABVD (Follows 2014), while the German evidence-based guidelines do not give recommendations regarding interim PET due to limited evidence, but state that the treating physician may, however, have special reasons for requesting interim PET as an aid to therapeutic decision-making (Rancea 2013). Thus, the decision-making process for or against interim PET is usually confusing for patients and physicians, as there are no clear recommendations for a consistent approach in international guidelines. Cancer burden, economic and societal impact are introduced in discussions on the best strategy as patients are usually young and will likely survive, however, they will carry a risk of developing a relapse or secondary malignancies.

To our knowledge, there is one systematic review on the potential prognostic value of interim PET in individuals with HL (Adams 2015). However, this review looked at 'treatment failure' as an outcome of the interim PET scan, which is different to the outcomes the current review will explore. Moreover, and despite the fact that it is entitled as a prognostic review, the methodology used is akin to diagnostic test evaluation (with calculations of diagnostic odds ratio, specificity and sensitivity) rather than using established prognostic methodology and crucially, the confidence in the calculated estimates was not rated. Last but not least, the review included studies published before December 2014, and hence important research published since that time is not included; we are aware of at least four studies (Miltenyi 2015; Rigacci 2015; Simon 2015; Simontacchi 2015), and there may be more. Moreover, the authors of the systematic review did not rate the confidence in the calculated estimates.

As the question of the prognostic role of interim PET is very important and will strongly influence decision-making, we will summarise all data available from identified studies and include a meta-analysis if the primary studies are sufficiently homogeneous. Our aim is to produce robust evidence based on the improved power that a meta-analysis provides over the limitations of individual primary studies, and grade the evidence. A reliable answer to the question of the potential prognostic role of interim PET scan in adults with HL will strongly influence decision-making at a crucial point of patients' treatment pathway. Moreover, the rating of the evidence about the prognostic role of an interim PET scan will provide readers with an estimate of how much they can rely on the calculated results.

The aim of this prognostic factor systematic review is to provide a comprehensive overview on the benefits and harms of interim PET for patients with HL. The meta-analysis and grading of the evidence will allow a conclusion, of whether interim PET is a prognostic factor which results translate into a clinical important difference. This comprehensive overview is necessary for clinical decision-making; it will have a great impact on international guidelines and clinical pathways, and will contribute to a high-grade decision support for effective, supportive strategies for the individual patient.

OBJECTIVES

Primary objective

The objective of this systematic review is to identify all studies evaluating interim PET scan results as a prognostic factor, describe the characteristics and risk of bias of included studies and if possible, meta-analyse results on the association between PET scan results and overall or progression-free survival and adverse events.

METHODS

This protocol for a systematic review of prognostic factors is an exemplar protocol of a new review type within the Cochrane Library. Methods have not been standardised by Cochrane.

Criteria for considering studies for this review

Types of studies

We will include both, retrospective and prospective studies evaluating an interim PET scan in at least 10 individuals with Hodgkin lymphoma (HL) and with at least five individuals with the outcome event.

Participants

We will include studies on adults (males and females aged ≥ 18 years) with histologically-confirmed HL receiving first-line chemotherapy and an interim PET-scan (after two or three cycles of chemotherapy), irrespective of stage of disease.

Types of prognostic factors

We will assess studies with an interim PET scan during first-line treatment without PET-guided treatment adaptation, thus individuals should be treated in the same way regardless of the of the PET scan outcome. For the grade of uptake, a validated scale should be used, such as the 5-PS Deauville criteria (Barrington 2014), the Lugano classification (Cheson 2014), the Imaging Subcommittee of International Harmonization Project in Lymphoma criteria (Juweid 2007) or the joint Italian-Danish study criteria (Gallamini 2007).
We will exclude studies which were published only as abstracts.

Type of outcome measures

Primary outcome

- Overall survival

We will include studies that assess overall survival as an outcome. We chose this outcome because it has the greatest clinical relevance and is most important for individuals with HL. Furthermore, death due to any cause is an objective endpoint not susceptible to be biased by the outcome assessor. To report meaningful findings, the mean follow-up period should be at least 12 months.

Secondary outcomes

- Progression-free survival
- Adverse events

We will include studies that evaluate progression-free survival, as people with HL with similar survival may nevertheless have differing lengths of time without symptoms or requirement for treatment, depending both on initial treatment and disease characteristics. Response is defined as the level of disease regression obtained with front-line treatment (Cheson 2014). Determination of which individuals are less likely to obtain a good response will help with decisions about which individuals might be treated with new, potentially more aggressive treatment strategies.
Adverse events are also considered clinically relevant as further treatment may cause toxicity and other unpleasant effects and PET scan may be used as an indication for treatment decisions.

Search methods for identification of studies

Electronic searches

Reporting and therefore retrieval of prognostic factor studies is very poor, as evaluation of guidelines on reporting of prognostic markers in cancer (Altman 2012; McShane 2005) have shown (Mallett 2010). Moreover, no specific search filter exists for this new methodological approach, therefore published filters have to be combined for a sensitive search strategy (Geersing 2012). However, as PET scans often are not reported as a prognostic factor, we will not combine our search strategy with a filter for prognostic research. Therefore, the search strategy will not be very specific, many hits are expected to be screened in detail by two review authors. We will search Cochrane Central Register of Controlled studies (CENTRAL) and MEDLINE and we will not apply a language restriction to reduce the language bias, according to chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).
We will search the following databases and sources.

- Databases of medical literature
  - CENTRAL latest issue (Appendix 1)
  - MEDLINE (1990 to present) (Appendix 2)
- Databases of ongoing studies
  - The *meta*Register of Controlled studies (*m*RCT) (http://www.controlled-trials.com/mrct/)
  - EU clinical studies register: https://www.clinicalstudiesregister.eu/ctr-search/search
  - Clinicalstudies.gov: https://clinicalstudies.gov/
  - WHO International Clinical studies Registry Platform (ICTRP)
- Conference proceedings of annual meetings of the following societies for abstracts (2000 to present)
  - American Society of Hematology
  - American Society of Clinical Oncology
  - European Hematology Association
  - International Symposium on Hodgkin Lymphoma

Searching other resources

- Handsearching of references
  - References of all identified studies, relevant review articles and current treatment guidelines for further literature

- Personal contacts
  - Authors of relevant studies, study groups, experts and investigators from transplantation centres worldwide who are known to be active in the field will be contacted for unpublished material or further information on ongoing studies

Data collection and analysis

Selection of studies

Two review authors (or, in case of large number of studies yielded by the search, then teams of two reviews authors at a time) will independently screen the results of the search strategies for eligibility for this review by reading the abstracts. In the case of disagreement the full-text publication will be obtained. If no consensus can be reached, we will ask a third review author (Higgins 2011).
We will document the results in a flow chart as recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher 2009), showing the total numbers of retrieved references and the numbers of included and excluded studies.

Data extraction and data management

Two review authors will independently extract the data, according to the adapted CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) and QUIPS (Quality In Prognosis Studies) checklists (Hayden 2013; Moons 2014) to investigate both, the reporting and the use of methods known to influence the quality of prognostic factor studies. We will contact authors of individual studies for additional information, if required. We will use a standardised data extraction form containing the following items.

- General information
  - Author, title, source, publication date, country, language, duplicate publications
- Source of data
  - (e.g., cohort, prospective planned study, randomised study participants, or registry data)
- Participants
  - Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centres, setting, inclusion and exclusion criteria)
  - Participant description (e.g. age, gender, stage of disease)
  - Details of treatments received
  - Study dates
- Prognostic factor
  - Definition and method for measurement of prognostic factor
  - Timing of prognostic factor measurement (number of chemotherapy cycles before and after measurement of the prognostic factor)
- Outcomes to be predicted
  - Definition and method for measurement of outcome
  - Was the same outcome definition (and method for measurement) used in all individuals?
  - Was the outcome assessed without knowledge of the prognostic factor (i.e. blinded)?
  - Time of outcome occurrence or summary of duration of follow-up
- Sample size
  - Number of participants and number of outcomes/ events
- Missing data
  - Number of participants with any missing value (include predictors and outcomes)
  - Handling of missing data (e.g., complete-case analysis, imputation, or other methods)
- Reported results
  - Overall survival (including duration of follow-up)
  - Progression-free survival (including duration of follow-up)

Assessment of methodological quality

For quality assessment of the prognostic role of interim PET we will use the QUIPS tool (Hayden 2013). Two review authors will independently assess the risk of bias for each study using the following items with the criteria mentioned in the QUIPS tool.

- Study participation
  - Does the study sample adequately represent the population of interest?
- Study attrition
  - Does the study data available (i.e. participants not lost to follow-up) adequately represent the study sample?
- Prognostic factor measurement
  - Is the prognostic factor measured in a similar way for all participants?
- Outcome measurement
  - Is the outcome of interest measured in a similar way for all participants?
- Study confounding
  - Are important potential confounding factors are appropriately accounted for?
- Statistical analysis and reporting
  - Is the statistical analysis appropriate, and are all primary outcomes reported?

We will make a judgement for every criterion, using one of the following three categories.

- 'Low risk': if the criterion is adequately fulfilled in the study, i.e. the study is at a low risk of bias for the given criterion.
- 'High risk': if the criterion is not fulfilled in the study, i.e. the study is at high risk of bias for the given criterion.
- 'Unclear': if the study report does not provide sufficient information to allow for a clear judgement or if the risk of bias is unknown for one of the criteria listed above.

Discussing reporting deficiencies

Methods and reporting in prognostic research often do not follow current methodological recommendations, limiting retrieval, reliability and applicability of these publications (Bouwmeester 2012; Peat 2014). There are some hints that prognosis research in cancer is cluttered with false-positive studies which would not have been published if the results were negative (Kyzas 2005; Kyzas 2007; Sauerbrei 2005). Moreover, studies evaluating prognostic factors are usually not prospectively registered and no protocol is published (Riley 2013; Peat 2014), making it difficult to identify all studies and assess potential risk of publication bias. We will use sensitive search filters for the disease (HL) and the prognostic factor (PET-scan) without any specific filter for prognostic research to increase retrieval.

Due to the expected large effect of odds ratios (ORs), tests for funnel plot asymmetry could result in publication bias being incorrectly indicated by the test far too often (Macaskill 2010). As a result of this, we will not evaluate risk of publication bias by funnel plot asymmetry, but describe potential reporting deficiencies.

Data synthesis

For overall survival and disease-free-survival, we will only pool hazard ratios (HRs), if adjusted analyses were based on the same co-variates, otherwise we will not pool data. We will stratify results across treatments as treatments may differ between patients. For meta-analyses, we will use the inverse variance method and random-effects model. Where a value of an HR is not available, we will attempt to estimate it using available data, and according to the methods suggested by Tierney and colleagues (Tierney 2007). Where we consider the data sufficiently similar to be combined, we will pool results by applying meta-analyses using the fixed-effect model, and the random-effects model as a sensitivity analysis. If the studies are clinically too heterogeneous to combine, we will show results without calculating an overall estimate. We will perform analyses according to the recommendations of Cochrane and will use the Cochrane statistical package Review Manager 5 for organising the text of the review, and where possible for the meta-analysis (Deeks 2011; Review Manager (RevMan)).

Grading the evidence

According to recommendations from the GRADE working group, we will rate and describe the confidence in estimates for each outcome by assessing potential risk of bias, inconsistency, imprecision, indirectness and publication bias. We will apply the adapted approach to rate the quality of prognostic factor evidence (Huguet 2013) to summarise the evidence of overall survival, progression-free survival, and adverse effects.

Investigation/description of heterogeneity

We will investigate and discuss clinical and statistical heterogeneity and design aspects of included studies mentioned in the section data extraction and data management. We will assess between-study heterogeneity using the I^2 statistic (I^2 greater than 30%, moderate heterogeneity; I^2 greater than 75%, considerable heterogeneity) (Deeks 2011). We will explore potential causes of heterogeneity by sensitivity (study design (prospective versus retrospective) and risk of bias (high versus low) and subgroup analyses (disease stage (early, intermediate, advanced), type of chemotherapy, and type of radiotherapy).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials search strategy

ID Search
#1 MeSH descriptor: [Lymphoma] this term only
#2 MeSH descriptor: [Hodgkin Disease] explode all trees
#3 Germinoblastom*
#4 Reticulolymphosarcom*
#5 Hodgkin*
#6 (malignan* near/2 (lymphogranulom* or granulom*))
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Positron-Emission Tomography] explode all trees
#9 (pet* or petscan*)
#10 tomograph*
#11 emission*
#12 MeSH descriptor: [Deoxyglucose] explode all trees
#13 MeSH descriptor: [Fluorodeoxyglucose F18] explode all trees
#14 (deoxyglucose* or desoxyglucose* or deoxy-glucose* or desoxy-glucose* or deoxy-d-glucose* or desoxy-d-glucose* or 2deoxyglucose* or 2deoxy-d-glucose* or fluorodeoxyglucose* or fluorodesoxyglucose* or fludeoxyglucose* or fluordeoxyglucose* or fluordesoxyglucose* or 18fluorodeoxyglucose* or 18fluorodesoxyglucose* or 18fluordeoxyglucose* or fdg* or 18fdg* or 18f-dg*)
#15 (fluor* or 2fluor* or fluoro* or fluorodeoxy* or fludeoxy* or fluorine* or 18f* or 18flu*)
#16 glucose*
#17 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #7 and #17 in trials

Appendix 2. MEDLINE Ovid search strategy

#	Searches
1	*LYMPHOMA/
2	exp HODGKIN DISEASE/
3	Germinoblastom$.tw,kf,ot.
4	Reticulolymphosarcom$.tw,kf,ot.
5	Hodgkin$.tw,kf,ot.
6	(malignan$ adj2 (lymphogranulom$ or granulom$)).tw,kf,ot.
7	or/1-6
8	POSITRON-EMISSION TOMOGRAPHY/
9	(pet$ or petscan$).tw,kf,ot.

(*Continued*)

10	tomograph$.tw,kf,ot.
11	emission$.tw,kf,ot.
12	exp DEOXYGLUCOSE/
13	FLUORODEOXYGLUCOSE F18/
14	(deoxyglucose$ or desoxyglucose$ or deoxy-glucose$ or desoxy-glucose$ or deoxy-d-glucose$ or desoxy-d-glucose$ or 2deoxyglucose$ or 2deoxy-d-glucose$ or fluorodeoxyglucose$ or fluorodesoxyglucose$ or fludeoxyglucose$ or fluordeoxyglucose$ or fluordesoxyglucose$ or 18fluorodeoxyglucose$ or 18fluorodesoxyglucose$ or 18fluordeoxyglucose$ or fdg$ or 18fdg$ or 18f-dg$).tw
15	(fluor$ or 2fluor$ or fluoro$ or fluorodeoxy$ or fludeoxy$ or fluorine$ or 18f$ or 18flu$).tw
16	glucose$.tw.
17	or/8-16
18	7 and 17
19	ANIMALS/ not HUMANS/
20	18 not 19

CONTRIBUTIONS OF AUTHORS

Nicole Skoetz: Protocol development

Karel Moons: Methodological input

Lise J Estcourt: Medical and content input

Andreas Engert: Medical and content input

Carsten Kobe: Nuclearmedical input

Bastian von Tresckow: Clinical input

Gary Collins: methodological input

Marialena Trivella: Statistical/methodological input

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Nicole Skoetz: Award of the national ministry grant by Federal Ministry of Education and Research for the University Hospital of Cologne to perform this systematic review does not lead to a conflict of interest

Karel Moons: none known

Lise J Estcourt: none known

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