Childhood cancer survivors: cardiac disease & social outcomes
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Clinical heart failure in children, adolescents and young adults treated with anthracyclines and/or irradiation involving the heart region

Protocol information

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Background

In children leukaemia is the most common malignancy, followed by central nervous system (CNS) tumours, sarcomas and lymphoma. Around 60% of children with cancer receive anthracyclines (doxorubicin, daunorubicin, epirubicin and/or idarubicin) as part of the treatment. Roughly 20% of the children will get irradiation involving the heart region (i.e., total body irradiation, left or whole abdominal irradiation, spinal irradiation and thoracic irradiation). Anthracyclines and irradiation are effective treatment modalities, however both modalities have been associated with deterioration of cardiac function. Anthracycline- and irradiation-associated heart failure (HF) can show as either diastolic or systolic dysfunction that may progress to either dilated or constricted cardiomyopathy. Cardiac dysfunction can be asymptomatic or symptomatic. It can occur not only during therapy, but also years after its completion. Clinical anthracycline- and irradiation-associated HF is a well-known problem in children: the incidence of clinical heart failure has been reported to be as high as 16% 0.9 to 4.8 years after treatment (anthracycline-associated) and between 0.3-22.8% ≤26.5 years after treatment (irradiation-associated). This review will focus on clinical heart failure (CHF). Although the mechanism of anthracycline-associated CHF is not fully understood, it is clear that free radicals play an important role in damaging cardiac myocyte membranes. The cause of irradiation-associated HF are micro vascular changes, which result in fibrosis mainly in the interstitial part of the myocardium. This may cause reduced contractility and thus a combination of diastolic and systolic dysfunction. Irradiation involving the heart region also affects other parts of the heart, including the pericardium, valves, coronaries and conduction system. Risk factors for developing anthracycline-associated and irradiation-associated CHF are contradictory in the literature. Many studies on cardioprotective strategies have been performed, like infusion duration, different anthracycline derivates and cardioprotective agents like dexrazoxane. However CHF remains a problem.

Why it is important to do this review

It is important to gain more insight in the incidence and associated risk factors of anthracycline- and irradiation-associated CHF. Due to the increase in survival of patients treated for childhood, adolescent and young
adult cancer, more people are at risk of developing this serious cardiac adverse event. And at the moment no adequate treatment is available for anthracycline-associated HF.\(^{17}\) Also treatment for radiation-associated CHF is limited.\(^{18}\) The occurrence of anthracycline and irradiation-associated CHF has immediate effect on the quality of life of children, adolescents and young adults treated with anthracyclines and/or irradiation involving the heart region and on medical costs in general. Furthermore when developing new treatment and screening protocols physicians should take CHF into account.

**Objectives**

To evaluate the existing evidence on the association between childhood, adolescent and young adult cancer treatment with anthracyclines and/or irradiation involving the heart region and the occurrence of both early and late CHF.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

All study designs, except case reports, case series (i.e. a description of non-consecutive patients) and studies including less than 100 patients, treated with potentially cardiotoxic therapy, examining the association between childhood, adolescent and young adult cancer treatment including anthracyclines and/or irradiation involving the heart region and the occurrence of CHF (or death due to CHF or heart transplant after CHF). We defined cohort studies as studies in which a group of consecutive patients was followed from a similar well defined point in the course of the disease. The described study group could be the original cohort or a subgroup of the original cohort based on well-defined inclusion criteria.

**Types of participants**

Children, adolescents and young adults treated with anthracyclines (doxorubicin, daunorubicin, epirubicin and/or idarubicin) and/or irradiation involving the heart region and who were between 0 and 25 years of age at the time of cancer diagnosis. Studies that both included child and adults are only eligible for inclusion of this review if the majority of the participants were children, adolescents or young adults until the age of 25.
at cancer diagnosis (i.e. either more than 90% between 0-25 year or the maximal age should not be over 30 years) or if the study presented results for children, adolescents and/or young adult cancer patients separately.

Types of interventions
Treatment with anthracyclines (doxorubicin, daunorubicin, epirubicin and/or idarubicin) and/or irradiation involving the heart region, which was given as treatment for a primary childhood, adolescent or young adult cancer. Studies also including patients who did not receive anthracyclines and/or irradiation involving the heart (i.e., total body irradiation, left or whole abdominal irradiation, spinal irradiation and thoracic irradiation) are only eligible for inclusion in this review if separate data are available for the patients treated with anthracyclines and/or irradiation involving the heart.

Types of outcome measures
- Anthracycline and/or irradiation associated CHF (symptoms, NYHA II, III and IV (http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/acute-chronic-heart-failure.aspx), CTCAE3.0 grade 3 and 4 or CTCAE4.0 grade 2, 3 and 4 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)
- Heart transplant because of anthracycline and/or irradiation associated CHF
- Death due to anthracycline and/or irradiation associated CHF (i.e. CTCAE3.0 or CTCAE4.0 grade 5)

Search methods for identification of studies
See: Cochrane Childhood Cancer Group methods used in reviews.19
We will not impose language restrictions.
We will update the searches every two years.

Electronic searches
We will search the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue), MEDLINE/PubMed (from 1945 to present), and EMBASE/Ovid (from 1980 to present).
The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in the appendices (See Appendix 1, Appendix 2, Appendix 3).
**Searching other resources**

We will locate information about trials not registered in CENTRAL, PubMed/MEDLINE or EMBASE, either published or unpublished, by searching the reference lists of relevant articles and review articles. We will hand search the conference proceedings of the International Society for Paediatric Oncology (SIOP), American Society of Clinical Oncology (ASCO), American Society of Pediatric Hematology/Oncology (ASPHO), European symposium on late complications after childhood cancer (ESLCCC), and International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (all last five years) Appendix 4 describes how these searches will be performed for the first 4 conference proceedings. The International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer will be searched on paper.

**Data collection and analysis**

**Selection of studies**

After performing the searches as described above, the appropriate articles will be independently selected by two authors; if they do not comply a third author will act as an arbiter. We will obtain in full any study which seems to meet the inclusion criteria on the grounds of the title or abstract, or both, for closer inspection. The full article of the plausible studies will be used to check if it meets all the inclusion criteria. All the reasons of exclusion will be collected and displayed. In order to assess the interobserver agreement a kappa statistic will be calculated. When articles are using data from the same study population, acknowledged by comparison of authors, location and cohort specifications (name cohort, year start and end etc) only one report will be included in the review, preferentially the report including the most included patients or most recent data.
Data extraction and management

Two reviewers will independently perform data extraction using standardised forms. We will extract data on the following items:

1. Study characteristics
   - Study design
   - Number of patients of the original cohort
   - Number of patients of the described study group
   - Number of patients with an outcome measure

2. Participants
   - Age at diagnosis
   - Age at follow-up
   - Gender
   - Malignancy
   - Follow-up
   - Subgroups (if the study assessed those)

3. Interventions
   - Number of patients who received anthracyclines
   - Number of patients who received Irradiation involving the heart region.
   - Number of patients who received anthracyclines and irradiation involving the heart region
   - Type of anthracycline
   - Cumulative dose of anthracycline
   - Cumulative weekly dose of anthracycline (as mentioned by the authors)
   - Infusion duration of anthracycline
   - Cumulative dose of irradiation involving the heart region

4. Outcome
   - Outcome definitions
   - Method of detection
   - Timepoint(s) at which outcome data were collected

5. Results
   - Incidence of CHF
   - Incidence of transplant due to CHF
   - Incidence of death due to CHF
• Subgroup analyses (like different therapy received, gender, age at cancer diagnosis, duration of follow-up)

6. Risk factors
7. Length of follow-up

In case of disagreement, we will re-examine the abstracts and articles and undertake discussion until consensus is achieved. If this is impossible, we will achieve final resolution using a third author acting as arbiter.

**Assessment of risk of bias in included studies**

Two authors will independently undertake the assessment of risk of bias of the included studies. For randomised controlled trials (RCTs) and controlled clinical trials (CCTs) we will use the risk of bias items as described in the module of the Childhood Cancer Group, which are based on the Cochrane Handbook for Systematic Reviews of Interventions. The assessment of risk of bias in observational studies will be based on earlier described checklists for observational studies according to Evidence-Based Medicine Criteria. The risk of bias assessment criteria for observational studies are described in Table 1. For the risk of bias assessment of case-control studies the criteria will be slightly adapted with regard to the selection of cases and controls, which should be based on comparable patient characteristics (like age at cancer diagnosis, gender, length of follow-up and cancer treatment). If the two authors not comply a third author will act as an arbiter. The risk of bias in included studies will be taken into account in the interpretation of the review's results.

**Measures of treatment effect**

Prevalence, cumulative incidence, mean difference, absolute and relative risk, odds ratio, attributable risk, and other associated outcomes.

**Dealing with missing data**

When relevant data regarding study selection, data extraction and risk of bias assessment are missing, we will attempt to contact the study authors to retrieve the missing data.

**Assessment of heterogeneity**

Heterogeneity will be assessed both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, that is the $I^2$ statistic. If significant heterogeneity ($I^2 < 50\%$) is identified, we will explore possible
reasons for the occurrence of heterogeneity and take appropriate measures.

Assessment of reporting biases
In addition to the evaluation of reporting bias as described in the 'Assessment of risk of bias' section, we will assess reporting bias by constructing a funnel plot where there are a sufficient number of included studies (that is at least 10 studies included in a meta-analysis). When there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry.20

Data synthesis
We will use a random effects model for the pooling of treatment effects. We will summarize studies descriptively for which pooling is not possible. All results will be presented with the corresponding 95% confidence interval. All analyses will be done according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions20, and with the statistical components of Review Manager 5.1. We will include outcome measures only if it was the intention of the study to perform the necessary assessments in all included patients (that is, not only optional or only performed in some centres). When the results of a particular outcome measure are available for less than 50% of the patients of a study, due to the associated high risk of attrition bias, we will not report the results of this outcome measure. We will perform pooling of results only if studies (in case of observational studies) or treatment groups (in case of RCTs and CCTs) are comparable, including the outcome definitions that were used. Different study designs will be taken into account in the analyses. We will summarize risk factors descriptively, and only the studies which performed a multivariate analysis (i.e. including two or more potential predictive factors) will be included, case control studies are also eligible.

Sensitivity analysis
For all outcomes for which pooling is possible we will perform sensitivity analyses for all risk of bias criteria separately. We will exclude studies with a high risk of bias and studies for which the risk of bias is unclear and compare the results of studies with a low risk of bias with the results of all available studies.
## Table 1. Risk of bias assessment criteria for observational studies

<table>
<thead>
<tr>
<th>Study group</th>
<th>Internal validity</th>
<th>External validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias (representative: yes/no)</td>
<td>• if the described study group consisted of more than 95% of the original cohort of children, adolescents and young adults treated with anthracyclines and/or irradiation involving the heart region • or if it was a random sample with respect to the cancer treatment</td>
<td>Reporting bias (well defined: yes/no) • if the mean, the median or the range of the cumulative anthracycline and irradiation dose, other potential cardiotoxic treatment (mitoxantrone, ifosfamide, cyclophosphamide and vincristine) was mentioned and prior cancer treatment (++). • if only the mean, the median or the range of the cumulative anthracycline and irradiation dose was mentioned (+)</td>
</tr>
<tr>
<td>Attrition bias (adequate: yes/no)</td>
<td>• if the outcome was assessed for more than 95% of the study group of interest (++). • or if the outcome was assessed for 65-95% of the study group of interest (+)</td>
<td>Reporting bias (well defined: yes/no) • if the length of follow-up was mentioned</td>
</tr>
<tr>
<td>Detection bias (blind: yes/no)</td>
<td>• if the outcome assessors were blinded to the investigated determinant</td>
<td>Reporting bias (well defined: yes/no) • if the outcome definition was objective and precise; according to symptoms, NYHA and/or CTCAEv3.0 or CTCAEv4.0</td>
</tr>
<tr>
<td>Confounding (adjustment for other factors: yes/no)</td>
<td>• if important prognostic factors (i.e. age, gender, co-treatment) or follow-up were taken adequately into account</td>
<td>Analyses (well defined: yes/no) • if a relative risk, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi² was calculated.</td>
</tr>
</tbody>
</table>
Acknowledgements

Leontien Kremer and Elvira van Dalen, the Coordinating Editors of the Childhood Cancer Group, are co-authors of this review and therefore they could not act as the Coordinating Editor for this review. Renée Mulder (Department of Paediatric Oncology of the Emma Children's Hospital/Academic Medical Center, Amsterdam, the Netherlands) was willing to take on this task, for which we would like to thank her. The editorial base of the Cochrane Childhood Cancer Group is funded by Stichting Kinderen Kankervrij (KiKa).

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References


17. Sieswerda E, Dalen v EC, Postma A, Cheuk DKL, Caron HN, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer (Review). Cochrane Database of Systematic Reviews. 2011(9).


Appendices

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Anthracyclines** the following text words will be used:
anthracyclines OR anthracyclin* OR anthracycline antibiotics OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR IMI 30 OR IMI30 OR IMI-30 OR idarubicin hydrochloride OR NSC 256439 OR NSC-256439 OR NSC256439 OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-epidoxorubicin OR 4' epidoxorubicin OR 4'-epidoxorubicin OR 4' epi doxorubicin OR 4'-epi-adriamycin OR 4' epi adriamycin OR 4'-epi-DXR OR 4' epi DXR OR epirubicin hydrochloride OR famorubicin OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942 OR epirubicin OR epirubic* OR adriablastine OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR doxorubicin hydrochloride OR doxorubic* OR adriamyc* OR daunorubidomycine OR dauno rubidomycin OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc* OR NSC-82151 OR NSC 82151 OR NSC82151 OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR liposomal doxorubicin OR myocet OR doxorubicin OR daunorubicin

2. For **Irradiation** the following text words will be used:
radiation OR radiation injuries OR radiation induced OR radiotherapy OR radiotherapies OR radiotherap* OR irradiation OR chest wall radiotherapy OR thoracic radiotherapy OR thorax radiation OR chest radiation OR radiotherapy heart OR heart irradiation OR lymph node radiotherapy OR lymph node irradiation OR Involved-Node Radiotherapy OR mediastinal irradiation OR radiation dose

3. For **Clinical heart failure** the following text words will be used:
Congestive heart failure OR CHF OR heart failure OR clinical heart failure OR clinical cardiototoxicity OR clinical cardiotoxicities OR clinical cardiotoxiciti* OR Cardiac Failure OR Myocardial Failure OR Left-Sided Heart Failure OR Left Sided Heart Failure OR Right-Sided Heart Failure OR Right Sided Heart
Failure OR Heart Failure, Congestive OR Heart Decompensation OR cardiomyopathy OR cardiomyopathies OR cardiomyopath* OR cardiac damage OR cardiac toxicity OR cardiac toxicities OR cardiac dysfunction OR cardiac dysfunctions OR cardiac failure OR cardiac failures OR heart pathology OR heart disease OR heart diseases

4. For **Children** the following text words will be used:
infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child OR school child* OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics OR pediatric* OR paediatric* OR paediatric* OR school OR school* OR prematur* OR preterm* OR young adult OR young adults OR young women OR young men OR young male OR young female
Final search (1 OR 2) and 3 and 4
The search will be performed in title, abstract or keywords
[*= zero or more characters]

**Appendix 2.** Search strategy for Medline/PubMed

1. For **Anthracyclines** the following MeSH headings and text words will be used: anthracyclines OR anthracyclin* OR anthracycline antibiotics OR antibiotics, anthracycline OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR IMI 30 OR IMI 30 OR IMI-30 OR idarubicin hydrochloride OR hydrochloride, idarubicin OR NSC 256439 OR NSC-256439 OR NSC256439 OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-epidoxorubicin OR 4' epidoxorubicin OR 4'-epi doxorubicin OR 4' epi doxorubicin OR 4'-epi-adriamycin OR 4' epi adriamycin OR 4'-epi-DXR OR 4' epi DXR OR epirubicin hydrochloride OR hydrochloride, epirubicin OR farmorubicin OR IMI-28 OR IMI 28 OR IMI 28 OR NSC 256942 OR NSC-256942 OR NSC256942 OR epirubicin OR epirubic* OR adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR doxorubicin hydrochloride OR hydrochloride, doxorubicin OR doxorubic* OR adriamyc* OR dauno-rubidomycine OR dauno rubidomycin OR rubidomycine OR rubomycin OR daunomycin OR...
cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc* OR NSC-82151 OR NSC 82151 OR NSC82151 OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR liposomal doxorubicin OR doxorubicin, liposomal OR myocet OR doxorubicin OR daunorubicin

2. For Irradiation the following MeSH headings and text words will be used: radiation OR radiation injuries OR radiation induced OR radiotherapy OR radiotherapies OR radiotherap* OR radiotherapy[sh] OR radiotherapy/adverse effects OR irradiation OR radiation effects[sh] OR chest wall radiotherapy OR thoracic radiotherapy OR thorax radiation OR chest radiation OR radiotherapy heart OR heart irradiation OR lymph node radiotherapy OR lymph node irradiation OR Involved-Node Radiotherapy OR mediastinal irradiation OR radiation dose

3. For Clinical heart failure the following MeSH headings and text words will be used: Congestive heart failure OR CHF OR heart failure OR clinical heart failure OR clinical cardiotoxicity OR clinical cardiotoxicities OR clinical cardiotoxicit* OR Cardiac Failure OR Myocardial Failure OR Heart Failure, Left-Sided OR Heart Failure, Left Sided OR Left-Sided Heart Failure OR Left Sided Heart Failure OR Heart Failure, Right-Sided OR Heart Failure, Right Sided OR Right-Sided Heart Failure OR Right Sided Heart Failure OR Heart Failure, Congestive OR Heart Decompensation OR Decompensation, Heart OR cardiomyopathy OR cardiomyopathies OR cardiomyopath* OR cardiac damage OR cardiac toxicity OR cardiac toxicities OR cardiac dysfunction OR cardiac dysfunctions OR cardiac failure OR cardiac failures OR heart pathology OR heart/radiation effects OR heart ventricles/radiation effects OR heart disease OR heart diseases

4. For Children the following MeSH headings and text words will be used: infant* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR
preterm* OR young adult OR young adults OR young women[tiab] OR young men[tiab] OR young male[tiab] OR young female[tiab]

5. For **Case reports** the following MeSH headings and text words will be used: case reports OR case report

Final search ((1 OR 2) and 3 and 4) NOT 5

{*= zero or more characters; tiab=title or abstract; sh=subject heading; mh=MeSH term}

**Appendix 3** Search strategy for EMBASE/OVID

1. For **Anthracyclines** the following Emtree terms and text words will be used:
   1. (anthracyclin$ or anthracyclines).mp. or exp Anthracycline/
   2. anthracycline antibiotics.mp. or exp Anthracycline Antibiotic Agent/
   3. exp Anthracycline Derivative/
   4. (4-demethoxydaunorubicin or 4 demethoxydaunorubicin or 4-desmethoxydaunorubicin or 4 desmethoxydaunorubicin).mp. or exp idarubicin/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
   5. (IMI 30 or IMI30 or IMI-30 or idarubicin hydrochloride).mp.
   6. (NSC 256439 or NSC-256439 or NSC256349 or idarubicin or idarubic$).mp.
   7. (4'-epiadriamycin or 4' epiadriamycin or 4'-epidoxorubicin or 4' epidoxorubicin or 4'-epi-doxorubicin or 4' epi doxorubicin).mp.
   8. (4'-epi-adriamycin or 4' epi adriamycin or 4'-epi-DXR or 4' epi DXR).mp.
   9. exp epirubicin/ or (epirubicin or epirubicin hydrochloride or epirubic$ or farmorubicin).mp.
   10. (IMI-28 or IMI 28 or IMI28 or NSC 256942 or NSC-256942 or NSC256942).mp.
   11. (adriablastine or adriblastin or adriablastin or adriamycin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
   12. (DOX-SL or DOX SL or doxorubicin hydrochloride or doxorubic$ or adramyc$).mp.
   13. (dauno-rubidomycine or dauno rubidomycin or rubidomycin or rubomycin or daunomycin).mp.
14. (cerubidine or daunoblastin or daunoblastine or daunorubicin hydrochloride or daunorubic$).mp.
15. (NSC-82151 or NSC 82151 or NSC82151).mp.
16. (daunoxome or daunoxom$ or daunosom$ or doxil or caelyx or liposomal doxorubicin or myocet or doxorubicin or daunorubicin).mp.
17. exp DAUNORUBICIN DERIVATIVE/ or exp DAUNORUBICIN/ or exp IDARUBICIN DERIVATIVE/ or exp IDARUBICIN/ or exp DOXORUBICIN DERIVATIVE/ or exp DOXORUBICIN/ or exp EPIRUBICIN/
18. or/1-17

2. For irradiation the following Emtree terms and text words will be used:
1. radiation.mp. or exp radiation/
2. radiation injuries.mp. or exp radiation injury/
3. radiation induced.mp.
4. exp radiotherapy/
5. (radiotherapy or radiotherapies or radiotherap$).mp.
6. radiotherapy.sh.
7. irradiation.mp. or exp irradiation/
8. (radiation dose distribution or radiation induced heart disease or radiation induced cardiomypathy or radiation induced cardiotoxicity or radiation induced cardiovascular disease).sh.
9. chest wall radiotherapy.mp.
10. thoracic radiotherapy.mp.
11. thorax radiation.mp.
12. chest radiation.mp.
13. radiotherapy heart.mp.
14. heart radiotherapy.mp.
15. heart irradiation.mp.
16. lymph node radiotherapy.mp. or exp lymph node irradiation/
17. lymph node irradiation.mp.
18. involved-node radiotherapy.mp.
19. mediastinal irradiation.mp.
20. radiation dose.mp. or exp radiation dose/
21. or/1-20
3. For **Clinical heart failure** the following Emtree terms and text words will be used:

1. exp congestive heart failure/
2. (congestive heart failure or CHF).mp.
3. heart failure.mp. or exp heart failure/
4. clinical heart failure.mp.
5. (clinical cardiotoxicity or clinical cardiotoxicities or clinical cardiotoxicit$).mp.
6. cardiac failure.mp. or exp heart failure/
7. Myocardial Failure.mp.
8. left sided heart failure.mp.
9. right sided heart failure.mp.
10. heart decompensation.mp.
11. exp cardiomyopathy/
12. (cardiomyopathy or cardiomyopathies or cardiomyopath$).mp.
13. cardiac damage.mp.
14. exp cardiotoxicity/
15. (cardiac toxicity or cardiac toxicities).mp.
16. (cardiac dysfunction or cardiac dysfunctions).mp.
17. (cardiac failure or cardiac failures).mp.
18. heart pathology.mp.
19. exp heart disease/
20. (heart disease or heart diseases).mp.
21. or/1-20

4. For **Children** the following Emtree terms and text words will be used:

1. infan$.mp.
2. (newborn$ or new-born$).mp.
3. (perinat$ or neonat$).mp.
4. baby/
5. (baby or baby$ or babies).mp.
6. toddler$.mp.
7. (minors or minors$).mp.
8. (boy or boys or boyfriend or boyhood).mp.
9. girl$.mp.
10. (kid or kids).mp.
11. child/
12. (child or child$ or children$).mp.
13. school child/
14. (schoolchild$ or schoolchild).mp.
15. (school child or school child$).ti,ab.
16. (adolescen$ or youth$ or teen$).mp.
17. (juvenil$ or under$age$).mp.
18. pubescen$.mp.
19. exp pediatrics/
20. (pediatric$ or paediatric$ or peadiatric$).mp.
21. (school or school$).mp.
22. (prematur$ or preterm$).mp.
23. (young adult or young adults or young adult$).mp.
24. (young women or young men or young male or young female).mp.
25. or/1-24
5. For **Case reports** the following Emtree terms and text words will be used:
1. case reports or case report
   Final search ((1 or 2) and 3 and 4) not 5
   [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title or abstract; / = Emtree term; $= zero to many characters]

**Appendix 4.** Search strategies for proceedings abstracts and trial registers
The pdf files of SIOP and ESLCCC abstracts will be searched for "cardiotox" and for "heart failure". The ASCO abstracts will be searched for "cardiotoxicity" and for "heart failure" in the abstract (http://www.asco.org/ASCOv2/Meetings/Abstracts). The ASPHO abstracts will be searched for "cardiotoxicity" and for "heart failure" in the abstract.