Using evidence of multiple study designs in systematic reviews

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Using evidence of multiple study designs in systematic reviews

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The research presented in this thesis was conducted at the School for Public Health and Primary Care (CAPHRI), Department of Family Medicine, Maastricht University. CAPHRI participates in the Netherlands School of Primary Care Research (CaRe), acknowledged by the Royal Dutch Academy of Science (KNAW). CAPHRI was classified as 'excellent' by the external evaluation committee of leading international experts that reviewed CAPHRI in December 2010.

Using evidence of multiple study designs in systematic reviews

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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CHAPTER 1

General introduction

In this chapter a description is given of the main characteristics of systematic reviews such as the aim and definition of a systematic literature review and the principles of developing a structured research question. A crucial part of a systematic review is to limit the inclusion criteria with regard to the study design. Subsequently, important issues of study designs are described such as explanatory and pragmatic study designs, the evaluation of adverse events, practical or ethical concerns that may arise with certain study designs, and the so-called hierarchy of evidence. Finally, the aim of the research project and the outline of this thesis are addressed.

Aim of a systematic review

Systematic reviews of health care interventions aim to summarize evidence in a systematic and transparent manner and by doing so to generate new knowledge that can help people make decisions relevant to health [1,2]. According to the Centre for Reviews and 'Dissemination's guidance for undertaking reviews in health care, systematic reviews aim to identify, evaluate and summarise the findings of all relevant individual studies, thereby making the available evidence more accessible to decisionmakers [3]. According to the Medical Research Council, the evaluation of complex interventions such as change of behavior or prevention is also within the scope of systematic review of interventions [4].

Definition of a systematic review

A meaningful definition of a systematic review is given in the Cochrane Handbook for systematic reviews of interventions [5], quote:

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made. The key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies;*
- an explicit, reproducible methodology;*
- a systematic search that attempts to identify all studies that would meet the eligibility criteria;*
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and*
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.*

Ideally, the pre-specified eligibility criteria and the planned methodological approaches are published in a protocol beforehand. The Cochrane Collaboration, for example, requires the publication of a protocol as an initial step in conducting a Cochrane systematic review. Moher 2013 addressed the problem of duplicate systematic reviews [6]. PROSPERO an international prospective register of systematic reviews [7] aims to avoid unplanned duplication by also providing information about other ongoing systematic reviews. Waugh 2013 enumerated potential barriers that may contest the effectiveness of PROSPERO [8]. For instance, people might use the published information to speed up their own secret review of the same topic or may copy the ideas. Progress may be hampered if the authors who registered their plans lose interest while this refrains others from writing a review on the same topic. The Cochrane Collaboration requests registration of all of their systematic reviews and thereafter rejects inquiries addressing the same topic. For example, the Cochrane Skin Group (CSG) accepted the title 'Balneophototherapy for chronic plaque type psoriasis' in 2006 [9]. In 2013, the authors withdraw their application after being unable to develop a protocol and the Cochrane Skin Group posted an announcement wanting authors to form a new group [10]. During this 7-year time period other persons interested in preparing this review were prevented from doing so.

In a systematic review, the applied search strategy and the assessment of studies as well as the analysis of results have to match the procedures pre-determined in the protocol. Authors should avoid deviations from the protocol or carefully explain the reasons.

There may be some difficulties to separate systematic reviews from nonsystematic reviews. First, some use the expression 'narrative review' to denote nonsystematic reviews. Popay 2006 explains the ambiguous nature of the term 'narrative' [11]. 'Narrative' means storytelling and 'narrative review' is used as a phrase by some to describe more traditional literature reviews that are neither systematic nor transparent. However, a 'narrative synthesis' is an integral part of a systematic review using words and text to summarize the findings/results. According to the Cochrane Handbook, analysis of included studies in a systematic review may be 'narrative' or quantitative and a 'narrative synthesis' may use subjective rather than statistical methods where meta-analysis may be either not feasible or not sensible [12]. Thus, 'narrative review' may be a misnomer and 'nonsystematic review' should be the preferred term.

Second, both publication types 'narrative and nonsystematic review' may appear comprehensive at a first glance. However, they are profoundly different. In a nonsystematic review, an expert provides a broad overview of relevant information about a particular field [13]. In general, it lacks methodological information about how and where the included publications were searched and how they were selected and it lacks the reasons why some studies were given more emphasis than others. An appraisal of the risk of bias and a quantitative summary of the literature is often absent [14]. The most distinctive characteristics that are present in a systematic review and

that are not present in a nonsystematic review may be a study protocol, an analysis plan, a literature search strategy, and a description of the selection of suitable studies in accordance with prospectively defined inclusion and exclusion criteria [15]. It is important to know whether a conclusion or recommendation concerning the benefit of a health care intervention is based on data summarized in a systematic or a nonsystematic review. The systematic review of randomized controlled trials (RCTs) is regarded as the highest level of evidence available if confined to effects of interventions [16]. Some systematic reviews, called overviews of reviews (umbrella reviews), are designed to compile evidence from multiple systematic reviews without evaluating primary studies [17]. In a previous paper, we applied the following minimal inclusion criteria to distinguish systematic reviews from nonsystematic reviews: The authors were required to report multiple literature sources including at least MEDLINE and The Cochrane Library and had to report the search strategy including the search date [18]. Difficulties in separating systematic from nonsystematic reviews may happen with experts in evidence-based medicine exemplified by an evidence report in which the experts classified 10 reviews as systematic although nine of those were in fact nonsystematic [19].

Developing a research question

Preparing a systematic review of interventions begins with a health care question to clarify which intervention provides more benefit and less harm to patients than an alternative. The starting point and fundamental component of a systematic review of health care interventions is a structured clinical question that should include four essential constituents, that is, the type of participants (P), intervention (I), comparator (C), and outcome (O) commonly denoted as PICO [3,20]. These four items can be supplemented by timing (T) and setting (S), two other important features of a systematic review, to create the so-called PICOTS typology [21]. A further extension embraces the study design (SD) to complete all major items of a search strategy (PICOTS-SD) [22]. PICOTS-SD also leads to a clear and comprehensive definition of the inclusion criteria relevant to a systematic review.

Explanatory and pragmatic study designs

A systematic review may evaluate benefit and harm of a health care intervention in the context of 'efficacy' and 'effectiveness' [23]. Both terms sound similar but may be easily mixed up. Therefore, we adopt the terms 'explanatory study design' and 'pragmatic study design' in the present thesis instead [24]. Explanatory study designs address the question whether the intervention of interest can work in principle in the ideal study setting (RCT) and typically provides a conclusion for an average patient only [25]. Con-

ducting an RCT can mean the exclusion of female gender, persons beyond a certain age, patients not treated in primary care hospitals, outpatient treatment, participants with co-morbidities, and an allocation to treatment groups by discretion of the medical doctor. In some situations RCTs are not feasible, for example, due to ethical concerns or strong patients' preferences and the results may not be applicable to everyday practice [26]. Pragmatic study designs aim to show that interventions will work under every day circumstances, for example, in a general practice [27]. As pragmatic study designs consider a variety of patients' characteristics, the conclusions based on the results may typically apply for certain subgroups of patients. The reporting of the range of applicability should always accompany the reporting of the estimated effect. Some authors criticized that many public commissioners provide predominantly funding for explanatory study designs research [27]. To accommodate the evaluation of various research questions concerning explanatory study designs and pragmatic study designs, the inclusion of more than one study design appears to be necessary. If multiple study designs are included in a systematic review then they should be well selected and customized to provide answers to the questions of interest. Efficiency, also known as cost-effectiveness, addresses the question whether the intervention of interest is value for money and should be paid for. The costs are usually not the issue of systematic reviews but of health technology assessments.

Adverse events

Concerning medical interventions such as surgery, drugs, or behavioural counselling, adverse events can be crucial for their legal approval or their restriction to particular indications. The detection of severe adverse events may give rise to their discontinuation and removal from the market. The comprehensive detection of adverse events may need a long-term observation of a large number of participants and an experimental research design could become a costly and unsuccessful enterprise.

Practical or ethical concerns

A practical concern may arise when the low number of patients with a specific rare disease such as acquired severe aplastic anemia makes it difficult to conduct an RCT. An ethical concern may arise with the treatment of certain severe diseases such as random allocation to a new experimental treatment in patients with pancreatic cancer. Another ethical concern may arise if a short-time survival is expected to differ between test and control intervention.

Hierarchy of evidence

There appears to be some variation in the hierarchy among some authors and institutions issuing evidence-based guidelines or systematic reviews. All agree that RCTs have the highest level of evidence with respect to minimising risk of bias. The prospective nonrandomized controlled clinical trial (CCT) has an experimental design and its internal validity should be regarded lower than a randomized trial but higher than an observational study. Prospective cohort studies have a potential for a lower risk of bias than retrospective cohort studies because they have lower risk of measurement bias and confounding [28]. In cohort studies groups are defined by exposure whereas in case-control studies groups are defined by disease status. Both points are acknowledged in the hierarchy of evidence by some but not all authors. Case series and case reports are descriptions of one or more individual cases. Some authors combine these two designs in one category while others place case series in a higher level. The Centre for Evidence-Based Medicine (CEBM), the National Institute of Health and Care Excellence (NICE), and the Centre for Reviews and Dissemination (CRD) [3,29,30] are some of major institutions that propose study design classification trees. A critical study characteristic is the concurrent versus the historical control group. Concurrent means that the participants in the test and in the control group are treated and followed within the same observation period. Historical means that the participants were treated and followed in a different observation period introducing potential bias that results, for example, from different study conditions due to medical progress. Another critical study characteristic is the allocation of participants to the test or control arm by random and concealed allocation versus by discretion of the study investigator. Single-arm studies such as case series and case reports cannot provide information whether the test intervention works better than a control intervention. Another single-arm study design is called the within group comparison which has also been referred to as before and after study in a previous CRD report.

A considerable proportion of researchers appears dichotomized to either accept only the randomized design for scientific evidence on health care interventions or to also accept designs without randomization as sufficient [31]. A 'hierarchy of evidence' was established that clearly downgrades designs other than randomized studies regardless of the type of outcome evaluated [16]. Some authors questioned this hierarchy [32,33]. Advantages and disadvantages of various designs have been reported repeatedly and some authors support the integration of multiple study designs with respect to the outcome of interest [31]. The selection of study design is dependent on the research question such as the intended effect under ideal or under daily health care conditions, the adverse event, or the health-related quality of life or costs of (the implementation of) an intervention. The effects of drug therapy, medical device therapy, or the treatment of life-threatening rare diseases may be best evaluated by different study designs. The limitations of exclusively using data from RCTs to evaluate

whether an intervention might work have been discussed [26]. The number of study participants may be too low to detect certain severe adverse events especially if the events are rare. Therefore, RCTs may not be appropriate to estimate the incidence of rare but important adverse events. Study designs that incorporate the data of a large number of participants of interest such as case control studies, case series, registry analyses, or cross-section or qualitative analyses may complement the information on severe adverse events.

Aim of the research project

The aim of this thesis is to investigate the advantages and disadvantages of using various study designs to answer specific clinical research questions within systematic reviews and to develop and pilot test an algorithm to guide systematic reviewers in their decision to choose appropriate study designs.

We will discuss the following research questions in this thesis:

1. What is known in the published literature about the pros and cons of integration of multiple study types in systematic reviews?
2. What can be learnt from conducting systematic reviews about topics that may require the inclusion of multiple study designs, assuming that more than one study design may be essential to gather sufficient data for answering the objectives of the review.
3. What is the preferred content and format of a straightforward algorithm for integration of various study designs in a systematic review, that incorporates major study characteristics as decision points and that allows consideration of practical concerns?
4. Can the algorithm hold its promise as a useful guide for choosing appropriate study designs by testing its feasibility and applying it to existing systematic reviews?

Outline of this thesis

Chapter 2 includes the main method paper 'Using multiple types of studies in systematic reviews of health care interventions – a systematic review' that answers research question 1. It contains the search strategy for literature retrieval about the characteristics of various study designs and recommendations for integrating them in systematic reviews of health care interventions. The specific abilities of individual study designs to answer particular research questions are presented. The data from studies are summarized that evaluated whether the effects reported in RCTs might have a direction or magnitude that vary in general from those in nonrandomized trials.

Chapter 3 to chapter 6 include papers of systematic reviews on various health care interventions that answer research question 2. All systematic reviews concern non-medicinal treatment. Two systematic reviews address hematopoietic stem cell transplantation in two distinct rare and severe diseases with scarce comparative studies. One systematic review concentrates on patient-centered outcomes in a low-risk stage of a frequent malignant disease. Another systematic review on a surgical intervention relies on RCTs only, but faces the need to compensate data on adverse events by other study designs.

Chapter 7 includes the method manuscript 'Development of an algorithm to provide awareness in choosing study designs for inclusion in systematic reviews of health care interventions – a method study' that answers research question 3. In this chapter, the construction of an algorithm is described as well as the reasoning for choosing specific decision points. It is also explained that the algorithm needs the consideration of practical or ethical concerns and the need to switch the design chosen at first sight to provide a sufficiently pragmatic and flexible tool that is fit for application in the real world. The manuscript also answers the research question 4. The practical application of the algorithm is described and it is tested whether the potential usefulness of the algorithm can be confirmed in principle by applying it to the four systematic reviews of health care interventions reported in chapters 3 to 6.

Chapter 8 accommodates the general discussion of this thesis. It contains the summary of the main findings, its strengths and limitations. It also contains the consideration of agreements and disagreements expressed in other studies or reviews. The concepts of evidence-based medicine and best available evidence are crucial for interpreting the findings. Therefore, a separate section was introduced to connect these concepts with the results of the thesis. Finally, conclusions and recommendations for decision makers and further research are drawn.

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CHAPTER 2

Using multiple types of studies in systematic reviews of health care interventions – a systematic review

Peinemann F, Tushabe DA, Kleijnen J. Using Multiple Types of Studies in Systematic Reviews of Health Care Interventions – A Systematic Review. PLoS One. 2013;8(12):e85035.

Abstract

Background A systematic review may evaluate different aspects of a health care intervention. To accommodate the evaluation of various research questions, the inclusion of more than one study design may be necessary. One aim of this study is to find and describe articles on methodological issues concerning the incorporation of multiple types of study designs in systematic reviews on health care interventions. Another aim is to evaluate methods studies that have assessed whether reported effects differ by study types.

Methods and findings We searched PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Methodology Register on 31 March 2012 and identified 42 articles that reported on the integration of single or multiple study designs in systematic reviews. We summarized the contents of the articles qualitatively and assessed theoretical and empirical evidence. We found that many examples of reviews incorporating multiple types of studies exist and that every study design can serve a specific purpose. The clinical questions of a systematic review determine the types of design that are necessary or sufficient to provide the best possible answers. In a second independent search, we identified 49 studies, 31 systematic reviews and 18 trials that compared the effect sizes between randomized and nonrandomized controlled trials, which were statistically different in 35%, and not different in 53%. Twelve percent of studies reported both, different and non-different effect sizes.

Conclusions Different study designs addressing the same question yielded varying results, with differences in about half of all examples. The risk of presenting uncertain results without knowing for sure the direction and magnitude of the effect holds true for both nonrandomized and randomized controlled trials. The integration of multiple study designs in systematic reviews is required if patients should be informed on the many facets of patient relevant issues of health care interventions.

Introduction

A systematic review may evaluate different aspects of a health care intervention such as efficacy, effectiveness, and adverse events [1]. To accommodate the evaluation of various research questions such as efficacy or effectiveness and outcomes such as survival or severe adverse events, the inclusion of more than one study design appears to be necessary. If multiple study designs are included in a systematic review they should be well selected and customized to answer to the questions of interest. Efficacy addresses the question whether the intervention of interest can work in the ideal study setting (randomized controlled trial) and typically provides a conclusion for an average patient only [2]. In some situations, RCTs are not feasible due to ethical concerns or due to strong patients' preferences and the results may not be applicable to everyday practice [3]. Some nonrandomized studies are designed to evaluate effectiveness and may show that interventions will work under every day circumstances, for example in a general practice [4]. Effectiveness typically provides a conclusion for a subgroup of patients that can be applied to individual patients. Adverse events can be crucial for approval, the restriction of application to particular indications, or the discontinuation of drugs or other interventions. The comprehensive detection of adverse events may need a long-term observation of a large number of participants and an experimental research design could become a costly and unsuccessful enterprise. It appears that many public commissioners provide predominantly funding for efficacy research [4].

A considerable proportion of researchers appears dichotomized to either require the randomized design for scientific evidence on health care interventions or to also accept designs without randomization as sufficient [5]. A 'hierarchy of evidence' was established that clearly downgrades designs other than randomized studies regardless of the type of outcome evaluated [6]. Some authors questioned this hierarchy [7,8]. Advantages and disadvantages of various designs have been reported repeatedly and some authors support the integration of multiple study designs with respect to the outcome of interest [5]. We did not find a report that systematically summarized methods papers about usefulness and complexity of integrating various designs in one systematic review. Therefore, we wanted to collect experiences, recommendations, and evidence based on clinical study data reported by others to infer whether one design is superior to others or not and whether alternative or more practical designs could complement or even replace a seemingly favorable design. One aim of this study is to find and describe articles on methodological issues concerning the incorporation of multiple types of study designs in systematic reviews on health care interventions. Another aim is to evaluate methods studies that have assessed whether reported effects differ by study types. Finally, we aimed to identify and summarize qualitative evidence sufficient enough to guide finding and integrating the right research design for answering various clinical questions within systematic reviews of health care interventions.

Methods

While preparing this systematic review, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist (Table S1; online at doi: 10.1371/journal.pone.0085035).

Inclusion criteria

We included articles reporting on how to integrate different study designs in systematic reviews of health care interventions. We did not include articles merely describing advantages and disadvantages of various designs. We also included articles reporting different results of a particular outcome that depend on the type of design such as in a comparison of a randomized vs. a nonrandomized controlled design. Since we concentrated on the reporting of various study designs, we did not specify on the type of participants, interventions, comparisons, outcomes.

Search strategy

We searched PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Methodology Register on 31 March 2012. The search strategy is detailed in Table 1. Terms and syntax used for the search in PubMed were also used for the Cochrane Library. The MeSH term "Randomized Controlled Trials as Topic"[MeSH] aims to specifically identify RCTs [9] while the MeSH term "Epidemiologic Studies"[Mesh] comprises nonrandomized study designs [10]. We combined terms of the controlled vocabulary MeSH with text words. We searched PubMed and the Related citations function in PubMed tool to find some pertinent articles that appeared to represent the topic of the present review. We adopted candidate text words reported by those articles in the title or the abstract to build a search strategy for nonrandomized or observational studies [11-13].

Study selection

We imported the bibliographic data of the search results into an EndNote X4 database. Two reviewers assessed independently title and/or abstract whether randomized controlled trials and nonrandomized studies were addressed at the same time in any type of article. Disagreements were resolved by discussion. Full texts were ordered if we agreed on potentially relevant references and if disagreements could not be resolved. The full text papers were assessed to see whether the methodology of how to integrate specific study designs in systematic reviews was addressed. We also marked studies that compared the results of randomized controlled trials and nonrandomized

studies on the same clinical topic to estimate possible effect size differences between the two design categories.

Table 1. Search strategy

No	Term
1	"Randomized Controlled Trials as Topic"[Mesh]
2	randomized controlled[tiab]
3	randomised controlled[tiab]
4	randomization[tiab]
5	randomisation[tiab]
6	random allocation[tiab]
7	"Epidemiologic studies"[Mesh] non random*[tiab]
8	nonrandom*[tiab]
9	non-random*[tiab]
10	observational[tiab]
11	quasi-experiment*[tiab]
12	quasi experiment*[tiab]
13	or/1-6
14	or/7-12
15	and/13-14

Searching PubMed, Cochrane database of systematic reviews, and the Cochrane database of methods studies on 31 March 2012.

Abbreviations and symbols. *: The asterisk represents truncation to find all terms that begin with a given text string; [Mesh]: Search field tag provided by PubMed for the search in Medical Subject Headings (MeSH) terms; [tiab]: Search field tag provided by PubMed for the search in the title and/or in the abstract

Data collection, analysis, and synthesis

We summarized the identified statements in a descriptive manner and did not quantitatively pool any data. We worked with 2 types of reviews, systematic reviews and other reviews. The systematic review category included Cochrane systematic reviews, other systematic reviews not issued by Cochrane, and health technology assessments. The other review category included non-systematic reviews, editorials, comments, and letters. We based the rationale to include non-systematic type papers on the following reflections. We wanted to build a comprehensive review of available methods papers. We wanted to acknowledge experience-based thoughts and reasonings and we wanted to include rationales and recommendations with respect to integrate various designs in systematic reviews that have been developed by others. We did not expect a large number of systematic reviews and we apprehended a limited scope of topics if we would have confined the data collection to systematic reviews only. Nevertheless, we stratified the results presentation by the two review types.

We identified 16 separately reported clinical fields and we used one additional category for articles that combined two or more clinical fields. The 17 categories were:

- Acupuncture: Intervention regarding acupuncture type of complementary and alternative medicine)
- Cardiology: Interventional procedures to reopen coronary arteries as opposed to surgical interventions
- Genetics: Genetic diseases and rare diseases
- HRT: Hormone replacement therapy for women
- Mental: Intervention to treat a mental disease such as depression
- Nephrology: Intervention regarding renal disease
- Nutrition: Influence of food on health
- Orthopedics: Intervention regarding orthopedic disease
- Palliation: Intervention regarding palliative treatment
- Pediatrics: Intervention regarding children
- Pharma: Drugs to treat patients
- Pregnancy: Intervention regarding pregnant women
- Social: Complex social interventions
- Surgery: Surgical intervention regarding various diseases
- Tele: Intervention regarding telehealth issues
- Transplant: Autologous or allogeneic transplantation of organs
- Various: Two or more different clinical fields

We created 8 distinct categories for classifying the type of study design:

- RCT: Randomized controlled trial
- NRCT: Nonrandomized controlled trial: prospective comparative trial with allocation of patients by physician
- Cohort study: Prospective or retrospective observational study with a control group without allocation of patients by physician, start is intervention
- CCS: Case-control study: retrospective study, start is events
- Regist: Registry of data from patients with particular diseases or interventions
- Admin: Administrative databases such as data from health care providers
- Survey: Survey or audit as well as postmarketing analysis Cases: Single case or case series

We identified a considerable number of different methodological topics relevant for the integration of various study designs in systematic reviews. As some of the topics were similar, we assigned these topics to 15 methodological categories. All major issues such as validity, applicability, and confounding were addressed in the papers.

- Adherence: Patients may adhere to the prescription or may not take drugs or doses as wanted

- Adverse events: Patients may experience unwanted effects or events that are associated with the intervention
- Applicability: Results may not be generalized to patients that have different characteristics than the study population
- Case load: The number of patients with a particular disease or intervention admitted to a hospital or treated by a physician
- Confounding: A known or unknown factor that is associated with the intervention and influences the outcome
- Exclusions: Certain patients are excluded from the recruitment such as elderly, pregnant women, children, patients with comorbidities
- Heterogeneity: Patients within one treatment group differ in baseline characteristics such as severity of disease
- Long term: Follow up more than 12 months after the intervention
- Participation: Eligible individuals who did not participate in trials
- Pathophysiol: Pathophysiological issues such as bacterial cause or various genetic constitution
- Preferences: Patients and physicians may have preferences about what treatment is best
- Rare disease: Rare diseases may not be represented in clinical trials and rare adverse events may not be detected by small studies
- Specialisation: The level of education and experience of a physician may influence the outcome
- Survival: Proportion of patients that sustain a specific wanted status after a certain time period
- Validity: To measure what should be measured; minimizing uncertainty and systematic error; dealing with selection bias

Results

Search results

We included 42 articles that report about the integration of study designs in systematic reviews (Figure 1) [5,7,8,14-52]. In the first step of the study selection process, we retrieved 6994 records from electronic databases including 6141 citations from PubMed and 803 citations from the Cochrane Library. The Cochrane Library citations were made of 188 systematic reviews and 526 methods studies. After excluding 6555 records not relevant to the topic of interest or duplicates, we assessed the fulltexts of 439 different articles. After a first screening process, we excluded 355 articles and after a repeated screening of the remaining potentially relevant fulltexts, we excluded another 42 articles. The reasons for exclusion are shown in Figure 1.

Figure 1. Literature retrieval and study selection.

Characteristics of included articles

The characteristics of included articles are shown in Table 2 and Table 3. We identified 8 systematic reviews [14,17-20,33,34,38] and 34 non-systematic reviews including editorials, comments, or letters. The articles containing concepts relevant to our research question were published between 1995 and 2012. Most of the articles were published between 2005 and 2012: 73% (31 of 42) of all reviews, 62% (5 of 8) systematic reviews and 76% (26 of 34) non-systematic reviews (Table 2). The systematic reviews covered 4 of 16 distinct clinical field categories with 5 of 8 reviews reporting on surgery and with 1 review reporting on acupuncture, cardiology, and various clinical fields, respectively (Table 2).

Table 2. Characteristics of included articles

Author	Year	Ref	Field	Type of design							
				RCT	NRCT	Cohort	CCS	Regist	Admin	Survey	Cases
Systematic review											
Archampong	2012	[14]	Surgery		1	1	1	1		1	
Britton	1998	[17]	Surgery	1	1						
Chambers	2009	[18]	Cardiology	1	1						1
Chambers	2010	[19]	Surgery	1				1			
Chou	2010	[20]	Surgery	1	1	1	1	1	1	1	1
Lewsey	2000	[33]	Surgery	1					1		
Linde	2002	[34]	Acupuncture	1	1	1	1			1	1
Norris	2005	[38]	Various		1	1	1				1
Non-systematic review											
Atkins	2007	[15]	Surgery	1	1	1	1	1	1	1	
Black	1996	[16]	Various			1	1				
Chumbler	2008	[21]	Tele	1	1	1					1
Concato (Comp)	2010	[7]	Surgery	1	1	1			1		
Concato (Observ)	2010	[22]	Various	1	1	1	1				
Essock	2003	[23]	Mental	1	1						
Fletcher	2002	[24]	Various	1	1	1	1				
Fletcher	2009	[25]	HRT	1	1	1					
Gale	2009	[26]	Transplant	1				1			
Grzeskowiak	2012	[27]	Pregnancy			1	1	1	1		1
Hadley	2009	[61]	Palliation	1		1		1		1	
Hartling	2005	[29]	Surgery		1	1	1				1
Hodgson	2007	[30]	Mental	1		1					
Hoppe	2009	[8]	Orthopedics	1		1	1				1
Horn	2010	[31]	Various	1	1						
Kovesdy	2012	[32]	Nephrology	1		1					
McCarthy	2008	[35]	Surgery	1	1	1					1
Mercer	2007	[36]	Various	1	1						1
Mitchell	1995	[37]	Pediatrics	1							
Norris	2011	[39]	Various		1	1	1	1			1
Ogilvie	2005	[40]	Social	1	1	1	1				1
Olivier	2006	[41]	Pharma	1	1	1	1	1	1		1
Reeves	2005	[42]	Nutrition	1		1	1				
Rosendaal	2001	[43]	Cardiology	1			1				
Sharma	2012	[44]	Social	1		1					
Shrier	2007	[45]	Various	1		1					
Silverman	2009	[46]	Pharma	1		1	1		1		
Vandenbroucke	1998	[47]	Various	1			1				
Vandenbroucke	2004	[48]	Various	1			1				
Vandenbroucke	2008	[5]	Various	1			1				
Vandenbroucke	2009	[49]	HRT	1		1					
Vandenbroucke	2011	[50]	Various	1	1						
Wilcken	2001	[51]	Genetics	1		1		1			
Zlowodzki	2006	[52]	Various	1	1	1	1				1
Frequency				36	22	28	21	10	7	5	14

Legend: Type of review. Systematic review (first 8 papers): Cochrane Systematic Review (Archampong 2012), Health Technology Assessment of National Health Service in UK (Britton 1998), other systematic reviews not issued by Cochrane or HTA (Chambers 2009, Chambers 2010, Chou 2010, Lewsey 2000, Linde 2002, Norris 2005). Non-systematic review (rest of 34 papers): narrative review or editorial or comment or letter.

Field. Acupuncture: Intervention regarding acupuncture type of complementary and alternative medicine; Cardiology: Interventional procedures to reopen coronary arteries as opposed to surgical interventions; Genetics: Genetic diseases and rare diseases; HRT: Hormone replacement therapy for women; Mental: Intervention to treat a mental disease such as depression; Nephrology: Intervention regarding renal disease; Nutrition: Influence of food on health; Orthopedics: Intervention regarding orthopedic disease; Palliation: Intervention regarding palliative treatment; Pediatrics: Intervention regarding children; Pharma: Drugs to treat patients; Pregnancy: Intervention regarding pregnant women; Social: Complex social interventions; Surgery: Surgical intervention regarding various diseases; Tele: Intervention regarding telehealth issues; Transplant: Autologous or allogeneic transplantation of organs; Various: Two or more different clinical fields

Type of design. RCT: Randomized controlled trial; NRCT: Nonrandomized controlled trial: prospective comparative trial with allocation of patients by physician; Cohor: Prospective or retrospective observational study without allocation of patients by physician, start is intervention; CCS: Case-control study: retrospective study, start is events; Regist: Registry of data from patients with particular diseases or interventions; Admin: Administrative databases such as data from health care providers; Survey: Survey or audit or postmarketing analysis; Cases: Single case or case series

Other abbreviations. Ref: reference

Table 3. Outcomes of included articles

Authors	Year	Ref	Outcomes addressed													
			Adherence	Adverse events	Applicability	Case-load	Confounding	Exclusions	Heterogeneity	Long term	Participation	Patho-physiol	Preferences	Rare disease	Specialisation	Survival
Systematic review																
Archampong	2012	[14]				1								1	1	
Britton	1998	[17]			1		1	1	1	1		1				
Chambers	2009	[18]		1	1					1						
Chambers	2010	[19]		1											1	
Chou	2010	[20]	1	1	1				1	1						1
Lewsey	2000	[33]			1											1
Linde	2002	[34]		1	1					1						
Norris	2005	[38]			1		1									1
Non-systematic review																
Atkins	2007	[15]		1	1				1							
Black	1996	[16]	1	1	1					1	1		1			1
Chumbler	2008	[21]														1
Concato (Comp)	2010	[7]			1											1
Concato (Observ)	2010	[22]					1									1
Essock	2003	[23]			1		1			1			1			1
Fletcher	2002	[24]			1		1									1
Fletcher	2009	[25]					1									1
Gale	2009	[26]			1		1				1					1
Grzeskowiak	2012	[27]		1			1									1
Hadley	2009	[61]		1					1							
Hartling	2005	[29]		1	1					1						
Hodgson	2007	[30]		1	1			1		1	1					1
Hoppe	2009	[8]			1		1			1	1		1			1

Authors	Year	Ref	Outcomes addressed														
			Adherence	Adverse events	Applicability	Case-load	Confounding	Exclusions	Heterogeneity	Long term	Participation	Patho-physiol	Preferences	Rare disease	Specialisation	Survival	Validity
Horn	2010	[31]			1												1
Kovesdy	2012	[32]	1		1		1		1	1							1
McCarthy	2008	[35]					1										1
Mercer	2007	[36]			1												1
Mitchell	1995	[37]		1			1										
Norris	2011	[39]			1		1		1	1		1					1
Ogilvie	2005	[40]			1			1									1
Olivier	2006	[41]		1						1							
Reeves	2005	[42]					1										1
Rosendaal	2001	[43]					1										1
Sharma	2012	[44]										1					
Shrier	2007	[45]					1										1
Silverman	2009	[46]	1		1					1							1
Vandenbroucke	1998	[47]		1			1					1					1
Vandenbroucke	2004	[48]		1			1										1
Vandenbroucke	2008	[5]		1			1			1							1
Vandenbroucke	2009	[49]		1			1	1									1
Vandenbroucke	2011	[50]		1													1
Wilcken	2001	[51]		1						1				1			
Zlowodzki	2006	[52]					1										1
Frequency			4	18	21	1	21	4	6	15	5	2	5	2	1	2	30

Legend. Outcomes addressed. Adherence: Patients may adhere to the prescription or may not take drugs or doses as wanted; Adverse events: Patients may experience unwanted effects or events that are associated with the intervention; Applicability: Results may not be generalized to patients that have different characteristics than the study population; Case load: The number of patients with a particular disease or intervention admitted to a hospital or treated by a physician; Confounding: A known or unknown factor that is associated with the intervention and influences the outcome; Exclusions: Certain patients are excluded from the recruitment such as elderly, pregnant women, children, patients with comorbidities; Heterogeneity: Patients within one treatment group differ in baseline characteristics such as severity of disease; Long term: Follow up more than 12 months after the intervention; Participation: Eligible individuals who did not participate in trials; Pathophysiol: Pathophysiological issues such as bacterial cause or various genetic constitution; Preferences: Patients and physicians may have preferences about what treatment is best; Rare disease: Rare diseases may not be represented in clinical trials and rare adverse events may not be detected by small studies; Specialisation: The level of education and experience of a physician may influence the outcome; Survival: Proportion of patients that sustain a specific wanted status after a certain time period; Validity: To measure what should be measured; minimizing uncertainty and systematic error, dealing with selection bias; other abbreviations. Ref: reference.

The non-systematic reviews covered 15 of 16 categories with 12 reporting on various topics, 4 reporting on surgery, no report on acupuncture, and 1 to 2 reporting on each of the rest of clinical entities.

Of the 15 methodological topics, which are relevant for the integration of various study designs in systematic reviews, 5 topics were frequently reported by more than 10 articles (Table 3). The rest were addressed by 1 article or up to 6 articles. Validity was reported by 30 reviews (systematic 3, non-systematic 27), applicability by 21 reviews (systematic 6, non-systematic 15), confounding by 21 reviews (systematic 2, non-systematic 19), adverse events by 18 reviews (systematic 4, non-systematic 14), and long-term follow up by 15 reviews (systematic 4, non-systematic 11). Systematic reviews reported 13 categories leaving pathogenesis and rare diseases out. Non-systematic reviews reported 12 categories and did not refer to case load, specialisation, and survival.

Key messages

We qualitatively summarized the key messages of the 42 included methods studies based on the extraction of major statements (Table S2). We identified a clear tendency in the message that nonrandomized studies should be conducted and integrated in systematic reviews to complement available RCTs or replace lacking RCTs in 85% (36 of 42) of all reviews. We judged the difference between systematic reviews 75% (6 of 8) and non-systematic reviews 88% (30 of 34) as not considerable. Thus the majority of identified reviews supported the view that nonrandomized studies are important and should be an integral part of assessing health care interventions. Only a minority of reviews regarded RCTs as the sole means of finding reliable answers to clinical research questions. Most papers acknowledged the advantages and the disadvantages of RCTs and nonrandomized studies with regard to specific methodologic topics or specific clinical outcomes. Some papers addressed the problem that RCTs are not possible for assessing certain questions and that case reports may have a considerable impact on safety issues.

Comparison of randomized vs. nonrandomized controlled design

We identified 49 studies, 18 trials and 31 systematic reviews that compared the effect measures found in randomized controlled trials with those in nonrandomized controlled trials (Table 4). Of these 49 studies, 39 reported about the same or similar intervention in both study designs and 10 studies that included different interventions in the analyses. In 35% (17 of 49) studies, there was a different direction or a statistically significant difference of the magnitude of effect between randomized and nonrandomized controlled trials. In 53% (26 of 49) studies, the effect did not differ considerably between those two designs. In 12% (6 of 49) studies, both results, a difference as well as no difference were reported.

Table 4. Reviews and studies comparing randomized vs. nonrandomized controlled results

First author	Year	Ref	Intervention	Difference R vs. N		
				Yes	Various	No
Abraham	2010	[62]	same			no
Algra	2012	[63]	same			no
Antman	1985	[64]	same	yes		
Aslani	2010	[65]	same			no
Benis	2002	[66]	same	yes		
Benson	2000	[67]	same			no
Bhandari	2004	[68]	same	yes		
Britton	1998	[17]	same			no
Carroll	1996	[69]	same	yes		
CASS	1984	[70]	same			no
Cheng	2012	[71]	same			no
Choi	2012	[72]	same			no
Claggett	1984	[73]	same			no
Colditz	1989	[74]	various	yes		
Conaty	2004	[75]	same			no
Concato	2000	[76]	same			no
Deeks	2003	[77]	various		various	
Edwards	2012	[78]	various			no
Flossman	2007	[79]	same			no
Franklin	2000	[80]	same			no
Furlan (Exam)	2008	[81]	same		various	
Furlan (Meth)	2008	[82]	same	yes		
Golder	2011	[83]	various			no
Gross	2005	[84]	same			no
Guyatt	2000	[85]	same	yes		
Hannan	2008	[86]	various		various	
Hlatky	1988	[87]	same			no
Ioannidis	2001	[58]	various	yes		
Kunz	2007	[54]	same	yes		
Kunz	1998	[53]	same	yes		
Kuss	2011	[88]	same			no
Lawlor	2004	[89]	same	yes		
Linde	2002	[34]	same			no
MacLehose	2000	[11]	various			no
Mueller	2010	[90]	same	yes		
Naudet	2011	[91]	same	yes		
Odgaard-Jensen	2011	[55]	various		various	
Papanikolaou	2006	[92]	various		various	
Phillips	1999	[93]	same			no

First author	Year	Ref	Intervention	Difference R vs. N		
				Yes	Various	No
RMIT	1994	[94]	same			no
Rovers	2001	[95]	same			no
Schmoor	2008	[96]	same			no
Shea	2010	[97]	same	yes		
Shikata	2006	[98]	various		various	
Tzoulaki	2011	[99]	same	yes		
Vis	2008	[100]	same	yes		
Vist	2008	[101]	same			no
Wilkes	2010	[102]	same			no
Wolfe	2004	[103]	same	yes		
Frequency				17	6	26

Legend: Abbreviations. CASS: Coronary artery surgery study; Difference R vs N: difference between randomized vs. nonrandomized results; Ref: reference; RMIT: Recurrent Miscarriage Immunotherapy Trialists

Discussion

We identified and summarized qualitative evidence sufficient enough to guide finding and integrating the right research design for answering various clinical questions within the conduct of systematic reviews of health care interventions.

It is obvious that intended effects of interventions such as the physician-reported outcomes of prevention of death and healing or improving of disease in ideal settings with financially affordable follow up and with ample number of available participants are best investigated in well planned RCTs. There is no equal or better alternative study design. The results may or may not be applicable to the general population. Many people with particular characteristics such as younger or older age, gender, pregnancy, or comorbidity may have been excluded and may have experienced opposing effects or an unfavorable and unwanted balance of benefit and harm. Pediatricians may seek information on drugs from observational studies if data on the treatment of children from RCTs are not available. Unintended, severe adverse events require long-term observation including postmarketing analysis, administrative databases, and case reports to identify harmful drugs that have to be withdrawn from the market. The types of different study design that need to be included in a systematic review depend on the nature of the clinical questions that the review addresses.

Oxman and collaborators assessed the effects of randomisation and concealment of allocation on the results of healthcare studies and reported their results in three papers within the time period from 1998 to 2011 [53-55]. The authors concluded that "the results of randomised and non-randomised studies – sometimes – differed". In many cases the results did not differ. The authors argued "that it is not generally pos-

sible to predict the magnitude, or even the direction, of possible selection biases and consequent distortions of treatment effects from studies with non-random allocation or controlled trials with inadequate or unclear allocation concealment". We believe that trials with random allocation and adequate allocation concealment may show contradictory results. We also believe that it is not possible to foresee the magnitude or the direction of bias in those adequately randomized trials with absolute certainty [56]. Nevertheless, the authors stated that "randomized controlled trials are a safeguard against biased estimates of treatment effects". Various design prerequisites and adjustment procedures in nonrandomized controlled trials can minimize bias and confounding, however, it is not known for certain in a particular trial whether the results reflect the reality or whether they are distorted. The same principle holds true for trials with adequate randomization and concealment of allocation. Even if the risk of a false estimate determined in a series of trials would be lower than in trials with inadequate randomization and concealment of allocation the fact is that the result of the primary outcome measure in a single specific trial cannot be regarded as an absolute and certain proof regardless of the p-values or confidence intervals. Ioannidis 2005 concluded that, quote: "Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones" [57]. The authors found that 5 of 6 highly cited nonrandomized studies had been contradicted or had found stronger effects versus 9 of 39 randomized controlled trials ($P = 0.008$). Our assessment adds to the existing work done by Oxman group and the Ioannidis group that the effect did not differ considerably between the randomized and the nonrandomized designs in more than half of the studies. The general postulate or dogma of the RCT as a safeguard against biased estimates of treatment effects may create deceptive promises and may give researchers a false sense of security. We infer from our findings just the same as Shrier 2007 has expressed before, quote: "(...)that excluding observational studies in systematic reviews a priori is inappropriate and internally inconsistent with an evidence-based approach" [45].

According to the Cochrane handbook, the Cochrane Collaboration focuses particularly on systematic reviews of RCTs and considers inclusion of nonrandomized studies mainly if RCTs are lacking. We see a vast number of clinical research questions that are not investigated by RCTs. There may be many reasons, for example, patients' and physicians' preferences that prevent the accumulation of true randomized study data. Our results suggest that the Cochrane Collaboration might be advised to consider more reasons for including nonrandomized studies on the condition of a rigorous risk of bias assessment and confinement to specific interventions and outcomes.

In general, a high risk of bias is inherent in all nonrandomized studies. Certain study characteristics such as prospective design, concurrent control group, adjustment of results with respect to different baseline values, and confounder control can limit additional bias. For example, Ioannidis 2001 [58] reported that discrepancies between

RCT and nonrandomized studies were less common when only nonrandomized studies with a prospective design were considered. The Cochrane Collaboration offers a guide for inclusion of nonrandomized studies [59] and it has developed a tool for assessing the risk of bias in both RCT and controlled nonrandomized studies [60].

Conclusions

Different study designs addressing the same question yielded varying results, with differences in about half of all examples. The risk of presenting uncertain results without knowing for sure the direction and magnitude of the effect holds true for both nonrandomized and randomized controlled trials, though, the risk of bias and confounding is probably higher in the nonrandomized ones. The integration of multiple study designs in systematic reviews is required if patients should be informed on the many facets of patient relevant issues of health care interventions.

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CHAPTER 3

Autologous hematopoietic stem cell transplantation following high dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas

Peinemann F, Smith LA, Bartel C. Autologous hematopoietic stem cell transplantation following high dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas. Cochrane Database of Systematic Reviews. 2013;8:CD008216.

Abstract

Background Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma. In patients with advanced local or metastatic disease, autologous hematopoietic stem cell transplantation (HSCT) applied after high-dose chemotherapy (HDCT) is a planned rescue therapy for HDCT-related severe hematologic toxicity. The rationale for this update is to determine whether any randomized controlled trials (RCTs) have been conducted and to clarify whether HDCT followed by autologous HSCT has a survival advantage.

Objectives To assess the effectiveness and safety of HDCT followed by autologous HSCT for all stages of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) in children and adults.

Search methods For this update we modified the search strategy to improve the precision and reduce the number of irrelevant hits. All studies included in the original review were considered for re-evaluation in the update. We searched the electronic databases CENTRAL (2012, Issue 11) in The Cochrane Library, MEDLINE, and EMBASE (05 December 2012) from their inception using the newly developed search strategy. Online trials registers and reference lists of systematic reviews were searched.

Selection criteria Terms representing STS and autologous HSCT were required in the title or abstract. In studies with aggregated data, participants with NRSTS and autologous HSCT had to constitute at least 80% of the data. Single-arm studies were included in addition to studies with a control arm because the number of comparative studies was expected to be very low.

Data collection and analysis Two review authors independently extracted study data. Some studies identified in the original review were re-examined and found not to meet the inclusion criteria and were excluded in this update. For studies with no comparator group, we synthesized the results for studies reporting aggregate data and conducted a pooled analysis of individual participant data using the Kaplan-Meier method. The primary outcomes were overall survival (OS) and treatment-related mortality (TRM).

Main results The selection process was carried out from the start of the search dates for the update. We included 57 studies, from 260 full text articles screened, reporting on 275 participants that were allocated to HDCT followed by autologous HSCT. All studies were not comparable due to various subtypes. We identified a single comparative study, an RCT comparing HDCT followed by autologous HSCT versus standard chemotherapy (SDCT). The overall survival (OS) at three years was 32.7% versus 49.4% with a hazard ratio (HR) of 1.26 (95% confidence interval (CI) 0.70 to 2.29, P value 0.44) and thus not significantly different between the treatment groups. In a subgroup of patients that had a complete response before treatment, OS was higher in both treatment groups and OS at three years was 42.8% versus 83.9% with a

HR of 2.92 (95% CI 1.1 to 7.6, P value 0.028) and thus was statistically significantly better in the SDCT group. We did not identify any other comparative studies. We included six single-arm studies reporting aggregate data of cases; three reported the OS at two years as 20%, 48%, and 51.4%. One other study reported the OS at three years as 40% and one further study reported a median OS of 13 months (range 3 to 19 months). In two of the single-arm studies with aggregate data, subgroup analysis showed a better OS in patients with versus without a complete response before treatment. In a survival analysis of pooled individual data of 80 participants, OS at two years was estimated as 50.6% (95% CI 38.7 to 62.5) and at three years as 36.7% (95% CI 24.4 to 49.0). Data on TRM, secondary neoplasia and severe toxicity grade 3 to 4 after transplantation were sparse. The one included RCT had a low risk of bias and the remaining 56 studies had a high risk of bias.

Authors' conclusions A single RCT with a low risk of bias shows that OS after HDCT followed by autologous HSCT is not statistically significantly different from standard-dose chemotherapy. Therefore, HDCT followed by autologous HSCT for patients with NRSTS may not improve the survival of patients and should only be used within controlled trials if ever considered.

Plain Language Summary

High-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for non-rhabdomyosarcoma soft tissue sarcomas

Review question

We reviewed the evidence about the effect of high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation compared to standard-dose chemotherapy on overall survival in people with non-rhabdomyosarcoma soft tissue sarcomas. We found one randomized controlled trial (RCT) comparing both treatments and 48 studies with results from transplantation only.

Background

Non-rhabdomyosarcoma soft tissue sarcomas are a group of rare cancers. People with inoperable or metastatic disease have a poor prognosis. It was believed that higher doses of chemotherapy might improve patients' survival. However, high doses of chemotherapy stop the production of blood cells in the bone marrow and are not compatible with life. Stem cells collected from people before highdose chemotherapy can be transplanted back to the patient if the blood cell count gets too low. Due to a lack of research studies, it has not been proven that patients treated with this procedure live any longer than patients treated with standard chemotherapy. We wanted to determine whether using high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation was better or worse than standard-dose chemotherapy.

Study characteristics

The evidence is current to 5 December 2012. The single RCT that was identified compared 38 patients in the transplantation group versus 45 patients in the chemotherapy only group and was judged to have a low risk of bias (high methodological quality). The participants were 18 to 65 years old, had various types of non-rhabdomyosarcoma soft tissue sarcomas and were observed for a median follow-up time of 55 months. The rest of the studies reported results for a series of or individual transplanted patients only, with various ages, tumor types and follow up times; they all had a high risk of bias. The treatment period among studies ranged from 1994 to 2008. The single RCT and some of the other studies were funded by non-profit organizations. Three studies reported financial support by biopharmaceutical companies. Most studies did not give details of funding.

Summary of findings for the main comparison

Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcoma					
Patient or population: patients with non-rhabdomyosarcoma soft tissue sarcoma					
Settings: Specialized hospital					
Intervention: Autologous hematopoietic stem cell transplantation following high-dose chemotherapy					
Comparison: standard-dose chemotherapy					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Standard-dose chemotherapy	Autologous hematopoietic stem cell transplantation following high-dose chemotherapy			
Overall survival Follow-up: median 55 months	489 per 1000	571 per 1000 (375 to 785)	HR 1.26 (0.7 to 2.29)	83 (1 study)	⊠⊠⊠⊠ High
Progression-free survival Follow-up: median 55 months	756 per 1000	849 per 1000 (681 to 955)	HR 1.34 (0.81 to 2.2)	83 (1 study)	⊠⊠⊠⊠ High
Treatment-related mortality See comment	See comment	See comment	Not estimable	163 (1 study)	⊠⊠⊠⊠ Very low
Health-related quality of life See comment	See comment	See comment	Not estimable	–	See comment
Disease-free survival Follow-up: 3 years	See comment	See comment	Not estimable	0 (1 study)	⊠⊠⊠⊠ Very low
Non-hematological toxicity grade 3 to 4 See comment	See comment	See comment	Not estimable	105 (9 studies ¹)	⊠⊠⊠⊠ ¹ Very low

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI**: Confidence interval; **HR**: Hazard ratio; **GRADE** Working Group grades of evidence; **High quality**: Further research is very unlikely to change our confidence in the estimate of effect; **Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **Very low quality**: We are very uncertain about the estimate. ¹case series

Key results

In the single RCT, the overall survival (OS) at three years was 32.7% in the transplantation group versus 49.4% in the chemotherapy only group, and this was not found to be significant. There was one case of treatment-related mortality in the transplantation group and none in the chemotherapy only group.

Quality of evidence

The overall quality of the data was based on a single RCT, which had a low risk of bias. The rest of the studies had a high risk of bias due to single-arm and retrospective study design and were not useful for comparing two treatments. Currently the research evidence indicates that patients with non-rhabdomyosarcoma soft tissue sarcomas should not be treated with high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. If this treatment is offered it should be done only within clinical controlled trials and after careful consideration.

Background

Description of the condition

Soft tissue sarcomas (STS) are a highly heterogeneous group of rare malignant solid tumors of non-epithelial extraskelatal body tissue and are classified on a histogenetic basis [Enzinger 2001]. STS have a significant risk of distant metastasis in addition to the potential for locally destructive growth and recurrence. Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise all STS except rhabdomyosarcoma, which primarily affects children and young adults. In this review we investigated NRSTS which are categorized as malignant according to the World Health Organization (WHO) 2002 classification [Fletcher 2002] as adopted by the European Society for Medical Oncology (ESMO) Guidelines Working Group [ESMO 2012]. This latter classification excludes the Ewing family of tumors (EFT).

NRSTS usually originate de novo and rarely from benign tumors. In most cases the pathogenesis is unknown; however, some factors have been found to be associated with the development of NRSTS [Enzinger 2001]. These include exposure to ionizing radiation, environmental carcinogenic substances, oncogenic viruses and immunologic factors. Genetic factors can also play a role since some inherited diseases such as neurofibromatosis type 1 are associated with a higher risk of NRSTS [Tsao 2000].

In Western countries about four new cases of NRSTS are estimated per 100,000 population every year [ESMO 2012], with rhabdomyosarcoma and the Ewing family of tumors excluded from this statistic. STS constitute about 1% of malignancies in adults and 7% in children [NCI 2009a]. Rhabdomyosarcoma represents about 50% of STS in

children [Gurney 1997; Miller 1995]. NRSTS are rare in both children and adults and the distribution of NRSTS differs significantly between children and adults (Table 1) according to [Spunt 2006].

Table 1. Frequency of subtypes of included NRSTS in patients of young versus advanced age

Young age (< 20 years)		Advanced age (>= 20 years)	
Synovial sarcoma	7.7%	Leiomyosarcoma	13.7%
Malignant fibrous histiocytoma	4.9%	Malignant fibrous histiocytoma	10.1%
Fibrosarcoma	4.5%	Liposarcoma	8.0%
Liposarcoma	2.8%	Hemangiosarcoma	2.5%
Epitheloid sarcoma	2.0%	Spindle cell sarcoma	2.3%

Estimates in the table according to [Spunt 2006]
 Abbreviations. NRSTS: non-rhabdomyosarcoma soft tissue sarcomas

Based on the Surveillance, Epidemiology and End Results (SEER) cancer statistics review (1975 to 2007) of the National Cancer Institute (NCI), in the US 10,520 new cases and 3920 deaths from STS were estimated for the year 2010 [NCI 2010a]. Separate data were not available for rhabdomyosarcoma and NRSTS. The distribution of STS increased with age according to SEER data from 2001 to 2005. Of all STS cases, 10.3% were in children and young adults less than 20 years of age [NCI 2008a]. The median age at diagnosis of STS, including tumors of the heart, was 57 years [NCI 2008b].

Staging

Disease progression may be dichotomized into the two categories of limited and extensive disease. Limited disease is typically a localized, small-sized, low-grade and operable and accessible tumor that has no regional lymph node involvement and no distant metastases. Extensive disease can also be denoted as advanced disease, defined as localized, large-sized and high-grade tumor that may not be completely removed by surgery, may be invasive and may have regional lymph node involvement or distant metastases. Both categories differ significantly in terms of prognosis and treatment. Where many patients with limited disease may be cured by surgery, extensive disease is associated with a poor outcome and many patients receive chemotherapy as palliative therapy.

The American Joint Committee on Cancer (AJCC) tumor-nodemetastasis (TNM) staging system combines grade, depth and size of the tumor as well as regional lymph node involvement and distant metastases and describes the extent of a cancer's spread from stage 0 to IV [AJCC 2002]. A review reported the five-year overall survival (OS) estimates for stage I (low-grade, superficial and deep), II (high-grade, superficial and deep), III (high-grade, large and deep) and IV (any metastasis to lymph nodes or

distant sites) as approximately 90%, 70%, 50% and 10% to 20%, respectively; information on treatment was not given [Clark 2005]. A multicenter study a total of 2185 participants with advanced STS revealed a median survival of 12 months [Van Glabbeke 1999]. In the same study, of the 1922 (26%) eligible participants who responded to chemotherapy the five-year OS was 10%; in univariate analyses the response to chemotherapy was not predicted by the same factors as was OS.

Symptoms

The location of the primary tumor can involve any area of the body. The distribution is 40% lower limb and girdle, 20% upper limb and girdle, 20% abdominal sites, 10% trunk and 10% head and neck [Clark 2005]. NRSTS can involve any type of tissue and typically affect muscles, tendons, adipose tissue, blood vessels and joints [Sondak 2001] and commonly present as a painless mass. The symptoms depend on the anatomical site of origin, the size of the mass and other aspects. Retroperitoneal sarcomas are most often asymptomatic, until the mass grows large enough to be clinically obvious or presses on vital organs and causes pain [Dileo 2005].

Patients who relapse or suffer progressive disease after therapy or metastasis are commonly called high-risk patients because these signs are associated with shorter survival time. Spontaneous recovery from NRSTS is unknown.

Description of the intervention

Standard therapy

Surgery is the standard treatment for localized NRSTS [ESMO 2012] and can be curative if distant dissemination is not present [Kotilingam 2006]. Chemotherapy is a standard treatment for patients with distant metastasis [ESMO 2012] and is regarded mainly as a palliative treatment for high-risk patients who are characterized by inoperable, locally advanced and metastatic disease. Doxorubicin, ifosfamide, gemcitabine, dacarbazine, docetaxel and trabectedin are used in monotherapy or in combinations [ESMO 2012]. [Riedel 2012] provides an overview of current systemic therapies and discusses possible novel therapeutic agents and treatment strategies.

High-dose chemotherapy [HDCT] followed by autologous hematopoietic stem cell transplantation [HSCT]

Autologous hematopoietic stem cell transplantation (HSCT) is defined as the transplantation of stem cells that have been collected previously from bone marrow or peripheral blood of the same person. High-dose chemotherapy (HDCT) uses higher doses of chemotherapeutic agents than are usually applied in standarddose chemotherapy. HDCT may be tolerated by the patient or it may ablate the patient's bone marrow reserves and create an absolute requirement for stem cell rescue. Instead of HDCT,

highdose radiation therapy may be used to treat NRSTS patients. Autologous HSCT applied after HDCT or high-dose radiation is a planned rescue therapy for HDCT-related severe hematologic toxicity [Banna 2007]. Ideally, a mega-therapy regimen should be used consisting of several non-cross resistant agents that have a steep dose-response curve and little extramedullary toxicity [Ladenstein 1997].

HDCT and autologous HSCT are not standard treatment options; they are an experimental approach mainly used to treat high-risk people with an unfavorable prognosis [stage IV with distant metastases]. HDCT and autologous HSCT may be used in special cases after careful consideration, usually for patients who respond well to standard chemotherapy according to Response Evaluation Criteria in Solid Tumors (RECIST) [Therasse 2000] criteria [Kasper 2005; Kasper 2007b]. Carboplatin, cisplatin, cyclophosphamide, etoposide, ifosfamide, melphalan, mitoxantrone and thiotepa, for example, have been used in HDCT regimens. Independent of the disease status, HDCT and autologous HSCT are hazardous interventions that carry the risk of life-threatening organ failure.

Adverse events

Non-hematological adverse events, such as short-term and longterm organ toxicities, must be considered when using HDCT [Ladenstein 1997]. Hematological adverse events as a result of autologous HSCT are usually manageable but life-threatening consequences of pancytopenia. They generally affect all patients and include, for example, graft failure, severe infections and bleeding.

Frequency

Of a total of 20,017 autologous HSCTs that were registered in Europe in the year 2010, by the European Group for Blood and Marrow Transplantation (EBMT), 45 were indicated for STS [Passweg 2012].

How the intervention might work

HDCT followed by autologous HSCT was adopted to treat highrisk patients because it was believed that escalating doses in chemotherapy might increase survival by capturing putatively remnant malignant cells and might overcome resistance to standarddose chemotherapy [Banna 2007]. High-dose chemotherapy may cause severe hematologic and non-hematologic toxicity and autologous HSCT is a planned rescue therapy for the HDCT-related demise of hematopoietic stem cells.

Why it is important to do this review

In the last two decades, from 1986 to 2007, the lack of evidence and need to conduct randomized controlled trials (RCTs) was stated by authors seeking to clarify the relevance of HDCT followed by autologous HSCT in high-risk patients with STS [Blay 2000; Carvajal 2005; Dumontet 1992; Ek 2006; Elias 1998; Kasper 2007a; Ladenstein 1997; Pinkerton 1986; Reichardt 2002; Rosti 2002; Schlemmer 2006; Seeger 1991; Woods 1999]. Some authors have warned against the use of HDCT followed by autologous HSCT, indicating the possibility of repositioning of malignant cells [Woods 1999]. Others have questioned the use of HDCT with reference to the potential existence of refractory cancer stem cells [Banna 2007; Bonnet 1997; Sanchez-Garcia 2007]. The rationale for this review update is to review the latest available evidence and to clarify whether RCTs have been conducted and whether results of any study show evidence of a survival advantage.

Objectives

To assess the effectiveness and safety of high-dose chemotherapy (HDCT) followed by autologous hematopoietic stem cell transplantation (HDCT) for all stages of non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) in children and adults.

Methods

Criteria for considering studies for this review

Types of studies

Inclusion criteria

Randomized controlled trials (RCTs). Since we expected to find few if any RCTs, non-RCTs were also included as follows. Prospective non-randomized controlled trials [denoted quasi-RCTs in the first version], other non-RCTs such as prospective and retrospective cohort studies, case-control studies, phase I and II prospective studies, case series and case reports.

Results from RCTs and controlled clinical trials (CCTs) may provide data for estimation of effects on overall survival (OS) and answer the question: does the intervention provide a significantly better survival than the control and does the quality of the studies fit with the assumption that the intervention is better than the control? Data from non-comparative studies (phase I and II prospective studies, case series and case reports) were collected to estimate treatment-related mortality (TRM) within a cohort of

participants. Due to the lack of a control group these studies do not provide data for estimation of treatment effect.

Exclusion criteria

None

Rationale for including non-RCTs

Authors of studies on HDCT with autologous HSCT have stated that RCTs are both necessary and feasible. However, NRSTS is a rare disease and, according to the results of a previous literature search, currently there are no published RCTs available. In addition, CCTs or studies with any comparative data may be unlikely or rare. If they do exist they may be of low methodological quality. Based on the assumption that it is unlikely that the intervention has been or will be studied in RCTs in the near future, this systematic report of the findings and the limitations of all available published studies will be useful, for example for informing the design of appropriate RCTs and providing a summary of all of the evidence on the topic to date.

Types of participants

Inclusion criteria

We have adopted the World Health Organization (WHO) classification of soft tissue tumors to define the population of patients with NRSTS [Fletcher 2002]. We present the designation of tumors that were regarded as (malignant) soft tissue sarcomas in the present review in Table 2. The clear delineation of soft tissue sarcomas to be included in the present report and the grounds for exclusion of some tumor types was hindered by the presence of more than 30 heterogeneous tumor entities, the distinction between categories of malignant tumors and categories of intermediate malignancies as described in the WHO classification (Fletcher 2002), and a complicated histology and terminology.

Studies were included as long as at least 80% of patients had NRSTS. Children as well as adults were investigated and age limits did not apply. Participants were included regardless of the severity of the disease and the clinical staging information, as long as they received autologous (from either a peripheral or bone marrow source, or both) HSCT.

Exclusion criteria

We present the terms for tumors that were not considered in the present review in Table 3. Whilst the WHO classification of NRSTS includes the Ewing family of tumors, that is extraosseous tumor types, we excluded these types because they are primarily bone sarcomas. Because extraosseous types are rarely diagnosed and share common features, they were regarded as one entity with osseous types and were excluded.

Table 2. Included non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)

Category*	Associated subtypes
Adipocytic tumors	
Anaplastic soft tissue sarcoma	
Angiosarcoma	Angiosarcoma of soft tissue; hemangiosarcoma; hemangiopericytoma; lymphangiosarcoma
Clear cell myomelanocytic tumor	
Clear cell sarcoma of soft tissue tumor	
Desmoplastic small round cell tumor	
Epitheloid sarcoma	
Fibrosarcoma	Adult fibrosarcoma; myxofibrosarcoma; low grade fibromyxoid sarcoma, hyalinizing spindle cell tumor; sclerosing epitheloid fibrosarcoma
Fibromyxoid sarcoma	
Epitheloid hemangioendothelioma	
Intimal sarcoma	
Leiomyosarcoma	
Liposarcoma	Dedifferentiated liposarcoma; myxoid liposarcoma; round cell liposarcoma; pleomorphic liposarcoma; mixed-type liposarcoma; liposarcoma, not otherwise specified; chondroid liposarcoma (added by authors)
Malignant fibrous histiocytoma	Pleomorphic malignant fibrous histiocytoma, undifferentiated pleomorphic sarcoma; giant cell malignant fibrous histiocytoma, undifferentiated pleomorphic sarcoma with giant cells; inflammatory malignant fibrous histiocytoma, undifferentiated pleomorphic sarcoma with prominent inflammation; undifferentiated pleomorphic sarcoma; spindle cell sarcoma
Malignant glomus tumor	
Malignant hemangiopericytoma	
Malignant mesenchymoma	
Mesenchymomal sarcoma	
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	
Rhabdoid sarcoma	Extrarenal rhabdoid tumor; extracerebral rhabdoid tumor
Synovial sarcoma	

*category of malignant tumors according to the World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Soft Tissue and Bone [Fletcher 2002]

Table 3. Excluded tumor types

Category	Associated subtypes
Atypical teratoid/rhabdoid tumors	
Chondrosarcoma	Mesenchymal chondrosarcoma; extraskeletal myxoid chondrosarcoma ('chondroid type')
Clear cell sarcoma of the kidney	
Dermatofibrosarcoma protuberans	
Endometrial stroma sarcoma	
Ewing family of tumors	Ewing sarcoma; skeletal Ewing sarcoma; extraskeletal Ewing sarcoma; peripheral primitive neuroectodermal tumor (pPNET); Askin tumor
Extragenital germ cell sarcoma	
Follicular dendritic cell sarcoma	
Ganglioneuroblastoma	
Gastrointestinal stromal tumor	
Giant cell fibroblastoma	
Giant cell tumor of bone	
Histiocytic sarcoma	
Interdigitating dendritic cell sarcoma	
Interdigitating reticulum cell sarcoma	
Kaposi sarcoma	
Lymphoblastic lymphosarcoma	
Malignant ectomesenchymoma	
Medulloblastoma	
Myeloid sarcoma	
Myxosarcoma (cardiac tumor)	
Nephroblastoma	
Neuroblastoma (Wilms tumor)	
Osteosarcoma	Extraskeletal osteosarcoma
Paraganglioma	
Peripheral nerve sheath tumor, malignant (neurofibrosarcoma)	
Rhabdoid tumor, renal	
Rhabdoid tumor, cerebral	
Rhabdomyosarcoma	
Schwannoma, malignant (Schwannosarcoma)	
Stromal cell sarcoma	
Unclassified sarcoma	
Undifferentiated sarcoma	
Uterine endometrial stromal sarcoma	

Types of interventions

Intervention: autologous hematopoietic stem cell transplantation (HSCT), stem cells from a peripheral source or the bone marrow, serving as a rescue therapy usually applied after high-dose chemotherapy (HDCT).

Comparison: standard-dose chemotherapy, which is defined as chemotherapy at a lower dose than HDCT without the need for stem cell rescue.

Types of outcome measures

Primary outcomes

- Overall survival (OS): the event was death by any cause, from diagnosis or start of HDCT and autologous HSCT.
- Treatment-related mortality (TRM): incidence of deaths that were classified as treatment related or the participants died of treatment complications.

Secondary outcomes

- Disease-free survival (DFS): time free of disease after diagnosis or start of HDCT and autologous HSCT. We provided the definitions reported in the studies.
- Progression-free survival (PFS): time staying free of disease progression after diagnosis or start of HDCT and autologous HSCT. We provided the definitions reported in the studies.
- Event-free survival (EFS): time staying free of any of a particular group of defined events after diagnosis or start of HDCT and autologous HSCT. We provided the definitions reported in the studies.
- Non-hematological toxicity grade 3 to 4: adverse events classified according to the common toxicity criteria [NCI 2009b] within 90 days of start of HDCT and autologous HSCT; grades 3 and 4 of toxicity were extracted for non-hematological (nausea, mucositis, kidney, liver, nervous system, heart, other) toxicities.
- Secondary neoplasia: as classified by the study authors.
- Health-related quality of life measured by validated questionnaires.

Search methods for identification of studies

Electronic searches

We conducted an electronic database search of MEDLINE (Ovid), including articles published between 1946 and 5 December 2012, by using the search strategy shown in Appendix 1. We searched EMBASE (Ovid), including articles published between 1980 and 5 December 2012, by using the search strategy shown in Appendix 2. We searched The Cochrane Library, including articles published from inception to 5 December 2012, by using the search strategy shown in Appendix 3. The original strategies which were

run on 5 February 2010 and are shown in Appendix 4 for MEDLINE (Ovid), in Appendix 5 for EMBASE (Ovid), and in Appendix 6 for The Cochrane Library. For this update we considered all studies that were included in the original review and re-evaluated them. We searched for ongoing trials by scanning the online registries ClinicalTrials.gov [ClinicalTrials.gov 2012] and the World Health Organization International Clinical Trials Registry Platform [ICTRP 2012] on 5 December 2012 for additional completed or ongoing studies using the search strategy "sarcoma AND chemotherapy AND transplantation". For the update of the present review we searched abstracts of annual meetings of the following societies via EMBASE (Ovid): American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), Bone Marrow Transplantation (BMT) Tandem Meeting of the American Society for Blood and Marrow Transplantation (ASBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR), and European Group for Blood and Marrow Transplantation (EBMT).

The search strategies used have been developed and executed by the author team.

Searching other resources

We located information about trials not registered in electronic databases by searching the reference lists of relevant articles and review articles such as [Banna 2007, Ek 2006, Pedrazzoli 2006, and Verma 2008a]. For the update, we did not identify more recent reviews. We contacted authors to replenish missing information.

Data collection and analysis

Selection of studies

We endorsed the PRISMA statement, adhered to its principles and conformed to its checklist [Moher 2009]. We re-ran the whole selection process including all records retrieved from the inception of each database. We retrieved all titles and abstracts by electronic searching and downloaded them to the reference management database EndNote Version X3 [Thomson Reuters Corp 2012]. We removed duplicates and two review authors examined the remaining references independently. We excluded those studies that clearly did not meet the inclusion criteria and we obtained copies of the full texts of potentially relevant references. Two authors assessed the eligibility of retrieved papers independently. We resolved disagreement by discussion and it was not necessary to consult a third review author. We considered studies written in languages other than English and asked peers familiar with the particular language and with the principles of study evaluation to translate major methodological issues. We also used the [Google Translate 2012] program. We documented reasons for the exclusion of studies.

Data extraction and management

We re-extracted the data from all selected studies identified from the inception of each database. Two review authors independently abstracted data on study characteristics, patients and interventions, duration of follow up, outcomes, and deviations from the protocol. In addition, two review authors independently assessed the risk of bias. We resolved differences between review authors by discussion or by appeal to a third review author. All included studies were full-text publications.

We extracted the following data.

- General information on author, title, source, publication date.
- Study characteristics: trial design, setting, inclusion and exclusion criteria, comparability of patients' characteristics between groups, treatment allocation, blinding, subgroup analysis, length of follow-up.
- Participant characteristics: age; gender; number of participants recruited, /allocated, affected, analyzed; additional diagnoses; participants lost to follow-up.
- Interventions: type of high-dose chemotherapy, source of stem cells, and type of standard-dose chemotherapy.
- Outcomes: overall survival, treatment-related mortality, disease-free survival, progression-free survival, event-free survival including type of event, toxicity, secondary neoplasia, healthrelated quality of life.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included studies using six criteria. We have used four criteria of The Cochrane Collaboration's tool for assessing risk of bias [Higgins 2011a]:

1. random sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of outcome assessment (detection bias);
4. selective reporting such as not reporting pre-specified outcomes (reporting bias).

We extended the tool for assessing risk of bias with five additional criteria that are specific for the inclusion criteria for the present review and that are critical for confidence in the results:

1. prospective design;
2. comparable baseline characteristics;
3. assignment of patients to treatment groups;
4. concurrent control;
5. loss to follow-up.

We applied The Cochrane Collaboration's criteria for judging risk of bias [Higgins 2011b]. In general, a 'low risk' of bias is judged if the bias is unlikely to seriously alter

the results, for example, participants and investigators enrolling participants could not foresee assignment. A 'high risk' of bias is judged if the bias seriously weakens confidence in the results, for example, participants or investigators enrolling participants could possibly foresee assignments. 'Unclear risk' of bias is judged if the bias raises some doubt about the results, for example, the method of concealment is not described or not described in sufficient detail to allow a definite judgement.

We judged studies as prospective if an explicit statement was reported or there were clues suggesting a prospective design (for example prior approval of treatment, informed consent). We judged studies as retrospective if an explicit statement was reported or was implied by a description that data were reviewed from an existing source. We regarded each of the following items as an indication of a retrospective design: registry reports and reviewing of medical records.

Measures of treatment effect

The primary effect measure was the hazard ratio (HR) for time-to-event data. If the HR was not directly given in the publication, we planned to estimate HRs according to methods proposed by [Parmar 1998] and [Tierney 2007].

We planned to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for dichotomous outcomes. In the case of rare events, we planned to use Peto odds ratio instead. We planned to analyze continuous data and to present them as mean differences, if all results were measured on the same scale (for example length of hospital stay). If this was not the case (for example pain or quality of life), we planned to use standardized mean differences. Studies reporting aggregate data that combined the results of several participants (including results from separately reported subpopulations that fulfilled the inclusion criteria) were distinguished from studies with individual data of single participants. Data from these studies were described as narrative summaries. In some studies diagnoses of NRSTS were mixed with non-NRSTS solid tumors and rhabdomyosarcomas to such an extent that the proportion of NRSTS participants was less than 80% of the study population. In this case, if data on single participants were identified that fulfilled the inclusion criteria of the present review we included the study and data for the individual participant in our data analysis.

Estimates of OS were considered for the evaluation if the use of the Kaplan-Meier method was reported in the study. We described survival estimates from studies reporting aggregate data independent of the start of the follow-up period on the condition that these estimates were not pooled with those of other studies.

A survival analysis was conducted of individual participant level data based on the Kaplan-Meier method. Pooling required binary information on OS [0 = alive; 1 = dead] and on follow-up. In the majority of cases, the starting point of follow-up was the beginning of treatment. However, we accepted other starting points such as the time

when the diagnosis or indication for treatment was established. Statistical analyses of time to event data were performed using SAS Version 9.2 [SAS Institute Corp 2012].

Unit of analysis issues

None

Dealing with missing data

We conformed to The Cochrane Collaboration's principal options for dealing with missing data and analysed only the available data [Higgins 2011c]. If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes among participants who were assessed. We contacted the authors of the studies by [Bui-Nguyen 2012, Ivanova 2010, Jordan 2010, Philippe-Chomette 2012, Schlemmer 2006] to ask for missing data about the histologic types that were combined as 'others'. The authors responded well and as a consequence we could base the inclusion or exclusion of patient data on the additional data.

Assessment of heterogeneity

We planned to assess heterogeneity between studies by visual inspection of forest plots; by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (I^2 statistic) [Higgins 2003]; by a formal statistical test of the significance of the heterogeneity (Cochran's Q) [Deeks 2011]; and, if possible, by subgroup analyses [see 'Subgroup analysis and investigation of heterogeneity']. We planned to investigate and report possible reasons if there was evidence of substantial heterogeneity. We planned to use the random-effects model with inverse variance weighting for statistical pooling [DerSimonian 1986]. We did not pool estimates.

Assessment of reporting biases

We conformed to The Cochrane Collaboration's criteria and planned to evaluate reporting biases such as publication bias, time lag bias, multiple (duplicate) publication bias, location bias, citation bias, language bias and outcome reporting bias [Sterne 2011]. We did not assess reporting bias because of the low number of identified studies.

Data synthesis

One review author entered the data into [Review Manager 2011]. Another review author checked the entered data. Methods of synthesizing the studies depended on the quality, design and heterogeneity of the studies identified.

We planned to synthesize data on mortality (HDCT and autologous HSCT versus SDCT) by using the hazard ratio (HR) as effect measure in a random-effects model.

However, data were too scarce to be reasonably pooled. Aggregate data were synthesized as narrative. In contrast, individual data were pooled and available time-to-event data were analyzed in a Kaplan-Meier survival analysis.

We used the software GRADEpro 3.2 [GRADEpro 2008] to create the 'Summary of findings' table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions [Schunemann 2011].

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses based on age, stage, and time period of treatment. However, we found no appropriate data to conduct these analyses.

Sensitivity analysis

We had planned sensitivity analyses to compare the results of studies with low versus high risk of bias. As all included studies had a high risk of bias, no sensitivity analyses were carried out.

Results

Description of studies

Clinical heterogeneity was substantial because tumor subdiagnosis varied considerable between patients. Furthermore, tumor stage was not reported for all participants. Study design was tenuously reported due to the identification of either aggregate data or individual patient data in one-arm studies. Overall, the likelihood of bias was very high except in the single randomized controlled trial (RCT). All studies were not comparable due to various subtypes.

Results of the search

For this update we modified the search strategy to improve the precision and reduce the number of irrelevant hits. In the original review, we applied a search strategy that was designed to include all solid tumors including the Ewing family of tumors and rhabdomyosarcoma. This strategy resulted in the retrieval of a large number of documents (4782) including a very high fraction of not relevant retrieved documents. We revised the search strategy and this retrieved a considerably reduced number of retrieved documents (1035) from the inception of each electronic databases. The new strategy did not identify some single-arm studies with individual data that were included in the original review. Some individual cases are hidden in articles that do not mention soft tissue sarcomas and transplantation in the title or abstract. Some of those are missed by the new strategy. It is impossible to identify all published cases of

transplanted patients with NRSTS. Therefore, the number of identified relevant cases will vary with different strategies. The retrieval information confirmed that the number of studies with comparative data and aggregate data did not vary and the number of these types of identified studies was robust. The new search strategy was more economical in terms of spending resources for study selection for the present review, and also for future updates. We did not ignore the results of the original review and re-evaluated all studies that were identified by the old strategy and were included in the original review.

We retrieved 1035 records applying the new search strategy. We also retrieved six ongoing studies. We imported 15 studies that were included in the original review but were not identified with the new search strategy. We screened 773 different articles after removal of duplicates (Figure 1). The titles and abstracts of 513 articles did not fulfil the inclusion criteria or they reported about ongoing studies. A total of 260 of the retrieved articles were evaluated in detail using the full text. Of these, a total of 62 records reporting about 57 studies were included in the present review and the other 198 references were excluded. We identified one randomized controlled trial (RCT), six single-arm studies with aggregate data, and 50 single-arm studies with individual data.

Eight studies were published after the original retrieval and were added to the included studies [Bisogno 2010; Buerk 2010; BuiNguyen 2012; Cook 2012; Etienne-Mastroianni 2002; Houet 2010; Jordan 2010; Philippe-Chomette 2012]. Nine further studies were included in the original review but were not identified by the new search strategy [Fang 2008; Graham 1997; Hawkins 2002; Kretschmar 1996; Krskova 2007; Matsuzaki 2002; Peters 1986; Peters 1989; Slease 1988] (Table 4; online at doi: 10.1002/14651858.CD008216.pub4). These 15 studies were included in the update in addition to the results of the new search strategy. Three studies were included in the original review and identified in the update but were excluded after re-evaluation [Ivanova 2010; Kaminski 2000; Kuehne 2000]. Three studies were excluded in the original review and identified in the update but were included after re-evaluation [Blay 2000; Fetscher 1996; Mingo 2005]. Six further studies were included in the original review and not identified in the update but were excluded after re-evaluation. Four studies reported about undifferentiated sarcoma, which is not included [Endo 1996; Frapier 1998; Mesia 1994; Nakamura 2008]. One study reported about rhabdoid tumor but without information about the localisation, which is required for identification of the extrarenal and the extracerebral rhabdoid tumors [Ronghe 2004]. One study reported on undifferentiated sarcoma and rhabdoid tumor without information about the localisation [Shaw 1996]. We retrieved a total of 49 studies in ClinicalTrials.gov 2012 and found 14 potentially relevant studies. We identified six ongoing studies, whereof two studies are currently recruiting [NCT00638898; NCT01288573] and four studies are not recruiting participants [NCT00002601; NCT00002854; NCT00141765; NCT00623077]. We identified three completed studies, one terminated study that was withdrawn due to slow accrual, and four studies with unknown status and information

that has not been verified recently. The investigators did not provide results via the registry and we did not found a publication in PubMed 2012 matching the data shown in the registry. Of the rest of the 35 studies, 15 studies did not include the diagnosis of interest, 15 studies did not include the intervention of interest, and five did not include the outcome of interest. We did not identify other relevant studies searching in the two trials registries [ICTRP 2012] and [ISRCTN 2012]. We did not identify any additional studies from screening the reference lists of included studies and reviews.

Figure 1. Literature search and study flow.

Included studies

We identified 57 studies including a total of 275 participants that received HDCT and autologous HSCT. The characteristics of the individual 57 included studies are described in the section Characteristics of included studies (online at doi: 10.1002/14651858.CD008216.pub4). We have provided a tabulated overview of the seminal characteristics of the included studies in Table 5.

Table 5. Overview of included studies

Study	Total, N	Diagnosis			Start of follow-up	Pros- pective	HDCT vs SDCT, N analyzed
		Not rel, N (%)	Rel, N	Affected patients, N type of included diagnosis			
Aggregate comparative data (HDCT & autologous HSCT vs SDCT)							
[Bui-Nguyen 2012]	87	18 (20)	69	16x LMS, 16x MFH, 10x LPS, 9x SYN, 6x ANG, 2x UDS, 2x MME, 2x DSRCT, 2x FIB, 1x LMS, 1x UCS, 1x CCS	Randomization	YES	38 vs. 45 in ITT*
<i>Subtotal comparative data in 1 study</i>							38 vs. 45
Aggregate case series data (HDCT & autologous HSCT only)							
[Bertuzzi 2003]	10	0 (0)	10	10x DSRCT	Therapy	YES	10
[Bisogno 2010]	14	0 (0)	14	14x DSRCT	Diagnosis	YES	14
[Blay 2000]	24	2 (10)	22	24x NRSTS	Therapy	YES	24
[Bokemeyer 1997]	18	2 (11)	16	5x MFH, 2x HAP, 3x SYN, 2x LMS, 2x MES	Therapy	No	36
[Cook 2012]	36	0 (0)	36	36x DSRCT	Therapy	No	36
[Philippe-Chomette 2012]	14	0 (0)	14	14x DSRCT	Diagnosis	No	14
<i>Subtotal case series in 6 studies</i>							114
Individual cases data (HDCT & autologous HSCT only)							
<i>Subtotal case series in 50 studies</i>							123
Summary of patient count							
<i>Subtotal HDCT & autologous HSCT in 57 studies</i>							275
<i>Subtotal SDCT in 1 study</i>							45
<i>Total in 57 studies</i>							320

*modified ITT: histologically ineligible patients excluded from primary group of analysis; HDCT group: 3 of 41 randomized data excluded; SDCT group: 1 of 46 randomized data excluded

Abbreviations: Diag: diagnosis; HDCT: high-dose chemotherapy (& autologous hematopoietic stem cell transplantation); HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; ITT: intention to treat; N: number of participants; Rel: relevant; SDCT: standard-dose chemotherapy; vs.: versus

Diagnoses: ANA: anaplastic soft tissue sarcoma; ANG: angiosarcoma; CCS: clear cell sarcoma; DSRCT: desmoplastic small round- cell tumor; EPI: epitheloid sarcoma; FIB: fibrosarcoma; FMS: fibromyxoid sarcoma; HAP: hemangiopericytoma; LIP: liposarcoma; LMS: leiomyosarcoma; MES: mesenchymal sarcoma; MFH: malignant fibrous histiocyoma; MHP: malignant hemangiopericytoma; MME: malignant myoepithelioma; NRSTS: various types of non-rhabdomyosarcoma soft tissues sarcomas; RHA: rhabdoid tumor; SCS: spindle cell sarcoma; SYN: synovial sarcoma; UCS: unclassified sarcoma; UDS: undifferentiated sarcoma

Design

We included one RCT with two parallel treatment groups, HDCT and autologous HSCT versus SDCT [Bui-Nguyen 2012]. It was an open, multicenter, randomized phase III study. All patients received the same baseline treatment. Patients were eligible for randomization if they had responded to chemotherapy or, for stable disease, if a complete surgical resection of all disease sites could be carried out. Randomization was carried out centrally. The intention-to-treat (ITT) modified population included all randomly assigned patients excluding patients found to be ineligible at central histology review.

We included six single-arm studies that reported aggregate data of participants that received HDCT and autologous HSCT and that consisted of at least 80% with relevant NRSTS [Bertuzzi 2003; Bisogno 2010; Blay 2000; Bokemeyer 1997; Cook 2012; Philippe-Chomette 2012]. Three of the studies collected the data prospectively [Bertuzzi 2003; Bisogno 2010; Blay 2000] and three retrospectively [Bokemeyer 1997; Cook 2012; Philippe-Chomette 2012]. The remaining 50 studies comprised single-arm studies without appropriate aggregate data. Relevant participants were considered in the survival analysis of pooled individual data.

Sample sizes

The authors of the RCT [Bui-Nguyen 2012] conducted an ITT analysis of 38 participants in the HDCT arm versus 41 participants in the SDCT arm. Six single-arm studies reported aggregate data of 10 [Bertuzzi 2003], 14 [Bisogno 2010], 24 [Blay 2000], 16 [Bokemeyer 1997], 36 [Cook 2012], and 14 [Philippe-Chomette 2012] participants with NRSTS who received HDCT and autologous HSCT. Fifty studies reported on 123 individual relevant participants. Overall survival and follow-up data were reported for 80 participants in 41 studies and subsequently those data could be considered in survival analysis of the pooled individual data.

Setting

The 57 studies were set in 12 different countries, eight countries in Europe (Czech Republic, France, Germany, Greece, Italy, Netherlands, Spain, United Kingdom), two in North America (Canada, United States), and two in Asia (Korea, Japan). Most of the transplanted patients were studied in the USA (79 of 260) and France (79 of 260). In four countries (France, Germany, Italy, USA) 10 or more patients were studied. The only RCT [Bui-Nguyen 2012] was set in France.

Participants

We included 275 patients with 15 different relevant histological diagnoses in 57 studies. Most patients (N = 109) had desmoplastic small round-cell tumor; 10 or more patients were reported for angiosarcoma, desmoplastic small round-cell tumor, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, and synovial sarcoma.

[Bui-Nguyen 2012] reported the age in the HDCT arm in a range of 18.5 to 65.0 years (median 45.8 years) and a comparable age in the SDCT arm with a range of 18.7 to 65.0 years (median 43.3 years). Males were 58.5% of participants (24 of 41) in the HDCT arm and 50% (23 of 46) in the CDCT arm.

[Bertuzzi 2003] reported a range of 15 to 60 years of age (median 29 years) for the 10 male patients that were included. [Bisogno 2010] included 13 males and one female, the age range was 2 to 17.8 years (median 10.3 years). [Blay 2000] reported on 30 patients of which 17 were males and 13 females. The age ranged from 17 to 57 years (median 34 years). [Bokemeyer 1997] reported the age range between 25 and 57 years with a median of 45 years. Gender was not specified. [Cook 2012] reported the age range between 8 and 46 years with a median of 19 years; 29 were males and 7 were females. [Philippe-Chomette 2012] reported an age range of 4 to 22.6 years for 14 transplanted patients in the HDCT arm; 12 of those patients were males and 2 females.

Age was provided for 113 of 123 individual patients ranging from 1 to 65 years with a median of 27 years. Gender was provided for 83 individual patients, of which 55 were male and 28 were female. Follow-up was provided for 80 individual patients, ranging from 0 to 120 months with a median of 17 months.

Interventions

Components and the dosage of various chemotherapeutic regimens are described in the Characteristics of included studies (shown in the unabridged article).

In the study by [Bui-Nguyen 2012], 87 patients received courses one to five of standard-dose chemotherapy. Forty-one patients were randomized to receive HDCT and transplantation of autologous peripheral stem cells as course six in the HDCT arm. Of these, 38 patients were analyzed in a modified ITT analysis. Forty-six patients were randomized to again receive standard-dose chemotherapy as course six. Of these, 45 patients were analyzed in a modified ITT analysis.

In the study by [Bertuzzi 2003], after a four-course induction phase 10 patients in complete or partial response received HDCT and autologous HSCT using peripheral blood as the stem cell source. In the study by [Bisogno 2010], after an induction phase of nine weeks 14 patients at various clinical stages received three consecutive intensified-dose combinations and autologous HSCT using peripheral blood as the stem cell source. In the study by [Blay 2000], after induction chemotherapy for most of the patients 24 patients with an advanced clinical stage including 87% with metastasis received HDCT and autologous HSCT. The stem cell source was mainly bone marrow (N = 25) and a few patients received stem cells from peripheral blood (N = 5). In the study by [Bokemeyer 1997], 16 patients received HDCT and autologous HSCT from peripheral blood. In the study by [Cook 2012], 36 patients received HDCT and autologous HSCT mainly from peripheral blood (N = 33) and a few from bone marrow (N = 2), with information missing in one patient. In the study by [Philippe-Chomette 2012], 14 patients received various regimens of HDCT and autologous HSCT. The source of stem cells was not reported.

Primary outcome

All seven included studies with aggregate data [Bertuzzi 2003; Bisogno 2010; Blay 2000; Bokemeyer 1997; Bui-Nguyen 2012; Cook 2012; Philippe-Chomette 2012] reported overall survival (OS). Among the 50 studies with individual data from 123 patients, OS and follow-up were reported for 80 patients. Ten studies reported treatment-related mortality (TRM), five of seven studies with aggregate data and five of 50 studies with individual data. There were 13 events in nine and zero events in one study.

Secondary outcomes

One study reported disease-free survival, five studies reported progression-free survival, nine reported non-hematological toxicity grade 3 to 4, and one study reported secondary neoplasia. Five studies reported on five severe adverse events.

Excluded studies

A total of 198 references of the potentially relevant articles were excluded (Figure 1) based on:

- not diagnosis of interest, NRSTS according to Table 2 or relevant data not reported separately (n = 95);
- not intervention of interest, not HDCT and autologous HSCT (n = 69);
- not outcome of interest or not reported separately (n = 2);
- not publication type of interest, a review, editorial, letter, duplicate data, or congress abstract (n = 32).

Excluded studies are described in the 'Characteristics of excluded studies table' (shown in the unabridged article).

Risk of bias in included studies

We have identified one comparative study with a randomized design [Bui-Nguyen 2012]. We think that this trial stands out and has substantially less risk of bias than the rest of the studies. Fifty-six of 57 studies were single-arm studies that subsequently had a very high risk of bias, see Characteristics of included studies. An overview of the risk of bias is shown in Figure 2 (online at doi: 10.1002/14651858.CD008216.pub4) and the risk of bias for each study is shown in Figure 3 (online at doi: 10.1002/14651858.CD008216.pub4).

Allocation

We have identified true randomization including highly probable adequate random sequence generation for [Bui-Nguyen 2012] and judged a low risk of bias for this study. We judged a high risk of bias for the rest of the studies.

Assignment of patients to treatment groups

In the study by [Bui-Nguyen 2012], patients were assigned to two different treatment arms in a randomized fashion. Thus we judged a low risk of bias for this study. The rest of the studies were singlearm studies with an observational design and we judged a high risk of bias for these studies.

Blinding

Blinding of outcome assessment was not addressed in all included studies. Thus, we judged a high risk of bias for all studies.

Incomplete outcome data

[Bui-Nguyen 2012] conducted a modified ITT analysis. The exclusion of histologically ineligible patients after randomization affected three of 41 patients in the HDCT arm and one of 46 patients in the SDCT arm. All other studies analyzed the patients as treated. Thus we judged a low risk of bias for [Bui-Nguyen 2012] and a high risk of bias for the rest.

Selective reporting

In the study by [Bui-Nguyen 2012], allocation was carried out centrally, though masking of allocation was not described in full detail. Thus we judged an unclear risk of bias for this study. We judged a high risk of bias for the rest of the studies.

Other potential sources of bias

Prospective design

The one RCT was prospective [Bui-Nguyen 2012], three of the six single-arm studies with aggregate data [Bertuzzi 2003; Bisogno 2010; Blay 2000] and 12 of the 50 single-arm studies with individual data [Fraser 2006; Graham 1997; Hawkins 2002; Jordan 2010; Kasper 2010; Kushner 1996; Kushner 2001; Lafay-Cousin 2000; Lashkari 2009; Patel 2004; Peters 1986; Peters 1989] had prospective parts. The prospective design may be advantageous for studies that present aggregate data from a series of patients treated in a certain time period. The prospective design is not relevant for individual data. Thus, we judged a low risk of bias for [Bui-Nguyen 2012, Bertuzzi 2003, Bisogno 2010, and Blay 2000] and we judged a high risk of bias for the rest.

Comparable baseline characteristics

[Bui-Nguyen 2012] had a randomized controlled design and the baseline characteristics of both treatment groups were comparable. Thus, we judged a low risk of bias for [Bui-Nguyen 2012] and a high risk of bias for the rest.

Concurrent control

We identified a concurrent control group in [Bui-Nguyen 2012] and judged a low risk of bias. The rest of the studies did not report a control group and we judged a high risk of bias. Note: [Philippe-Chomette 2012] reported the results of some cases with conventional chemotherapy. The data for those cases were probably observed and not part of an experimental design, collected retrospectively in different time periods.

Loss to follow-up

Bui-Nguyen 2012 conducted a modified ITT analysis. The exclusion of histologically ineligible patients after randomization affected three of 41 patients in the HDCT arm and one of 46 patients in the SDCT arm. All other studies analyzed the participants as treated. Thus we judged a low risk of bias for [Bui-Nguyen 2012] and a high risk of bias for the rest.

Effects of interventions

See: **Summary of findings for the main comparison** Autologous hematopoietic stem cell transplantation following high-dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcoma

Primary outcome

Overall survival

Overall survival (OS) was not statistically significantly different between HDCT and autologous HSCT versus SDCT at three years in the RCT by [Bui-Nguyen 2012]: 32.7% versus 49.4% with a HR of 1.26 (95% CI 0.70 to 2.29, $P = 0.44$) (Table 6). The authors separately analyzed patients that had achieved a complete response to induction therapy before HDCT. OS was higher in the complete response patients compared to all patients and OS was statistically significantly different between the treatment arms. The OS among the patients that have achieved a complete response at three years before HDCT was 42.8% versus 83.9% with a HR of 2.92 (1.1 to 7.6, $P = 0.028$) (Table 6).

The single-arm studies with aggregate data reported an OS at two years ranging from 20% to 51.4% and at three years ranging from 38.9% to 40% (Table 6). [Blay 2000] and [Cook 2012] compared patients that had achieved versus not achieved a complete response before HDCT. [Blay 2000] reported an OS at two years of 63% versus 27%, and [Cook 2012] reported an OS at three years of 57% versus 28% (Table 6). Again, the achievement of a complete response before HDCT was favorable with respect to OS. We conducted a survival analysis using individual data on the condition that survival status and time to event were reported. This was true for 65% (80 of 123) of the patient data; for 43 patients, follow-up data were not available. We estimated an OS at two years of 50.6% (95% CI 38.7 to 62.5) and at three years of 36.7% (95% CI 24.4 to

49.0) (Table 6). Both estimates were within the range of the other studies. We provided the OS for each individual case in Table 7 (online at doi: 10.1002/14651858.CD008216.pub4). The graphical presentation of the Kaplan-Meier graph of all 80 included patients at risk is shown in Figure 4. We also analyzed the subgroup of patients with the diagnosis of desmoplastic small round-cell tumor because this diagnosis constituted the largest proportion, 34% (27 out of 80), of individual patients considered for the survival analysis (Figure 5; online at doi: 10.1002/14651858.CD008216.pub4). Of the individual data from patients with desmoplastic small round-cell tumor, 77% (27 of 35) had follow-up information. Both survival curves do not appear to be considerably different, though the median survival was 2.8 years within the subgroup of 27 patients with desmoplastic small round-cell tumor versus 2.2 years within the total population of 80 patients.

Table 6. Overall survival (OS)

Study	Overall survival, % (95% CI)		
	All patients assessed	Complete response before the time of HSCT	Not complete response before the time of HSCT
Aggregate comparative data (HDCT & autologous HSCT vs SDCT)			
[Bui-Nguyen 2012]	3 years: 32.7% vs. 49.4% HR 1.26 (0.70 to 2.29, $p = 0.44$)	3 years: 42.8% vs. 83.9% HR 2.92 (1.1 to 7.6, $p = 0.028$)	n/r
Aggregate case series data (HDCT & autologous HSCT only)			
[Bertuzzi 2003]	2 years: 20%	n/r	n/r
[Bisogno 2010]	2 years: 48% 3 years: 38.9%	n/r	n/r
[Blay 2000]	n/r	2 years: 63%	2 years: 27%
[Bokemeyer 1997]	Median: 13 mo; range: 3 to 19	n/r	n/r
[Cook 2012]	3 years: 40% (24 to 58)	3 years: 57% (29 to 83)	3 years: 28% (9 to 51)
[Philippe-Chomette 2012]	2 years: 51.4% (23.2 to 79.6)	n/r	n/r
Individual cases data (HDCT & autologous HSCT only)			
50 studies	2 years: 50.6% (38.7 to 62.5) 3 years: 36.7% (24.4 to 49.0) 5 years: 29.9% (16.7 to 43.1)	n/r	n/r

Some estimates were deduced from Kaplan-Meier plots. Bisogno 2010: 1 of 14 patients was reported to have achieved complete response before HDCT. Blay 2000: all patients in subgroup N = 24, patients that achieved complete remission before HDCT N = 8, patients that did not achieve complete remission before HDCT N = 16. Bui-Nguyen 2012: all patients N = 38 vs. N = 45, patients that achieved complete remission before HDCT N = 20 vs. N = 19. Cook 2012: all patients N = 36, patients that achieved complete remission before HDCT N = 13, patients that did not achieve complete remission before HDCT N = 18.

Abbreviation: CI: confidence interval; HDCT: high-dose chemotherapy; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; n/a: not applicable; n/r: not reported; OS: overall survival; $p = p$ value; SDCT: standard-dose chemotherapy.

Figure 4. Kaplan-Meier analysis of overall survival of individual cases data from patient with various NRSTS

X-axis below line: years

X-axis above line: number of patients at risk

Y-axis: probability of overall survival

Number of subjects at risk after each additional year of follow up.

The Kaplan-Meier analysis of overall survival was conducted using individual data of patients with NRSTS with available follow-up information (total 80, failed 46, censored 34) from 41 case series and case reports. Information about outcome (dead or alive) and follow-up (time of survival after diagnosis or begin of treatment) was required for each individual.

Abbreviations: NRSTS: non-rhabdomyosarcoma soft tissue sarcoma

Treatment-related mortality

Treatment-related mortality (TRM) was addressed in 12 studies (163 transplanted participants). Ten of 12 studies reported a procedure-related death for 15 participants and two of 12 studies reported zero treatment-related deaths (Table 8). A conservative estimate of TRM was 5.5% (15 procedure-related deaths of a total of 275 transplanted patients).

Secondary outcomes

Disease-free survival

Cook 2012 reported an OS at three years of 23% regarding all patients and 40% versus 9% regarding patients with and without a complete response before HDCT respectively (Table 9).

Table 8. Treatment-related mortality (TRM)

Study	Events (N)	Cause of death
Aggregate comparative data (HDCT & autologous HSCT vs SDCT)		
[Bui-Nguyen 2012]	1	Treatment-related leukemia death 2 years after HSCT
Aggregate case series data (HDCT & autologous HSCT only)		
[Bertuzzi 2003]	0	n/a
[Bisogno 2010]	0	n/a
[Blay 2000]	1	Sudden toxic death of unknown cause at day 29
[Bokemeyer 1997]	n/r	n/a
[Cook 2012]	2	n/r
[Philippe-Chomette 2012]	1	Died of treatment toxicity 12 months after HSCT
Individual cases data (HDCT & autologous HSCT only)		
[Doros 2008]	1	n/r
[Engelhardt 2007]	3	Sepsis; sepsis; pulmonary metastases
[Kasper 2007]	1	Cardiac arrest of unknown origin
[Navid 2006]	1	Hepatic and renal failure
[Saab 2007]	2	Acute myocardial infarction; veno-occlusive disease
[Sleese 1988]	2	Staphylococcus sepsis; progressive encephalopathy
<i>Sum in 12 studies</i>	<i>15</i>	

Blay 2000: The authors did not specify, whether the patient was among the 24 patients with adult-type sarcomas or among the 6 patients with rhabdomyosarcoma and Ewing's sarcoma both of which are not included in the present review.
Cook 2012: 1 death within 100 days.

Abbreviation: HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation; n/a: not applicable; n/r: not reported; $p = p$ value; SDCT: standard-dose chemotherapy; TRM: treatment-related mortality.

Table 9. Disease-free survival (DFS)

Study	Disease-free survival, % (95% CI)		
	All patients assessed	Complete response before the time of HSCT	Not complete response before the time of HSCT
Aggregate case series data (HDCT & autologous HSCT only)			
[Cook 2012]	3 years: 23% (10 to 39)	3 years: 40% (15 to 69)	3 years: 9% (0 to 29)

Cook 2012: all patients N = 36, patients that achieved complete remission before HDCT N = 13, patients that did not achieve complete remission before HDCT N = 18.

Abbreviation: CI: confidence interval; HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation; n/a: not applicable; n/r: not reported; DFS: disease-free survival.

Progression-free survival

Progression-free survival (PFS) was not statistically significantly different between HDCT and autologous HSCT versus SDCT in the RCT by [Bui-Nguyen 2012] at three years (9.3% versus 21.6% with a HR of 1.34 (95% CI 0.81 to 2.20, $P = 0.25$)) (Table 10). The authors separately analyzed patients that had achieved a complete response to induction therapy before HDCT. PFS was higher in the complete response patients

compared to all patients and OS was statistically significantly different between the treatment arms: PFS among the patients that have achieved complete response at three years before HDCT was 20.0% versus 62.3% with a HR of 2.87 (95% CI 1.3 to 6.3, $P = 0.009$) (Table 10). [Blay 2000] reported a considerable difference between the PFS of patients with complete response before HDCT at two and five years (62% versus 5%).

Non-hematological toxicity grade 3 to 4

Non-hematological toxicity grade 3 to 4 was addressed in nine studies and 38 serious adverse event were described for 105 participants in nine studies (Table 11). A conservative estimate was 13.8% (38 events of non-hematological toxicity grade 3 to 4 in a total of 275 transplanted patients).

Secondary neoplasia

Secondary neoplasia was addressed in one case report (Table 12).

Health-related quality of life

Health-related quality of life scales were not addressed in the included studies.

Table 10. Progression-free survival (PFS)

Study	Progression-free survival, % (95% CI)		
	All patients assessed	Complete response before the time of HSCT	Not complete response before the time of HSCT
Aggregate comparative data (HDCT & autologous HSCT vs SDCT)			
[Bui-Nguyen 2012]	3 years: 9.3% vs. 21.6% HR 1.34 (0.81 to 2.20, $p = 0.25$)	3 years: 20.0% vs. 62.3% HR 2.87 (1.3 to 6.3, $p = 0.009$)	n/r
Aggregate case series data (HDCT & autologous HSCT only)			
[Bertuzzi 2003]	2 years: 0%	n/r	n/r
[Bisogno 2010]	2 years: 23%	n/r	n/r
	3 years: 15.5%		
[Blay 2000]	n/r	2 years: 62%	2 years: 5%
		5 years: 62%	5 years: 5%
[Bokemeyer 1997]	Median: 8 mo; range: 2 to 19	n/r	n/r
Individual cases data (HDCT & autologous HSCT only)			
50 studies	2 years: 50.6% (38.7 to 62.5)	n/r	n/r
	3 years: 36.7% (24.4 to 49.0)		
	5 years: 29.9% (16.7 to 43.1)		

Some estimates were deduced from Kaplan-Meier plots. Disease-free survival (DFS), event-free survival (EFS), failure-free survival (FFS), or health-related quality of life (HRQL) not reported. Bisogno 2010: Definition of endpoint: "For event-free survival (EFS), the interval between diagnosis and the date of latest follow-up, relapse or death was considered." In figure 1 of the article, the endpoint was designated as progression-free survival, which also is meaningful regarding the definition. Blay 2000: including 5 patients with rhabdomyosarcoma and 1 patient with primitive neuroectodermal tumor. Abbreviation: CI: confidence interval; HDCT: high-dose chemotherapy; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; PFS: progression-free survival; SDCT: standard-dose chemotherapy

Table 11. Non-hematological toxicity grade 3 to 4

Study	Non-hematological toxicity (N)							Remarks
	Nausea	Mucositis	Kidney	Liver	Nerv	Heart	Other	
Aggregate comparative data (HDCT & autologous HSCT only)								
[Bui-Nguyen 2012]	3	4	n/r	n/r	n/r	n/r	3	Other: infection (2); pain (1)
Aggregate case series data (HDCT & autologous HSCT only)								
[Bisogno 2010]	1	n/r	n/r	n/r	n/r	n/r	n/r	No grade 4 organ dysfunction
[Blay 2000]	8	n/r	5	n/r	1	0	n/r	n/r
[Bokemeyer 1997]	n/r	2	2	n/r	1	n/r	1	Nerv: central neurotoxicity; Other: septic episode
Individual cases data (HDCT & autologous HSCT only)								
[Garrido 1998]	n/r	n/r	n/r	n/r	1	n/r	n/r	Neuroleptic malignant syndrome
[Kozuka 2002]	1	n/r	n/r	n/r	n/r	n/r	n/r	n/r
[Kushner 2001]	n/r	n/r	n/r	n/r	1	n/r	n/r	n/r
[Patel 2004]	n/r	n/r	1	1	n/r	n/r	1	Other: respiratory distress
[Yonemoto 1999]	n/r	n/r	n/r	1	n/r	n/r	n/r	n/r
Sum	12	7	8	2	4	0	5	38 events in 105 patients of 9 studies

Single-arm studies, only transplanted patients. Toxicity defined by National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE), [NCI 2009b].

Abbreviation. HSCT: autologous haematopoietic stem cell transplantation following high-dose chemotherapy; n/a: not applicable; n/r: not reported; N: number.

Table 12. Secondary neoplasia

Study	Events (N)	Diagnosis
Individual cases data (HDCT & autologous HSCT only)		
[Yamamura 2003]	1	Chronic myelogenous leukemia

Single-arm studies, only transplanted patients.

Abbreviation: HDCT: high-dose chemotherapy; HSCT: hematopoietic stem cell transplantation.

Discussion

Summary of main results

Unlike in the first Cochrane systematic review published in 2011, we identified a randomized controlled trial (RCT) comparing HDCT followed by autologous HSCT to standard chemotherapy (SDCT) [Bui-Nguyen 2012]. The authors reported a difference in overall survival (OS) after the treatment in favor of SDCT (32.7% versus 49.4%) but the difference was not statistically significant (HR 1.26, 95% CI 0.70 to 2.29, $P = 0.44$). Progression-free survival was also in favor of SDCT (9.3% versus 21.6%) but again the difference was not significant (HR 1.34, 95% CI 0.81 to 2.20, $P = 0.25$). Therefore, there is evidence that patients may not have a better survival after HDCT followed by autologous HSCT. If at all, this intervention should only be offered after careful consideration and only within controlled clinical trials. Of the participants, 20% have diagnoses not relevant to the present review and the 80% of participants with relevant diagnoses have 12 different types of NRSTS. The heterogeneity of types of NRSTS may be important because the OS may differ between the tumor types and the results of frequent types may overlay those of infrequent types.

We identified six case series reporting aggregate data that represented at least 80% of patients with NRSTS. These results described observed survival after a single experimental treatment. The results do not allow conclusions about an effect or benefit of this treatment that is not established. Of the six studies, four case series reported on transplanted patients with desmoplastic small round-cell tumors. OS at two years ranged between 20% and 51.4%. Two case series had a variety of NRSTS. Unfortunately they did not report Kaplan-Meier survival estimates. Our estimated OS of 50.6% at two years for the remaining studies with participant level data falls slightly below the upper limit of the range of 20% to 51.4% reported for six studies with aggregate data. Follow-up information was available for 65% (80 out of 123) of participants that could be included in the survival analysis. For treatment-related mortality (TRM), even the more conservative estimate of 5.5% (15 out of 275 transplanted patients) is considerably higher than the 2.0% TRM within the first days following HSCT reported by the European Group for Blood and Marrow Transplantation (EBMT) Registry [EBMT 2009] for the year 1998 [Rosti 2002]. Secondary neoplasia was reported for just one participant, which was probably an extreme underestimation of the true frequency because of the relatively short follow-up in the included studies and the fact that the included studies were not designed to specifically detect secondary neoplasia. The detection of secondary neoplasia depends on a long follow-up, which might be provided by cancer registers. This reported incidence compares with a frequency of 4.0% for secondary neoplasia based on register data [Neglia 2001] and 6.9% [Baker 2003] after a long observation period of 20 years. Non-hematological severe organ toxicity grade 3 to 4 was reported for 36% (38 of 105) transplanted patients with relevant NRSTS in nine

studies. Lower grade and hematological toxicity were not included and should be accounted for to get a full picture of adverse events.

Overall completeness and applicability of evidence

Many of the studies we identified had to be excluded because they included participants with different heterogeneous tumors without separate reporting, or the proportion of participants with NRSTS was fewer than 80%. Furthermore, some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today. It is also a possibility that the results reflect the course of the disease and a consequence of the prior therapy rather than a consequence of the test intervention.

Quality of the evidence

The one RCT has a low risk of bias, whereas the remaining 48 studies were judged as having a high risk of bias. The characteristics of these single-arm studies showed that there are many different tumor types of NRSTS treated by transplantation, though each individual NRSTS entity was scarce. We found that a pooled survival analysis of individual participant data was considerably hampered. Specifically, the required follow-up information was incomplete or missing for 34% (37 out of 108) of participants and, therefore, corresponding data could not be included in the survival analysis. Each tumor type may carry an individual risk profile and, therefore, ideally should be evaluated separately. The body of evidence does not allow robust conclusions to be made in relation to the objectives of the review.

Potential biases in the review process

Strengths

The search strategy was broad and it is very likely that all relevant studies were identified. The WHO classification of NRSTS was adopted and modified to define a clear terminology for the study selection process. Studies were excluded if the proportion of noneligible participants were greater or equal to 20% of the total population. Authors were contacted to ask for additional data.

Limitations

The results of studies may be difficult to compare because followup started at different time points, that is at diagnosis or at start oftreatment. The delay between diagnosis and starting high-dose chemotherapy can be considerable. The median delay between diagnosis and intensification was four to 39 months in a study on 22 partici-

pants with STS including 11 NRSTS and 11 rhabdomyosarcoma patients [Dumontet 1992]. We did a sensitivity analysis restricting the pooled analysis to individual cases that were followed from the start of the treatment and we excluded cases that were followed from diagnosis. However, we found only a very marginal difference in survival estimates.

We identified one RCT with a low risk of bias. This means that the results of this RCT may be used as evidence for the evaluation of the efficacy of autologous HSCT following HDCT for NRSTS. All other identified studies were single-arm studies with an inherent very high risk of bias. This means that the results of the singlearm studies are not helpful to decide whether autologous HSCT following HDCT for NRSTS is a meaningful treatment option. Many studies were excluded because participants with NRSTS were mixed with participants with other malignant diseases. The heterogeneity of NRSTS and the possible different terminology used in publications may have led us to overlook studies with eligible participants. This may be more an issue for case series but it is highly unlikely for controlled trials. The pooled survival analysis of individual data was based on less than half of all the individual data available and the exclusion of these data, whilst intending to reduce bias, may also have introduced bias.

Agreements and disagreements with other studies or reviews

We agree with [Pedrazzoli 2006] that the potential benefit of this treatment option has not been investigated sufficiently in comparative studies. A systematic review [Verma 2008a] was performed to determine whether first-line dose-intensive chemotherapy supported by growth factor or autologous bone marrow or stem cell transplantation improves outcomes compared with standard-dose chemotherapy in patients with inoperable, locally advanced or metastatic soft tissue sarcoma. [Verma 2008a] included only one case series [Schlemmer 2006] with HDCT followed by autologous HSCT, which was excluded from the present review because 40% of patients were not diagnosed with the disease of interest. [Kasper 2005] concluded that the use of HDCT for locally advanced or metastatic adult (soft tissue and bone) sarcomas still remains highly investigational and should not be performed outside clinical trials.

Authors' Conclusions

Implications for practice

The evidence base does not support the use of HDCT followed by autologous HSCT in high-risk patients with NRSTS. If this treatment is offered it should only be after careful consideration and integrated within a prospective concurrent, preferably randomized, controlled trial.

Implications for research

It is doubtful whether further studies are necessary to clarify the relevance of HDCT followed by autologous HSCT in patients with NRSTS. If non-randomized controlled studies are conducted, a low risk of bias should be achieved. Single-arm studies are not helpful. Criteria for the included tumor types should adhere to the WHO classification.

Differences between protocol and review

Differences between the recent version and the updated version of the review

It is not clear that the unclassified and the undifferentiated tumor types are non-rhabdomyosarcoma soft tissue sarcomas. Therefore, we did not consider these tumor types for the present review and relocated both types from the list of included to the list of excluded tumor types. As a result, the following seven studies were included in the original review but excluded in the update: [Endo 1996; Frapier 1998; Mesia 1994; Nakamura 2008; Ronghe 2004; Shaw 1996; Watanabe 2006].

In contrast to the recent version, we excluded the article by [Ivanova 2007]. According to e-mail correspondence with the author AB Shvarova of a related article [Ivanova 2010] and co-worker at the same research institution, the proportion of patients with NRSTS was less than 50%. Most of the retrospectively observed patients were children diagnosed with rhabdomyosarcoma. In contrast to the recent version, we included the study by [Blay 2000] because we accepted the results of a subgroup analysis comprising 91% (22 out of 24) relevant patients. In agreement with the recent version, the exclusion of the study by [Schlemmer 2006] based on a proportion of NRSTS patients below 80% was confirmed according to a recent author contact.

We complemented PFS estimates. We conducted an updated search and included five further studies [Bisogno 2010; Buerk 2010; Hara 2010; Houet 2010; Jordan 2010] that were identified in the update and therefore not reported in the recent version. One study reported aggregate data of 14 participants [Bisogno 2010] and three studies reported individual data of nine participants which were suitable for inclusion in the meta-analysis [Buerk 2010; Hara 2010; Jordan 2010].

Concerning the two articles by [Kasper 2007a] and [Kasper 2010], we stated in the recent version that some participants were reported in both articles. In the present updated version, we evaluated these duplicate data and identified six participants by coincidental information on age, histology, and metastatic sites. We included eight instead of 14 participants reported by [Kasper 2007a] and seven participants reported by [Kasper 2010]. Consequently, we removed the duplicate data of six participants from the pooled analysis. We did not find additional reviews in the updated search.

We changed the search strategy to increase the fraction of the identified relevant documents of all identified relevant and not relevant documents (precision). The new search strategy is more economical in terms of spending resources for study selection for the present review and also for future updates. The new search strategy was not only used for the time period to be updated but was used from inception of all electronic databases searched. The screening process was redone regarding the complete retrieved records. All identified studies were evaluated in detail regardless of being part of the original review. We considered and re-evaluated all studies that were included in the original review. Therefore, the search strategy is composed of two parts. The new more narrow strategy is spanning the time from inception to 5 December 2012. The old more broad strategy is spanning from inception to 5 February 2010.

References

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CHAPTER 4

First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia

Peinemann F, Grouven U, Kroger N, Bartel C, Pittler MH, Lange S. First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia. PLoS One. 2011;6(4):e18572.

Abstract

Introduction Acquired severe aplastic anemia (SAA) is a rare and progressive disease characterized by an immune-mediated functional impairment of hematopoietic stem cells. Transplantation of these cells is a first-line treatment option if HLA-matched related donors are available. First-line immunosuppressive therapy may be offered as alternative. The aim was to compare the outcome of these patients in controlled trials.

Methods A systematic search was performed in the bibliographic databases MEDLINE, EMBASE, and The Cochrane Library. To show an overview of various outcomes by treatment group we conducted a meta-analysis on overall survival. We evaluated whether studies reported statistically significant factors for improved survival.

Results 26 non-randomized controlled trials (7,955 patients enrolled from 1970 to 2001) were identified. We did not identify any RCTs. Risk of bias was high except in 4 studies. Young age and recent year of treatment were identified as factors for improved survival in the HSCT group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the IST group. In 19 studies (4,855 patients), summary statistics were sufficient to be included in meta-analysis. Considerable heterogeneity did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies.

Conclusions Young age and recent year of treatment were identified as factors for improved survival in the transplant group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the immunosuppressive group. Considerable heterogeneity of non-randomized controlled studies did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies.

Introduction

Acquired severe aplastic anemia (SAA) is a rare [1] and potentially fatal disease which is characterized by hypocellular bone marrow and pancytopenia, and mainly affects young adults. The incidence rate was estimated at less than 4 per million people per year [2]. The major signs and symptoms are severe infections, bleeding, and exhaustion. The underlying pathophysiology is thought to be an aberrant immune response involving the T-cell mediated destruction of hematopoietic stem cells. In most cases, the cause is unknown, although various triggers such as drugs, toxins, and viruses have been reported [3,4].

The treatment of SAA mainly includes immunosuppressive therapy (IST) with antithymocyte globulin (ATG)/antilymphocyte globulin (ALG) and cyclosporine A (CSA), or allogeneic hematopoietic stem cell transplantation (HSCT) [3,4,5]. Allogeneic HSCT is seen as the treatment of choice for selected patients with an HLA-matched related donor [6,7]. Allogeneic HSCT is associated with graft failure, graft-versus-host disease (GVHD), and organ toxicities. On the other hand, patients may not respond to IST and long-term IST is associated with the development of clonal diseases [8]. Clinical treatment algorithms have been suggested to find a decision that meets individual conditions, personal preferences, and prognostic factors [9].

The present systematic review and meta-analysis compares the outcome after first-line HLA-matched related donor HSCT vs. IST in SAA patients in published controlled trials.

Methods

While preparing this systematic review and meta-analysis, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist [10,11].

Study inclusion criteria

We included patients with acquired severe aplastic anemia who received, as first-line treatment, allogeneic HSCT from HLA-matched related donors (MRD) as the test intervention and IST as the control intervention. Study design was limited to randomized controlled trials (RCTs) and non-randomized intervention studies [12]. We did not set a minimum sample size to be considered. Fulltext publications in English language were considered. We set no limits on year of publication or year of treatment. A protocol is not available.

Search strategy

MEDLINE (1950 to 2010), EMBASE (1980 to 2010) and The Cochrane Library (to 2010) were searched without restrictions on study design and publication year (final search 10 January 2010). The first database search was conducted 24 January 2006. The final search 10 January 2010 included a modified strategy to consider MeSH changes and to render the exclusion of animal studies more precisely. The MeSH term BONE MARROW TRANSPLANTATION was deleted from one category [13]. For MeSH 2008 there was a major revision of Publication Types (PT) and the phrase "as Topic" was added [14]. We introduced (ANIMALS not (ANIMALS and HUMANS)).sh. and replaced (ANIMALS not HUMANS).sh. To account for these changes, both searches were not restricted to any publication year. The terms and the syntax used for the search in MEDLINE via Ovid as shown in Table 1 were tailored to the requirements of the other 2 databases. Reference lists of all included original articles and 5 recent reviews (2007 to 2009) [8,9,15,16,17] were handsearched. Abstracts of the American Society of Hematology Annual Meeting 2004 to 2009 [18] and information on studies registered at ClinicalTrials.gov [19] were searched online (April 2010).

Study selection

First, articles were excluded if the title and/or the abstract clearly referred to other diagnoses than severe aplastic anemia and in addition clearly referred to other interventions than allogeneic hematopoietic stem cell transplantation. Second, articles not excluded in the first step were evaluated whether patients were analyzed in a test group after first-line allogeneic HSCT from a MRD and were compared with patients after first-line IST in a control group. Reporting of extractable information about overall survival was required for all included studies. For each excluded study, an appropriate reason was documented. All steps of the literature screening process were performed by two independent reviewers. Any disagreements were resolved by discussion. Criteria for classification of severity of aplastic anemia and quality of response after immunosuppressive treatment were applied according to the EBMT [20].

Risk of bias

Risk of bias within studies was evaluated by assessing study design, such as retropro prospective planning, concurrent control group, criteria for assignment of patients to treatment arms, control for confounding factors, and other criteria, such as unclear selection of patients and analysis of the same patients in both treatment groups, that may increase the risk of bias especially in non-randomized trials [21]. A low risk of bias required a 'yes' for all three of the following topics: concurrent control group, control for confounding factors, and no other risk of bias factors.

Table 1. Search strategy used in MEDLINE via Ovid

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1950 to Present>

Search Strategy: row number, search term (number of retrieved records)

1	exp ANEMIA, APLASTIC/ (12718)
2	(aplast\$ anem\$ or aplast\$ anaem\$).tw,kf,ot. (6906)
3	or/1-2 (14343)
4	exp STEM CELL TRANSPLANTATION/ (33962)
5	exp BONE MARROW TRANSPLANTATION/ (37050)
6	exp TRANSPLANTATION, HOMOLOGOUS/ (68947)
7	transplant\$.tw,kf,ot. (271774)
8	graft\$.tw,kf,ot. (187569)
9	(allograft\$ or allo-graft\$).tw,kf,ot. (42157)
10	(homograft\$ or homo-graft\$).tw,kf,ot. (4829)
11	or/4-10 (443058)
12	RANDOMIZED CONTROLLED TRIALS AS TOPIC.sh. (63488)
13	RANDOMIZED CONTROLLED TRIAL.pt. (279602)
14	random\$.tw,kf,ot. (484356)
15	CONTROLLED CLINICAL TRIAL.pt. (79896)
16	RANDOM ALLOCATION.sh. (66150)
17	DOUBLE BLIND METHOD.sh. (102937)
18	SINGLE BLIND METHOD.sh. (13347)
19	(ANIMALS not HUMANS).sh. (3331490)
20	exp CLINICAL TRIALS AS TOPIC/ (221553)
21	CLINICAL TRIAL.pt. (452572)
22	(clin\$ adj25 trial\$).tw,kf,ot. (173070)
23	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw,kf,ot. (105483)
24	PLACEBOS.sh. (28204)
25	placebo\$.tw,kf,ot. (122048)
26	RESEARCH DESIGN.sh. (57641)
27	COMPARATIVE STUDY.pt. (1453016)
28	exp EVALUATION STUDIES AS TOPIC/ (779364)
29	FOLLOW-UP STUDIES.sh. (391452)
30	PROSPECTIVE STUDIES.sh. (267034)
31	(control\$ or prospectiv\$ or volunteer\$).tw,kf,ot. (2222508)
32	(metaanal\$ or (meta and anal\$) or ((review or search\$) and (medical database\$ or medline or pubmed or embase or cochrane or systemat\$))).tw,kf,ot. (80827)
33	META-ANALYSIS AS TOPIC.sh. (9714)
34	META-ANALYSIS.pt. (22757)
35	exp REGISTRIES/ (37774)
36	(registr\$ or register\$ or ibmtr\$ or ebmt\$).tw,kf,ot. (129832)
37	((group or regist\$) and (blood or stem cell or marrow) and transplant\$ and (europ\$ or international)).tw,kf,ot. (1120)
38	or/12-37 (7025740)
39	(ANIMALS not (ANIMALS and HUMANS)).sh. (3331490)
40	and/3,11,38 (1160)
41	40 not 39 (1087)
42	from 41 keep 1-1087 (1087)

Primary outcome: overall survival

The primary effect measure for meta-analyses was the hazard ratio. If the hazard ratio was not directly given in the publication, we extracted summary statistics from Kaplan Meier survival functions and estimated hazard ratios according to methods proposed by Parmar 1998 [22]. For estimation, we applied a tool which uses p values of the appropriate log-rank test comparing the two survival functions of interest, number of patients analyzed, and number of events on each arm [23]. If this information was not available, hazard ratios were deduced from the graphical display of the survival curves, if possible. Meta-analyses were conducted using the generic variance approach [24,25] and the random effects model [26]. Calculations were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). The results of the meta-analyses were graphically displayed by means of a forest plot. Heterogeneity of the results was visually assessed and quantified using the I² value [27]. A funnel plot was prepared by using The Cochrane Collaboration's Review Manager 5 (<http://www.cc-ims.net/revman>). In the case of considerable heterogeneity (I² ≥ 50%), a pooled estimate is not reasonable and, therefore, was not calculated [28].

Subgroup analysis

Sensitivity analysis: We tried to explain heterogeneity identified in the meta-analysis of overall survival by evaluating dichotomized subpopulations of study and patients characteristics in several sensitivity analyses [29]. Subgroups in individual studies: We extracted overall survival data of subgroups to reproduce survival functions from some individual studies if reported for both treatments. Data on subgroup analyses were extracted if available. The difference between the estimates of 2 subgroups was evaluated by conducting a test of interaction based on meta-regression models [30]. Calculations were conducted using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Factors for improved survival

We extracted statistically significant results from multivariate analyses on factors for improved survival, such as age, disease severity, treatment period, and type of IST, if reported in the included studies.

Data collection and analysis

All steps of the data collection process were performed by two independent reviewers. Any disagreements were resolved by discussion. We collected study characteristics such as the number and region of participating centers, the treatment period, the

number of analyzed patients per treatment arm, the proportion of patients with diseases other than SAA, a regimen other than firstline treatment, and median follow-up. Median age, gender, and time interval from diagnosis to treatment were extracted as patients' characteristics. For the HSCT arm we extracted the number of patients who were treated with conditioning irradiation and conditioning ATG or ALG. For the IST arm we extracted the number of patients treated with ATG or ALG alone or in combination with CSA.

The primary outcome was overall survival from the beginning of HSCT or IST. Kaplan Meier estimates were extracted directly from the text or deduced from survival curves given in the publication. The principal summary measure was the hazard ratio as specified in the meta-analysis section. We extracted the p value of the log-rank test of the overall survival functions and the 5-year estimate of both treatment arms. Results from subgroup analyses were also extracted.

The secondary outcomes were overall mortality, graft failure, GVHD, no response to IST, and health-related quality of life.

Graft failure included both primary and secondary types; acute GVHD was considered if grade II–IV was reported and chronic GVHD was considered if an extensive course was reported.

Results

Search results

Of 3,085 retrieved publications, 358 full-text papers were obtained for further assessment, and 26 non-randomized controlled clinical trials were identified that met the inclusion criteria and were included in the present study [31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56] (Figure 1). We did not identify any RCTs.

An overview of the study characteristics is presented in Table 2. Patients were recruited between 1970 and 2002 in 24 studies, whereas in 2 studies, year of treatment was not reported. In 13 studies [31,34,35,39,41,42,43,44,45,46,47,49,54], disease severity (SAA or VSAA) or first-line treatment was clearly classified for all patients. The proportion of patients with moderate aplastic anemia, unknown disease severity, or second-line treatment was less than 20% in 6 studies [32,36,38,40,50,52] and was 20% or more in 7 studies [33,37,48,51,53,55,56]. 25 included trials used information about the availability of MRD to allocate patients to comparison groups, called Mendelian (genetic) randomization [57,58]. In 3 studies [41,52,53], relevant data were not reported for the total study population but were reported separately for subgroups.

Figure 1. Literature search and study flow.

Abbreviations: HSCT: hematopoietic stem cell transplantation;
IST: immunosuppressive therapy; SAA: severe aplastic anemia.

Baseline data

An overview of characteristics of 7,955 analyzed patients in 26 studies is presented in Table 3. Median age (HSCT vs. IST: 9–24 vs. 5–55 years) was reported in 15 of 26 studies and the difference between groups was not statistically different (sign test: $p = 0.119$). Gender (HSCT vs. IST: 44–76 vs. 43–78 percent males) was reported in 19 of 26 studies and median of the time from diagnosis to treatment (HSCT vs. IST: 27–300 vs. 12–150 days) was reported in 15 of 26 studies.

An overview of the treatment characteristics is presented in Table 4. Conditioning irradiation was reported in 22 of 26 studies (0%–100%) and ATG or ALG was used in 9 studies (2%–100%) in the HSCT arms. In the IST arms, ATG or ALG (8%–100%) and CSA (0%–100%) was reported in 25 of 26 studies. IST was composed of ATG or ALG in 25 studies and was combined with CSA in 13 studies.

Table 2. Study characteristics

No	Included studies	Group, region (N. centers)	Treatment period in years	N. analyzed patients; subgroups indicated HSCT vs. IST	N. patients other* than SAA (%); HSCT vs. IST	N. patients other† than first-line treatment (%); HSCT vs. IST	Median follow-up in years
1	Ahn 2003 [31]	Seoul, Korea (10)	1990-2001	64 vs. 156	0 vs. 0	0 vs. 0	–
2	Arranz 1994 [32]	Madrid, Spain (1)	1983-1991	21 vs. 29. Subgroup age 20-40 years: 11 vs. 13	0 vs. 2 (7)	5 (24) vs. 1 (3)	–
3	Bacigalupo 1988 [33]	EBMT, Europe (57)	1981-1986	218 vs. 291. Subgroup age + PMN: <20 ys + <0.2 G/L: 55 vs. 46; <20 ys + ≥0.2 G/L: 63 vs. 57; ≥20 ys + <0.2 G/L: 32 vs. 89; ≥20 ys + ≥0.2 G/L: 44 vs. 36	45 (21) vs. 92 (32)	47 (22) vs. 0	2.6 vs. 2.7
4	Bacigalupo 2000 [34]	EBMT, Europe (?)	1976-1998	Subgroup year (IST = ALG) 1976-1989: 915 vs. 523; 1990-1998: 844 vs. 116. Subgroup year (IST = ALG+CSA) 1976-1989: 915 vs. 56; 1990-1998: 844 vs. 53	0 vs. 0	0 vs. 0	–
5	Bayever 1984 [35]	Los Angeles, USA (1)	1977-1982	35 vs. 22	0 vs. 0	0 vs. 0	–
6	Champlin 1984 [36]	Los Angeles, USA (1)	unclear	61 vs. 69. Subgroup age <20: 35 vs. 21; 20-<35: 21 vs. 21; ≥35: 5 vs. 27	0 vs. 0	0 vs. 5 (7)	–
7	De Planque 1990 [37]	Leiden, Netherlands (1)	1974-1987	19 vs. 63	0 vs. 0	8 (42) vs. 19 (30)	2.8 vs. 1.8
8	Doney 1997 [38]	Seattle, USA (1)	1978-1991	168 vs. 227. Subgroup age (<6 ys: 12 vs. 25), 6-<20 ys: 63 vs. 62; 20-<40 ys: 82 vs. 73; ≥40 ys: 11 vs. 67. Subgroup PMN <0.2 G/L: 70 vs. 94; ≥0.2 G/L: 98 vs. 133	0 vs. 34 (15)	0 vs. 0	–
9	Fouladi 2000 [39]‡	Toronto, Canada (1)	1987-1997	21 vs. 20	0 vs. 0	0 vs. 0	–
10	Fuhrer 1998 [40]	SAA 94, Germany (37)	1993-1997	28 vs. 86	2 (7) vs. 7 (8)	0 vs. 0	4.3 vs. 3.0
11	Fuhrer 2005 [41]	Germany (53)	1993-2001	Subgroup PMN <0.2 G/L: 40 vs. 97; <0.2-<0.5 G/L: 27 vs. 49	0 vs. 0	0 vs. 0	–
12	Ghavamzadeh 2004 [42]	Tehran, Iran (1)	1990-2001	29 vs. 24	0 vs. 0	0 vs. 0	–
13	Gillio 1997 [43]	New York, USA (1)	1983-1992	25 vs. 23. Subgroup year 1983-1987: not extractable; 1988-1992: not extractable	0 vs. 0	0 vs. 0	–
14	Gluckman 1979 [44]§	Paris, France (1)	unclear	37 vs. 28	0 vs. 0	0 vs. 0	6.8 vs. 7.2

No	Included studies	Group, region (N. centers)	Treatment period in years	N. analyzed patients; subgroups indicated HSCT vs. IST	N. patients other* than SAA (%); HSCT vs. IST	N. patients other† than first-line treatment (%); HSCT vs. IST	Median follow-up in years
15	Halperin 1989 [45]	Toronto, Canada (1)	1977-1987	14 vs. 12	0 vs. 0	0 vs. 0	–
16	Kahn 2002 [46]	Kansas City, USA (1)	1977-1999	15 vs. 16	0 vs. 0	0 vs. 0	6.0 vs. 2.0
17	Kim 2003 [47]	Seoul, Korea (1)	1990-1999	22 vs. 74	0 vs. 0	0 vs. 0	0.4 vs. 4.4
18	Kojima 2000 [48]	Nagoya, Japan (2)	1984-1998	37 vs. 63	7 (19) vs. 14 (22)	0 vs. 0	–
19	Lawlor 1997 [49]	Vancouver, Canada (1)	1982-1994	9 vs. 18	0 vs. 0	0 vs. 0	3.0 vs. 2.7
20	Locasciulli 1990 [50]	EBMT, Europe (29)	1970-1988	171 vs. 133	0 vs. 0	23 (13) vs. 0	–
21	Locasciulli 2007 [51]	EBMT, Europe (257)	1991-2002	1567 vs. 912. Subgroup year (HSCT among patients with MSD) 1991-1996: 614 vs. 608; 1997-2002: 550 vs. 304. Subgroup age (IST among patients with PMN ≥ 0.2 G/L (vs. PMN < 0.2 G/L)); < 16 ys: 607 vs. 129 (vs. 175); ≥ 16 ys: 960 vs. 442 (vs. 141)	1183 (75) vs. 368 (40)	197 (13) vs. 0	4.6 vs. 4.7
22	Paquette 1995 [52]	Los Angeles, USA (1)	1977-1989	Subgroup year 1977-1983: 37 vs. 40; 1984-1989: 18 vs. 16	0 vs. 0	0 vs. 3 (5)	2.4 vs. 4.5
23	Pitcher 1999 [53]	London, UK (1)	1973-1996	Subgroup year 1973-1988: unclear, 1989-1996: unclear	unclear	unclear	–
24	Tzeng 1989 [54]	Taipei, ROC (1)	1985-1988	9 vs. 7	0 vs. 0	0 vs. 0	–
25	Viollier 2005 [55]**	Basel, Switzerland (1)	1976-1999	52 vs. 155	14 (27) vs. 50 (32)	0 vs. 0	2.0 vs. 0.5
26	Werner 1989 [56]††	Cincinnati, USA (2)	1981-1986	6 vs. 9	0 vs. 2 (22)	0 vs. 0	11.5 vs. 11.3

*other than SAA; MAA or not reported degree of severity; †other than first-line MRD; second-line HSCT, first-line mismatched related HSCT, first-line- unrelated HSCT; ‡Fouladi 2000: 5 patients in the IST group received second-line HLA-matched unrelated donor transplantation after failed IST; §Gluckman 1979: 5 patients of the IST group received second-line HLA-identical sibling donor transplantation after failed IST; 2 patients with Fanconi anemia and 2 patients with paroxysmal nocturnal hemoglobinemia were included; ||Kojima 2000: 11 patients in the IST group received second-line unrelated donor transplantation after failed IST; ¶Pitcher 1999: outcome from 1973-1988 has been reported by Webb 1991 [69]; number of patients other than SAA estimated; **Viollier 2005: Follow-up of Nissen 1999 [70], Speck 1994 [71], Tichelli 1988 [72], Speck 1986 [73], Speck 1984 [74], Speck 1983 [75], Speck 1981 [76], Speck 1980 [77], Speck 1977 [78]; 8 patients of the IST group received HSCT; ††Werner 1989: 1 patient in the IST group received second-line haploidentical transplantation after failed IST; Abbreviations: HLA: human leukocyte antigen; IST immunosuppressive therapy; PMN: polymorphonuclear neutrophil granulocytes; ROC: Republic of China; UK: United Kingdom of Great Britain and Northern Ireland; USA: United States of America

Table 3. Patients' characteristics

No	Study	Age; median years (range); H SCT vs. IST	Gender; N, males : N, females (% males); H SCT vs. IST	Time interval from diagnosis to treatment; median days (range); H SCT vs. IST
1	Ahn 2003 [31]	(14-24) vs. (14-24)	33 : 31 (57) vs. 72 : 84 (46)	–
2	Arranz 1994 [32]	24 (12-46) vs. 38 (8-71)	–	50 (8-1145) vs. 60 (2-1889)
3	Bacigalupo 1988 [33]	(0-50) vs. (0-50)	135 : 82 (62) vs. 162 : 126 (56)	(0->90) vs. (0->90)
4	Bacigalupo 2000 [34]	–	–	90 vs. 35
5	Bayever 1984 [35]	17 (2-24) vs. 15 (1-23)	23 : 12 (66) vs. 15 : 7 (68)	60 (9-2520) vs. 58 (8-2669)
6	Champlin 1984 [36]	17 (1-44) vs. 31 (1-76)	43 : 18 (71) vs. 41 : 28 (59)	60 (7-1440) vs. 64 (3-2671)
7	De Planque 1990 [37]	27 (13-85) across groups	42 : 40 across groups	–
8	Doney 1997 [38]	22 (2-53) vs. 25 (1-74)	101 : 67 (60) vs. 102 : 125 (45)	30 (6-6822) vs. 42 (3-4590)
9	Fouladi 2000 [39]	9 (2-16) vs. 10 (1-17)	16 : 5 (76) vs. 11 : 9 (55)	54 (18-165) vs. 12 (0-60)
10	Fuhrer 1998 [40]	10 (2-16) vs. 9 (1-15)	12 : 16 (43) vs. 53 : 33 (62)	49 (18-272) vs. 23 (3-168)
11	Fuhrer 2005 [41]	9 (1-17) across groups	125 : 88 across groups	27 (1-268) across groups
12	Ghavamzadeh 2004 [42]	19 vs. 25 mean	19 : 10 (63) vs. 18 : 6 (75)	–
13	Gillio 1997 [43]	12 (2-19) vs. 14 (1-20)	14 : 11 (56) vs. 18 : 5 (78)	27 (5-2124) vs. 35 (10-4383)
14	Gluckman 1979 [44]	19 (3-31) vs. 21 (4-56)	23 : 14 (62) vs. 15 : 13 (54)	90 (8-2520) vs. 120 (15-1152)
15	Halperin 1989 [45]	8 (1-18) across groups	21 : 15 across groups	27 (15-120) vs. 30 (6-180)
16	Kahn 2002 [46]	22 (6-59) vs. 55 (9-78)	8 : 7 (53) vs. 10 : 6 (63)	38 (14-866) vs. 12 (2-183)
17	Kim 2003 [47]	22 (14-43) vs. 34 (15-75)	16 : 6 (73) vs. 37 : 37 (50)	300 (30-3540) vs. 150 (30-10920)
18	Kojima 2000 [48]	10 (0-16) vs. 9 (1-17)	18 : 19 (49) vs. 31 : 32 (49)	38 (20-2040) vs. 24 (12-2490)
19	Lawlor 1997 [49]	13 (4-17) vs. 7 (2-14)	4 : 5 (44) vs. 9 : 9 (50)	–
20	Locasciulli 1990 [50]	(0-15) vs. (0-15)	97 : 74 (57) vs. 71 : 62 (53)	(0->90) vs. (0->90)
21	Locasciulli 2007 [51]	19 (1-67) vs. 24 (1-94)	959 : 605 (61) vs. 520 : 390 (57)	81 (1-3661) vs. 23 (1-1375)
22	Paquette 1995 [52]	(16-30) vs. (16-30)	–	–
23	Pitcher 1999 [53]	(1-14) across groups	40 : 35 across groups	–
24	Tzeng 1989 [54]	20 (10-35) vs. 27 (19-56)	5 : 4 (56) vs. 3 : 4 (43)	–
25	Vollmer 2005 [55]	19 (2-55) vs. 23 (2-74)	27 : 25 (52) vs. 85 : 70 (55)	51 (6-420) vs. 36 (1-11340)
26	Werner 1989 [56]	(3-15) vs. (1-16)	4 : 2 (67) vs. 5 : 4 (56)	(7-56) vs. (7-406)

–: information not extractable from publication; Abbreviations: H SCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy

Table 4. Treatment characteristics

No	Study	HSCT; N. treated / N. total (%)		IST; N. treated / N. total (%)	
		Irradiation*	ATG or ALG	ATG or ALG	CSA
1	Ahn 2003 [31]	6 / 64 (9)	53 / 64 (83)	148 / 156 (95)	67 / 156 (43)
2	Arranz 1994 [32]	20 / 21 (95)	–	29 / 29 (100)	0
3	Bacigalupo 1988 [33]	110 / 218 (50)	–	291 / 291 (100)	0
4	Bacigalupo 2000 [34]	433 / 1759 (25)	28 / 1759 (2)	–	–
5	Bayever 1984 [35]	35 / 35 (100)	0	22 / 22 (100)	0
6	Champlin 1984 [36]	59 / 61 (97)	0	69 / 69 (100)	0
7	De Planque 1990 [37]	15 / 19 (79)	1 / 19 (5)	83 / 83 (100)	0
8	Doney 1997 [38]	0	21 / 168 (24)	225 / 227 (99)	1 / 227 (1)
9	Fouladi 2000 [39]	12 / 21 (57)	5 / 21 (24)	20 / 20 (100)	19 / 20 (95)
10	Fuhrer 1998 [40]	–	28 / 28 (100)	86 / 86 (100)	86 / 86 (100)
11	Fuhrer 2005 [41]	0	0	VSAA: 97 / 97 (100) SAA: 49 / 49 (100)	VSAA: 97 / 97 (100) SAA: 49 / 49 (100)
12	Ghavamzadeh 2004 [42]	0	29 / 29 (100)	2 / 24 (8)	24 / 24 (100)
13	Gillio 1997 [43]	17 / 25 (68)	3 / 25 (12)	23 / 23 (100)	0
14	Gluckman 1979 [44]	10 / 37 (27)	9 / 37 (24)	28 / 28 (100)	0
15	Halperin 1989 [45]	14 / 14 (100)	14 / 14 (100)	12 / 12 (100)	0
16	Kahn 2002 [46]	8 / 15 (53)	0	16 / 16 (100)	16 / 16 (100)
17	Kim 2003 [47]	17 / 22 (77)	2 / 22 (9)	74 / 74 (100)	17 / 74 (23)
18	Kojima 2000 [48]	26 / 37 (70)	9 / 37 (24)	27 / 63 (43)	2 / 63 (3)
19	Lawlor 1997 [49]	2 / 9 (22)	1 / 9 (11)	18 / 18 (100)	15 / 18 (83)
20	Locasciulli 1990 [50]	59 / 171 (35)	34 / 171 (20)	133 / 133 (100)	0
21	Locasciulli 2007 [51]	282 / 1567 (18)	319 / 1567 (20)	495 / 912 (54)	846 / 912 (93)
22	Paquette 1995 [52]	–	–	1977-1983: 40 / 40 (100) 1984-1989: 16 / 16 (100)	0
23	Pitcher 1999 [53]	–	–	1973-1988: 18 / 18 (100) 1989-1996: 25 / 25 (100)	1973-1988: 0 1989-1996: 14 / 25 (56)
24	Tzeng 1989 [54]	9 / 9 (100)	0	7 / 7 (100)	0
25	Viollier 2005 [55]	–	–	155 / 155 (100)	0
26	Werner 1989 [56]	2 / 6 (33)	–	8 / 9 (89)	2 / 9 (22)

*Irradiation: conditioning irradiation: thoraco-abdominal irradiation, total body irradiation, or total lymphoid irradiation.

Abbreviations: ALG: anti-lymphocyte globulin; ATG: anti-thymocyte globulin; CSA: cyclosporine A; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy

Primary outcome: overall survival

An overview of the overall survival is presented in Table 5. 5-year overall survival was reported in 17 studies (HSCT vs. IST: 32%–98% vs. 37%–92%). 5 studies reported a statistically significant difference of survival functions in favor of HSCT [38,47,48,50,51] and 1 study in favor of IST [46]. 9 studies [31,33,35,40,42,43,49,54,55] did not find a statistically significant difference of survival functions and 11 studies did not report a significance test.

We included 19 studies (4,855 patients) [31,32,33,35,37,38,39,40,42,43,45,46,47, 48,49,50,51,54,55] in a meta-analysis on overall survival, which provided summary statistics required for estimating the hazard ratio. The pooled hazard ratio was statistically not significant and was characterized by a considerable heterogeneity indicated by an I² value of 75% (Figure 2). A pooled estimate was not justified.

Figure 2. Meta-analysis of all studies with available data.

Meta-analysis of overall survival using hazard-ratio as effect measure after first-line HSCT vs. first-line IST. Pooled estimate not justified because of considerable heterogeneity and of not sufficient external validity. Abbreviations: HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; SAA: severe aplastic anemia; SE: standard error.

Table 5. Five-year overall survival

No	Study	Total		Subgroups		Comments
		Yes	Meta-analysis HSCT vs. IST in % (p value\$)	Meta-analysis HSCT vs. IST in % (p value\$)	HSCT vs. IST in % (p value\$)	
1	Ahn 2003 [31]	Yes	79* vs. 72* (0.83)	-	-	-
2	Arranz 1994 [32]	Yes	71† vs. 62† (-)	-	3 years (20-40 ys: 63† vs. 47†)	-
3	Bacigalupo 1988 [33]	Yes	63† vs. 61† (0.1)	Age PMN	Subgroup age + PMN: <20 ys + <0.2 G/L: 64† vs. 38† (0.01); <20 ys + ≥0.2 G/L: 58† vs. 62† (0.1); 4 years (≥20 ys + <0.2 G/L: 62† vs. 82† (0.002)); 4 years (≥20 ys + ≥0.2 G/L: 44† vs. 43† (0.06))	Younger patients (<20 ys) had a better survival with HSCt than with IST, p=0.01. This result remained stable for patients with <0.2 G/L (p=0.01) but not with ≥0.2 G/L (p=0.1). Patients aged ≥20 ys had a better survival with IST than with HSCt, p=0.0008. This result remained stable for patients with ≥0.2 G/L (p=0.002) but not with <0.2 G/L (p=0.06).
4	Bacigalupo 2000 [34]	-	-	Year	Subgroup IST = ALG: 1976-1989: 56† vs. 50† (-); 1990-1998: 80† vs. 63† (-); Subgroup IST = ALG + CSA; 1976-1989: 56† vs. 64† (-); 1990-1998: 80† vs. 83† (-)	HSCt: Age 1990-1998: <17 ys (77) vs. 17-40 ys (68) vs. ≥41 ys (54), p=0.001. The outcome among transplanted patients was better with younger age. Survival has improved in all age groups over time and the effect of age remained. Patients receiving radiation had no survival advantage but a higher incidence of chronic GVHD and malignant disease. IST: Age (unclear treatment period): <17 (64) vs. 17-40 (71) vs. ≥41 (59). There was no age effect on outcome of IST patients.
5	Bayever 1984 [35]	Yes	4 years (72* vs. 45* (0.18))	-	-	-
6	Champlin 1984 [36]	-	61† vs. 56† (-)	Age	Subgroup age: 4 years (<20: 79† vs. 37* (0.02)); 20-<35: 41† vs. 68* (not sign.); 2 years (≥35: 20* vs. 60* (0.02))	Survival function reported only for subgroups
7	De Planque 1990 [37]	Yes	32† vs. 63† (-)	-	-	-
8	Doney 1997 [38]	Yes	72* vs. 48*	Age	Subgroup age: <6 ys: 100* vs. 55*	-

No	Study	Total		Subgroups		Comments	
		Meta-analysis		Meta-analysis		HSCT vs. IST	
		HSCT vs. IST in % (p value\$)		HSCT vs. IST in % (p value\$)		HSCT vs. IST in % (p value\$)	
		(0.01 favors HSCT)		PMN		(0.006); 6-<20 ys: 78* vs. 55* (0.001); 20-<40 ys: 69* vs. 57* (0.04); ≥40 ys: 37* vs. 39* (0.2). Subgroup PMN: <0.2 G/L: 74* vs. 38* (-); ≥0.2 G/L: 74* vs. 58* (-)	
9	Fouladi 2000 [39]	Yes	95* vs. 65*	-	-	-	-
10	Fuhrer 1998 [40]	Yes	4 years (84† vs. 87† (0.43))	-	-	-	-
11	Fuhrer 2005 [41]	-	-	-	-	Subgroup PMN: <0.2 G/L: 89† vs. 93† (-); ≥0.2 G/L: 96† vs. 81† (-)	Survival function reported only for IST group; significant difference within the IST group, p<0.001.
12	Chavamazadeh 2004 [42]	Yes	67† vs. 37† (0.3)	-	-	-	-
13	Gillio 1997 [43]	Yes	83* vs. 86* (0.98)	-	-	Subgroup year: 1983-1987: 72* vs. 85* (not sign.); 1988-1992: 100* vs. 89* (not sign.)	Number of patients not reported for treatment periods.
14	Gluckman 1979 [44]	-	-	-	-	-	-
15	Halperin 1989 [45]	Yes	78* vs. 43* (-)	-	-	-	-
16	Kahn 2002 [46]	Yes	33* vs. 70* (0.047 favors IST)	-	-	-	-
17	Kim 2003 [47]	Yes	95† vs. 70† (0.04 favors HSCT)	-	-	-	-
18	Kojima 2000 [48]	Yes	98* vs. 80* (0.004 favors HSCT)	-	-	-	-
19	Lawlor 1997 [49]	Yes	75† vs. 92† (0.15)	-	-	-	-
20	Locasciulli 1990 [50]	Yes	64* vs. 52* (0.002 favors HSCT)	-	-	-	-
21	Locasciulli 2007 [51]	Yes	74* vs. 75*	Age	Subgroup year (HSCT among patients	HSCT: The outcome among patients with MSD has	

No	Study	Total		Subgroups		Comments	
		Meta-analysis	HSCT vs. IST in % (p value\$)	Meta-analysis	HSCT vs. IST in % (p value\$)		
			(0.002 favors HSCT)	Year PMN	with MSD): 1991-1996: 75* vs. 76* (-); 1997-2002: 80* vs. 73* (-). Subgroup age (IST among patients with PMN: ≥ 0.2 (vs. <0.2 G/L); <16 ys: 76* vs. 78* (vs. 83*) (-); ≥ 16 ys: 64* vs. 73* (vs. 65*) (-)	improved over time (p=0.03). IST: The outcome among patients with <0.2 G/L was better in children (<16 ys) than in adults (≥ 16 ys), p=0.0002. The outcome among patients with ≥ 0.2 G/L was similar between age groups, p=0.2.	
22	Paquette 1995 [52]	-	-	Year	1977-1983: 42* vs. 54* (not sign.); 1984-1989: 72* vs. 45* (0.25)	-	
23	Pitcher 1999 [53]	-	-	-	1973-1988: 68* vs. 44* (-); 1989-1996: 92* vs. 86* (-)	Unclear number of patients	
24	Tzeng 1989 [54]	Yes	2 years (75† vs. 43† (>0.1))	-	-	-	
25	Viollier 2005 [55]	Yes	57* vs. 68* (0.2)	-	-	Survival, event-free survival, and quality-adjusted time without symptoms and toxicity are similar between HSCT and IST. There were differences in terms of mean duration in years of some health states (HSCT vs. IST): Treatment-related toxicity 0.27 vs. 0.36, p<0.001; transfusion dependency 0.1 vs. 0.66, p<0.001; secondary clonal disorder 0.04 vs. 0.68, p<0.001; extensive chronic GVHD 0.96 vs. 0, p<0.023	
26	Werner 1989 [56]	-	-	-	-	-	

-: information not extractable from the publication; *5-year overall survival point estimate deduced from Kaplan Meier curve.; †5-year overall survival point estimate extracted from text.; ‡Kahn 2002: 5-year overall survival 33% vs. 78% (text), 33% vs. 70% (figure).; \$p value of log-rank test; Abbreviations: CI: 95% confidence interval, lower-upper limit; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; PMN: polymorphonuclear neutrophil granulocytes

Risk of bias

Risk of bias within studies was high for 21 of 26 included studies mainly due to flaws of study design, assignment of patients to treatment groups, and missing control for confounding (Table 6). In 7 studies, an upper age limit was applied as additional assignment criteria.

Table 6. Risk of bias

No	Included studies	Prospective design	Concurrent control	No other assignment criteria than MRD	Control for confounding factors*	No other risk of bias factors†	Risk of bias‡
1	Ahn 2003 [31]	no	YES	YES	YES	YES	LOW
2	Arranz 1994 [32]	no	YES	no (age 40)§	no	YES	high
3	Bacigalupo 1988 [33]	no	YES	YES	YES	YES	LOW
4	Bacigalupo 2000 [34]	no	YES	YES	YES	YES	LOW
5	Bayever 1984 [35]	no	YES	YES	no	YES	high
6	Champlin 1984 [36]	no	YES	no (age 45)§	no	no (selection unclear)	high
7	De Planque 1990 [37]	no	YES	no (second-line)	no	YES	high
8	Doney 1997 [38]	no	YES	no (age 55)§	no	YES	high
9	Fouladi 2000 [39]	no	YES	YES	no	YES	high
10	Fuhrer 1998 [40]	no	YES	YES	no	YES	high
11	Fuhrer 2005 [41]	YES	YES	YES	no	YES	high
12	Ghavamzadeh 2004 [42]	no	YES	no (age 45)§	no	YES	high
13	Gillio 1997 [43]	no	YES	YES	no	YES	high
14	Gluckman 1979 [44]	no	YES	YES	no	no (5 in both groups)	high
15	Halperin 1989 [45]	no	YES	YES	no	YES	high
16	Kahn 2002 [46]	no	no	no (age 40)§	no	YES	high
17	Kim 2003 [47]	no	YES	no (age 50)§	no	YES	high
18	Kojima 2000 [48]	no	YES	YES	no	YES	high
19	Lawlor 1997 [49]	no	YES	YES	no	YES	high
20	Locasciulli 1990 [50]	no	YES	YES	YES	YES	LOW
21	Locasciulli 2007 [51]	no	YES	no (alternate donor)	no	YES	high
22	Paquette 1995 [52]	no	YES	YES	no	no (selection unclear)	high
23	Pitcher 1999 [53]	no	YES	YES	no	YES	high
24	Tzeng 1989 [54]	no	YES	YES	no	YES	high
25	Viollier 2005 [55]	YES	YES	no (age 40)§	no	YES	high
26	Werner 1989 [56]	no	YES	YES	no	YES	high

*Control for confounding factors; no: no adjusted analysis.

†No other risk of bias factors; no: selection of patients unclear; except Gluckman 1979: no: 5 patients with failed first-line IST followed by second-line HSCT were analyzed in both treatment groups.

‡Risk of bias: LOW required concurrent control group (YES), control for confounding factors (YES), and no other risk of bias factors (YES).

§Upper age limit in years.

Abbreviations: HSCT: hematopoietic stem cell transplantation; IST immunosuppressive therapy; MRD: HLA-matched related donor; PMN: polymorphonuclear neutrophil granulocytes

The funnel plot of 19 studies included in meta-analysis shows no asymmetry (Figure 3), which may be consistent with absent publication bias. In 7 of 26 included studies, data of the primary outcome were not sufficiently reported to be included in the main meta-analysis.

Figure 3. Funnel plot using data from Figure 2.
Distribution of estimates can be regarded as funnel-shaped and compatible with a moderate publication bias. Abbreviations: SE: standard error.

Subgroup and sensitivity analysis

The difference between the estimates was not statistically significant in both approaches and for all evaluated items, except for age, which was statistically significant in the evaluation of subgroups from individual studies and not statistically significant in the sensitivity analysis (Table 7).

Factors for improved overall survival

We evaluated patient characteristics that were evaluated in multivariate regression analyses (Table 8). 11 studies reported statistically significant factors for improved survival and 15 studies did not. Frequency of reporting the main factors, that is, age, year of transplant and type of IST is presented in Table 9.

Young age was identified as a statistically significant factor for improved overall survival for patients in the HSCT group in 5 studies. The results for patients in the IST group were less clear because advanced age was a favorable factor in 3 studies and

young age a favorable factor in 2 studies. The actual age limit, which was used to dichotomize participants into young vs. advanced age varied across studies. Level of polymorphonuclear neutrophilic granulocytes (PMN) between 0.2 G/L and 0.5 G/L

was found to be an important factor for improved survival after IST in 5 studies. Only 1 study found an advantage with less than 0.2 G/L in patients who were younger than 17 years. Recent year of treatment was an important factor for improved survival after HSCT in 4 studies and after IST in 1 study. Improvement of outcome over time was accompanied with treatment refinement, such as combination of methotrexate with CSA for GVHD prophylaxis and reduction of conditioning irradiation. Another example of improvement of outcome with treatment refinement is the combination of ALG and CSA instead of monotherapy of ALG. This combination was identified as factor for improved survival in 2 studies.

Table 7. Sensitivity analysis

Characteristic	Type of analysis	Subgroups	Included studies	Statistics*
Age	Sensitivity analysis	Median age in HSCT or IST group ≥ 18 years vs. < 18 years	[32,38,46,47,51,54,55] vs. [35,39,40,43,48,49]	p = 0.449
Age	Subgroups in individual studies	Advanced vs. young age (various definitions)	[33,36,38,51]	p = 0.040
Year of treatment	Sensitivity analysis	Center year of observation period (HSCT or IST) ≥ 1995 vs. < 1995	[31,42,50,31] vs. [32,33,35,37,38,39,40,43,45,46,47,48,49,54,55]	p = 0.945
Year of treatment	Subgroups in individual studies	Recent vs. early year of treatment (various definitions)	[33,51,52]	p = 0.884
Severity of disease	Subgroups in individual studies	high PMN (SAA without VSAA) vs. low PMN (VSAA)	[33,38,51]	p = 0.086
Study population	Sensitivity analysis	Number of patients per study ≥ 100 vs. < 100	[31,33,38,40,48,50,51,55] vs. [32,35,37,39,42,43,45,46,47,49,54]	p = 0.604
Time interval HSCT	Sensitivity analysis	Median interval from diagnosis to HSCT ≥ 50 days vs. < 50 days	[32,35,39,47,51,55] vs. [38,40,43,45,46,48]	p = 0.809
Time interval IST	Sensitivity analysis	Median interval from diagnosis to IST ≥ 50 days vs. < 50 days	[32,35,47] vs. [38,39,40,43,45,46,48,50,55]	p = 0.530
Location	Sensitivity analysis	Multicenter study vs. single center	[31,33,40,48,50,51] vs. [32,35,37,38,39,42,43,45,46,47,49,54,55]	p = 0.474

*Statistics: test of interaction

Table 8. Factors influencing overall survival with statistical significance

No	Included studies	Characteristic	Favors HSCT	Favors IST
1	Ahn 2003 [31]	n/r	n/a	n/a
2	Arranz 1994 [32]	n/r	n/a	n/a
3	Bacigalupo 1988 [33]	Age (years)	<20	≥20
		PMN (G/L)	<0.2	0.2-<0.5
4	Bacigalupo 2000 [34]	Age (years)	<17; <41	No effect
		Year of transplant	≥1990	n/r
		Type of IST	n/a	ALG+CSA (vs. ALG or CSA alone)
5	Bayever 1984 [35]	n/r	n/a	n/a
6	Champlin 1984 [36]	Age (years)	<20	≥20
7	De Planque 1990 [37]	Age (years)	No effect	<45
		PMN (G/L)	No effect	≥0.2
8	Doney 1997 [38]	Age (years)	<40	–
		PMN (G/L)	No effect	≥0.2
9	Fouladi 2000 [39]	PMN (G/L)	No effect	≥0.2
10	Fuhrer 1998 [40]	n/r	n/a	n/a
11	Fuhrer 2005 [41]	PMN (G/L)	–	<0.2 (among patients aged 0 to 17 years)
12	Ghavamzadeh 2004 [42]	n/r	n/a	n/a
13	Gillio 1997 [43]	n/r	n/a	n/a
14	Gluckman 1979 [44]	n/r	n/a	n/a
15	Halperin 1989 [45]	n/r	n/a	n/a
16	Kahn 2002 [46]	n/r	n/a	n/a
17	Kim 2003 [47]	n/r	n/a	n/a
18	Kojima 2000 [48]	n/r	n/a	n/a
19	Lawlor 1997 [49]	n/r	n/a	n/a
20	Locasciulli 1990 [50]	Year of transplant	≥1981	No effect
		Age (years)	No effect	≥6 (among patients with PMN <0.2 G/L)
		PMN (G/L)	No effect	≥0.2
21	Locasciulli 2007 [51]	Age (years)	<16	<16 (among patients with PMN <0.2 G/L)
		Year of treatment	≥1997	No effect
		Type of IST	n/a	ALG+CSA
		PMN (G/L)	n/r	No effect
22	Paquette 1995 [52]	n/r	n/a	n/a
23	Pitcher 1999 [53]	Year of transplant	≥1989	≥1989
24	Tzeng 1989 [54]	n/r	n/a	n/a
25	Viollier 2005 [55]	Quality-adjusted time without symptoms and toxicity	Treatment-related toxicity; transfusion dependency; secondary clonal disorder	Extensive chronic GVHD
26	Werner 1989 [56]	n/r	n/a	n/a

–: information not extractable from the publication.

*5-year overall survival point estimate deduced from Kaplan Meier curve

†5-year overall survival point estimate extracted from text

‡Kahn 2002: 5-year overall survival 33% vs. 78% (text), 33% vs. 70% (figure)

§p value of log-rank test

Abbreviations: ALG: anti-lymphocyte globulin; CSA: cyclosporine A; GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; n/a: not applicable; n/r: not reported; PMN: polymorphonuclear neutrophil granulocytes

Table 9. Frequency of reporting statistically significant factors of improved survival

Characteristic	HSCT	IST
Age (years): young vs. advanced	5 [34,35,37,39,52]	2 [38,52]
Age (years): advanced vs. young	0	3 [34,37,51]
PMN (G/L): <0.2 vs. 0.2 to <0.5	1 [34]	1 [42]
PMN (G/L): 0.2 to <0.5 vs. <0.2	0	5 [34,38-40,51]
Year of treatment: recent vs. earlier period	4 [35,51,52,54]	1 [54]
Type of IST: ALG+CSA vs. ALG	n/a	2 [35,52]

Abbreviations: ALG: anti-lymphocyte globulin; CSA: cyclosporine A; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy; n/a: not applicable; PMN: polymorphonuclear neutrophil granulocytes

Secondary outcomes

An overview of graft failure, GVHD, no response, and overall mortality is presented in Table 10. Graft failure (reported in 15 studies) ranged from 1% to 43%, acute GVHD grade II to IV (reported in 16 studies) ranged from 0% to 88%, and extensive chronic GVHD (reported in 10 studies) ranged from 3 to 27%. No response to IST (extractable from 14 studies) ranged from 6% to 71%. Overall mortality was reported in 23 studies (HSCT vs. IST: 3%–67% vs. 9%–58%).

Table 10. Adverse events: graft failure, GVHD, no response, overall mortality

No	Study	HSCT; N. affected / N. evaluable (%)			IST; N. affected / N. evaluable (%)	HSCT vs. IST; N. affected / N. evaluable (%)
		Any graft failure	Acute GVHD grade II-IV	Extensive chronic GVHD	No response	Overall mortality
1	Ahn 2003 [31]	11 / 61 (18)	20 / 50 (40)	12 / 50 (24)	–	13 / 64 (20) vs. 37 / 156 (24)
2	Arranz 1994 [32]	–	–	–	–	9 / 71 (13) vs. 8 / 62 (13)
3	Bacigalupo 1988 [33]	–	–	–	–	87 / 218 (40) vs. 75 / 291 (26)
4	Bacigalupo 2000 [34]	211 / 1759 (12)	228 / 1759 (13)	176 / 1759 (10)		611 / 1759 (35) vs. 540 / 1592 (34)
5	Bayever 1984 [35]	1 / 35 (3)	10 / 34 (29)	7 / 34 (21)	14 / 22 (64)	9 / 35 (26) vs. 9 / 22 (41)
6	Champlin 1984 [36]	3 / 61 (9)	25 / 58 (43)	9 / 58 (16) any type	33 / 69 (48)	23 / 61 (38) vs. 26 / 69 (38)
7	De Planque 1990 [37]	3 / 19 (16)	14 / 16 (88)	3 / 11 (27)	16 / 82 (20)	8 / 19 (42) vs. 25 / 63 (40)
8	Doney 1997 [38]	18 / 168 (11)	46 / 150 (31)	26 / 150 (17)	122 / 227 (54)	50 / 168 (30) vs. 130 / 227 (57)
9	Fouladi 2000 [39]	1 / 21 (5)	3 / 20 (15)	1 / 20 (5)	–	1 / 21 (5) vs. 6 / 20 (30)
10	Fuhrer 1998 [40]	–	–	–	–	4 / 28 (14) vs. 8 / 86 (9)
11	Fuhrer 2005 [41]	–	–	–	–	–
12	Ghavamzadeh 2004 [42]	–	14 / 29 (48)	–	14 / 24 (58)	9 / 29 (31) vs. 14 / 24 (58)
13	Gillio 1997 [43]	1 / 25 (4)	2 / 25 (8) III-IV	2 / 25 (8)	13 / 23 (57)	5 / 25 (20) vs. 5 / 23 (22)
14	Gluckman 1979 [44]	16 / 37 (43)	8 / 37 (22)	–	20 / 28 (71)	20 / 37 (54) vs. 14 / 29 (48)
15	Halperin 1989 [45]	–	–	–	1 / 12 (8)	3 / 14 (21) vs. 7 / 12 (58)
16	Kahn 2002 [46]	3 / 15 (20)	7 / 15 (47) any type	1 / 15 (7) any type	1 / 16 (6)	10 / 15 (67) vs. 5 / 16 (31)
17	Kim 2003 [47]	1 / 22 (5)	2 / 21 (10)	3 / 21 (14)	41 / 74 (55)	2 / 22 (9) vs. 20 / 74 (27)
18	Kojima 2000 [48]	1 / 37 (3)	2 / 36 (6)	1 / 36 (3)	31 / 63 (49)	1 / 37 (3) vs. 21 / 63 (33)
19	Lawlor 1997 [49]	1 / 9 (11)	5 / 9 (56)	3 / 9 (33) any type	5 / 18 (28)	2 / 9 (22) vs. 2 / 18 (11)
20	Locasciulli 1990 [50]	–	–	–	–	58 / 171 (34) vs. 57 / 133 (44)
21	Locasciulli 2007 [51]	–	42 / 1567 (3) any	–	–	371 / 1567 (24) vs. 228 / 912 (25)
22	Paquette 1995 [52]	–	–	–	–	–
23	Pitcher 1999 [53]	–	–	–	–	–
24	Tzeng 1989 [54]	2 / 9 (22)	0 / 9 (0)	2 / 9 (22) any type	4 / 7 (57)	2 / 9 (22) vs. 4 / 7 (57)
25	Viollier 2005 [55]	5 / 52 (1)	–	12 / 52 (23)	41 / 155 (27)	24 / 52 (46) vs. 61 / 155 (39)
26	Werner 1989 [56]	–	–	–	–	0 / 6 (0) vs. 1 / 9 (11)

–: information extractable from publication.

*Bayever 1984: acute GVHD including interstitial pneumonia; chronic GVHD including moderate or severe types. Abbreviations: GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy

†Bacigalupo 2000: less acute GVHD with methotrexate plus cyclosporine A vs. methotrexate or cyclosporine A alone; incidence of acute GVHD III to IV has been reduced from 20% to 6% with time ($p < 0.00001$), however, survival for patients with acute GVHD >I has not improved with time; incidence of extensive chronic GVHD has been reduced from 15% to 5% with time ($p < 0.00001$), however, survival for patients with extensive chronic GVHD beyond day 100 after HSCT has not been improved with time.

Abbreviations: GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; IST: immunosuppressive therapy

Discussion

Primary outcome

We found high risk of bias among 26 identified non-randomized controlled studies. Considerable heterogeneity of 19 studies included in a meta-analysis of overall survival did not justify a pooled estimate. The aim to compare the primary outcome between treatment groups in an overall synthesis of available data was not achieved. We were able to identify statistically significant factors for improved overall survival reported in the studies. Young age (rather than advanced age) and recent (rather than earlier) year of treatment were associated with a better overall survival in the HSCT group. Advanced age (rather than young age), SAA without VSAA (rather than VSAA), and combination of ALG and CSA (rather than ALG alone) were associated with a better overall survival in the IST group. While pooling data on overall survival of all participating patients did not appear sensible, we conducted sensitivity meta-analysis of subgroups to explain heterogeneity and of subgroups reported in individual studies. Unfortunately, these evaluations were hampered by the fact that individual patient data were not available and instead of that we relied on published aggregate data if reported. It should be mentioned that ALG is no longer available.

Although young age was recognized as a major influence factor on overall survival, the appropriate definition for young age varies considerably across studies. For example, the cut-off for young vs. advanced age was 16 years in the study of Bacigalupo 2008 [16], 30 years in the study of Ljungman 2009 [59], and 40 years in the study of Marsh 2009 [9].

Bacigalupo 2008 [16] reported that the outcome has improved since 1996 for HSCT but not for IST. This result was supported by 4 studies whereas 1 study did find an improvement for the IST group as well. Several factors may have contributed to recent improvements for HSCT, such as detailed HLA-matching, less irradiation-based conditioning, less acute GVHD with a prophylaxis combination of methotrexate plus CSA instead of methotrexate alone [34], refinement of the type and dosage of conditioning drugs, and general advancement of medical and nursing clinical science.

We found that a combination therapy of ALG plus CSA favored overall survival in the IST group, underscoring that refinement of therapy obviously has also improved the outcome with IST. Gafter-Gvili 2008 [60] concluded in a systematic review and metaanalysis that combination of ALG plus CSA should be considered the gold standard for IST for patients with SAA.

6 studies [33,37,38,39,41,50] evaluated whether the disease severity of VSAA (PMN < 0.2 G/L) vs. SAA (without VSAA; PMN 0.2 to < 0.5 G/L) had an impact on overall survival. 5 studies [33,37,38,39,50] consistently found that SAA without VSAA favored the outcome in IST group when compared to VSAA. 2 studies [39,50] included only children and 3 studies [33,37,38] included also adults. These results may suggest that

HSCT may be the preferred treatment option for patients with VSAA and that IST may be the preferred option for patients with SAA without VSAA. However, Fuhrer 2005 [41] reported contradictory results that VSAA favored the outcome in IST group. The results may be relevant for children only because all analyzed patients were younger than 17 years of age. We did not find another study confirming the results, especially not in 2 studies mentioned above.

We believe that this is the first comprehensive systematic review and meta-analysis about studies comparing first-line HSCT versus first-line IST in patients with SAA.

Secondary outcomes

Studies inconsistently reported adverse events and their frequencies varied significantly across studies. Graft failure was highest in early studies but could affect up to 18% of patients in recent studies. Rates for acute GVHD grade III to IV reached up to 40% and for extensive chronic GVHD reached up to 24% in recent studies. A considerable number of patients not responding to IST may indicate the importance of unrelated donor transplantation.

Duplicate publication bias

Identical data may have been included twice in the present systematic review. We searched for follow-up papers of a single study to include the update version and exclude former presentations. Register analyses can provide results based on a large number of patients but registers may use data that may have been published previously by the contributing study centers. We identified 5 studies published on behalf of the EBMT [33,34,50,51] which are probably based on overlapping data. Locasciulli 2007 [51] presented an update of the EBMT data and, therefore, investigated considerably more patients (2,479 patients) than Locasciulli 1990 [50] (304 patients). The courses of the survival functions are clearly different between the 2 studies. In Locasciulli 1990 [50] (Figure 1 of the article), in the majority of the follow-up period the course of the Kaplan-Meier curve after HSCT is above that after IST (congruent in the first 12 months), indicating an advantage from HSCT. In Locasciulli 2007 [51] (Figure 1 of the article), in the majority of the follow-up period the course of the Kaplan-Meier curve after HSCT is below that after IST (in the first 60 months). Only at the very end of the follow-up period (from 100 to 120 months) is the HSCT curve above the IST curve. The difference between the 2 survival functions was assessed by a log-rank test. The authors stated that 10-year survival was significantly superior in patients treated with BMT than in those in whom immunosuppression was used (73% versus 68%, $p = 0.002$). On the contrary, we are convinced that the survival functions clearly show that IST was statistically significantly better than HSCT. Our interpretation of the results is supported by Linden 2007 [61], who addressed the specific problem of inter-

preting the crossing of the survival functions using Locasciulli 2007 [51] as an example. Locasciulli 1990 [50] clearly reported that only data from SAA patient were included. In contrast, Locasciulli 2007 [51] included a considerable proportion of patients with moderate aplastic anemia or with unknown severity of disease. A study population with different patients' characteristics with respect to disease severity might have contributed to the different results. Medical advancement after a time difference of 17 years between publication dates of both studies might have had a greater impact on improved survival after HSCT than on survival after IST.

Outcome reporting bias

Outcome reporting bias [62] is defined as the selection of a subset of the originally recorded outcome variables for publication. Systematic reviews need to address the issue of missing outcome data because outcome reporting bias can affect their conclusions [63]. We identified considerable outcome reporting bias. A major flaw of all studies was the lack of statistical summary data such as standard error or confidence interval for point estimates and p values of logrank test. To pool as many studies as possible, we estimated the hazard ratio. The number of patients at risk was scarcely reported.

Study publication bias

Study publication bias is defined as publication of research results depending on their results [64]. Funnel plots of both reported meta-analyses show moderate asymmetry and do not indicate considerable publication bias. The strengths of the present systematic review are the broadness of the search strategy and the comprehensiveness of the published data included. Nevertheless, there may be a slight possibility that an unknown number of studies were not registered and not published.

Language bias

Results in English language articles could be different from those of articles written in other languages [65]. Non-English language articles require expensive translations to prevent selective outcome extraction and misinterpretation of results. Funding for translation was not provided and we excluded all non-English language articles, including German articles. Restricting the inclusion of studies to English articles may have little effect on summary treatment effect estimates [66,67] and German language articles may not play a preeminent role in the dissemination of medical research [68].

Internal validity

We identified a high risk of bias within all non-randomized controlled studies except for 4 studies. Assignment of patients to treatment groups was reported to be based on availability of MRD in all 26 studies, although, in 7 studies an upper age limit was applied as additional assignment criteria. This type of allocation has specific requirements, such as allelic vs. serologic typing, number of analyzed loci, time spent searching for donors, documentation of all individuals analyzed including families of IST patients, number of analyzed individuals per family, intent-to-treat analysis. However, these requirements were not reported in the included studies.

Heterogeneity

We included as many controlled studies as possible in order to not miss any valuable outcome information. Consequently, we accepted studies that considered a considerable number of patients with moderate aplastic anemia or unknown disease severity. Pooling of data from patients with varying characteristics may have compromised the generalizability of results. Furthermore, important subgroups such as young and advanced age were confused in the meta-analysis.

In an attempt to reduce heterogeneity we strictly confined the meta-analysis to studies that clearly included at least 80% of patients with SAA and first-line treatment (data not shown). We found a moderate heterogeneity and a statistically significant pooled estimate that favored HSCT. Many studies including large and recently published ones were excluded. The result suggested a global preference for one treatment disregarding conditions other than the treatment that might have a determined impact on the outcome. We believe that this procedure would have introduced a study selection bias and a misleading conclusion and was therefore not pursued.

Strengths and limitations of the present review

The strengths of this review are the broadness of the search strategy and the comprehensiveness of the published data included. Significant factors that may influence the survival of the patients were considered in the present systematic review. We estimated hazard ratios from published aggregate survival functions and did not use individual patient data. Subgroup analysis was not helpful to explain considerable heterogeneity found in meta-analysis. While the results of the meta-analysis may not be conclusive, they can provide useful summaries of the state of knowledge.

Conclusions

Young age and recent year of treatment were identified as factors for improved survival in the transplant group. Advanced age, SAA without very severe aplastic anemia, and combination of anti-lymphocyte globulin with cyclosporine A were factors for improved survival in the immunosuppressive group. Considerable heterogeneity of non-randomized controlled studies did not justify a pooled estimate. Adverse events were inconsistently reported and varied significantly across studies.

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CHAPTER 5

Permanent interstitial low-dose-rate brachytherapy for patients with localised prostate cancer: a systematic review of randomised and nonrandomised controlled clinical trials

Peinemann F, Grouven U, Bartel C, Sauerland S, Borchers H, Pinkawa M, Heidenreich A, Lange S. Permanent interstitial low-dose-rate brachytherapy for patients with localised prostate cancer: a systematic review of randomised and nonrandomised controlled clinical trials. *European Urology*. 2011;60(5):881-93.

Abstract

Context Prostate cancer (PCa) is the most common cancer in men. Permanent interstitial low-dose-rate brachytherapy (LDR-BT) is a short-distance radiation therapy in which low-energy radioactive sources are implanted permanently into the prostate.

Objective To assess the effectiveness and safety of LDR-BT compared to treatment alternatives in men with localised PCa.

Evidence acquisition Bibliographic databases (Medline, Embase, and the Cochrane Library) were searched from inception until June 2010 for randomised and nonrandomised controlled trials comparing LDR-BT with radical prostatectomy (RP), external-beam radiation therapy (EBRT), or no primary therapy (NPT). Primary outcome was overall survival (OS). Secondary outcomes were disease-free survival (DFS), biochemical recurrence-free survival (bRFS), physician-reported severe adverse events (SAE), and patient-reported outcomes (PRO).

Evidence synthesis A total of 31 studies, including 1 randomised controlled trial (RCT), were identified. Risk of bias was high for all 31 studies. OS was reported in one nonrandomised controlled study; however, these data were not interpretable because of strong residual confounding. DFS was not reported. Comparison of bRFS between treatment groups is not validated; thus, results were not interpretable. Physician-reported urogenital late toxicity grade 2 to 3 was more common in the LDR-BT group when compared to the EBRT group. With respect to PRO, better scores for sexual and urinary function as well as urinary incontinence were reported for LDR-BT compared to RP. Better scores for bowel function were reported for LDR-BT compared to EBRT.

Conclusions We found a low amount of evidence in studies that exclusively compared LDR-BT with other treatment modalities. LDR-BT may have some different physician-reported SAE and patient-reported outcomes. The current evidence is insufficient to allow a definitive conclusion about OS. Randomised trials focusing on long-term survival are needed to clarify the relevance of LDR-BT in patients with localised PCa.

1. Introduction

Localised prostate cancer (PCa) is defined by the categories T1 to T2 of the TNM staging system [1] if combined with an absence of both regional lymph node metastasis (N0) and distant metastasis (M0). The European Association of Urology suggested four different treatment concepts for localised PCa [2].

Brachytherapy [2] is short-distance radiation therapy (RT) that places radiation sources with different durations and rates of dose delivery in or near tumours [3]. Permanent interstitial low-dose rate brachytherapy (LDR-BT) refers to implanting low-energy radioactive sources that emit radiation at a rate < 2 Gy/h [4]. The radioisotopes iodine-125 or palladium-103 are contained in titanium pellets of the size of rice grains, which are called seeds. Sixty to 100 seeds are typically inserted into the prostate through a transperineal route guided by transrectal ultrasound. LDRBT is a minimally invasive procedure that can be carried out as an outpatient treatment and is completed in 45–90 min under spinal or general anaesthesia. However, a large prostate volume (≥ 60 ml) can be technically challenging and basically represents a relative contraindication to LDRBT. LDR-BT has to be distinguished from high-dose brachytherapy (HDR-BT), which uses the radioisotope iridium 192 as a high-energy-emitting radiation source with a rate of ≥ 12 Gy/h [4]. The source is placed temporarily in the prostate using needles as applicators.

The term primary (rather than definitive) therapy was suggested to convey a clear message concerning both the intent and the nature of RT and surgical operation, including LDR-BT, radical prostatectomy (RP), and external-beam RT (EBRT) [5]. The term no primary therapy (NPT) is used in the present systematic review to accommodate all types of observation, including active surveillance, watchful waiting, and observing without distinctive management.

LDR-BT, as compared to RP and EBRT, may have similar survival outcomes but may reduce the incidence of local adverse events and may provide better health-related quality of life (HRQL) [6,7]. However, randomised controlled trials (RCT) are lacking [8,9]. The aim of this systematic review was to assess the benefit and harm of LDR-BT relative to RP, EBRT, or NPT in men with localised PCa.

2. Evidence Acquisition

While preparing this systematic review, we endorsed the Preferred Reporting Items for Systematic Reviews and MetaAnalyses statement, adhered to its principles, and conformed to its checklist [10]. Data are based on works conducted by the Institute for Quality and Efficiency in Health Care and commissioned by the Federal Joint Committee of the selfgoverning statutory health insurance system in Germany [11,12].

2.1. Study inclusion criteria

We included RCTs and nonrandomised controlled trials evaluating LDR-BT as monotherapy in patients with localised PCa. The proportion of relevant patients had to be at least 80% of the study population, and the response rate of questionnaires was expected to be at least 70%. For nonrandomised studies to be included, comparable baseline characteristics between treatment groups or adjustment for imbalances of these data were required. Limits on year of publication or language were not applied.

2.2. Search strategy

Medline, Embase, and the Cochrane Library were searched without restrictions on study design, publication year, or language. The last database searches were conducted in June 2010. Terms and syntax used for the search in Medline via Ovid (Table S1; online at doi: 10.1016/j.eururo.2011.06.044) were tailored to the requirements of the other two databases. Reference lists of all included primary articles and two recent reviews [8,9] were handsearched for further information. Information on studies registered at ClinicalTrials.gov [13], World Health Organisation International Clinical Trials Registry Platform [14], International Standard Randomised Controlled Trial Number Register [15], National Institute for Health Research UK Clinical Research Network's Portfolio Database [16], and National Cancer Institute Physician Data Query Clinical Trial [17] were searched online (June 2010) for RCTs.

2.3. Study selection

The study population included patients (no age limit) with localised PCa as classified by the TNM classification system [1]. Test intervention was LDR-BT; HDR-BT was not included. The control intervention was RP, EBRT, or NPT.

In the first step of study selection, bibliographic records were excluded if the title or the abstract clearly referred to other diagnoses than localised PCa or if a single-arm study was reported. In the second step, articles not excluded in the first step were evaluated to determine whether the test intervention were compared to at least one of the defined control interventions using an included study design. For each excluded study of the second step, an appropriate reason was documented (Fig. 1). All steps of the literature screening process were performed by two independent reviewers; any disagreements were resolved by discussion.

Figure 1. Literature retrieval and study selection.

Abbreviations: EBRT: external-beam radiation therapy; ISRCTN: International Standard Randomised Controlled Trial Number Register; LDR-BT: low-dose rate brachytherapy; NCI PDQ: National Cancer Institute Physician Data Query Clinical Trials; NIHR UKCRN: National Institute for Health Research UK Clinical Research Network's Portfolio Database; NPT: no primary therapy; PRO: patient-reported outcome; RCT: randomised controlled trial; RP: radical prostatectomy; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform.

2.4. Data collection and analysis

For included studies, data on study characteristics, patients and interventions, risk of bias, duration of follow-up, and outcomes were abstracted independently by two review authors. Differences between reviewers were resolved by discussion or by appeal

to a third review author. Primary outcome was overall survival (OS). Secondary outcomes were clinically defined disease-free survival (DFS), biochemical recurrence-free survival (bRFS), physician-reported severe adverse events (SAE), and patient-reported outcomes (PRO) such as function and bother scores as well as generic HRQL.

bRFS, also called prostate-specific antigen (PSA)-based recurrence-free survival, is a widely used laboratory-reported outcome. We believe that it should not be regarded as a validated surrogate for comparing different treatment groups in patients with a localised PCa—a problem further addressed in the discussion section. SAE included sexual problems, urinary problems such as lower urinary tract symptoms and urinary incontinence, bowel problems such as rectal incontinence, toxicity—for example, urogenital or gastrointestinal acute or late toxicity according to modified Radiation Therapy Oncology Group radiation scale [18]—and other SAE such as secondary neoplasia. The questionnaires included in this systematic review to assess function, bother, and generic HRQL are listed in Table 1.

The primary effect measure for survival outcomes was the hazard ratio (HR). For nonrandomised studies, either comparability of baseline characteristics or an appropriate adjustment from a multiple regression analysis was required. We identified bRFS data qualified for quantitative pooling in a meta-analysis. However, we regard bRFS as an unvalidated surrogate for a pooled estimate may draw conclusions that are too far from reality. We did not identify OS and DFS data appropriate for pooling. Therefore, details of planned extraction of summary statistics and estimation of pooled data are not reported.

Results were accepted as adjusted if at least one of six predefined confounding factors was considered in a multiple regression model or in a stratified or matched analysis: age, T stage of the TNM classification, PSA, Gleason score, prostate size, and comorbidity. Unadjusted results were used from RCTs and from nonrandomised studies if no adjusted analysis were available and baseline characteristics were comparable. Other accepted effect measures were risk difference, risk ratio, odds ratio (OR), and mean difference. The reporting of a statistically significant effect in at least two studies and at the same time no reporting of contradicting results after a follow-up of at least 6 mo were required to determine whether the data were in favour of LDR-BT or the compared treatment.

2.5. Assessment of risk of bias and quality of reporting

Two reviewers independently assessed the quality of RCTs. A low risk of bias required a "yes" for all five of the following criteria: (1) adequate generation of the randomisation sequence; (2) adequate allocation concealment; (3) blinding of outcome assessors; (4) completeness of outcome data, including reporting of dropouts before and losses to follow-up after the beginning of treatment; and (5) an analysis based on intention to treat (ITT) of patients at the time of randomisation. In studies reporting PROs, the presence of baseline scores was evaluated in addition to the other six confounders.

Table 1. Endpoints

Study	LDR-BT vs.				Endpoints			Type of PRO score		
	RP	EBRT	NPT	OS	brFS	SAE	PRO	Function	Bother	HRQL
Randomized										
Giberti 2009 [30]	YES	no	no	no	YES ¹	YES ²	YES	IIEF, IPSS, QLQ-PR25	n/r	QLQ-C30
Nonrandomized										
Abdel-W 2008 [19]	no	YES	YES	no	no	YES ³	no	n/a	n/a	n/a
Beyer 2000 [20,69]	no	YES	no	no	YES ^{4,5}	no	no	n/a	n/a	n/a
Borchers 2004 [21]	YES	no	no	no	no	no	YES ⁶	n/r	n/r	QLQ-C30
Bradley 2004 [22,70]	YES	no	no	no	no	no	YES ⁷	IPSS; BSFI	n/r	FACT-G
Burdick 2009 [23]	YES	YES	no	no	YES ³	no	no	n/a	n/a	n/a
Buron 2007 [24]	YES	no	no	no	no	no	YES ^{8,9}	n/r	n/r	QLQ-C30
D'Amico 1998 [25]	YES	YES	no	no	YES ^{4,5}	no	no	n/a	n/a	n/a
D'Amico 2003 [26] ¹⁰	YES	no	no	no	YES ⁴	no	no	n/a	n/a	n/a
Davis 2001 [27]	YES	YES	no	no	no	no	YES ⁹	UCLA-PCI	UCLA-PCI	SF-36
Eade 2008 [18] ³	no	YES	no	no	YES ³	YES ³	no	n/a	n/a	n/a
Elliot 2007 [28]	YES	YES	YES	no	no	YES ³	no	n/a	n/a	n/a
Ferrer 2008 [29] ¹¹	YES	YES	no	no	no	no	YES ¹²	EPIC	n/r	n/a
Huang 2010 [31]	YES	YES	no	no	no	no	YES ¹³	UCLA-PCI	UCLA-PCI	SF-36
Kirschner-H 2008 [32]	YES	no	no	no	no	no	YES ¹⁴	IPSS, ICSmale	ICSmale	QLQ-C30
Kobuke 2009 [33]	YES	no	no	no	no	no	YES ¹⁵	IPSS, UCLA-PCI	UCLA-PCI	SF-36
Kupelian 2004 [34, 71] ¹⁰	YES	YES	no	no	YES ⁴	no	no	n/a	n/a	n/a
Lee 2001 [35]	YES	YES	no	no	no	no	YES ⁹	IPSS	n/r	FACT-GIP
Malcolm 2010 [36]	YES	no	no	no	no	no	YES ¹⁶	UCLA-PCI	UCLA-PCI	n/r
Nieder 2008 [37]	YES	YES	no	no	no	YES ³	no	n/a	n/a	n/a
Ojha 2010 [38]	YES	YES	YES	no	no	YES ³	no	n/a	n/a	n/a

Study	LDR-BT vs.				Endpoints				Type of PRO score		
	RP	EBRT	NPT	OS	bRFS	SAE	PRO	Function	Bother	HRQL	
Pe 2009 [39]	no	YES	no	no	YES ³	no	no	n/a	n/a	n/a	
Pickles 2010 [40]	no	YES	no	no	YES ¹⁷	YES ¹⁸	no	n/a	n/a	n/a	
Pinkawa 2010 [41]	no	YES	no	no	YES ³	no	no	n/a	n/a	n/a	
Sharkey 2005 [42,72]	YES	no	no	no	YES ^{4,5}	no	no	n/a	n/a	n/a	
Smith 2009 [43]	YES	YES	YES	no	no	no	YES ¹⁹	UCLA-PCI	UCLA-PCI	SF-12	
Talcott 2003 [44]	YES	YES	YES	no	no	no	YES ²⁰	n/a	n/a	SF-36	
Vassil 2010 [45]	YES	YES	no	no	YES ³	no	no	n/a	n/a	n/a	
Wong 2009 [46]	no	YES	no	no	YES ³	no	no	n/a	n/a	n/a	
Zelevsky 1999 [47] ¹⁰	no	YES	no	no	YES ⁴	YES ⁴	no	n/a	n/a	n/a	
Zhou 2009 [48]	YES	YES	YES	YES ³	no	no	no	n/a	n/a	n/a	

Abbreviations: Bother: bother score; bRFS: biochemical (prostate-specific antigen) recurrence-free survival; BSF: brief sexual function inventory; EBRT: external beam radiotherapy; EPIC: Expanded prostate cancer index composite; Function: function or symptom score; FACT: Functional assessment of cancer therapy; FACT-G: Functional assessment of cancer therapy general; FACT-P: Functional assessment of cancer therapy prostate; HRQL: health-related quality of life score; IC-Smale: International Continence Society male; IIEF: International index of erectile function; IPSS: International prostate symptom score; LDR-BT: low-dose rate brachytherapy; n/a: not applicable; n/r: not reported; NPT: no primary therapy including active surveillance, watchful waiting or observation of patients with prostate cancer; OS: overall survival or/and disease-free survival; UCLA-PCI: University of California Los Angeles prostate cancer index; PRO: patient-reported outcome; QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire cancer 30 items; QLQ-PR25: European Organisation for Research and Treatment of Cancer quality of life questionnaire prostate cancer 25 items; RP: radical prostatectomy; SAE: severe adverse events; SF-12: Medical Outcomes Study 12-item short-form health survey; SF-36: Medical Outcomes Study 36-item short-form health survey

1 proportions; 2 not reported; 3 time to event (adjusted hazard ratio by Cox proportional hazards model); 4 Kaplan-Meier survival analysis (log-rank test); 5 stratified; 6 mean scores (Wilcoxon rank-sum test); 7 mean scores (F test); 8 Buron 2007: QLQ-PR25 effect measure not adjusted, thus not indicated; 9 mean scores (ANCOVA analysis of covariance); Davis 2001: IPSS not adjusted; 10 D'Amico 2003; Kupelian 2004; Zelevsky 1999: no Cox model and not stratified; 11 Ferrer 2008: FACT, IPSS, and SF-36 effect measure not adjusted, thus not indicated; 12 mean scores (generalized estimating equations); 13 mean scores (repeated measures mixed model); 14 mean scores (Kruskal-Wallis test); 15 mean scores (Mann-Whitney U test); 16 time to return to 90% of baseline score (Cox proportional hazards model); 17 prevalence rates (Mann-Whitney test); 18 Kaplan-Meier survival analysis (matched-pairs analysis); 19 odds ratio (proportional odds model); 20 mean scores (multivariate regression)

All nonrandomised studies were assigned per se a high risk of bias because of their nonrandomised design. To further differentiate risk of bias in these nonrandomised studies, additional flaws were categorised as small or large. The category small additional flaws required a "yes" for all four of the following criteria: (1) concurrent control group; (2) consecutive recruitment; (3) control for at least three out of the six predefined confounding factors age, T stage, PSA, Gleason score, prostate size, and comorbidity; and (4) reporting of patient flow or missing data. When there was evidence of multiple publications of the same study population, results were only included if they came from a different subpopulation.

3. Evidence synthesis

3.1. Search results

After exclusion of duplicates, 3785 bibliographic records were screened for potential eligibility, and 462 full-text papers were obtained for further assessment (Fig. 1). A total of 31 studies [18–48] met the inclusion criteria. The present systematic review included 1 RCT [30] and 30 nonrandomised studies.

3.2. Baseline data

An overview of the study characteristics, such as data obtained from registries, study location, treatment period, follow-up, EBRT dose, and number of included patients, is presented in Table 2. Median age in the EBRT group was up to 7 yr higher than in the LDR-BT group and in the LDR-BT group up to 9 yr higher than in the RP group in the majority of studies. Most studies included only the T1 and T2 categories of TNM classification, with a few studies reporting on patients with T3 or T4 categories (42% per group). Although the majority of patients in the primary studies had a Gleason score < 7 and a PSA level < 10 ng/ml, most studies also included a considerable proportion (about 20–30%) of patients with a PSA level ≥ 10 ng/ml. Prostate size and comorbidity were reported only in a few studies. LDR-BT was mostly performed using iodine-125 as the isotope, but in a few studies, palladium-103 was used instead. EBRT was conducted with different radiation doses between and among studies. Median total dose ranged from 68 Gy to 78 Gy. Neoadjuvant or adjuvant androgen-deprivation therapy differed among patients. RP was carried out with or without a nerve-sparing technique using either a retropubic or perineal route.

Of 30 nonrandomised studies, 7 reported results from registries [19,28,31,37, 38,43,48]. Table S2 (online at doi: 10.1016/j.eururo.2011.06.04) shows categorisation of six different patients' characteristics (age, TNM stage, PSA, Gleason score, size of prostate, comorbidity) as comparable between treatment groups, adjusted for as a confounder, or not considered in data analysis.

Table 2. Study characteristics

Included studies	Registries	No. of centers (country)	Treatment period, yr	Follow-up, mo, median	EBRT dose, Gy (range)	No. of included patients			
						LDR-BT	RP	EBRT	NPT
Randomized									
Giberti 2009 [30]	–	1 (Italy)	1999–2002	Mean: 68	n/r	100	100	–	–
Not-randomized									
Abdel-W 2008 [19] ¹	SEER	> 1 (USA)	1988–2002	40 vs 64 vs 52	n/r	–	10 223	48 400	40 733
Beyer 2000 [20,69]	–	1 (USA)	1988–1995	51 vs 41	67	–	695	1 527	–
Borchers 2004 [21]	–	1 (Germany)	1999–?	26 all	–	42	52	–	–
Bradley 2004 [22,70]	–	1 (USA)	1997–2000	26 vs 19	–	77	130	–	–
Burdick 2009 [23]	–	1 (USA)	1996–2005	54 all	Minimum: 70	310	127	268	–
Buron 2007 [24]	–	11 (France)	2001–2002	Mean: 25 vs 25	–	127	308	–	–
D'Amico 1998 [25]	–	2 (USA)	1989–1997	41 vs 38 vs 38	66	888	218	766	–
D'Amico 2003 [26]	–	1 (USA)	1997–2002	48 vs 48	–	406	227	–	–
Davis 2001 [27] ²	–	1 (USA)	1995–1999	22 vs 38 vs 30	70	269	142	222	–
Eade 2008 [18] ³	–	1 (USA)	1998–2004	48 vs 43	(74–78)	–	158	216	–
Elliott 2007 [28] ⁴	CaPSURE	> 1 (USA)	1995–2006	32 all	n/r	3 310	799	645	378
Ferrer 2008 [29]	–	10 (Spain)	2003–2005	Minimum: 24	74	134	275	205	–
Huang 2010 [31]	CaPSURE	> 1 (USA)	1995–2006	n/r	n/r	757	219	154	–
Kirschner-H 2008 [32]	–	1 (Germany)	1999–2002	Minimum: 12	–	61	33	–	–
Kobuke 2009 [33]	–	1 (USA)	2004–2005	Minimum: 12	–	37	36	–	–
Kupelian 2004 [34,71] ⁵	–	2 (USA)	1990–1998	56 all	68 vs 78	1 034	950	785	–
Lee 2001 [35]	–	1 (USA)	1998–1999	12 all	70	23	44	23	–
Malcolm 2010 [36]	–	1 (USA)	2000–2008	30 all	–	135	122	–	–
Nieder 2008 [37]	SEER	> 1 (USA)	1988–2003	49 all	n/r	109 178	22 889	93 059	–
Ojha 2010 [38] ⁶	SEER	> 1 (USA)	1988–2003	45 vs 79 vs 67 vs 53	n/r	84 031	10 259	41 986	323 336

Included studies	Registries	No. of centers (country)	Treatment period, yr	Follow-up, mo, median	EBRT dose, Gy (range)	No. of included patients			
						LDR-BT	RP	EBRT	NPT
Pe 2009 [39]	–	1 (USA)	1993–2006	37 vs 51	74	171	–	189	–
Pickles 2010 [40]	–	1 (Canada)	1998–2001	68 vs 67	(52–70)	139	–	139	–
Pinkawa 2010 [41]	–	1 (Germany)	2000–2003	76 vs 67	70	94	–	135	–
Sharkey 2005 [42,72]	–	1 (USA)	1993–2002	36 all	–	869	208	–	–
Smith 2009 [43]	NSWCCR	> 1 (Australia)	2000–2002	n/r	n/r	58	981	123	–
Talcott 2003 [44] ⁸	–	> 1 (USA)	1994–2000	24 all	n/r	80	129	182	19
Vassil 2010 [45]	–	> 1 (USA)	1996–2005	65 all	(70–80)	256	354	305	–
Wong 2009 [46] ⁹	–	1 (USA)	1993–2004	58 all	68 vs 76	225	–	584	–
Zelevsky 1999 [47] ¹⁰	–	1 (USA)	1988–1997	24 vs 36	(70–81)	145	–	137	–
Zhou 2009 [48] ¹¹	OCISS	> 1 (USA)	1999–2001	n/r	n/r	644	936	876	2 306

Abbreviations: – not applicable; CaPSURE: Cancer of the Prostate Strategic Urologic Research Endeavor, USA; EBRT: external beam radiotherapy; LDR-BT: low-dose rate brachytherapy; mo: months; n/r: not reported; NPT: no primary therapy including active surveillance, watchful waiting or observation of patients with prostate cancer; NSWCCR: New South Wales central cancer registry, Australia; OCISS: Ohio Cancer Incidence Surveillance System, Medicare, and death certificate files; RP: radical prostatectomy; SEER: Surveillance, Epidemiology and End Results, cancer register, Bethesda, Maryland, USA; yr: years

1 Abdel-W 2008: NPT: patients with prostate cancer, no radiotherapy, no surgery

2 Davis 2001: reported also 137 data of a non-diseased control population

3 Eade 2008: BT 1998 to 2004; EBRT: 2001 to 2004

4 Elliott 2007: NPT: watchful waiting for 378 patients with prostate cancer

5 Kupelian 2004: 484 EBRT < 72 Gy vs. 301 EBRT ≥ 72 Gy

6 Ojha 2010: NPT: no definitive therapy

7 Smith 2009: reported also 495 data of a non-diseased control population

8 Talcott 2003: NPT: observation (no initial treatment)

9 Wong 2009: 270 3D-CRT 1993–2000 vs. 314 IMRT 2000 to 2004

10 Zelevsky 1999: EBRT from 1988 to 1995 and LDR BT from 1988 to 1997

11 Zhou 2009: NPT: no definitive therapy within 6 months after prostate cancer diagnosis. The type of brachytherapy, especially the dose, is not specified in the article. According to e-mail contact on 23 May 2011, the authors identified all brachytherapy patients without differentiating specific radiation dose but assumed that over 80% was low-dose rate, as high-dose rate is not prevalent in Ohio.

3.3. Risk of bias and quality of studies

Risk of bias of the RCT by Giberti 2009 [30] was evaluated as high. Patients were randomised, using a computerised blocked random number list, into 2 groups of 100 patients each. Randomisation was performed by a urologist not participating in the surgical operations; however, concealment of allocation was not reported. Outcome assessment was performed by another urologist blinded to patient treatment. Furthermore, a considerable number of patients were lost to follow-up (15% in the brachytherapy group and 11% in the RP group), management of the missing data was not addressed, and no ITT analysis was performed. There was no information on prior sample size calculation and no statement about funding and competing interests.

Risk of bias was high for all 30 nonrandomised studies because of the nonrandomised design (Table 3). Additional large flaws were identified in 63% of studies (19 of 30) [18–21, 24–28,32,37–39,41,42,44,45,47,48], and additional small flaws were identified in the other 37% (11 of 30).

3.4. Primary outcome: overall survival

An overview of conclusions based on the available data is presented in Table 4. Only one nonrandomised study reported improvement in overall mortality (HR: 0.40; 95% confidence interval [CI], 0.32–0.52) for monotherapy of localised disease in the LDR-BT group compared to the NPT group [48] at 7-yr follow-up, as listed in the overview of reported end points in Table 1. Improvement of disease-specific mortality (HR: 0.45; 95% CI, 0.23–0.87) was also reported in this study, but not in any other identified study. As detailed later, results were deemed not interpretable in the present systematic review.

3.5. Secondary outcomes

An overview of conclusions based on the available data is presented in Table 4. Table 1 shows the end points that were reported by the accordant studies. DFS was not identified in the included studies; bRFS was reported in 14 studies (Table 5). Time-to-event data were in favour of LDR-BT compared to RP in three of seven studies and were not significantly different in four of seven studies. Concerning EBRT, time-toevent data were in favour of LDR-BT compared to EBRT in 3 of 10 studies and were not significantly different in 7 of 10 studies. In an additional study, Kupelian 2004 [34] reported results after EBRT for two subgroups stratified by dose level. The outcome was in favour of LDR-BT compared to low-dose EBRT and was not significantly different after high-dose EBRT. In all four studies [34,40,41,46] applying low-dose EBRT, outcome was in favour of LDR-BT, although Wong et al. evaluated two different types of EBRT with different dose levels (Table 2).

Table 3. Risk of bias within studies

Study	Concurrent groups ¹	Consecutive enrolment reported ²	Prospective design ³	Confounder control adequate ⁴	Blinded end point assessment ⁵	Patient flow, lost data reported ⁶	Risk of bias ⁷	Additional flaws ⁸
Nonrandomized								
Abdel-W 2008 [19]	YES	no	no	no	no	YES	High	Large
Beyer 2000 [20,69]	YES	no	no	YES	no	no	High	Large
Borchers 2004 [21]	YES	YES	YES	(YES) ⁹	no	YES	High	Large
Bradley 2004 [22,70]	YES	YES	no	YES	no	YES	High	SMALL
Burdick 2009 [23]	YES	YES	Unclear	YES	no	YES	High	SMALL
Buron 2007 [24]	YES	no	YES	YES	no	YES	High	Large
D'Amico 1998 [25]	YES	no	no	YES	no	YES	High	Large
D'Amico 2003 [26]	YES	no	YES	YES	no	YES	High	Large
Davis 2001 [27]	YES	no	no	no	no	YES	High	Large
Eade 2008 [18]	(YES) ¹⁰	YES	no	YES	no	YES	High	Large
Elliott 2007 [28]	YES	no	no	YES	no	YES	High	Large
Ferrer 2008 [29]	YES	YES	YES	YES	(YES) ¹¹	YES	High	SMALL
Huang 2010 [31]	YES	YES	no	YES	no	YES	High	SMALL
Kirschner-H 2008 [32]	YES	no	no	YES	no	no	High	Large
Kobuke 2009 [33]	YES	YES	YES	YES	no	YES	High	SMALL
Kupelian 2004 [34,71]	YES	YES	no	YES	no	YES	High	SMALL
Lee 2001 [35]	YES	YES	YES	YES	no	YES	High	SMALL
Malcolm 2010 [36]	YES	YES	YES	YES	no	YES	High	SMALL
Nieder 2008 [37]	YES	no	no	YES	no	YES	High	Large
Ojha 2010 [38]	YES	no	no	YES	no	YES	High	Large
Pe 2009 [39]	YES	no	no	no	no	YES	High	Large
Pickles 2010 [40] ¹²	YES	YES	YES	YES	no	YES	High	SMALL
Pinkawa 2010 [41]	YES	YES	no	(no) ¹³	no	YES	High	Large

Study	Concurrent groups ¹	Consecutive enrolment reported ²	Prospective design ³	Confounder control adequate ⁴	Blinded end point assessment ⁵	Patient flow, lost data reported ⁶	Risk of bias ⁷	Additional flaws ⁸
Sharkey 2005 [42,72]	YES	no	no	YES	no	YES	High	Large
Smith 2009 [43]	YES	YES	YES	YES	no	YES	High	SMALL
Talcott 2003 [44]	YES	no	YES	YES	no	YES	High	Large
Vassil 2010 [45]	YES	no	no	YES	no	YES	High	Large
Wong 2009 [46]	YES	YES	no	YES	no	YES	High	SMALL
Zelefsky 1999 [47]	(YES) ¹⁴	no	no	no	no	no	High	Large
Zhou 2009 [48]	YES	no	no	YES	no	YES	High	Large

Abbreviations: PRO: patient-reported outcome such as disease-specific symptom/function scores and bother scores or generic health-related quality of life scores; PSA: prostate-specific antigen; TNM: Tumor-Nodus-Metastasis (classification of cancer).

1 Concurrent groups: both groups were evaluated at the same time period, although, an overlap of less than 50% was accepted

2 Consecutive enrolment: recruiting one patient after another in uninterrupted succession

3 Prospective design: description of prospective elements of the study such as plans or protocols; analyses of data from registers were generally regarded as retrospective design

4 Confounder control adequate: either all 6 predefined baseline characteristics (age, tumor node metastasis stage, prostate-specific antigen, Gleason score, prostate size, comorbidity) were comparable or the results were adjusted for at least 3 of these confounders; studies were excluded if confounders were not comparable and were not used for adjustments of results

5 Blinded endpoint assessment: the reporting of assessment of endpoints by persons not aware of group assignment was required

6 Patient flow, lost data reported: description of the number of patients recruited, of dropouts after randomization but before begin of treatment, of lost to follow-up after treatment, and the description of the reasons for the loss of data from these patients was required

7 Risk of bias of non-randomized studies: regarded as high for all studies because of the non-randomized study design

8 Additional flaws: flaws in addition to a high risk of bias were regarded as small if the combined requirements for concurrent groups, consecutive enrolment, confounder control, and reporting of patient flow and reasons for lost data were met

9 Borchers 2004: baseline characteristics comparable (BT vs. RP) according to author's communication; BT vs. nerve-sparing RP was not addressed because baseline characteristics were not comparable

10 Eade 2008; BT 1998-2004, EBRT 2001-2004; not fully concurrent, however, overlap was greater than 50%

11 Ferrer 2008: the statistical analyst was blinded to treatment assignment

12 Pickles 2010: matched-pairs structure not accounted for in statistical analysis

13 Pinkawa 2010: adjustment not possible or ineffective because of 0 of 0% high-risk patients in BT group (vs. 39% in EBRT group)

14 Zelefsky 1999: BT 1988-1997, EBRT 1988-1995; not fully concurrent, however, overlap was greater than 50%

Table 4. Overview of conclusions

Endpoint	LDR-BT vs		
	NPT	EBRT	RP
Primary end points			
Overall survival	n/i	n/i	n/i
Cause-specific survival	n/i	n/i	n/i
Secondary end points			
Disease-free survival	n/r	n/r	n/r
Biochemical recurrence-free survival	n/r	n/i	n/i
Physician-reported severe adverse events			
Toxicity			
Gastrointestinal (acute or late), urogenital (acute), grade 2-3	n/r	↔	n/r
Urogenital (late toxicity, grade 2-3)	n/r	↓	n/r
Urinary tract			
Urethral stricture	↔	↔	↔
Urinary incontinence	n/r	n/r	↔
Secondary neoplasia	↔	↔	↔
Patient-reported outcomes			
Sexual			
Function	↔	↔	↑
Bother function	↔	↔	↔
Erectile dysfunction	n/r	n/r	↔
Urinary			
Function	↔	↔	↑
Bother function	↔	↔	↔
Irritation	n/r	↔	↔
(Stress) incontinence	n/r	↔	↑
Bother (stress) incontinence	n/r	n/r	↔
Bowel			
Function	↔	↑	↔
Bother function	↔	↔	↔
Generic HRQL			
Physical component score	↔	↔	↔
Mental component score	↔	↔	↔

Abbreviations: EBRT: external beam radiotherapy; HRQL: health-related quality of life; LDR-BT=low-dose-rate brachytherapy; n/i: not interpretable; n/r: not reported; NPT=no primary therapy including active surveillance, watchful waiting, or observation of patients with prostate cancer; RP: radical prostatectomy.

↑: At least 2 studies reporting statistically significant effect in favor of LDR-BT in the accordant category and no contradicting effects in other studies

↓: At least 2 studies reporting statistically significant effect in favor of control treatment in the accordant category and no contradicting effects in other studies

↔: Fewer than 2 studies reporting statistically significant effects or contradicting effects or difference between groups not statistically significant

Table 5. Biochemical recurrence-free survival at 5 years

Study	LDR-BT vs EBRT			LDR-BT vs RP	
	LDR-BT, 5-yr survival, %	EBRT, 5-yr survival, %	HR (95% CI); <i>p</i> value	RP, 5-yr survival, %	HR (95% CI); <i>p</i> value
Randomized					
Giberti 2009 [30] ²	n/r	–	–	n/r	0.96 (0.35–2.42); 0.875 ³
Not-randomized					
Beyer 2000 [20,69] ⁴	71	69	n/r; 0.94	–	–
Burdick 2009 [23]	n/r	n/r	1.04 (0.56–1.94); 0.9	n/r	0.44 (0.25–0.77); 0.004
D'Amico 1998 [25] ⁵	88	89	n/r; > 0.250	85	n/r; > 0.250
D'Amico 2003 [26] ⁶	95	–	–	93	n/r; 0.160
Eade 2008 [18] ⁷	94	100	4.00 (0.80–20.03); 0.09	–	–
Kupelian 2004 [34,71]	83	–	–	81	0.96 (0.76–1.21); 0.72
Kupelian 2004 [34,71] < 72 Gy	83	51	0.43 (0.28–0.66); n/r	–	–
Kupelian 2004 [34,71] ≥ 72 Gy	83	81	0.89 (0.51–1.55); n/r	–	–
Pe 2009 [39]	96	95	0.850 (n/r); 0.780	–	–
Pickles 2010 [40] ⁸	95	85	0.32 (0.16–0.63); 0.001	–	–
Pinkawa 2010 [41] ⁹	n/r	n/r	0.50 (0.30–0.80); < 0.010	–	–
Sharkey 2005 [42,72]	93	–	n.a.	85	0.44 (0.27–0.73); < 0.002
Vassil 2010 [45]	90	86	0.99 (0.62–1.58); 0.969	80	0.52 (0.33–0.78); 0.003
Wong 2009 [46]	94	87; 74 ¹⁰	n/r; < 0.001 ¹¹	–	–
Zelevsky 1999 [47] ¹²	82	88	n/r; 0.090	–	–

Abbreviations: –: not applicable; bRFS: Biochemical recurrence-free survival; CI: confidence interval; EBRT: external beam radiotherapy; HR: hazard ratio; LDR-BT: low-dose rate brachytherapy; n/r: not reported; RP: radical prostatectomy; TNM: Tumor-Nodus-Metastasis (classification of cancer); yr: year

1 *p* value: Table 5 specifies statistical test

2 Giberti 2009: presented frequency rates without censoring, thus relative risk was based on these rates

3 *p* value calculated using unconditioned test for comparing two independent proportions by Andres 1994 [73]

4 Beyer 2000: baseline data were not comparable, although data were not statistically different between treatment groups after stratification according to PSA, Gleason score, T category of TNM, and age.

5 D'Amico 1998: baseline data were not comparable, although data were not statistically different between treatment groups after stratification according to PSA, Gleason score, and T category of TNM.

6 D'Amico 2003: baseline data were not comparable and neither adjusted nor stratified for

7 Eade 2008: 4-year Brfs

8 Pickles 2010: HR was estimated from summary time-to-event data using the tool provided by Tierney 2007 [74]; median dose was less than 72 Gy

9 Pinkawa 2010: median dose was less than 72 Gy

10 Wong 2009: intensity-modulated radiotherapy (IMRT); 3-dimensional conformal radiotherapy (3D-CRT)

11 Wong 2009: *p* value relates to a statistical test of a group of 4 values: LDR-BT, EBRT-IMRT, EBRT-3D-CRT, and a fourth not relevant item characterized by a low number of participants

12 Zelevsky 1999: baseline data were not comparable and neither adjusted nor stratified for

Physician-reported SAE were reported in one RCT [30] and seven nonrandomised studies [18,19,28,37,38,40,47] (Table 1). Results comprising type of control intervention, proportion of events, HR and p value, and interpretation of effect are listed in Table 6. An effect was defined as a statistically significant difference between intervention groups. A better score was defined as at least two effects in one direction without contrasting effect after a minimum 6-mo follow-up. Urogenital late toxicity grade 2 to 3 was significantly more common in three studies in the LDR-BT group compared to the EBRT group. The difference between groups of other SAE was not significant. An effect was reported in a single study only, or the results were contradictory among several studies.

PROs such as function or bother scores as well as generic HRQL were reported in 13 studies (Table 1) [21,22,24, 27,29–33,35,36,43,44], including the single RCT. Concerning sexual function or bother, better scores were reported for the LDR-BT group compared with RP (Table S3; online at doi: 10.1016/j.eururo.2011.06.04). Concerning urinary tract problems, urinary function scores and urinary incontinence scores were better for the LDR-BT group than the RP group (Table S4; online at doi: 10.1016/j.eururo.2011.06.04). Concerning bowel scores, better scores were reported for the LDR-BT group than the EBRT group (Table S5; online at doi: 10.1016/j.eururo.2011.06.04). Concerning generic HRQL, we found only two contrasting effects (Table S6; online at doi: 10.1016/j.eururo.2011.06.04). Differences between groups that were not statistically different and failure to report results of statistical tests were major reasons.

Table 6. Results: Severe adverse events

End point	LDR-BT versus...	Study	Events, %	HR (95% CI); <i>p</i> value	Effect ¹
Toxicity					
Gastrointestinal early ²	EBRT	Pickles 2010 [40]	4 vs 5	n/r; 0.852 ³	n/s
Gastrointestinal late ⁴	EBRT	Eade 2008 [18]	n/r	3.18 (1.00–10.05); 0.050	Pro EBRT (1)
	EBRT	Pickles 2010 [40]	1.0 vs 3.8	n/r; 0.018 ⁵	Contra EBRT (1)
Urogenital early ²	EBRT	Pickles 2010 [40]	2.9 vs 0.7	n/r; 0.211 ³	n/s
Urogenital late ⁴	EBRT	Eade 2008 [18]	19.2 vs 3.5	9.90 (3.70–26.47); < 0.001	Pro EBRT (1)
	EBRT	Pickles 2010 [40]	6.5 vs 0.0	n/r; < 0.001 ⁵	Pro EBRT (2)
	EBRT	Zelevsky 1999 [47]	n/r	7.19 (3.68–13.96); < 0.001	Pro EBRT (3)
Urinary tract					
Urethral stricture	RP	Elliott 2007 [28]	1.8 vs 8.4	0.16 (0.01–1.87); n.r.	n/s
	RP	Giberti 2009 [30]	2.0 vs 6.5	n/r; 0.221 ³	n/s
	EBRT	Elliott 2007 [28]	1.8 vs 1.7	0.95 (0.07–12.78); n.r.	n/s
	EBRT	Eade 2008 [18]	7.0 vs 0.0	n/r; < 0.001 ³	Pro EBRT (1)
	NPT	Elliott 2007 [28]	1.8 vs 1.1	1.68 (0.46–6.14); 0.430	n/s
Urinary bladder catheterisation	EBRT	Pickles 2010 [40]	15.0 vs 0.0	n/r, < 0.001	Pro EBRT (1)
Urinary incontinence	RP	Giberti 2009 [30]	0.0 vs 18.4	n/r; < 0.001 ³	Contra RP (1)
Urinary irritation	RP	Giberti 2009 [30]	20.0 vs 5.0	n/r; < 0.001 ³	Pro RP (1)
Secondary neoplasia					
Second primary tumor	EBRT	Abdel-W 2008 [19]	4.7 vs 10.3	0.84 (0.73–0.97); n/r	Contra EBRT (1)
	NPT	Abdel-W 2008 [19]	4.7 vs 7.9	0.96 (0.87–1.06); 0.397	n/s
Urinary bladder carcinoma	RP	Nieder 2008 [37]	0.5 vs 0.7	1.52 (1.24–1.87); n/r	Pro RP (1)
	EBRT	Nieder 2008 [37]	0.5 vs 1.3	0.81 (0.60–1.10); n/r	n/s
Rectal carcinoma	RP	Nieder 2008 [37]	0.2 vs 0.3	1.08 (0.77–1.54); n/r	n/s
	EBRT	Nieder 2008 [37]	0.2 vs 0.4	0.86 (0.52–1.43); n/r	n/s
Acute myeloid leukaemia	RP	Ojha 2010 [38]	0.1 vs 0.1	0.98 (0.23–4.18); n/r	n/s
	EBRT	Ojha 2010 [38]	0.1 vs 0.2	0.60 (0.14–2.50); n/r	n/s
	NPT	Ojha 2010 [38]	0.1 vs 0.1	1.22 (0.46–3.22); n/r	n/s

Abbreviations: CI: confidence interval; EBRT: external beam radiotherapy; HR: hazard ratio; LDR-BT: low-dose rate brachytherapy; n/r: not reported or insufficient data; n/s: difference between treatment groups not statistically significant; NPT: no primary therapy including active surveillance, watchful waiting or observation of patients with prostate cancer; RP: radical prostatectomy

¹ Count of statistically significant effects per category

² Gastrointestinal toxicity (early, grade 2-3); urogenital toxicity (early, grade 2-3)

³ *p* value calculated using unconditioned test for comparing two independent proportions by Andres 1994 [73]

⁴ Gastrointestinal toxicity (late, grade 2-3); urogenital toxicity (late, grade 2-3)

⁵ *p* value calculated using chi-square test

3.6. Discussion

3.6.1. Outcomes

We found a high risk of bias among all 31 identified studies, including 1 RCT. Recent systematic reviews [8,9,49,50] also addressed the lack of RCTs investigating brachytherapy. Wilt 2008 [49] pointed out that long-term, adequately powered randomised trials to provide reliable estimates about the relative effectiveness of treatments are needed.

Only one nonrandomised study reported equivalent improvement of overall and disease-specific mortality for localised disease 7 yr after LDR-BT compared to NPT [48]. The mortality–incidence ratio of PCa can be estimated at 15%, and the overall 5-yr relative survival of patients in comparison to the general population was reported at 99.1% [51]. Both statistics are compatible with a long life expectancy compared to other cancers. Thus, even significant improvement of disease-specific mortality is not expected to have an important impact on overall mortality. Yet, a large difference in OS is reported, which strongly indicates structural differences in the patient populations between the treatment groups, possibly resulting in biased effect estimates because of considerable residual confounding.

Concerning physician-reported SAE, a statistically significant effect in favour of LDR-BT in at least two studies and no contradicting effects in other studies were found for urogenital late toxicity grade 2 to 3 when compared to EBRT. Concerning PROs, a statistically significant effect in favour of LDR-BT in at least two studies and no contradicting effects in other studies compared with RP was identified for sexual function, urinary function, and urinary incontinence. Some of the results are not unexpected considering the treatment-specific impact on physical integrity. An advantage for LDR-BT in urinary and sexual domains was similarly observed at 5-yr follow-up in the Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial [52]. An analogous effect in favour of LDR-BT was identified for bowel function when compared to EBRT. Some of the results are also not unexpected, because the bowel may be affected by EBRT.

The current evidence does not allow a determination of whether LDR-BT has an additional benefit or harm compared to other treatment alternatives in patients with localised PCa. Informed decision-making requires detailed and unbiased description of possible benefits and harms for each intervention with respect to the individual needs and health preferences of the patients. Unfortunately, conflicts of interest may hamper unbiased counselling [53], and experts such as urologists or radiotherapists prefer the modality they deliver [54,55]. Thus, individual preferences by patients and physicians play a central role in the decision whether to treat or to pursue active surveillance [56]. Ethical issues such as patient and physician preferences as well as transparent counselling should be considered in study designs. RCTs on surgical treatment of cancer are especially threatened by low rates of accrual, and physicians offered the

following main explanations in questionnaire: concern that the doctor–patient relationship would be affected by an RCT, difficulty with informed consent, and dislike of open discussions involving uncertainty [57].

3.6.2. Biochemical recurrence-free survival

We found inconsistent results for bRFS. Some studies found significant differences between LDR-BT versus RP and LDRBT versus EBRT, whereas others reported insignificant differences. All studies in favour of LDR-BT over EBRT reported application of low-dose EBRT. These results are in agreement with the results of a meta-analysis by Viani 2009, who concluded that high doses are superior to low-dose RT in preventing biochemical failure [58].

BRFS is the most commonly used end point in the included studies and may be the best tool available for detecting recurrence of PCa in individuals. However, for the purpose of statistical comparison of different treatments, bRFS is not an appropriate end point. BRFS represents a surrogate end point and is not validated for comparing LDRBT to RP, EBRT, or NPT. Different definitions of this surrogate and serious reservations for interpreting comparative results are in effect. Therefore, this outcome is presented as supporting data only to allow a description of available information.

PSA-based recurrence was traditionally considered an attractive surrogate end point for survival [59], but this was mainly based on data after RP. It has not been validated for any treatment of localised PCa. Different definitions exist for bDFS after EBRT (Phoenix definition) [60] and after RP [61]. The term is not defined for follow-up after LDR-BT and is not helpful for comparing two treatment alternatives, especially not for comparing LDR-BT to RP [62]. Sensitivity and specificity of the Phoenix criteria to detect late clinical recurrence range between 60% and 80% for patients after EBRT [60]. More than half of the patients who have a biochemical recurrence-free survival (bRFS) according to the Phoenix definition subsequently die from other causes than PCa [63]. The predictive value of a BCR after LDR-BT using the Phoenix definition depends on the duration of follow-up [64]. Short-term studies focussing on PSA-based RFS, therefore, tend to overestimate the efficacy of LDR-BT compared to RP, because PSA recurrence—by its very definition—is unlikely to occur within the first months after LDR-BT. The proportion of false-positive values in PSA bounce can be considerable for accurate estimates of treatment efficacy after brachytherapy if the follow-up is < 3 yr [64,65]. All these points raise serious questions about the validity of BCR-free survival as an outcome measure.

3.6.3. Strengths and limitations of the present review

The strengths of this review are the broadness of the search strategy and the comprehensiveness of the published data included. However, the lack of RCT data and the poor methodologic quality of the included studies imply that the validity and the over-

all robustness of results are limited. In addition, the included studies were heterogeneous with regard to patient characteristics, isotopes used in LDR-BT, surgical approaches in RP, and radiation dose in EBRT. As in any systematic review, the limitations in drawing conclusions are directly dependent on the quality and homogeneity of the primary studies.

We identified a high risk of bias within all studies. As the different treatment options in localised PCa (LDR-BT, RP, EBRT, and NPT) differ substantially with regard to techniques, possible benefits, and possible harms, clinical guidelines recommend these treatments to specific patient subgroups, causing selection bias and covariate imbalance in observational studies. Because statistical adjustment is unable to fully control for such strong confounding factors, this problem may be overcome only by RCTs.

3.6.4. Future prospects

We have identified three ongoing RCTs that may provide sufficient evidence in upcoming years to allow conclusions about the comparative effectiveness of LDR-BT. With support from the German statutory health care system, a preference-based multicentre RCT comparing LDR-BT, RP, EBRT, and active surveillance is planned to start recruitment in 2011 [66]. Standard Treatment Against Restricted Treatment (START) is an international (Canada, United States, United Kingdom) two-arm multicentre RCT to investigate the outcome of active surveillance in patients with low-risk PCa compared to LDR-BT, EBRT, or RP [67]. Surgery Against Brachytherapy (SABRE 1), a randomised evaluation, is an international (United Kingdom, Canada) multicentre RCT to compare LDR-BT against RP [68].

4. Conclusions

We found a low amount of evidence in studies that exclusively compared LDR-BT with other treatment modalities. LDR-BT may have some different physician-reported SAE and PROs. The current evidence is insufficient to allow a definitive conclusion about OS. Randomised trials focussing on long-term survival are needed to clarify the relevance of LDR-BT in patients with localised PCa.

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Supplementary tables associated with this article can be found, in the online version, at doi: 10.1016/j.eururo.2011.06.044.

CHAPTER 6

Negative-pressure wound therapy: Systematic review of randomized controlled trials

Peinemann F, Sauerland S. Negative-pressure wound therapy: systematic review of randomized controlled trials. *Deutsches Arzteblatt International*. 2011;108(22):381-9.

Abstract

Background In negative-pressure wound therapy (NPWT), a wound is covered with an airtight dressing, and negative pressure is applied. This is thought to promote healing. We evaluated NPWT with an updated, systematic review of the literature.

Methods We systematically searched the PubMed and Cochrane Library databases for randomized, controlled trials (RCTs) of NPWT for the treatment of acute or chronic wounds. The primary outcome was complete wound closure.

Results We found reports of 9 RCTs in addition to the 12 covered by earlier IQWiG reviews of this topic. Five of the 9 new trials involved NPWT systems that are not on the market. The frequency of complete wound closure is stated in only 5 of the 9 new reports; a statistically significant effect in favor of NPWT was found in only two trials. The results of 8 of the 9 new trials are hard to interpret, both because of apparent bias and because diverse types of wounds were treated.

Conclusion Although there may be a positive effect of NPWT, we did not find clear evidence that wounds heal any better or worse with NPWT than with conventional treatment. Good RCTs are still needed to evaluate NPWT.

Introduction

Negative-pressure wound therapy (NPWT) is a sealed wound-care system and is particularly indicated for large chronic persistent wounds and acute complicated wounds [1, 2]. The system consists of an electronically controlled pump and a foam dressing that drains the wound. An adjustable negative pressure is applied via an airtight adhesive film that covers the wound. NPWT drains wound exudate and is thought to promote blood circulation and healing.

This systematic review aims to update the systematic reviews on NPWT previously published by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) [3–5]. The aim of these reports was to evaluate wound healing and adverse events following NPWT in comparison to conventional treatment in patients with acute or chronic wounds.

Methods

The reports within this systematic review were compiled in accordance with the principles of the PRISMA statement [e1].

Inclusion criteria

The research included randomized controlled trials (RCTs) involving patients with acute and chronic wounds. Because of the increasing number of RCTs conducted in recent years, non-randomized trials were not included in the evaluation. The intervention under examination was NPWT. As in the previous reports, studies of systems not commercially available were included in addition to commercially available systems. In the systems that were not commercially available, negative pressure was generated by a suction pump for chest drainage, a central vacuum system or Redon bottles, for example. The comparator treatment was conventional dressings, generally saline-soaked gauze dressings. There was no minimum number of patients per trial. There was no restriction on language or year of publication. However, articles in languages other than English or German were only included in the review if there were translations available that made it possible to assess the trials concerned.

Search strategy

Unlike the earlier IQWiG reports, this review included only RCTs [3, 4]. The simplified search strategy used (eTable 1) identified all 12 RCTs already included in PubMed and the Cochrane Library's Clinical Trials on November 7, 2010. EMBASE and CINAHL were not searched, as they had not yielded any additional relevant results in previous

searches [6]. The search results from the two included databases were imported into EndNote X3 (Thomson Reuters) and duplicates were deleted manually.

The electronic trial registers ClinicalTrials.gov (URL: <http://clinicaltrials.gov/>; registration numbers: NCT followed by eight digits) and the International Standard Randomised Controlled Trial Number Register (URL: www.controlled-trials.com/; registration numbers: ISRCTN followed by eight digits) were searched for completed and ongoing trials on January 15, 2011, using the following search terms: "vacuum assisted closure"; "vac"; "negative pressure wound therapy"; "npwt".

Study selection

First of all, articles were excluded on the basis of their title and abstract if these did not mention NPWT or it was clear that the trials were not randomized. The full text of the remaining articles was then examined. The reasons for excluding each individual study were recorded internally. All stages of study selection were performed independently by two separate individuals. Differences of opinion were discussed until a common decision could be made. Potential for bias

The risk of bias within trials was examined using the criteria stated in Table 1. A positive answer in all five categories was established at the outset as indicating a low potential for bias. The potential effect of publication bias was assessed by updating a previous study [6] identifying all the trials that were terminated early.

Data collection and analysis

All stages of data extraction were performed by one person and checked by another. Where there were differences of opinion, consensus was reached following discussion. The results were subjected to descriptive analysis. Study characteristics were extracted as shown in Table 2.

Complete wound closure, a variable used both as raw data and as a Kaplan–Meier estimator, was the primary endpoint. The U.S. Food and Drug Administration's (FDA) 2006 Guidance for Industry [7] defines complete wound closure as "skin closure without drainage or dressing requirements". No meta-analysis was performed, as the primary trials were highly heterogenous.

The following dependent variables were used as secondary endpoints:

- Adverse events, such as:
 - Death
 - Secondary amputations
 - Fistula formation
 - Wound infection
- Time to complete wound closure
- Reduction in wound size
- Health-related quality of life

Table 1. Potential for bias

RCT	Suitable allocation to groups* ¹	Allocation to groups suitably concealed* ²	Assessment of endpoints blinded* ³	Reasons given for any data loss* ⁴	Adequate ITT analysis* ⁵	Potential for bias* ⁶
Commercially available systems						
Blume 2008 [8]	+	+	-	+	-	High
Chio 2010 [9]	+	+	-	-	-	High
Keskin 2008 [10]	?	?	-	+	-	High
Stannard 2009 [11]	+	?	-	+	-	High
Systems not commercially available						
Bee 2008 [12]	+	+	-	+	-	High
Mody 2008 [13]	+	?	-	-	-	High
Perez 2010 [14]	?	?	-	-	+	High
Saaq 2010 [15]	+	?	-	+	+	High
Sepulveda 2009 [16] ⁷	+	+	+	+	+	Low

Abbreviations: +: Yes; -: No; ? Unclear; ITT: intention to treat; RCT: randomized controlled trial

*¹ Suitable allocation to groups: A precise description of the randomization sequence generating procedure was required (e.g. computer-generated lists).

*² Allocation to groups suitably concealed: Information on how allocation to groups was then blinded was required (e.g. centrally by telephone or using sealed, opaque envelopes).

*³ Assessment of endpoints blinded: Information on who (patient and/or researcher) assessed which endpoint under blinding conditions (without knowing the group to which the patient had been allocated) was required.

*⁴ Reasons given for any data loss: The requirement was either no data loss or, if data loss was reported, identification of all patients whose data could not be fully evaluated after randomization and the reasons for this (e.g. patients who dropped out before the beginning of treatment or during follow-up).

*⁵ Adequate ITT analysis: Evaluation using the number of randomized patients as the size of the population was required.

*⁶ Potential for bias: High or low; all five criteria had to be met for the potential for bias to be described as low.

*⁷ Sepulveda 2009: The blinded parameter was assessment of the percentage of wound granulation.

Table 2. Trial and patient characteristics in the newly-identified randomized controlled trials (RCTs)

RCT	Sites	Recruitment period	FU (days)	Randomized patients	Dropout or LTFU	Dropout or LTFU by ITT	Mean age	Gender: % male	Mean wound surface area (cm ²)	Comorbidities (%)
				I vs. C	I vs. C	I vs. C	I vs. C	I vs. C	I vs. C	I vs. C
Commercially available systems										
Blume 2008 [8] ^{*1}	5 (USA)	2002 to 2005	112	172 vs. 169	59 vs. 52	3 vs. 3	58 vs. 59	83 vs. 73	14 vs. 11	n/a
Chio 2010 [9] ^{*2}	1 (USA)	2007 to 2009	30	27 vs. 27	4 vs. 0	4 vs. 0	62 vs. 58	61 vs. 60	73 vs. 69	39 vs. 26
Keskin 2008 [10] ^{*3}	1 (Turkey)	n/a	10	20 vs. 20	n/a	n/a	n/a	n/a	n/a	0 vs. 0
Stannard 2009 [11] ^{*4}	1 (USA)	2001 to 2006	840	35 vs. 23	0	0	n/a	74 vs. 57	65 vs. 58	n/a
Systems not commercially available										
Bee 2008 [12]	1 (USA)	2003 to 2007	n/a	31 vs. 20	2 vs. 1	2 vs. 1	44 vs. 37	81 vs. 85	n/a	n/a
Mody 2008 [13] ^{*5}	1 (India)	n/a	214	19 vs. 36	5 vs. 15	4 vs. 3	54	72	67 vs. 121	n/a
Perez 2010 [14] ^{*6}	1 (Haiti)	2007 to 2007	n/a	25 vs. 24	5 vs. 4	5 vs. 4	49 vs. 44	60 vs. 45	45 vs. 40	35 vs. 30
Saaq 2010 [15]	1 (Pakistan)	2007 to 2009	n/a	50 vs. 50	n/a	n/a	33	86	65	n/a
Sepulveda 2009 [16] ^{*7}	1 (Chile)	2006 to 2007	n/a	12 vs. 12	0	0	62 vs. 62	83 vs. 75	n/a	42 vs. 33

Abbreviations: C: Control group; n/a: Not available; I: Intervention group = negative-pressure wound therapy (NPWT); ITT: intention to treat; LTFU: Lost to follow-up;

*1 Blume 2008: Allocation to groups: 172 NPWT vs. 169 control; NPWT/control group: 3/3 no NPWT + 1/5 LTFU + 54/43 trial terminated + 1/1 incomplete data = 59/52 dropout or LTFU

*2 Chio 2010: Comorbidities were diabetes mellitus, peripheral vascular disease, hypothyroidism, and long-term steroid treatment.

*3 Keskin 2008: Comorbidities were diabetes mellitus; 40 patients: mean age 38 years, 60% male.

*4 Stannard 2009: Mean length of observation period (days); wound surface area was calculated from length and breadth.

*5 Mody 2008: Mean length of observation period (days); dropouts after randomization, before treatment 4:3; LTFU before wound closure 1:12; mean wound surface area calculated on the basis of data on 4 wound categories.

*6 Perez 2010: Comorbidities were diabetes mellitus.

*7 Sepulveda 2009: Comorbidities were dyslipidemia receiving drug treatment; proportion of patients with hypertension not stated.

Results

Search of the literature

Of the 249 articles initially imported, 176 remained after duplicates had been deleted. In 137 cases it was clear from the title and/or abstract that the article did not meet the inclusion criteria (eFigure; online at doi: 10.3238/arztebl.2011.0381). A further 30 potentially relevant articles were excluded after they had been read in full. A total of nine new RCTs were identified in the updated search [8–16]. Five of the nine new RCTs examined systems that were not commercially available [12–16]. This left a total of 21 RCTs available for our research: seven [e2–e8] from IQWiG's Final Report N04–03 [3], five RCTs in four articles [e9–e12] from IQWiG's Rapid Report N06–02 [4], and nine RCTs from the updated search.

Underlying data

An overview of trial characteristics is provided in Table 2. The mean age of the participants, most of whom were male, was generally over 50. The mean wound surface area was numerically slightly greater in intervention groups than in control groups in all trials in which this information was given separately. Detailed descriptions of inclusion and exclusion criteria, treatments under research, comparator treatments, analyzed endpoints, and their definitions can be found in eTables 2 and 3 (online at doi: 10.3238/arztebl.2011.0381). In most trials comorbidities were not reported. The trials examined many different types of acute and chronic wound (eTable 4; online at doi: 10.3238/arztebl.2011.0381).

Potential for bias

Eight of the nine trials had a high potential for bias (Table 1). The conditions for generating randomization sequences and treatment blinding were unclear in some trials, with the result that random allocation of patients to treatment groups was not traceable in these trials. In eight of the nine trials it was not reported or not clear that endpoints had been measured in blinded conditions, although this was feasible. It should be stressed that quality-of-life results from non-blinded trials are prone to a particularly high potential for bias. Only one of the trials met all five criteria for low potential for bias. In six of the nine new trials, up to 20% of the data from randomized patients were not included in the evaluation, and there was thus no appropriate intention-to-treat analysis.

Investigation of publication bias revealed a further four RCTs that had been terminated early, in addition to the five that had already been reported on: NCT00121537, NCT00691821, NCT00837096, and NCT01108276.

The following reasons were given for terminating trials early:

- Inclusion criteria not met
- Patient withdrawal
- Low recruitment levels
- Changes in clinical practice
- Errors in study planning

Eight ongoing RCTs were also identified among the registered trials (NCT00582179, NCT00582998, NCT00635479, NCT01200563, NCT01191567, NCT00548314, and NCT00789659).

Primary endpoint

The proportion of patients with complete wound closure was reported in only five of the nine new trials [8, 12–15] (Table 3). In four trials the difference between groups was statistically insignificant. Only two trials showed a statistically significant effect in favor of NPWT [15].

Secondary endpoints

Time to wound closure was reported in four of the nine new trials [8, 13, 14, 16] (Table 4). Three trials showed a statistically significant difference between groups in favor of NPWT [8, 14, 16], and in one trial the difference was statistically insignificant [13]. There was a statistically significant difference in reduction in wound size in favor of NPWT in one of the nine new trials [8].

Adverse events were investigated in eight of the nine new trials [8, 9, 11, 12]. Statistically significant differences in favor of NPWT were reported in three trials. The adverse events concerned were secondary amputations [8], the proportion of patients with deep wound infections [11], and the secondary surgery rate [14].

Differences in mortality rates between treatment groups were statistically insignificant [8, 12, 15, 16]. This was also the case for most of the wound complication rates in four trials [8, 9, 12, 13].

One trial investigated health-related quality of life, using questionnaires [11]. The results for the physical component (following treatment) were better in the NPWT group, and the difference was statistically significant. For the mental component, meanwhile, the results were comparable.

Another trial revealed more fear of treatment, e.g. due to possible pain, in the NPWT group than in the control group, and the difference was statistically significant [10].

Table 3. Systematic review results on primary endpoint

RCT	Endpoint	NPWT	Control	P value	Remarks
Commercially available systems					
Blume 2008 [8]	No. of cases of complete wound closure; n (%)	73 (43)	48 (29)	p = 0.007	Observation period 112 days; no data on 6 or 9 month follow-up
Chio 2010 [9]	n/a	n/a	n/a	n/a	-
Keskin 2008 [10]	n/a	n/a	n/a	n/a	-
Stannard 2009 [11]	n/a	n/a	n/a	n/a	-
Systems not commercially available					
Bee 2008 [12]	Abdominal wall closed by sewing together the fascia; n (%)	15 (31)	5 (26)	Insig.	Unclear figures in Table 2 of article: closure (total) 14 (48) but NPWT + control = 20 (70). No confidence interval or p value stated in article, only qualitative interpretation: no difference
Mody 2008 [13]	No. of cases of complete wound closure; n (%)	7 (48)	16 (48)	n/a	Percentages relate to no. of patients treated, not no. of patients randomized; few patient characteristics reported
Perez 2010 [14]	No. of cases of complete wound closure; n (%)	18 (90)	19 (95)	p = 0.302	30 days after wound closure or skin transplantation
Saaqi 2010 [15]	No. of cases of complete wound closure; n (%)	45 (90)	9 (18)	p < 0.001	2 weeks after skin transplantation; 3 categories (2 weeks, 3 to 4 weeks and 5 or more weeks) instead of mean no. of days to wound healing
Sepulveda 2009 [16]*7	n/a	n/a	n/a	n/a	-

Abbreviations: -: None; Insig.: statistically insignificant; n/a: not available; NPWT: negative-pressure wound therapy; RCT: randomized controlled trial

Table 4. Systematic review results on secondary endpoints

RCT	Endpoint	NPWT	Control	p value	Remarks
Commercially available systems					
Blume 2008 [8]	No. of days to complete wound closure; median (95% CI)	96 (75 to 114)	>112	p = 0.001	Results based on Kaplan-Maier analysis
Blume 2008 [8]	Reduction in wound surface area (cm ²)	-4.3	-2.5	p = 0.021	Measured 28 days after beginning of treatment
Blume 2008 [8]	Secondary amputations; n (%)	7 (4)	17 (10)	p = 0.035	-
Blume 2008 [8]	Mortality; n (%)	3 (2)	3 (2)	n/a	-
Blume 2008 [8]	No. of wound complications (edema, infection of wound, cellulitis, osteomyelitis); n (%)	16 (10)	11 (7)	-	No statistically significant difference in any individual adverse event
Chio 2010 [9]	No. of wound complications; n (%)	7 (30)	12 (44)	p = 0.816	However, according to Table 2 of article NPWT 35% (8 of 23), not 30% (7 of 23) as stated in text
Keskin 2008 [10]	Increase in STAI; mean (SD)	14.0 (2.3)	2.6 (1.2)	p < 0.001	Increase in fear during the first 10 days of treatment
Keskin 2008 [10]	Increase in HAM; mean (SD)	4.4 (0.6)	1.3 (0.6)	p < 0.001	Increase in fear during the first 10 days of treatment
Stannard 2009 [11]	Wound complications: rate of deep wound infections; n (%)	2 (5)	7 (28)	p = 0.024	-
Stannard 2009 [11]	Physical quality of life according to SF-36 after 6 months; mean (95% CI)	43 (35 to 50)	34 (29 to 39)	p = 0.049	Results after 3 and 9 months also showed a statistically significant benefit for NPWT.
Stannard 2009 [11]	Mental quality of life according to SF-36 after 6 months; mean (95% CI)	n/a	n/a	n/a	Results after 3, 6, and 9 months all failed to show any statistically significant difference.
Systems not commercially available					
Bee 2008 [12]	Mortality; n (%)	7 (26)	5 (25)	n/a	3 patients died within 7 days and were excluded from analysis. NPWT failed in a further 2 patients, who were successfully treated using the control therapy.
Bee 2008 [12]	Intestinal fistula formation; n (%)	(21)	(5)	p = 0.14	-
Bee 2008 [12]	Abdominal abscess; n (%)	12 (44)	9 (47)	n/a	-
Mody 2008 [13]	Days to complete wound closure; mean (SD)	36 (45)	28 (19)	p = 0.66	-
Mody 2008 [13]	No. of wound complications; n (%)	6 (32)	2 (6)	n/a	-
Perez 2010 [14]	Days to complete wound closure; mean (R)	16 (14 to 23)	25 (23 to 32)	p = 0.013	-
Perez 2010 [14]	Secondary surgery rate	7	4	p = 0.038	-

RCT	Endpoint	NPWT	Control	p value	Remarks
Saaq 2010 [15]	≥ 95% acceptance of skin transplant; n (%)	45 (90)	9 (18)	p < 0.001	No patient characteristics reported for either treatment group. Categories from 1 to 3 given for endpoints.
Saaq 2010 [15]	Mortality; n (%)	0	0	n/a	-
Saaq 2010 [15]	No. of patients with complete wound closure within 2 weeks; n (%)	45 (90)	9 (18)	p < 0.001	-
Saaq 2010 [15]	No. of cases needing repeat skin transplantation; n (%)	0	4 (8)	n/a	-
Sepulveda 2009 [16]	Hospital mortality; n (%)	0	0	n/a	-
Sepulveda 2009 [16]	Days to 90% wound granulation; mean (SD)	19 (6)	32 (14)	p = 0.007	-

Abbreviations: -: not applicable; CI: Confidence interval; HAM: Hamilton Rating Scale; n/a: not available; NPWT: negative-pressure wound therapy; R: range; RCT: Randomized controlled trial; SD: standard deviation; SF 36: short form (36) health survey; STAI: State-Trait Anxiety Inventory;

Summary of results

Table 5 shows the qualitative results of all 21 RCTs included in the present systematic review, in terms of the endpoints studied. The quantitative results of the 12 older RCTs covered in IQWiG reports can be found in the corresponding publications [3, 4], and the results of the nine new RCTs are shown in Tables 3 and 4.

Table 5. Summary of results of all 21 randomized controlled trials (RCTs) included to date

RCT	Primary endpoint	Secondary endpoints			
	Complete wound closure	Time to complete wound closure	Reduction in wound size ^{*1}	Mortality	Other adverse events ^{*2,3}
Armstrong 2005 [e2]	+++	+++	n/a	(+)	(+)
Bee 2008 [12]	(+)	n/a	n/a	(-)	(-)
Blume 2008 [8]	+++	+++	+++	(+)	(+)
Braakenburg 2006 [e9]	n/a	(+)	(+)	(+)	(-)
Chio 2010 [9]	n/a	n/a	n/a	n/a	(+)
Eginton 2003 [e3]	n/a	n/a	+++	n/a	n/a
Ford 2002 [e4]	(-)	n/a	(+)	n/a	(-)
Joseph 2000 [e5]	n/a	+++	+++	n/a	+++
Keskin 2008 [10] ^{*4}	n/a	n/a	n/a	n/a	n/a
Llanos 2006 [e10]	n/a	n/a	+++	n/a	n/a
Mody 2008 [13]	(-)	(-)	n/a	n/a	(-)
Moisisdis 2004 [e6]	n/a	n/a	n/a	n/a	n/a
Mouës 2004 [e6]	n/a	(+)	+++	n/a	n/a
Perez 2010 [14]	(-)	+++	n/a	n/a	---
Saaqi 2010 [15]	+++	+++	n/a	0	n/a
Sepulveda 2009 [16]	n/a	+++	n/a	0	n/a
Stannard 2006a [e11] ^{*5}	n/a	n/a	n/a	n/a	(-)
Stannard 2006b [e11]	n/a	n/a	n/a	n/a	0
Stannard 2009 [11] ^{*6}	n/a	n/a	n/a	n/a	---
Vuerstaek 2006 [e12]	n/a	+++	+++	(-)	(-)
Wanner 2003 [e8]	n/a	(+)	(+)	n/a	n/a

Abbreviations: +++: statistically significant difference in favor of negative-pressure wound therapy (NPWT); ---: statistically significant difference in favor of comparator treatment; (+): insignificant difference in favor of NPWT; (-): insignificant difference in favor of comparator treatment; 0: no difference; n/a: not available

^{*1} Wound size: Surface area or volume, statistically significant results reported primarily

^{*2} Pain: Braakenburg 2006 referred to a study on pain but did not report its results; Vuerstaek 2006 reported a statistically significant benefit of NPWT, but there were already statistically significant differences in pain between the two groups initially (pain was lower at baseline in the NPWT group). This was not suitably taken into account in the evaluation.

^{*3} Further results that were only reported singly and were therefore not included in the table: amputations: Armstrong 2005: (+); Blume 2008: +++; Braakenburg 2006 (+). Quality of life: Keskin 2008: ---; Stannard 2009: +++; Vuerstaek 2006: --- (in the first week of treatment)

^{*4} Keskin 2008: fear during the first 10 days

^{*5} Stannard 2006a: trial on hematomas; Stannard 2006b: trial on incisions in fractures

^{*6} Stannard 2009: statistically significant difference after 3, 6 and 9 months

Discussion

Primary endpoint: complete wound closure

The results on complete wound closure are not homogenous, and it is impossible to be sure that NPWT performs better than the control treatments. Effects in favor of NPWT were reported in some trials, and no opposing effects could be detected in other trials. As a result, other systematic reviews also currently conclude that an additional benefit of NPWT in comparison to other types of wound treatment has not been proved [17, 18].

Secondary endpoints

Time to wound closure: In terms of the endpoint "time to wound closure," effects in favor of NPWT groups were reported in most cases. However, there were considerable differences between trials in terms of the methods used to measure and evaluate wound closure; particularly problematic is the fact that no blinding was used when this endpoint was measured. In addition, most trials did not investigate whether wounds that had healed successfully actually remained closed in the longer term. The results thus cannot be interpreted as showing definitively that any one treatment is superior.

Adverse events: The results on adverse events were not homogenous. For some specific complications, such as secondary amputations, statistically significant effects in favor of NPWT groups were reported, but for a number of other adverse events no statistically significant difference was detected. No opposing results, i.e. statistically significant effects in favor of comparator groups, were recorded.

The difference between the number of patients included in trials and the number of patients treated worldwide is particularly striking when describing adverse effects. Data from the RCTs are of only limited use in evaluating the frequency of adverse events. It would be more appropriate if sufficiently large-scale RCTs were conducted.

The FDA recently issued a report on six deaths and 77 other complications that were reported within a two-year period in connection with NPWT [19]. All the deaths were caused by acute hemorrhages, and known contraindications for NPWT (e.g. a large blood vessel exposed) had clearly been overlooked. Many of the deaths occurred in outpatient care or care homes, which highlights the need to monitor therapy. In this regard, it should be noted that trials of NPWT were generally conducted in hospitals.

Potential for bias

Of the nine included RCTs, eight have a high potential for bias. This limits the value of the results on the endpoints reported on. The difficulties of conducting RCTs and the

arguments for and against including non-randomized trials when assessing medical devices and surgeries have been extensively described [e13, e14].

Heterogeneity

Strikingly, almost all the trials of commercially available NPWT systems were conducted in the USA. It seems that in developing countries the commercially available systems are very difficult to afford, and as a result such countries have developed their own NPWT systems, sometimes from very simple materials. Trials of these are now being conducted. This wide variety of NPWT systems makes the data considerably more difficult to interpret, although it is still largely unclear whether or not there are genuine differences between commercially available NPWT systems and those that are not commercially available. Also, the treatments administered to comparator groups (conventional dressings) were defined in different ways in different trials, probably as a result of differences between patient populations. This too can cause heterogeneity between trials and so limit the comparability of trial results.

Publication bias

According to the website of manufacturer KCI (August 2010), NPWT has been prescribed to more than 3 million patients, and some 600 peer-reviewed articles have been published on the subject. This and the low total number of RCTs make it astonishing that despite the frequency of acute and chronic wounds and the widespread use of NPWT a considerable number of trials have apparently had to be terminated due to recruitment problems. Although it seems that some planned RCTs had not even been started or were terminated soon after they began, the fact that there are RCTs on which nothing has been published casts doubt on the completeness of the data available for assessment of the benefits of NPWT.

Summary

Pool of trials

As the wounds for which NPWT is used vary greatly in their etiology, chronicity, size, and location, there is considerable variation between trials in the selection and definition of endpoints. This alone makes a quantitative summary of all trials of questionable value. In trials that provide results on wound healing, these results are mostly favorable for NPWT. These results are partly supported by statistically significant effects regarding the primary endpoint "complete wound closure" and the secondary end-

points "time to complete wound closure", "reduction in wound size", and "amputations".

The results on overall mortality and total adverse events are inconsistent. A considerable proportion of the total deaths were probably not caused by treatment. Individual adverse events are reported too infrequently and inconsistently for conclusions to be drawn. Also, the group of adverse events as a whole is highly heterogeneous. Some of the few results on quality of life are limited to the endpoint "fear" alone. Only a few trials investigated pain (in particular when dressings were changed).

The available pool of only 21 RCTs remains too small to provide a clear answer to the question of whether or not NPWT is superior to conventional wound treatment. The difficulty of interpreting the RCTs is caused essentially by the heterogeneity of the various indications for NPWT on the one hand, and the considerable qualitative and quantitative shortcomings of the trials on the other.

Outlook

Germany's statutory health insurers jointly invited tenders for two RCTs on NPWT in July 2010 [20, e15]. Patients with diabetic foot ulcers or iatrogenic wounds must be randomized to receive NPWT or conventional wound treatment, and patient numbers must be sufficient in each treatment group and for each indication. It is hoped that these trials will provide the further evidence needed for a decision on NPWT to be made. Eight other ongoing registered RCTs were also identified.

Conclusion

Although NPWT may have a positive effect on wound healing, there is no proof that it is either superior or inferior to conventional wound treatment. Further RCTs of good methodological quality are required.

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Supplementary eReferences, eFigures, and eTables associated with this article can be found, in the online version, at doi: 10.3238/arztebl.2011.0381.

CHAPTER 7

Development of an algorithm to provide awareness in choosing study designs for inclusion in systematic reviews of health care interventions – a method study

Manuscript submitted

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Abstract

Objectives We developed an algorithm that aims to provide guidance and awareness for various design characteristics suitable to answer distinct research questions in health care interventions.

Design In a method study, we transferred information from electronic databases and major institutional handbooks into a non-systematic review. Based on the retrieved data, we developed an algorithm to provide guidance for allocating various study designs to specific research questions.

Setting There were no limits on the level of care and the geographical location.

Participants There were no limits on the type of diagnosis and the characteristics of patients.

Interventions There were no limits on the type of medical treatment or public health intervention.

Primary and secondary outcome measures The primary outcome was the development of an algorithm that incorporates the length of follow up (long, short), the frequency of events (rare, frequent), the types of outcome (death, disease, discomfort, disability, dissatisfaction), considers practical or ethical concerns, and unavailable best evidence. The secondary outcome was to show the usefulness of the algorithm while applying it to selected systematic reviews.

Results We developed a guidance-support tree and provided examples for explaining the critical guidance points and for testing the usefulness of the algorithm. We could follow and confirm the appropriateness of the pathways for all described examples of four selected systematic reviews. The algorithm cannot be applied without the consideration of disease-specific circumstances and aims of interventions.

Conclusions We are confident that the algorithm can assist to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. It aims to provide awareness not regulation. We think that it may reduce the time burden on review authors and may contribute to the production of a higher quality review.

Strengths and limitations of this study

- We developed an algorithm to provide guidance for allocating various study designs to specific research questions. This can be viewed as a response to the lack of comprehensive guidance in major published methods documents.
- The terms used for defining the critical decision points of the algorithm, such as short versus long follow-up and rare versus frequent events need to be interpreted in the context of the disease and may be unclear and not useful if used as general terms.

- Disease-specific circumstances and aims of interventions always have to be taken into account during application of the algorithm.
- We could follow and confirm the appropriateness of the pathways during the application of the algorithm on four selected systematic reviews.
- The testing was conducted retrospectively with systematic reviews that were already completed. This approach is far from the everyday working condition and the approach may be considerably biased by the expectations of the authors.

Abbreviation	Term
AE	Adverse events
CCT	Nonrandomised controlled clinical trial
CEBM	Centre of Evidence-Based Medicine
CRD	Centre for Reviews and Dissemination
EBM	Evidence-based medicine
EBRT	External beam radiotherapy
HDCT	High-dose chemotherapy
HRQL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
IST	Immunosuppressive therapy
LDR-BT	Permanent interstitial low-dose-rate brachytherapy
MSD	Human leukocyte antigen matched sibling donors
NICE	National Institute for Health and Care Excellence
NPT	No primary therapy
NPWT	Negative pressure wound therapy
NRSTS	Nonrhabdomyosarcoma soft tissue sarcomas
ORDR	Office of Rare Diseases Research
OS	Overall survival
PCa	Prostate cancer
PICOTS-SD	Population – Intervention – Comparator – Outcome – Time – Setting – Study design
RCT	Randomised controlled trial
RP	Radical prostatectomy
SAA	Acquired severe aplastic anaemia
SDCT	Standard-dose chemotherapy

Introduction

When evaluating health care interventions, different categories of intervention such as medicinal versus non-medicinal therapy, and different categories of outcomes such as intended effects, adverse events, or health-related quality of life may sometimes be best answered by multiple study designs. Some designs have features, which preferably match the requirements of specific parts of a research question. Exclusively using data from randomised trials (RCTs) to evaluate whether an intervention might work has a number of limitations [1]. For example, RCTs may not be appropriate to estimate the incidence of rare (adverse) events. Study designs that incorporate the data of a large number of participants of interest such as case control studies, case series, registry analyses, or cross-sectional analyses may complement the information on such rare, but important events. We have gathered some examples of research questions that cannot or only with great difficulty be investigated in RCTs (Table S1). A practical concern may arise with low numbers of patients with a rare disease. It might be difficult to conduct an RCT to evaluate patients with acquired severe aplastic anaemia. An ethical concern may arise with the treatment of severe diseases or life-threatening treatments. It might be obsolete to conduct an RCT to evaluate a new experimental treatment of patients with pancreatic cancer.

The methods of conducting systematic reviews of health care interventions are major components of 'evidence-based' medicine (EBM). In 2000, Sackett et al. defined EBM as the integration of 'best' research evidence with individual clinical expertise, patient values and expectations, and 'best' external research evidence [2]. This definition may be visualized by three overlapping circles in a Venn diagram [3]. The area of intersection, where all three different resources meet, should represent the EBM. To classify more valid and less valid information, the 'levels of evidence' specify a hierarchical order for various research designs based on their internal validity. The highest level of valid data, that is, the 'best' evidence, however, is not always available. In Table S2, we present the classification of some of the major study designs for intended effects of therapy. There appears to be some variation in the hierarchy among some authors and institutions issuing 'evidence-based' guidelines or systematic reviews. All authors agree that RCTs have the highest 'level of evidence' with respect to minimising the risk of bias. The prospective nonrandomised controlled clinical trial (CCT) has an experimental design and its internal validity should be regarded lower than a randomised trial but higher than an observational study. Prospective cohort studies have a potential for a lower risk of bias than retrospective cohort studies because they have lower risk of recall bias and confounding [4]. In cohort studies groups are defined by exposure whereas in case-control studies groups are defined by outcome status. Both points are acknowledged in the 'hierarchy of evidence' by some but not all authors. Case series and case reports are descriptions of one or more individual cases. Some authors combine both designs in one category while others place case series a higher level.

Table S1. Research questions that cannot or that can only with difficulty be investigated in RCTs.

Topic	Reason
Research questions that in certain circumstances cannot be investigated in RCTs	
Life-threatening intervention, for example, intervention with high early treatment-related mortality.	Allocation to intervention group endangers life.
Certain second-line interventions reserved for refractory patients that did not respond to first-line standard therapy	Ultimo ratio and therefore no control group by definition. Example: Haematopoietic stem cell transplantation from unrelated versus related donors for patients with acquired severe aplastic anaemia
Pregnant women	Ethical concerns against inclusion in experiments.
Infants	Ethical concerns against inclusion in experiments.
Interventions that have been shown to produce a dramatic effect.	The magnitude of benefit of one particular intervention such as insulin to treat diabetes mellitus would render any intervention a neglect of health care if insulin would be omitted unless the new treatment does also has a dramatic effect.
Lack of consent to participate.	Cheating persons is not legal
Studies that do not comply with the Declaration of Helsinki.	The set of ethical principles regarding human experimentation is regarded as the cornerstone document of human research ethics.
Research questions that can with difficulty be investigated in RCTs	
Rare adverse events and other rare safety outcomes	Number of study participants is too low
Allocation of alternative interventions is dominated by patients' preferences	Treatment group is chosen by a patient because of specific expectations of effectiveness, adverse events, or health-related quality of life.

Table S2. Definition, classification, and hierarchy of study designs for intended effects of therapy.

Category	Contr	Prosp	Design	Description	Evidence level by some institutions or authors							
					I	II	III	IV	V	VI	VII	VIII
Experimental	Yes	Yes	Randomized controlled trial	Random, concealed allocation of participants to an intervention and a control group.	1	1	1	1	1	1	1	1
Experimental	Yes	Yes	Prospective non-randomized controlled clinical trial	The method of allocation by the researcher falls short of genuine randomization and fails to conceal the allocation sequence.	2	2	n.r.	n.r.	2	1	n.r.	n.r.
Observational	Yes	Yes	Prospective cohort study	Comparison of outcome rates between treatment groups (intervention vs. comparator)	3	2	2	2	3	2	2	2
Observational	Yes	Yes	Nested case-control study	Case-control study nested in a prospective cohort study, combines advantage of two study designs	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Observational	Yes	No	Retrospective cohort study	Comparison of outcome rates between treatment groups (intervention vs. comparator)	3	3	3	2	3	2	2	2
Observational	Yes	No	Case-control study	Comparison of treatment rates between outcome groups (cases vs. controls)	4	4	3	3	3	2	2	2
Observational	No	No	Registry analysis	Description of the outcome in many patients collected with a wide range of settings and patients' characteristics	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Observational	No	No	Case series	Description of the outcome in a number of 1 or more cases of an intervention.	5	5	4	4	3	3	3	3
Observational	No	No	Case report	Description of the outcome in a number of 1 or more cases of an intervention.	5	5	5	n.r.	n.r.	4	3	3
Observational	No	No	Health outcomes research	Intervention and outcome data collected at one particular time.	n.r.	n.r.	n.r.	2	n.r.	n.r.	n.r.	n.r.
Observational	No	No	Ecological study		n.r.	n.r.	n.r.	2	n.r.	n.r.	n.r.	n.r.
Observational	No	No	Cross-sectional study		5	n.r.	n.r.	n.r.	n.r.	3	n.r.	n.r.
Observational	No	No	Within-group comparison	Also known as before-and-after study. Comparison of outcomes before and after an intervention.	5	n.r.	n.r.	n.r.	2	3	n.r.	n.r.
Others	n.a.	No	Expert opinion		5	n.r.	5	5	n.r.	4	4	4

Category	Contr	Prosp	Design	Description	Evidence level by some institutions or authors							
					I	II	III	IV	V	VI	VII	VIII
Others	n.a.	No	Consensus recommendation		5	n.r.	5	n.r.	n.r.	n.r.	4	n.r.
Others	n.a.	No	Pathophysiological study		5	n.r.	5	5	n.r.	4	n.r.	n.r.
Others	n.a.	No	Animal study		5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

Experimental: In an experimental study, the researcher allocates participants to different treatment groups. Observational: In an observational study, the participants are not allocated by the researcher. Control: yes: with control group (comparative study), no: no control group (single-arm study).

Evidence level by some institutions or authors: I: Present review; II: Vandenbroucke 2008 [35]35; III: Gemeinsamer Bundesausschuss (G-BA) Federal Joint Committee [36]; Centre for Evidence-based Medicine (CEBM) [37]; V: Centre for Reviews and Dissemination (CRD) [7]; VI: Khan 2011 [24]; VII: National Institute for Health and Clinical Excellence (NICE): levels of evidence were specified in 2004 [38] but not in the updated versions in 2008 and 2013; VIII: Scottish Intercollegiate Guidelines Network (SIGN) [39]

Abbreviation. CCS: case-control study; Contr: control group; CR: case report; CS: case series; HOR: Health outcome research; NRCCT: nonrandomized controlled clinical trial; n.a.: not applicable; NCC: nested case-control study; PCS: prospective cohort study; Prosp: prospective design; RCS: retrospective cohort study; RCT: randomized controlled trial.

In Figure 1 we show a study design classification tree including the main features of study designs that makes them distinct from others conforming with the reports of the Centre for Evidence-Based Medicine (CEBM), the National Institute for Health and Care Excellence (NICE), and the Centre for Reviews and Dissemination (CRD) [5-7]. Examples of distinguishing study characteristics are the concurrent vs. the historical control group or the participants being or not being allocated to the treatment groups by the investigator. Within group comparison has also been referred to as a before and after study in a previous CRD report.

Methods

The aim of this paper is to develop an algorithm as a guidance to choose study designs that are most appropriate to answer various health care questions and to guide systematic reviewers in considering multiple study designs for evaluation of the many facets of health care interventions. We searched the internet sites of not-for-profit publishers of systematic reviews and health technology assessments of health care interventions to identify published guidelines on the topic. We developed an algorithm as a guidance for choosing appropriate study design using the following decision points (Figure 2): length of follow up (long, short), frequency of events (rare, frequent), types of outcome (death, disease, discomfort, disability, dissatisfaction), and practical or ethical concerns. These decision points follow implicitly when considering the main characteristics of frequently used different study designs. E.g. cohort studies are done when randomisation is not practical or ethical, case-control studies are done when cohort studies are not practical due to low frequency of outcomes. Studies without control groups may be done when a disease is extremely rare, or for certain outcomes such as dissatisfaction or for assessing compliance.

Figure 1. Decision algorithm to help define study designs.

Figure 2. Algorithm

Explanation.

RCT: prospective randomized controlled trial, allocating experimental units via random assignment to a treatment or control condition with concealment of the allocation procedure

CCT: prospective nonrandomized controlled clinical trial, allocating experimental units via nonrandom assignment to a treatment or control condition; discomfort etc: discomfort, disability, and dissatisfaction

Nested case-control study: case-control study nested within a prospective, observational cohort study

Cohort study: prospective, observational cohort study

Case series: retrospective, observational tabulation of data from participants without consecutive enrolment

Case report: retrospective, observational report of data from one participants up to 3 patients

Registry analysis: retrospective, observational analysis of participants data from various sources transferred to and collected in a database

Abbreviation. CCT: controlled clinical trial; nested case contr: nested case-control study within a prospective cohort study; RCT: prospective randomized controlled trial, allocating experimental units via random assignment to a treatment or control condition with concealment of the allocation procedure

Length of follow up

The outcomes can be evaluated early or at a late time point after start of treatment. The terms short vs. long are relative depending on the disease, intervention and outcome of interest. We list some examples with a cut-off between short and long follow up that ranges from 30 days to 5 years (Table S3). The disease may be invasive, severe and fast progressing and a short follow up may capture the majority of the events of interest. Symptoms may aggravate a long time period after the onset of some diseases and a long follow-up is necessary to observe events. A long follow-up is also required if events occur distributed over a wide time range. The intervention of interest might have an instantaneous impact on the patients' well-being such as dextrose given to a patient in hypoglycemic coma or acute cardioversion and defibrillation in a patient with malignant arrhythmia that can occur after a heart attack. The effects of these events can be detected within a short observation period. Some patients receive life-long medicinal therapies that are intended to prevent the appearance of life-threatening symptoms of an underlying disease. In this situation, a long observation will be required to detect a number of beneficial or adverse events sufficient for comparing a test with a control intervention.

Frequency of events

The condition of interest may be rare and hard to encounter at all and may require specific study designs that allow to observing patients with these rare diseases to collect sufficient data for analysis and to draw conclusions supported by the data. A rare disease may be defined according to the Office of Rare Diseases Research (ORDR): "In the United States, a rare disease is generally considered to be a disease that affects fewer than 200,000 people. There are more than 6,800 rare diseases. Altogether, rare diseases affect an estimated 25 million to 30 million Americans." [8]. Disease-specific

registration of patients may provide information about the number and characteristics of patients that are in need of health care. Multicentre studies may need the information gathered by these registers and may arrange a treatment regimen of interest applicable to all participants. An example might be the German neuroblastoma study group [9]. A total of 96% of all German patients registered at the German childhood cancer registry with a specific type of neuroblastoma entered one of the trials. Randomization may be possible to compare two different chemotherapeutic substances but may not be feasible to investigate some other questions. In a retrospective analysis, the investigators found that spontaneous regression is regularly seen in infants with localized neuroblastoma and is not limited to the first year of life and that a wait-and-see strategy is justified in those patients [10]. Adverse events after the start of treatment may be rare and can be serious. The number of observed randomized patients may not be sufficient to detect a representative number of events. An observation of a large number of patients in single-arm studies or the recognition of selected case reports may provide information about serious drawbacks of a promising treatment. The terms rare vs. frequent events are relative depending on the disease, intervention and outcome of interest. We list some examples with a cut-off between rare and frequent events in Table S4.

Types of outcomes

We classified the outcomes according to Fletcher 2005 into the 5 groups of death, disease, discomfort, disability, and dissatisfaction (Table S5) [11]. In case of short follow-up and rare events and regarding all types of outcome, data of a large number of participants may be needed to estimate a realistic event rate (Figure 1; Table 1). Thus, prospectively designed RCT or CCT may not be appropriate because they usually recruit a limited number of participants. In case of long follow-up and rare events, this might similarly be true for the outcomes death and disease, which might be studied in observational studies that include large numbers of participants including registry analyses (Figure 1; Table 1). Discomfort, disability, and dissatisfaction may be subjective outcomes and may be reported only by participants. These outcomes should be measured with the highest possible validity and should be studied in RCTs to prevent a potential high risk of confounding. Alternatively, they might be studied in case control studies nested within prospective cohort studies to retrieve data from a large population. In case of short follow-up and frequent events, disease should be evaluated in trials with a high internal validity including prospectively design randomised and non-randomised controlled trials (Figure 1; Table 1). Due to the frequent number of events, a realistic event rate can be achieved, though the number of participants may be limited. It might not be appropriate to randomly allocate participants to treatment groups if death occurs frequently primarily in one of the groups. Again, discomfort, disability, and dissatisfaction should be measured with the highest possible validity and should

be studied only in RCTs. In case of long follow-up and frequent events regarding all outcomes, there is no reason to include other study designs than RCTs or alternatively CCTs, if RCTs are not available (Figure 1; Table 1). The RCT is appropriate because of its highest possible validity and a number of events, which can be expected to be sufficient high to enable a realistic rate.

Study design labels

After deciding whether the follow-up is short or long and after deciding whether the event is rare or frequent, one or several appropriate study designs are recommended. We used the following study design labels: RCT, CCT, nested case-control study, cohort study, case-control study, case series, case report, and registry analysis. We provided a description and classification of these and other possible study design labels in Table S2. The prospective design may be considered on two separate levels. This first level concerns the prospective direction of studying the exposure and outcome relationship, which can be call prospective in any RCT, CCT or cohort study (and retrospective in a case control study). The second level of prospective design of any study predefines the timing of the data collection. If data were collected in the past or from the past, the study would be considered retrospective (e.g. a retrospective cohort study), if data are collected in the present or future, the study would be considered prospective. It is always important to be explicit which level is meant when talking about prospective or retrospective study features to avoid confusions. Some health interventions are difficult to randomize because they are implemented at a regional-level rather than at a facility- or patient-level. Therefore, it is important to consider multiple study designs including CCT or other nonrandomized study designs for these types of interventions [12].

Practical or ethical concerns

Practical or ethical concerns may emerge as reasons to override the earlier decisions or to switch to a more appropriate study design. Therefore, we remind the reader at the bottom of the Figure 2 to reconsider the chosen path. Some study designs may be more suited for answering specific research questions than others. However, availability of high-quality evidence can only be determined by searching for it. It does not seem like a sound strategy to apply an algorithm that excludes RCTs from consideration because of ex ante assumptions that relevant RCTs may not exist. Therefore, the practical and ethical concerns provide a flexible handling of the algorithm if required. We provide some examples that follow the outlined structure of the algorithm in Table S6.

Table S3. Short versus long follow up depending on the type of disease and intervention/exposure

Diagnosis and intervention	Follow up		Reference
	Short (early)	Long (late)	
Shortening the duration and reducing the severity of the common cold treated by vitamin C	< 3 days	≥ 1 week	[40]
Early versus late radiation morbidity	< 30 days	≥ 30 days	[41]
Cancer-specific survival after recurrence in patients with recurrent renal cell carcinoma	< 5 years	≥ 5 years	[42]
Early or late diagnosis on patient survival in gastric cancer	< 3 years	≥ 3 years	[43]
Early or late mortality after isolated first coronary bypass surgery in multivessel disease in patients with diabetes	< 30 days	≥ 30 days	[44]
Early or late major adverse cardiac events after percutaneous coronary intervention in cardiac patients	< 6 months	≥ 6 months	[45]

Table S4. Rare versus frequent events depending on the type of disease and intervention/exposure

Diagnosis and intervention	Event		Reference
	Rare	Frequent	
Dying from lung cancer: lifelong nonsmokers versus current smokers (≥ 25 cigarettes per day)	= 17 per 100,000 per year	= 415 per 100,000 per year	[46]
Prevalence of chronic obstructive pulmonary disease in 2118 lifelong never-smokers without versus with exposure to environmental tobacco smoke (ever at home and at both previous and current work)	= 4.2%	= 14.7%	[47]
Maternal mortality goal of the Healthy People objective in 2000	< 3.3 per 100,000 live births	≥ 3.3 per 100,000 live births	[48]
Relative risk of lung cancer in current smokers versus nonsmoker	not applicable	24.0	[46]
Relative risk of lung cancer in nonsmoker exposed versus not exposed to environmental tobacco smoke	not applicable	2.4	[49]

Table S5. Outcomes of disease

Outcome	Description	Type of outcome
Death	A bad outcome if untimely	Investigator reported
Disease	A set of symptoms, physical signs, and laboratory abnormalities	Investigator reported
Discomfort	Symptoms such as pain, nausea, dyspnea, itching, and tinnitus	Participant-reported disease-related symptoms
Disability	Impaired ability to go about usual activities at home, work, or recreation	Participant-reported disease-related impaired function
Dissatisfaction	Emotional reaction to disease and its care, such as sadness or anger	Participant-reported disease-related bother about impaired function and generic health-related quality of life

Table 1. Examples for outcomes depending on lengths of follow up and frequency of events

Outcome	Short follow up		Long follow up	
	Rare events	Frequent events	Rare events	Frequent events
Death	<p>Population: Hypertrophic cardiomyopathy</p> <p>Intervention: Physical activity</p> <p>Aim: Incidence of sudden death after recreational sports</p> <p>Practical: Ethical concerns against experimental allocation</p>	<p>Population: Malignancies</p> <p>Intervention: Unrelated and mismatched haematopoietic stem cell transplantation</p> <p>Aim: Incidence of death due to graft rejection</p> <p>Practical: Ethical concerns may arise to randomize patients</p>	<p>Population: Acquired severe aplastic anaemia</p> <p>Intervention: Long-term immunosuppressive therapy</p> <p>Aim: Incidence of secondary malignancies</p> <p>Practical: Ethical concerns against randomized allocation</p>	<p>Population: High-risk neuroblastoma</p> <p>Intervention: Retinoic acid as postconsolidation therapy after high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation</p> <p>Aim: Event-free survival in comparable groups</p> <p>Practical: Randomized allocation is required to provide comparable groups</p>
Disease	<p>Population: Neuroblastoma</p> <p>Intervention: Watchful waiting</p> <p>Aim: Incidence of spontaneous regression</p> <p>Practical: Ethical concerns against experimental allocation</p>	<p>Population: Malignancies</p> <p>Intervention: Unrelated and mismatched haematopoietic stem cell transplantation</p> <p>Aim: Incidence of acute graft versus host disease</p> <p>Practical: Randomized allocation is required to provide comparable groups</p>	<p>Population: Malignancies</p> <p>Intervention: Radiotherapy</p> <p>Aim: Incidence of myelodysplastic syndrome</p> <p>Practical: Ethical concerns against randomized allocation</p>	<p>Population: Diabetic foot ulcer</p> <p>Intervention: Negative pressure wound therapy</p> <p>Aim: Incidence of wound closure</p> <p>Practical: Randomized allocation is required to provide comparable groups</p>
Discomfort Disability Dissatisfaction	<p>Population: Acquired severe aplastic anaemia</p> <p>Intervention: Matched sibling donor haematopoietic stem cell transplantation</p> <p>Aim: Incidence of graft failure as an early and rather unexpected serious complication only observed in the transplant group not in the non-transplant group</p> <p>Practical: Ethical concerns against experimental allocation</p>	<p>Population: Low-risk localized prostate</p> <p>Intervention: Radical prostatectomy</p> <p>Aim: Incidence of erectile dysfunction and urinary incontinence</p> <p>Practical: Randomized allocation provides comparable groups</p>	<p>Population: Advanced prostate cancer</p> <p>Intervention: hormonal androgen deprivation therapy</p> <p>Aim: Incidence of emotional distortion</p> <p>Practical: Randomized allocation provides comparable groups</p>	<p>Population: Diabetic foot ulcer</p> <p>Intervention: Negative pressure wound therapy</p> <p>Aim: Incidence of amputation</p> <p>Practical: Randomized allocation is required to provide comparable groups</p>

Table S6. Examples for outcomes of respiratory tract diseases depending on lengths of follow up and frequency of events

Outcome	Short follow up		Long follow up	
	Rare events	Frequent events	Rare events	Frequent events
Death	Viral infection may aggravate to acute myocarditis and subsequent heart failure	Lack of nourishment and lack of medicines may cause general susceptibility to life-threatening disease	Infection may affect organs such as the heart. Fibrous replacement of organ tissue may result in late arrhythmia and subsequent cardiac arrest.	Lung cancer is the most common cause of cancer-related death in men and women
Disease	Bacterial infection may aggravate to community acquired pneumonia	Infection may develop to acute sinusitis that may worsen and prolong the condition	Streptococcal pharyngitis may be complicated by chronic rheumatic heart disease	Long-term exposure to tobacco smoke is the most often cause of lung cancer
Discomfort Disability Dissatisfaction	Common cold may confine to bed and cause sick leave	Acute sinusitis may cause drowsiness, headache, and sleepiness	Streptococcal pharyngitis may be complicated by rheumatic fever, which may have an involuntary movement disorder called Sydenham's chorea as a main symptom	In non-smokers, secondhand smoke may be the cause of about 20% of cases of chronic obstructive pulmonary disease, which is characterized by shortness of breath and cough.

Testing the usefulness of the algorithm

We have conducted four systematic reviews on various diseases, interventions, and outcomes. We wanted to reproduce the process of deciding what study design would best fit the respective conditions, treatments, and patient centered endpoints. We wanted to practice the pathways of the algorithm and to test whether it works for the selected systematic reviews. Thus, the algorithm has been tested on them. The information on the PICOTS-SD frame regarding each systematic review is shown in Table 2. We introduced the main topics of each systematic review and discussed whether the algorithm was helpful in choosing the best study designs. We reflected on potential advantages and disadvantages of various study designs in each example. Figure 3 is modified from Figure 2 to delineate the pathways of 6 examples described in detail in the results chapter without altering the basic structure of the algorithm.

Results

Statements on research design

We looked at a sample of 12 high profile not-for-profit publishers of systematic reviews and health technology assessments of health care interventions, detailed in Table 3. Of those, 10 have published guidance about their methodological procedure for preparing the systematic reviews [5-7,13-19]. A range of other books or guidance documents on systematic reviews exist [20-25]. We extracted the major statements of their methods guidance with respect to choosing the appropriate research design in Table S7. We did not identify an algorithm or a comprehensive guidance focussing on finding the appropriate research design in any of these methods guidance documents.

Algorithm to find the appropriate research design

We propose an algorithm, which is shown in Figure 2. The algorithm has four decision points. First, it should be decided whether the follow-up is regarded as short or long. Second, it should be decided whether the events of interest are regarded as rare or frequent. Third, the outcome of interest needs to be considered. Fourth, the appropriate study design will be assigned. In addition, it should be considered whether it is justified to stay with the chosen study designs or whether it is warranted to switch the study design depending on possible practical and/or ethical reasons. We provide various specific examples for all outcome categories and want to show in detail in what way these outcomes depend on the length of follow up and the frequency of events (Table 1).

Table 2. PICOTS-SD frames of the included systematic reviews

Examples	References	P	I	C	O	T	S	SD
Example 1: Nonrhabdomyosarcoma soft tissue sarcomas	[26-28]	Patients with high-risk nonrhabdomyosarcoma soft tissue sarcomas (NRSTS)	High-dose chemotherapy (HDCT) followed by autologous haematopoietic stem cell transplantation (autoHSCT)	Standard-dose chemotherapy (SDCT)	Overall survival (OS), treatment- related mortality (TRM)	5-year follow up (FU)	Units in university hospitals specialized in transplantation	Randomized controlled trials (RCT)
Example 2: Acquired severe aplastic anaemia	[29-31]	Patients with acquired severe aplastic anaemia (SAA)	Allogeneic haematopoietic stem cell transplantation (alloHSCT) from HLA- matched related donors	Immunosuppressive therapy (IST) using ciclosporin A (CSA) and anti-thymocyte globulin (ATG)	Overall survival (OS), treatment- related mortality (TRM)	5-year follow up (FU)	Units in university hospitals specialized in transplantation	Randomized controlled trials (RCT), comparative clinical studies
Example 3: Localized prostate cancer	[32]	Patients with localized prostate cancer	Permanent interstitial low-dose rate brachytherapy (LDR-BT)	Radical prostatectomy (RP), external beam radiotherapy (EBRT), or no primary therapy (NPT)	Overall survival (OS), function and bother as well as health-related quality of life	5-year follow up (FU)	Surgery and radiotherapy units in general hospitals	Randomized controlled trials (RCT)
Example 4: Negative pressure wound therapy	[34]	Patients with chronic wounds	Negative pressure wound therapy (NPWT)	conventional gauze dressing	Complete wound closure, severe adverse events such as bleeding	6-months follow up (FU)	General hospitals	Randomized controlled trials (RCT)

Figure 3. Algorithm with paths of 6 examples shown.

Table 3. Methods guidance by publishers of systematic reviews

ID [Reference]	Country	Name of Institution	Title of handbook
AHRQ 2009 [13]	USA	Agency for Healthcare Research and Quality	Methods (section of a completed report)
ASERNIP-S 2009 [14]	Australia	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical; Royal Australasian College of Surgeons	General Guidelines for Assessing, Approving & Introducing New Surgical Procedures into a Hospital or Health Service
CADTH 2003 [15]	Canada	Canadian Agency for Drugs and Technologies in Health	Guidelines for Authors of CADTH Health Technology Assessment Reports
CEBM 2014 [5]	UK	Centre for Evidence Based Medicine	Study designs
Cochrane 2011 [16]	UK, World	The Cochrane Collaboration	Cochrane Handbook for Systematic Reviews of Interventions; Version 5.1.0; [updated March 2011]
CRD 2011 [7]	UK	Centre for Reviews and Dissemination	Systematic Reviews. CRD's guidance for undertaking reviews in health care
HAS 2007 [17]	France	French National Authority for Health	General method for assessing health technologies
IQWiG 2013 [18]	Germany	Institute for Quality and Efficiency in Health Care	Methoden Version 4.0
MRC 2008 [19]	UK	Medical Research Council	Developing and evaluating complex interventions: new guidance
MSAC	Australia	Medical Services Advisory Committee	No handbook found
NICE 2013 [6]	UK	National Institute for Health and Clinical Excellence	Guide to the Methods of Technology Appraisal
OHTAC	Canada	Ontario Health Technology Advisory Committee	No handbook found

Abbreviation. ID: Identifier

Table S7. Major statements in manuals or articles about choosing study designs in systematic reviews

ID [Reference]	Major statements
Institutions	
AHRQ 2009 [13]	<p>Inclusion and exclusion criteria for studies to be used in the review are determined based on the specific questions to be addressed. Criteria may vary for each question in the review.</p> <p>Key Questions</p> <p>Does any single NPWT system or any component of a NPWT system have a substantial therapeutic distinction in terms of wound healing outcomes compared to any other NPWT system or any other similar component of a NPWT system for the treatment of acute or chronic wounds?</p> <p>Do patients being treated with one NPWT system have a substantial therapeutic distinction in terms of less pain, bleeding, infection, other complications, or mortality than other NPWT systems?</p> <p>What are the reported occurrences of pain, bleeding, infection, other complications, and mortality for NPWT systems?</p> <p>Inclusion Criteria: Study Design: For Key Question 1 and 2, study must have been a controlled study comparing one NPWT system or components of a system to another NPWT system or components. Randomization to a NPWT system group was not required. For Key Question 3, no control group was required, because the focus of the question was simply to identify adverse events rather than compare rates across systems or components. However, because of the potential for bias in case series studies, no analyses were performed using adverse event data from these studies.</p> <p>Interpretation of assessments should take into consideration the likely robustness of the evidence, as indicated by the type of study design</p> <p>If only a limited number of poor quality RCTs can be identified, other study designs can be considered. In some cases, even if RCTs are available, studies of other types should be reviewed by the authors, e.g. to identify long-term effectiveness and/or rare or long-term adverse effects.</p> <p>The type of study can generally be worked at by looking at three issues:</p> <p>What was the aim of the study, descriptive or analytic?</p> <p>If analytic, was the intervention randomly allocated? Yes: RCT; No: Observational study.</p> <p>If observational, when were the outcomes determined? After the exposure: prospective (typically cohort study); at the same time as the exposure: cross sectional study; before the exposure: retrospective (typically case-control study).</p>
ASERNIP-S [14]	
CADTH 2003 [15]	
CEBM 2014 [5]	

ID [Reference]	Major statements
Cochrane 2011 [16]	<p>Randomization is the only way to prevent systematic differences between baseline characteristics of participants in different intervention groups in terms of both known and unknown (or unmeasured) confounders.</p> <p>For some Cochrane reviews, the question of interest cannot be answered by randomized trials, and review authors may be justified in including non-randomized studies. Non-randomized studies (NRS) are defined here as any quantitative study estimating the effectiveness of an intervention (harm or benefit) that does not use randomization to allocate units to comparison groups.</p> <p>There are three main reasons for including NRS in a Cochrane review:</p> <ul style="list-style-type: none"> To examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available NRS To provide evidence of the effects (benefit or harm) of interventions that cannot be randomized, or which are extremely unlikely to be studied in randomized trials. To provide evidence of effects (benefit or harm) that cannot be adequately studied in randomized trials, such as long-term and rare outcomes <p>Key issues about the inclusion of non-randomized studies in a Cochrane review</p> <p>Susceptibility to selection bias (understood in this Handbook to mean differences in the baseline characteristics of individuals in different intervention groups. Confounding occurs when selection bias gives rise to imbalances between intervention and control groups (or case and control groups in case-control studies) on prognostic factors, i.e. the distributions of the factors differ between groups AND the factors are associated with outcome.</p> <p>Determining which of non-randomized study designs to include (Chapter 13.2.1.3 of the Cochrane handbook): The diversity of NRS designs raises two related questions. First, should all NRS designs of a particular effectiveness question be included in a review? Second, if review authors do not include all NRS designs, what criteria should be used to decide which study designs to include and which to exclude?</p>
CRD 2009 [7]	<p>Randomised controlled trials (RCTs) and controlled trials for the objective to assess the clinical effectiveness of treatments. If information from controlled trials is not available, cohort studies are eligible for inclusion provided that data from a comparison group are reported.</p> <p>In some cases a range of study designs may be needed to address different questions within the same review. For example, a review seeking to include information on adverse events will often include case-control and/or case-series whilst a review incorporating participants' experiences of an intervention is likely to include qualitative studies.</p> <p>In cases where it is unworkable or unethical to randomise participants (e.g. when evaluating the effects of smoking on health), researchers may instead have to use a quasi-experimental or an observational design.</p>
HAS 2007 [17]	<p>Literature search and analysis of scientific data. A level of scientific evidence (HAS grading scheme) is allocated to each study.</p> <ul style="list-style-type: none"> I- High powered randomised controlled trials, meta-analyses, decision analyses. II- Low powered randomised controlled trials, or non-randomised trials, cohort studies. III- Case-control studies. IV- Retrospective studies, case series, descriptive epidemiological studies, and controlled trials with bias.

ID [Reference]	Major statements
IQWiG 2013 [18]	Für die Nutzenbewertung von Interventionen ist an erster Stelle eine Kontrollgruppe zu fordern. Aus einem reinen Vorher-nachher-Vergleich in einem Design mit abhängigen Stichproben ohne Kontrollgruppe lässt sich in der Regel kein Beleg für einen Effekt einer Intervention ableiten. Gütekriterien, die die Aussagekraft kontrollierter Studien erhöhen, sind Randomisierung und Verblindung. Den ersten Informationsgewinn gibt es häufig aus Fallberichten oder Fallserien. Grundsätzlich sind prospektive Studien retrospektiven Designs vorzuziehen. Allerdings sind zum Beispiel Fall-Kontroll-Studien häufig die einzige praktikable Möglichkeit, Informationen über Zusammenhänge zwischen Expositionen und selteneren Erkrankungen zu gewinnen. Neuere Studiendesigns der modernen Epidemiologie enthalten Elemente sowohl von Fall-Kontroll-Studien als auch von Kohortenstudien und sind nicht mehr eindeutig als retrospektiv oder prospektiv zu klassifizieren. Zumindest im Rahmen von Therapiestudien wird der höchste Evidenzgrad RCTs und systematischen Übersichten von RCTs zugeordnet. Auf den nächsten Plätzen folgen nicht randomisierte Interventionsstudien, prospektive Beobachtungsstudien, retrospektive Beobachtungsstudien, nicht experimentelle Studien (Fallserien und Fallberichte) und – mit niedrigstem Evidenzgrad – Expertenmeinungen ohne wissenschaftliche Begründung.
MRC 2008 [19]	There are many study designs to choose from, and different designs suit different questions and different circumstances. ⁴⁵ Awareness of the whole range of experimental and non-experimental approaches should lead to more appropriate methodological choices. You should always consider randomization when assessing effectiveness. An experimental approach may not be feasible or randomization may be unnecessary and other designs preferable. Examples where non-randomised designs have been used successfully: to ban smoking in public places, for studying rare adverse events, to evaluate the impact on the incidence of sudden infant deaths using case-control methods.
MSAC	No handbook found
NICE 2013 [6]	RCTs directly comparing the technology under appraisal with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.
OHTAC	No handbook found
Authors	
Black 1996 [20]	The view is widely held that experimental methods (randomised controlled trials) are the "gold standard" for evaluation and that observational methods (cohort and case control studies) have little or no value. This ignores the limitations of randomized trials, which may prove unnecessary, inappropriate, impossible, or inadequate.
Deeks 2003 [21]	There must be hundreds of examples of interventions for which RCTs would be possible but have not yet been carried out, leaving the medical and policy community to rely on nonrandomised evidence. It is therefore essential to have an understanding of the biases that may influence non-randomised studies.

ID [Reference]	Major statements
Egger 2006 [22]	<p>Etiological hypothesis, however, cannot generally be tested in randomized experiments. Due to the limited size of such trials, less common adverse effects of drugs may only be detected in case-control studies, or in analyses of databases from postmarketing surveillance schemes. Also, because follow-up is generally limited, adverse effects occurring later will not be identified. Women, the elderly, and minority ethnic groups are often excluded from randomized trials. Similarly, the university hospital typically participating in clinical trials differ from the settings where most patients are treated. Finally, both patient and therapist preferences may preclude a randomized controlled experiment. Example: ingesting your own urine. Even if adjustments for confounding factors have been made in the analysis, residual confounding remains a potentially serious problem in observational research. It is well known that people from less favourable social circumstances are more likely to be non-responders in studies evaluating patient-reported outcomes. The thorough consideration of possible sources of heterogeneity between observational study results will provide more insights than the mechanistic calculation of an overall measure of effect, which may often be biased. That different recall of past exposures may introduce bias. Sensitivity analysis is important to test the stability of findings across different study designs, different approaches to exposure ascertainment and to selection of study participants.</p> <p>Randomized controlled trials to assess treatment. Observational studies to assess harm. Ideally, we would also look to randomized trials to address issues of harm. However, for many potentially harmful exposures, randomly allocating patients is neither practical nor ethical. For instance, one could not suggest to potential study participants that an investigator will decide by the flip of a coin whether or not they smoke during the next 20 years or whether they will be exposed to potentially harmful ionizing radiation. For exposures like smoking and radiation, the best one can do is identify studies in which personal choice, or happenstance, determines whether people are exposed or not exposed.</p> <p>Some reviewers consider certain study designs to be superior because they feel that the design has an inherent value in itself. For example, they may focus exclusively on randomized studies when conducting reviews. Such a view ignores the fact that addressing different types of questions may require the use of different study designs. Assessment of long-term or rare outcomes, particularly when examining the safety of interventions, would be more suited to an observational design, not an experimental study. RCTs may be unethical. There may be the case that no RCT has been published. Educational interventions are often studied using a range of designs. It is improbable that rare harmful outcomes are detected by RCTs.</p> <p>Sources of bias in different study designs should be accounted for. Systematic reviews of NRS may be helpful in three situations.</p>
Guyatt 2005 [23]	
Khan 2011 [24]	
Reeves 2005 [25]	

Abbreviation. ID: Identifier; further abbreviations see Table 3

Testing the usefulness of the algorithm

Example 1: Non-rhabdomyosarcoma soft tissue sarcomas

The PICOTS-SD frame and the respective references associated with the systematic review on autologous haematopoietic stem cell transplantation (autoHSCT) following high-dose chemotherapy (HDCT) versus standard-dose chemotherapy (SDCT) in patients with nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) are shown in Table 2. In the first version of this systematic review, we assumed a long follow-up and frequent events regarding death by disease or complication: **NRSTS** in Figure 3 [26]. Thus, an RCT would be the best choice for all outcomes. We evaluated patients with a rare disease of interest that are treated rarely with the intervention of interest. The disease is a malignant tumor and treatment of cancer may frequently be followed up to allow estimation of the 5-year overall survival. Many authors recommended the conducting of RCTs as a requirement for the decision whether HDCT followed by autoHSCT results in a better survival than standard-dose chemotherapy (SDCT). In the first version of the Cochrane review, we did not find any RCT and we did not find any comparative study [26]. We identified only single-arm studies including a few case series and a lot of individual case data. We decided to include any study design with primary patient data to provide an overview of the available evidence. We were able to estimate overall survival and to describe adverse events. We were unable to draw conclusions on the benefit of the intervention of interest. We conducted an update 2.5 years after the first version was published and identified a single RCT [27]. There was consensus among the reviewers that we should restrict the study design to RCTs only in a future update under the condition that at least two RCTs are available for evaluation. Although the algorithm would have guided us to initially use RCTs, we switched to include observational data in the first version because RCTs were lacking completely. This represents an example of the principle of 'best' available evidence that we described in the preceding section. We had to downgrade the 'levels of evidence' to find and include data matching the prespecified PICOTS-SD frame. Using different study types provided advantages such as the presentation of data from other sources on overall survival after realizing that RCTs were not available in the first version. The update showed that we could present data on adverse events beyond the scope of an RCT. We brought to public attention that RCTs were requested for a long time and by many authors and we published the message that a meaningful decision on the usefulness of the intervention of interest might be impeded until RCTs are available. We were astounded when we identified an RCT during the search for the update. Thus, the presentation of a lack of quality studies might have fostered the conduction of a long desired study. Otherwise, it was not possible to estimate the effect of the intervention of interest because single-arm studies do not provide data that allow comparison between two different interventions. We tried to estimate overall survival from pooled individual data, which created a considerable heterogeneity not to mention the very

high risk of bias. We pooled different subtypes, which may have diverse courses of disease. The pooled cases were treated in different hospitals and countries and the variation in treatment condition was presumably very large. We think that the absence of study data was the cause for the inability to draw conclusions but not the use of different study types. We conducted another systematic review addressing the similar PICOTS-SD items but concentrated on metastatic rhabdomyosarcoma, the single soft tissue sarcoma entity excluded by the NRSTS review [28]. Again, the algorithm would have guided us to initially use RCTs but we switched to include observational data because RCTs were again lacking completely.

Example 2: Acquired severe aplastic anaemia

The PICOTS-SD frame and the respective references associated with the systematic review on allogeneic haematopoietic stem cell transplantation (alloHSCT) from matched sibling donors (MSD) versus immunosuppressive therapy (IST) in patients with acquired severe aplastic anaemia (SAA) are shown in Table 2. In this systematic review, we assumed a long follow-up and frequent events regarding death by disease or complication: **SAA** in Figure 3 [29]. Thus, an RCT would be the best choice for all outcomes. We evaluated patients with a rare disease of interest that are treated frequently with the intervention of interest. The disease is acquired severe aplastic anaemia caused by an autodestructive action against bone marrow stem cells. Immunosuppressive therapy interferes with selfdestruction but some patients may be refractory and long-term treatment may result in secondary malignancies. Allogeneic stem cell transplants from HLA-matched sibling donors is potentially curative opposed to IST and may have a favorable survival compared to IST. We did not find any RCT. We subsequently included any comparative study. We tried to lower the risk of bias by restricting the inclusion criteria to studies that were prospective, that met the requirements of 'Mendelian randomization', and that were confined to HLA-matched sibling donors [30]. Three studies were left for the evaluation. Unfortunately, the extracted data were generated more than 10 years ago and hardly applicable to the current medical care status. Although the algorithm would have guided us to initially use RCTs, we switched to include prospective nonrandomized controlled trials that met the criteria for 'Mendelian randomization' because RCTs were lacking completely. A considerable proportion of patients with acquired severe aplastic anaemia do not respond to immunosuppressive therapy and they have neither an HLA-matched sibling donor nor an HLA-matched related donor. The only treatment alternative left is to offer transplantation from an unrelated donor, preferably with a matched HLA status. The inherent practical concern may limit expectations of a control treatment. In our systematic review, we identified, as expected, only single-arm studies [31]. Nevertheless, we were able to quantitatively pool the data and specify estimated survival and adverse effects. Using different study types provided advantages such as the presentation of data from a lot of other comparative studies on overall survival after realizing

that RCTs were not available in the first version. These studies presented a large number of factors that may have influenced the course of the disease, for example age of participants and year of transplantation. We analysed the data qualitatively. The variety of those factors and also the data on adverse events may have been beyond the scope of an RCT. It was possible to estimate the effect of the intervention of interest and put them in context to reports published by others. However, high risk of bias due to the nonrandomized study design limited validity and high level of heterogeneity limited applicability of the study results considerably.

Example 3: Localized prostate cancer

The PICOTS-SD frame and the respective references associated with the systematic review on permanent interstitial low-dose-rate brachytherapy (LDR-BT) versus radical prostatectomy (RP) versus external beam radiotherapy (EBRT) and no primary therapy (NPT) in patients with localised prostate cancer are shown in Table 2. In this systematic review, we assumed a long follow-up and rare events concerning death: **PCa: OS** in Figure 3 [32]. Localized prostate cancer as opposed to advanced prostate cancer is believed to be associated with a very good overall survival regardless of the intervention. According to the algorithm, a cohort study would be appropriate to estimate long-term overall survival. Concerning patient-reported outcomes such as discomfort, disability and dissatisfaction, we assume that we have short follow-up and frequent events: **PCa: HRQL** in Figure 3. According to the algorithm, an RCT would be the best choice. The different treatment options might result in non-relevant differences of overall survival, too small to be detected. However, they are believed to have considerably different impact on physical and psychological well-being. For example, radical prostatectomy may promise to completely remove the malignant tumor but may also disrupt erectile function in a considerable proportion of patients. Loss of function, increase of bother, and constrained quality of life may be perceived by many men shortly after the intervention. We found that physician-reported urogenital late toxicity grade 2 to 3 was more common in the LDR-BT group when compared to the EBRT group. With respect to patient-reported outcomes, better scores for sexual and urinary function as well as urinary incontinence were reported for LDR-BT compared to RP. Better scores for bowel function were reported for LDR-BT compared to EBRT. We think that the algorithm matches well with the study design requirements generated by the research question. Restricting the study design to RCTs only resulted in a systematic review reporting the results of only a single study because only one RCT was available [33]. The information about discomfort, disability and dissatisfaction reported in numerous studies, though, with limited validity, was consequently ignored. Using different study types provided the main advantage to address two different research questions inherent in the systematic review. Evaluating overall survival needed a different approach than evaluating patient-reported outcomes. The obvious reluctance of

patients and physicians alike to participate in RCTs corroborated the consideration of other study designs such as nonrandomized controlled clinical trials and/or cohort studies with a set of inclusion criteria prospectively designed to request a minimal level of quality to meet potential high risk of bias. The single included RCT provided valuable information but was limited to some issues and did not cover all relevant questions. The nonrandomised studies had a high risk of bias due to study design and various additional flaws such as the lack of reporting of a consecutive enrollment, a retrospective design, and no adequate confounder control.

Example 4: Negative pressure wound therapy

The PICOTS-SD frame and the respective references associated with the systematic review on negative pressure wound therapy (NPWT) versus standard wound dressing in patients with wounds are shown in Table 2. In this systematic review, we assumed a short follow-up and frequent events concerning complete wound closure: **NPWT: Closure** in Figure 3 and we assumed a long follow-up and rare events concerning the outcome of severe adverse events **NPWT: AE** in Figure 3 [34]. NPWT is believed to facilitate wound closure faster than other treatment options and enable closure of chronic wounds that have failed to heal after other treatments. According to the algorithm, an RCT or a CCT would have been appropriate to evaluate the successful treatment of the disease. Serious adverse events may be detected in study designs of lower hierarchy such as registry analyses or case reports. For instance, in the year 2009, the US Food and Drug Administration issued a report on six deaths and 77 other complications that were reported within a two-year period in connection with NPWT. All the deaths were caused by acute hemorrhages, and known contraindications for NPWT (e.g. a large blood vessel exposed) had clearly been overlooked. Many of the deaths occurred in outpatient care or care homes, which highlights the need to monitor therapy. In this regard, it should be noted that trials of NPWT were generally conducted in hospitals. Using different study types provided the main advantage to address different research questions inherent in the systematic review. Evaluating complete wound closure needed a different approach than evaluating adverse events. The consideration of registry analyses and case reports were very helpful to draw attention to possible dangerous and life-threatening events and to point the finger at home care where indeed a considerable number of deaths were reported. A decision whether the intervention of interest can close wounds better than other alternative treatments apparently relies on the presence of high quality data from RCTs.

Discussion

We did not identify an existing algorithm or comprehensive guidance focussing on finding the appropriate research design. Therefore, we developed an algorithm as a guidance, which aims to guide the reasonable inclusion of various study designs in systematic reviews of health care interventions. The proposed algorithm cannot be applied without considering disease-specific circumstances and aims of interventions, in other words, it is not intended to be an absolute guide that in all cases will lead to appropriate study designs. The terms used for defining the critical decision points of the algorithm such as short versus long follow-up need to be interpreted in the context of the disease and may be unclear and not useful if used as general terms. We provided examples to show that short versus long follow-up can vary considerably depending on the disease. Similarly, we provided examples to show that the definition of rare versus frequent events has to be interpreted in the context of the type of intervention or exposure as well as the type of event. For some research questions, the algorithm may recommend the use of studies with the highest possible validity. For alternative research questions, the algorithm may recommend the use of studies with qualities other than methodological validity. The recommended study design may not be reported in the identified studies and, thus, may not be available. In this case, a study design of the next lower level of validity may be used as a replacement.

We tested the constructed algorithm in four systematic reviews to evaluate whether our reasoning in theory concerning the algorithm may solidify in practice. Each work clearly explained why it was necessary to include multiple study designs. The number of our systematic reviews was limited. However, we could cover most of the pathways. We judged in a retrospective view, whether the pathways of the algorithm could have been useful at the time of designing the review. We could follow and confirm the appropriateness of the pathways for all described examples of systematic reviews. In one example, the algorithm selected RCTs as the best choice but due to the lack of RCTs it was decided to rely on nonrandomized studies. This example showed that it is important to build a flexibility into the algorithm, which enables the systematic reviewer to extend or change the inclusion criteria to other study designs in case that certain unexpected conditions may emerge or practical concerns exists. We are confident that the algorithm is a tool helping to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. It has the potential to help to reorientate oneself to major features of the studies eligible for an evaluation of a health care intervention. The benefit is the provision of awareness, and it is not a new regulation. The intention is to provide a guide and a decision support that might be used fully or partially by persons who are going to prepare a systematic review. While preparing a systematic review, it may be important at an early time point to identify the relevant and the most appropriate study designs necessary to find answers for a variety of prespecified outcomes. It might also be of interest for persons

who evaluate the quality of systematic reviews and might want to check whether the all study designs have been considered that should have been considered. Therefore, we think that it may reduce the time burden on review authors and contribute to the production of a higher quality review.

Although it appeared that the algorithm is proper for projection of various research questions on the delineated pathways, we want to draw the attention to some limitations of this study. Disease-specific circumstances and aims of interventions always have to be taken into account during application of the algorithm. It is not intended to be an absolute guide always leading to appropriate study designs but meant to support systematic reviewers in their decisions. The testing was conducted retrospectively with systematic reviews that were already completed. This approach may have the advantage that potential pitfalls and a complicated matter are already known. However, this situation is far from the everyday working condition and the approach may be considerably biased by the expectations of the authors, to name just one potential cause. A testing more adapt to the real world should be included prospectively and should start while a systematic review is planned. Testing the algorithm prospectively and applying it at the start of a systematic review may have other results than those reported in the present study. Nevertheless, the results of this testing certainly need to be confirmed by other systematic reviewers, in other PICOTS-SD frames, and in a higher number of applications.

Conclusions

We are confident that the algorithm can assist to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. It aims to provide awareness not regulation. We think that it may reduce the time burden on review authors and may contribute to the production of a higher quality review.

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CHAPTER 8

General discussion

Summary of main findings

A review of 42 articles about the use of multiple study designs in systematic reviews of health care interventions showed a tendency that nonrandomized studies should be conducted and integrated in systematic reviews to complement available RCTs or replace lacking RCTs in 85% (36 of 42) of these articles. Most papers acknowledged the advantages and the disadvantages of RCTs and nonrandomized studies with regard to specific methodologic topics or specific clinical outcomes. In general, it was acknowledged that only RCTs can achieve the lowest risk of bias. Many papers highlighted that results of RCTs may not be applicable to a considerable number of the actual target population. Alternative study designs may be needed to confirm that the intervention of interest does work under real everyday conditions. Some papers addressed the problem that RCTs are not possible for assessing certain questions and that case reports may have a considerable impact on safety issues.

In a Cochrane Review on 'Autologous hematopoietic stem cell transplantation following high dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas', several single-arm studies were included with aggregate data, and many single arm studies with individual data to complement the results of a single available RCT. A time-to-event analysis was conducted on overall survival to incorporate individual data from non-comparative single-arm studies. The required follow-up information was incomplete or missing in a considerable number of participants. Neither the individual data, which were used in a time-to-event analysis on overall survival, nor the aggregate data from single-arm studies could contribute to the decision-making whether the test intervention was associated with a longer overall survival than the control intervention. The number of participants in the RCT was low and the individual data contributed to address serious adverse events associated with the test intervention. Some treatments were performed 10 to 20 years ago. Thus, the results may not be applicable to patients who are treated today.

In a systematic review on 'First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia', nonrandomized controlled trials with a prospective design were included because RCTs on the topic were not identified. The available data enabled a pooled estimate of overall survival for the test and the control intervention. Potential duplicate publication bias was identified due to identical data that may have been reported in a hospital-based study and in a registry analysis. Considerable outcome reporting bias, which is defined as the selection of a subset of the originally recorded outcome variables for publication, was also identified. A high risk of bias was identified within almost all non-randomized controlled trials limiting any meaningful inferences.

In a systematic review on 'Permanent interstitial low-dose-rate brachytherapy for patients with localised prostate cancer: a systematic review of randomised and non-randomised controlled clinical trials', 30 comparative nonrandomized studies were

included in addition to a single RCT because data on health-related quality of life was limited in the RCT. Due to the stage of the condition of interest, health-related quality of life rather than overall survival was the preeminent outcome of interest. The comparative nonrandomized studies provided useful information for decision-making. Individual preferences by patients and physicians may have played a central role in the decision whether to treat or to pursue active surveillance.

In a systematic review on 'Negative-pressure wound therapy: systematic review of randomized controlled trials', only RCTs were included because a large number of RCTs were identified. RCTs provided sufficient data on the primary outcome 'complete wound closure'. However, data on treatment-related complications were limited due to a low number of participants. A postmarketing surveillance system was consulted to complement data on a considerable number of serious complications connected with the test intervention. These data changed the overall picture of the possible benefits and harms of the intervention of interest.

The inclusion of various study designs may be required if a systematic review aims to answer different research questions. A decision tree was constructed that may guide systematic reviewers to choose a single design or multiple study designs appropriate to answer these research questions. For some research questions, the algorithm may recommend the use of studies with the highest possible validity. For alternative research questions, the algorithm may recommend the use of studies with qualities other than methodological validity. The recommended study design may not be reported in the identified studies and, thus, may not be available. In this case, a study design of the next lower level of validity may be used as a replacement. The usefulness and functionality of the algorithm was evaluated by applying it to four systematic reviews. These systematic reviews were conducted to evaluate the prospects of using multiple study designs. The systematic reviews provided short and long follow-ups, rare and frequent events, and various outcomes, that all suited well for a projection on the various pathways offered by the algorithm. The theoretical algorithm proved to be useful in various practical situations and helped to choose the appropriate study designs for inclusion in each systematic review.

Strengths and limitations

The search for published information on the advantages and disadvantages of various study designs, the corresponding data extraction, and data synthesis were performed systematically. For example, the definition of the search strategies, the inclusion criteria and study selection, the data analyses and result interpretation were independently done by at least two authors. The PRISMA statement were endorsed, adhered to its principles and conformed to its checklist. As in any systematic review, the limitations in

drawing conclusions are directly dependent on the quality and homogeneity of the primary studies.

One strength of the thesis lies in the broad search strategy. The retrieved information was designated to provide an objective view on the possible merits of every individual study design to support decision-making in health care. However, different authors and readers may have varying preconceptions about the way, how the term 'objective' should be conceived. It was tried to provide a comprehensive view of the published knowledge concerning the topic of this thesis. The comprehensiveness of the process of data collection required to include not only systematic reviews and meta-analyses but also nonsystematic reviews, method studies and opinions. The qualitative data were summarised by extracting the major identified contents. Thus, in every step of acquisition and judgement of data, personal preferences may have influenced the results.

The documentation of the applied methods enables others to repeat the work. It is possible that another person might come to different results. While reading through hundreds of papers, I perceived a polarized dispute on randomized versus nonrandomized and on experimental versus observational study designs among some authors. Some put RCTs on a pedestal and claimed that results are only valid and trustworthy if derived from high quality RCTs regarding all possible research questions. Others demanded that only data from observational studies are able to answer some research questions especially in the context of proving that an intervention might work under real world conditions. Thus, the inferences made in many included papers may be influenced by the authors' preoccupations. While building the algorithm, I aligned the decision points and paths according to seminal published information. The algorithm follows strict binary decision points and it retains sufficient flexibility to consider certain conditions such as ethical or practical issues or to react if the best possible evidence is not available.

The proposed algorithm cannot be applied without considering disease-specific circumstances and aims of interventions. The information base included nonsystematic reviews, which some may dislike as invalid opinions. The terms used for defining the critical decision points of the algorithm such as short versus long follow-up need to be interpreted in the context of the disease and may be unclear and not useful if used as general terms. We provided examples to show that short versus longterm follow-up can vary considerably depending on the disease. Similarly, we provided examples to show that the definition of rare versus frequent events has to be interpreted in the context of the type of intervention or exposure as well as the type of event.

The prospects of using multiple study designs were evaluated in four systematic reviews. The various characteristics of follow-up, frequency of adverse events, and type of outcomes of the included systematic reviews qualified to test almost every pathway of the algorithm. Although it appeared that the algorithm is proper for projection of various research questions on the delineated pathways, we wanted to draw

the attention to some limitations of this study. Disease-specific circumstances and aims of interventions always have to be taken into account during application of the algorithm. It is not intended to be an absolute guide always leading to appropriate study designs. The testing was conducted retrospectively with systematic reviews that were already completed. This approach may have the advantage that potential pitfalls and a complicated matter are already known. However, this situation is far from the everyday working condition and the approach may be considerably biased by the expectations of the authors, to name just one potential cause. A testing more adapt to the real world should be included prospectively and should start while a systematic review is planned. Testing the algorithm prospectively and applying it at the start of a systematic review may have other results than those reported in the present study. Nevertheless, the results of this testing certainly need to be confirmed by other systematic reviewers, in other PICOTS-SD frames, and in a higher number of applications.

Agreements and disagreements with other studies or reviews

We have not identified another algorithm published by other authors. It appears that our algorithm may be the first comprehensive decision tree available. Thus, we cannot compare our guidance tool for systematic reviewers with a similar one. Nevertheless, there are numerous papers reporting about issues concerning including multiple study designs. We want to address some salient aspects of this topic reported by some renowned authors.

The view of RCTs as the sole means of finding reliable answers to clinical research questions was perpetuated only by a minority of the evaluated reviews [1]. For example, McCarthy 2008 recommended to perform more RCTs in surgery because they provide the most rigorous way of determining a cause-effect relationship between treatment and outcome [2]. Mitchell 1995 stated that rigorous and large RCTs are required for valid estimations of rare and serious adverse events [3]. Reeves 2005 referred to the drawbacks of nonrandomized designs and pointed out that they are associated with selection bias, performing bias, detection bias, and attrition bias [4]. It is conceivable that a high level of evidence associated with RCTs certainly prevents a number of major biases considering effects of interventions [5-6]. Therefore, RCTs should be used if feasible.

We found that the majority of trials and systematic reviews reported effects that did not differ considerably between randomized and nonrandomized controlled trials [7]. About one third of the trials showed a different direction or a statistically significant difference of the magnitude of effect between those two designs. The estimated treatment effect may underestimate or overestimate the real effect. For example, Hernan 2012 noticed that the intention-to-treat analyses may underestimate the treatment effect in placebo-controlled randomized clinical trials [8]. A Cochrane review

compared RCTs versus historically or concurrently controlled nonrandomized trials in 2007 [10]. The authors concluded that, on average, the nonrandomized controlled trials tend to result in larger estimates of effect than RCTs. The latest update of this Cochrane review in 2011 amended the research question and compared RCTs versus concurrently controlled nonrandomized trials and excluded historically controlled ones [11]. The authors concluded that the results of randomized and nonrandomized controlled trials sometimes differed, namely, in some instances nonrandomized studies yielded larger estimates of effect and in other instances vice versa. It appears that the early firm statement expressing larger estimates in the nonrandomized controlled trials changed to a less decided message. Systematic biases can arise from time trends of changing outcomes in historically controlled studies in contrast to concurrently controlled studies [12]. Thus, the change was probably caused by the exclusion of studies with a historically controlled group and thereby removing a source of additional risk of bias. A new Cochrane review is on the way to assess the impact of study design on the effect measures estimated in RCTs compared to various observational study designs such as prospective or retrospective cohorts [13]. However, nonrandomized controlled trials may presumably not be included. We want to emphasize the important difference between observational comparative studies (no assignment by study investigator to treatment groups) and nonrandomized controlled trials (experimental design with assignment).

We found that the majority, at least three quarters of relevant identified reviews, inferred that nonrandomized studies should be included in systematic reviews [1]. In a landmark paper, Black 1998 explained that RCTs can be unnecessary (e.g. dramatic effect such as instant healing by insulin), inappropriate (e.g. act of random allocation may reduce the effectiveness), impossible (e.g. some interventions cannot be allocated on a random basis), or inadequate (e.g. limited applicability) [14]. Lewsey 2000 provided an example that an RCT is not possible to study early versus late surgery for subarachnoid haemorrhage [15]. Hartling 2005 addressed the issue of applicability and noticed that RCTs tend to enroll younger and healthier patients [16] and Hodgson 2007 further added that older patients, women, and patients with comorbid disorders are underrepresented in RCTs [17]. Olivier 2006 stressed the importance of case reports and postmarket monitoring of adverse events and described that case reports lead to the withdrawal of 19 of 21 drugs for safety reasons in a specific time period in France [18]. Concato 2010 noticed that contradictions among RCTs themselves are well described [19]. Britton 1998 concluded that a well-designed nonrandomized study may be preferable to a small, poorly designed and exclusive RCT [20]. Studies of lower levels may be necessary when RCTs are not feasible. For example, a considerable number of eligible individuals may be excluded from an RCT that have characteristics different from those of the included ones [20]. Eligible patients excluded from an RCT are usually not observed further, which may cause important limitations to judgements about applicability [21].

We concluded that the risk of presenting uncertain results without knowing for sure the direction and magnitude of the effect holds true for both nonrandomized and randomized controlled trials. Vandembroucke 2009 elucidated that conflicting results between observational studies and RCTs with respect to hormone replacement therapy (HRT) finally fell in line mainly by adjusting different time intervals [22]. He concluded that the discrepancies between RCTs and observational studies cannot be automatically attributed to randomization itself but may be related to systematic differences in characteristics of participants. Conflict #1 concerns the question whether HRT increases coronary heart disease. HRT caused an initial increased risk, which waned in later years. RCTs truly identified an increased risk because the data were observed since the start of HRT. The time lag caused the difference in risk not the study design. Observational studies falsely showed a reduced risk for coronary heart disease because the users were observed beyond a time interval since start HRT and were in a phase of decreased incidence. Conflict #2 concerns the question whether HRT increases breast cancer. Observational studies truly identified an increased risk after combined oestrogen-progestin. RCTs falsely did not identify this risk because the users were observed beyond a longer time interval after menopause than in the observational studies. The varying time interval between menopause and start of HRT caused the difference in risk not the study design. Hoppe 2009 acknowledged that RCTs are the most objective design but admitted that RCTs may not provide all of the information a clinician might need [23]. We concluded that the integration of multiple study designs in systematic reviews is required if patients should be informed on the many facets of patient relevant issues of health care interventions such as survival, cure of disease, improvement of symptoms, treatment-related complications, other adverse events, health-related quality of life. In a recent methods paper written under contract of the Agency for Healthcare Research and Quality, Seida 2013 found a considerable diversity across the comparative effectiveness reviews with respect to methods used to search for, select, appraise, and analyze observational studies [24]. The authors inferred that it was not always clear whether the inclusion of observational studies added value. As mentioned in the introduction chapter of the present thesis, Ijaz 2014 concluded that reporting of nonrandomized studies in Cochrane reviews requires an improved guidance [25].

Best available evidence

Evidence-based medicine (EBM) was defined as the integration of best research evidence with individual clinical expertise, patient values and expectations, and best external research evidence [26]. This definition of EBM may be appropriately illustrated by the Venn diagram in Figure 1 [27].

Figure 1. Definition of Evidence-Based Medicine [27].

Sackett 1996 judged: "Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients." [28]. The term 'best external evidence' may be described as a rigorous analysis of published study data primarily from RCT and quantitative (meta-analysis) and/or qualitative summary of these data within a systematic review. The term 'evidence' means information and the term 'best evidence' means the most valid and reliable information [29]. To classify more valid and less valid information, the 'levels of evidence' specify a hierarchical order for various research designs based on their internal validity. The highest level of valid data, that is, the 'best' evidence, however, is not always available. For instance, if RCTs are lacking and only case reports are available, then, case reports may constitute the best available evidence.

EBM proponents who might be inclined to narrow the view down to statistics may always demand RCTs. A spoof systematic review evaluated whether the imposition of a parachute versus no parachute results in a better survival when jumping out of a plane [30]. The article's effect was probably to contest idealization of RCTs. It is very important to keep the other circles of EBM always in mind. Many aspects of health care depend on individual circumstances and preferences and it may not be possible to evaluate those important issues. The term *evidence-based* medicine may imply that health care decisions are based solely on the best external evidence circle and not on the individual clinical expertise circle and not on the patient value and expectations circle. Therefore, the term *evidence informed* healthcare may be more appropriate [31]. Sackett 1996 warned: "Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate

for an individual patient." [28]. Berguer 2004 criticized that the name 'evidence-based medicine' is self-righteous in that it singles out one approach to the analysis of clinical data as the one embodying scientific truth [32]. He further pointed out that results from RCT are average numbers referable to an average individual. However, the 'average' risk may be meaningless when you are the patient. Feinstein and Horwitz 1997 [33] apprehended: "The laudable goal of making clinical decisions based on evidence can be impaired by the restricted quality and scope of what is collected as 'best available evidence'. The authoritative aura given to the collection, however, may lead to major abuses that produce inappropriate guidelines or doctrinaire dogmas for clinical practice." There may be perceivable hints that dogma and ideology prevail at least in some areas. It is certainly not a scientific characteristic to oppress other opinions including those by experts in various fields. Spence 2014 [34] criticized: "Today EBM is a loaded gun at clinicians' heads and that you better do as the evidence says, leaving no room for discretion or judgment. The current incarnation of EBM is corrupted, let down by academics and regulators alike." The letters by Hicks 2012 [35] and Hicks 2013 [36] may serve as an example for a heated dispute including the accusation that the authors of an EBM article did not take the clinical and the patient part sufficiently into account. They noted that the work "lacks appropriate clinical perspective", that the authors have "apparent misunderstanding of the values and principles of EBM", that the authors "have presented an analysis that is so lacking in scientific rigor that it can be fairly judged to have provided a prejudiced appraisal of the evidence pertaining to the patient benefits", and that the authors "potentially misguide policymakers and individuals about appropriate use of this technology. In our view, this is a disservice to our patients that must be strenuously resisted and hence the tone of our prior letter."

In summary, the term 'evidence-informed healthcare' mounts on three different equally important foundations. These three cornerstones comprise the patients and their values and expectations, the clinicians and their expertise and experience, and the epidemiologists and statisticians and their interpretation of study data. Subsequently, the term 'best available evidence' should not be confined to medical biometrical views but should include all three aspects.

Conclusions

The use of multiple study designs in systematic reviews clearly showed that various study designs increased the information that should be considered in decision-making. The impact of the extra information may not be foreseen very well. The extra information may complement the best available evidence adding new important data and may open the horizon to bring attention to issues that may be overlooked but are nevertheless pertinent to health care. Sometimes information from multiple study designs can induce prudence in those who decide about an acclaimed new interven-

tion. RCTs may not be the typical study design to provide sufficient evidence for market withdrawals.

Recommendations for decision makers

We recommend decision makers to avoid building their decisions only on data emerging from a single study design. Methods groups are on their way to improve the bias control and the reporting standards of nonrandomized controlled clinical trials. Other groups bring out suggestions to better search for and find studies on adverse events. Some Cochrane Groups demand two primary outcomes, one associated with the most wanted treatment effect and one associated with a serious unwanted effect. Patient-reported outcomes are important in evaluations that apply patient-centered outcomes and invite consumers to participate in conducting systematic reviews. We recommend considering multiple study designs to enable Cochrane Reviews and other systematic reviews accomplishing these goals more effectively. The algorithm is foreseen to function as a tool helping to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. It helps to reorientate oneself to major features of the studies eligible for an evaluation of a health care intervention. The benefit is the provision of awareness not a new regulation. The intention is to provide a guide that might be used fully or partially by persons who are going to prepare a systematic review. While conducting a systematic review, it may be important at an early time point to identify the relevant and the most appropriate study designs necessary to find answers for a variety of prespecified outcomes. It might also be of interest for persons who evaluate the quality of systematic reviews and might want to check whether the all study designs have been considered that should have been. The algorithm should be embedded in an article, which provides introduction and explanation of its target population, aims purposes, and its optimal use. The article should be published in an open access journal, a scholarly journal that is available online worldwide to all potential readers who can use the internet. The article will have a particular internet site, which contains tools for instant feedback to the authors, general comments, recommendations passed on to others, and links to social networks such as twitter.

Recommendations for further research

First, we recommend continuing the refinement of requirements for nonrandomized controlled clinical trials. Second, we recommend evaluating whether all Cochrane Reviews should include multiple study designs to cover the various main objectives. Third, we recommend elaborating whether the implementation of an algorithm can support the quality and scope of a systematic review. The algorithm should be applied prospectively and used as a tool for the process of choosing appropriate study designs

for inclusion in a systematic review of health-care interventions. We imagine a trial with random allocation of using versus not using the algorithm. The satisfaction of convenience of the users might be evaluated by a questionnaire and may be used as the effect measure. At least, the algorithm should be tried by more than just one person to allow any conclusions on its usefulness. Experience with the algorithm should be collected with 10 or more author groups. The systematic reviews conducted with the use of the algorithm should have other types of population, intervention, comparator, and outcome than those contained in the systematic reviews of this thesis.

Recommendations for instructing the algorithm

There might be an educational challenge of instructing end users of the algorithm. Persons who are planning to conduct a systematic review and use the algorithm should make themselves acquainted with the scope of possible study designs, their purposes, advantages, and drawbacks. Many pathways might lead to choose only RCTs for the evaluation of the efficacy of a health care intervention. Nevertheless, other study designs should be kept in mind and considered for additional inclusion depending on the particular disease and intervention of interest. We recommend a flexible and pragmatic approach without the obligation to rigidly exclude study designs. In the case that, for example, the RCT should be chosen, we have already implemented a strategy of considering ethical and practical issues. These issues should not be overlooked and might be reasons to replace RCT with another study design. If available publications do not report the study design of interest, then the hierarchical structure of study designs should be considered and the next lower level of evidence might be considered. The algorithm will be published preferably in an open access journal. Beginners might find it helpful to find a framework that offers already some potential study designs and objective reasons to favor specific study designs for inclusion. The algorithm is supposed to assist a group of experienced scientists while gaining a consensus about choosing study designs for inclusion in systematic reviews. It is not intended to replace the dialog among those experts. Knowledge and application of general rules and experience in methodological issues relevant for the conduct of systematic reviews described comprehensively in particular in the Cochrane Handbook for Systematic Reviews of Interventions is mandatory.

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Summary

Background and rationale

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. The most distinctive characteristics that are present in a systematic review and that are not present in a nonsystematic review may be a study protocol, an analysis plan, a literature search strategy, and a description of the selection of suitable studies in accordance with prospectively defined inclusion and exclusion criteria. The starting point and fundamental component of a systematic review of health care interventions is a structured clinical question.

A systematic review may evaluate benefit and harm of a health care intervention and may include a specific set of studies. Explanatory study designs address the question whether the intervention of interest can work in principle in the ideal study setting and typically provide a conclusion for an average patient only. The intervention and the control group may differ only with respect to the intervention of interest. Known and unknown characteristics are equally distributed among the two treatment groups. The resulting structural equality facilitates a decision whether an observed effect was actually caused by the intervention. Randomization may be the best approach to provide this structural equality and may provide a low risk of bias. However, in some situations, randomization is not feasible, not appropriate, or the results may not be applicable to everyday practice. Pragmatic study designs aim to show that interventions will work under every day circumstances but may have a high risk of bias. To accommodate the evaluation of various research questions, the inclusion of more than one study design appears to be necessary.

Research questions and answers

The aim of this thesis is to investigate the advantages and disadvantages of using various study designs to answer specific clinical research questions within systematic reviews and to develop and pilot test an algorithm to guide systematic reviewers in their

decision to choose appropriate study designs. The following research questions are discussed in the present thesis:

What is known in the published literature about the pros and cons of integration of multiple study types in systematic reviews?

A review of 42 articles about the use of multiple study designs in systematic reviews of health care interventions showed a tendency that nonrandomized studies should be conducted and integrated in systematic reviews to complement available randomized controlled trials or replace lacking trials in 85% (36 of 42) of these articles. It was acknowledged that only randomized controlled trials can achieve the lowest risk of bias. Many papers highlighted that results of randomized trials may not be applicable to a considerable number of the actual target population. The risk of presenting uncertain results without knowing for sure the direction and magnitude of the effect holds true for both nonrandomized and randomized controlled trials.

What can be learnt from conducting systematic reviews about topics that may require the inclusion of multiple study designs, assuming that more than one study design may be essential to gather sufficient data for answering the objectives of the review.

If no comparative study is available, then the data of single-arm studies might provide, for example, an estimation of overall survival. Data on adverse events can be presented beyond the scope of a randomized controlled trial. Discussing the limitations of the results may bring the public attention to a lack of certain data, which might foster the conduction of a long desired trial. In another example, the test but not the control intervention may cure patients, however, the test intervention might be associated with a higher early treatment-related mortality than the control intervention. This situation might create a conflict. Ethical concerns may prevent trials with a random allocation of patients to the treatment groups. The principles of 'Mendelian randomization' could be applied for evaluating transplantation by restricting transplant donors to siblings. Another example shows that patients with a localized as opposed to an advanced cancer might have a very good overall survival regardless of the type of intervention. Though, the health-related quality of life as measured by patient-reported outcomes may vary considerably among the treatment options, which is caused by the varying degrees of their invasiveness. Reluctance of patients and physicians alike to participate in randomization corroborates the consideration of alternative approaches. A report on deaths was issued in connection with a particular medical device. It showed that the consideration of registry analyses and case reports can be very helpful to draw attention to possible dangerous and life-threatening events. It was also helpful to point at the home setting where a considerable number of deaths happened.

What is the preferred content and format of a straightforward algorithm for integration of various study designs in a systematic review that incorporates major study characteristics as decision points and that allows consideration of practical concerns?

A decision tree was constructed using length of follow-up, frequency of events, and type of outcomes as main decision points. It was ensured that the preset pathways retain sufficient flexibility to consider ethical and practical issues as well as unavailable best evidence. The outcomes may be evaluated after a short or long follow-up. The events of interest may be rare or frequent. The outcomes can be classified into the five major groups of death, disease, discomfort, disability, and dissatisfaction. Then, appropriate study designs are recommended with respect to the type of outcome. Practical or ethical concerns or lack of recommended study designs may emerge as reasons to override the earlier decisions or to switch to a more appropriate study design. Therefore, the reader is reminded to reconsider the chosen path.

Can the algorithm hold its promise as a useful guide for choosing appropriate study designs by testing its feasibility and applying it to existing systematic reviews?

The appropriateness of the pathways of the decision tree was confirmed during the application of the algorithm on four selected systematic reviews. These systematic reviews were conducted to evaluate the prospects of using multiple study designs and were well suited for a projection on the various pathways offered by the algorithm. The theory-based algorithm proved to be useful in various practical situations and helped to choose the appropriate study designs for inclusion in each tested systematic review.

Strengths and limitations

One strength of the thesis lies in the broad search strategy. The retrieved information was designated to provide an objective view on the possible merits of every individual study design to support decision-making in health care. Nevertheless, personal preferences may have influenced the results in every step of acquisition and judgement of data. While reading through hundreds of papers, I perceived a polarized dispute on randomized versus nonrandomized and on experimental versus observational study designs among some authors. Thus, the inferences made in many included papers may be influenced by the authors' preoccupations.

The testing of the algorithm was conducted retrospectively by backtracing systematic reviews that were already completed. This approach is far from the everyday working condition. It may be considerably biased by my expectations that the algorithm should have been worked if applied prospectively. Thus, the results of this testing need to be confirmed by other systematic reviewers who plan to use the algorithm

from the start. The algorithm is not intended to be an absolute guide always leading to appropriate study designs. Disease-specific circumstances and aims of interventions always have to be taken into account during application of the algorithm.

Recommendations

The algorithm is foreseen to function as a guide helping to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. It is recommended to confirm this assumption by its prospective application, possibly within a trial. It is also recommended to test its usefulness with respect to other types of population, intervention, comparator, and outcome than those contained in the systematic reviews of this thesis. The algorithm may help to reorientate oneself to major features of the studies eligible for an evaluation of a health care intervention. There might be an educational challenge of instructing end users of the algorithm. Persons who are planning to conduct a systematic review and use the algorithm should make themselves acquainted with the scope of possible study designs, their purposes, advantages, and drawbacks. Persons without extensive practice in conducting systematic reviews might be asked to share their opinion concerning its usefulness for beginners. In general, a flexible and pragmatic approach without the obligation to rigidly exclude study designs is recommended.

Valorisation

The work of the thesis gained extensive insight into the using of evidence of multiple study designs in systematic reviews. A review of a comprehensive literature showed a tendency that nonrandomized studies should be conducted and integrated in systematic reviews to complement available randomized controlled trials or replace lacking those trials. The risk of presenting uncertain results without knowing for sure the direction and magnitude of the effect holds true for both nonrandomized and randomized controlled trials. The consideration of registry analyses and case reports can be very helpful to draw attention to possible dangerous and life-threatening events beyond the scope of a randomized controlled trial. Ethical concerns may prevent trials with a random allocation of patients to treatment groups. Health-related quality of life may vary considerably if the treatment options are characterized by varying degrees of invasiveness. In this case, reluctance of patients and physicians alike to participate in randomization corroborates the consideration of alternative approaches. The work showed the importance of using multiple study designs in systematic reviews and provided many examples. A decision tree was constructed to facilitate the choosing of study designs for particular research questions, as shown below. Length of follow-up, frequency of events, and type of outcomes were the main decision points. It was ensured that the preset pathways retain sufficient flexibility to consider ethical and practical issues as well as unavailable best evidence. The appropriateness of the pathways of the decision tree was confirmed by backtracing four systematic reviews. The theory-based algorithm proved to be useful in various practical situations and helped to choose the appropriate study designs for inclusion in each tested systematic review.

Relevance

The use of multiple study designs in systematic reviews clearly showed that various study designs increased the information that should be considered in decision-making. The impact of the extra information may not be foreseen very well. The extra information may complement the best available evidence based on randomized controlled trials by adding new important data and by opening the horizon to bring attention to issues that may be overlooked but are nevertheless pertinent to health care. Sometimes information from multiple study designs can induce prudence in those who decide about an acclaimed new intervention. For example, randomized controlled trials may not be the typical study design to provide sufficient evidence for market withdrawals.

Target groups

The algorithm is foreseen to function as a tool helping to bring seminal features of a systematic review to the attention of anyone who is planning to conduct a systematic review. This includes persons working in organizations or institutes that prepare health technology assessment reports, evidence reports, or systematic reviews on health care interventions. It helps to reorientate oneself to major features of the studies eligible for an evaluation of a health care intervention. This is not meant to add a new regulation, but the benefit is the provision of awareness of the value of different study designs in systematic reviews. The intention is to provide a guide that might be used fully or partially by persons who are going to prepare a systematic review. While conducting a systematic review, it may be important at an early time point to identify the relevant and the most appropriate study designs necessary to find answers for a variety of pre-specified outcomes. It might also be of interest for persons who evaluate the quality of systematic reviews and might want to check whether all study relevant designs have indeed been considered. This may include individual physicians who intend to make evidence-based decisions on the treatment of their patients, although it will not be easy for busy clinicians to do so. It should also include persons with positions on a more collective level of evidence synthesis, such as scientists of academic institutions and members of guideline committees who critically assess the published evidence on various health care interventions, and staff of governmental administrations that make political decisions on the reimbursement of public health care services.

Activities/Products

Five of the six results chapters have been published in article format. The results of one remaining chapter are submitted to a journal and the manuscript will hopefully be accepted for publication in the near future. The publication will provide introduction and explanation of its target population, aims purposes, and its optimal use. The article is planned to be published in an open access journal, a scholarly journal that is available online worldwide to all potential readers who can use the internet. In general, an article published in this way will have a particular internet site, which contains tools for instant feedback to the authors, general comments, recommendations passed on to others, and links to social networks such as Twitter. The algorithm is embedded in a manuscript and, as mentioned earlier, is submitted to an open access journal. It is also planned to submit the work to the Cochrane Colloquium, a meeting of persons who are international experts in the field of conducting and assessing systematic reviews.

Innovation

I looked at the methods guidance documents of high profile not-for-profit publishers of systematic reviews and health technology assessments of health care interventions. I did not find an existing algorithm providing guidance for systematic reviewers to choose the most appropriate study designs. It appears that the algorithm may be the first comprehensive decision tree available. Subsequently, I developed a decision support tree using length of follow-up, frequency of events, and type of outcomes as main decision points. It was ensured that the preset pathways retain sufficient flexibility to consider ethical and practical issues as well as unavailable best evidence. The constructed algorithm was tested in four systematic reviews to evaluate whether our reasoning based on theory is applicable in practice. Although it appeared that the algorithm is proper for projection of various research questions on the delineated pathways, disease-specific circumstances and aims of interventions have always to be taken into account during application of the algorithm.

Schedule & Implementation

The algorithm should be tried by more than just one person to allow any conclusions on its usefulness. The systematic reviews conducted with the use of the algorithm should have other types of population, intervention, comparator, and outcome than those contained in the systematic reviews of this thesis. First, it is recommended to continue the refinement of requirements for nonrandomized controlled clinical trials. Second, it is recommended to evaluate whether all Cochrane Reviews should include

multiple study designs to cover the various main objectives. Third, it is recommended to elaborate whether the implementation of an algorithm can support the quality and scope of a systematic review. Persons who are willing to use the algorithm should be provided with an instruction manual that includes further interpretations and explanations. Training needs should be predicted and addressed. Educational seminars should be offered to elucidate the various pathways of the algorithm and the process of choosing the most appropriate study designs required to answer the important research questions of a systematic review.

Curriculum vitae

Frank Peinemann was born on 27 December 1959 in Northeim, Germany. In 1987, he graduated from Medical School and in 1989 he was promoted Dr. med. for his dissertation in the field of molecular genetics at the University of Gottingen, Germany (uni-goettingen.de). He is recipient of two grants from the DFG German Research Foundation (dfg.de), a 2-year fellowship grant to conduct molecular genetic research at Emory University, Atlanta, USA (emory.edu), and a financial support for laboratory equipment in Gottingen (humangenetik.gwdg.de). During his stay in the USA, he passed the exams of the ECFMG Educational Commission of Foreign Medical Graduates, Philadelphia, Pennsylvania, USA (ecfm.org).

After various employments in medical care of infants, children, and adolescents ([uniklinik-duesseldorf](http://uniklinik-duesseldorf.de); klinikumfrankfurt.de; herzzentrum.uk-koeln.de/de/kinderkardiologie), and after continuing medical education, the medical board authorities awarded him certificates in pediatrics, medical genetics, pediatric cardiology, neonatology, medical informatics, and medical quality management. During his employment with the BQS German National Institute for Quality Measurement in Health Care, Dusseldorf, Germany (bqs-institut.de), he participated in the development of quality indicators in various fields to conduct external quality assurance and benchmarking of German hospitals. Then he started his current employment with the IQWiG Institute for Quality and Efficiency in Health Care, Koln, Germany (iqwig.de). His main job is to conduct systematic reviews on interventions in health care in various fields, which are commissioned by the G-BA Federal Joint Committee, Berlin, Germany (g-ba.de).

He was promoted Master of Science in Epidemiology after completing his studies and master thesis at the universities in Mainz and Essen, Germany (unimedizin-mainz.de/imbei; imibe.de). He is lecturer in Pediatrics at the Children's Hospital of the University of Cologne, Germany (kinderklinik.uk-koeln.de). He is also lecturer in Public Health on a freelance basis at FOM University of Applied Science for Economics & Management, Essen, Germany (fom.de). He works with several Cochrane Review Groups to conduct Cochrane systematic reviews on interventions in health care. He publishes articles in international peer-reviewed journals (pubmed.gov), presentations at international meetings, and provides peer reviews for prestigious scholarly journals (publons.com).

Publications

Chapters 2 to 6 are based on the following published articles

Peinemann F, Tushabe DA, Kleijnen J. Using multiple types of studies in systematic reviews of health care interventions - a systematic review. PLoS One. 2013;8(12):e85035.

Peinemann F, Smith LA, Bartel C. Autologous hematopoietic stem cell transplantation following high dose chemotherapy for non-rhabdomyosarcoma soft tissue sarcomas. Cochrane Database of Systematic Reviews. 2013;8:CD008216.

Peinemann F, Grouven U, Kroger N, Bartel C, Pittler MH, Lange S. First-line matched related donor hematopoietic stem cell transplantation compared to immunosuppressive therapy in acquired severe aplastic anemia. PLoS One. 2011;6(4):e18572.

Peinemann F, Grouven U, Bartel C, Sauerland S, Borchers H, Pinkawa M, Heidenreich A, Lange S. Permanent interstitial low-dose-rate brachytherapy for patients with localised prostate cancer: a systematic review of randomised and nonrandomised controlled clinical trials. European Urology. 2011;60(5):881-93.

Peinemann F, Sauerland S. Negative-pressure wound therapy: systematic review of randomized controlled trials. Deutsches Arzteblatt International. 2011;108(22):381-9.

Chapter 7 is based on the following submitted manuscript

Peinemann F, Kleijnen J. Development of an algorithm to provide awareness in choosing study designs for inclusion in systematic reviews of health care interventions – a method study.