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[Intervention Review]

Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer

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ABSTRACT

Background

Improvements in diagnostics and treatment for paediatric malignancies resulted in a major increase in survival. However, childhood cancer survivors (CCS) are at risk of developing adverse effects caused by multimodal treatment for their malignancy. Nephrotoxicity is a known side effect of several treatments, including cisplatin, carboplatin, ifosfamide, radiotherapy and nephrectomy, and can cause glomerular filtration rate (GFR) impairment, proteinuria, tubulopathy, and hypertension. Evidence about the long-term effects of these treatments on renal function remains inconclusive. It is important to know the risk of, and risk factors for, early and late adverse renal effects, so that ultimately treatment and screening protocols can be adjusted. This review is an update of a previously published Cochrane Review.

Objectives

To evaluate existing evidence on the effects of potentially nephrotoxic treatment modalities on the prevalence of renal dysfunction in survivors treated for childhood cancer with a median or mean survival of at least one year after cessation of treatment, where possible in comparison with the general population or CCS treated without potentially nephrotoxic treatment. In addition, to evaluate evidence on associated risk factors, such as follow-up duration, age at time of diagnosis and treatment combinations, as well as the effect of doses.

Search methods

On 31 March 2017 we searched the following electronic databases: CENTRAL, MEDLINE and Embase. In addition, we screened reference lists of relevant studies and we searched the congress proceedings of the International Society of Pediatric Oncology (SIOP) and The American Society of Pediatric Hematology/Oncology (ASPHO) from 2010 to 2016/2017.

Selection criteria

Except for case reports, case series and studies including fewer than 20 participants, we included studies with all study designs that reported on renal function (one year or longer after cessation of treatment), in CCS treated before the age of 21 years with cisplatin, carboplatin, ifosfamide, radiation involving the kidney region, a nephrectomy, or a combination of two or more of these treatments. When not all treatment modalities were described or the study group of interest was unclear, a study was not eligible for the evaluation of prevalence. We still included it for the assessment of risk factors if it had performed a multivariable analysis.

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Data collection and analysis

Two review authors independently performed study selection, 'Risk of bias' assessment and data extraction using standardised data collection forms. We performed analyses according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

Apart from the remaining 37 studies included from the original review, the search resulted in the inclusion of 24 new studies. In total, we included 61 studies; 46 for prevalence, six for both prevalence and risk factors, and nine not meeting the inclusion criteria, but assessing risk factors. The 52 studies evaluating the prevalence of renal dysfunction included 13,327 participants of interest, of whom at least 4499 underwent renal function testing. The prevalence of adverse renal effects ranged from 0% to 84%. This variation may be due to diversity of included malignancies, received treatments, reported outcome measures, follow-up duration and the methodological quality of available evidence.

Seven out of 52 studies, including 244 participants, reported the prevalence of chronic kidney disease, which ranged from 2.4% to 32%.

Of these 52 studies, 36 studied a decreased (estimated) GFR, including at least 432 CCS, and found it was present in 0% to 73.7% of participants. One eligible study reported an increased risk of glomerular dysfunction after concomitant treatment with aminoglycosides and vancomycin in CCS receiving total body irradiation (TBI). Four non-eligible studies assessing a total cohort of CCS, found nephrectomy and (high-dose (HD)) ifosfamide as risk factors for decreased GFR. The majority also reported cisplatin as a risk factor. In addition, two non-eligible studies showed an association of a longer follow-up period with glomerular dysfunction.

Twenty-two out of 52 studies, including 851 participants, studied proteinuria, which was present in 3.5% to 84% of participants. Risk factors, analysed by three non-eligible studies, included HD cisplatin, (HD) ifosfamide, TBI, and a combination of nephrectomy and abdominal radiotherapy. However, studies were contradictory and incomparable.

Eleven out of 52 studies assessed hypophosphataemia or tubular phosphate reabsorption (TPR), or both. Prevalence ranged between 0% and 36.8% for hypophosphataemia in 287 participants, and from 0% to 62.5% for impaired TPR in 246 participants. One non-eligible study investigated risk factors for hypophosphataemia, but could not find any association.

Four out of 52 studies, including 128 CCS, assessed the prevalence of hypomagnesaemia, which ranged between 13.2% and 28.6%. Both non-eligible studies investigating risk factors identified cisplatin as a risk factor. Carboplatin, nephrectomy and follow-up time were other reported risk factors.

The prevalence of hypertension ranged from 0% to 50% in 2464 participants (30/52 studies). Risk factors reported by one eligible study were older age at screening and abdominal radiotherapy. A non-eligible study also found long follow-up time as risk factor. Three non-eligible studies showed that a higher body mass index increased the risk of hypertension. Treatment-related risk factors were abdominal radiotherapy and TBI, but studies were inconsistent.

Because of the profound heterogeneity of the studies, it was not possible to perform meta-analyses. Risk of bias was present in all studies.

Authors' conclusions

The prevalence of adverse renal effects after treatment with cisplatin, carboplatin, ifosfamide, radiation therapy involving the kidney region, nephrectomy, or any combination of these, ranged from 0% to 84% depending on the study population, received treatment combination, reported outcome measure, follow-up duration and methodological quality. With currently available evidence, it was not possible to draw solid conclusions regarding the prevalence of, and treatment-related risk factors for, specific adverse renal effects. Future studies should focus on adequate study designs and reporting, including large prospective cohort studies with adequate control groups when possible. In addition, these studies should deploy multivariable risk factor analyses to correct for possible confounding. Next to research concerning known nephrotoxic therapies, exploring nephrotoxicity after new therapeutic agents is advised for future studies. Until more evidence becomes available, CCS should preferably be enrolled into long-term follow-up programmes to monitor their renal function and blood pressure.

PLAIN LANGUAGE SUMMARY

Early and late adverse effects on the kidney after treatment for childhood cancer

Review question

This review evaluated how common (the prevalence), and what might cause (the risk factors), early and late adverse effects (side effects), of the kidney in childhood cancer survivors (CCS).

Background

Improvements in diagnostics and treatment for childhood cancer has resulted in a major increase in survival. However, CCS are at risk of developing adverse effects as a result of their cancer treatment, including adverse effects on the kidneys. Little is known about the

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prevalence and risk factors of kidney function problems in long-term CCS. The kidneys can compensate for problems in their functioning, however, some symptoms can be experienced over time, depending on which kidney functions are affected.

Study characteristics

The evidence is current to March 2017. We included 61 studies; 46 on prevalence, six for both prevalence and risk factors, and nine studies that did not meet all the requirements for this review, but evaluated risk factors (non-eligible studies). Participants in the studies had been treated before the age of 21 years with chemotherapy (i.e. cisplatin, carboplatin, ifosfamide), radiation, or surgery involving the kidneys, or a combination of these treatments. The studies took place at least one year after the participants had finished their treatment. The 52 studies that evaluated prevalence of adverse kidney effects included 13,327 participants, of whom 4499 underwent kidney function tests. The studies were very different from each other, in the types of participants and treatments, length of follow-up and how they measured treatment results, and their methods were of variable quality.

Key results

The percentage of CCS with kidney problems ranged from 0% to 84%. Reported risk factors were often inconsistent among studies.

The prevalence of chronic kidney disease ranged from 2.4% to 32% in 244 participants (7/52 studies).

Thirty-six out of 52 studies, including at least 432 participants, carried out a kidney function test called glomerular filtration rate (GFR). An abnormal GFR was found to be present in 0% to 73.7% of participants. One eligible study found an increased risk of abnormal GFR in participants who had been treated with total body irradiation (TBI) and received certain types of antibiotics (aminoglycosides and vancomycin). Four non-eligible studies reported an increased risk of abnormal GFR for participants treated with surgery of the kidney and ifosfamide. Some studies also reported that cisplatin and long follow-up duration were risk factors.

Twenty-two out of 52 studies, including 851 participants, assessed an abnormal amount of proteins in the urine, which they found in 3.5% to 84% of participants. Risk factors, evaluated by three non-eligible studies, included cisplatin, ifosfamide, TBI, and a combination of surgery and radiation involving the kidney. However, the results of these studies did not agree, and we could not analyse their results together because they used different definitions.

Eleven out of 52 studies looked at a low level of phosphate in the blood (hypophosphataemia), or problems with the reabsorption of phosphate by the kidneys in 246 participants. Prevalence of hypophosphataemia ranged between 0% and 36.8% in 287 participants. The studies found problems with the reabsorption of phosphate by the kidneys in 0% to 62.5% of participants. One non-eligible study investigated risk factors, but could not find any association with hypophosphataemia.

Four out of 52 studies, including 128 CCS, evaluated a low level of magnesium in the blood (hypomagnesaemia). Prevalence ranged between 13.2% and 28.6%. Two non-eligible studies identified cisplatin as risk factor for hypomagnesaemia. Other reported risk factors were carboplatin, surgery of the kidney, and follow-up time. However, studies were contradictory.

The prevalence of high blood pressure ranged from 0% to 50% in 2464 participants (30/52 studies). Risk factors reported by one eligible study were older age at screening and radiation involving the kidney. A high body mass index was reported as a risk factor by three non-eligible studies. Other reported risk factors included follow-up time, and radiation involving the kidney or TBI. However, studies were contradictory.

Quality of evidence

All studies showed problems that could affect our confidence in their results. More, and especially higher-quality research is needed to gain better insight into kidney adverse effects and related risk factors.

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BACKGROUND

Improvements in diagnostics and treatment for malignant disease in childhood have led to a major increase in survival, with five-year survival reaching 80% in Europe (Gatta 2014). Despite this rise in survival, childhood cancer survivors (CCS) are at high risk of developing late effects caused by their oncological therapies. Three large cohort studies found that up to 88% of all survivors suffer from at least one long-term effect after a follow-up of 30, 17 and 7 years, respectively (Geenen 2007; Oeffinger 2006; Wasilewski-Masker 2010).

Nephrotoxicity is a known side effect of certain childhood cancer therapies, resulting in a decline in glomerular filtration rate (GFR), deterioration of tubular function, development of albuminuria and hypertension during or after treatment (Jones 2008). Impaired renal function may progress towards end-stage renal failure, an independent risk factor for cardiovascular disease (Manjunath 2003). Potentially nephrotoxic agents include ifosfamide and the platinum compounds cisplatin and carboplatin (English 1999; Jones 2008; Rossi 1999; Womer 1985). Studies have shown that ifosfamide and platinum toxicities persist during follow-up even up to 10 years after treatment, with the prevalence of adverse renal effects ranging from 0% to 45% depending on the study group and the measured outcome variable (Oberlin 2009; Skinner 2009). Abdominal and total body irradiation may cause radiation nephropathy, characterised by hypertension, a decline in GFR and, (intermittent) proteinuria (Breitz 2004). Kidney surgery may also play a role in the long-term course of renal function, for example, by causing hyperfiltration in unilateral nephrectomised survivors, which may ultimately lead to hypertension and glomerular impairment (De Graaf 1996; Schell 1995). With the current high survival rates for unilateral Wilms' tumour, the focus in recent research has been more on therapeutic changes to reduce treatment morbidity while maintaining oncological outcome. Recent studies have shown in small cohorts of carefully selected participants that nephron-sparing surgery reduces adverse renal effects while maintaining the high survival rates for patients with nonsyndromic unilateral Wilms' tumour compared to standard nephrectomy (Cost 2014; Cozzi 2012; Cozzi 2013a; Cozzi 2017a).

Several treatment-related risk factors for the development of late renal effects have been mentioned in the literature, but these effects were often examined in small, selected study populations and produced inconsistent results. Recently, larger cohort studies investigating nephrotoxicity in CCS have been performed (Dekkers 2013; Knijnenburg 2012; Mulder 2013), but very long-term follow-up studies are still lacking. Risk factors such as cumulative chemotherapy and radiotherapy doses, age at diagnosis, duration of follow-up and infusion schemes have all been investigated, but conclusive evidence is missing. Systematic review and meta-analysis of the literature may elucidate which risk factors are associated with renal impairment and which are not.

In 2008, Jones and colleagues published an evidence summary for the American Childhood Oncology Group (COG), delineating exposure-based risks of potentially nephrotoxic treatment modalities accompanied by health screening recommendations and considerations for the treatment and management of associated late effects (Jones 2008). The focus of management of nephrotoxicity lies in blood pressure control, electrolyte supplementation and, when needed, consultation with or referral to a nephrologist. The COG evidence summary served as a basis for the COG Long-Term Follow-up Guidelines (Children's Oncology Group 2018). Skinner published two overviews of the literature regarding nephrotoxicity during and after treatment for childhood cancer (Skinner 2010a; Skinner 2011) and O'Sullivan recently reviewed late adverse renal effects in CCS, but only for chemotherapeutic agents (O'Sullivan 2017). To reduce the number of (long-term) nephrotoxic events in CCS, treatment and screening protocols should be adjusted.

This is an update of the first systematic review of Knijnenburg 2013, evaluating the current available evidence on adverse renal effects of potentially nephrotoxic treatment for childhood cancer. In the initial review prevalence of renal adverse effects ranged between 0% and 84% after treatment with cisplatin, carboplatin, ifosfamide, radiotherapy involving the kidney, or nephrectomy. Due to large heterogeneity among studies in the initial review, the authors could not draw any conclusions about the prevalence of, and risk factors for nephrotoxicity for CCS treated with potentially nephrotoxic treatment. Therefore, an update of this systematic review of the literature is required to gain more evidence-based insight into the role of possible nephrotoxic treatments in early and long-term function of the kidneys.

OBJECTIVES

To evaluate existing evidence of the effects of potentially nephrotoxic treatment modalities on the prevalence of renal dysfunction in survivors treated for childhood cancer with a median or mean survival of at least one year after cessation of treatment, where possible in comparison with the general population or CCS treated without potentially nephrotoxic treatment. In addition, to evaluate evidence on associated risk factors, such as follow-up duration, age at time of diagnosis and treatment combinations, as well as the effect of doses.

METHODS

Criteria for considering studies for this review

Types of studies

All study designs, except case reports and case series, examining the effects of specific (multimodal) treatments of childhood cancer on adverse renal effects.

Types of participants

CCS diagnosed between the ages of 0 and 21 years with a mean or median survival of at least one year after the end of treatment and related controls, if available. If the study did not mention follow-up time after the end of treatment, at least 90% of the study group had to have finished treatment. Studies had to include at least 20 survivors previously treated with potentially nephrotoxic therapies.

Types of interventions

Treatment with cisplatin, carboplatin, ifosfamide, radiotherapy involving the kidney region, including total body irradiation, or surgery involving the kidney, or a combination of two or more of these treatments.

When studies did not describe all the above-mentioned treatment modalities, and we could not assume that any of these treatments had been given (based on information about tumour type and/

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or treatment protocol), we found the study not eligible for the evaluation of prevalence of adverse renal effects. Moreover, when it was unclear what the study group of interest consisted of, or if results were not described for the study group of interest separately, we excluded the study for the evaluation of prevalence. When a study was not eligible for evaluating prevalence, we could still include it for the assessment of risk factors, but only when it had performed multivariable analysis. To summarise, we included three types of studies in this systematic review, that is, studies for prevalence, studies assessing both prevalence and risk factors, and studies that did not fulfil the inclusion criteria, but performed multivariable analyses for risk factors. We have described results separately for the eligible and non-eligible studies, as the results of the latter group could be less reliable.

Types of outcome measures

We decided to limit included outcome measures to those that were most often reported, most consistent, and had the greatest clinical relevance. Included outcome measurements were:

1. chronic kidney disease (CKD)/renal insufficiency;
2. (estimated) GFR;
3. proteinuria;
4. serum phosphate/hypophosphataemia;
5. tubular phosphate regulation parameters (tubular phosphate threshold and fractional phosphate reabsorption);
6. serum magnesium/hypomagnesaemia; and
7. blood pressure.

We did not impose any restrictions on the outcome definitions. We included studies that reported on composite outcome measures, that included one of the above-mentioned outcomes. We excluded studies investigating blood pressure as part of a cardiovascular assessment or metabolic syndrome.

Search methods for identification of studies

The objective of the literature search was to identify all studies reporting on adverse renal effects of potentially nephrotoxic treatment modalities in CCS, except for case reports and case series; hence we included randomised controlled trials, case-control studies and cohort studies.

We did not impose any language restriction.

Electronic searches

We searched the following electronic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL, Issue 6, 2017), in the Cochrane Library;
2. MEDLINE/PubMed (from 1945 to 31 March 2017); and
3. EMBASE/Ovid (from 1980 to 31 March 2017).

We have provided the search strategies for the different electronic databases (using a combination of controlled vocabulary and text words), in the appendices (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We screened the reference lists of relevant articles and reviews for additional relevant studies. In addition, we handsearched the congress proceedings of the International Society of Pediatric Oncology (SIOP) from 2010 to 2016 and The American Society of Pediatric Hematology/Oncology (ASPHO) from 2010 to 2017. The key words of the search are shown in Appendix 4.

Data collection and analysis

Selection of studies

After performing the search strategy described above, two review authors independently selected studies meeting the inclusion criteria based on title and abstract. We obtained full-text papers for closer inspection of any study that seemed to meet the inclusion criteria based on title and abstract. We resolved discrepancies between review authors by consensus. If this proved impossible, final resolution was achieved by consulting a third review author. We have constructed a flow diagram (Figure 1). We have provided details of reasons for exclusion of any study considered for this review in the Characteristics of excluded studies.

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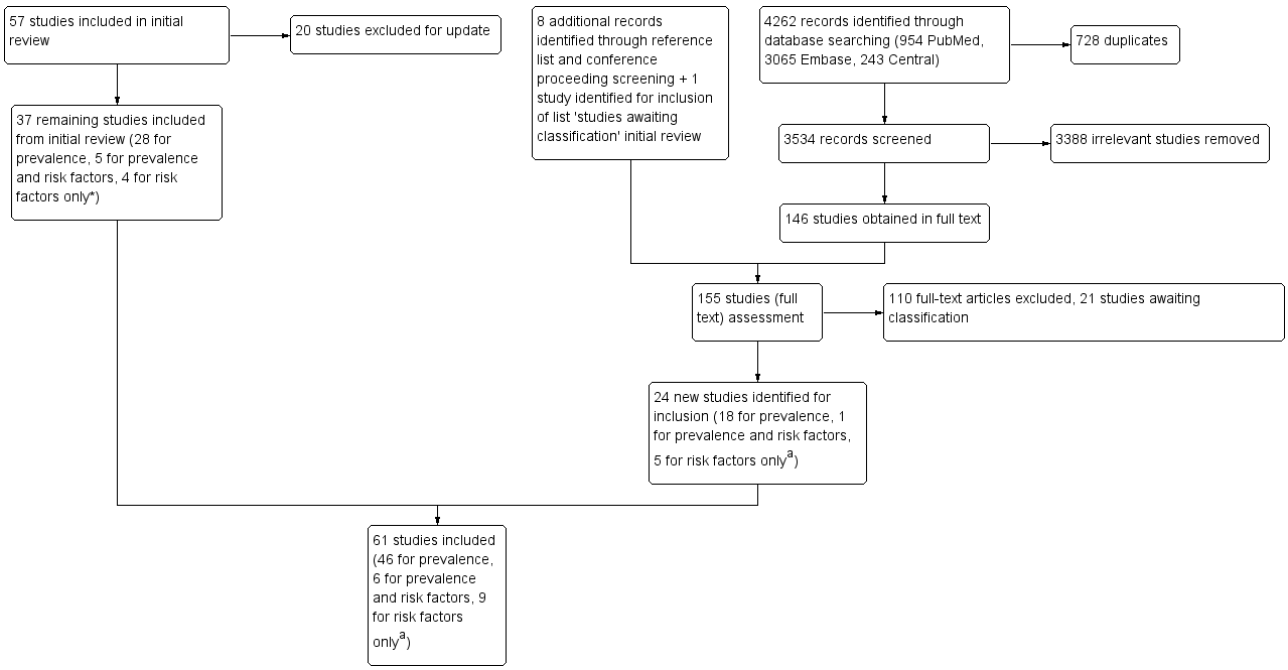
Figure 1. Study flow diagram [a]Studies that did not fulfil the inclusion criteria, but performed multivariable risk analyses



Data extraction and management

Two review authors performed data extraction independently using standardised data extraction forms. We retrieved data on the following items.

1. Study characteristics
   a. Study design
   b. Number of participants in the original cohort*
   c. Number of participants in the described study group*
   d. Number of participants in the study group of interest*
   e. Number of participants tested for adverse renal effects*
   f. Number of controls
2. Study participants
   a. Age at diagnosis or at treatment
   b. Time period diagnosis/treatment
   c. Age at follow-up
   d. Duration of follow-up
   e. Completion of follow-up
   f. Sex
   g. Tumour type
3. Interventions
   a. Number of participants treated with ifosfamide, cisplatin and carboplatin
   b. Cumulative doses of ifosfamide, cisplatin and carboplatin
   c. Number of participants treated with other types of chemotherapy
   d. Number of participants treated with radiotherapy including the kidney region
   e. Cumulative radiotherapy dose
   f. Number of participants treated with (partial), unilateral or bilateral nephrectomy
4. Outcome measurements, as defined by the authors of the original studies
5. Risk factors for nephrotoxicity, as defined by the authors of the original studies

*The participants in the original cohort represent the whole group of CCS. The described study group encompasses CCS from the original cohort included in the study. The study group of interest consists of the CCS within the described study group who received potentially nephrotoxic treatment as defined by this review. Finally, within the study group of interest we evaluated the study group tested for adverse renal effects.

In cases of disagreement, both review authors re-assessed the abstracts and full-text articles and discussed until consensus was achieved. If consensus was not achieved, we consulted a third review author for resolution.

Assessment of risk of bias in included studies

We based the 'Risk of bias' assessment on earlier described checklists for observational studies, based on evidence-based medicine criteria (Grimes 2002; Laupacis 1994), as adapted by Mulder 2010. Two review authors independently assessed all included studies on the risk of bias related to the composition of the study population, the follow-up assessments and the outcome assessments, as well as the methods used to assess risk factors for nephrotoxicity in each study. We have presented the criteria for the 'Risk of bias' assessment in Table 1. When a study explicitly stated that they gave radiotherapy or chemotherapy, or both, they had to describe cumulative doses to justify a classification of 'well-defined'.

For the 'Risk of bias' assessment in case-control studies, we used adapted criteria related to the selection of cases and controls.

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Selection of cases and controls had to be based on similar participant characteristics (i.e. age, sex and cancer treatment).

For randomised controlled trials (RCTs) and non-randomised controlled trials (CCTs), we used the criteria put forth by the Childhood Cancer Group (Module CCG).

In case of disagreement between two review authors, both re-assessed the abstracts and full-text articles to achieve consensus. If this proved impossible, we consulted a third review author for resolution.

Measures of treatment effect

Prevalence, cumulative incidence, mean difference, risk ratio, odds ratio, attributable risk and other associated risk measures.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots, and by the I^2 statistic, the formal statistical test for heterogeneity, which defines substantial heterogeneity as I^2 greater than 50% (Higgins 2011). We reported cases of substantial heterogeneity. We performed pooling of results only if studies were comparable, including the study population, follow-up duration, co-treatment, definition of outcome, and the method of assessment.

Assessment of reporting biases

We planned to make funnel plots to assess possible publication bias. Heterogeneity prevented us from performing meta-analysis; therefore, it was not possible to construct any funnel plots (Higgins 2011).

Data synthesis

We entered data into Review Manager 5 (RevMan 5 (Review Manager 2014)), and analysed them according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used random-effects models throughout the review. We used the generic inverse variance function of RevMan 5 to analyse the prevalence of adverse renal effects. When a study measured an outcome several times during follow-up, we used the result at latest follow-up for data synthesis in this review. When a study used multiple methods to assess prevalence of decreased GFR, we used the result of the estimation using an exogenous marker (i.e. inulin clearance, 51Cr-EDTA clearance, Tc-99m DTPA clearance, and 125-I-iothalamate clearance), for analyses in this review, as this is more accurate than equations using endogenous markers to estimate GFR (KDIGO 2013; Stevens 2009). When studies estimated GFR using an endogenous marker of GFR (eGFR), we only included this in the review if the estimating equation had been applied correctly. An overview of estimating equations and its calibration material can be found in Table 2. In case studies estimated GFR using different tests in a given paper, we used the arithmetic mean for analysis in this review.

It was not possible to pool the data, so we provided descriptive results of the studies. Because of the substantial heterogeneity, it was not feasible to perform multivariable meta-regression analyses on any of the outcome variables.

Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analyses of studies based on age at diagnosis and follow-up duration, and of studies that reported on a single treatment modality (cisplatin, carboplatin, ifosfamide, nephrectomy or radiotherapy). However, it was not feasible to perform these analyses, again because of the high degree of heterogeneity and the variety of treatment regimens given within the included studies.

Sensitivity analysis

Due to substantial heterogeneity, it was not possible to pool study outcomes for any of the included outcomes; therefore, we did not perform sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Original review

The original search in 2011 identified 5504 references through searching the electronic databases, CENTRAL, MEDLINE (PubMed) and Embase (Ovid). After initial screening of the titles and abstracts, we excluded 5138 references that clearly did not meet all the inclusion criteria defined for this systematic review. We obtained a total of 366 full-text articles for further screening. Of these 366, we excluded another 293 for not meeting the inclusion criteria. The reasons for exclusion are described in the Characteristics of excluded studies section. Another 16 studies were awaiting classification because they were still waiting to be translated, because we could not retrieve the full-text article, or because the full-text was not yet available (Cohen 2010; Cozzi 2010; D'Angio 1978; Eckstein 2010; Janda 1993; Kieran 2010; Li 2006; Madden 2010; Matsuyama 2002; Pugachev 2004; Radvansky 2010; Sakellari 2010a; Schwartz 2001; Sierota 2005; Stronska 2003; Terenziani 2010). The details of these studies can be found in the Characteristics of studies awaiting classification table. As a result, we included a total of 57 studies in the initial review on adverse renal effects after potentially nephrotoxic treatment for childhood cancer. We added one further study to the Characteristics of studies awaiting classification section during the review process because that was suggested by a review author (Bailey 2002).

Update in 2017

In 2017 the above-mentioned search in electronic databases revealed an additional 3534 potential relevant references after removal of 728 duplicates. Initial screening of titles and abstracts excluded 3388 references that did not meet the inclusion criteria. We read the full texts of the remaining 146 references. Screening of reference list revealed six additional studies, and congress proceedings in SIOP and ASPHO resulted in two additional studies. In total, we excluded 110 studies for different reasons (see Characteristics of excluded studies table). There were 21 possible relevant references moved to Characteristics of studies awaiting classification because the full-text was not yet available (Baassiri 2016; Bate 2012; Begun 2011; Bom-Sucesso 2014; Bruce 2014; Cozzi 2016; Godzinski 2016; Green 2016; Grylli 2016; Medeiros 2016; Moczulska 2011; Moczulska 2013; Moneib 2016; Okur 2014; Oz 2015; Schiavetti 2016; Vanrenterghem 2014; Wilde 2013; Yanagisawa 2016; Yazal Erdem 2016), or the full text could not be retrieved (Ikram 2011). In total, the search revealed 23 studies that we

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included; 18 for the evaluation of prevalence of adverse renal affects (and risk factors if applicable), and five studies that did not fulfil the inclusion criteria but performed multivariable risk analysis.

For this update we refined the selection criteria. As a result, 20 out of 57 studies that were first included in the original Cochrane Review are now excluded (Bergeron 2005; Bolling 2010; Breslow 2005; Cosentino 1993; English 1999; Ferrari 2005; Fujieda 2009; Hamilton 2011; Laverdiere 2005; Loebstein 1999; Oberlin 2009; Patzer 2001; Prasad 1996; Rossi 1993; Rossi 1994a; Rossi 1994b; Rossi 1999; Skinner 2009; Stefanowicz 2009; Trahair 2007). We have described the reasons for exclusion in the Characteristics of excluded studies section. Four studies that we had previously included for both prevalence and risk factors, failed to meet all the revised inclusion criteria, but we still included them for risk factors, as they performed multivariable analysis (Cardous-Ubbink 2010; Hoffmeister 2010; Stohr 2007a; Van Why 1991).

We were able to include one study in this review update from the studies awaiting classification in the original Cochrane Review (Bailey 2002). We excluded seven studies from the previous studies awaiting classification, but we also identified one through the search which was a duplicate (Cohen 2010 which is now referred to as Cohen 2012; Cozzi 2010 which is now referred to as Cozzi 2017a; D'Angio 1978; Li 2006; Matsuyama 2002; Pugachev 2004; Schwartz 2001).

In summary, 37 remaining studies from the original review, combined with 24 new inclusions from the current update, results in a total of 61 studies included in this review; 46 studies for the evaluation of prevalence only, six for the evaluation of both prevalence and risk factors (Frisk 2002; Geenen 2010; Kantor 1989; Lange 2011; Stohr 2007b; Van Dijk 2010), and nine studies that did not fulfil the inclusion criteria, but did perform risk factor analysis (Cardous-Ubbink 2010; Dekkers 2013; Hoffmeister 2010; Knijnenburg 2012; Mudi 2016; Mulder 2013; Ramirez 2016; Stohr 2007a; Van Why 1991). We have summarised the characteristics of these studies below and also in the Characteristics of included studies section. Figure 1 is the study flow diagram, that illustrates the flow of the search.

Based on the author lists and study and treatment characteristics, readers should take note that there may be potential overlap of participants in the studies included for prevalence of Aronson 2011, Geenen 2010 and Van Dijk 2010; the studies of Stefanowicz 2010, Stefanowicz 2011 and Stefanowicz 2012; the studies of Frisk 2002 and Frisk 2007; the studies of Di Tullio 1996 and Indolfi 2001; the studies of Cozzi 2005 and Cozzi 2012; and of Rossi 1994 and Rossi 1997. There might also be overlap of participants in the studies assessing risk factors of Cardous-Ubbink 2010 and Van Dijk 2010; and the studies of Dekkers 2013, Knijnenburg 2012 and Mulder 2013.

Included studies

We have described results separately for the 52 studies included for prevalence (and risk factors if applicable), and nine studies that did not meet the inclusion criteria, but did perform risk factor analysis.

Methods

Studies included for prevalence (and risk factors if applicable)

We identified a total of 19 cross-sectional cohort studies, as well as 16 prospective cohort studies, 11 retrospective cohort studies, one case-control study, and five cohort studies, for which the direction of inclusion was unclear. Diagnosis or treatment periods of included participants started as early as 1931 (Kantor 1989), and went on until 2014 (Davidoff 2015; Interiano 2017; Schiavetti 2015a), with a median enrolment period of 16 years per study. Eight studies did not report the diagnosis or treatment period of included participants. The earliest study was published in 1986 (Wikstad 1986), and the latest in 2017 (Interiano 2017).

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

Studies that did not fulfil the inclusion criteria, but did perform risk factor analyses consisted of three cross-sectional cohort studies, three retrospective cohort studies, and two prospective cohort studies. Additionally, we obtained one nested case-control study (Cardous-Ubbink 2010). The median enrolment period was 35 years per study and diagnosis or treatment periods started in 1964 (Dekkers 2013), and went on until 2005 (Dekkers 2013). Two studies did not mention the diagnosis or treatment period (Mudi 2016; Ramirez 2016). The earliest study was published in 1991 (Van Why 1991), and the latest in 2016 (Mudi 2016; Ramirez 2016).

Participants

Studies included for prevalence (and risk factors if applicable)

The total number of participants of interest described in the 52 included studies was 13,327. Of these 13,327 participants of interest, at least 4499 participants from 51 studies underwent renal function testing. One study (Lange 2011), did not mention the number of participants who underwent renal function tests. Study sizes ranged from 22 (Wikstad 1986) to 7950 participants (Lange 2011). Thirty-nine studies included only survivors of unilateral or bilateral Wilms' tumour (Aronson 2011; Bailey 2002; Chevallier 1997; Cost 2014; Cozzi 2005; Davidoff 2015; De Graaf 1996; Di Tullio 1996; Elli 2013; Finklestein 1993; Geenen 2010; Indolfi 2001; Interiano 2015; Interiano 2017; Janeczko 2015; Kantor 1989; Kern 2014; Kishore 2015; Kostel Bal 2016; Kubiak 2004; Lange 2011; Levitt 1992; Makipernaa 1991; Mancini 1996; Mavinkurve-Groothuis 2016; Mpofu 1992; Othman 2002; Oue 2014; Paulino 2000; Sasso 2010; Srinivas 1998; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012; Sudour 2012; Trobs 2001; Van Dijk 2010; Weirich 2004; Wikstad 1986). Furthermore, two studies included only participants with a renal tumour (Cozzi 2012; Schiavetti 2015a), three studies included only survivors with a sarcoma (Rossi 1997; Skinner 2010b; Stohr 2007b), one study included only participants with hepatoblastoma (von Schweinitz 1997), two studies included only participants with leukaemia and/or lymphoma (Frisk 2002; Frisk 2007), one study included only participants treated for central nervous system malignancies (Musiol 2016), and four studies included participants with diagnoses of miscellaneous tumours.

Forty-six studies mentioned the median or mean participant age at diagnosis, which ranged from 12 months (von Schweinitz 1997), to 14 years (Rossi 1997). Twenty-five studies reported median or mean participant age at follow-up, which ranged from 3.6 years (De Graaf 1996), to 29 years (Kantor 1989). Follow-up duration of survivors also varied widely, from a median of 12 months (Schell

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1995), up to 25 years (Kantor 1989). Follow-up duration was better reported than participant age at follow-up: all except two studies mentioned the follow-up duration. Forty-six studies reported sex distribution. The percentage of included male participants ranged from 28% to 69%, but the median percentage of male participants in the 46 studies that reported sex was 47.5%.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

The nine studies that did perform risk factor assessment, but did not meet the inclusion criteria included at least 6318 participants with a renal function test. However, either we could not clarify the number of participants of interest in these studies or they did not describe the results separately for the study group of interest. All studies included participants with diagnoses of miscellaneous tumours. Eight studies mentioned the median or mean age at diagnosis, which ranged from 5.7 years (Ramirez 2016), to 11.6 years (Stohr 2007a). The median or mean age at follow-up ranged from 13.3 years (Ramirez 2016), to 28 years (Cardous-Ubbink 2010), and was reported in seven studies. All the studies mentioned follow-up duration, which went from 17 months (Van Why 1991), up to 20.4 years (Cardous-Ubbink 2010). The median percentage of male participants was 55.5% (8/9 studies).

Treatment

We have only described below details of potential nephrotoxic treatment modalities for the 52 studies included for the evaluation of prevalence, because the nephrotoxic treatment, as defined by the review, was not clearly described in the non-eligible studies.

Cisplatin

In nine out of 52 studies, participants were definitely treated with cisplatin, while in 31 studies it was clear that participants definitely did not receive cisplatin. Whether participants did or did not receive cisplatin remained unspecified in 12 studies. For these studies, we assumed that participants did not receive cisplatin, based on tumour type or treatment protocol, or both. At least 385 participants were treated with cisplatin, and the percentage of participants treated with cisplatin within a cohort varied widely from 2% (Mancini 1996), to 100% (Brock 1991; Musiol 2016; von Schweinitz 1997). Eight out of nine studies reported median or mean cumulative doses including cisplatin, ranging from 180 mg/m^2 (Di Tullio 1996) to 800 mg/m^2 (Chevallier 1997), although most studies reported a mean or median cumulative cisplatin dose prescription between 300 and 500 mg/m^2 (Brock 1991; Musiol 2016; Rossi 1994; Schell 1995; Stohr 2007b).

Carboplatin

At least 163 participants from 15 studies reported carboplatin use. Twenty-five studies did not administer carboplatin, and 12 studies did not report carboplatin use, but based on tumour type or treatment protocol, or both, we assumed that they did not use it. The average percentage of participants treated with carboplatin was 16%, although this varied widely from 3% (Mancini 1996), to 74% (Musiol 2016). Six studies did not report the exact number of participants, but those studies included at least one participant with carboplatin (Davidoff 2015; Mudi 2016; Oue 2014; Stefanowicz 2011; Stefanowicz 2012; Trobs 2001). Eleven studies did not report cumulative carboplatin dose (Bardi 2004a; Cozzi 2012; Davidoff 2015; Interiano 2017; Janeczko 2015; Oue 2014; Schiavetti 2015a; Stefanowicz 2011; Stefanowicz 2012; Trobs 2001; Weirich 2004). Median carboplatin cumulative doses ranged from 1100 mg/m^2 to 2500 mg/m^2.

Ifosfamide

Out of 52 studies, 21 reported prescription of ifosfamide for at least 863 participants, 22 studies did not use ifosfamide, and nine studies did not report ifosfamide use. We assumed that these nine studies did not use ifosfamide based on tumour type or treatment protocol, or both. In five out of 21 ifosfamide studies, all participants received ifosfamide (Rossi 1994; Rossi 1997; Skinner 2010b; Stohr 2007b; von Schweinitz 1997). Median cumulative dose varied between 18 g/m^2 (Di Tullio 1996), and 106 g/m^2 (Skinner 2010b) in nine studies and 12 studies did not report it.

Radiotherapy involving the kidney

Forty-four out of 52 studies used radiotherapy involving the kidney in the treatment regimen of at least 1932 participants. Five studies did not include participants who received radiotherapy involving the kidney. Three studies did not mention administration of radiotherapy, but based on tumour type or treatment protocol, or both, we assumed that they did not include radiotherapy as part of treatment. Radiotherapy included total body irradiation (TBI) only in two studies (Frisk 2002; Frisk 2007), and abdominal irradiation only in 31 studies. One study included participants treated with both TBI and participants treated with abdominal irradiation (Skinner 2010b), and 10 other studies did not specify the field. Median doses ranged between 7.5 Gy and 12 Gy for the TBI group and between 10.4 Gy and 45 Gy for the abdominal irradiation group. Eighteen studies did not report the radiation dose.

Nephrectomy

A total of 44 studies included nephrectomised participants, while eight studies did not. In 41 out of 44 studies, 100% of the included participants underwent a nephrectomy (Aronson 2011; Bailey 2002; Chevallier 1997; Cost 2014; Cozzi 2005; Cozzi 2012; Davidoff 2015; De Graaf 1996; Di Tullio 1996; Elli 2013; Finklestein 1993; Geenen 2010; Indolfi 2001; Interiano 2015; Interiano 2017; Janeczko 2015; Kantor 1989; Kern 2014; Kishore 2015; Kostel Bal 2016; Kubiak 2004; Lange 2011; Levitt 1992; Makipernaa 1991; Mancini 1996; Mavinkurve-Groothuis 2016; Mpofu 1992; Othman 2002; Oue 2014; Paulino 2000; Schell 1995; Schiavetti 2015a; Srinivas 1998; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012; Sudour 2012; Trobs 2001; Van Dijk 2010; Weirich 2004; Wikstad 1986). All but three of these 41 studies performed nephrectomy for the treatment of Wilms' tumour. Eleven studies mentioned that they also included participants who underwent bilateral surgery in cases of bilateral disease (Aronson 2011; Davidoff 2015; Interiano 2017; Janeczko 2015; Kantor 1989; Mancini 1996; Oue 2014; Paulino 2000; Sudour 2012; Trobs 2001; Weirich 2004). Three studies reported on renal function after nephron-sparing surgery compared to radical nephrectomy for unilateral renal tumour (Cost 2014; Cozzi 2005; Cozzi 2012). One study investigated bilateral nephron-sparing surgery for bilateral Wilms' tumour (Davidoff 2015).

Forty out of 52 studies described other chemotherapeutics; 12 studies did not report other treatments. Types of other chemotherapy varied widely between studies; detailed descriptions per study can be found in the Characteristics of included studies.

We divided the included studies into subgroups based on the combination of treatments described in the article, as

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the five different included treatments can be given in various combinations. We considered a study to include participants with a certain treatment when a study included at least one participant who was given that treatment. The subgroups and the studies per subgroup are provided in Table 3.

Outcome definitions

The 52 studies included for prevalence reported a total of 129 adverse renal outcomes. As we noted profound heterogeneity in the reported outcome measures, we limited this review to the following outcome parameters based on reported frequency and clinical relevance: chronic kidney disease (CKD)/renal insufficiency, (estimated) GFR, proteinuria, serum phosphate, tubular phosphate absorption parameters, serum magnesium, and blood pressure. Even in these selected outcome measures, we observed considerable differences in defined cut-off points for abnormal test results and measurement methods. In addition, studies differed in reporting dichotomous or continuous outcome variables.

Chronic kidney disease/renal insufficiency

Prevalence

Seven studies reported the prevalence of (chronic) renal insufficiency or end-stage renal disease only, without specifying the cut-off value used to assess the GFR (Aronson 2011; Geenen 2010; Lange 2011; Paulino 2000; Sasso 2010; Stefanowicz 2011; Sudour 2012).

Risk factors of eligible studies

Lange 2011 also provided risk factors for end-stage renal disease in non-WT1 syndromic Wilms' tumour survivors.

Risk factors of non-eligible studies

None of the studies not fulfilling the inclusion criteria performed risk factor analysis for CKD/renal insufficiency.

(Estimated) glomerular filtration rate (GFR)

Prevalence

(Estimated) GFR was the most frequently assessed outcome parameter (36 studies). However, we noted great methodological variation in the assessment of this outcome parameter. A number of studies measured GFR directly using a gold-standard technique such as 51Cr-EDTA clearance (Bailey 2002; Brock 1991; Frisk 2002; Frisk 2007; Levitt 1992; Makipernaa 1991; Skinner 2010b), inulin clearance (Chevallier 1997; Schell 1995; Wikstad 1986), Tc-99m DTPA clearance (Interiano 2017; Kishore 2015; Srinivas 1998; Stefanowicz 2011), or by 125-I-iothalamate clearance (De Graaf 1996). The majority of studies used GFR estimation formulae (eGFR), such as the Schwartz formula (Cost 2014; Interiano 2017; Janeczko 2015; Kern 2014; Kostel Bal 2016; Kubiak 2004; Mpofu 1992; Musiol 2016; Rossi 1994; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012), the bedside Schwartz formula (Cozzi 2012; Davidoff 2015; Mavinkurve-Groothuis 2016), the new Schwartz formula (Musiol 2016; Stefanowicz 2011; Stefanowicz 2012), the CKiD Schwartz formula (Interiano 2017), the Modification of Diet in Renal Disease (MDRD) formula (Cozzi 2012; Schiavetti 2015a), the Filler formula (Stefanowicz 2011; Stefanowicz 2012), the Counahan formula (Bardi 2004a; Interiano 2017), or the CKD-EPI formula (Interiano 2015; Schiavetti 2015a). An overview of GFR estimation formulae can be found in Table 2. Five studies used more than one method to assess the GFR: Stefanowicz 2011 compared Tc-99m DTPA clearance with the Filler formula, the Schwartz formula and the new Schwartz formula, whereas Stefanowicz 2012 compared the Filler formula, the old Schwartz formula and the new Schwartz formula, Schiavetti 2015a compared the MDRD formula with the CKD-EPI formula, and Musiol 2016 compared the Schwartz formula with the new Schwartz formula. Interiano 2017 performed a comprehensive assessment of renal function by using different GFR assessments (Tc-99m DTPA clearance, Schwartz formula, CKiD Schwartz formula and Counahan formula).

Five studies investigated the GFR, but did not mention the assessment method used (Di Tullio 1996; Indolfi 2001; Mancini 1996; Van Dijk 2010; von Schweinitz 1997).

Studies also varied in the defined cut-off point for glomerular dysfunction: they used values of GFR below 90, 80, 75, 70 and 60 mL/min/1.73m^2. Three studies used a different definition for glomerular dysfunction. Van Dijk 2010 assessed glomerular dysfunction as defined by the CTCAE 3.0. Kishore 2015 defined a decreased GFR as below the reference of healthy individuals. Kern 2014's definition of decreased GFR was 1 standard deviation below age-adjusted published GFR norms. Two studies did not mention the cut-off value for a decreased (e)GFR (Indolfi 2001; von Schweinitz 1997).

Risk factors of eligible studies

Frisk 2002 assessed risk factors for a decreased (e)GFR.

Risk factors of non-eligible studies

Five studies not meeting the inclusion criteria performed risk factor analysis for a diminished (e)GFR (Dekkers 2013; Knijnenburg 2012; Mulder 2013; Mudi 2016; Van Why 1991). Among these studies there was a large variation in the methods used to estimate GFR as well: MDRD formula (Dekkers 2013), Schwartz formula (Knijnenburg 2012; Van Why 1991), bedside Schwartz formula (Mudi 2016), and CKD-EPI formula (Knijnenburg 2012; Mulder 2013).

Proteinuria

Prevalence

Twenty-three studies reported proteinuria, and used a variety of urinary protein measurements to investigate it. Two studies reported more than one proteinuria measure: Stefanowicz 2011 reported on the urinary albumin-to-creatinine ratio and the urinary albumin level, whereas Levitt 1992 reported on microalbuminuria and urinary albumin-creatinine ratio.

Albuminuria

Prevalence

Nine studies reported on albuminuria and used cut-off points of 20 mg/24 hours (Di Tullio 1996; Indolfi 2001; Makipernaa 1991), 30 mg/24 hours (Schiavetti 2015a; Srinivas 1998) or 20 mg/L (Bardi 2004a; Mancini 1996; Stefanowicz 2011; Stefanowicz 2012). Four studies did not mention any cut-off value (Janeczko 2015; Levitt 1992; Musiol 2016; Wikstad 1986). Six studies reported urinary albumin-to-creatinine ratios (U-ACR) and used cut-off points of 2 mg/mmol (Chevallier 1997; Cozzi 2005), 10 mg/mmol (Bailey 2002), 20 mg/mmol (Mpofu 1992) and 30 mg/g (i.e. 3.33 mg/mmol

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(Stefanowicz 2011)). One study did not mention a cut-off value for the U-ACR (Levitt 1992).

Total proteinuria

Prevalence

Two studies measured qualitative proteinuria by use of a dipstick (Interiano 2015; Interiano 2017). Sudour 2012 considered treatment with angiotensin-converting enzyme inhibitors as proteinuria. Kostel Bal 2016 reported on urinary protein-to-creatinine ratio without mentioning a cut-off point.

Two studies did not further specify how they measured proteinuria (Kishore 2015; Schell 1995).

Risk factors of eligible studies

Studies included for the assessment of proteinuria did not evaluate risk factors.

Risk factors of non-eligible studies

Three studies that were not eligible for the assessment of prevalence investigated risk factors for proteinuria by use of multivariable analysis (Dekkers 2013; Knijnenburg 2012; Ramirez 2016). Dekkers 2013 used different cut-off points depending on micro- and macroalbuminuria and sex; microalbuminuria: U-ACR greater than 3.5 mg/mmol (women) and greater than 2.5 mg/mmol (men), macroalbuminuria: U-ACR greater than 35 mg/mmol (women) and greater than 25 mg/mmol (men). The other studies used a dipstick to measure qualitative proteinuria (Knijnenburg 2012; Ramirez 2016).

Serum phosphate/hypophosphataemia

Prevalence

Eight studies reported serum phosphate levels (Bailey 2002; Frisk 2007; Janeczko 2015; Mancini 1996; Musiol 2016; Othman 2002; Schell 1995; Skinner 2010b). The cut-off value for hypophosphataemia was age-dependent in Frisk 2007 , less than 0.90 mmol/L in Skinner 2010b, less than 0.81 mmol/L in Bailey 2002, and less than 4.49 mEq/L (i.e. 2.25 mmol/L) in Janeczko 2015; four studies did not mention any cut-off value (Musiol 2016; Mancini 1996; Othman 2002; Schell 1995).

Risk factors of eligible studies

The eight studies assessing prevalence of hypophosphataemia did not perform risk factor analysis.

Risk factors of non-eligible studies

One study investigated risk factors for hypophosphataemia and used different cut-off points for children and adults (Knijnenburg 2012). For adults, they used a cut-off value of less than 0.81 mmol/L. For children age-dependent cut-off values were used.

Tubular phosphate regulation parameters

Prevalence

Six studies reported an outcome measure describing tubular phosphate reabsorption. Three studies reported the renal tubular phosphate threshold (TmP/GFR; Bailey 2002; Musiol 2016; Skinner 2010b). The low cut-off value of the renal tubular phosphate threshold was less than 1.0 mmol/L in Bailey 2002, less than 1.15 mmol/L in Musiol 2016, and less than 0.99 mmol/L in Skinner 2010b. Four studies reported the fractional phosphate reabsorption (Chevallier 1997; Musiol 2016; Rossi 1994; Rossi 1997). Rossi 1994 compared the fractional phosphate reabsorption with previously established normal data, Musiol 2016 used less than 85%, and two studies did not report a cut-off value (Chevallier 1997; Rossi 1997). Musiol 2016 used a combination of renal tubular phosphate threshold and fractional phosphate reabsorption.

Risk factors of eligible studies

None of the eligible studies performed multivariable analyses to assess risk factors for a decreased tubular phosphate reabsorption.

Risk factors of non-eligible studies

Studies not fulfilling the inclusion criteria did not analyse risk factors for a decreased tubular phosphate reabsorption.

Serum magnesium/hypomagnesaemia

Prevalence

Four studies assessed hypomagnesaemia by serum magnesium measurements (Bailey 2002; Brock 1991; Musiol 2016; Othman 2002). Brock 1991 used an age-dependent cut-off to define hypomagnesaemia, Othman 2002 used less than 0.80 mmol/L, Bailey 2002 used less than 0.63 mmol/L, and Musiol 2016 did not report which cut-off value they used.

Risk factors of eligible studies

The eligible studies assessing hypomagnesaemia did not evaluate risk factors.

Risk factors of non-eligible studies

Two studies that did not meet the inclusion criteria analysed risk factors for hypomagnesaemia (Knijnenburg 2012; Stohr 2007a). Knijnenburg 2012 used different cut-off values for serum magnesium for male participants (< 0.75 mmol/L), female participants (< 0.71 mmol/L), and children aged under 15 years (< 0.68 mmol/L). Stohr 2007a defined hypomagnesaemia as a serum magnesium level less than 0.70 mmol/L.

Blood pressure

Prevalence

Thirty-two studies investigated blood pressure. Thirty-one studies investigated office blood pressure of CCS (Bailey 2002; Chevallier 1997; Cozzi 2005; Davidoff 2015; Di Tullio 1996; Finklestein 1993; Geenen 2010; Indolfi 2001; Interiano 2015; Interiano 2017; Janeczko 2015; Kantor 1989; Kubiak 2004; Kishore 2015; Kostel Bal 2016; Levitt 1992; Makipernaa 1991; Mancini 1996; Mavinkurve-Groothuis 2016; Mpofu 1992; Paulino 2000; Sasso 2010; Schell 1995; Schiavetti 2015a; Srinivas 1998; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012; Trobs 2001; Van Dijk 2010; Wikstad 1986). Elli 2013 investigated ambulatory blood pressure measurement of CCS compared to matched general population controls. Thirty studies reported high blood pressure or hypertension prevalence and two studies provided only mean/median blood pressure measurements (Mancini 1996; Wikstad 1986). Definition of high blood pressure/hypertension used per study can be found in the Characteristics of included studies.

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Risk factors of eligible studies

Two studies included for prevalence, also presented risk factors for high blood pressure (Geenen 2010; Kantor 1989).

Risk factors of non-eligible studies

Three non-eligible studies performed multivariable analyses (Cardous-Ubbink 2010; Hoffmeister 2010; Knijnenburg 2012). All studies used an office blood pressure measurement, and the definitions of high blood pressure/hypertension are shown in the Characteristics of included studies.

Composite outcome measures

Prevalence

Six studies reported composite outcome measures that included at least one of the six outcome measures mentioned above (Oue 2014; Schiavetti 2015a; Stohr 2007b; Weirich 2004; Van Dijk 2010; von Schweinitz 1997). Two of these used a composite outcome to capture general renal function by defining their own grading system (Oue 2014; Schiavetti 2015a), or by using a set of predefined criteria (Weirich 2004). Two studies used a composite outcome to report on renal tubular function (Stohr 2007b; von Schweinitz 1997); they used their own definitions, combining hypophosphataemia, glycosuria and proteinuria (Stohr 2007b), or tubular phosphate reabsorption and amino acid reabsorption (von Schweinitz 1997). One study combined blood pressure, glomerular- and tubular function in a composite outcome (Van Dijk 2010). Detailed description of the composite outcome measures can be found in the Characteristics of included studies table.

Risk factors of eligible studies

Two studies used multivariable analysis to assess risk factors for, respectively, tubulopathy and nephrological adverse events (Stohr 2007b; Van Dijk 2010).

Risk factors of non-eligible studies

No additional study performed risk factor analyses for composite outcome measures.

Risk of bias in included studies

Data on the risk of bias of the included studies are reported in the Characteristics of included studies section and are summarised in Figure 2 and Figure 3. The criteria for the 'Risk of bias' assessments are listed in Table 1.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

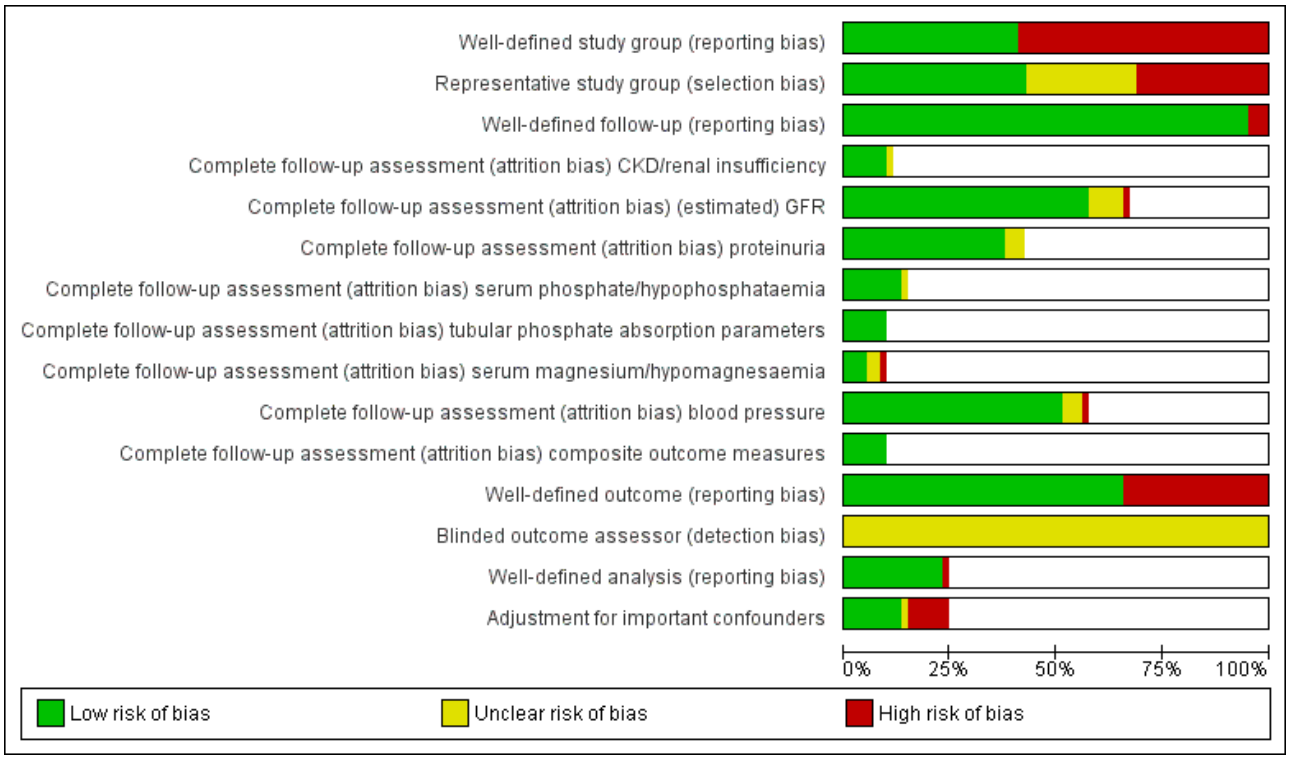

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Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

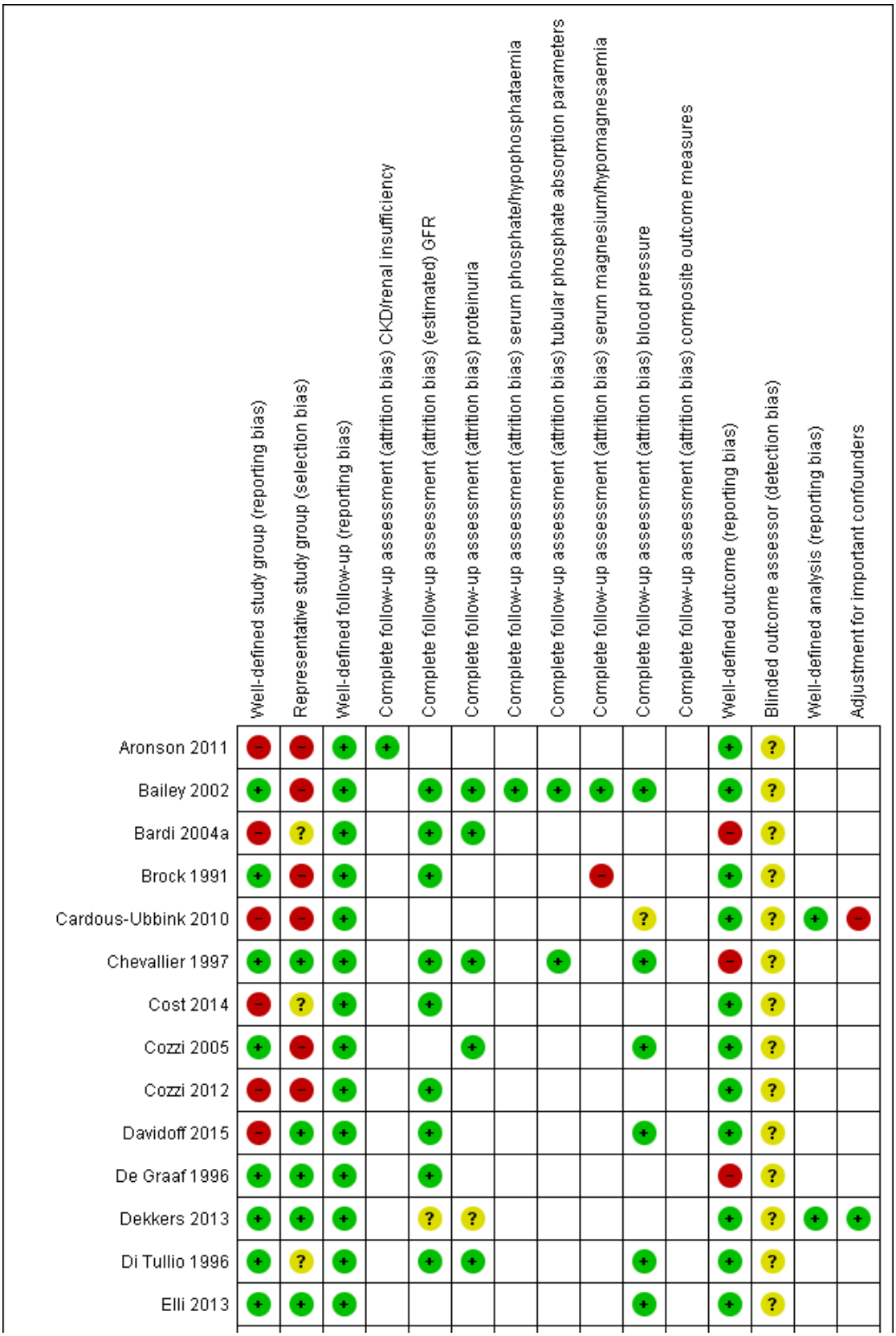

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Figure 3. (Continued)

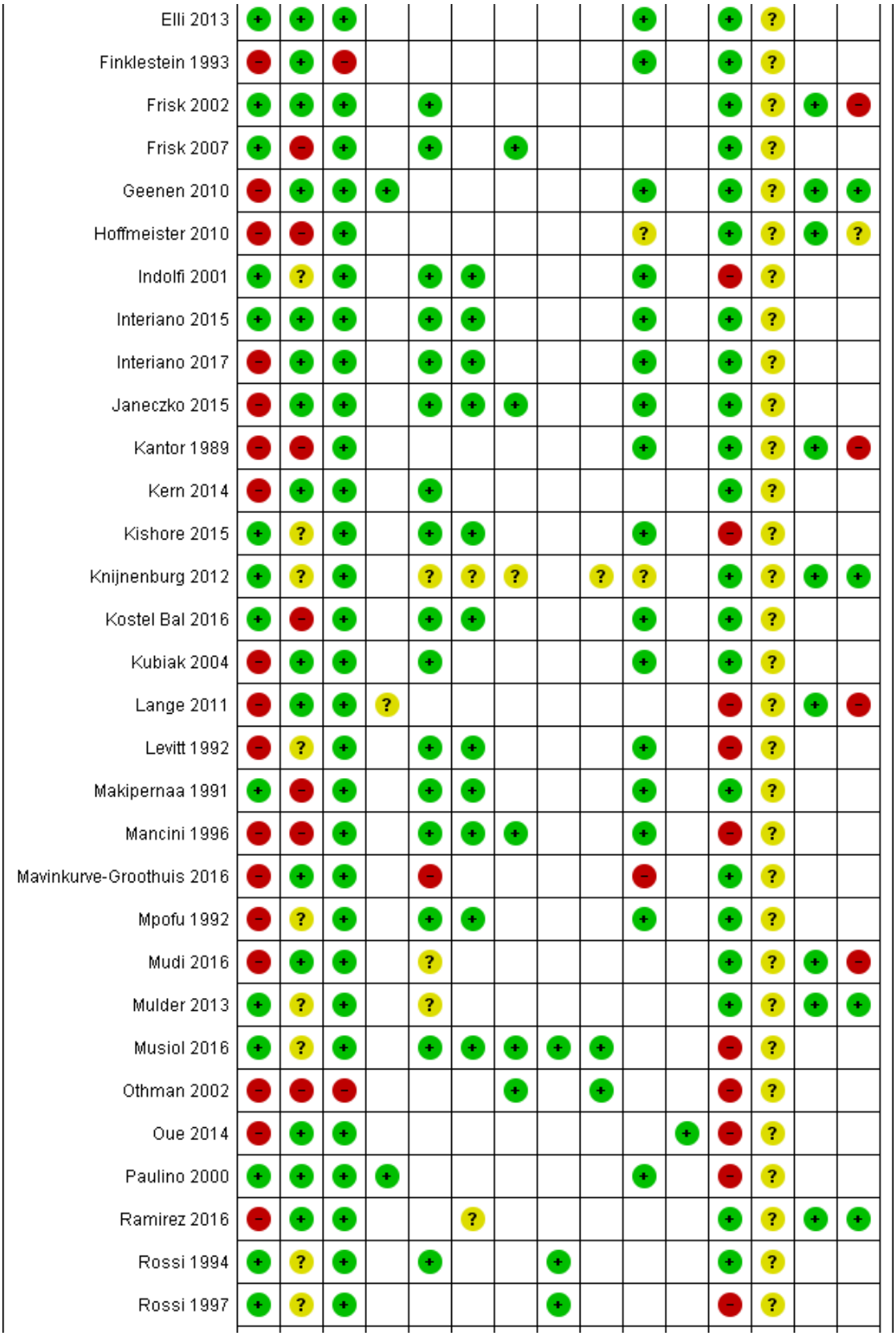

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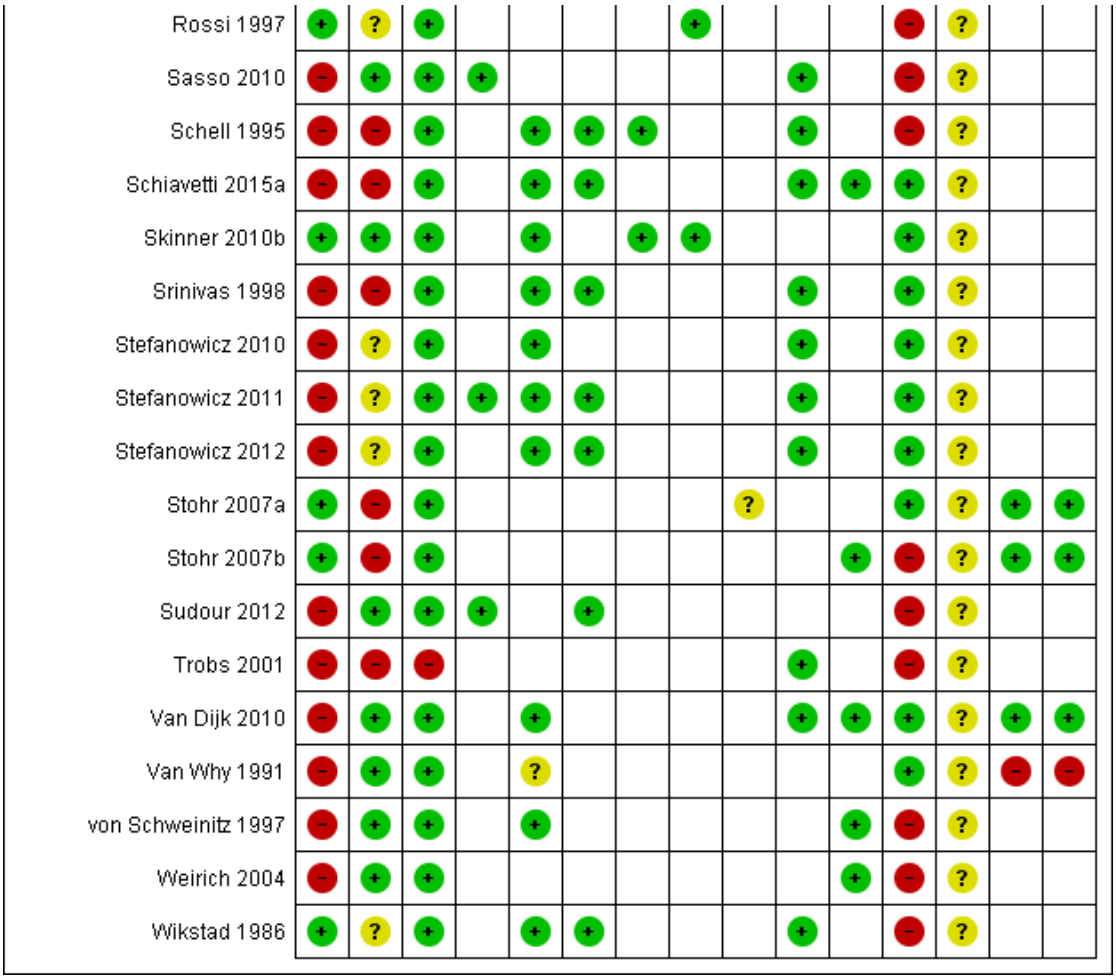
Figure 3. (Continued)



Internal validity

To determine the internal validity of the included studies, we assessed the risks of selection bias, detection bias, attrition bias, and confounding.

Selection bias

Studies included for prevalence (and risk factors if applicable)

Risk of selection bias was low in 22 out of 52 (42.3%), included studies for prevalence (Chevallier 1997; Davidoff 2015; De Graaf 1996; Elli 2013; Finklestein 1993; Frisk 2002; Geenen 2010; Interiano 2015; Interiano 2017; Janeczko 2015; Kern 2014; Kubiak 2004; Lange 2011; Mavinkurve-Groothuis 2016; Oue 2014; Paulino 2000; Sasso 2010; Skinner 2010b; Sudour 2012; Van Dijk 2010; von Schweinitz 1997; Weirich 2004). These studies provided enough information for the review authors to conclude that they consisted of a representative study group, including more than 90% of the original cohort or a random sample of the original cohort. Sixteen studies (30.8%), included less than 90% of the original cohort, and this group did not represent a random sample, resulting in a high risk of selection bias. In the other 14 studies (26.9%), the risk of selection bias was unclear due to unreported size of their original cohort.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

From the nine studies that did not fulfil the inclusion criteria, but performed risk factor analyses, four (44%), had a low risk of selection bias (Dekkers 2013; Mudi 2016; Ramirez 2016; Van Why 1991), three (33%), had a high risk of selection bias (Cardous-Ubbink 2010; Hoffmeister 2010; Stohr 2007a), and it was unclear in two (22%), studies (Knijnenburg 2012; Mulder 2013)

Detection bias

The risk of detection bias, defined as outcome assessment by blinded investigators, could not be determined in any of the 61 studies (0%). Although most of the reported outcomes were not at risk for detection bias, as they represent objective laboratory measurements, some outcomes (e.g. blood pressure) could have been influenced by non-blinded outcome assessors.

Attrition bias

Chronic kidney disease/renal insufficiency

Studies included for prevalence and risk factors (if applicable)

Except for one study (14.3%), for which the risk of attrition bias was unclear due to unclear number of participants with a renal function test (Lange 2011), all the other six studies (85.7%),

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investigating CKD/renal insufficiency had a low risk of attrition bias with adequate follow-up, defined as assessment of outcome parameters in more than 90% of the study group (Aronson 2011; Geenen 2010; Paulino 2000; Sasso 2010; Stefanowicz 2011; Sudour 2012).

(Estimated) glomerular filtration rate

Studies included for prevalence and risk factors (if applicable)

The majority of the studies investigating GFR (29/36; 80.6%), had an adequate follow-up. For six additional studies (16.7%), follow-up was acceptable, with an outcome assessment for 60% to 90% of the study group (Davidoff 2015; Indolfi 2001; Interiano 2017; Makipernaa 1991; Mpofu 1992; von Schweinitz 1997), resulting in a low risk of bias for 35 studies. One study had a high risk of bias, as the outcome parameter was assessed in less than 60% of the study group (Mavinkurve-Groothuis 2016).

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

The five studies assessing risk factors for GFR, but not fulfilling inclusion criteria, had an unclear risk of attrition bias for GFR as the size of the study group of interest is unclear (Dekkers 2013; Knijnenburg 2012; Mudi 2016; Mulder 2013; Van Why 1991)

Proteinuria

Studies included for prevalence and risk factors (if applicable)

Out of 23 studies assessing proteinuria, two studies (8.7%; Bailey 2002; Indolfi 2001), had an acceptable outcome assessment, and 21 studies (91.3%), had an adequate outcome assessment, resulting in a low risk of attrition bias for all studies investigating proteinuria.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

Attrition bias was unclear for the three studies that were not eligible for the review but performed multivariable analyses (Dekkers 2013; Knijnenburg 2012; Ramirez 2016).

Serum phosphate/hypophosphataemia

Studies included for prevalence and risk factors (if applicable)

All eight studies (100%), investigating hypophosphataemia had an adequate outcome assessment (Bailey 2002; Frisk 2007; Janeczko 2015; Mancini 1996; Musiol 2016; Othman 2002; Schell 1995; Skinner 2010b), and therefore a low risk of attrition bias.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

The outcome assessment of Knijnenburg 2012 was unclear, as no separate data for the study group of interest were available, resulting in an unclear risk of bias.

Tubular phosphate absorption parameters

Studies included for prevalence and risk factors (if applicable)

The six studies assessing tubular phosphate absorption parameters all had a low risk of attrition bias, with one study having an acceptable outcome assessment (16.7%; Rossi 1994), and the others having an adequate outcome assessment (83.3%; Bailey 2002; Chevallier 1997; Musiol 2016; Rossi 1997; Skinner 2010b).

Serum magnesium/hypomagnesaemia

Studies included for prevalence and risk factors (if applicable)

Hypomagnesaemia was assessed in more than 90% of the study group in three out of four studies (75%; Bailey 2002; Musiol 2016; Othman 2002), resulting in a low risk of attrition bias for those studies. One study (25%), showed a high risk of attrition bias (Brock 1991), assessing hypomagnesaemia in less than 60% of the study group.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

The two studies not meeting the inclusion criteria, but that performed multivariable analyses for the risk factors of hypomagnesaemia had an unclear risk of attrition bias (Knijnenburg 2012; Stohr 2007a).

Blood pressure

Studies included for prevalence and risk factors (if applicable)

The majority of the studies (26/32; 81.3%), investigating blood pressure had an adequate outcome assessment. In addition, five studies (15.6%), had an acceptable outcome assessment (Bailey 2002; Davidoff 2015; Elli 2013; Finklestein 1993; Indolfi 2001). Thirty-one studies (96.9%), had a low risk of attrition bias, and one study (3.1%), had a high risk of attrition bias (Mavinkurve-Groothuis 2016).

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

Studies assessing risk factors for blood pressure, but not eligible for the rest of the review, had an unclear risk of attrition bias (Cardous-Ubbink 2010; Hoffmeister 2010; Knijnenburg 2012).

Composite outcome measure

Studies included for prevalence and risk factors (if applicable)

Studies using a composite outcome measure all had al low risk of attrition bias with an adequate outcome assessment in four out of six studies (66.7%; Schiavetti 2015a; Stohr 2007b; Van Dijk 2010; Weirich 2004), and an acceptable outcome assessment in two out of six studies (33.3%; Oue 2014; von Schweinitz 1997).

Confounding

Only six of the 52 eligible studies assessed possible risk factors for the development of early or late adverse renal effects using multivariable analyses (11.5%). The remaining 46 studies did not assess risk factors and could therefore not correct for confounding. In addition, nine non-eligible studies performed risk factor analyses.

Studies included for prevalence and risk factors

Only three out of six studies (50%), adjusted their risk factor analyses adequately for potential confounders (Geenen 2010; Stohr 2007b; Van Dijk 2010), resulting in a low risk of bias. The other half of the studies (50%), that did perform risk factor analyses, did not adequately adjust for possible confounders and hence we scored them as having a high risk of potential bias (Frisk 2002; Kantor 1989; Lange 2011).

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Studies that did not fulfil inclusion criteria, but performed risk factor analysis

The risk of bias for adjustment for potential confounders was low in five out of nine studies (55.6%; Dekkers 2013; Knijnenburg 2012; Mulder 2013; Ramirez 2016; Stohr 2007a). The other three studies (33.3%), had a high risk of potential bias (Cardous-Ubbink 2010; Mudi 2016; Van Why 1991). One study (11.1%), did not mention for which factors multivariable analyses were adjusted and had an unclear risk of bias (Hoffmeister 2010).

External validity

To determine the external validity of the included studies, we assessed four aspects of possible reporting bias in the included studies.

Well-defined study group

Studies included for prevalence and risk factors (if applicable)

As a first requirement, studies had to adequately describe the treatment regimen, including cumulative doses of the chemotherapeutic agents of interest (cisplatin, carboplatin and/or ifosfamide), as well as (cumulative) doses of radiotherapy, as long as these therapies were part of the study's main treatment protocol. Only 21 studies (40.4%), met this criterion and had a low risk of bias (Bailey 2002; Brock 1991; Chevallier 1997; Cozzi 2005; De Graaf 1996; Di Tullio 1996; Elli 2013; Frisk 2002; Frisk 2007; Indolfi 2001; Interiano 2015; Kishore 2015; Kostel Bal 2016; Makipernaa 1991; Musiol 2016; Paulino 2000; Rossi 1994; Rossi 1997; Skinner 2010b; Stohr 2007b; Wikstad 1986). Thirty-one studies (59.6%), provided insufficient or no information on the treatment regimen and we judged them as having a high risk of reporting bias regarding the included study group.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

Four studies specified treatment regimens (44.4%; Dekkers 2013; Knijnenburg 2012; Mulder 2013; Stohr 2007a). These studies had a low risk of bias. Five studies (55.6%), did not meet this criterion, resulting in a high risk of bias.

Well-defined follow-up

Studies included for prevalence and risk factors (if applicable)

The second requirement was to mention the follow-up duration for the study group of interest. This was reported better than the treatment regimen, with only three studies (5.8%), not reporting the exact follow-up period and therefore having a high risk of bias (Finklestein 1993; Othman 2002; Trobs 2001). From these studies, at least 90% of the study group of interest was off-treatment, or we could derive follow-up duration from reported age at treatment and age at time of study, or both. The other 49 studies (94.2%), had a low risk of bias, as they mentioned a minimum, median or mean follow-up period.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

All studies (100%), that did not fulfil the inclusion criteria, but performed risk analyses, had a low risk of bias, as they mentioned follow-up adequately (Cardous-Ubbink 2010; Dekkers 2013; Hoffmeister 2010; Knijnenburg 2012; Mudi 2016; Mulder 2013; Ramirez 2016; Stohr 2007a; Van Why 1991).

Well-defined outcome

Studies included for prevalence and risk factors (if applicable)

Outcome definitions had to be objective, precise and had to include a description of the upper or lower limits of the reported outcome. Studies had to provide outcome definitions for more than 50% of their included outcomes. Although the outcome definitions were highly heterogeneous, 31 out of 52 studies (59.6%), described outcomes objectively and precisely, resulting in a low risk of bias (Aronson 2011; Bailey 2002; Brock 1991; Cost 2014; Cozzi 2005; Cozzi 2012; Davidoff 2015; Di Tullio 1996; Elli 2013; Finklestein 1993; Frisk 2002; Frisk 2007; Geenen 2010; Interiano 2015; Interiano 2017; Janeczko 2015; Kantor 1989; Kern 2014; Kostel Bal 2016; Kubiak 2004; Makipernaa 1991; Mavinkurve-Groothuis 2016; Mpofu 1992; Rossi 1994; Schiavetti 2015a; Skinner 2010b; Srinivas 1998; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012; Van Dijk 2010). The other 21 studies (40.4%), we judged to have a high risk of bias, because they did not provide outcome definitions for most of their included outcomes, or the given definitions were not objective and precise.

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

All nine studies (100%), that performed risk factor analyses, but not being eligible for the rest of the review, had well-defined outcomes, and therefore a low risk of bias (Cardous-Ubbink 2010; Dekkers 2013; Hoffmeister 2010; Knijnenburg 2012; Mudi 2016; Mulder 2013; Ramirez 2016; Stohr 2007a; Van Why 1991).

Well-definded analysis

The last criterion for the external validity assessment was that studies had to provide relevant risk measures for more than 90% of the study group. As mentioned before, six out of 52 eligible studies (11.5%), investigated potential risk factors for the development of early or late adverse renal effects using multivariable analyses. Forty-six studies (88.5%), did not investigate potential risk factors and hence we scored them as having an unclear risk of bias. In addition, nine non-eligible studies investigated potential risk factors for nephrotoxicity.

Studies included for prevalence and risk factors

All six studies (100%), included for prevalence and risk factors had a well-defined risk estimation, resulting in a low risk of bias (Frisk 2002; Geenen 2010; Kantor 1989; Lange 2011; Stohr 2007b; Van Dijk 2010).

Studies that did not fulfil inclusion criteria, but performed risk factor analysis

Out of nine studies, we judged one study to have a high risk of bias despite performing multivariable logistic regression analyses, because they did not present relevant risk measures (Van Why 1991). The other eight studies had a low risk of bias (93.3%; Cardous-Ubbink 2010; Dekkers 2013; Hoffmeister 2010; Knijnenburg 2012; Mudi 2016; Mulder 2013; Ramirez 2016; Stohr 2007a).

Effects of interventions

Chronic kidney disease/renal insufficiency

Seven studies, including at least 244 participants, reported chronic kidney disease (CKD) or renal insufficiency (Aronson 2011; Geenen

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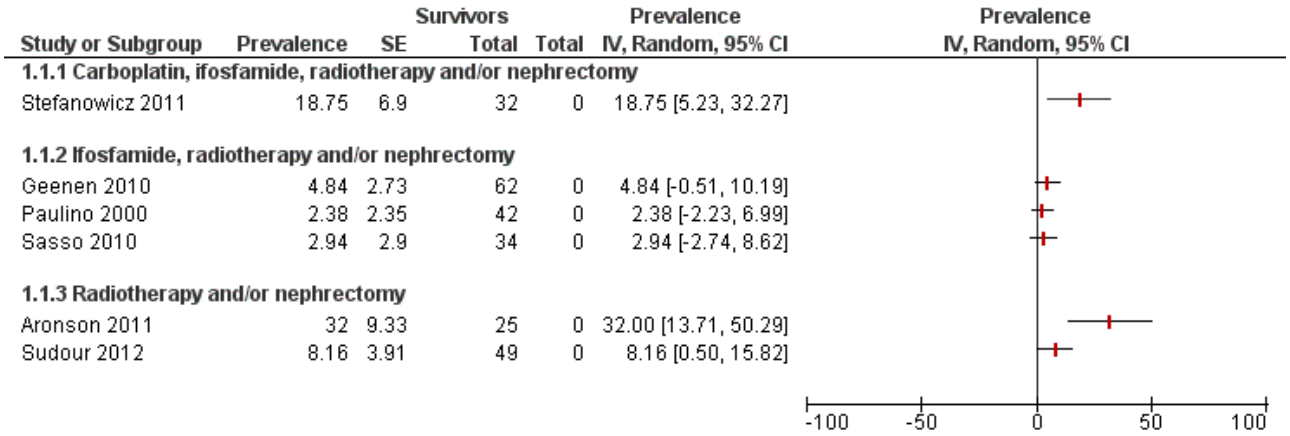
2010; Lange 2011; Paulino 2000; Sasso 2010; Stefanowicz 2011; Sudour 2012). We could not include Lange 2011 in the analysis because it was unclear how many of the 7950 participants of the study group of interest had received a renal function test. Prevalence of CKD/renal insufficiency ranged between 2.4% and 32%. Despite the comparable study population of Wilms' tumour survivors, studies showed large variation in the outcome definitions that they used, follow-up duration, and treatment regimens. Due to high clinical and statistical heterogeneity (I^2 = 66%), it was not feasible to pool data on CKD/renal insufficiency. See also Analysis 1.1 and Figure 4.

Figure 4. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.1, chronic kidney disease/renal insufficiency as defined by study authors. It should be noted that the method used in Review Manager 5 to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%



Risk factors of eligible studies

Lange 2011 showed an increased risk for end-stage renal disease in children with non-WT1 syndromic Wilms' tumour, with predominant stromal histology, an age at diagnosis of less than 24 months, and intralobar nephrogenic rests. See Table 4 for more details.

Risk factors of non-eligible studies

No additional study performed multivariable analyses to assess risk factors for CKD or renal insufficiency.

(Estimated) glomerular filtration rate (GFR)

Cut-off less than 90 mL/minute/1.73 m²

Twelve studies presented a prevalence of decreased GFR using a cut-off value of 90 mL/minute/1.73 m^2 in a total of 432 survivors (Bailey 2002; Cozzi 2012; Davidoff 2015; Interiano 2015; Interiano 2017; Kostel Bal 2016; Kubiak 2004; Musiol 2016; Schiavetti 2015a; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012). Reported prevalences ranged from 0% to 73.7%. Studies varied widely in the methods they used to assess GFR, participant characteristics, follow-up duration, and treatment modalities used. Due to profound clinical and statistical heterogeneity (I^2 = 94%), it was not feasible to pool study results. See also Analysis 1.2 and Figure 5.

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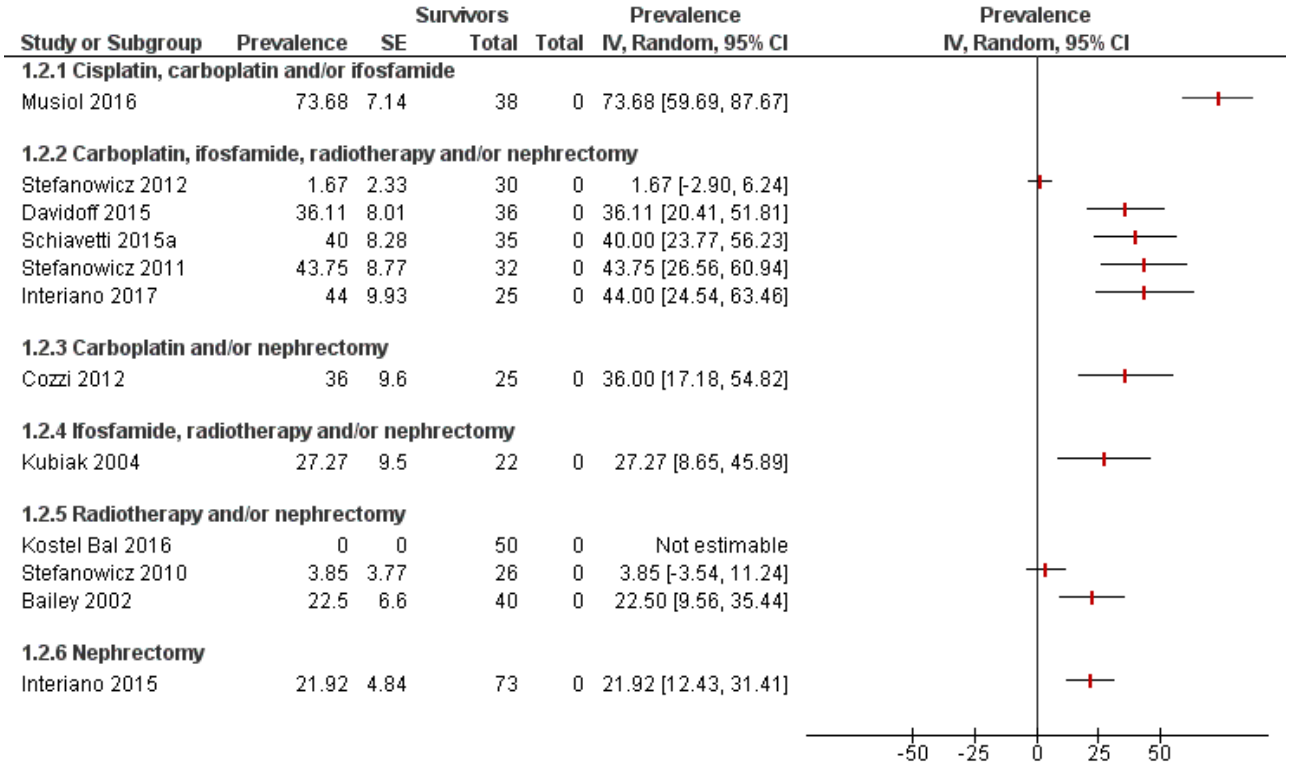
Figure 5. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.2, (estimated) glomerular filtration rate < 90 mL/min/1.73m². It should be noted that the method used in Review Manager 5 to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%



Risk factors of eligible studies

None of the studies included for the assessment of decreased GFR less than 90 mL/minute/1.73 m² evaluated risk factors.

Risk factors of non-eligible studies

Three studies that did not fulfil all the inclusion criteria for this review investigated possible risk factors for glomerular dysfunction, defined as a GFR less than 90 mL/minute/1.73 m² in multivariable analysis (Knijnenburg 2012; Mulder 2013; Mudi 2016). These studies' risk analyses revealed that nephrectomy and ifosfamide were treatment-related risk factors for decreased GFR. Knijnenburg 2012 and Mulder 2013 identified two additional treatment-related risk factors: cisplatin and high-dose (HD) cyclophosphamide. Mulder 2013 also found carboplatin as a risk factor. Knijnenburg 2012 found that a longer follow-up duration was related to a decrease in GFR over time in the total cohort of CCS; Mulder 2013 only found an association with follow-up time for cisplatin, carboplatin and HD-cyclophosphamide. Mulder 2013 also found that an older age at diagnosis when undergoing a nephrectomy was a significant risk factor for a decreased GFR.

The risk factors described above in Knijnenburg 2012 are from analyses including the overall cohort of CCS. They also performed risk factor analyses for mutually exclusive treatment groups. These results can be found in Table 5, together with more detailed information of investigated risk factors by the above mentioned studies.

Cut-off less than 80 mL/minute/1.73 m²

Seven studies with a total of 315 participants used a cut-off value of 80 mL/minute/1.73 m² to assess the GFR (Bailey 2002; Brock 1991; Di Tullio 1996; Levitt 1992; Mpofu 1992; Rossi 1994; Srinivas 1998). Reported prevalences ranged from 0% to 42.5%. Again, studies were clinically incomparable due to differences in the methods used to assess GFR, the diversity of included malignancies and treatment combinations, and dissimilarity of follow-up. Statistical heterogeneity made it impossible to pool these study results as well (I^2 = 82%). See also Analysis 1.3 and Figure 6.

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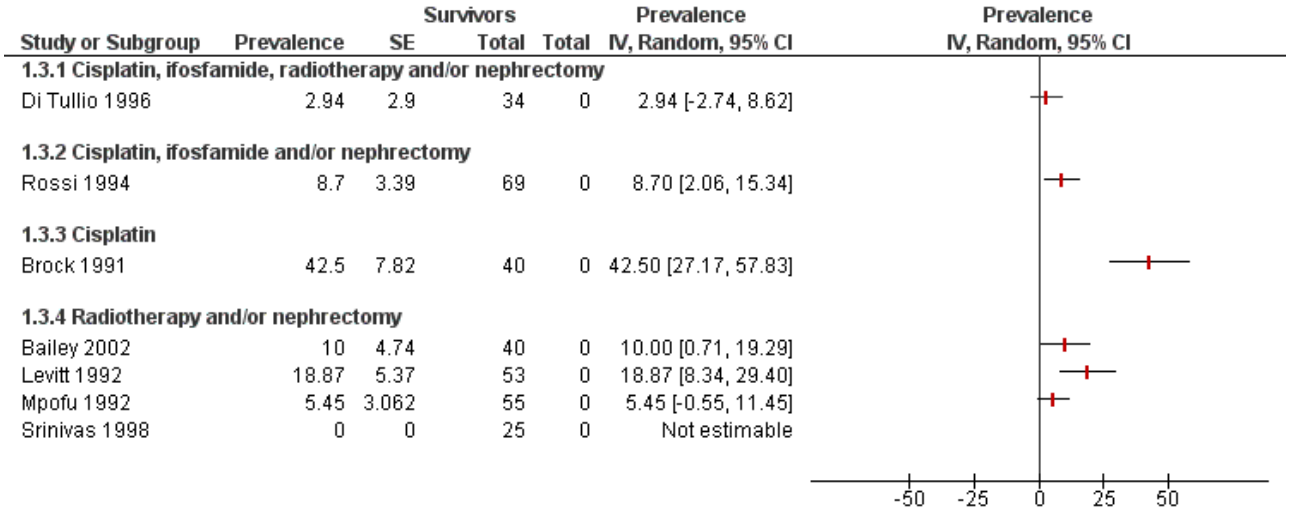
Figure 6. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.3, (estimated) glomerular filtration rate < 80 mL/min/1.73 m². It should be noted that the method used in Review Manager 5 to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%



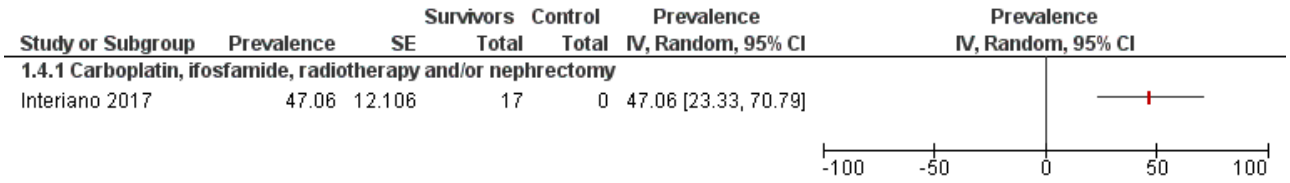
Risk factors

Neither eligible nor non-eligible studies performed risk factor analyses for a decreased GFR defined as less than 80 mL/minute/1.73 m².

Cut-off less than 75 mL/minute/1.73 m²

Interiano 2017 used a cut-off value of 75 mL/minute/1.73 m² for GFR and reported a prevalence of 47.1% in a total cohort of 17 bilateral Wilms' tumour survivors. See also Analysis 1.4 and Figure 7.

Figure 7. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.4 (estimated) glomerular filtration rate < 75 mL/min/1.73m²



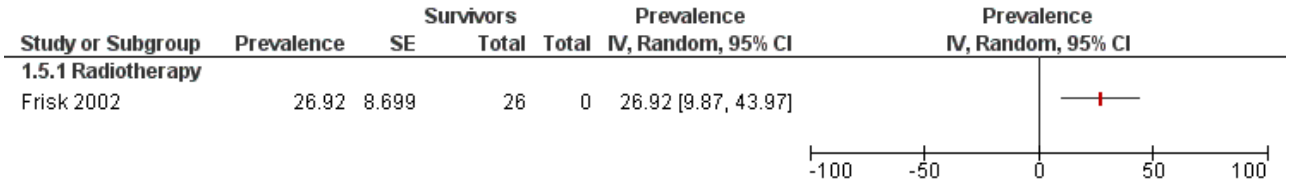
Risk factors

Neither eligible nor non-eligible studies performed risk factor analyses for a decreased GFR defined as less than 75 mL/minute/1.73 m².

Cut-off less than 70 mL/minute/1.73 m²

Frisk 2002 was the only study that used a cut-off value of 70 mL/minute/1.73 m² to assess GFR, and found a prevalence of 26.9% in 26 survivors treated with TBI as a conditioning regimen before autologous bone marrow transplantation. See also Analysis 1.5 and Figure 8.

Figure 8. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.5, (estimated) glomerular filtration rate < 70 mL/min/1.73 m²



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Risk factors of eligible studies

Frisk 2002 also performed multivariable analysis and found that concomitant treatment with aminoglycosides and vancomycin was significantly related to the decrease in GFR among survivors treated with TBI. More detailed information can be found in Table 6.

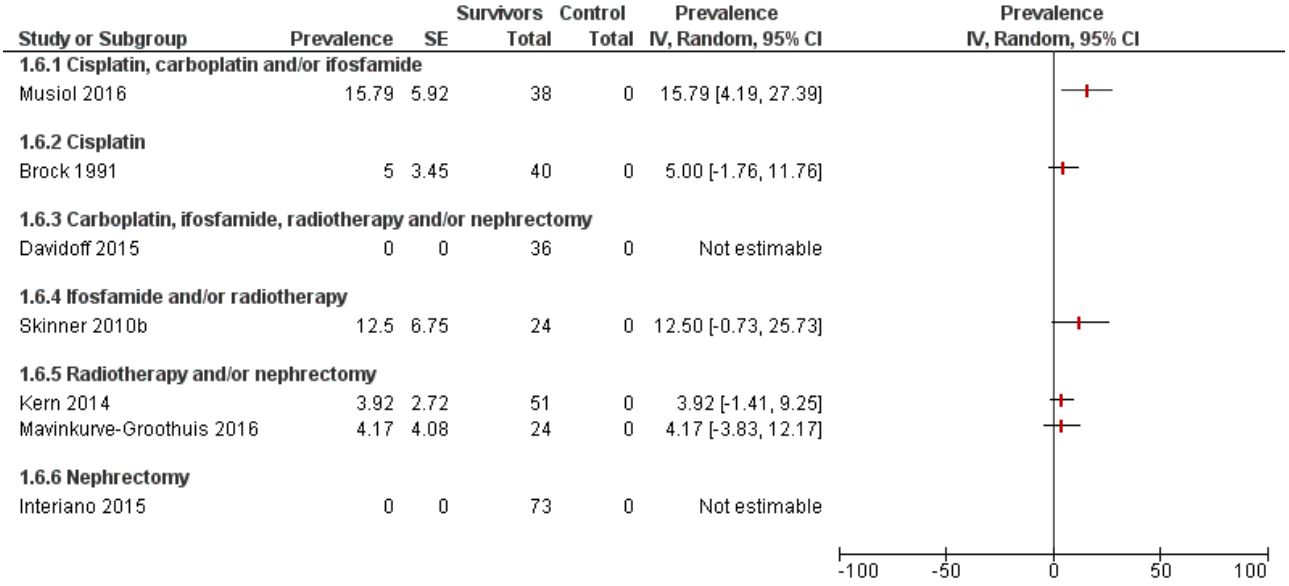
Risk factors of non-eligible studies

No non-eligible studies performed multivariable analyses to investigate risk factors for a GFR less than 70 mL/minute/1.73 m^2.

Cut-off less than 60 mL/minute/1.73 m^2

Seven studies used a cut-off value of 60 mL/minute/1.73 m^2 and prevalence ranged between 0% and 15.8% in a total of 286 participants (Brock 1991; Davidoff 2015; Interiano 2015; Kern 2014; Mavinkurve-Groothuis 2016; Musiol 2016; Skinner 2010b). Analysis showed low statistical heterogeneity (I^2 = 12%). However, due to clinical heterogeneity consisting of variation in the assessment of GFR, the follow-up duration, the study population and the received treatment, we could not pool study results. See also Analysis 1.6 and Figure 9.

Figure 9. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.6, (estimated) glomerular filtration rate < 60 mL/min/1.73m². It should be noted that the method used in Review Manager 5 to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%



Risk factors of eligible studies

No eligible studies performed risk factor analyses for glomerular dysfunction with a GFR less than 60 mL/minute/1.73 m^2.

Risk factors of non-eligible studies

Dekkers 2013 was the only study not eligible for the assessment of prevalence that investigated risk factors for glomerular dysfunction defined as a GFR less than 60 mL/minute/1.73 m^2. Treatment modalities that were associated with a decreased GFR in multivariable analysis included nephrectomy with or without abdominal radiotherapy, HD-ifosfamide, and HD-cisplatin. The definitions used for high-doses and more details about the investigated risk factors for decreased GFR can be found in Table 5.

Other definition or definition of decreased GFR not mentioned

Five studies did not mention a definition of decreased GFR or used a different definition from the above (Indolfi 2001; Kern 2014; Kishore 2015; Van Dijk 2010; von Schweinitz 1997). These studies included 329 CCS in total, and prevalence ranged from 0% to 20.7%. Studies varied in the assessment of GFR, the outcome definition, follow-up time, and types of paediatric malignancies included and their treatment. This resulted in clinical heterogeneity. Together with statistical heterogeneity (I^2 = 64%), it was not feasible to pool results. Results are shown in Analysis 1.7 and Figure 10.

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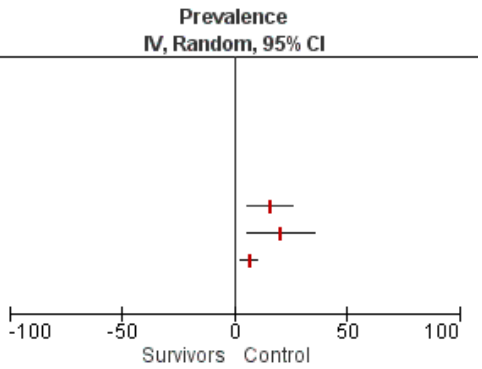
Figure 10. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome, 1.7 (estimated) glomerular filtration rate: other definition or definition not mentioned

Study or Subgroup	Prevalence	SE	Survivors Total	Control Total	Prevalence IV, Random, 95% CI
1.7.1 Cisplatin and/or ifosfamide					
von Schweinitz 1997	0	0	41	0	Not estimable
1.7.2 Radiotherapy and/or nephrectomy					
Indolfi 2001	0	0	27	0	Not estimable
Kern 2014	15.69	5.1	51	0	15.69 [5.69, 25.69]
Kishore 2015	20.69	7.52	29	0	20.69 [5.95, 35.43]
Van Dijk 2010	6.63	1.85	181	0	6.63 [3.00, 10.26]



Risk factors of eligible studies

The five studies that had a different definition of decreased GFR did not investigate risk factors for glomerular dysfunction.

Risk factors of non-eligible studies

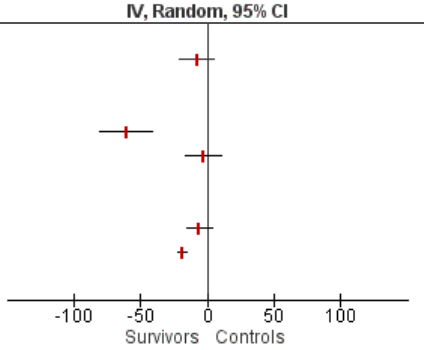
Van Why 1991 investigated 39 survivors treated with a bone marrow transplant (BMT). They defined glomerular dysfunction as a GFR less than 50 mL/minute/1.73 m^2 or doubling of baseline serum creatinine concentration. Treatment with TBI, amphotericin B and cyclosporin A 60 days after BMT were independent predictors for late renal insufficiency. More detailed information, together with non-significant risk factors, is shown in Table 5.

Comparison of GFR

Five studies reported a mean GFR at follow-up in 126 CCS in comparison with 172 controls (Bardi 2004a; Mavinkurve-Groothuis 2016; Schell 1995; Stefanowicz 2012; Wikstad 1986). All studies investigated Wilms' tumour survivors who received a unilateral nephrectomy. Bardi 2004a noted the most profound decrease in GFR. After a median follow-up of seven years, Wilms' tumour survivors had a mean GFR of 71 mL/minute/1.73 m^2 at follow-up; a decrease of 61 mL/minute/1.73 m^2 in comparison with controls without any renal or urinary tract disease. Two studies used a control group of children who received a unilateral nephrectomy for non-malignant disease and both found a non-significant difference (Mavinkurve-Groothuis 2016; Schell 1995). Wikstad 1986 reported a difference between Wilms' tumour survivors and healthy controls (−18.9 mL/minute/1.73 m^2), as well as a significant difference between Wilms' tumour survivors and children nephrectomised for hydronephrosis (−10.6 mL/minute/1.73 m^2). Stefanowicz 2012 compared Wilms' tumour survivors with children with unilateral renal agenesis, which showed a non-significant mean difference of −2.7 mL/minute/1.73m^2. It was not feasible to pool these study results due to clinical and statistical heterogeneity (I^2 = 87%), including variation in GFR measurement, received treatment, follow-up duration, and different control groups. See also Analysis 2.1 and Figure 11.

Figure 11. Forest plot of comparison 2. Mean glomerular filtration rate in mL/min/1.73 m^2 at least 1 year after diagnosis, outcome 2.1, mean (estimated) glomerular filtration rate in studies that included internal or healthy controls

Study or Subgroup	Mean Difference	SE	Survivors Total	Controls Total	Mean Difference IV, Random, 95% CI
2.1.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schell 1995	-8	6.46	21	6	-8.00 [-20.66, 4.66]
2.1.2 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Bardi 2004a	-61	10.28	22	86	-61.00 [-81.15, -40.85]
Stefanowicz 2012	-2.7	7.04	30	17	-2.70 [-16.50, 11.10]
2.1.3 Radiotherapy and/or nephrectomy					
Mavinkurve-Groothuis 2016	-6	4.81	31	57	-6.00 [-15.43, 3.43]
Wikstad 1986	-18.9	1.64	22	6	-18.90 [-22.11, -15.69]



Proteinuria

The prevalence of proteinuria ranged between 3.5% and 84%, and was reported in 22 studies with a total of 851 participants (Bailey 2002; Bardi 2004a; Chevallier 1997; Cozzi 2005; Di Tullio 1996; Indolfi 2001; Interiano 2015; Interiano 2017; Janeczko 2015; Kishore 2015; Kostel Bal 2016; Levitt 1992; Makipernaa 1991; Mancini 1996; Mpofu 1992; Musiol 2016; Schell 1995; Schiavetti 2015a; Srinivas 1998; Stefanowicz 2011; Stefanowicz 2012; Sudour 2012). Wikstad 1986 did not provide prevalence of proteinuria in their cohort and we could not, therefore, include it in our analysis. It should be noted that the 23 studies that reported proteinuria used five different

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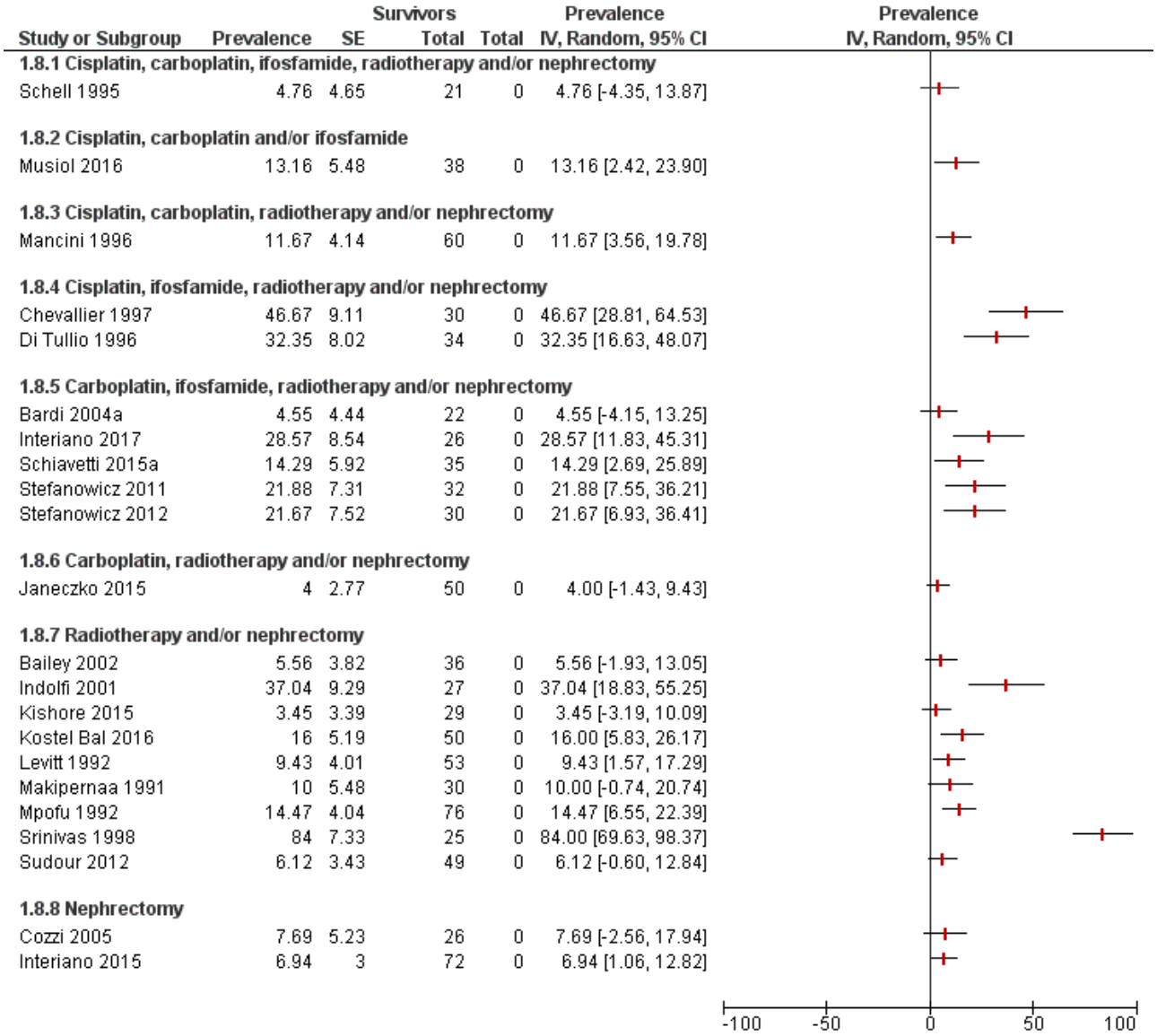
methods of proteinuria assessment, and outcome definitions varied. In addition, there was a lot of variation in follow-up duration, study population, and treatment combinations. Because of clinical and high statistical heterogeneity, it was not possible to pool results (I^2 = 87%). See also Analysis 1.8 and Figure 12.

Figure 12. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.7, proteinuria as defined by study authors. It should be noted that the method used in Review Manager 5 to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%



Risk factors of eligible studies

None of the eligible studies assessed risk factors for proteinuria using multivariable analysis.

Risk factors of non-eligible studies

Three studies that did not meet the inclusion criteria, investigated risk factors for proteinuria, whilst correcting for possible confounders (Dekkers 2013; Knijnenburg 2012; Ramirez 2016). It should be noted that these studies were not comparable with regard to the definition and assessment of proteinuria. Dekkers 2013 showed that participants treated with HD-cisplatin or a combination treatment of nephrectomy and abdominal radiotherapy, had a higher risk of developing proteinuria. Ramirez 2016 found that significant risk factors for proteinuria were HD-ifosfamide and TBI. Knijnenburg 2012 revealed ifosfamide as the only risk factor for proteinuria in the total cohort of CCS. Reported risk factors by Knijnenburg 2012 when assessing mutually exclusive treatment groups are shown in Table 7, together with more detailed information on the other multivariable analyses.

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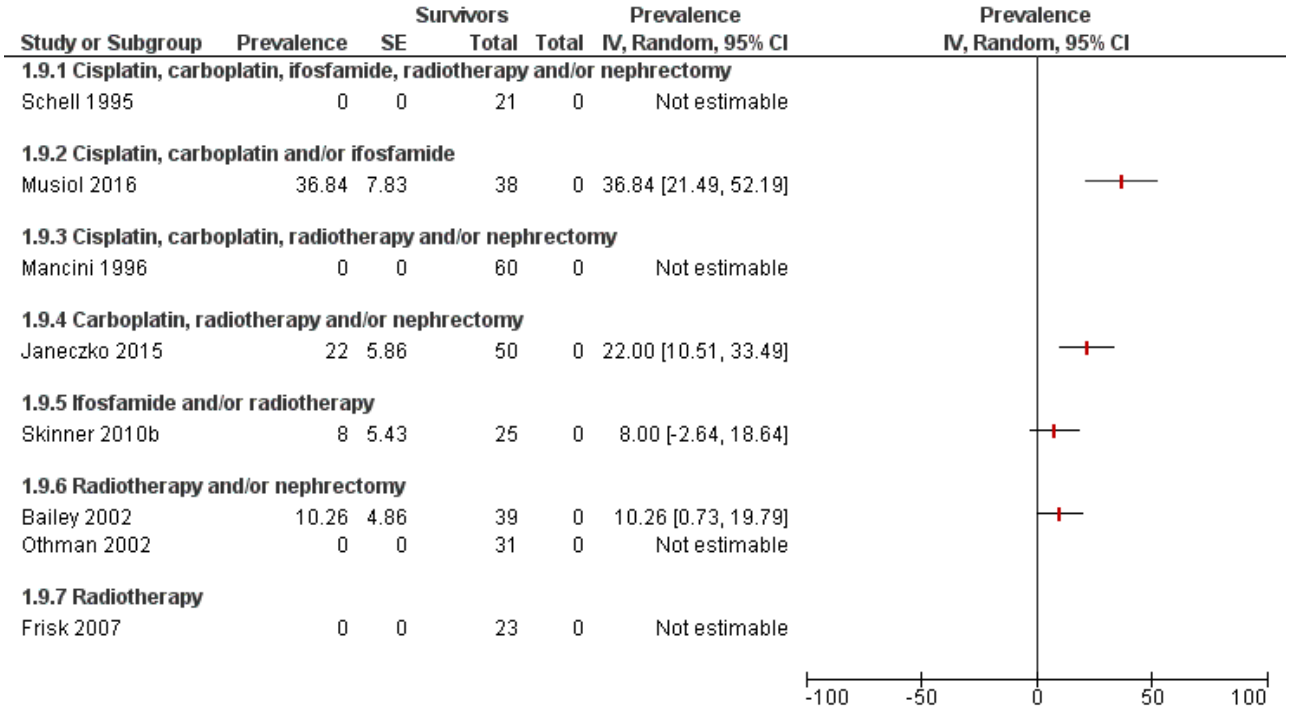
Serum phosphate/hypophosphataemia

Eight studies investigated serum phosphate levels in 287 survivors and prevalence ranged between 0% and 36.8% (Bailey 2002; Frisk 2007; Janeczko 2015; Mancini 1996; Musiol 2016; Othman 2002; Schell 1995; Skinner 2010b). Results are presented in Analysis 1.9 and Figure 13. Again, variation in outcome definitions, study populations, treatment regimens, and follow-up durations resulted in profound clinical and statistical heterogeneity (I^2 = 74%), precluding pooling of results.

Figure 13. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.8, serum phosphate/hypophosphataemia as defined by study authors. It should be noted that the method used in Reviw Manager to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%



Risk factors of eligible studies

None of the eligible studies investigated risk factors for hypophosphataemia.

Risk factors of non-eligible studies

Only one study that did not meet the inclusion criteria performed a multivariable analysis, but did not find any treatment-related risk factors for hypophosphataemia (Knijnenburg 2012), see also Table 8.

Tubular phosphate regulation parameters

Six studies, including 246 participants, investigated the phosphate reabsorption capacity of the renal tubuli, using fractional phosphate reabsorption or the tubular phosphate threshold as an outcome measure (Bailey 2002; Chevallier 1997; Musiol 2016; Rossi 1994; Rossi 1997; Skinner 2010b). Prevalence ranged between 0% and 62.5%. Results are presented in Analysis 1.10 and Figure 14. It should be noted that participants of the two studies investigating tubular phosphate handling, Rossi 1994 and Rossi 1997, may have been included in multiple studies. Again, variation in outcome definitions, included malignancies and their treatment, and follow-up duration resulted in profound clinical and statistical heterogeneity (I^2 = 58%), making pooling of results unfeasible.

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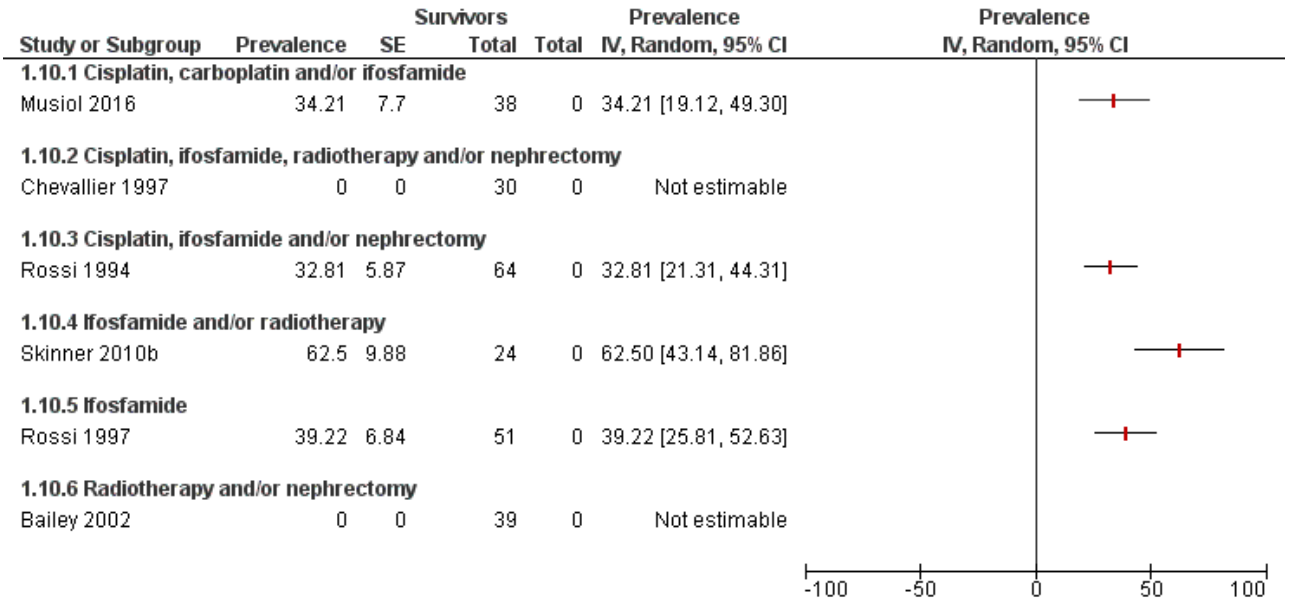
Figure 14. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.9, tubular phosphate regulation parameters as defined by study authors



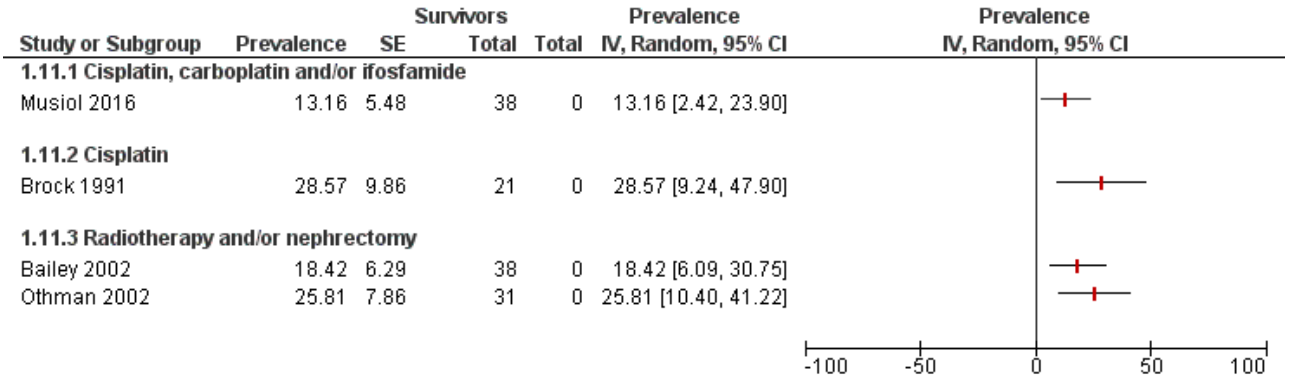
Risk factors

None of the eligible or non-eligible studies performed multivariable analyses to assess risk factors for a decreased tubular phosphate reabsorption.

Serum magnesium/hypomagnesaemia

Four studies, with a total of 128 participants, reported hypomagnesaemia prevalences in CCS, which ranged from 13.2% to 28.6% (Bailey 2002; Brock 1991; Musiol 2016; Othman 2002), as shown in Analysis 1.11 and Figure 15. Follow-up duration ranged from 2.5 to 8.8 years. Othman 2002 did not mention follow-up duration. Despite the statistical analysis finding no statistical heterogeneity (I^2 = 0%), it was not feasible to pool study results due to clinical heterogeneity. This included difference in outcome definitions, study population, treatment modalities, and follow-up duration.

Figure 15. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.10, serum magnesium/ hypomagnesaemia as defined by study authors



Risk factors of eligible studies

None of the eligible studies evaluated risk factors for hypomagnesaemia by use of multivariable analysis.

Risk factors of non-eligible studies

Two studies not fulfilling the inclusion criteria for this review, investigated possible risk factors for hypomagnesaemia, whilst taking into account appropriate measures to prevent confounding (Stohr 2007a; Knijnenburg 2012). It should be mentioned that these studies differed in their definition of hypomagnesaemia. Stohr 2007b found that sarcoma survivors treated with carboplatin or

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cisplatin, or both, had significantly lower serum magnesium levels compared to sarcoma survivors not treated with these compounds. Knijnenburg 2012 showed that cisplatin treatment and having had a nephrectomy were significant risk factors for hypomagnesaemia in a total cohort of CCS. They also found follow-up duration as a significant risk factor. Results of their analysis with mutually exclusive treatment groups can be found in Table 9, as well as more details of the assessed risk factors in multivariable analyses.

Blood pressure

Thirty studies, including 2464 CCS treated with potentially nephrotoxic therapy, reported the prevalence of hypertension or high blood pressure, as defined by the study authors (Bailey 2002; Chevallier 1997; Cozzi 2005; Davidoff 2015; Di Tullio 1996; Elli 2013; Finklestein 1993; Geenen 2010; Indolfi 2001; Interiano 2015; Interiano 2017; Janeczko 2015; Kantor 1989; Kishore 2015; Kostel Bal 2016; Kubiak 2004; Levitt 1992; Mavinkurve-Groothuis 2016; Makipernaa 1991; Mpofu 1992; Paulino 2000; Sasso 2010; Schell 1995; Schiavetti 2015a; Srinivas 1998; Stefanowicz 2010; Stefanowicz 2011; Stefanowicz 2012; Trobs 2001; Van Dijk 2010). We could not include two studies in the analysis, because they did not provide prevalence (Mancini 1996; Wikstad 1986). Prevalence of hypertension ranged from 0% (Bailey 2002; Chevallier 1997; Di Tullio 1996; Indolfi 2001; Mavinkurve-Groothuis 2016; Schell 1995; Srinivas 1998) to 50% (Davidoff 2015). In particular, studies that included only radiotherapy and nephrectomy as potentially nephrotoxic treatments investigated hypertension (see Analysis 1.12 and Figure 16). Overall, the differences in outcome definition, study population, treatment, and follow-up duration caused profound clinical and statistical heterogeneity, making it impossible to pool the results (I^2 = 67%).

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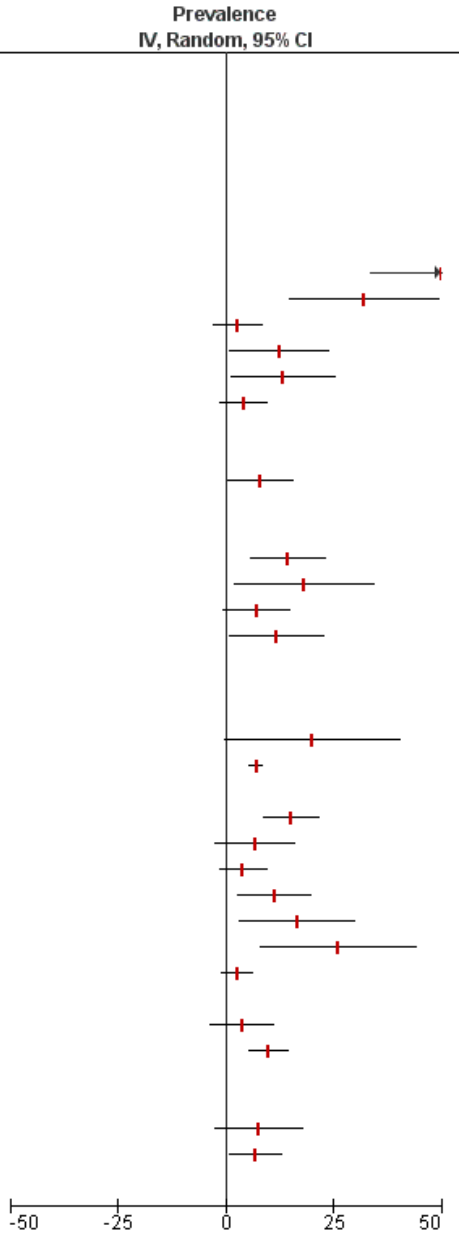
Figure 16. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.11, blood pressure. It should be noted that the method used in Review Manager 5 to calculate 95% confidence intervals is not accurate in percentages close to 0, leading to confidence intervals that are below 0%

Study or Subgroup	Prevalence	SE	Survivors Total	Total	Prevalence IV, Random, 95% CI
1.12.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schell 1995	0	0	21	0	Not estimable
1.12.2 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy					
Chevallier 1997	0	0	30	0	Not estimable
Di Tullio 1996	0	0	34	0	Not estimable
1.12.3 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Davidoff 2015	50	8.33	36	0	50.00 [33.67, 66.33]
Interiano 2017	32.14	8.82	28	0	32.14 [14.85, 49.43]
Schiavetti 2015a	2.86	2.82	35	0	2.86 [-2.67, 8.39]
Stefanowicz 2011	12.5	5.85	32	0	12.50 [1.03, 23.97]
Stefanowicz 2012	13.33	6.21	30	0	13.33 [1.16, 25.50]
Trobs 2001	4.08	2.83	49	0	4.08 [-1.47, 9.63]
1.12.4 Carboplatin, radiotherapy and/or nephrectomy					
Janeczko 2015	8	3.84	50	0	8.00 [0.47, 15.53]
1.12.5 Ifosfamide, radiotherapy and/or nephrectomy					
Geenen 2010	14.52	4.47	62	0	14.52 [5.76, 23.28]
Kubiak 2004	18.18	8.22	22	0	18.18 [2.07, 34.29]
Paulino 2000	7.14	3.97	42	0	7.14 [-0.64, 14.92]
Sasso 2010	11.76	5.52	34	0	11.76 [0.94, 22.58]
1.12.6 Radiotherapy and/or nephrectomy					
Bailey 2002	0	0	36	0	Not estimable
Elli 2013	20	10.33	15	0	20.00 [-0.25, 40.25]
Finklestein 1993	7.09	0.75	1171	0	7.09 [5.62, 8.56]
Indolfi 2001	0	0	27	0	Not estimable
Kantor 1989	15.13	3.29	119	0	15.13 [8.68, 21.58]
Kishore 2015	6.9	4.71	29	0	6.90 [-2.33, 16.13]
Kostel Bal 2016	4	2.77	50	0	4.00 [-1.43, 9.43]
Levitt 1992	11.32	4.35	53	0	11.32 [2.79, 19.85]
Makipernaa 1991	16.67	6.8	30	0	16.67 [3.34, 30.00]
Mavinkurve-Groothuis 2016	26.09	9.16	23	0	26.09 [8.14, 44.04]
Mpofu 1992	2.63	1.84	76	0	2.63 [-0.98, 6.24]
Srinivas 1998	0	0	25	0	Not estimable
Stefanowicz 2010	3.85	3.77	26	0	3.85 [-3.54, 11.24]
Van Dijk 2010	9.94	2.22	181	0	9.94 [5.59, 14.29]
1.12.7 Nephrectomy					
Cozzi 2005	7.69	5.23	26	0	7.69 [-2.56, 17.94]
Interiano 2015	6.94	3	72	0	6.94 [1.06, 12.82]



Risk factors of eligible studies

Two eligible studies reported risk factors for hypertension as a result of multivariable analysis (Geenen 2010; Kantor 1989). No significant risk factors were found by Kantor 1989. Geenen 2010 showed that an older age at time of screening and treatment with abdominal irradiation were associated with hypertension. Please note that these studies used different definitions of hypertension. More details of the risk factor analyses for hypertension can be found in Table 10.

Risk factors of non-eligible studies

Risk factors for hypertension were also investigated by three studies not fulfilling the inclusion criteria of this review (Cardous-Ubbink 2010; Hoffmeister 2010; Knijnenburg 2012). All studies showed an association of a higher body mass index with hypertension. In addition, Hoffmeister 2010 revealed the following significant risk factors for hypertension: acute kidney injury; TBI; stem cell donor type; and growth hormone therapy. One determinant significantly decreased the risk of hypertension: previous hepatitis C infection. Significant risk factors in the total cohort of CCS in Knijnenburg 2012 were abdominal radiotherapy, age at diagnosis, longer follow-up time, and male gender. Table

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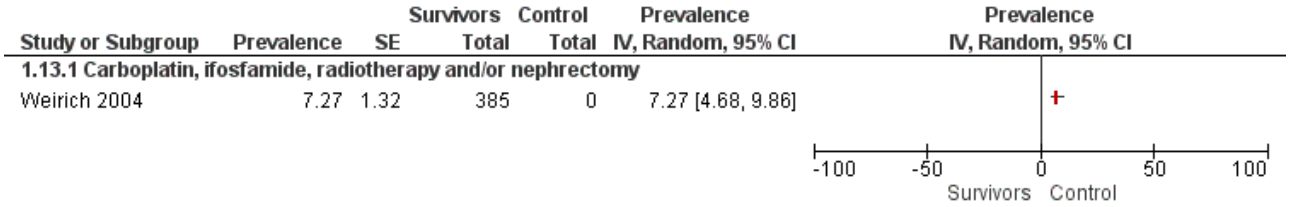
11 lists all risk factors investigated in these studies, as well as Knijnenburg 2012's multivariable analysis results with mutually exclusive treatment groups.

Composite outcome measures

Six studies including 1260 survivors reported on renal toxicity by using a composite outcome that incorporated one of the included outcome measures for this review (Oue 2014; Schiavetti 2015a; Stohr 2007b; Van Dijk 2010; von Schweinitz 1997; Weirich 2004). The content of composite outcomes differed among studies. Therefore, we have described the results separately for each study.

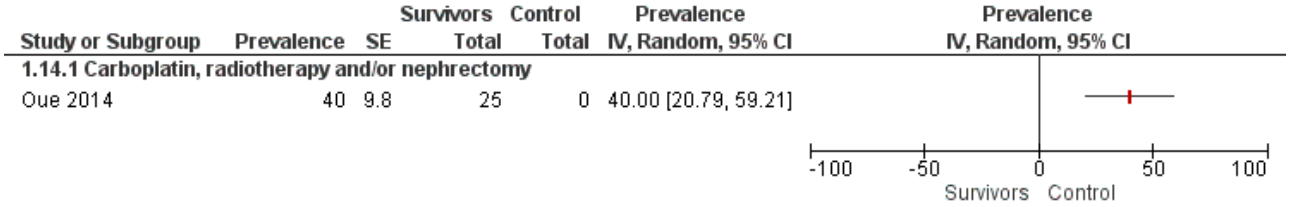
Weirich 2004 used the CTCAE v2 criteria to assess renal and urinary dysfunction and found toxicity in 28 out of 385 (7.3%), Wilms' tumour survivors. Fifteen survivors (3.9%), needed treatment for renal or urinary system impairment; including hypertension, proteinuria, electrolyte wasting, recurrent infections for vesico-urethral reflux, and urinary retention. See also Analysis 1.13 and Figure 17.

Figure 17. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.13, composite outcome as defined by Weirich 2004



Oue 2014 reported a nephrotoxicity prevalence of 40% in a cohort of 25 survivors of bilateral Wilms' tumours, defined as creatinine or BUN level elevated 1.5 times the maximum of the normal range, or both. Results are shown in Analysis 1.14 and Figure 18.

Figure 18. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome:1.14, composite outcome as defined by Oue 2014



Two studies used a composite outcome measure to report on renal tubular function (Stohr 2007b; von Schweinitz 1997). Stohr 2007b assessed ifosfamide toxicity in 593 sarcoma survivors and reported on the prevalence of tubular dysfunction, defined as having at least two of the three following criteria: hypophosphataemia, glycosuria and proteinuria. After a median follow-up period of 12.6 months, 18 of the 593 survivors (3%), were diagnosed with a tubulopathy (see Analysis 1.15 and Figure 19). von Schweinitz 1997 defined a tubulopathy as impaired tubular phosphate reabsorption and/or impaired amino acid reabsorption, although they did not give cut-off values for measurements. Out of 41 assessed hepatoblastoma survivors, seven had tubulopathy (17.1%), after a median follow-up duration of 5.3 years, as is shown in Analysis 1.16 and Figure 20.

Figure 19. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.15, composite outcome as defined by Stohr 2007b

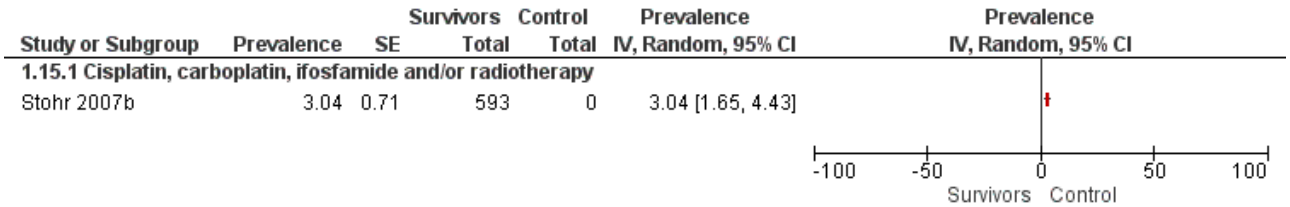


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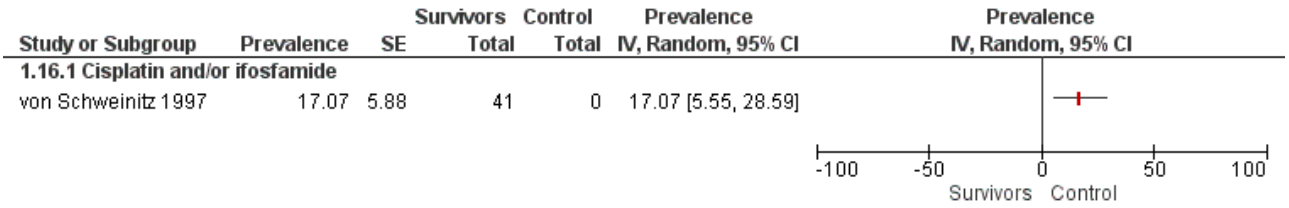
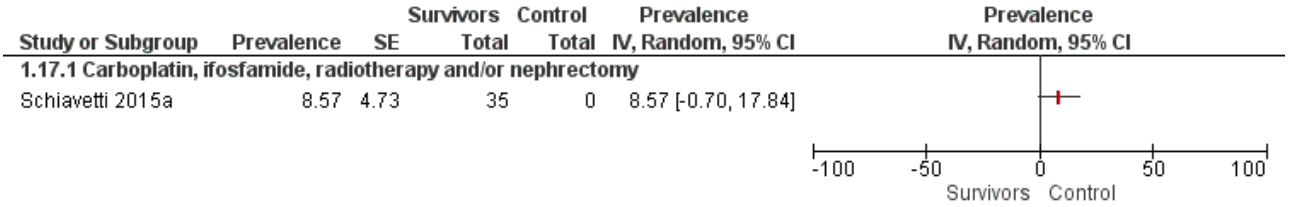
Figure 20. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.16, composite outcome as defined by von Schweinitz 1997



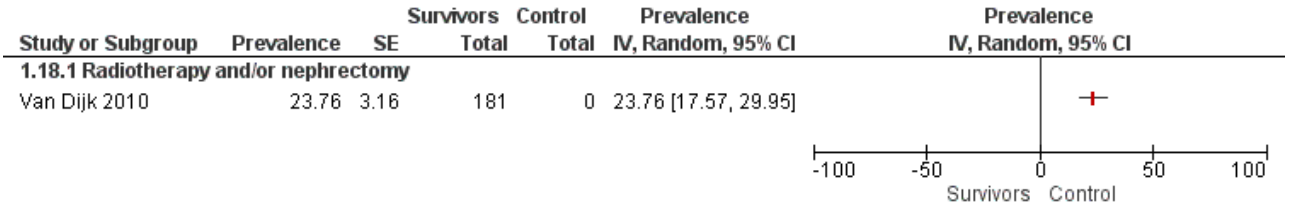
Schiavetti 2015a investigated CKD, defined as abnormalities in kidney structure or function, or a decreased eGFR (Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI)), less than 60 mL/minute/1.73 m^2, for more than three months. They classified three of the 35 renal tumour survivors (8.6%), as having CKD. Results are presented in Analysis 1.17 and Figure 21.

Figure 21. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.17, composite outcome as defined by Schiavetti 2015a



Finally, Van Dijk 2010 combined hypertension, glomerular dysfunction, and tubular dysfunction for the composite outcome nephrological adverse events. As can be seen in Analysis 1.18 and Figure 22, nephrological adverse events were present in 43 out of 181 (23.8%), survivors of Wilms' tumour.

Figure 22. Forest plot of comparison 1. Prevalence of renal dysfunction, outcome 1.18, composite outcome as defined by Van Dijk 2010



Risk factors of eligible studies

Two eligible studies assessed risk factors by use of multivariable analysis for a composite outcome (Stohr 2007b; Van Dijk 2010). Stohr 2007b assessed risk factors for tubulopathy. Associated risk factors were a high dose of ifosfamide and an age at diagnosis under four years. Van Dijk 2010 investigated risk factors for nephrological adverse events in general but found no significant risk factors. Details of the multivariable analyses of composite outcomes are presented in Table 12.

Risk factors of non-eligible studies

No additional studies performed risk factor analysis for a composite outcome.

DISCUSSION

Summary of main results

In this systematic review of the literature, we evaluated all existing evidence on the prevalence of and risk factors for renal dysfunction in CCS treated with potentially nephrotoxic treatments (i.e. ifosfamide, carboplatin, cisplatin, radiotherapy involving the kidney region and nephrectomy). This is an update of the first systematic review, Knijnenburg 2013. We were able to include 24 new studies in this update, together with the 37 remaining studies from the initial review, resulting in a total of 61 studies assessed in this review; 46 for evaluation of prevalence of renal dysfunction, six for assessment of both prevalence and risk factors, and nine studies that did not meet the inclusion criteria, but performed risk factor analysis. The prevalence of adverse renal effects ranged from 0% to 84%. This variation can be explained by variation in included malignancies, prescribed treatments, reported outcome measures and their cut-off values, follow-up duration, and the

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methodological quality of available evidence. Gaps in evidence remain regarding which specific nephrotoxic treatments, and at which doses, put CCS at greatest risk of developing early or late renal adverse effects.

The prevalence of CKD/renal insufficiency ranged between 2.4% and 32%. One eligible study analysed risk factors. Risk factors for end-stage renal disease in non-WT1 syndromic Wilms' tumour patients included being aged under two years at the time of diagnosis, having a predominant stromal histology and intralobar nephrogenic rest. None of the included studies analysed treatment-related risk factors for CKD.

The studies that investigated an impaired (estimated) GFR showed a wide range of prevalence ranging from 0% to 73.7%, regardless of the cut-off value they used. This raises the suspicion that glomerular function deteriorates slowly over time, with end-stage renal disease as the worst outcome. The decline in GFR is a physiological process during the normal aging process. Glomerular function slowly declines with a mean GFR decline rate of 0.95 mL/minute/year after the age of 50 years (Eriksen 2017). Therefore, a GFR below 90 mL/minute/1.73 m^2 usually does not manifest until late adulthood (Hoang 2003), whilst most of the included studies show an increased prevalence of impaired GFR in a relatively young population. This is supported by Mulder 2013, who showed that GFR declined over time in CCS treated with and without potential nephrotoxic therapy with no differences in time trends, but a significant mean difference with a lower GFR in participants treated with nephrotoxic therapy. However, no evident relation could be found between follow-up duration and prevalence rate of decreased (e)GFR among studies included for this review. Very long-term follow-up (> 25 years), studies have not been performed yet, in part because of the low survival rates for paediatric malignancies treated more than 25 years ago. For this reason, it is of great importance to assess glomerular function in these survivors in relation to glomerular function in the normal population in the forthcoming decennia.

Still, the question which of the potential nephrotoxic treatment places CCS at greatest risk for glomerular dysfunction is not fully clarified. Only one eligible study conducted multivariable analysis and found an association of aminoglycosides and vancomycin with decreased GFR in participants receiving TBI. The four non-eligible studies that performed risk analysis in a total cohort of CCS found nephrectomy and (HD)-ifosfamide to be significant risk factors for impaired GFR. In addition, cisplatin was also reported as risk factor in the majority of these studies. For the other treatment-related risk factors, studies were inconclusive. Two non-eligible studies also reported an increased risk of glomerular dysfunction after a longer follow-up period.

Proteinuria is one of the early and sensitive markers for CKD, and it is an independent predictor of mortality in the general population (Matsushita 2010; National Kidney Foundation 2002). The prevalence of proteinuria ranged between 3.5% and 84% in 22 studies. Part of this heterogeneity may be due to the variation of measures used to assess proteinuria. Risk factors for proteinuria were only analysed by non-eligible studies and results were inconsistent. Due to inconsistent results and the heterogeneity between studies, it was not possible to draw any conclusions regarding the prevalence or risk factors for proteinuria. More valid research is needed regarding proteinuria in CCS, as it can be a valuable, non-invasive and low-cost tool for screening purposes.

The literature describes hypophosphataemia in CCS as being most often associated with impairment of proximal tubular reabsorption of phosphate caused by ifosfamide toxicity (Liamis 2010). Hypomagnesaemia and hypokalaemia are associated with renal phosphate wasting, as well as phosphate depletion (Liamis 2010). Hypophosphataemia prevalence varied between 0% and 36.8% among different studies. There was no relation between the prevalence and the variation in treatment modality or follow-up duration; nor did it reflect the definitions of abnormal values provided. A remarkable difference in the prevalence of hypophosphataemia was found in two studies in which the majority of participants received ifosfamide, with prevalences of 35.8% and 8% respectively (Musiol 2016; Skinner 2010b). Although Skinner 2010b reported a relatively low prevalence of hypophosphataemia after a long follow-up period of 10 years, they did observe impaired tubular phosphate reabsorption with a prevalence of 62.5% indicating sub-clinical phosphate wasting. Other studies that solely investigated ifosfamide survivors also reported high prevalences of impaired tubular phosphate reabsorption, ranging from 32.8 to 39.2%. The high prevalence of impaired tubular phosphate reabsorption parameters emphasises the need for longitudinal follow-up to recognise hypophosphataemia and initiate phosphate supplementation in order to prevent osteomalacia in adults and hypophosphataemic rickets in children. The studies did not find any treatment-related risk factors for hypophosphataemia, but multivariable analysis was only performed by one (non-eligible) study.

Damage to the proximal and distal tubulus of the kidney from platinum toxicity caused by cisplatin or carboplatin treatment, or both, can cause (chronic) magnesium wasting, leading to hypomagnesaemia (Lajer 1999). Hypomagnesaemia may result in various symptoms depending on the severity and duration of shortage, ranging from leg cramps and tiredness to seizures and coma (Viering 2017). The prevalence of hypomagnesaemia among 128 participants in four included studies varied between 13.2% and 28.6%, and could not be pooled due to clinical heterogeneity. Two non-eligible studies performed multivariable analysis for hypomagnesaemia (Stohr 2007a; Knijnenburg 2012). They both identified cisplatin as a treatment-related risk factor for reduced serum magnesium. Other risk factors found for hypomagnesaemia are carboplatin, nephrectomy, and follow-up time. However, the two studies were conflicting, and we could not compare results due to differences in the outcome definitions that the studies used. Longitudinal studies with repeated serum magnesium measurements, preferably in a cohort of CCS that included all malignancies and treatments, would provide the opportunity for investigators to assess in greater detail risk factors for hypomagnesaemia and its course.

Uncontrolled hypertension is the number one risk factor associated with high mortality rates throughout the world, as high blood pressure is closely correlated with coronary heart disease and stroke (Beevers 2007; World Health Organization 2002). Many CCS are already at risk for cardiovascular disease from anthracycline- or radiation-induced cardiotoxicity (Kremer 2002; Van Dalen 2006; Van der Pal 2012). In the studies included in this review, the prevalence of hypertension varied between 0% and 50%. Substantial heterogeneity among studies prevented us from performing a meta-analysis. The studies that corrected for possible confounders for hypertension were not concordant either. One out of two eligible studies assessing risk factors showed a

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significant negative effect of radiation therapy and a longer follow-up duration on blood pressure. These risk factors were also found by one non-eligible study, but other studies did not report this association. Hoffmeister 2010 reported that survivors with hepatitis C virus infection were almost 50% less likely to develop hypertension than their HCV-negative counterparts. Although they did not have an explanation for this phenomenon, investigators in a large study of 171,665 veterans reported a similar finding (Butt 2009). Three non-eligible studies showed that higher body mass index was a significant risk factor for hypertension in CCS (Cardous-Ubbink 2010; Hoffmeister 2010; Knijnenburg 2012), a well-known association in the epidemiology of hypertension and cardiovascular disease. Targeting obesity and its related lifestyle factors may be an important approach in the prevention of cardiovascular events and subsequently renal late adverse effects in this population. In addition, future studies should correct for BMI when assessing treatment-related risk factors for hypertension in CCS.

Six studies used a composite outcome that incorporated one of the included outcome measures of this review. However, they all used a different composite outcome, precluding pooling of results. One study that used a composite outcome for renal tubular dysfunction (i.e. hypophosphataemia, glycosuria and/or proteinuria), performed multivariable analysis (Stohr 2007b). HD-ifosfamide and a young age at diagnosis were associated with tubular dysfunction. This finding supports the high prevalences of impaired tubular phosphate reabsorption, a consequence of tubular dysfunction, found by studies investigating CCS treated with ifosfamide in this review.

Overall completeness and applicability of evidence

The studies included in this review varied widely in study population, treatment modalities used, follow-up duration, and reported outcome measures and their definitions, resulting in substantial clinical heterogeneity and precluding pooling of results.

A matter of concern was the large variation in the methods used to determine or estimate the GFR. The studies included in this review used at least 14 different measurement techniques to determine the GFR, either by obtaining renal clearance measurements or by estimating the GFR using estimation formulae based on endogenous markers of renal function (i.e. creatinine, cystatin C, blood urea nitrogen). In addition, they used different cut-off values. When a study used different equations to estimate GFR, we used the arithmetic mean for analysis in this review. We chose this approach because one of the main limitations of the currently available GFR estimation equations is the lack of universality across the multiple clinical settings in which it is applied. This approach is in part supported by several recent studies, which have shown that the average of a cystatin C and a creatinine-based eGFR has higher diagnostic accuracy in comparison with estimations based on a single marker (Den Bakker 2018; Leion 2017). Nevertheless, it should be noted that we also combined more/other eGFR outcomes than used in these studies. Our overall combined measure has not been validated and is not yet a generally accepted measure of renal function.

Four studies showed that there may be large differences in the GFR based on which method or equation is used (Musiol 2016; Schiavetti 2015a; Stefanowicz 2011; Stefanowicz 2012). Depending on the method, these differences were as large as 35.6 mL/minute/1.73 m^2, causing variation in the prevalence of participants with a GFR less than 90 mL/minute/1.73 m^2 between 0% and 43.8% in the same study. In these studies, cystatin C informed significantly better than creatinine in survivors of Wilms' tumour (Stefanowicz 2011; Stefanowicz 2012), and central nervous system malignancies (Musiol 2016). These studies indicate that equations that only use creatinine give an overestimation of glomerular function, which would implicate that the prevalence of glomerular dysfunction is higher than reported in this review. This may be explained by the fact that there is compensatory tubular secretion of creatinine when GFR starts to decline, while cystatin C does not undergo tubular secretion (Roos 2007). Therefore, cystatin C is a more accurate marker than creatinine, in particular for mildly impaired glomerular dysfunction (Hojs 2006; Shlipak 2013). This better diagnostic accuracy of cystatin C was also demonstrated in a cohort of children receiving cancer treatment (Blufpand 2011). A larger cohort study could investigate the value of cystatin C as a marker for eGFR in CCS, as this group may benefit from early detection of glomerular dysfunction to prevent further deterioration by timely intervention. Besides, effort should be put into (international) guideline harmonisation for the follow-up of glomerular function after childhood cancer to facilitate comparability among studies.

The 22 studies investigating proteinuria showed large variation in their outcome measurements as well; at least five different measurements were reported. Four studies measured proteinuria by use of qualitative urine dipstick test, which is inferior to quantitative measurement in collected urine. Current clinical practice guidelines recommend albumin:creatinine ratios and protein:creatinine ratios in untimed urine samples as optimal screening method for evaluating albuminuria or proteinuria (Stevens 2013). This method was used in seven of the 23 studies investigating proteinuria.

Quality of the evidence

We assessed the internal validity of the included studies by applying criteria for selection bias, attrition bias, detection bias and confounding. Assessment of the risk of bias showed that all included studies suffered from methodological limitations. Not a single study stated that investigators blinded the outcome assessor to the treatment exposure. Of course, this may not be applicable to simple laboratory tests, but assessment of blood pressure, for example, would be susceptible to detection bias. Apart from this bias, the methodological quality of studies varied widely. Only three studies assessing prevalence had a low risk of bias on all five remaining criteria listed in Table 1 (Elli 2013; Interiano 2015; Skinner 2010b). Selection bias could not be excluded in 57.7% of all eligible studies. Selection bias may lead to distortion of the observed effects in a study in relationship to the 'real' effect. When a study includes only a non-random subsample of the original cohort, the risk that selection of survivors is based on factors related to the specific outcome of interest, is substantial. The results of such studies should be interpreted with caution, as reported prevalences and risk factors may overestimate or underestimate the real prevalence. If selection bias can be ruled out, attrition bias (incomplete follow-up), poses another threat to the validity of the study. The risk for attrition bias was low in all except for three out of 52 studies included for prevalence in this review.

The last criterion related to the internal validity of studies was confounding. Did studies take important (confounding) variables into account in the analysis of possible risk factors for renal adverse

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outcomes? For the majority of eligible studies for this review, the answer was no; only six studies used multivariable analysis, and three of them corrected adequately for possible confounders. Out of the nine studies assessing risk factors that did not fulfil the inclusion criteria for this review, eight used adequate risk factor analysis and five corrected for possible confounders. This poses a problem for the interpretation of risk factor analyses in the remaining studies. Without control for potential confounders, the results of risk factor analysis may overestimate or underestimate the actual effect.

To a considerable extent, external validity determines the generalisability of study results to other populations or to individual participants. We assessed external validity by applying four criteria of study reporting: the characteristics of the study group, the follow-up duration, the outcome definition and the statistical analysis. Although duration of follow-up was mentioned in most studies, reporting of the other three items was limited. If substantial information is missing regarding the treatment that participants received, the definition of the outcome measured or the statistical relevance of the results, it is difficult to interpret the results of the study correctly. To improve the external validity of studies, authors should adhere to published guidelines regarding high-quality reporting, such as the STROBE statement (von Elm 2007).

Potential biases in the review process

A strength of this Cochrane Review is our comprehensive search strategy, including handsearching of conference proceedings and reference list screening, which limits the risk of selection bias.

This systematic review does have a number of limitations. Although we could translate a number of the articles, we are still waiting for translation of four relevant studies that were not published in English. These language limitations may have resulted in language bias, as it is known that authors of studies are more likely to publish in English if their results are significant (Egger 1997). Selection of outcome measures that had the highest clinical relevance and were reported most often and most consistently also may have introduced reporting bias, as reporting of a certain outcome may be related to the nature and direction of study results. This may have caused selection of outcome measures that showed the most desirable or significant results. However, selection of the outcome measures for this review was predominantly based on clinical relevance and existing screening guidelines for renal function in CCS, such as the guidelines of Skinner 1991. Another limitation is that we included studies with possible overlap of study cohorts. This might have influenced the estimating effect of certain outcomes when pooling data. However, due to large heterogeneity, we did not pool data in this Cochrane Review.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that CCS are at risk for developing early and late adverse renal effects, including CKD/renal insufficiency, impaired (estimated) GFR, proteinuria, hypomagnesaemia, hypophosphataemia, impaired tubular phosphate reabsorption, and arterial hypertension. CCS are advised to be screened for these adverse effects, preferably according to systematic, prespecified protocols based on the treatment modalities provided. Because current evidence is not conclusive regarding possible risk factors for adverse renal effects, we believe that all CCS who receive potentially nephrotoxic therapy, including (partial) unilateral of bilateral nephrectomy, radiotherapy including the kidney region, ifosfamide, cisplatin and carboplatin, need renal function testing at fixed time intervals. A longer follow-up duration was a risk factor for impaired renal function in several studies; therefore, screening could be continued during adulthood. However, recommendations about the exact time interval for renal function surveillance cannot be made based on current evidence. When additional evidence becomes available, treatment regimens and follow-up protocols can be adjusted. Alternatives for nephrotoxic treatment might be explored, yet without compromising the high childhood cancer survival rates. CCS need life-style counselling on topics such as avoidance of obesity and smoking, non-steroidal anti-inflammatory drug (NSAID) use, excessive alcohol use and salt intake, and avoidance of dehydration, to minimise the risk of developing (progressive) kidney disease and/or hypertension (Jones 2008; Nathan 2009).

Implications for research

All studies included in this Cochrane Review showed methodological limitations. Future research on the prevalence of and risk factors for renal dysfunction after childhood cancer should be designed as prospective cohort studies, preferably in large and complete (nationwide) cohorts including information on specific combination of treatments given, as well as cumulative doses. In this Cochrane Review, cyclophosphamide was not systematically reviewed, as it is thought not to induce glomerular toxicity because the metabolism of cyclophosphamide differs from its isomer ifosfamide (Chang 1993). Nevertheless, some studies included in this Cochrane Review did report an association between HD-cyclophosphamide and a decline in GFR in multivariable analyses. Therefore, this possible association could be considered for investigation in a large cohort of CCS and cyclophosphamide might be taken into account as possible nephrotoxic treatment in future systematic reviews. In addition, for future studies and systematic reviews it is advised to focus on nephrotoxicity following treatment with new therapeutic agents as well, such as biologicals.

Very little evidence is available on the development of renal function over time in CCS and very long-term follow-up studies are lacking. Study investigators should perform longitudinal analyses of renal function and, if possible, include a matched control population (preferably siblings) because normative data on glomerular and tubular function in healthy children and in young adults are scarce. The development of adverse renal effects after childhood cancer can have several causes. Therefore, studies should use multivariable analysis to assess risk factors and to correct for possible confounders. As the reporting quality of many of the included studies was inadequate, we recommend that authors of future reports adhere to one of the existing reporting guidelines for clinical studies, such as the STROBE checklist (von Elm 2007). To facilitate comparability among studies an international guideline could be established.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aronson 2011

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants in original cohort: 29; N of participants described study group: 25; N of participants in study group of interest: 25; N of participants with renal function tests: 25 Tumour: bilateral WT: 25/25 (100%). Time period diagnosis/treatment: 1967-2007. % M/F: 28%/72% Age at diagnosis: median: 1.03 years (range 0.27-5.35 years); age at follow-up: median: 15.0 years (range 5.4-34.0 years); follow-up duration: median: 10.5 years (range 5.5-34 years); completion of follow-up: 25/25 (100%) Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 25/25 (100%); NP details: bilateral total NP: 3/25 (12%); unilateral total NP + contralateral partial NP: 14/25 (56%); bilateral partial NP: 8/25 (32%) N of participants RT including the kidney region: 5/25 (20%); RT field: n/m; radiation dose: n/m
Outcomes	**CKD/renal insufficiency** Definition of renal adverse effect: serum creatinine > 1.2 mg/100 mL Observed values of renal adverse effects: median: 0.7 mg/100 mL (range 0.5-2.8) N of participants with renal adverse effect: 8/25 (32%), of whom 5 received a renal transplant (3 after bilateral NP, 2 for ESRD), and 3 with mild renal insufficiency (creatinine > 1.2) **Risk factors** No multivariable risk analysis performed
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type and treatment protocol (SIOP). Possible overlap between the study groups of Geenen 2010, Van Dijk 2010, Aronson 2011 and Cardous-Ubbink 2010

Risk of bias

Bias	Authors' judgement	Support for judgement

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Aronson 2011 *(Continued)*

Well-defined study group (reporting bias)	High risk	Relevant CT and RT regimens were not specified
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was no random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Follow-up duration was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Bailey 2002

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 58; N of participants described study group: 40; N of participants study group of interest: 40; N of participants with renal function tests: 40 for GFR, 36 for proteinuria, 39 for hypophosphataemia, 39 for TmP/GFR, 38 for hypomagnesaemia and 36 for BP Tumour: WT (40/40). Time period diagnosis/treatment: 1966-1998. % M/F: 40%/60% Age at diagnosis: median 4.3 years (range 3 months-11.8 years); age at follow-up: n/m; follow-up duration: median 8.8 years (range 0.06-27.5 years); completion of follow-up: depending on outcome completion of follow-up ranges from 36/40 (90%)-40/40 (100%) Controls: n/a
Interventions	N of participants ifosfamide: 0/40 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/40 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/40 (0%); carboplatin cumulative dose: n/a Other types of CT: actinomycin 34/40 (85%), vincristine 36 (90%), doxorubicin 12 (30%), cyclophosphamide 1/40 (2%); other CT cumulative doses: n/m N of participants NP: 40/40 (100%); NP details: unilateral NP 39/40 (98%), wedge resection 1 kidney and complete removal other 1/40 (2%) N of participants RT including the kidney region: 19/40 (47.5%); RT field: abdominal 5/19 (26%), flank 14/19 (74%); radiation dose: the median dose to the kidney bed (i.e. on tumour side) was 30 Gy (range 19.8 – 34) given in a median of 16 fractions (range 10 – 22). median dose of 3.3 Gy to remaining kidney
Outcomes	**Glomerular filtration rate by 51Cr-EDTA plasma clearance** Definition of renal adverse effect: 1. GFR < 90 mL/min/1.73 m^2 2. GFR < 80 mL/min/1.73 m^2 Observed values of renal adverse effects: median of 100 mL/min/1.73 m^2 (range 61 – 150)

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Bailey 2002 *(Continued)*

N of participants with renal adverse effect:

1. 9/40 (23%) participants had a GFR < 90 mL/min/1.73 m^2
2. 4/40 (10%) had a GFR < 80 mL/min/1.73 m^2

Risk factors

No multivariable risk analysis performed

Proteinuria measured by U-ACR

Definition of renal adverse effect: < 10 mg/mmol

Observed values of renal adverse effects: median 1.43 mg/mmol (range 0.02–46.7)

N of participants with renal adverse effect: 2/36 (5%)

Risk factors

n/m

Serum phosphate/hypophosphataemia

Definition of renal adverse effect: serum phosphate < 0.81 mmol/L

Observed values of renal adverse effects: median 1.3 mmol/L

N of participants with renal adverse effect: 4/39 (10%)

Risk factors

n/m

Tubular phosphate regulation parameters measured by renal tubular phosphate threshold (TmP/GFR)

Definition of renal adverse effect: tmP/GFR ≤ 1.0 mmol/L

Observed values of renal adverse effects: median 1.30 mmol/L (range 0.8 – 2.35)

N of participants with renal adverse effect: no participants had an abnormal fractional excretion in the presence of abnormal serum electrolytes. 0/39 (0%)

Risk factors

n/m

Serum Mg/hypomagnesaemia

Definition of renal adverse effect: serum Mg < 0.63 mmol/L

Observed values of renal adverse effects: median 0.74 mmol/L

N of participants with renal adverse effect: 7/38 (18%)

Risk factors

n/m

BP

Definition of renal adverse effect: n/m

Observed values of renal adverse effects:

1. median SBP 108 mmHg (range 80-120); median z-score related to the medians for age (Task Force, 1987) −0.24 (range −1.51 to 1.80);

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Bailey 2002 *(Continued)*

2. median DBP 70 mmHg (range 46-80 mmHg); median z-score for age 0.23 (range −1.57 to 1.27).

N of participants with renal adverse effect: there were no abnormal SBP or DBPs in the participants studied. 0/36 (0%)

Risk factors

n/m

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of 69 % of original cohort and is not a random sample of original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for 90% of the study group of interest (+)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) tubular phosphate absorption parameters	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum magnesium/hypomagnesaemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for 90% of the study group of interest (+)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for 5/6 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

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Bardi 2004a

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 115; N of participants study group of interest: 22; N of participants with renal function tests: 22 Tumour: WT: 22/22 (100%). Time period diagnosis/treatment: 1984-2001 (total described cohort). % M/F: 57%/43% (total described cohort) Age at diagnosis: median: 5 years (range 0.3-20) (total described cohort); age at follow-up: median: 13 years (range 3-24) (total described cohort); follow-up duration: median: 7 years (range 2-23) (total described cohort); completion of follow-up: 100% Controls: 86 children with no renal or urinary tract disease (46 male/40 female; median age 10 years; age range: 2-20 years)
Interventions	N of participants ifosfamide: 4/22 (18%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/22 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 4/22 (18%); carboplatin cumulative dose: n/m Other types of CT: n/m; CT cumulative doses: n/m N of participants NP: 22/22 (100%); NP details: 21/22 hemiNP, 1/22 polar resection N of participants RT including the kidney region: 11/22 (50%); RT field: flank radiation; radiation dose: n/m
Outcomes	**GFR: estimated glomerular filtration rate by Counahan formula** Definition of renal adverse effect: n/m Observed values of renal adverse effects: 1. Controls: 132 (79) mL/min/1.73 m^2 2. WT: 71 (27) mL/min/1.73 m^2 ($P < 0.05$ vs controls Mean difference WT vs controls -61 (10.28) mL/min/1.73 m^2 N of participants with renal adverse effect: n/m **Risk factors** n/m **Proteinuria measured by microalbuminuria in 24-hurine** Definition of renal adverse effect: > 20 mg/L Observed values of renal adverse effects: mean (SD) in mg/L: WT: 16.6 (2.4); controls: 15.8 (1.2) N of participants with renal adverse effect: WT: 1/22 (4.5%) controls: n/m **Risk factors** n/m
Notes	Cisplatin 0 is an assumption based on tumour type. Only a part of the described cohort were eligible for this Cochrane Review.

Risk of bias

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Bardi 2004a *(Continued)*

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Relevant cumulative CT and RT doses were not specified
Representative study group (selection bias)	Unclear risk	Original cohort size was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definition was not mentioned for 1 of 2 outcome measures
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Brock 1991

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 55; N of participants described study group: 40; N of participants study group of interest: 40; N of participants with renal function tests: 40 for GFR, 21 for hypomagnesaemia. Tumour: NB: 27/40 (68%), germ cell tumour: 8/40 (20%), hepatoblastoma: 3/40 (8%), osteogenic sarcoma: 2/40 (5%). Time period diagnosis/treatment: 1979-1988. % M/F: 62%/38% Age at diagnosis: median: 15 months (range 13 days-13 years 8 months); age at follow-up: n/m; follow-up duration: median: 2.5 years (range 1.5-7); completion of follow-up: 100% for GFR, 52.5% for hypomagnesaemia Controls: n/a
Interventions	N of participants ifosfamide: 0/40 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 40/40 (100%); cisplatin cumulative dose: median: 500 mg/m^2 (range 120-1860) N of participants carboplatin: 0/40 (0%); carboplatin cumulative dose: n/a Other types of CT: NB: cyclophosphamide, vincristine, teniposide-etoposide and HD melphalan; germ cell tumour: bleomycin, vinblastine-etoposide; hepatoblastoma: doxorubicin; osteosarcoma: doxorubicin and MTX; other CT cumulative doses: n/m N of participants NP: 0/40 (0%); NP details: n/a N of participants RT including the kidney region: 0/40 (0%); RT field: n/a; radiation dose: n/a
Outcomes	**Glomerular filtration rate by 51Cr-EDTA clearance**

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Brock 1991 *(Continued)*

Definition of renal adverse effect: GFR < 80 mL/min/1.73 m^2

Observed values of renal adverse effects: median GFR in mL/min/1.73 m^2 (range); end of treatment: 74 (13-184); at follow-up: 90 (27-135)

N of participants with renal adverse effect: end of treatment: 13/40 (33%) 60-80 mL/min/1.73 m^2; 11/40 (28%) < 60 mL/min/1.73 m^2

At follow-up: 15/40 (38%) 60-80 mL/min/1.73 m^2; 2/40 (5%) < 60 mL/min/1.73 m^2

Risk factors
No multivariable risk analysis performed

Serum Mg/hypomagnesaemia

Definition of renal adverse effect: age-specific reference values

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 6/21 (29%)

Risk factors

No multivariable risk analysis performed

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum magnesium/hypomagnesaemia	High risk	Outcome was assessed for < 60% of the study group of interest
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Cardous-Ubbink 2010

Methods **Included for risk factors only**

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Cardous-Ubbink 2010 *(Continued)*

	Nested case-control study
Participants	N of participants original cohort: 1362; N of participants described study group: 1080; N of participants study group of interest: unclear; N of participants with renal function tests: 1080. All following data represent the 44 cases and 123 matched controls (N = 167) Tumour: leukaemia: 26/167 (15.6%), lymphoma: 44/167 (26.3%), WT: 47/167 (28.1%), brain/CNS: 18/167 (10.8%), bone: 9/167 (5.4%), soft tissue sarcoma: 16/167 (9.6%), other: 7/167 (4.2%). Time period diagnosis/treatment: 1966-1996. % M/F: 56%/44% Age at diagnosis: median 7.7 years; age at follow-up: median 28.0 years; follow-up duration: median 20.4 years; completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 9/167 (5.4%); ifosfamide cumulative dose: n/m N of participants cisplatin: 7/167 (4.2%); cisplatin cumulative dose: n/m N of participants carboplatin: 0/167 (0%); carboplatin cumulative dose: n/a Other types of CT: any CT: 146/167 (87.4%). Chemo besides cisplatin/ifosfamide: 134/167 (80.2%); other CT cumulative doses: n/m N of participants NP: 47/167 (28.1%); NP details: n/m N of participants RT including the kidney region: any RT: 102/167 (61.1%); RT field: abdominal RT: 54/167 (32.3%); radiation dose: n/m
Outcomes	**BP** Definition of renal adverse effect: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg at ≥ 3 consecutive visits Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 11
Notes	Unclear how many of the described survivors were originally treated with nephrotoxic treatment according to our inclusion criteria Possible overlap between the study groups of Aronson 2011; Geenen 2010 and Van Dijk 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative CT and RT doses, and NP details were not specified
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) blood pressure	Unclear risk	Study group of interest unclear

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Cardous-Ubbink 2010 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	High risk	Not all important prognostic factors were taken into account using multivariable logistic regression

Chevallier 1997

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 30; N of participants described study group: 30; N of participants study group of interest: 30; N of participants with renal function tests: 30 Tumour: WT 30/30 (100%). Time period diagnosis/treatment: 1986-1993. % M/F: n/m Age at diagnosis: mean 3.4 years (SD 2.5); age at follow-up: n/m; follow-up duration: mean 4.6 years (SD 3.1); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 2/30 (6.6%); ifosfamide cumulative dose: 60 g/m^2 and 3.3 g N of participants cisplatin: 1/30 (3.3%); cisplatin cumulative dose: 35 mg N of participants carboplatin: 0/30 (0%); carboplatin cumulative dose: n/a Other types of CT: vincristine, actinomycin and adriamycin (28/30) and other regimens in 2/30; other CT cumulative doses: n/m N of participants NP: 30/30 (100%); NP details: unilateral NP N of participants RT including the kidney region: 6/30 (20%); RT field: abdomen; radiation dose: 15 Gy + 20 Gy boost to the tumour
Outcomes	**GFR: glomerular filtration rate by inulin clearance** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean GFR 93 mL/min/1.73 m^2 (SD 13) N of participants with renal adverse effect: n/m **Risk factors** No multivariable risk analysis performed **Proteinuria measured by U-ACR** Definition of renal adverse effect: > 2 g/mol Observed values of renal adverse effects: mean (SD): 2.8 g/mol (2.2 g/mol) N of participants with renal adverse effect: 14/30 (47%) had a U-ACR > 2 g/mol **Risk factors**

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Chevallier 1997 *(Continued)*

No multivariable risk analysis performed

Tubular phosphate regulation parameters measured by fractional phosphate reabsorption

Definition of renal adverse effect: n/m.

Observed values of renal adverse effects: mentioned only for subgroups

N of participants with renal adverse effect: 0/30 (0%)

Risk factors

No multivariable risk analysis performed

BP

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 0/30 (0%)

Risk factors
No multivariable risk analysis performed

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) tubular phosphate absorption parameters	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definition was objective but not precise; no cut-off values were mentioned for 3/4 outcomes

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Chevallier 1997 *(Continued)*

Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Cost 2014

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: unclear; N of participants described study group: 30; N of participants study group of interest: 30; N of participants with renal function tests: 30 Tumour: unilateral non-syndromal WT 30/30 (100%). Time period diagnosis/treatment: 2000-2012. % M/F: 53%/47% Age at diagnosis: NSS cohort mean 2.5 years (range 0.19-8.2 years), RN cohort mean 3.7 years (range 0.3-7.4 years); age at follow-up: n/m; follow-up duration: NSS cohort median 8.4 years (range 0.54-31.8 years), RN cohort median 2.1 years (range 0.6-10 years); completion of follow-up: NSS cohort 14/15 (93.3 %), RN cohort 15/15 (100%) Group 1: NSS 15/30 (50%) Group 2: RN 15/30 (50%) Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: presurgical CT 8/30 (27%); 6/15 (40%) NSS, 2/15 (13%) RN. Adjuvant CT 28/30 (94%); NSS 13/15 (87%) RN 15/15 (100%) Actinomycin-D, vincristine; other CT cumulative doses: n/m N of participants NP: 30/30 (100%); NP details: NSS 15/30 (50%); RN 15/30 (50%) N of participants RT including the kidney region: 4/30 (13%); NSS 1/15 (6,7%), RN 3/15 (20%) RT field: n/m; radiation dose: n/m
Outcomes	**eGFR calculated by Schwartz formula** Definition of renal adverse effect: participants were staged according to the National Kidney Foundation CKD system Observed values of renal adverse effects: median eGFR (range) NSS cohort at diagnosis vs NSS cohort at last follow-up 91.7 (39.4-237.7, 49.1) vs 135.3 (57.5-185.8, 55.1) P = 0.013 Median eGFR (range) RN cohort at diagnosis vs RN cohort at last follow-up 149.9 (93.8-215.9, 38.1) vs 131.0 (98.6-161.2, 15.8) P = 0.046 Median eGFR (range) NSS cohort at diagnosis vs RN cohort at diagnosis 91.7 (39.4-237.7, 49.1) vs 149.9 (93.8-215.9, 38.1) P = 0.026 Median eGFR (range) NSS cohort at last follow-up vs RN cohort at last follow-up 135.3 (57.5-185.8, 55.1) vs 131.0 (98.6-161.2, 15.8) P = 0.946 Change in eGFR (range) during study period for NSS vs change in eGFR during study period for RN 28.6 (−51.9 to 83.0, 45.8) vs −19.1 (−54.7 to 25.2, 30.9) P = 0.007 N of participants with renal adverse effect: n/m **Risk factors**

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Cost 2014 *(Continued)*

	No multivariable analysis performed
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of CT and RT were not mentioned
Representative study group (selection bias)	Unclear risk	No information about original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Cozzi 2005

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 30; N of participants described study group: 26; N of participants study group of interest: 26; N of participants with renal function tests: 26 Tumour: WT 26/26 (100%). Time period diagnosis/treatment: 1992-2003. % M/F: 35%/65% Age at diagnosis: mean (SD): NP: 60.0 months (40.7); NSS: 42.7 months (42.0); age at follow-up: n/m; follow-up duration: mean (SD): NP: 71.9 months (41.0); NSS: 65.3 months (38.6); completion of follow-up: 100% Group 1: NP (NP, 16/26) Group 2: NSS (NSS, 10/26) Controls: n/a
Interventions	N of participants ifosfamide: 0/26 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/26 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/26 (0%); carboplatin cumulative dose: n/a Other types of CT: NP 12/16 (75%): vincristine + actinomycin D (N = 2); vincristine + actinomycin D + epirubicin (N = 10); NSS 7/10 (70%): vincristine + actinomycin D (N = 2); vincristine + actinomycin D + epirubicin (N = 5); other CT cumulative doses: n/m

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Cozzi 2005 *(Continued)*

	N of participants NP: 26/26 (100%); NP details: group 1: unilateral NP (NP, N = 16); group 2: NSS (NSS, N = 10) N of participants RT including the kidney region: 0/26 (0%); RT field: n/a; radiation dose: n/a
Outcomes	**Proteinuria measured by U-ACR (in mg/mmol)** Definition of renal adverse effect: > 20 mg/mmol Observed values of renal adverse effects: mean (SD) in mg/mmol: NP: 12.6 (9.38); NSS: 11.02 (5.46); P = 0.63 N of participants with renal adverse effect: total cohort 2/26 (7,7%) NP: 2/16 (12.5%); NSS: 0/10 (0%) **Risk factors** n/m **BP** Definition of renal adverse effect: BP > 2 SDs of expected mean for age and sex Observed values of renal adverse effects: mean (SD) in mmHg: SBP NP: 112.5 (8.6); SBP NSS: 100.0 (9.1) P < 0.001; DBP NP: 72.5 (8.4); DBP NSS: 63.5 (7.1) P < 0.001; SBP SDS NP: 0.72 (0.74); SBP SDS NSS: -0.10 (0.92) P = 0.01; DBP SDS NP: 0.87 (0.77); DBP SDS NSS: 0.19 (0.62) P = 0.01 N of participants with renal adverse effect: total cohort 2/26 (7,7%) with a SBP SDS > 2 SD NP: 2/16 (12.5%) ; NSS: 0/10 (0%) **Risk factors** n/m
Notes	Possible overlap between Cozzi 2005 and Cozzi 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise

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Cozzi 2005 *(Continued)*

Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Cozzi 2012

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 34; N of participants described study group: 25; N of participants study group of interest: 25; N of participants with renal function tests: 25 Tumour: WT 20/25 (80%), renal cell carcinoma 1/25 (4%), cystic nephroma 3/25 (12%), oncocytoma 1/25 (4%). Time period diagnosis/treatment: 1992-2003. % M/F: 60%/40% Age at diagnosis: NP group mean 55.4 months (41.4 SD), NSS group mean 42.7 months (42.0 SD); age at follow-up: n/m; follow-up duration: NP group mean 148,6 months (48.54 SD), NSS group mean 147.9 months (48.52 SD); completion of follow-up: 25/25 (100%) Group A: NP 15/25 (60%) Group B: NSS (NSS) 10/25 (40%) Controls: n/a
Interventions	N of participants ifosfamide: 0/25 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/25 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 1/25 (4%); carboplatin cumulative dose: n/m Other types of CT: postoperative chemo 18/25 (72%): vincristine, doxorubicin, epirubicin. Cumulative dose other types of CT: n/m N of participants NP: 25/25 (100%); NP details: NP 15/25 (60%), NSS 10/25 (40%) N of participants RT including the kidney region: 0/25 (0%); RT field: n/a; radiation dose: n/a
Outcomes	**eGFR calculated by bedside Schwartz equation (≤ 17 years) or MDRD equation (≥ 18 years)** **Definition** CKD I = eGFR > 90 mL/min/1.73 m^2 CKD II = eGFR 60-89 mL/min/1.73 m^2 CKD III = eGFR 30-59 mL/min/1.73 m^2 CKD IV = eGFR 15-29 mL/min/1.73 m^2 CKD V = eGFR < 15 mL/min/1.73 m^2 **Observed values** Mean eGFR NP group 88.63 mL/min/1.73 m^2 (13.54 SD), NSS group 106.20 mL/min/1.73 m^2 (24.13SD) (P = 0.029) N of participants with renal adverse effect: total eGFR < 90 mL/min/1.73 m^2 9/25 (36%) CKD I total cohort 16/25 (64%); NP group 7/15 (47%), NSS group 9/10 (90%) CKD II total cohort 9/25 (36%); NP group 8/15 (53%), NSS group 1/10 (10%) **Risk factors**

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Cozzi 2012 *(Continued)*

	n/m
Notes	Possible overlap between Cozzi 2005 and Cozzi 2012

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	All types of therapy were mentioned except for cumulative dose carboplatin
Representative study group (selection bias)	High risk	Described study group consisted of 74% of original cohort and was not a random sample of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Davidoff 2015

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 42; N of participants described study group: 42; N of participants study group of interest: 42; N of participants with renal function tests: 36 Tumour: synchronous bilateral WT 42/42 (100%). Time period diagnosis/treatment: 2001-2014. % M/F: 45%/55% Age at diagnosis: median 2.2 years (range 0.3-10.8 years); age at follow-up: median 6.7 years (range 1.3-14.6 years); follow-up duration: median 3.7 years (range: 0.03–13.4 years); completion of follow-up: 36/42 (85.7%) Controls: n/a
Interventions	N of participants ifosfamide: unclear, at least 1 with a maximum 15/42 (36%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/42 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: unclear, at least 1 with a maximum 15/42 (36%); carboplatin cumulative dose: n/m Other types of CT: pre-operative CT: vincristine 42/42 (100%), dactinomycin 41/42 (98%), doxorubicin 41/42 (98%). Postoperative CT 15/42 (36%): cyclophosphamide, ifosfamide, etoposide, carboplatin. Other CT cumulative doses: n/m N of participants NP: 42/42 (100%); NP details: bilateral NSS 39/42 (93%), unilateral NP & contralateral NSS (7%)

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Davidoff 2015 *(Continued)*

	N of participants RT including the kidney region: 24/42 (57%); RT field: abdomen 24/24; 18 postoperative (unilateral flank 12, bilateral flank 6), 6 for recurrent or progressive disease; radiation dose range: n/m
Outcomes	**eGFR calculated by the modified Schwartz equation for children** Definition of renal adverse effect: 1. eGFR < 90 mL/min/1.73 m^2 2. eGFR < 60 mL/min/1.73 m^2 Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1. eGFR < 90 mL.min/1.73 m^2 n= 13/36 (36%) 2. eGFR < 60 mL/min/1.73 m^2 n= 0/36 (0%) eGFR > 90 mL/min/1.73 m^2 n = 23/36 (64%) **Risk factors** No analysis performed **BP** Definition of renal adverse effect: participants were considered hypertensive if they had repeated SBP or DBP readings ≥ 95th percentile, or prehypertensive if the BP was between the 90th and the 95th percentiles recorded at > 1 outpatient visit, or if antihypertensive medication was prescribed for BP control Observed values of renal adverse effects: n/m N of participants with renal adverse effect: total 18/36 (50%); hypertensive 2/36 (6%), antihypertensive medication 11/36 (31%), prehypertensive 5/36 (14%) **Risk factors** No analysis performed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of CT and RT were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for 86% of the study group of interest (+)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for 86% of the study group of interest (+)

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Davidoff 2015 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

De Graaf 1996

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 48; N of participants described study group: 41; N of participants study group of interest: 41; N of participants with renal function tests: 41 Tumour: WT: 41/41 (100%). Time period diagnosis/treatment: n/m. % M/F: 39%/61% Age at diagnosis: median: 3 years 3 months (range 5 months-9 years 9 months); age at follow-up: median (range): radiated group: 62 months (25-125); no-radiation group: 43 months (18-139); follow-up duration: median: 13 months (range 11-22); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0/41 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/41 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/41 (0%); carboplatin cumulative dose: n/a Other types of CT: vincristine, actinomycin D: 41/41 (100%) Doxorubicin: 12/41 (29%); other CT cumulative doses: median doxorubicin dose: 300 mg/m^2 (range 150-480); n/m for vincristine and actinomycin D N of participants NP: 41/41 (100%); NP details: unilateral NP N of participants RT including the kidney region: 12/41 (29%); RT field: fields including the kidney region; radiation dose: range: 1000-2250 cGy
Outcomes	**GFR using 125-I-iothalamate clearance, expressed as SD scores** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean GFR (SD): all participants: —0.57 (1.74); no-radiation group: —0.27 (1.82); irradiated group: —1.51 (1.05); P = 0.022 for non-radiated versus irradiated participants Percentage of GFR for normal age-match children: no irradiation: 94.6%; radiation: 72.7% N of participants with renal adverse effect: n/m **Risk factors** No multivariable analysis performed
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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De Graaf 1996 *(Continued)*

Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of only 85% of the original cohort but was a random sample with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definition was objective but not precise, with no cut-off values mentioned
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Dekkers 2013

Methods	**Included for risk factors only** Cross-sectional cohort study
Participants	N of participants original cohort: 885; N of participants described study group: 763; N of participants study group of interest: unclear; N of participants with renal function tests: 763 Tumour: ALL/T-NHL 216/763 (28.3%), AML 26/763 (3.4%), B-NHL 68/763 (8.9%), HL 80/763 (10.5%), bone tumour 35/763 (4.6%), renal tumour 85/763 (11.1%), NB 50/763 (6.6%), LCH 14/763 (1.8%), germ cell tumour 18/763 (2.4%), malignant mesenchymal tumour 67/763 (8.8%), brain tumour 76/763 (9.9%), other 28/763 (3.7%). Time period diagnosis/treatment: 1964-2005. % M/F: 54%/46% Age at diagnosis: median 7.3 years (range 0.0-18.0 years); age at follow-up: median 26.9 years (17.8-65.8 years); follow-up duration: median 18.3 years (range 5.0–58.2); completion of follow-up: unclear Controls: age-specific SD scores were calculated to compare eGFR data with data from healthy Dutch references retrieved from the Nijmegen Biomedical study (N = 3732, aged 18–85 years)
Interventions	N of participants ifosfamide: 75/763 (10%); ifosfamide cumulative dose: 18000 mg/m^2 (range 4-96000) N of participants cisplatin: 51/763 (7%); cisplatin cumulative dose: 450 mg/m^2 (range 18-900) N of participants carboplatin: 16/763 (2%); carboplatin cumulative dose: 2050 mg/m^2 (range 500-7150) Other types of CT: cyclophosphamide 305/763 (39.9%), MTX 319/763 (41.8%): intrathecal 277, IV 236, oral 250 N of participants NP: 85/763 (11%); NP details: unilateral NP 85/85 (100%) N of participants RT including the kidney region: 47/763 (6%); RT field: abdominal 47, TBI 26; radiation dose: abdominal 23 Gy (range 10-40), TBI 10 Gy (6-20)
Outcomes	**eGFR using the abbreviated MDRD equation** Definition of renal adverse effect: kidney disease was categorised according to the Kidney Disease Outcomes Quality Initiative guidelines: stage 3 eGFR = 30–59 mL/min per 1.73 m^2, stage 4 eGFR = 15–29 mL/min per 1.73 m^2, and stage 5 eGFR < 15 mL/min per 1.73 m^2 with or without renal replacement therapy Observed values of renal adverse effects: n/a

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Dekkers 2013 *(Continued)*

	N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 5 **Proteinuria measured by the U-ACR** Definition of renal adverse effect: microalbuminuria: U-ACR > 3.5 mg/mmol (women) and > 2.5 mg/mmol (men) macroalbuminuria: U-ACR > 35 mg/mmol (women) and > 25 mg/mmol (men) Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 7
Notes	Unclear how many of the described survivors were originally treated with nephrotoxic treatment according to our inclusion criteria Possible overlap with Knijnenburg 2012; Mulder 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the eligible cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Unclear risk	Study group of interest unclear
Complete follow-up assessment (attrition bias) proteinuria	Unclear risk	Study group of interest unclear
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account

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Di Tullio 1996

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: unclear; N of participants described study group: 34; N of participants study group of interest: 34; N of participants with renal function tests: 34 Tumour: WT: 34/34 (100%). Time period diagnosis/treatment: n/m. % M/F: 35%/65% Age at diagnosis: n/m; age at follow-up: mean: 12.1 years (range 2.1-19.6); follow-up duration: mean: 8.6 years (range 2.7-15.8); completion of follow-up: 34/34 (100%) Controls: n/a
Interventions	N of participants ifosfamide: 1/34 (3%); ifosfamide cumulative dose: 18 g/m^2 N of participants cisplatin: 1/34 (3%); cisplatin cumulative dose: 180 mg/m^2 N of participants carboplatin: 0/34 (0%); carboplatin cumulative dose: n/a Other types of CT: actinomycin D + vincristine (+ adriamycin); other CT cumulative doses: actinomycin D: 15 mcg/g per course; vincristine: 1.5 mg/m^2 per course; adriamycin: 50 mg/m^2 N of participants NP: 34/34 (100%); NP details: unilateral NP in all cases N of participants RT including the kidney region: 23/34 (68%); RT field: tumour bed and/or abdomen, with shielding for contralateral kidney; radiation dose: 15-35 Gy
Outcomes	**GFR using creatinine clearance, method not mentioned** Definition of renal adverse effect: < 80 mL/min/1.73 m^2 Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1/34 (3%) **Risk factors** No multivariable analysis performed **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: urinary albumin excretion > 20 mg/24 h Observed values of renal adverse effects: mean microalbuminuria: 48 mg/24 h (SD 94) N of participants with renal adverse effect: 11/34 (32%) with urinary albumin > 20 mg/24 h; 4/34 (12%) with proteinuria (> 4 mg/m^2/h) **Risk factors** No multivariable analysis performed **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 0/34 (0%) **Risk factors** No multivariable analysis performed
Notes	Same study group as Indolfi 2001

Risk of bias

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Di Tullio 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was given for 2 of the 3 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Elli 2013

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 40; N of participants described study group: 25; N of participants study group of interest: 25; N of participants with renal function tests: 15 Tumour: unilateral WT 25/25 (100%). Time period diagnosis/treatment: 1985-2010. % M/F: 36%/64% Age at diagnosis: median 3.8 years (range 1-13.8 years); age at follow-up: n/m; follow-up duration: median 9.9 years (range 2-21 years); completion of follow-up: 15/25 (60%) Controls: 33 age-, weight- and height-matched healthy children were considered as a control group for an echocardiographic study. Also, 20 age-, weight- and height-matched healthy children were considered as a control group for the ABPM monitoring study
Interventions	N of participants ifosfamide: 0/25 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/25 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/25 (0%); carboplatin cumulative dose: n/a Other types of CT: anthracyclines 9/25 (36%); other CT cumulative doses: anthracyclines mean cumulative doses 361.11 mg/m² (+/- 98.80) N of participants NP: 25/25 (100%); NP details: unilateral NP 25/25 (100%)

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Elli 2013 *(Continued)*

	N of participants RT including the kidney region: 18/25 (72%); RT field: flank 5/18, abdominal 13/18; radiation dose: 900-3450 cGy
Outcomes	**BP measured by 24-h ABPM** Definition of renal adverse effect: a participants was accepted as hypertensive if the mean of 3 measurements was > 95 percentile for age, sex and height according to the criteria of Tümer 1999 for casual BP recordings in Turkish children. Dipping was defined as a > 10% drop in the mean SBP or DBP between the daytime and the night-time Observed values of renal adverse effects: the 24-h SBP, daytime SBP, night-time SBP, night-time DBP measurements were found to be significantly increased in the participants group compared with healthy children (all P values < 0.05) N of participants with renal adverse effect: 3/15 WT participants (20%) and 1/ 20 control participants (5%) **Risk factors** No multivariable analysis performed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of 63% of original cohort but is a random sample of original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for 60% of the study group of interest (+)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Finklestein 1993

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 2243; N of participants described study group: 2243; N of participants study group of interest: 2243; N of participants with renal function tests: 1528 Tumour: unilateral WT. Time period diagnosis/treatment: 1969-n/m. % M/F: at 1st measurement: 48%/52%

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Finklestein 1993 *(Continued)*

	Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: at least 5 years; completion of follow-up: 1528/2243 (68%) Controls: n/a
Interventions	N of participants ifosfamide: 0/2243 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/2243 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/2243 (0%); carboplatin cumulative dose: n/a Other types of CT: NWTS-1, NWTS-2 and NWTS-3 regimens (including actinomycin-D, vincristine, doxorubicin, cyclophosphamide); other CT cumulative doses: n/m N of participants NP: 2243/2243(100%); NP details: unilateral NP N of participants RT including the kidney region: at least 48 of 62 with high BP; RT field: n/m; radiation dose: median 25 Gy (10-40 Gy)
Outcomes	**DBP** Definition of renal adverse effect: > 95th percentile for age and sex Observed values of renal adverse effects: n/a N of participants with renal adverse effect: overall: 62/1528 (4.1%) with DBP > 90 mmHg at any time point; 1st measurement after 5 years > 95th percentile for age and sex: 83/1171 (7.1%) **Risk factors** n/m
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	CT doses were not described, and no RT information was provided for the whole cohort, only for those with hypertension
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	High risk	No length of follow-up was mentioned
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for 68% of the study group of interest (+)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Frisk 2002

Methods	**Included for both prevalence and risk factors**

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Frisk 2002 *(Continued)*

	Prospective cohort study
Participants	N of participants original cohort: 44; N of participants described study group: 40; N of participants study group of interest: 26 (+ TBI); N of participants with renal function tests: 26 Tumour: ALL, AML, LBL, LCAL and HL. Time period diagnosis/treatment: October 1985-August 1997. % M/F: + TBI: 62%/38% Age at diagnosis: + TBI: median 8.4 years (range 3.6-17.7); age at follow-up: n/m; follow-up duration: median: + TBI 120 months; completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0/26 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/26 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/26 (0%); carboplatin cumulative dose: n/a Other types of CT: + TBI group: prednisolone, teniposide, daunorubicin, vincristine, cyclophosphamide and ara-C; other CT cumulative doses: n/m N of participants NP: 0/26 (0%); NP details: n/a N of participants RT including the kidney region: 26/26 (100%); RT field: TBI; radiation dose: 7.5 Gy (N = 22); 12 Gy (N = 4)
Outcomes	**GFR using 51Cr-EDTA clearance** Definition of renal adverse effect: chronic renal impairment defined as GFR < 70 mL/min/1.73 m^2 Observed values of renal adverse effects: mean GFR before BMT (95% CI): + TBI: 124 (114-134) Mean GFR 6 months after BMT (95% CI): +TBI: 99 (82-115) (P < 0.001) After 6 months GFR stabilised After 60 months, mean GFR for this group was 76 mL/min/1.73 m^2 (range 67-85) N of participants with renal adverse effect: + TBI: 7/26 (27%) had a GFR < 70 mL/min/1.73 m^2 after 6 months **Risk factors (multivariable analysis)** Details can be found in Table 6
Notes	Only a part of the described cohort (26 participants with TBI) was eligible for this Cochrane Review. Possible overlap with the study group of Frisk 2007

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Details of relevant treatments were provided
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Frisk 2002 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	High risk	Sex was not taken into account as prognostic factor

Frisk 2007

Methods	**Included for prevalence only** Cohort study with unclear direction
Participants	N of participants original cohort: 40; N of participants described study group: 35; N of participants study group of interest: 23; N of participants with renal function tests: 23 Tumour: AML 7/35 (20%), LCAL 2/35 (6%), HL 3/35 (9%), ALL 21/35 (60%), LBL 2/35 (6%). Time period diagnosis/treatment: October 1985-August 1997. % M/F: non-TBI group: 75%/25%; TBI group: 65%/35% Age at diagnosis: median age at BMT: non-TBI: 13.2 years (range 1.9-17.0); TBI: 8.6 years (range 3.6-17.7); age at follow-up: n/m; follow-up duration: median non-TBI: 2 years (0.5-5.0); TBI: 4 years (0.5-9.0); completion of follow-up: 100% N of participants TBI group: 23. N of participants non-TBI group: 12 Controls: n/a
Interventions	N of participants ifosfamide: 0/23 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/23 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/23 (0%); carboplatin cumulative dose: n/a Other types of CT: miscellaneous, including busulphan, cyclophosphamide, carmustine, etoposide, ara-C, teniposide, daunorubicin, vincristine, prednisolone; other CT cumulative doses: n/m N of participants NP: 0/23 (0%); NP details: n/a N of participants RT including the kidney region: 23/23 (100%); RT field: TBI; radiation dose: 7.5 Gy single fraction (N = 20); 12 Gy in six fractions (N = 3)
Outcomes	**GFR using 51Cr-EDTA clearance or endogenous creatinine clearance** Definition of renal adverse effect: mean laboratory reference value for GFR was 119 (SD 9) mL/min/1.73 m^2 Observed values of renal adverse effects: GFR (mL/min/1.73 m^2) before BMT was 130 (SD 24) in non-TBI group and 119 (SD: 20) in TBI group GFR decreased 5 years after BMT to 119 (SD 25) in non-TBI group (P = 0.028) and to 101 (SD 20) in TBI group (P = 0.029) GFR, which was also measured in 16 participants 10 years after BMT in TBI group: 104 (SD 19) N of participants with renal adverse effect: n/m **Risk factors**

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Frisk 2007 *(Continued)*

	n/m **Serum phosphate/hypophosphataemia** Definition of renal adverse effect: reference normal ranges: 1.1-2.0 mmol/L from 1-3 years of age, 1.0-1.8 mmol/L from 4-6 years of age, 0.9-1.8 mmol/L from 7-10 years of age, 0.8-1.6 mmol/L from 11-15 years of age and 0.74-1.54 mmol/L in adult participants Observed values of renal adverse effects: n/m N of participants with renal adverse effect: "There were sporadic cases of mild hyperphosphataemia, but no case of hypophosphataemia" **Risk factors** n/m
Notes	Possible overlap with the study group of Frisk 2002

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Geenen 2010

Methods	**Included for both prevalence and risk factors** Cross-sectional cohort study
Participants	N of participants original cohort: 308; N of participants described study group: 141; N of participants study group of interest: 62; N of participants with renal function tests: 62 Tumour: WT: 62/62 (100%). Time period diagnosis/treatment: 1966-1991. % M/F (N = 141): 45%/55%

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Geenen 2010 *(Continued)*

	Age at diagnosis: RT + CT: mean 3.7 years (SD 2.3); CT: mean 3.6 years (SD 2.2); age at follow-up: RT + CT: mean 28.3 years (SD 5.2); CT: mean 23.5 years (SD 4.0); follow-up duration: RT + CT: mean 24.7 years (SD 5.6); CT: mean 19.9 years (SD 5.0); completion of follow-up: 100% N of participants RT + CT group: 37/62 (59.7%); CT group: 25/62 (40.3%) Controls: 69 siblings of survivors
Interventions	N of participants ifosfamide: unclear, but 5/62 (8%) treated with alkylating agents, including ifosfamide; ifosfamide cumulative dose: n/m N of participants cisplatin: 0/62 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/62 (0%); carboplatin cumulative dose: n/a Other types of CT: anthracyclines: 16/62 (26%); dactinomycin: 58/62 (94%); vincristine: 53/62 (85%); other CT cumulative doses: n/m N of participants NP: not mentioned, but supposedly 62/62 (100%); NP details: n/m N of participants RT including the kidney region: 31/62 (50%); RT field: abdomen: 31/31 (100%); radiation dose: n/m
Outcomes	**CKD/renal insufficiency** Definition of renal adverse effect: receiving renal replacement therapy, kidney transplantation or a GFR < 50 mL/min/1.73 m^2 Observed values of renal adverse effects: n/a N of participants with renal adverse effect: total: 3/62 (4.8%). RT + CT: 3/37 (8.1%); CT: 0/25; controls: 0/69. P = 0.016 for RT + CT vs controls. P = 0.14 for RT + CT vs CT **Risk factors** No multivariable analysis performed **BP** Definition of renal adverse effect: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg Observed values of renal adverse effects: mean (SD) SBP in mmHg: RT + CT: 126 (14.6); CT: 120 (10.2); controls: 120 (10). P < 0.05 for RT + CT vs controls Mean (SD) DBP in mmHg: RT + CT: 79 (9.2); CT: 78 (8.4); controls: 73 (8). P < 0.05 for RT + CT vs controls and CT vs controls N of participants with renal adverse effect: total cohort: 9/62 (14.5%) RT + CT: 8/37 (21.6%); CT: 1/25 (4%); controls: 1/69 (1.4%). P < 0.001 for RT + CT vs controls. P = 0.45 for CT vs controls. P = 0.053 for RT + CT vs CT **Risk factors (multivariable analysis)** Details can be found in Table 10
Notes	Possible overlap between the study groups of Aronson 2011; Cardous-Ubbink 2010 and Van Dijk 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Specific types of treatment and cumulative doses of CT and RT were not mentioned
Representative study group (selection bias)	Low risk	Study group consisted of only 50% of the original cohort but was a random sample of the original cohort

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Geenen 2010 *(Continued)*

Well-defined follow-up (reporting bias)	Low risk	Follow-up duration was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account using multivariable logistic regression analysis

Hoffmeister 2010

Methods	**Included for risk factors only** Retrospective cohort study
Participants	N of participants original cohort: 789; N of participants described study group: 689; N of participants study group of interest: 480; N of participants with renal function tests: 480 Tumour: ALL: 204/689 (30%); AML: 157/689 (23%); aplastic anaemia: 106/689 (15%); CML: 55/689 (8%); NB: 39/689 (6%); other: 128/689 (19%). Time period diagnosis/treatment: 1969-2004. % M/F (n = 689): 59%/41% Age at diagnosis: median age at BMT (n = 689): 9.2 years (range 0.3-18.0); age at follow-up: age at onset of hypertension (N = 120): median: 25 years (range 3-46.) Follow-up duration (n = 689): median 16 years (range 5-36); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0/689 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/689 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/689 (0%); carboplatin cumulative dose: n/a Other types of CT: cyclophosphamide, busulphan, fludarabine, MTX; other CT cumulative doses: n/m N of participants NP: 13/689 (2%); NP details: n/m N of participants RT including the kidney region: single fraction TBI: 79/689 (11%); fractionated TBI: 356/689 (52%); LD TBI: 10/689 (1%); pre-HCT abdominal radiation: 22/689 (3%); RT field: TBI: 445/689 (65%); abdominal: 22/689 (3%); radiation dose: single fraction: 10 Gy; fTBI: 12-15.75 Gy; LD: 2-6 Gy. Abdominal: n/m
Outcomes	**BP**

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Hoffmeister 2010 *(Continued)*

	Definition of renal adverse effect: in participants < 18 years: SBP or DBP ≥ 95th percentile according to age, sex and height. In adult participants: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg (participants with diabetes: 130/80). Onset of hypertension was defined as having high BP at 2 consecutive readings or at start of drug therapy for hypertension Observed values of renal adverse effects: n/m N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 11
Notes	Extracted study characteristics under participants and interventions are from the described study group as no separate data were available for the study group of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	NP details were not mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) blood pressure	Unclear risk	No separate data for the study group of interest were available
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Unclear risk	Unclear if important prognostic factors were adequately taken into account using multivariable Cox regression analysis

Indolfi 2001

Methods	**Included for prevalence only** Prospective cohort study
Participants	All tumour and age-related characteristics were described for the 27 participants with renal function tests N of participants original cohort: unclear; N of participants described study group: 34; N of participants study group of interest: 34; N of participants with renal function tests: 27 Tumour: WT 27/27 (100%). Time period diagnosis/treatment: n/m. % M/F: 33%/66%

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Indolfi 2001 *(Continued)*

	Age at diagnosis: mean 3.4 years (SD 2.7); age at follow-up: n/m; follow-up duration: 1: mean 8.5 years (3.5); 2: mean 14.5 years (SD 3.5); completion of follow-up: 27/34 (79%) Controls: n/a
Interventions	N of participants ifosfamide: 0/27 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/27 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/27 (0%); carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 27/27 (100%); NP details: 27/27 unilateral NP N of participants RT including the kidney region: 19/27 (70%); RT field: abdominal, contralateral kidney shielded when > 12 Gy; radiation dose: range: 1500-3000 cGy
Outcomes	**GFR using creatinine clearance** Definition of renal adverse effect: n/m Observed values of renal adverse effects: creatine clearance mean values (SD) in mL/min/1.73 m^2 after mean follow-up of 8.5 years: 117 (46); after mean follow-up of 14.5 years: 118 (34) N of participants with renal adverse effect: 0/27 survivors with a low clearance **Risk factors** No multivariable analysis performed **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: > 20 mg/24 h Observed values of renal adverse effects: mean values (SD) in mg/24 h: measurement 1: 42 (79); measurement 2: 47 (81) N of participants with renal adverse effect: measurement 1: 8/34 (24%); measurement 2: 10/27 (37%) **Risk factors** No multivariable analysis performed **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 0/27 survivors with hypertension **Risk factors** n/m
Notes	Same study group as Di Tullio 1996

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and doses of relevant CT and RT were mentioned

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Indolfi 2001 *(Continued)*

Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for 79% of the study group of interest (+)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for 79% of the study group of interest (+)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for 79% of the study group of interest (+)
Well-defined outcome (reporting bias)	High risk	Outcome definition was objective and precise for only one of the three outcome measures
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Interiano 2015

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 75; N of participants described study group: 75; N of participants study group of interest: 75; N of participants with renal function tests: 73 for eGFR, 72 for proteinuria, 72 for BP Tumour: nonsyndromic WT 75/75 (100%). Time period diagnosis/treatment: 1962-2001. % M/F: 41%/59% Age at diagnosis: median 3.2 years (range 0.2-12.1 years); age at follow-up: n/m; follow-up duration: median 19.6 years (range 10.0-32.8 years); completion of follow-up: 97% for eGFR, 96% for proteinuria, 96% for BP Controls: n/a
Interventions	N of participants ifosfamide: 0/75 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/75 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/75 (0%); carboplatin cumulative dose: n/a Other types of CT: vincristine 8/75 (11%), actinomycin D 8/75 (11%), doxorubicin 3/75 (4%); other CT cumulative doses: n/m N of participants NP: 75/75 (100%); NP details: unilateral RN 75/75 (100%) N of participants RT including the kidney region: 0/75 (0%); RT field: n/a; radiation dose: n/a
Outcomes	**eGFR was calculated using CKD-EPI equation** Definition of renal adverse effect:

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Interiano 2015 *(Continued)*

1. eGFR <90 mL/min/1.73 m^2
2. eGFR < 60mL/min/1.73m^2

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect:

1. eGFR <90 mL/min/1.73 m^2 16/73 (21.9%)
2. eGFR < 60mL/min/1.73m^2 0/73 (0%)

Risk factors
n/m

Proteinuria measured by random urinalysis

Definition: proteinuria measuring > trace on an isolated random urinalysis was considered abnormal

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 5/72 (6.9%)

Risk factors
n/m

BP

Definition of renal adverse effect: elevated BP was defined as a SBP reading of > 140 mm Hg or a DBP reading of > 90 mm Hg, whereas hypertension was defined as elevated BP or the use of antihypertensive medication(s)

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 5/72 (6.9%)

Risk factors
n/m

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	All types of treatment were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of < 90 % of original cohort but is a random sample size with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Interiano 2015 *(Continued)*

Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Interiano 2017

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 42; N of participants described study group: 28; N of participants study group of interest: 28; N of participants with renal function tests: 25 for GFR, 26 for proteinuria, 28 for BP Tumour: synchronous bilateral WT 28/28 (100%). Time period diagnosis/treatment: 2001-2014. % M/F: 44%/56% Age at diagnosis: median 2.4 years (range 0.3-10.8); age at follow-up: median 7.9 years (range 2.4-14.6); follow-up duration: median 5.2 years (range 1.4-13.6); completion of follow-up: 60.7-89% for GFR, 93% for proteinuria, 100% for BP Controls: n/a
Interventions	N of participants ifosfamide: 1/28 (3.6%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/28 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 4/28 (14.3%); carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 28/28 (100%); NP details: bilateral NSS (NSS) 26/28 (92.9%), unilateral NP with contralateral NSS 2/28 (7.1%). 7 participants treated with bilateral NSS required a repeat NSS, with 1 requiring a 3rd partial NP. N of participants RT including the kidney region: 14/28 (50%); RT field: flank 13/14, whole abdomen 1/14; radiation dose: range 10.5-10.8 Gy
Outcomes	**GFR measured by 1. eGFR Schwartz, 2. eGFR Counahan-Barratt, 3. eGFR CKiD, 4. 99mTC-DTPA** Definition of renal adverse effect: 1. mGFR < 90 mL/min/1.73 m^2 2. eGFR CKiD < 75 mL/min/1.73 m^2 Observed values of renal adverse effects: median at last follow-up eGFR 1. Schwartz 103.3 mL/min/1.73 m^2 (range 67.8 - 159.5), 2. eGFR Counahan-Barrat 103.5 mL/min/1.73 m^2 (range 70.6- 163.4) 3. eGFR CKiD 79.7 mL/min/1.73 m^2 (range 58.3-180.7) 4. mGFR 99mTC-DTPA 97 mL/min/1.73 m^2 (range 56-155) N of participants with renal adverse effect: 1. mGFR < 90 mL/min/1.73 m^2 11/25 (44.0%)

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Interiano 2017 *(Continued)*

2. eGFR CKiD < 75 mL/min/1.73 m^2 8/17 (47.1%)

Risk factors

n/m

Proteinuria measured by dipstick urinalysis

Definition of renal adverse effect: ≥ 1+ proteinuria by dipstick urinalysis

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 8/26 (28.6%)

Risk factors

n/m

BP

Definition of renal adverse effect: prehypertension was defined as persistent (≥ 2 measurements three months apart) SBP or DBP ≥ 90th and < 95th percentile adjusted for age and height

Hypertension was defined as persistent SBP or DBP ≥ 95th percentile or the use of antihypertensive medication

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: prehypertension 6/28 (21.4%), hypertension 9/28 (32.1%)

Risk factors

n/m

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Doses of relevant CT were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of 66.7% of original cohort but is a random sample of original cohort
Well-defined follow-up (reporting bias)	Low risk	Follow-up time was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Depending on GFR equation outcome was assessed for 60%-90% of the study group of interest (+)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Interiano 2017 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for 2/3 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Janeczko 2015

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 50; N of participants described study group: 50; N of participants study group of interest: 50; N of participants with renal function tests: 50 Tumour: unilateral WT 48/50 (96%), bilateral WT 2/50 (4%). Time period diagnosis/treatment: 2000-2012. % M/F: 44%/56% Age at diagnosis: median 3.1 years (range 2 months-12 years); age at follow-up: n/m; follow-up duration: 2 years; completion of follow-up: 50/50 (100%) Controls: n/a
Interventions	N of participants ifosfamide: 0/50 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/50 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 5/50 (10%); carboplatin cumulative dose: n/m Other types of CT: vincristine 50/50 (100%), actinomycin 48/50 (96%), cyclophosphamide 5/50 (10%); other CT cumulative doses: n/m N of participants NP: 50/50 (100%); NP details: total NP 41/50 (82%), partial NP/NSS 9/50 (18%) N of participants RT including the kidney region: 6/50 (12%); RT field: local/abdominal 6/50 (12%); radiation dose: n/m
Outcomes	**eGFR calculated using the Schwartz formula** Definition of renal adverse effect: GFR was analysed according to the age of the child, and evaluated as correct when > 39 mL/min/1.73 m^2 of BSA in children 1-6 months old, > 49 mL/min/1.73 m^2 in children 6–12 months old, > 62 mL/min/1.73 m^2 in children 12–23 months old and > 90 mL/min/1.73 m^2 in children > 2 years old Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1 year after the end of treatment 19/50 (38%), 2 years after the end of the therapy 12/50 (24%) **Risk factors** No multivariable analysis performed **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1 year after end of treatment 2/50 (4%), 2 years after end of treatment 2/50 (4%) **Risk factors**

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Janeczko 2015 *(Continued)*

n/m

Serum phosphate/hypophosphataemia

Definition of renal adverse effect: phosphorus value < 4.49 mEq/L

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 1 year after end of treatment 9/50 (18%), 2 years after end of treatment 11/50 (22%)

Risk factors

n/m

BP assessed during a physical examination

Definition of renal adverse effect: abnormally high BP was defined as values > 95th percentile according to centile charts for the weight and height of the children based the results of the OLAF Project setting standards for BP of children and young people in Poland.

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 1 year after end of treatment 5/50 (10%), 2 years after end of treatment 4/50 (8%)

Risk factors

n/m

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Doses of relevant CT were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90 % of original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Janeczko 2015 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for 3/4 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Kantor 1989

Methods	**Included for both prevalence and risk factors** Cross-sectional cohort study
Participants	N of participants original cohort: 152; N of participants described study group: 119; N of participants study group of interest: 119; N of participants with renal function tests: 119 Tumour: WT (116/119, 97.5%); renal cell carcinoma (3/119, 2.5%). Time period diagnosis/treatment: 1931-1972. % M/F: 43%/57% Age at diagnosis: n/m; age at follow-up: median: 29 years (range 18-58); follow-up duration: median: 25 years (range 14-53); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: dactinomycin alone or with other drugs: 80/119 (67%); other CT cumulative doses: n/m N of participants NP: 119/119 (100%); NP details: unilateral NP (plus partial NP in case of bilateral disease) N of participants RT including the kidney region: 91/119 (76%); RT field: whole or partial abdominal irradiation; radiation dose: n/m
Outcomes	**BP measured by a physician/nurse, taken from recent medical records or by personal recall from a recent visit** Definition of renal adverse effect: definite hypertension: > 160 mmHg SBP or > 95 mmHg DBP or receiving treatment for hypertension Borderline hypertension: 140-160 mmHg SBP or 90-95 mmHg DBP, no medication Observed values of renal adverse effects: n/m N of participants with renal adverse effect: definite hypertension: 18/119 (15%), significantly > expected from normal population; borderline hypertension: 6/119 (5%) **Risk factors (multivariable analysis)** Details can be found in Table 10
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Kantor 1989 *(Continued)*

Well-defined study group (reporting bias)	High risk	CT and RT regimens were not specified
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	High risk	Follow-up duration was not taken into account

Kern 2014

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 55; N of participants described study group: 55; N of participants study group of interest: 55; N of participants with renal function tests: 51 Tumour: non-syndromic unilateral WT 55/55 (100%). Time period diagnosis/treatment: 1995-2011. % M/F: 40%/60% Age at diagnosis: mean 3.25 years; age at follow-up: n/m; follow-up duration: median 6.3 years; completion of follow-up: 51/55 (93%) Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: 51/55 (92.7%) participants CT (not further specified) N of participants NP: 55/55 (100%); NP details: 53 RN, 2 partial NP N of participants RT including the kidney region: 27/55 (49%); RT field: n/m; radiation dose: n/m
Outcomes	**Age-adjusted GFR calculated using the Schwartz formula** Definition of renal adverse effect: 1. GFR 1 SD below age-adjusted published GFR norms 2. Age-adjusted GFR < 60 mL/min/1.73 m^2

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Kern 2014 *(Continued)*

	Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1. GFR 1 SD below age-adjusted published GFR norms 8/51 (15.7%) 2. Age-adjusted GFR < 60 mL/min/1.73 m^2 2/51 (3.9%) **Risk factors** No multivariable analysis performed
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Types and cumulative doses of relevant CT and RT were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcomes were assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Kishore 2015

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 42; N of participants described study group: 29; N of participants study group of interest: 29; N of participants with renal function tests: 29 Tumour: unilateral WT 29/29 (100%). Time period diagnosis/treatment: 1996-2003. % M/F: n/m Age at diagnosis: median 2.87 years (range 0.5-7.5, SD 1.8); age at follow-up: median 7.9 years (range 2.5-18, SD 3.8); follow-up duration: median 4.78 years (range 1-8.8, SD 2.6); completion of follow-up: 29/29 (100%) Controls: n/a
Interventions	N of participants ifosfamide: 0/29 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/29 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/29 (0%); carboplatin cumulative dose: n/a

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Kishore 2015 *(Continued)*

	Other types of CT: vincristine, actionomycin-D, doxorubicin: N unclear, only mention of 27 participants receiving pre-operative CT; cumulative dose: n/m N of participants NP: 29/29 (100%); NP details: complete RN 29/29 (100%) N of participants RT including kidney region: 4/29 (13.8%); irradiation field: flank 4/29 (13.8%), radiation dose: 10.4 Gy
Outcomes	**GFR using Tc-99m clearance** Definition of renal adverse effect: below the reference range for healthy individuals Observed values of renal adverse effects: mean GFR was 109 ± 31.8 mL/min/1.73 m^2 (range: 59–182 mL/min/1.73 m^2) N of participants with renal adverse effect: 6/29 (20.6%) **Risk factors** No multivariable analysis performed **Proteinuria not further specified** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1/29 (3.4%) **Risk factors** n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: hypertension was observed in 2/29 participants (6.9%) **Risk factors** n/m
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of RT were mentioned
Representative study group (selection bias)	Unclear risk	Described study group consisted of 69 % of original cohort and unclear if it is a random sample of original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Kishore 2015 *(Continued)*

Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definitions were not objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Knijnenburg 2012

Methods	**Included for risk factors only** Cross-sectional cohort study
Participants	N of participants original cohort: 1845; N of participants described study group: 1442; N of participants study group of interest: 896; N of participants with renal function tests: 1313 Tumour: bone tumours 108 (7.5%), hepatic tumours 20 (1.4%), germ cell tumours 52 (3.6%), renal tumours 207(14.4%), soft tissue sarcoma 153 (10.6%), NB 96 (6.7%), retinoblastoma 13 (0.9%), CNS tumour 85 (5.9%), leukaemia 376 (26.1%), lymphoma 302 (20.9%), other 30 (2.1%). Time period diagnosis/treatment: 1966-2003. % M/F: 55/45 Age at diagnosis: median 5.9 years (interquartile range 2.9-10.9); age at follow-up: median 19.3 years (interquartile range 15.6-24.5); follow-up duration: median 12.1 years (range 7.8-17.5); completion of follow-up: 1313/1442 (91%) Controls: n/a
Interventions	N of participants ifosfamide: 202/1442 (14.0%); ifosfamide cumulative dose: 30.0 g/m^2 (17.3–54.0) N of participants cisplatin: 112/1442 (7.8%); cisplatin cumulative dose: 320 mg/m^2 (276–480) N of participants carboplatin: 111/1442 (7.7%); carboplatin cumulative dose: 2.0 g/m^2 (1.2–2.8) Other types of CT: HD MTX 368/1442 (25.5%), HD cyclophosphamide 124/1442 (8.6%); cumulative dose: HD MTX 15.0 g/m^2 (6.0–36.0), HD Cyclophosphamde 3.0 g/m^2 (3.0–6.8) N of participants NP: 212/1442 (14.7%); NP details: total NP + partial NP N of participants RT including kidney region: 125/1442 (8.7%); irradiation field: abdominal 103/1442 (7.1%), TBI 22/1442 (1.5%), radiation dose: abdominal 20.0 Gy (15.0–30.0), TBI 7.5 Gy (7.5–12.0)
Outcomes	**eGFR using the Schwartz formula as adapted by Zappitelli for survivors ≤ 18 years of age, and CKD-EPI formula for all adult survivors** Definition of renal adverse effect: decreased GFR was defined as an eGFR < 90 mL/min per 1.73 m^2, as recommended by the Kidney Disease Outcomes Quality Initiative guidelines Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 5

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Knijnenburg 2012 *(Continued)*

Proteinuria measured by dipsticks for albuminuria

Definition of renal adverse effect: normal: negative, abnormal: high 150 mg/dL, moderate 75 mg/dL, equivocal 25 mg/dL

Observed values of renal adverse effects: n/a

N of participants with renal adverse effect: n/a

Risk factors (multivariable analysis)

Details can be found in Table 7

Serum phosphate/hypophosphataemia

Definition of renal adverse effect: adults, < 0.81 mmol/L; children, age-dependent. Additionally, survivors receiving a phosphate supplement were regarded as having abnormal serum levels.

Observed values of renal adverse effects: n/a

N of participants with renal adverse effect: n/a

Risk factors (multivariable analysis)

Details can be found in Table 8

Serum Mg/hypomagnesaemia

Definition of renal adverse effect: serum Mg: male, < 0.75 mmol/L; female, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L. Survivors receiving a Mg supplement were regarded as having abnormal serum levels.

Observed values of renal adverse effects: n/a

N of participants with renal adverse effect: n/a

Risk factors (multivariable analysis)

Details can be found in Table 9

BP

Definition of renal adverse effect: in adult survivors, elevated BP was defined as having a SBP or DBP > 140 or 90 mmHg, respectively. In paediatric survivors, elevated BP was defined as having a SBP and/or DBP that was ≥ 95th percentile for sex, age, and height, using height z-scores for Dutch children. Survivors using antihypertensive medication were considered hypertensive.

Observed values of renal adverse effects: n/a

N of participants with renal adverse effect: n/a

Risk factors (multivariable analysis)

Details can be found in Table 11

Notes	Extracted study characteristics under participants and interventions are from the described study group as no separate data were available for the study group of interest. Possible overlap with Mulder 2013 and Dekkers 2013

Risk of bias

Bias	Authors' judgement	Support for judgement

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Knijnenburg 2012 *(Continued)*

Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Unclear risk	Described study group consisted of 78.2 % of original cohort and unclear if it is a random sample of original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Unclear risk	No separate data for the study group of interest were available
Complete follow-up assessment (attrition bias) proteinuria	Unclear risk	No separate data for the study group of interest were available
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Unclear risk	No separate data for the study group of interest were available
Complete follow-up assessment (attrition bias) serum magnesium/hypomagnesaemia	Unclear risk	No separate data for the study group of interest were available
Complete follow-up assessment (attrition bias) blood pressure	Unclear risk	No separate data for the study group of interest were available
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for 5/5 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account

Kostel Bal 2016

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants in original cohort: 250; N of participants described study group: 50; N of participants in study group of interest: 50; N of participants with renal function tests: 50 Tumour: unilateral WT: 50/50 (100%). Time period diagnosis/treatment: 1975-2011. % M/F: 54%/46% Age at diagnosis: median: 3.4 years (range 0.6-19 years); age at follow-up: n/m; follow-up duration: median: 8.8 years (range 2.3-35.4 years); completion of follow-up: 50/50 (100%)

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Kostel Bal 2016 *(Continued)*

	Controls: n/a
Interventions	N of participants ifosfamide: 0/50 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/50 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/50 (0%); carboplatin cumulative dose: n/a Other types of CT: vincristine-actinomycin D 34/50 (68%), Vincristine-actinomycin D-adriamycin 10/50 (20%), vincristine-actinomycin D-adriamycin-etoposide 6/50 (12%); other CT: cumulative dose adriamycin 335 mg/m^2 N of participants NP: 50/50 (100%); unilateral NP 40/50 (80%), extended surgery 10/50 (20%) N of participants RT including the kidney region: 20/50 (40%); in 8/20 the remaining kidney was in the field too; radiation dose: median 1500 cGy
Outcomes	**eGFR by the Schwartz formula and using 24-h creatinine clearance** Definition of renal adverse effect: eGFR < 90 mL/min/1.73 m^2 Observed values of renal adverse effects: variations in mean GFR according to follow-up time: 2-4 years = 125 mL/min/1.73 m^2, 5-9 years = 135 mL/min/1.73 m^2 (P = 0.012), 10-14 years = 115 mL/min/1.73 m^2 (P = 0.012), > 15 years = 113 mL/min/1.73 m^2. Variations in GFR according to follow-up time < 10 years = 131 mL/min/1.73 m^2, > 10 years = 113 mL/min/1.73 m^2 (P = 0.002) N of participants with renal adverse effect: at initial diagnosis 5/50 (8%), at time of study 0/50 (0%) **Risk factors** No multivariable analysis performed **Proteinuria measured by urinary protein-creatinine ratio in 24-hurine** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 8/50 (16%) **Risk factors** No multivariable analysis performed **BP** Definition of renal adverse effect: BP > 95 percentile for the age and sex standards among Turkish children Observed values of renal adverse effects: n/m N of participants with renal adverse effect: at diagnosis 11/50 (22%); at time of study 2/50 (4%) (P < 0.05) **Risk factors** n/m
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned

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Kostel Bal 2016 *(Continued)*

Representative study group (selection bias)	High risk	Study group only 20% of original cohort and is not a random sample
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for 2/3 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Kubiak 2004

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 25; N of participants described study group: 23; N of participants study group of interest: 23; N of participants with renal function tests: 22 Tumour: bilateral WT 23/23 (100%). Time period diagnosis/treatment: 1973-2002. % M/F: 30%/70% Age at diagnosis: median 19 months (range 5-65); age at follow-up: n/m; follow-up duration: median 57 months (range 12.5-297); completion of follow-up: 22/23 (96%) Controls: n/a
Interventions	N of participants ifosfamide: 1/23 (4.3%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/23 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/23 (0%); carboplatin cumulative dose: n/a Other types of CT: vincristine, actinomycin D, etoposide, cyclophosphamide, doxorubicin; other CT cumulative doses: n/m N of participants NP: 23/23 (100%); NP details: 18/46 kidneys in 23 participants nephrectomised 28/46 kidneys salvaged (21 excisions, 5 enucleations, 2 bench surgical procedures with autotransplantation) N of participants RT including the kidney region: n/m, but at least 1; RT field: n/m; radiation dose: n/m
Outcomes	**eGFR using the Schwartz formula** Definition of renal adverse effect: < 90 mL/min/1.73 m^2

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Kubiak 2004 *(Continued)*

Observed values of renal adverse effects: median: 101.5 mL/min/m^2 (range 60-169 mL/min/m^2) in 20/20 survivors without renal failure

N of participants with renal adverse effect: 6/22 (27%) including 2 with renal failure

Risk factors
n/m

BP

Definition of renal adverse effect: mean SBP and/or DBP pressure was ≥ 95th percentile in relation to age and sex

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 4/22 (18.2%)

Risk factors
n/m

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT doses or RT regimens were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Lange 2011

Methods

Included for both prevalence and risk factors

Prospective cohort study

Participants

N of participants original cohort: 9237; N of participants described study group: 7950; N of participants study group of interest: 7950; N of participants with renal function tests: unclear

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Lange 2011 *(Continued)*

	Tumour: 7950 non-WT1 syndromic WT (WT): synchronous bilateral WT 512/7950 (6.5%), unilateral WT 7351/7950 (92.5%), metachronous bilateral WT 87/7950 (1%). Time period diagnosis/treatment: n/m. % M/F: 45%/55% Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: median 14.2 years; completion of follow-up: unclear Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: 0; other CT cumulative doses: n/m N of participants NP: 7950/7950 (100%); NP details: n/m N of participants RT including the kidney region: 944/7848 (12%); RT field: contralateral kidney; radiation dose: N = 221 > 15.0 Gy, N = 723 0.1-14.9 Gy
Outcomes	**ESRD** Definition of renal adverse effect: require long-term dialysis or kidney transplant, or died of renal failure before treatment for ESRD was initiated Observed values of renal adverse effects: cumulative incidence at 20 years unilateral WT 0.7% (95% CI 0.4-1.0), bilateral WT 3.1% (95% CI 0.9-5.3). Estimated hazard ratio was 5.9 (95% CI 3.2-10.6) for bilateral WT vs unilateral WT, P < 0.001 N of participants with renal adverse effect: prevalence unclear as N of participants with renal function tests is not known; absolute numbers: 40 unilateral WT, 14 synchronous bilateral WT, 1 metachronous bilateral WT **Risk factors (multivariable analysis)** Details can be found in Table 4
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of relevant CT and NP details were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of < 90% of the original cohort, but was a random sample with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Unclear risk	Number of participants with renal tests unclear
Well-defined outcome (reporting bias)	High risk	Outcome definition was not precise

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Lange 2011 *(Continued)*

Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	High risk	Sex was not taken into account as prognostic factor.

Levitt 1992

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 82; N of participants described study group: 53; N of participants study group of interest: 53; N of participants with renal function tests: 53 Tumour: WT 53/53 (100%). Time period diagnosis/treatment: 1970-1980. % M/F: 51%/49% Age at diagnosis: mean 3.4 years (SD 0.7, range 0.6-10.2); age at follow-up: mean 16.1 years (SD 3.6, range 9.5-24.1); follow-up duration: mean 12.9 years (SD 3.0, range 7.8-19); completion of follow-up: 53/53 (100%) Controls: the values of U-ACR were compared with those from 77 normal children.
Interventions	N of participants ifosfamide: 0/53 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/53 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/53 (0%); carboplatin cumulative dose: n/a Other types of CT: vincristine, +/- actinomycin, +/- doxorubicin +/- cyclophosphamide, N unclear, maximum 37/53 (70%); other CT cumulative doses: n/m N of participants NP: 53/53 (100%); NP details: unclear N of participants RT including the kidney region: 40/53 (75%); RT field: unclear numbers renal bed/abdominal; radiation dose: 23/40 (58%) < 1200 cGy, 17/40 (42%) > 1200 cGy
Outcomes	**GFR was measured from the plasma clearance of 51-Cr-EDTA** Definition of renal adverse effect: GFR < 80 mL/min/1.73 m^2 BSA Observed values of renal adverse effects: mean 89.9 mL/min/1.73 m^2 BSA (13.7 SD) N of participants with renal adverse effect: 10/53 (19%) **Risk factors** No multivariable analysis performed **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: n/m Observed values of renal adverse effects: range 2.1-23.25 mg/mL N of participants with renal adverse effect: 5/53 (9.4%) **Risk factors** n/m

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Levitt 1992 *(Continued)*

Proteinuria measured by U-ACR

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: the mean for the WT participants was 0.45 (range 0.09-23.26 mg/mL), not significantly different from the mean of the controls 0.32 mg/mol (range 0.05-1.95)

N of participants with renal adverse effect: n/m

Risk factors

No multivariable analysis performed

BP

Definition of renal adverse effect: SBP SDS > 2.0 or on treatment for hypertension

Observed values of renal adverse effects: mean SBP SDS 0.84 +/- 1.03 (range −1.80 to 3.80). Mean DBP SDS was 1.15 (+/- 1.11, range −1.4 to 4.3). Both SBP and DBP were significantly > 0 (t = 7.3 P < 0.001)

N of participants with renal adverse effect: 6/53 (11%)

Risk factors

No multivariable analysis performed

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Details of NP were not mentioned
Representative study group (selection bias)	Unclear risk	Described study group consisted of 65% of original cohort and unclear if this is a random sample of original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definitions were objective and precise for 2/4 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

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Makipernaa 1991

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 34; N of participants described study group: 30; N of participants study group of interest: 30; N of participants with renal function tests: 27 for GFR, 30 for proteinuria and 30 for BP Tumour: WT: 30/30 (100%). Time period diagnosis/treatment: 1960-1976. % M/F: 50%/50% Age at diagnosis: mean 2.6 years (range 0.3-7.2); age at follow-up: mean 21.8 years (range 12.2-29.6); follow-up duration: mean 19.2 years (range 10.8-27.7); completion of follow-up: 90% for GFR, 100% for proteinuria and 100% for BP Controls: n/a
Interventions	N of participants ifosfamide: 0/30 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/30 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/30 (0%); carboplatin cumulative dose: n/a Other types of CT: dactinomycin: 26/30 (86.7%), cyclophosphamide: 3/30 (10%), vincristine: 3/30 (10%); other CT cumulative doses: dactinomycin: 15 mcg/kg daily in 5-day courses. 1 course: 6/26; 6-8 courses: 7/26; ≥ 9 courses: 13/26. Not mentioned for cyclophosphamide and vincristine N of participants NP: 30/30 (100%); NP details: unilateral NP N of participants RT including the kidney region: 27/30 (90%); RT field: abdominal radiation (27/30) but excluding the remaining kidney; radiation dose: median: 30 Gy (range 20-49)
Outcomes	**GFR using 51-Cr-EDTA clearance** Definition of renal adverse effect: no cut-off mentioned Observed values of renal adverse effects: mean GFR 108 mL/min/1.73 m^2 (range 74-151) in 27/30 N of participants with renal adverse effect: n/m **Risk factors** No multivariable analysis performed **Proteinuria measured by urinary albumin excretion** Definition of renal adverse effect: urinary albumin excretion > 20 mg/24 h Observed values of renal adverse effects: n/m N of participants with renal adverse effect: overall: 3/30 (10%); normal: 25/30 (83.3%); 10-20 mg/24 h: 2/30 (6.7%); > 20 mg/24 h: 3/30 (10%) **Risk factors** No multivariable analysis performed **BP** Definition of renal adverse effect: BP > 140 mmHg SBP and/or 90 mmHg DBP Observed values of renal adverse effects: in normotensive participants, mean BP was 110/75 mmHg (range 100/70-140/85 mmHg) N of participants with renal adverse effect: 5/30 (16.7%) **Risk factors**

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Makipernaa 1991 *(Continued)*

	No multivariable analysis performed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for 90% of the study group of interest (+)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Objective and precise outcome definitions were given for 2/3 outcome measurements
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Mancini 1996

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 89; N of participants described study group: 60; N of participants study group of interest: 60; N of participants with renal function tests: 60 Tumour: WT: 60/60 (100%). Time period diagnosis/treatment: 1973-1992. % M/F: 48%/52% Age at diagnosis: median: 3.1 years (range 0.7-10.8); age at follow-up: median: 13.4 years (range 4.2-22.7); follow-up duration: median: 9.3 years (range 1.7-21.1); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0/60 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 1/60 (2%); cisplatin cumulative dose: 800 mg/m^2 N of participants carboplatin: 2/60 (3%); carboplatin cumulative dose: 2500 mg/m^2 (2000 and 3000 mg/m^2)

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Mancini 1996 *(Continued)*

	Other types of CT: actinomycin D only: 1/60 (2%); actinomycin D + vincristine: 38/60 (63%); actinomycin D + vincristine + adriamycin: 15/60 (25%); cyclophosphamide: 2/60 (3%); other CT cumulative doses: n/m N of participants NP: 60/60 (100%); NP details: 59/60 (98%) unilateral NP, 1/60 (2%) bilateral NP N of participants RT including the kidney region: 29/60 (48%); RT field: 21 on renal bed, 5 abdomen, 3 other; radiation dose: n/m
Outcomes	**GFR using creatinine clearance, no further method specified** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean GFR: 97.6 mL/min/1.73 m^2 (SD 12.4, range 67.6-134.6) N of participants with renal adverse effect: n/m **Risk factors** No multivariable risk analysis performed **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: > 20 mcg/mL Observed values of renal adverse effects: mean: 15.2 mcg/mL (SD 23.4) N of participants with renal adverse effect: 7/60 (12%) **Risk factors** No multivariable risk analysis performed **Serum phosphate/hypophosphataemia** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 0/60 (0%) **Risk factors** n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean SBP: 113.9 mmHg (SD 12.9) Mean DBP: 71.9 mmHg (SD 12.3) N of participants with renal adverse effect: n/m **Risk factors** No multivariable risk analysis performed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Mancini 1996 *(Continued)*

Well-defined study group (reporting bias)	High risk	RT doses not specified
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definition was mentioned for only 1 of the 4 outcome measures
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Mavinkurve-Groothuis 2016

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 108; N of participants described study group: 79; N of participants study group of interest: 79; N of participants with renal function tests: 24 for GFR, 23 for BP Tumour: unilateral WT without associated syndromes such as WAGR and Denys-Drash syndrome. Time period diagnosis/treatment: 1987-2011. % M/F: 50%/50% Age at diagnosis: mean 3.7 years (SD 2.5); age at follow-up: mean 12.4 years (SD 5.9); follow-up duration: mean 9.1 years (SD 5.7); completion of follow-up: GFR 24/79 (30%), BP 23/79 (29%) Controls: KIMONO cohort: 184 participants with solitary functioning kidney for non-oncological reasons
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 79/79 (100%); NP details: unilateral NP 79/79 (100%)

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Mavinkurve-Groothuis 2016 *(Continued)*

	N of participants RT including the kidney region: 19/79 (24%); RT field: n/m; radiation dose: n/m
Outcomes	**eGFR using the revised Schwartz formula** Definition of renal adverse effect: eGFR < 60 mL/min/1.73 m^2 Observed values of renal adverse effects: the eGFR remained stable over the follow-up period. Mean (SD) eGFR at follow-up WT: 2.5 years 86 (25), 5 years 89 (23), 10 years 82 (22), 15 years 83 (14) Mean eGFR (SD) at 15 years WT 83 (14 SD), controls 89 (31 SD); mean difference -6 (4.81) mL/min/1.73 m^2 N of participants with renal adverse effect: at a follow-up of 15 years: WT 1/24 (4%), controls 7/57 (12%) **Risk factors** No multivariable analysis performed **BP was measured using either a manual auscultatory or an automatic oscillometric device** Definition of renal adverse effect: high BP was defined as SBP and/or DBP values > 95th percentile (z-score > 1.65) adjusted for age, gender, and height Observed values of renal adverse effects: mean SBP z-score and DBP z-score at diagnosis 2.1 (SD 1.4) and 1.8 (SD 1.3). At discharge from the hospital 0.3 (SD 1.3) and 0.2 (SD 0.7), after 2.5 years 0.0 (SD 0.9) and 0.8 (SD 1.0), after 5 years 0.2 (SD 1.0) and 0.1 (SD 0.6), after 10 years 0.6 (SD 1.5) and 0.0 (SD 0.7), after 15 years 0.6 (SD 1.5) and 0.0 (SD 0.7). During follow-up, BP z-scores remained stable on average (and none of the survivors used renoprotective drugs during follow-up) N of participants with renal adverse effect: at a follow-up of 15 years: WT 6/23 (26%) KIMONO 6/57 (11%) **Risk factors** No multivariable analysis performed
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type and treatment protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of CT and RT were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of 73% of original cohort but is a random sample of original cohort with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	High risk	Outcome was assessed for < 60% of the study group of interest
Complete follow-up assessment (attrition bias) blood pressure	High risk	Outcome was assessed for < 60% of the study group of interest

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Mavinkurve-Groothuis 2016 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Mpofu 1992

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 76; N of participants study group of interest: 76; N of participants with renal function tests: 55 for GFR, 76 for proteinuria, 76 for BP Tumour: WT: 76/76 (100%). Time period diagnosis/treatment: 1970-1989. % M/F: 47%/53% Age at diagnosis: mean: 3.41 years; age at follow-up: n/m; follow-up duration: mean 9.0 years (range 2-23); completion of follow-up: 72% for GFR, 100% for proteinuria, 100% for BP Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 76/76 (100%); NP details: n/m N of participants RT including the kidney region: 41/76 (54%); RT field: renal bed only: 31/76; whole abdomen: 7/76; other: 3/76; radiation dose: with proteinuria: 2820 cGy; without proteinuria: 2000 cGy
Outcomes	**eGFR using the Schwartz formula (or 51Cr-EDTA clearance in 4 participants)** Definition of renal adverse effect: GFR < 80 mL/min/1.73 m^2 Observed values of renal adverse effects: EMU p/c > 20 mg/mmol group, mean GFR (range): 88.6 (39.0-121.6); EMU p/c < 20 mg/mmol group, mean GFR (range): 104.5 (96.0-132.4) N of participants with renal adverse effect: 3/55 (5%), all 3 had EMU p/c > 20 mg/mmol **Risk factors** No multivariable analysis performed **Proteinuria measured by EMU p/c** Definition of renal adverse effect: EMU p/c > 20 mg/mmol Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 11/76 (14.5%) **Risk factors** No multivariable analysis performed **BP in SDs from normal (derived from the Second Task Force on BP in Children)**

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Mpofu 1992 *(Continued)*

	Definition of renal adverse effect: receiving treatment for hypertension Observed values of renal adverse effects: mean SBP (SD): 0.72 (1.29), median: 0.77; mean DBP (SD): 0.48 (1.14), median: 0.54 N of participants with renal adverse effect: 2/76 (2.6%) **Risk factors** n/m
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT regimens and NP details were mentioned
Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for 72% of the study group of interest (+)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Mudi 2016

Methods	**Included for risk factors only** Cross-sectional cohort study
Participants	N of participants original cohort: 130; N of participants described study group: 130; N of participants study group of interest: unclear; N of participants with renal function tests: 130 Tumour: leukaemias 26%, lymphomas 22%, renal tumours 20%, sarcomas 8%, germ cell tumours 8%, hepatoblastoma 4%, others 12%. Time period diagnosis/treatment: n/m. % M/F: 53%/47% Age at diagnosis: n/m; age at follow-up: 2-18 years; follow-up duration: median 2 years; completion of follow-up: 130/130 (100%)

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Mudi 2016 *(Continued)*

	Controls: n/a
Interventions	N of participants ifosfamide: n/m, but at least 1; ifosfamide cumulative dose: range cumulative dose 4800-100,800 mg N of participants cisplatin: n/m, but at least 1; cisplatin cumulative dose: range cumulative dose 140-720 mg N of participants carboplatin: n/m, but at least 1; carboplatin cumulative dose: range cumulative dose 900-4860 mg Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m, but at least 1; NP details: n/m N of participants RT including the kidney region: n/m, but at least 1; RT field: n/m; radiation dose: cumulative dose range 10.5-59.4 Gy
Outcomes	**eGFR was calculated using the modified Schwartz formula** Definition of renal adverse effect: eGFR < 90 mL/min per 1.73 m^2 was considered abnormal according to the Kidney Disease Outcomes Quality Initiative guidelines Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 5
Notes	Unclear how many of the described survivors were originally treated with nephrotoxic treatment according to our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Types of treatment were not well mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Unclear risk	Study group of interest unclear
Well-defined outcome (reporting bias)	Low risk	Outcome was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	High risk	Not all important prognostic factors were taken into account using multivariable logistic regression analysis

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Mulder 2013

Methods	**Included for risk factors only** Prospective cohort study
Participants	N of participants original cohort: 1502; N of participants described study group: 1251; N of participants study group of interest: unclear; N of participants with renal function tests: 1122 Tumour: leukaemia 267/1122 (23.8%), lymphoma 259/1122 (23.1%), brain/CNS tumour 77/1122 (6.9%), bone tumour 99/1122 (8.8%), soft tissue sarcoma 125/1122 (11.1%), renal tumour 144/1122 (12.8%), hepatic tumour 10/1122 (0.9%), germ cell tumour 45/1122 (4%), NB 57/1122 (5.1%), retinoblastoma 11/1122 (1%), other 28/1122 (2.5%). Time period diagnosis/treatment: 1966-2003. % M/F: 53%/47% Age at diagnosis: median 7.6 years (range 0.0-17.8); age at follow-up: median 21.2 years (range 18.0-47.7); follow-up duration: median 7.3 years (range 0.8-14.3); completion of follow-up: 920/1122 (83%) Controls: 444 CCS without potentially nephrotoxic therapy
Interventions	N of participants ifosfamide: 155/1122 (13.8%); ifosfamide cumulative dose: median 30.0 mg/m^2 (range 3.0-132.0) N of participants cisplatin: 88/1122 (7.8%); cisplatin cumulative dose: median 365.0 mg/m^2 (range 180.0-1600.0) N of participants carboplatin: 64/1122 (5.7%); carboplatin cumulative dose: median 1900.0 mg/m^2 (range 480.0-6400.0) Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 147/1122 (13.1%); NP details: partial 7/147, complete 140/147 N of participants RT including the kidney region: 116/1122 (10.3%); RT field: abdominal 95/116, TBI 21/116; radiation dose: median cumulative 20.0 Gy (range 5.0-46.0)
Outcomes	**GFR calculated using CKD-EPI formula for adult CCS** Definition of renal adverse effect: glomerular dysfunction was defined as a GFR < 90 mL/min/1.73 m^2 as recommended by the Kidney Disease Outcome Quality Initiative guidelines Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 5
Notes	Unclear how many of the described survivors were originally treated with nephrotoxic treatment according to our inclusion criteria possible overlap with Knijnenburg 2012; Dekkers 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Unclear risk	Described study group consisted of 83% of original cohort and unclear if it is a random sample of original cohort

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Mulder 2013 *(Continued)*

Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Unclear risk	Study group of interest unclear
Well-defined outcome (reporting bias)	Low risk	Outcome definition was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account using multivariable logistic regression analysis

Musiol 2016

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: unclear; N of participants described study group: 38; N of participants study group of interest: 38; N of participants with renal function tests: 38 Tumour: medulloblastoma 19/38 (50%), ependymoma anaplasticum 4/38 (10%), astrocytoma anaplasticum 4/38 (10%), oligodendroglioma anaplasticum 1/38 (3%), oligoastrocytoma anaplasticum 2/38 (5%), PNET 1/38 (3%), glioblastoma multiforme 2/38 (5%), germinoma 4/38 (10%), carcinoma plexus choroidei 1/38 (1%). Time period diagnosis/treatment: 2004-2013. % M/F: 47%/53% Age at diagnosis: median 9.75 years (range 0.92-17.7); age at follow-up: median 13.7 years (range 2.1-22); follow-up duration: mean 3.2 years (range 0.16-6.5); completion of follow-up: 38/38 (100%) Controls: n/a
Interventions	N of participants ifosfamide: 20/38 (53%); ifosfamide cumulative dose: 18 participants 9-36 mg/m^2, 2 participants unclear N of participants cisplatin: 38/38 (100%); cisplatin cumulative dose: 18 participants < 450 mg/m^2, 20 participants > 450 mg/m^2 N of participants carboplatin: 28/38 (74%); carboplatin cumulative dose: 22 participants > 1100 mg/m^2, 6 participants < 1100 mg/m^2 Other types of CT: cyclophosphamide 13/38 (34%); other CT cumulative doses: n/m N of participants NP: 0/38 (0%); NP details: n/a N of participants RT including the kidney region: 0/38 (0%); RT field: n/a; radiation dose: n/a
Outcomes	**eGFR with Schwartz formula and updated CKD Schwartz equation (new Schwartz formula)** Definition of renal adverse effect: nephrotoxicity was defined according to indicates of National Kidney Foundation 1. Stage 2 CKD = eGFR 90–60 mL/min/1.73 m^2 2. Stage 3 CKD = eGFR 60–30 mL/min/1.73 m^2

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Musiol 2016 *(Continued)*

3. Stage 4 CKD = eGFR 30–15 mL/min/1.73 m^2
4. Stage 5 CKD = eGFR < 15 mL/min/1.73 m^2

Observed values of renal adverse effects: the mean GFR estimated using Schwartz formula in the whole group was 76 mL/min/1.73 m^2, while GFR estimated using revised Schwartz formula was 63 mL/min/1.73 m^2 (P < 0.0001)

N of participants with renal adverse effect:

1. Stage 2 CKD 22/38 (58%)
2. Stage 3 CKD 6/38 (16%)
3. Total eGFR < 90 mL/min/1.73 m^2 (stage 2 + 3 CKD) 28/38 (74%)
4. Total eGFR < 60 mL/min/1.73 m^2 6/38 (16%)
5. No nephrotoxicity (eGFR > 90 mL/min/1.73m^2) 10/38 (26.5%)

Risk factors

No multivariable analysis performed

Proteinuria measured by microalbuminuria

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 5/38 (13%)

Risk factors

n/m

Serum phosphate/hypophosphataemia

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 14/38 (36%)

Risk factors

n/m

Tubular phosphate regulation parameters measured by TRP and Tmp/GFR

Definition of renal adverse effect: TRP dysfunction was defined as TRP < 85 %. References ranges for Tmp/GFR for children aged 2–15 years were 1.15– 2.6 mmol/L (21–47 mg/dL)

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 13/38 (34%)

Risk factors

n/m

Serum Mg/hypomagnesaemia

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 5/38 (13%)

Risk factors

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Musiol 2016 *(Continued)*

	n/m
Notes	22 participants of the study group of interest received spinal lumbar and sacral RT. It was assumed that there was negligible scatter of radiation to the kidney region. The Schwartz formula was used to assess the GFR in all subgroups of different nephrotoxic therapies, the new Schwartz formula was only used to compare the mean GFR of the total cohort with the results of the original Schwartz formula.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	All types of treatment and cumulative doses of relevant CT were mentioned
Representative study group (selection bias)	Unclear risk	No information about original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) tubular phosphate absorption parameters	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum magnesium/hypomagnesaemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Mentioned for < 50% of all outcomes (2/5 outcomes)
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Othman 2002

Methods	**Included for prevalence only** Cross-sectional cohort study

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Othman 2002 *(Continued)*

Participants	N of participants original cohort: 49; N of participants described study group: 31; N of participants study group of interest: 31; N of participants with renal function tests: 31 Tumour: WT: 31/31 (100%). Time period diagnosis/treatment: n/m. % M/F: 35%/65% Age at diagnosis: mean: 3.6 years; median: 3 years (range 0.75-9); age at follow-up: mean: 13.7 years; median: 13 years (range 4-32); follow-up duration: n/m; completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 31/31 (100%); NP details: n/m N of participants RT including the kidney region: 15/31 (48%); RT field: abdomen: 15/31; radiation dose: n/m
Outcomes	**Serum phosphate/hypophosphataemia** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean: 1.41 mmol/L (SD 0.38 mmol/L) N of participants with renal adverse effect: 0/31 (0%) **Risk factors** n/m **Serum Mg/hypomagnesaemia** Definition of renal adverse effect: < 0.80 mmol/L Observed values of renal adverse effects: mean serum Mg: 0.83 mmol/L (SD 0.14 mmol/L) N of participants with renal adverse effect: 8/31 (25.8%) **Risk factors** n/m
Notes	N of participants treated with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	CT regimens, RT doses and NP details were not mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	High risk	Length of follow-up was not mentioned
Complete follow-up assessment (attrition bias)	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Othman 2002 *(Continued)*

serum phosphate/hypophosphataemia		
Complete follow-up assessment (attrition bias) serum magnesium/hypomagnesaemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definitions were not mentioned for one of the two outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Oue 2014

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 31; N of participants described study group: 28; N of participants study group of interest: 28; N of participants with renal function tests: 25 Tumour: bilateral synchronous WT 31/31 (100%). Time period diagnosis/treatment: 1996-2011. % M/F: 52%/48% Age at diagnosis: mean 15.5 +/- 13.0 months (range 7-62); age at follow-up: n/m; follow-up duration: median 8.0 years (range 1.3-13.1); completion of follow-up: 25/28 (89%) Controls: n/a
Interventions	N of participants ifosfamide: 0/28 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/28 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: unclear, at least one with a maximum 9/28 (32%); carboplatin cumulative dose: n/m Other types of CT: vincristine 25/28 (89%) dactinomycin 25/28 (89%) doxorubicin 13/28 (46%). Cyclophosphamide unclear, maximum 9/28 (32%); other CT cumulative doses: n/m N of participants NP: 28/28 (100%); NP details: bilateral NSS 10/28 (36%), total NP one kidney and NSS contralateral kidney 15/28 (54%), bilateral NP 3/28 (11%) N of participants RT including the kidney region: 4/28 (14%); RT field: kidney region 4/4; radiation dose: median 16 Gy (range 10-30)
Outcomes	**Composite outcome using creatinine and/or BUN** Definition of renal adverse effect: creatinine and/or BUN level elevated 1.5 times the maximum of the normal range Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 10/25 (40%). Of which 4 renal failure requiring haemodialysis, and 1 renal transplant. The participants with residual renal parenchyma estimated to be > that of a single kidney (100%) had a normal renal function. On the other hand, most of the participants with residual renal parenchyma estimated to be < that of a single kidney developed an impaired renal function after 10 years of follow-up **Risk factors**

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Oue 2014 *(Continued)*

	n/m
Notes	6 participants genitourinary abnormalities, 2 participants Denys-Drash Syndrome (+ WT1 mutation tumour tissue)

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Carboplatin dose was not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) composite outcome measures	Low risk	Outcome was assessed for 89% of the study group of interest (+)
Well-defined outcome (reporting bias)	High risk	Outcome definition was objective but not precise: composite outcome
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Paulino 2000

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 42; N of participants described study group: 42; N of participants study group of interest: 42; N of participants with renal function tests: 42 Tumour: WT: 42/42 (100%). Time period diagnosis/treatment: 1968-1994. % M/F: 40%/60% Age at diagnosis: median: 48 months (range 7-126); age at follow-up: median (range) in years: a: 13.7 (6.7-20.0); B: 19.9 (13.3-28.9); c: 19.7 (9.3-27.1); follow-up duration: median: 181 months (range 60-306); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: at least 1; ifosfamide cumulative dose: n/m N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: actinomycin D/vincristine/adriamycin: 13/42 (31%); actinomycin D/vincristine: 18/42 (43%); other: n/m; other CT cumulative doses: n/m N of participants NP: 42/42 (100%); NP details: unilateral NP: 41/42 (97.6%); bilateral partial NP: 1/42 (2.4%)

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Paulino 2000 *(Continued)*

	N of participants RT including the kidney region: 42/42 (100%); RT field: 36/42 (86%): hemiabdomen or tumour bed. 6/42 (14%): whole abdomen; radiation dose: a: 12/42: 1000-1200 cGy; B: 11/42: 1201-2399 cGy; c: 19/42: 2400-4000 cGy
Outcomes	**CKD/renal insufficiency** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 1/42 (2%) with chronic renal insufficiency **Risk factors** n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 3/42 (7.1%) **Risk factors** n/m
Notes	N of participants treated with cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definitions were not mentioned
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Ramirez 2016

Methods	**Included for risk factors only**

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Ramirez 2016 *(Continued)*

	Retrospective cohort study
Participants	N of participants original cohort: 821; N of participants described study group: 773; N of participants study group of interest: unclear; N of participants with renal function tests: 773 Tumour: leukaemia/lymphoma 460/773 (59.5%), CNS 48/773 (6.2%), germ cell 13/773 (1.7%), NB 62/773 (8.0%), other solid tumours 21/773 (2.7%), renal tumour 83/773 (10.7%), sarcomas 86/773 (11.1%). Time period diagnosis/treatment: n/m. % M/F: 57%/43% Age at diagnosis: abnormal urinalysis mean 6.2 years (range < 1.0-15.8), normal urinalysis mean 5.7 years (range < 1.0- 7.7); age at follow-up: abnormal urinalysis mean 13.3 years (range 6.0-20.6), normal urinalysis mean 13.3 years (range 2.8-21.8); follow-up duration: abnormal urinalysis mean 5.8 years (range 2.0-13.0), normal urinalysis mean 6.1 years (range 2.0-20.7); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 95/773 (12.3%); ifosfamide cumulative dose: < 30 g/m^2 47/95, ≥ 30 g/m^2 48/95 N of participants cisplatin: 108/773 (14.0%); cisplatin cumulative dose: n/m N of participants carboplatin: 93/773 (12.0%); carboplatin cumulative dose: n/m Other types of CT: cyclophosphamide 546/773 (70.6%), MTX 409/773 (52.9%); other CT cumulative doses: cyclophosphamide < 3 g/m^2 201/546, cyclophosphamide ≥ 3 g/m^2 345/546 N of participants NP: 87/222 (39.2%); NP details: n/m N of participants RT including the kidney region: 222/773 (28.7%); RT field: TBI 53/222, bladder 86/222, renal 83/222; radiation dose: n/m
Outcomes	**Proteinuria** Definition of renal adverse effect: > 1+ protein via urine dipstick or automated analysis Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 7
Notes	Unclear how many of the described survivors were originally treated with nephrotoxic treatment according to our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of relevant CT and RT, and NP details were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of original cohort
Well-defined follow-up (reporting bias)	Low risk	Follow-up time was mentioned
Complete follow-up assessment (attrition bias) proteinuria	Unclear risk	Study group of interest unclear

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Ramirez 2016 *(Continued)*

Well-defined outcome (reporting bias)	Low risk	Outcome was objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account

Rossi 1994

Methods	**Included for prevalence only** Cohort study with unclear direction
Participants	N of participants original cohort: n/m; N of participants described study group: 72; N of participants study group of interest: 72; N of participants with renal function tests: 69 for eGFR, 64 for TPR Tumour: Ewing's/soft tissue sarcoma: 22/72 (30.5%), osteosarcoma: 18/72 (25%), ALL/B-NHL: 15/72 (20.8%), NB: 3/72 (4.2%), WT: 3/72 (4.2%), other: 11/72 (15.3%). Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: n/m; age at follow-up: median: 13.4 years (range 1.7-16.9); follow-up duration: median: 15.8 months (range 3.5-123); completion of follow-up: 96% for eGFR, 89% for TPR Controls: n/a
Interventions	N of participants ifosfamide: 72/72 (100%); ifosfamide cumulative dose: < 15 g/m^2: 8/72; 15-40 g/m^2: 30/72; > 40 g/m^2: 27/72 N of participants cisplatin: 33/72 (45.8%); cisplatin cumulative dose: 100-300 mg/m^2: 8/72; > 300 mg/m^2: 25 N of participants carboplatin: 0/72 (0%); carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/a N of participants NP: 5/72 (6.9%); NP details: unilateral NP N of participants RT including the kidney region: 0/72 (0%); RT field: n/a; radiation dose: n/a Group definitions: Group 1: LD ifosfamide (N = 15, < 15 g/m^2, median 8 g/m^2) Group 2: medium-dose ifosfamide (N = 20, 15-40 g/m^2, median 27 g/m^2) and cisplatin > 300 mg/m^2 Group 3: HD ifosfamide (N = 21, > 40 g/m^2, median > 68 g/m^2) but no cisplatin
Outcomes	**eGFR using the Schwartz formula** Definition of renal adverse effect: eGFR < 80 mL/min/1.73 m^2 Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 6/69 (8.7%) **Risk factors** No multivariable analysis performed

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Rossi 1994 *(Continued)*

	Tubular phosphate regulation parameters measured by TP/Cr Definition of renal adverse effect: normal TP/Cr: mean 1.50 micromol/mL; TP/Cr < —2 SD: < 1.07 micromol/mL; TP/Cr < —3 SD: < 0.84 micromol/mL Observed values of renal adverse effects: n/m N of participants with renal adverse effect: total 21/64 (32.8%); TP/Cr between —2 SD and —3 SD: 15/64 (23.4%); TP/Cr < —3 SD: 6/64 (9.4%) Repeat measurement 8 months after first measurement (N = 28): all normal (14) stayed normal; 11/14 abnormal showed further deterioration; 3/14 abnormal regained normal phosphate reabsorption **Risk factors** No multivariable analysis performed
Notes	Possible overlap with the study groups of Rossi 1997

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) tubular phosphate absorption parameters	Low risk	Outcome was assessed for 89% of the study group of interest (+)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Rossi 1997

Methods	**Included for prevalence only** Cohort study with unclear direction
Participants	N of participants original cohort: n/m; N of participants described study group: 51; N of participants study group of interest: 51; N of participants with renal function tests: 51 Tumour: sarcoma (soft tissue or Ewing's): 51/51 (100%). Time period diagnosis/treatment: n/m. % M/F: n/m

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Rossi 1997 *(Continued)*

	Age at diagnosis: median (range): continuous infusion: 14 years (0-19); short infusion: 12 years (2-19); age at follow-up: n/m; follow-up duration: median: continuous infusion: 4.5 years; short infusion: 1.5 years; completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 51/51 (100%); ifosfamide cumulative dose: median (range) in g/m^2: CI: 67 (36-81); SI: 69 (37-92) N of participants cisplatin: 0/51 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/51 (0%); carboplatin cumulative dose: n/a Other types of CT: adriamycin, actinomycin D and vincristine; other CT cumulative doses: n/m N of participants NP: 0/51 (0%); NP details: n/a N of participants RT including the kidney region: 0/51; RT field: n/a; radiation dose: n/a
Outcomes	**Tubular phosphate regulation parameters measured by TP/Cr** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: total 20/51 (39%); 18 months off-therapy: continuous infusion: 2/14 (14%); short infusion: 6/27 (22%) (P = NS) Continuous infusion: 12/23 (52%); short infusion: 8/28 (29%) (P = NS) **Risk factors** n/m
Notes	Continuous infusion of ifosfamide (48 h) Short infusion (3 × 3 h in 3 days) N of participants with RT including the kidney region 0 is an assumption based on tumour type. Possible overlap with the study groups of Rossi 1994

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT were mentioned
Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) tubular phosphate absorption parameters	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definition was not mentioned

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Rossi 1997 *(Continued)*

Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Sasso 2010

Methods	**Included for prevalence only** Cohort study with unclear direction
Participants	N of participants original cohort: 34; N of participants described study group: 34; N of participants study group of interest: 34; N of participants with renal function tests: 34 Tumour: WT 34/34 (100%). Time period diagnosis/treatment: April 1981-April 2000. % M/F: 41%/59% Age at diagnosis: median 48 months (range 2-151); age at follow-up: not mentioned; follow-up duration: median 181 months (range 60-264); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: n/m, but at least 6; ifosfamide cumulative dose: n/m N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: neoadjuvant CT: not defined (6/34, 18%); other CT cumulative doses: n/m N of participants NP: 33/34 (97%); NP details: all 33 unilateral NP N of participants RT including the kidney region: 34/34 (100%); RT field: whole abdomen only (17/34), hemiabdomen only (9/34), other (8/34); radiation dose: range: 15-35 Gy
Outcomes	**CKD/renal insufficiency** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/a N of participants with renal adverse effect: chronic renal failure: 1/34 (3%) **Risk factors** n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/a N of participants with renal adverse effect: 4/34 (12%) **Risk factors** n/m
Notes	All 5 CCS with renal toxicity were treated with ifosfamide and > 12 Gy RT to the unaffected kidney (P < 0.05) N of participants with cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

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Sasso 2010 *(Continued)*

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT regimens were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	No outcome definitions were given
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Schell 1995

Methods	**Included for prevalence only** Cohort study with unclear direction
Participants	N of participants original cohort: 57; N of participants described study group: 34; N of participants study group of interest: 21; N of participants with renal function tests: 21 Tumour: WT: 21/21 (100%). Time period diagnosis/treatment: 1986-1992. % M/F: n/m Age at diagnosis: WT: mean 42 months (SD 39); age at follow-up: n/m; follow-up duration: WT: median 12 months (range 2-60); completion of follow-up: 100% Control group: 6 children who underwent NP for a non-malignant disease, without radiological and ultrasound evidence of abnormalities in the contralateral kidney
Interventions	N of participants ifosfamide: WT: 4/21 (19%); ifosfamide cumulative dose: n/m N of participants cisplatin: WT: 1/21 (5%); cisplatin cumulative dose: WT: 400 mg/m^2 N of participants carboplatin: WT: 1/21 (5%); carboplatin cumulative dose: WT: 1750 mg/m^2 Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 21/21 (100%); NP details: unilateral NP N of participants RT including the kidney region: WT: 7/21 (33%); RT field: WT: local irradiation; radiation dose: n/m
Outcomes	**GFR using inulin clearance** Definition of renal adverse effect: n/m

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Schell 1995 *(Continued)*

Observed values of renal adverse effects: mean GFR (SD) in mL/min/1.73 m^2: WT: 85 (17); controls: 93 (13); mean difference WT vs controls -8 (6.46) mL/min/1.73 m^2

N of participants with renal adverse effect: n/m

Risk factors

No multivariable analysis performed

Proteinuria not further specified

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: WT: 1/21 (5%) with mild proteinuria

Risk factors
n/m

Serum phosphate/hypophosphataemia

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: WT: 0/21 (0%), all levels were normal in all children

Risk factors
n/m

BP

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: WT: 0/21 (0%)

Risk factors
n/m

Notes	Only a part of the described cohort was eligible for this Cochrane Review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Not all cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Schell 1995 *(Continued)*

Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definitions were not mentioned
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Schiavetti 2015a

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: 82; N of participants described study group: 35; N of participants study group of interest: 35; N of participants with renal function tests: 35 Tumour: WT 29/35 (83%), clear cell sarcoma 1/35 (3%), renal cell carcinoma 4/35 (11%), congenital mesoblastic nephroma 1/35 (3%). Time period diagnosis/treatment: 1978-2014. % M/F: 40/60 Age at diagnosis: mean 5 years, median 5 years (range 0.1-13); age at follow-up: mean 25 years (SD 5.43), median 24 years (range 17-35.4); follow-up duration: mean 20 years (SD 6.67), median 19 (range 8-34); completion of follow-up: 35/35 (100%) Control group: n/a
Interventions	N of participants ifosfamide: 2/35 (6%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/35; cisplatin cumulative dose: n/a N of participants carboplatin: 4/35 (11%); carboplatin cumulative dose: n/m Other types of CT: vincristine, actinomycin-D, epirubicin, etoposide, interferon, doxorubicin, cyclophosphamide; other CT cumulative doses: n/m N of participants NP: 35/35 (100%); NP details: unilateral NP 35/35 (100%) N of participants RT including the kidney region: 8/35 (23%); RT field: abdomen 8/8 (+ 2 lung); radiation dose: range 15-34 Gy
Outcomes	**eGFR was classified by both CKD-EPI equation and MDRD equation** Definition of renal adverse effect: decreased GFR was classified as an eGFR < 90 mL/min/1.73 m^2 and decline in GFR category (> 90 (G1), 60–89 (G2), 45–59 (G3a), 30–44 (G3b), 15–29 (G4), <15 (G5) mL/min/1.73 m^2) Observed values of renal adverse effects: for the 8/35 (22.9%) cases with an eGFR CKD–EPI < 90 mL/min/1.73 m^2, G2 category; the mean value was 80 +/- 9.78 mL/min/ 1.73m^2, (median 84.5, range 63–89).

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Schiavetti 2015a *(Continued)*

For the 27/35 (77.1%) cases with an eGFR CKD–EPI > 90 mL/min/ 1.73m^2, the mean value was 105 +/- 11 mL/min/1.73 m^2 (median 104, range 90–129)

N of participants with renal adverse effect: eGFR CKD–EPI < 90 mL/min/1.73 m^2 = 8/35 (23%); eGFR MDRD < 90 mL/min/1.73 m^2 = 20/35 (57%); WT survivors eGFR CKD–EPI < 90 mL/min/1.73 m^2 = 6/29 (21%)

Mean prevalence eGFR using the MDRD formula and CKD-EPI formula total cohort 14/35 (40%)

Risk factors

No multivariable analysis performed

Proteinuria measured by urinary albumin excretion

Definition of renal adverse effect: albuminuria was expressed according to A1-3 categories. A threshold for urinary albumin excretion of > 30 mg/24 h sustained for > 3 months was considered pathological. A1 normal to mildly increased (< 30 mg/g, < 3 mg/mmol). A2 moderately increased (30-300 mg/g, 3-30 mg/mmol). A3 severely increased (> 300 mg/g, > 30 mg/mmol)

Observed values of renal adverse effects: the albuminuria category was A2 (30– 300 mg/g) in all affected cases

N of participants with renal adverse effect: 5/35 (14%) survivors

Risk factors

n/m

BP

Definition of renal adverse effect: high BP was defined as SBP or DBP > 140 or 90 mmHg respectively

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 1/35 (3%)

Risk factors

n/m

Composite outcome: CKD

Definition of renal adverse effect: CKD was defined as abnormalities in kidney structure or function or a decreased eGFR CKD–EPI < 60 mL/min/1.73 m^2 (GFR categories G3a–G5) for > 3 months

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: all renal tumour survivors 3/35 (8.6%); G2 A2 category in 1 case and G1 A2 category in 2 cases. WT survivors 2/29 (6.9%)

Risk factors

No multivariable analysis performed

Notes	The mean result of the MDRD formula and CKD-EPI formula was used for eGFR prevalence in analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of CT and RT were not mentioned

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Schiavetti 2015a *(Continued)*

Representative study group (selection bias)	High risk	Described study group consisted of 43% of original cohort and is not a random sample
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) composite outcome measures	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	3/4 outcome definitions were objective and precise, 1 outcome definition was a composite outcome
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Skinner 2010b

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 29; N of participants described study group: 25; N of participants study group of interest: 25; N of participants with renal function tests: 25 Tumour: rhabdomyosarcoma 12/25 (48%), soft tissue sarcoma 6/25 (24%), Ewing's sarcoma 6/25 (24%), PNET 1/25 (4%). Time period diagnosis/treatment: 1986-1996. % M/F: 64%/36% Age at diagnosis: median: 6.0 years (range 0.6-17.7); age at follow-up: n/m; follow-up duration: 1 year: median 1.1 years (range 0.9-2.1); 10 year: median 10.5 years (range 9.3-11.4); completion of follow-up: 21/25-25/25 (92%/100%), depending on time point and outcome Controls: n/a
Interventions	N of participants ifosfamide: 25/25 (100%); ifosfamide cumulative dose: median 106 g/m^2 (range 12-153) N of participants cisplatin: 0/25 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/25 (0%); carboplatin cumulative dose: n/a Other types of CT: melphalan (N = 2), actinomycin D, cyclophosphamide, doxorubicin, etoposide and vincristine (N = n/m); other CT cumulative doses: n/m N of participants NP: 0/25 (0%); NP details: n/a

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Skinner 2010b *(Continued)*

	N of participants RT including the kidney region: 3/25 (12%); RT field: kidney (N = 2), TBI (N = 1); radiation dose: kidney: n/m; TBI: 12 Gy
Outcomes	**GFR using 51Cr-EDTA clearance** Definition of renal adverse effect: age-related reference ranges for subclinical nephrotoxicity, < 60 mL/min/1.73 m^2 for clinical nephrotoxicity Observed values of renal adverse effects: median (range) in mL/min/1.73 m^2: end of treatment: 101 (65-147); 1 year post-treatment: 82 (59-131); 10 years post-treatment: 88 (40-151) N of participants with renal adverse effect: end of treatment: 26%; 1 year post-treatment: 72%; 10 years post-treatment: 50% GFR < 60 mL/min/1.73 m^2: end of treatment: 0%; 1 year post-treatment: 4%; 10 years post-treatment: 13% **Risk factors** No multivariable analysis performed **Serum phosphate/hypophosphataemia** Definition of renal adverse effect: < 0.90 mmol/L Observed values of renal adverse effects: median (range) in mmol/L: end of treatment: 1.20 (0.43-1.61); 1 year post-treatment: 1.19 (0.57-1.62); 10 years post-treatment: 1.07 (0.74-1.58) N of participants with renal adverse effect: end of treatment: 22%; one year post-treatment: 28%; 10 years post-treatment: 8% **Risk factors** No multivariable analysis performed **Tubular phosphate regulation parameters measured by Tmp/GFR** Definition of renal adverse effect: < 0.99 mmol/L Observed values of renal adverse effects: median (range) in mmol/L: end of treatment: 0.90 (0.19-1.41); 1 year post-treatment: 0.85 (0.01-1.46); 10 year post-treatment: 0.85 (0.43-1.49) N of participants with renal adverse effect: end of treatment: 48%; 1 year post-treatment: 50%; 10 years post-treatment: 62% **Risk factors** No multivariable analysis performed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of 86% of the original cohort but was a random sample with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned

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Skinner 2010b *(Continued)*

Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) serum phosphate/hypophosphataemia	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) tubular phosphate absorption parameters	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Srinivas 1998

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 56; N of participants described study group: 25; N of participants study group of interest: 25; N of participants with renal function tests: 25 Tumour: WT: 25/25 (100%). Time period diagnosis/treatment: 1985-1995. % M/F: 56%/44% Age at diagnosis: mean: 2.8 years (SD 1.9 years); age at follow-up: mean: 7.7 years (range 2-20); follow-up duration: mean: 4.9 years (range 1-15); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 25/25 (100%); NP details: 25/25 (100%) unilateral NP N of participants RT including the kidney region: 6/25 (24%); RT field: n/m; radiation dose: n/m
Outcomes	**GFR using Tc-99m DTPA clearance** Definition of renal adverse effect: < 80 mL/min/1.73 m^2 Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 0/25 (0%) **Risk factors** n/m **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: > 30 mg/24 h urinary albumin

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Srinivas 1998 *(Continued)*

Observed values of renal adverse effects: mean U-ACR: 28.82 (SD 10.08)

N of participants with renal adverse effect: overall: 21/25 (84%); 30-100 mg/24 h: 15/25 (60%); > 100 mg/24 h: 6/25 (24%)

Risk factors
n/m

BP

Definition of renal adverse effect: n/m

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 0/25 (0%)

Risk factors
n/m

Notes	N of participants with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT regimens were specified, and no RT doses were specified
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample with respect to treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for two of the three outcome measures
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Stefanowicz 2010

Methods	**Included for prevalence only** Cross-sectional cohort study

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Stefanowicz 2010 *(Continued)*

Participants	N of participants original cohort: unclear; N of participants described study group: 26; N of participants study group of interest: 26; N of participants with renal function tests: 26 Tumour: nephroblastoma 26/26; stage 1 7/26 (27%), stage 2N— 9/26 (34%), stage 2N+ 3/26 (12%) and stage 3 7/26 (27%). Time period diagnosis/treatment: 1992-2007. % M/F: 50%/50% Age at diagnosis: n/m; age at follow-up: mean 11.2 years (SD 4.8; range 2.3-20.4); follow-up duration: mean 7.1 years (SD 4.8 range 0.4-16.4); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0/26 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/26 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/26 (0%); carboplatin cumulative dose: n/a Other types of CT: 5/26 treated with nephrotoxic CT not further specified; other CT cumulative doses: n/m N of participants NP: 26/26 (100%); NP details: unilateral NP N of participants RT including the kidney region: 11/26 (42.3%); RT field: n/m; radiation dose: n/m
Outcomes	**eGFR using the Schwartz formula** Definition of renal adverse effect: < 90 mL/min/1.73 m^2 Observed values of renal adverse effects: normal CysC group: median 120 mL/min/1.73 m^2 (range 102-165); high CysC group: median 102 mL/min/1.73 m^2 (range 74-142) N of participants with renal adverse effect: 1/26 (4%) **Risk factors** n/m **BP** Definition of renal adverse effect: mean SBP/DBP compared with sex/age/height corrected reference values Observed values of renal adverse effect: n/m N of participants with renal adverse effect: 1/26 (4%) **Risk factors** n/m
Notes	There may be overlap between participants in this study and Stefanowicz 2011 and Stefanowicz 2012.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT was specified, no cumulative doses, no RT doses
Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned

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Stefanowicz 2010 *(Continued)*

Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Stefanowicz 2011

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: unclear; N of participants described study group: 32; N of participants study group of interest: 32; N of participants with renal function tests: 32 Tumour: unilateral WT: 32/32 (100%). Time period diagnosis/treatment: 1987-2008. % M/F: 59%/41% Age at diagnosis: mean: 8.5 years (SD 5.7 years); median: 2.9 years (range 0.08-11.4); age at follow-up: mean: 13 years (SD 5.4 years); median: 12.2 years (range 3.6-24.3); follow-up duration: mean: 9.3 years (SD 5.4 years); median: 7.75 years (range 0.3-20.6); completion of follow-up: 100%. Controls: n/a
Interventions	N of participants ifosfamide: unclear, at least 1 with maximum: 7/32 (22%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/32 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: unclear, at least 1 with maximum: 7/32 (22%); carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 32/32 (100%); NP details: unilateral NP: 32/32 (100%) N of participants RT including the kidney region: 12/32 (37.5%); RT field: tumour bed or total abdomen: 9/32 (28%); remnant kidney: 3/32 (9%); radiation dose: n/m
Outcomes	**CKD/renal insufficiency** Definition of renal adverse effect: CKD staging according to National Kidney Foundation guidelines Observed values of renal adverse effects: n/m N of participants with renal adverse effect: CKD stage I: GFR > 90 mL/min/1.73 m^2 with no signs of kidney damage: 8/32 (25%); GFR > 90 mL/min/1.73 m^2 with signs of kidney damage: 10/32 (32%). CKD stage II: GFR 60-89 mL/min/1.73 m^2 with no signs of kidney damage: 8/32 (25%); GFR 60-89 mL/min/1.73 m^2 with signs of kidney damage: 6/32 (19%) **Risk factors** n/m

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Stefanowicz 2011 *(Continued)*

(e)GFR using 99Tc-DTPA clearance, old Schwartz formula, new Schwartz formula and Filler formula

Definition of renal adverse effect:

1. 99Tc-DTPA clearance GFR < 90 mLl/min/1.73 m^2
2. old Schwartz formula eGFR < 90 mLl/min/1.73 m^2
3. new Schwartz formula eGFR < 90 mLl/min/1.73 m^2
4. Filler formula eGFR < 90 mLl/min/1.73 m^2

Observed values of renal adverse effects:

1. 99Tc-DTPA clearance: mean: 94.3 mL/min/1.73 m^2 (SD 10.24). Mean GFR nephrotoxic chemo (N = 7): 92.7 (SD 8.7); mean GFR non-nephrotoxic chemo (N = 25): 88.9 (SD 18.3) (P = 0.43)
2. old Schwartz formula: mean: 122.3 mL/min/1.73 m^2 (SD 19.92)
3. new Schwartz formula: mean: 94.3 mL/min/1.73 m^2 (SD 10.2)
4. Filler formula: mean: 129.8 mL/min/1.73 m^2 (SD 23.9)

N of participants with renal adverse effects:

1. 99Tc-DTPA clearance 14/32 (44%)
2. old Schwartz formula 1/32 (3%)
3. new Schwartz formula 11/32 (34%)
4. Filler formula 0/32 (0%)

Risk factors
m/m

Proteinuria measured by U-ACR

Definition of renal adverse effect: U-ACR > 30 mg/g

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 7/32 (22%)

Risk factors
n/m

Proteinuria measured by U-ACR

Definition of renal adverse effect: U-ACR > 20 mg/L

Observed values of renal adverse effects: n/m

N of participants with renal adverse effect: 6/32 (19%)

Risk factors
Not mentioned

BP

Definition of renal adverse effect: arterial or DBP > 95th percentile

Observed values of renal adverse effects:
n/m

N of participants with renal adverse effect:
4/32 (12.5%)

Risk factors

n/m

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Stefanowicz 2011 *(Continued)*

Notes	There may be overlap between participants in this study and Stefanowicz 2010 and Stefanowicz 2012. For data-analysis we used the results of the 99Tc-DTPA clearance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT was specified, no cumulative doses, no RT doses
Representative study group (selection bias)	Unclear risk	Size of original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Stefanowicz 2012

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: unclear; N of participants described study group: 30; N of participants study group of interest: 30; N of participants with renal function tests: 30 Tumour: unilateral WT 30/30 (100%). Time period diagnosis/treatment: 1987-2008. % M/F: 67%/33% Age at diagnosis: mean 3.4 years (SD 2.3, range 0.1-8.2); age at follow-up: mean 12.8 years (SD 5.4); follow-up duration: mean 9.1 years (SD 5.3), median 10.2 years (range 0.3-20.5); completion of follow-up: 30/30 (100%) Controls: 17 participants with unilateral renal agenesis (URA)

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Stefanowicz 2012 *(Continued)*

Interventions	N of participants ifosfamide: unclear, at least 1 with maximum 7/30 (23%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/30 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: unclear, at least 1 with maximum 7/30 (23%); carboplatin cumulative dose: n/m Other types of CT: 23/30 (77%): vincristine, actinomycin D and doxorubicin; other CT cumulative doses: n/m N of participants NP: 30/30 (100%); NP details: unilateral NP: 30/30 (100%) N of participants RT including the kidney region: 6/30 (20%); RT field: total abdomen 3/6 (50%), bed of removed kidney 3/6 (50%); radiation dose: n/m
Outcomes	**eGFR using the old Schwartz formula, Filler formula and new Schwartz formula** Definition of renal adverse effect: eGFR < 90 mL/min/1.73 m^2 Observed values of renal adverse effects: 1. old Schwartz formula: mean eGFR WT 121.7 (20.3 SD) URA 126.0 (24.4 SD) P = 0.517. The eGFR values did not differ between groups. 2. Filler formula: mean eGFR WT 129.2 (24.9), URA 130.3 (22.6) P = 0.877. The eGFR values did not differ between groups. 3. new Schwartz formula: mean eGFR WT 94.2 (10.9), URA 91.9 (11.4) P = 0.518. The eGFR values did not differ between groups. Mean difference of old Schwartz and Filler formulas WT 125.45 (22.60 SD) vs URA 128.15 (23.50) = - 2.70 (7.04) N of participants with renal adverse effects: 1. old Schwartz formula: 1/30 (3%) 2. Filler formula: 0/30 (0%) 3. new Schwartz formula: 9/30 (30%) Mean prevalence old Schwartz and Filler formula 0.5/30 (1.67%) **Risk factors** No multivariable analysis was performed **Proteinuria measured by U-ACR** Definition of renal adverse effect: U-ACR> 30 mg/g Observed values of renal adverse effects: U-ACR median 13.5 mg/g (range 2.7–112.3) N of participants with renal adverse effects: 7/30 (23%) **Risk factors** No multivariable analysis was performed **Proteinuria measured by urinary albumin concentration** Definition of renal adverse effect: albumin > 20mg/L Observed values of renal adverse effects: WT: albumin median 9.5 mg/mL (range 1.8–106.31) N of participants with renal adverse effects: 6/30 (20%) **Risk factors**

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Stefanowicz 2012 *(Continued)*

	n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effects: total 4/30 (13%) 4/30 children (13%) demonstrated an average DBP/SBP > 95th percentile, 1/30 (3%) child demonstrated 95th percentile DBP, and 2/30 (7%) children demonstrated 95th percentile SBP. An average DBP and/or SBP > 90th percentile was observed in 2/30 (7%) participants. 1/30 (3%) participants had DBP > 90th percentile **Risk factors** n/m
Notes	There may be overlap between participants in this study and Stefanowicz 2010 and Stefanowicz 2011. We did not take into account the results of eGFR of the new Schwartz formula for analyses because it was calibrated differently.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Cumulative doses of CT and RT were not mentioned
Representative study group (selection bias)	Unclear risk	No information about original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for 2/3 outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Stohr 2007a

Methods	**Included for risk factors only**

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Stohr 2007a *(Continued)*

	Prospective cohort study
Participants	N of participants original cohort: 757; N of participants described study group: 651; N of participants study group of interest: unclear; N of participants with renal function tests: mg: 435. GFR: 618 Tumour: in the Mg analyses (N = 435): osteosarcoma 139/435 (32%), soft tissue sarcoma 167/435 (38%), Ewing's sarcoma 109/435 (25%). In the GFR analyses (N = 618): osteosarcoma 212/618 (34%), soft tissue sarcoma 258/618 (42%), Ewing's sarcoma 148/618 (24%). Time period diagnosis/treatment: 1998-2002. % M/F: in the Mg analyses: 56%/44%. In the GFR analyses: 57%/43% Age at diagnosis: in the Mg analyses: median 11.6 years (IQR 6.5-14.9). In the GFR analyses: "similar to Mg group"; age at follow-up: n/m; follow-up duration: In the Mg analyses: median 23 months (range 0-59). In the GFR analyses: "similar to Mg group"; completion of follow-up: mg: 67%. GFR: 95% Controls: n/a
Interventions	N of participants ifosfamide: in the Mg analyses: 410/435 (94%). In the GFR analyses: "similar to Mg group"; ifosfamide cumulative dose: in the Mg analyses: median 51 g/m² (range 6-105). In the GFR analyses: "similar to Mg group" N of participants cisplatin: in the Mg analyses: 158/435 (36%). In the GFR analyses: 234/618 (38%); cisplatin cumulative dose: in the Mg analyses: median 360 mg/m² (range 120-600). In the GFR analyses: "similar to Mg group" N of participants carboplatin: in the Mg analyses: 60/435 (14%). In the GFR analyses: 114/618 (18%); carboplatin cumulative dose: in the Mg analyses: median 1.5 g/m² (range 0.5-4.2). In the GFR analyses: "similar to Mg group" Other types of CT: actinomycin D, busulphan, doxorubicin, epirubicin, etoposide, melphalan, MTX or vincristine; other CT cumulative doses: n/m N of participants NP: 0/618 (0%); NP details: n/a N of participants RT including the kidney region: in the Mg analyses: 53/435 (12%). In the GFR analyses: "similar to Mg group"; RT field: abdominal; radiation dose: median 45 Gy (IQR 36-51)
Outcomes	**Serum Mg/hypomagnesaemia** Definition of renal adverse effect: serum Mg < 0.7 mmol/L or receiving Mg supplementation Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 9
Notes	Unclear how many of the described survivors were originally treated with nephrotoxic treatment according to our inclusion criteria

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned

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Stohr 2007a *(Continued)*

Complete follow-up assessment (attrition bias) serum magnesium/hypomagnesaemia	Unclear risk	Study group of interest unclear
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account

Stohr 2007b

Methods	**Included for both prevalence and risk factors** Prospective cohort study
Participants	All tumour and age-related characteristics were described for the 593 participants with renal function tests N of participants original cohort: 754; N of participants described study group: 648; N of participants study group of interest: 648; N of participants with renal function tests: 593 Tumour: Ewing's sarcoma 154/593 (26%), osteosarcoma 217/593 (37%), soft tissue sarcoma 222/593 (37%). Time period diagnosis/treatment: 1998-2002. % M/F: 55%/45% Age at diagnosis: median 11.7 years (range 0.4-17.6); age at follow-up: n/m; follow-up duration: median 19 months (IQR 8-36) after end of therapy; completion of follow-up: 92% Controls: n/a
Interventions	N of participants ifosfamide: 593/593 (100%); ifosfamide cumulative dose: 51 g/m^2 (range 6-105) N of participants cisplatin: 217/593 (37%); cisplatin cumulative dose: 360 mg/m^2 (range 120-960) N of participants carboplatin: 84/593 (14%); carboplatin cumulative dose: 1.5 g/m^2 (range 0.5-4.2) Other types of CT: variable combinations of actinomycin D, doxorubicin, epirubicin, etoposide, MTX, or vincristine according to the appropriate protocols; other CT cumulative doses: n/m N of participants NP: 0/593 (0%); NP details: n/a N of participants RT including the kidney region: 63/593 (11%); RT field: abdominal (tumour) field; radiation dose: median cumulative dose: 45 Gy (range 27-59)
Outcomes	**Composite outcome: tubulopathy, including hypophosphataemia, glucosuria, proteinuria, at least at 2 consecutive examinations 4 weeks apart** Definition of renal adverse effect: having met at least 2 of the 3 above-mentioned criteria Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 27/593 (4.6%), of which 9/27 were diagnosed during therapy and 18/27 after cessation of therapy (median follow-up 12.6 months (range 0-22.6))

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Stohr 2007b *(Continued)*

	Risk factors (multivariable analysis) Details can be found in Table 12
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatment and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and no random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) composite outcome measures	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definition was objective but not precise: composite outcome
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account

Sudour 2012

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 49; N of participants described study group: 49; N of participants study group of interest: 49; N of participants with renal function tests: 49 Tumour: synchronous bilateral nephroblastoma (stage IV) 49/49 (100%). Time period diagnosis/treatment: 1993-2001. % M/F: 37%/63% Age at diagnosis: median 2.3 years (range 1.7 months-8.4 years); age at follow-up: n/m; follow-up duration: median 8.0 years (95% CI (7.9-9.1); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/a N of participants cisplatin: 0; cisplatin cumulative dose: n/a N of participants carboplatin: 0; carboplatin cumulative dose: n/a Other types of CT: Oncovin, dactinomycin, etoposide; other CT cumulative doses: n/m

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Sudour 2012 *(Continued)*

	N of participants NP: 49/49 (100%); NP details: bilateral NSS 19/49 (39%); total NP 1 kidney and NSS contralateral kidney 29/49 (59%); bilateral NP 1/49 (2%) N of participants RT including the kidney region: 11/49 (22%); RT field: total abdomen 4 (8%) healthy renal parenchyma region; radiation dose: median 15 Gy (range 10-30 Gy)
Outcomes	**Renal insufficiency; ESRD** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effects: 7/49 (14%); 3 (6.1%) because of their syndrome (2 Denys-Drash and 1 WAGR); 4 (8.2%) by consequence of the treatment (NSS with small nephrogenic rest and/or RT) **Risk factors** n/m **Proteïnuria** Definition of renal adverse effect: treatment with conversion enzyme inhibitors Observed values of renal adverse effects: n/m N of participants with renal adverse effects: 3/49 (6%) (one has Denys-Drash syndrome) **Risk factors** n/m
Notes	N of participants with ifosfamide, cisplatin and carboplatin 0 is an assumption based on tumour type.

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Number of participants receiving and cumulative doses of possible relevant CT were not mentioned
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) CKD/renal insufficiency	Low risk	Outcomes were assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcomes were assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Outcome definitions were not objective and precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

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Trobs 2001

Methods	**Included for prevalence only** Retrospective cohort study
Participants	N of participants original cohort: 54; N of participants described study group: 49; N of participants study group of interest: 49; N of participants with renal function tests: 49 Tumour: WT 54/54 (100%). Time period diagnosis/treatment: 1974-1996. % M/%F: 57%/43% Age at diagnosis: median 2.6 years (range 0-12); age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: n/m, but was included in at least one of the given protocols; ifosfamide cumulative dose: n/m N of participants cisplatin: 0/49 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: n/m, but was included in at least one of the given protocols; carboplatin cumulative dose: n/m Other types of CT: cyclophosphamide, actinomycin D, vincristine, doxorubicin, VP16; other CT cumulative doses: n/m N of participants NP: 49/49 (100%); NP details: 6 bilateral nephrectomies, other unilateral N of participants RT including the kidney region: n/m, but was included in at least one of the given protocols; RT field: n/m; radiation dose: range 15-35 Gy
Outcomes	**BP** Definition of renal adverse effect: hypertension requiring medication Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 2/49 (4.08%) CCS had arterial hypertension **Risk factors** n/m
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No relevant CT regimens were specified, no cumulative doses, no number of participants treated with RT
Representative study group (selection bias)	High risk	Described study group consisted of < 90% of the original cohort and was not a random sample of the original cohort with respect to cancer treatment
Well-defined follow-up (reporting bias)	High risk	Length of follow-up was not mentioned
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)

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Trobs 2001 *(Continued)*

Well-defined outcome (reporting bias)	High risk	Outcome definition was not precise
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Van Dijk 2010

Methods	**Included for both prevalence and risk factors** Cross-sectional cohort study
Participants	N of participants original cohort: 185; N of participants described study group: 185; N of participants study group of interest: 185; N of participants with renal function tests: 181 Tumour: WT: 185/185 (100%). Time period diagnosis/treatment: 1966-1996. % M/F: 52%/48% Age at diagnosis: median: 3.7 years (range 0.3-16.5); age at follow-up: median: 22.9 years (range 6.8-42.0); follow-up duration: median: 18.9 years (range 5.0-36.7); completion of follow-up: 181/185 (98%) Controls: n/a
Interventions	N of participants ifosfamide: 0; ifosfamide cumulative dose: n/m N of participants cisplatin: 0; cisplatin cumulative dose: n/m N of participants carboplatin: 0; carboplatin cumulative dose: n/m Other types of CT: anthracyclines, alkylating agents, vincristine, vinblastine, dactinomycin; other CT cumulative doses: n/m N of participants NP: 185/185 (100%); NP details: n/m N of participants RT including the kidney region: 78/185 (42%); flank only: 53/78 (68%); abdomen only: 12/78 (15%); flank + abdomen: 13/78 (17%); radiation dose: median EQD2 for flank/abdomen: 27.7 Gy (range 11.6-39.0)
Outcomes	**Glomerular function** Definition of renal adverse effect: as defined by the CTCAE 3.0, not explicitly mentioned Observed values of renal adverse effect: n/m N of participants with renal adverse effect: overall: 12/181 (6.6%). Survivors treated with RT: grade 1: 3/12; grade 2: 2/12; grade 3,4,5: 2/12. Survivors treated without RT: grade 1: 2/12; grade 2: 0/12; grade 3,4,5: 3/12 **Risk factors** n/m **BP** Definition of renal adverse effect: as defined by the CTCAE 3.0, not explicitly mentioned Observed values of renal adverse effects: n/m N of participants with renal adverse effect: overall: 18/181 (9.9%). Survivors treated with RT: grade 1: 2/18; grade 2: 8/18; grade 3,4,5: 0/18. Survivors treated without RT: grade 1: 1/18; grade 2: 7/18; grade 3,4,5: 0/18 **Risk factors** n/m

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Van Dijk 2010 *(Continued)*

	Composite outcome: nephrological adverse events Definition of renal adverse effect: hypertension, glomerular dysfunction not further specified and tubular dysfunction not further specified Observed values of renal adverse effects: n/m N of participants with renal adverse effect: overall 43/181 (23.8%) **Risk factors (multivariable analysis)** Details can be found in Table 12.
Notes	N of participants cisplatin, carboplatin and ifosfamide 0 is an assumption based on tumour type. Possible overlap with the study groups of Aronson 2011; Cardous-Ubbink 2010 and Geenen 2010

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	CCT regimes cumulative doses of CT, and NP details were not specified
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Follow-up duration was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) composite outcome measures	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise for > 50% of outcomes
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	Low risk	Relevant risk measures were provided
Adjustment for important confounders	Low risk	Important prognostic factors were taken into account

Van Why 1991

Methods	**Included for risk factors only**

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Van Why 1991 *(Continued)*

	Retrospective cohort study
Participants	N of participants original cohort: 64; N of participants described study group: 64; N of participants study group of interest: 39; N of participants with renal function tests: 39 Tumour: haematological malignancies 36/64 (56%), solid tumours 5/64 (8%), immunodeficiency/other non-malignancies 23/64 (36%). Time period diagnosis/treatment: 1975-1988. % M/F: n/m Age at diagnosis (n = 64): mean age 7.6 years (range 1 month-18 years); age at follow-up: n/m; follow-up duration (n = 64): mean 17 months (range 2 months-11 years); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: 53/64 any conditioning CT regimen; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: 39/64 (61%); RT field: TBI; radiation dose: 1320 cGy in 8 fractions
Outcomes	**eGFR using the Schwartz formula or serum creatinine concentration** Definition of renal adverse effect: eGFR < 50 mLl/min/1.73 m^2 or doubling of baseline serum creatinine concentration Observed values of renal adverse effects: n/a N of participants with renal adverse effect: n/a **Risk factors (multivariable analysis)** Details can be found in Table 5
Notes	N of participants treated with ifosfamide, cisplatin, carboplatin and NP n/m, but cannot be assumed. Extracted study characteristics under participants and interventions are from the described study group as no separate data were available for the study group of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	No CT and NP data were given
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Unclear risk	No separate data were available for the study group of interest
Well-defined outcome (reporting bias)	Low risk	Outcome definitions were objective and precise

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Van Why 1991 *(Continued)*

Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant
Well-defined analysis (reporting bias)	High risk	multivariable logistic regression was performed, but the results were not presented
Adjustment for important confounders	High risk	Not all important prognostic factors were taken into account

von Schweinitz 1997

Methods	**Included for prevalence only** Prospective cohort study
Participants	N of participants original cohort: 56; N of participants described study group: 54; N of participants study group of interest: 54; N of participants with renal function tests: 41 Tumour: hepatoblastoma: 54/54 (100%). Time period diagnosis/treatment: 1988-1993. % M/F (N = 72, including 18 deceased participants): 66%/34% Age at diagnosis (N = 72, including 18 deceased participants): median: 12 months (range 1 day-11 years); age at follow-up: n/m; follow-up duration: median: 64 months (range 28-82 months); completion of follow-up: 41/54 (76%) Controls: n/a
Interventions	N of participants ifosfamide: 54/54 (100%); ifosfamide cumulative dose: n/m (0.5 g/m^2 bolus + 3.0 g/m^2 over 72 h per cycle) N of participants cisplatin: 54/54 (100%); cisplatin cumulative dose: n/m (20 mg/m^2 × 5 per cycle) N of participants carboplatin: 0/54 (0%); carboplatin cumulative dose: n/a Other types of CT: doxorubicin: 54/54 (100%); other CT cumulative doses: 60 mg/m^2 over 48 h per cycle N of participants NP: 0/54 (0%); NP details: n/a N of participants RT including the kidney region: 0/54 (0%); RT field: n/a; radiation dose: n/a
Outcomes	**GFR using creatinine clearance, method not specified** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 0/41 (0%) had an abnormal clearance at follow-up **Risk factors** n/m **Renal tubular function as a composite outcome of tubular phosphate reabsorption and amino acid reabsorption** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 7/41 (17%) with a subclinical renal tubulopathy of which: 5/41 (12%) with mild tubulopathy; 2/41 (5%) with more severe tubulopathy **Risk factors**

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von Schweinitz 1997 *(Continued)*

	n/m
Notes	All participants received at least 2 cycles of CT

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	CT dosages given only per cycle, no cumulative doses
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for 76% of the study group of interest (+)
Complete follow-up assessment (attrition bias) composite outcome measures	Low risk	Outcome was assessed for 76% of the study group of interest (+)
Well-defined outcome (reporting bias)	High risk	No outcome definitions were given for the outcome measurements
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Weirich 2004

Methods	**Included for prevalence only** Prospective cohort study
Participants	Tumour and age-related characteristics were described for all 392 participants without tumour- or therapy-related death. All other characteristics related to the 385/392 participants with a follow-up duration > 5 years N of participants original cohort: 385; N of participants described study group: 385; N of participants study group of interest: 385; N of participants with renal function tests: 385 Tumour: unilateral WT: 369/392 (94.1%), bilateral WT: 23/392 (5.9%). Time period diagnosis/treatment: 1989-1994. % M/F: n/m for follow-up cohort Age at diagnosis: median 2.9 years; mean 3.5 years; age at follow-up: 157/392 (40.1%) > 13 years; follow-up duration: > 5 years in 385/392 (98.2%). median: 8 years (range 0.25-12.6); completion of follow-up: 100% Controls: n/a
Interventions	N of participants ifosfamide: 25/385 (6.4%); ifosfamide cumulative dose: range 24-30 g/m^2 N of participants cisplatin: 0/385 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 26/385 (6.7%); carboplatin cumulative dose: n/m

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Weirich 2004 *(Continued)*

	Other types of CT: adriamycin: 204/385 (52.9%), etoposide 26/385 (6.7%); other CT cumulative doses: adriamycin: range 250-400 mg/m^2 N of participants NP: 385/385 (100%); NP details: bilateral surgery with > 50% loss of renal tissue: 11/385 (2.8%) Unilateral surgery: 374/385 (97.1%) N of participants RT including the kidney region: 84/385 (21.8%); RT field: abdominal irradiation; radiation dose: n/m
Outcomes	**Composite outcome renal/urinary dysfunction** Definition of renal adverse effect: according to CTCAE v2 criteria Observed values of renal adverse effects: n/m N of participants with renal adverse effect: overall: 28/385 (7.2%); mild: 13/385 (3.4%); moderate: 7/385 (1.8%); severe: 5/385 (1.3%); disabling: 3/385 (0.8%) 15/385 (3.9%) needed treatment for renal or urinary system impairment **Risk factors** n/m
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	High risk	Carboplatin and RT cumulative dose was not specified
Representative study group (selection bias)	Low risk	Described study group consisted of > 90% of the original cohort
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) composite outcome measures	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	Composite outcome
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

Wikstad 1986

Methods	**Included for prevalence only** Cross-sectional cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 37 (22 WT survivors + 15 Hn); N of participants study group of interest: 22; N of participants with renal function tests: 22

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Wikstad 1986 *(Continued)*

	Tumour: WT 22/22 (100%). Time period diagnosis/treatment: 1950-1978. % M/F: Wt: 50%/50%; Hn: 40%/60% Age at diagnosis: WT: mean 2.6 years (SD 0.4); Hn: mean 7.9 years (SD 1.2); age at follow-up: WT: mean 16.2 years (SD 1.8); Hn: mean: 25 years (SD 2.7); follow-up duration: WT: mean 13.2 years (SD 1.7); Hn: mean: 17.1 years (SD 2.5); completion of follow-up: 100% Controls: 6 healthy participants (3 male); mean age 35 years (SD 3 years)
Interventions	N of participants ifosfamide: 0/22 (0%); ifosfamide cumulative dose: n/a N of participants cisplatin: 0/22 (0%); cisplatin cumulative dose: n/a N of participants carboplatin: 0/22 (0%); carboplatin cumulative dose: n/a Other types of CT: actinomycin D: 18/22; other CT cumulative doses: actinomycin D: 70 mcg/kg IV 3-7 times in 11/18 and once in 7/18 N of participants NP: WT: 22/22 (100%); Hn :15/15 (100%); NP details: all unilateral nephrectomies N of participants RT including the kidney region: 22/22 (100%); RT field: abdominal radiation; radiation dose: 5-15 Gy to the contralateral kidney
Outcomes	**GFR using inulin clearance** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean (SD); WT: 85.6 mL/min/1.73 m^2 (3.4); Hn: 96.2 mL/min/1.73 m^2 (3.6); controls: 104.5 mL/min/1.73 m^2 (3.6) Mean difference WT vs healthy controls −18,9 mL/min/1.73 m^2 (1.64) $P < 0.05$ between WT and Hn N of participants with renal adverse effect: n/m **Risk factors** No multivariable analysis performed **Proteinuria measured by urinary albumin excretion** Definition of renal adverse effect: n/m Observed values of renal adverse effect: mean (SD): WT: 16.7 mcg/min (11.9); Hn: 72.9 mcg/min (23.1); controls: 17.2 mcg/min (3.7); $P < 0.05$ for WT vs Hn; no difference between WT and controls, neither when corrected for BSA N of participants with renal adverse effects: n/m **Risk factors** n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean SBP in mmHg (SD): WT: 117 (2); Hn: 125 (3); controls: 122 (6); mean DBP in mmHg (SD): WT: 76 (2); Hn: 81 (2); controls: 81 (2). No significant differences between the subgroups N of participants with renal adverse effect: n/m **Risk factors** n/m

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Wikstad 1986 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Well-defined study group (reporting bias)	Low risk	Types of treatments and cumulative doses of relevant CT and RT were mentioned
Representative study group (selection bias)	Unclear risk	Number of participants in original cohort was not mentioned
Well-defined follow-up (reporting bias)	Low risk	Length of follow-up was mentioned
Complete follow-up assessment (attrition bias) (estimated) GFR	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) proteinuria	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Complete follow-up assessment (attrition bias) blood pressure	Low risk	Outcome was assessed for > 90% of the study group of interest (++)
Well-defined outcome (reporting bias)	High risk	No outcome definitions were given for the outcome measurements
Blinded outcome assessor (detection bias)	Unclear risk	Unclear whether outcome assessors were blinded to the investigated determinant

% M/F: percentage male/female; **51Cr-EDTA:** 51-chromium-ethylenediaminetetraacetic acid; **ALL:** acute lymphoblastic leukaemia; **AML:** acute myeloid leukaemia; **ara-C:** cytarabine; **APBM:** ambulant blood pressure monitoring; **BMT:** bone marrow transplantation; **B-NHL:** B-cell non-Hodgkin lymphoma; **BP:** blood pressure; **BSA:** body surface area; **BUN:** blood urea nitrogen; **CCS:** childhood cancer survivors; **cGy:** centiGray; **CI:** confidence interval; **CKD:** chronic kidney disease; **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration; **CKiD:** Chronic Kidney Disease in Chilren; **CML:** chronic myeloid leukaemia; **CNS:** central nervous system; **CT:** chemotherapy; **CTCAE:** Common Terminology Criteria for Adverse Events; **DBP:** diastolic blood pressure; **eGFR:** estimated glomerular filtration rate; **EMU p/c:** early morning urine protein-to-creatinine ratio; **EQD2:** equivalent dose in 2 Gray fractions; **ESRD:** end-stage renal disease; **fTBI:** fractionated total body irradiation; **GFR:** glomerular filtration rate; **Gy:** Gray; **h:** hour **H(S)CT:** hematopoietic (stem) cell transplantation; **HD:** high-dose; **HL:** Hodgkin lymphoma; **Hn:** hydronephrosis; **IQR:** interquartile range; **IV**: intravenous; **LCH:** Langerhans cell histiocytosis; **LBL:** lymphoblastic lymphoma; **LCAL:** large cell anaplastic lymphoma; **LD:** low-dose; **mcg:** microgram; **MDRD:** modification of diet in renal disease; **Mg:** magnesium; **mGFR:** measured glomerular filtration rate; **MTX:** methotrexate; **N:** number; **n/a:** not applicable; **NB:** neuroblastoma; **n/m:** not mentioned; **NP:** nephrectomy; **NS:** not significant; **NSS:** nephron-sparing surgery; **NWTS:** National Wilms' Tumour Study; **PNET:** primitive neuroectodermal tumour; **RN:** radical nephrectomy; **RT:** radiotherapy; **SBP:** systolic blood pressure; **SD:** standard deviation; **SDS:** standard deviation score; **SIOP:** International Society of Paediatric Oncology; **T-NHL:** T-cell non-Hodgkin lymphoma **TBI:** total body irradiation; **Tc-99m DTPA:** technetium-99m diethylenetriaminepentaacetic acid; **TmP/GFR:** renal tubular phosphate threshold; **TP/Cr:** fractional tubular phosphate reabsorption (tubular phosphate/creatinine ratio); **TRP:** tubular reabsorption of phosphate; **U-ACR:** urinary albumin-to-creatinine ratio; **URA:** unilateral renal agenesis; **VP16:** etoposide; **WAGR:** Wilms' tumour, Aniridia, Genitourinary abnormalities, and Retardation; **WT:** Wilms' tumour

Characteristics of excluded studies *[ordered by study ID]*

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Study	Reason for exclusion
Abboud 2009	No distinction between nephrotoxic therapy and other therapy
Abd-El-Aal 2005	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Abedi 1990	No CCS
Ahn 2013	No CCS
Aksnes 2009	No distinction between nephrotoxic therapy and other therapy
Aleksa 2001	Review
Aleksa 2004	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Amato 1995	No CCS
Anderson 1979	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Anderson 2010	Editorial
Anderson 2016	Review
Antman 1989	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Arai 1998	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Arakelyan 2010	No CCS
Arga 2015	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Argueso 1992	< 20 CCS
Ariceta 1997	< 20 participants tested for early or late effects
Arjmandi-Rafsanjani 2008	No distinction between nephrotoxic therapy and other therapy
Armstrong 2010	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Arndt 1997	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Arndt 1999	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Arriagada 2009	Review
Ashraf 1994	< 20 participants tested for early or late effects
Ater 2016	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Aurer 2016	No CCS
Bacci 2002	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Bachrach 2014	No CCS

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Study	Reason for exclusion
Baker 2010	Review
Barahmani 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Bardi 2004b	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Bardi 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Bashir 2007	Case report
Baudoin 1993	< 20 CCS
Berg 2006	Case report
Berger 2013	No distinction between nephrotoxic therapy and other therapy
Bergeron 2005	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Beyzadeoglu 2008	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Bhatia 2003	Review
Bhisitkul 1991	< 20 CCS
Bobowski 2016	No distinction between CCS and adult cancer survivors
Boddy 1996	< 20 CCS
Bodei 2008	No CCS
Boer 2015	No distinction between CCS and adult cancer survivors
Bolling 2010	Age at diagnosis not 0-21 years
Bonsib 2010	Review
Bosl 1988	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Bouillet 2012	Review
Brade 1991	Review
Bradley 1998	No distinction between nephrotoxic therapy and other therapy
Breslow 2005	Unclear if the total described cohort received nephrotoxic treatment as defined by Cochrane Review
Brock 1992	< 20 CCS with early or long-term follow-up as defined in our inclusion criteria
Bunjes 2002	No CCS
Burk 1990	< 20 CCS
Bürger 1985	Review

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Study	Reason for exclusion
Cachat 1996	Review
Cai 2010	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Carlson 1993	No CCS
Cassady 1995	Review
Castleberry 1991	No nephrotoxicity
Chao 2016	No distinction between nephrotoxic and other therapy
Chen 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Chen 2016	< 20 CCS
Cheng 2008	Review
Chintagumpala 2015	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Chow 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Chow 2010	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Chow 2011	No distinction between nephrotoxic therapy and other therapy
Chu 2014	No relevant outcome measures
Coccia 2012	Guideline
Cohen 1995	Case series
Cohen 2008	No CCS
Cohen 2012	< 20 CCS, no distinction between adult and CCS
Cole 1994	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Conn 1972	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Cosentino 1993	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Cosset 1994	Review
Cost 2012	No distinction between CCS and adult cancer survivors
Couto-Silva 2001	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Coze 1997	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Cozzi 1997	Letter to the editor
Cozzi 2001	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria

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Study	Reason for exclusion
Cozzi 2007	No relevant outcome measures
Cozzi 2013a	Age at time of diagnosis not clear for total described cohort
Cozzi 2013b	Letter to the editor
Cozzi 2014a	Letter to the editor
Cozzi 2014b	Letter to the editor
Cozzi 2015a	Letter to the editor
Cozzi 2015b	Letter to the editor
Cozzi 2017a	Not all nephrotoxic therapies as defined by this Cochrane Review are mentioned and cannot be assumed
Cozzi 2017b	Letter to the editor
Crist 2001	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Crom 1981	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Culine 1994	No CCS
Curigliano 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
D'Angio 1976	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
D'Angio 1978	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
D'Aoust 1979	No CCS
Dantonello 2014	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Daw 2011	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
De Gislain 1990	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
De Kraker 1989	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Delpassand 2008	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Demchak 1991	No CCS
Demirjian 2014	No CCS
Desai 2016	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Detaille 2007	Review
Dhaliwal 1980	Case report
Diavolitsis 2010	No CCS

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Study	Reason for exclusion
Dome 1993	Review
Doz 1994	Review
Druley 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Duarte 2017	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Dunkel 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Edgar 2009	Review
Eghbali 1994	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Ehrlich 1974	Case report
Eklof 1976	No relevant outcome measures
Emminger 1992	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
England 2011	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
English 1999	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Erginel 2014	No relevant outcome measures
Escobar 2006	No distinction between nephrotoxic therapy and other therapy
Esiashvili 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Featherstone 2011	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Feig 2009	Review
Felice 2016	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Ferrari 2005	Follow-up duration of the study group of interest unclear
Ferrari 2005a	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Feusner 2008	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Feyer 1989	No distinction between childhood and adult cancer survivors
Finkel 2014	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Flentje 1998	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Fossa 2002	No distinction between adult and CCS
Fouladi 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Friedman 2007	Case report

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Study	Reason for exclusion
Fujieda 2009	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Gallegos-Castorena 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Galsky 2007	No CCS
Garaventa 1994	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Garvin 2012	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Gaynon 1994	Review
Geenen 2007	No distinction between nephrotoxic therapy and other therapy
Gerke 2000	No CCS
Gerstein 2009	No relevant outcome measures
Gillis 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Gobel 1993	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Goren 1986	< 20 CCS
Goren 2003	Review
Goyal 2011	No CCS
Graf 2003	Review
Gratton 2006	Review
Green 1995	Review
Green 2008	Review
Green 2013	Review
Greene 2013	Review
Gronroos 2008	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Gunes 2010	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Haddy 2009	No distinction between nephrotoxic therapy and other therapy
Hadley 2006	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Haecker 2013	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Hagleitner 2012	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Halim 2012	No distinction between CCS and adult cancer survivors

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Study	Reason for exclusion
Hallet 2012	Review
Hamilton 2011	Unclear if the total described cohort received nephrotoxic treatment as defined by Cochrane Review
Hanly 2009	Review
Hanna 2008	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Harel 2013	Review
Hartmann 2000	No CCS
Hayashi 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Hayes-Jordan 2010	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Hazar 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Hegde 2009	Review
Heikens 1998	Review
Heikens 2000	No distinction between nephrotoxic therapy and other therapy
Helenglass 1988	< 20 CCS
Henderson 2008	Review
Herrera-Pereza 2016	Review
Hingorani 2008	Review
Hong 2015	< 20 participants tested for early or late effects
Horwich 1991	< 20 CCS
Hou 2015	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Hovi 1989	Nephrotoxic treatment given in < 20 participants
Hu 2013	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Huang 2016	No CCS
Hubertus 2015	Follow-up period unclear
Hudson 2008	Review
Iida 2008	No CCS
Inai 2013	No CCS
Indolfi 2013	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria

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Study	Reason for exclusion
Ippolito 2006	No CCS
Jackson 2011	Review
Janeway 2010	Review
Jenkins 2013	Review
Jeon 2013	No CCS
Jeon 2014	No CCS
Jereb 1997	Review
Jiménez-Triana 2015	Not all nephrotoxic therapies as defined by this Cochrane Review are mentioned and cannot be assumed
Jones 1995	Review
Jones 2008	Review
Kal 2006	Review
Kallingal 2016	No CCS
Kandula 2015	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Kantarjian 1996	No CCS
Katzenstein 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Kawamura 2016	No CCS
Keaney 2005	Review
Kenney 2010	No nephrotoxic treatment
Kesik 2015	Not all nephrotoxic therapies as defined by this Cochrane Review are mentioned and cannot be assumed
Kibirige 1988	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Kieran 2013	< 20 CCS
Kieran 2014	< 20 CCS
Kieran 2015	Review
Kim 1980	No CCS
Kim 2009	No distinction between nephrotoxic therapy and other therapy
Kim 2015	No CCS
Kirch 1997	Review

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Study	Reason for exclusion
Kist-van Holthe 2002	No distinction between nephrotoxic therapy and other therapy
Kist-van Holthe 2005	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Komninos 2015	No CCS
Kopp 2012	Review
Koren 2007	Review
Kourti 2005	No distinction between nephrotoxic therapy and other therapy
Kremens 2002	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Kremers 2003	Review
Kubeš 2014	Review
Kumar 1996	< 20 participants tested for early or late effects
Kung 1995	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Kurt 2008	Review
Kusumi 2008	No CCS
Künkele 2013	No relevant outcome measures
Labrador 2014	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Landier 2008	Review
Landier 2012	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Lane 2013	No CCS
Langer 2004	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Laverdiere 2005	Age at time of diagnosis not 0-21 years
Le Bourgeois 1979	No distinction between CCS and adult cancer survivors
Le Deley 2014	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Leahey 1999	No distinction between nephrotoxic therapy and other therapy
Lee 2001	Early or late nephrotoxicity as defined in our inclusion criteria in < 20 participants
Leow 2016	Review
Levi 1993	No CCS
Levitt 2012	Review
Li 2006	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria

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Study	Reason for exclusion
Li 2016	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Liesner 1994	Nephrotoxic treatment given in < 20 participants
Liu 2016	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Loebstein 1999	Age at time of diagnosis not 0-21 years
Lonnerholm 1991	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Ludwig 1992	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Macklis 1991	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Macleod 1988	No CCS
Magnan 2015	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Majhail 2009	No distinction between nephrotoxic chemotherapy and other therapy
Makari 2010	Review
Mandell 1999	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Marina 1994	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Marina 2000	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Marina 2004	Review
Marina 2016	No distinction between CCS and adult cancer survivors
Mashhadi 2011	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Mashhadi 2013	No CCS
Massimi 2007	Review
Matsuyama 2002	Definition of nephrotoxic treatment wider than definition used in this Cochrane Review and no multivariable risk factors analyses performed
Mburu 2012	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
McCune 2004	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
McCune 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
McDonald 1993	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Meacham 2010	No nephrotoxic therapy
Meadows 1985	Review
Meck 2006	Review

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Study	Reason for exclusion
Mendez 2006	No CCS
Mertens 1997	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Meyer 2006	No CCS
Millar 2011	< 20 CCS
Millar 2017	Review
Minard-Colin 2012	No relevant outcome measures
Miralbell 1996	No CCS
Miralbell 2004	No CCS
Mitchell 2009	Review
Moghrabi 1998	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Mohammadianpanah 2004	Case report
Morgan 2016	< 20 CCS with early or long-term follow-up as defined in our inclusion criteria
Morris 1991	Review
Muramaki 2012	No CCS
Naguib 2008	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Nath 2007	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Ngo 2013	No CCS
Niethammer 1998	Review
Nieto 2005	< 20 survivors with nephrotoxic treatment
Nogueira 1998	< 20 CCS
Nunez 2007	Review
Oberlin 2009	Age at time of diagnosis 0-21 years
Oeffinger 2001	No nephrotoxic therapy
Oeffinger 2009	No nephrotoxic therapy
Ota 1993	Review of cisplatin studies in adults
O'Sullivan 2016	Review
Pahernik 2007	No CCS
Parigi 2003	No distinction between nephrotoxic therapy and other therapy

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Study	Reason for exclusion
Parisi 1999	Review
Patte 1991	No nephrotoxic treatment
Patzer 1997	No distinction between nephrotoxic therapy and other therapy
Patzer 2001	Age at time of diagnosis not 0-21 years
Paulides 2008	Review
Pectasides 2010	No CCS
Pentheroudakis 2007	Review
Pereira 2005	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Perwein 2011	< 20 CCS
Petersen 1992	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Petersen 1999	No CCS
Phillips 2008	Review
Pietila 2005	< 20 CCS
Pietila 2009	No distinction between nephrotoxic therapy and other therapy
Pinter 2003	No distinction between nephrotoxic therapy and other therapy
Plowman 1999	Review
Pochedly 1973	Review
Ponisch 2006	Review
Poon 2007	No CCS
Prasad 1996	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Pratt 1981	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Pratt 1991	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Pratt 1996	Review
Pugachev 2004	No CCS were included
Raney 1994	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Regazzoni 1998	No CCS
Reisi 2009	No nephrotoxic therapy

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Study	Reason for exclusion
Renal tumours and hypertension	Review/editorial
Richie 2013	Letter to the editor
Ritchey 1996	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Ritchey 2008	Review
Roback 1971	Case report
Romanini 1981	No CCS
Romao 2016	Review
Rossi 1993	Unclear if the total described cohort received nephrotoxic treatment as defined by Cochrane Review
Rossi 1994a	Age at time of diagnosis not 0-21 years
Rossi 1994b	Not all nephrotoxic therapies as defined by Cochrane Review are mentioned and cannot be assumed
Rossi 1999	Age at time of diagnosis not 0-21 years
Rossi 1999a	Review
Ruggiero 2013	Review
Ruggiero 2016	Review
Sadak 2012	Review
Saddadi 2009	No CCS
Saez 1995	No CCS
Sagerman 1969	Case series
Sagstuen 2005	No CCS
Sakellari 2010b	Duplicate study of Sakellari 2010a
Sanpakit 2013	< 20 participants tested for early or late effects
Sastry 2005	Review
Schenkein 1994	No CCS
Schiavetti 2015b	Letter to the editor
Schiff 1977	No CCS
Schmidt 2010	Review

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Study	Reason for exclusion
Schmoll 2003	No CCS
Schwartz 2001	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Schwartz 2007	No CCS
Shamash 2000	No CCS
Shirasaki 2004a	No CCS
Shirasaki 2004b	No CCS
Shkalim-Zemer 2015	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Shnorhavorian 2009	Review
Sieber 2004	No CCS
Silberzweig 1992	Case report
Simpson 2002	No CCS
Skinner 1991	Review
Skinner 1992	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Skinner 1993	Review
Skinner 2000	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Skinner 2003	< 20 CCS
Skinner 2009	Unclear if the total described cohort received nephrotoxic treatment as defined by Cochrane Review
Skinner 2010a	Review
Skinner 2011	Review
Skinner 2012	Review
Skinner 2013	Guideline
Sloetjes 2000	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Smith 1998	Case series
Sonn 2008	Review
Spira 2009	No CCS
Spreafico 2014	Letter to the editor
Springate 1997	Review

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Study	Reason for exclusion
Stava 2007	Review
Stefanowicz 2009	Definition nephrotoxic treatment wider than definition used in this Cochrane Review and no multivariable risk factor analyses performed
Stefanowicz 2011a	Review
Steinbach 1995	Review
Stern 2002	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Suarez 1991	No relevant outcome measures
Sudour-Bonnange 2015	Review
Sukarochana 1972	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Talvensaari 1996	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Talvensaari 1997	Review
Tamaro 1997	Review
Taylor 1997	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Taylor 2003	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Tefft 1977	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Termuhlen 2011	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Thomas 1983	No relevant outcome measures
Tichelli 1991	Review
Tokuc 1997	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Torricelli 2012	No CCS
Trahair 2007	Unclear if the total described cohort received nephrotoxic treatment as defined by Cochrane Review
Trimis 2007	No nephrotoxic therapy
Turna 2008	No CCS
Van den Heuvel-Eibrink 2011	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Van Waas 2010a	No nephrotoxic therapy
Van Waas 2010b	Review
Veringa 2011	No nephrotoxic treatment
Vio 1970	Review

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Study	Reason for exclusion
Von Der Weid 1999	< 20 participants treated with nephrotoxic therapy
Voute 1992	Review
Voute 1996	Review
Wallace 2013	Review
Watanabe Nemoto 2014	< 20 CCS
Waters 2015	Review
Weijl 2004	No CCS
Welch 1987	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Wistow 1979	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Womer 1985	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Wright 2009	Review
Wu 2005	Review
Xu 2016	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Yanagisawa 2009	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Yao 1997	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Yaris 2005	No nephrotoxic therapy
Yoshimura 1997	No CCS
Zagars 1987	No CCS
Zani 2005	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Zerin 1996	No relevant outcome measures
Zielinska 2003	No evaluation of early or late nephrotoxicity as defined in our inclusion criteria
Zorn 2007	No CCS
Zubowska 2013	Definition nephrotoxic treatment wider than definition used in this Cochrane Review and no multi-variable risk factor analyses performed

CCS: childhood cancer survivors

Characteristics of studies awaiting assessment *[ordered by study ID]*

Baassiri 2016

Methods	Cross-sectional cohort study

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Baassiri 2016 *(Continued)*

Participants	N of participants original cohort: n/m; N of participants described study group: 114; N of participants study group of interest: 114; N of participants with renal function tests: n/m Tumour: AML 114/114 (100%). Time period diagnosis/treatment: n/m. % M/F: male 46%/54% Age at diagnosis: n/m; age at follow-up: median 30 years (range 19-51); follow-up duration: median 19.3 years (range 10.7 - 37.6); completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m 44% received H(S)CT N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: 45%; RT field: n/m; radiation dose: n/m
Outcomes	Chronic health conditions in adult survivors of childhood AML, no specific mention of renal outcome
Notes	The full text of this study has not yet been published (as of 7 August 2017), but has been presented at the 48th Congress of the International Society of Pediatric Oncology, SIOP 2016, Dublin, Ireland (abstract PD060). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Bate 2012

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: 56; N of participants described study group: 56; N of participants study group of interest: 56; N of participants with renal function tests: 42 Tumour: WT (56/56). Time period diagnosis/treatment: n/m. % M/F: n/m. Age at diagnosis: median 3.7 years (range 0.4-18.9 years); age at follow-up: n/m; follow-up duration: mean 11.6 years (range 5.9-33.3 years); completion of follow-up: 42/56 (75%)
Interventions	N of participants ifosfamide: 0/56 (0%); ifosfamide cumulative dose: n/m N of participants cisplatin: 0/56 (0%); cisplatin cumulative dose: n/m N of participants carboplatin: unclear, at least 1 with maximum 5/56 (9%); carboplatin cumulative dose: n/m Other types of CT: melphalan, at least 1 with maximum 5/56 (9%); other CT cumulative doses: n/m N of participants NP: 55/56 (98%); NP details: n/m N of participants RT including the kidney region: 17/56 (30%); RT field: n/m; radiation dose: n/m
Outcomes	**eGFR** Definition of renal adverse effect: < 90 mL/min/1.73 m^2 Observed values of renal adverse effects: mean GFR was 96.5 mL/min/1.73 m^2 (range 72-150 mL/min/1.73 m^2)

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Bate 2012 *(Continued)*

	N of participants with renal adverse effect: 15/42 (35.7%); 6 participants received renal field RT, 1 had nephrotoxic CT and 2 participants received both. **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 44th Congress of SIOP 2012, London, UK (abstract PQ019). N of participants ifosfamide and cisplatin 0 is an assumption based on tumour type.

Begun 2011

Methods	Case-control study
Participants	25 WT survivors with single kidney. Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: estimated time in 7-12 age group 4.5 years (SD 2.2) and in 13-18 age group 7.5 years (SD 3.4); completion of follow-up: n/m Controls: 16 healthy children (group C)
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: n/m; RT field: n/m; radiation dose: n/m
Outcomes	**GFR measured by creatinine clearance** Definition of renal adverse effect: n/m Observed values of renal adverse effects: an average basal level of GRF in 7-12 years in WT was 125% compared with C and 82.6% in 13-18 years (in WT compared with C accordingly). GRF after the protein loading in 7-12 age of WT group was 141.32 ± 10.7 mL/min/1.73 m^2 (120.85 ± 5.54 in group C, NS), and in WT participants aged 13-18 was 97.92 ± 6.22 mL/min/1.73 m^2 (143.13 ± 6.93 in group C, $P < 0.01$) N of participants with renal adverse effect: n/m Risk factors: n/m **RFR** Definition of renal adverse effect: n/m Observed values of renal adverse effects: RFR percentage in WT group aged 7-12 was 16.68 ± 8.39% (24.76 ± 3.47% in group C, NS), and in 13-18 years was 14.31 ± 6.34% (38.11 ± 6.98% in group C, $P < 0.05$). RFR decreased in mL/min and in % for WT group 13-18 years compared with control N of participants with renal adverse effect n/m **Risk factors** n/m

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Begun 2011 *(Continued)*

Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 22nd Annual Congress of ESPNIC 2011, Hannover, Germany (poster 286). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Bom-Sucesso 2014

Methods	Retrospective cohort study
Participants	N of participants original cohort: 60; N of participants described study group: 52; N of participants study group of interest: n/m; N of participants with renal function tests: n/m Tumour: renal tumours 8/52 (15%), brain tumours 8/52 (15%), retinoblastomas 7/52 (13%), Ewing family of tumours 7/52 (13%), neurogenic tumours 4/52 (8%), leukaemias 5/52 (10%), rhabdomyosarcomas 4/52 (8%), others 7/52 (13%), nephrological pathology with a tumour predisposition syndrome without actual cancer 2/52 (4%). Time period diagnosis/treatment: n/m. % M/F: 52%/48% Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	CT 43/52 (83%) types and cumulative doses: unclear from the currently available information N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 7/52 (13%); NP details: unclear from the currently available information N of participants RT: 3/52 (6%); RT field: craniospinal and pelvic; radiation dose: unclear from the currently available information
Outcomes	Within CT treated participants, 13 had cortical lesions, 12 tubulopathy, 4 stage 2 renal insufficiency and 1 stage 1 renal insufficiency
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 47th Annual Congress of the ESPN 2014, Porto, Portugal (poster 382). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Bruce 2014

Methods	Retrospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 51; N of participants study group of interest: 51; N of participants with renal function tests: 51 Tumour: solid tumours 51/51 (100%). Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m

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Bruce 2014 *(Continued)*

Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: 51/51 (100%), cisplatin cumulative dose: n/m. N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 7/51 (14%); NP details: unclear from the currently available information N of participants RT: 3/51 (6%); RT field: craniospinal and pelvic; radiation dose: unclear from the currently available information
Outcomes	**Nephrotoxicity (composite outcome)** Definition of renal adverse effect: nephrotoxicity was graded as follows, 0: normal renal function, 1: asymptomatic electrolytes disorders in blood work, grade 2: need for electrolyte supplementation and/or increase in serum creatinine 1.5-1.9 times from baseline, grade 3: increase in serum creatinine 2-2.9 times from baseline or need for electrolyte supplementation for > 3 months after treatment completion, grade 4: renal replacement therapy Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 38/51 participants had nephrotoxicity (74.5%). Grade 1 was observed in 16/51 (31.4%) and Grade 2 in 22/51 (43.1%). Hypophosphatemia was found in 34/51 (66.7%) participants, hypomagnesaemia in 21/51 (41.2%), hypokalaemia in 18/51 (35.3%) participants **Risk factors** No multivariable analysis performed
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 6th Annual Meeting of the Canadian Society of Pharmacology and Therapeutics, 2014, Manitoba, Canada (abstract ID 11). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Cozzi 2016

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: 79; N of participants described study group: 79; N of participants study group of interest: unclear from the currently available information; N of participants with renal function tests: 79 Tumour: n/m Time period diagnosis/treatment: 1960-2014. % M/F: n/m. Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m. N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 79/79 (100%); NP details: unilateral NP N of participants RT: n/m; RT field: n/m radiation dose: n/m

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Cozzi 2016 *(Continued)*

Outcomes	**eGFR** Definition of renal adverse effect: eGFR < 90 mL/min/1.73 m^2 Observed values of renal adverse effects: n/m N of participants with renal adverse effect: n/m **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th Congress of SIOP 2016, Dublin, Ireland (abstract O159). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Eckstein 2010

Methods	Prospective cohort study
Participants	N of participants original cohort: 32; N of participants described study group: 32; N of participants study group of interest: unclear from the currently available information; N of participants with renal function tests: unclear from the currently available information Tumour: craniospinal tumours: 32/32 (100%). Time period diagnosis/treatment: 2002-2009. % M/F: 47%/53% Age at diagnosis: median 66 months; age at follow-up: n/m; follow-up duration: median 502 days; completion of follow-up: n/m Controls: unclear from the currently available information
Interventions	Conditioning regimens included carboplatin/thio-tepa/etoposide (61%), carboplatin/thiotepa (21%), carboplatin/thiotepa/etoposide (5%), thiotepa/etoposide (5%) and other (8%) N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m. N of participants carboplatin: 87%; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	Unclear from the currently available information, but abstract reports hypertension and renal failure
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 2010 BMT Tandem Meetings Orlando, FL, USA (abstract S247). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Godzinski 2016

Methods	Unclear from the currently available information
Participants	N of participants original cohort: 26; N of participants described study group: 26; N of participants study group of interest: 26; N of participants with renal function tests: 24

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Godzinski 2016 *(Continued)*

	Tumour: bilateral WT 26/26 (100%). Time period diagnosis/treatment: 2006-2015. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: 24/26 (92%) Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 26/26 (100%); NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	Renal function impairment; details unclear from the currently available information
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th Congress of SIOP 2016, Dublin, Ireland (abstract PD046). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Green 2016

Methods	Unclear from the currently available information
Participants	N of participants original cohort: unclear from the currently available information; N of participants described study group: 2314; N of participants study group of interest: 2314; N of participants with renal function tests: 2314 Tumour: n/m. Time period diagnosis/treatment: n/m. % M/F: 52%/48% Age at diagnosis: median 6.9 years (range 3.2-12.6); age at follow-up: median 31 years (range 25.3-37.0); follow-up duration: median 23 years (range 17.3-29.4); completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	**Hypomagnesemia** Definition of renal adverse effect: < 1.3 mEq/dL or taking supplement Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 39/2314 (1.7%) **Risk factors** n/m **CKD**

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Green 2016 *(Continued)*

	Definition of renal adverse effect: defined according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative Observed values of renal adverse effects: n/m N of participants with renal adverse effect: CCS with no CKD or CKD Grades 1-5 were 93.6%, 4.1%, 0.9%, 1.2%, 0.1%, and 0.1%, respectively **Risk factors** In multivariable analysis, non-Hispanic black race (OR 2.19, 95% CI 1.43 to 3.34), history of NP (OR 2.74, 95% CI 1.39 to 5.41), increased BMI 35-40 vs 25 (OR 2.36, 95% CI 1.38 to 4.05), BMI 40 vs > 0-25 (OR 2.15, 95% CI 1.21 to 3.82), history of treatment with ifosfamide (OR 2.24, 95% CI 1.23 to 4.06), or cis-platinum (OR 1.89, 95% CI 1.10 to 3.23) were associated with CKD Grade 1-5 vs no CKD. Age at RF evaluation 50 years vs 18-30 years (OR 6.72, 95% CI 1.06 to 42.79), history of treatment with ifosfamide (OR 7.23, 95% CI 2.47 to 21.12), or cis-platinum (OR 5.25, 95% CI 2.14 to 12.85) exposure were risk factors for CKD = Grade 3-5 vs No CKD. HD cyclophosphamide (1000 mg/m2/course) was not associated with CKD
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the ASCO Annual Meeting 2016, Chicago, USA (abstract 10571). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Grylli 2016

Methods	Prospective cohort study
Participants	N of participants original cohort: unclear from the currently available information; N of participants described study group: 66; N of participants study group of interest: unclear from the currently available information; N of participants with renal function tests: n/m Tumour: CNS tumour 66/66 (100%). Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: n/m; age at follow-up: median 12.6 years; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	**eGFR** Definition of renal adverse effect: n/m Observed values of renal adverse effects: mean eGFR was 156.9 + 28.2 mL/min/1.73 m^2 N of participants with renal adverse effect: n/m **Risk factors** n/m **BP**

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Grylli 2016 *(Continued)*

	Definition of renal adverse effect: n/m Observed values of renal adverse effects: BP was ≤ 90 percentile in all children N of participants with renal adverse effect: 0/66 (0%) **Risk factors** n/m **Tubular function** Definition of renal adverse effect: n/m Observed values of renal adverse effects: tubular function assessment did not demonstrate any abnormal values N of participants with renal adverse effect: 0/66 (0%) **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 21st annual scientific meeting and education day of the Society for Neuro-Oncology, Scottsdale, Arizona, USA (abstract QOS-52). From currently available data, it is unclear whether this study is eligible for inclusion in this review.

Ikram 2011

Methods	Unclear from the currently available information
Participants	N of participants original cohort: unclear from the currently available information; N of participants described study group: 30; N of participants study group of interest: 30; N of participants with renal function tests: 30 Tumour: solid tumour 30/30 (100%). Time period diagnosis/treatment: n/m. % M/F: 67%/33% Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	Treatment with platinum compounds (carboplatin, cisplatin) N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	**GFR** Definition of renal adverse effect: n/m Observed values of renal adverse effects: GFR ranged between 22 mL/min/1.73 m^2 and 160 mL/min/1.73 m^2 N of participants with renal adverse effect: n/m

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Ikram 2011 *(Continued)*

	Risk factors There was significant deterioration in GFR associated with cumulative doses of cisplatin and carboplatin (P = 0.01) From currently available information, it is unclear if these results are based on univariable or multivariable analysis. **Serum Mg/hypomagnesaemia** Definition of renal adverse effect: serum Mg < 1.5 mg/dL Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 13.7% of participants with cisplatin and 12.1% of participants with carboplatin therapy **Risk factors** n/m
Notes	We could not retrieve the full text of this study. Based on currently available information, it is unclear whether this study meets all inclusion criteria.

Janda 1993

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 20; N of participants study group of interest: 20; N of participants with renal function tests: 20 Tumour: unilateral WT: 20/20 (100%). Time period diagnosis/treatment: n/m. % M/F: 45%/55% Age at diagnosis: n/m; age at follow-up: mean 15.5 years (range 8-25 years); follow-up duration: mean 11.1 years (range 3-24 years); completion of follow-up: 20/20 (100%) Controls: number unknown, participants with a solitary kidney due to agenesis or NP due to other causes than WT
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 20/20 (100%); NP details: unilateral NP N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	**eGFR using the Schwartz formula** Definition of renal adverse effect: < 1.33 mL/sec/1.73 m^2 Observed values of renal adverse effects: mean 1.66 mL/sec/1.73 m^2 (SD 0.27) N of participants with renal adverse effect: 1/20 (5%) **Risk factors** n/m **Proteinuria measured by biuret reaction** Definition of renal adverse effect: > 100 mg/m^2/24 h

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Janda 1993 *(Continued)*

	Observed values of renal adverse effects: mean 34.7 mg/m^2/24 h (SD 145) N of participants with renal adverse effect: 1/20 (5%) **Risk factors** n/m **Proteinuria measured by microalbuminuria** Definition of renal adverse effect: > 10 mg/m^2/24 h Observed values of renal adverse effect: mean 16.8 mg/m^2/24 h (SD 30.1) N of participants with renal adverse effect: 7/20 (35%) **Risk factors** n/m **BP** Definition of renal adverse effect: SBP or DBP > 97th percentile according to the 2nd Task Force report on hypertension in children Observed values of renal adverse effects: n/m N of participants with renal adverse effect: SBP: 1/20 (5%); DBP: 4/20 (20%) **Risk factors** n/m
Notes	The study is written in Czech. We are awaiting the translation. Based on currently available information, it is unclear whether this study meets all inclusion criteria

Kieran 2010

Methods	Retrospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 72; N of participants study group of interest: n/m; N of participants with renal function tests: n/m Tumour: 40 (55.6%) leukaemia, 8 (11.1%) lymphoma, 15 (20.8%) CNS tumours, and 9 (12.5%) other solid tumours. Time period diagnosis/treatment: 2004-2009. % M/F: 56%/44% Age at diagnosis: mean: 8.3 years (range: 0.7-18.9 years); age at follow-up: mean 19.5 (range: 1.2-46.7) years; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	35 (48.6%) participants received CT, 4 (5.6%) received RT, 31 (43.1%) received both, and 2 (2.8%) participants were treated with surgical resection alone, further information unclear from the currently available information
Outcomes	Unclear from the currently available information, but including serum creatinine, serum electrolytes and urine electrolytes
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 2010 Annual Meeting of the American Urological Association, AUA San Francisco, CA USA (abstract e409). From currently available data it is unclear if this study is eligible for inclusion in this review

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Madden 2010

Methods	Prospective cohort study
Participants	N of participants original cohort: 47; N of participants described study group: 44; N of participants study group of interest: 44; N of participants with renal function tests: n/m Tumour: medulloblastoma: 49/49 (100%). Time period diagnosis/treatment: 1994-2009. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: unclear from the currently available information
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: yes, but number unclear from currently available information, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: lomustine, vincristine, cyclophosphamide, but numbers unclear from currently available information; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	Unclear from the currently available information, but the abstract mentions long-term renal insufficiency
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 14th International Symposium on Pediatric Neuro-Oncology, Vienna, Austria (abstract ii111). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Medeiros 2016

Methods	Retrospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 73; N of participants study group of interest: 73; N of participants with renal function tests: 73 Tumour: solid tumour 73/73 (100%). Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: minimum follow-up 1 year after completion of treatment; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: 73/73 (100%), cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	**Nephrotoxicity**

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Medeiros 2016 *(Continued)*

	Definition of renal adverse effect: • Grade 0: normal renal function • Grade 1: asymptomatic electrolyte disorders, including an increase in serum creatinine, up to 1.5 times baseline value • Grade 2: need for electrolyte supplementation < 3 months and/or increase in serum creatinine 1.5-1.9 times from baseline • Grade 3: increase in serum creatinine 2-2.9 times from baseline or need for electrolyte supplementation for > 3 months after treatment completion • Grade 4: increase in serum creatinine ≥ 3 times from baseline or renal replacement therapy Observed values of renal adverse effect: n/m N of participants with renal adverse effect: 53 developed nephrotoxicity (72.6%), no nephrotoxicity (grade 0) was observed in 20 participants (27.3%). Grade 1 was observed in 20 participants (27.3%), grade 2 in 8 participants (10.9%) and grade 3 in 25 participants (34.2%) **Risk factors** Participants with nephrotoxicity were younger than participants with non-nephrotoxicity, median age 5.9 years vs 13.4 years respectively (P = 0.006) From currently available information, it is unclear if these results are based on univariable or multivariable analysis.
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 17th Congress of the IPNA, 2016, Iguacu, Brazil (abstract PO-120). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Moczulska 2011

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 23; N of participants study group of interest: 23; N of participants with renal function tests: n/m Tumour: nephroblastoma 23/23 (100%). Time period diagnosis/treatment: n/m. % M/F: 48/52 Age at diagnosis: mean 3 years (2 months-9 years); age at follow-up: mean 8 years (7–17.5 years); follow-up duration: mean 8 years (minimum 5-12.5 years); completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 23/23 (100%); NP details: unilateral NP N of participants RT involving the kidney region: n/m; RT field: n/m radiation dose: n/m
Outcomes	**GFR calculated with Iohexol method** Definition of renal adverse effect: unclear from the currently available information Observed values of renal adverse effect: n/m

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Moczulska 2011 *(Continued)*

	N of participants with renal adverse effect: hyperfiltration with GRF > 120 mL/min/1.73 m^2 was measured in 5 children aged 7–14 (mean 10 years). CKD stage 2 was diagnosed in 4 participants aged 11–14 (mean 12.6 years) and in 2 of them proteinuria was observed **Risk factors** n/m **BP by use of APBM** Definition of renal adverse effect: n/m Observed values of renal adverse effect: n/m N of participants with renal adverse effect: ABPM showed hypertension in 6 children **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 15th tri-annual congress of the IPNA 2010, New York, USA (abstract PS3-SAT-409). From currently available data, it is unclear whether this study is eligible for inclusion in this review.

Moczulska 2013

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 42; N of participants study group of interest: 42; N of participants with renal function tests: n/m Tumour: kidney tumour 42/42 (100%). Time period diagnosis/treatment: n/m. % M/F: 40/60 Age at diagnosis: n/m; age at follow-up: 11+/-3.37, 5-17.5 years; follow-up duration: mean 7.7+/- 2.6 years; completion of follow-up: n/m Controls: control group consisted of 30 age-matched children with kidney agenesis (M = 14; F = 16), aged 10.81+/- 3.91, 4-17 years)
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 42/42 (100%); NP details: unilateral NP N of participants RT: n/m; RT field: n/m radiation dose: n/m
Outcomes	**GFR** Definition of renal adverse effect: n/m Observed values of renal adverse effect: participants in the control group showed significant higher GFR (117.9 vs 106.7 mL/min/sBSA, P = 0.021) than nephrectomised participants treated in early childhood with CT N of participants with renal adverse effect: n/m **Risk factors** n/m

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Moczulska 2013 *(Continued)*

	BP by 24 h APBM Definition of renal adverse effect: n/m Observed values of renal adverse effect: n/m N of participants with renal adverse effect: in result 15 participants were treated with ACEI as nephroprotection for albuminuria, hyperfiltration and hypertension **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 16th tri-annual congress of the IPNA 2013, Shanghai, China (abstract P-SUN341). From currently available data, it is unclear whether this study is eligible for inclusion in this review.

Moneib 2016

Methods	Retrospective cohort study
Participants	N of participants original cohort: 25; N of participants described study group: 25; N of participants study group of interest: 25; N of participants with renal function tests: 23 Tumour: bilateral WT 25/25 (100%). Time period diagnosis/treatment: 2007-2012. % M/F: n/m Age at diagnosis: median 2.7 years (range 0.3-8.6); age at follow-up: n/m; follow-up duration: median 49 months, completion of follow-up: 23/25 (92%) Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: vincristine 25/25 (100%), actinomycin D 25/25 (100%), doxorubicin 25/25 (100%); other CT cumulative doses: unclear from the currently available information N of participants NP: 23/23 (100%); NP details: bilateral partial NP 5/23, RN one side + partial NP other side 18/23 N of participants RT including the kidney region: 13/23 (56.5%); RT field: abdominal 13/13; radiation dose: unclear from the currently available information
Outcomes	**ESRD** Definition of renal adverse effect: n/m Observed values of renal adverse effect: n/m N of participants with renal adverse effect: 2/23 (8.7%) **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th Congress of SIOP 2016, Dublin, Ireland (abstract P0761). From currently available data, it is unclear whether this study is eligible for inclusion in this review

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Okur 2014

Methods	Retrospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 56; N of participants study group of interest: 56; N of participants with renal function tests: n/m Tumour: WT 56/56 (100%). Time period diagnosis/treatment: 1991-2004. % M/F: 23.1/76.9 Age at diagnosis: mean 50.7 +/- 40.3 (8-204) months; age at follow-up: 100.5 +/- 84.9 (1-274) months; follow-up duration: mean 7.7+/- 2.6 years; completion of follow-up: n/m Controls: n/m
Interventions	All participants received CT N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT: 35/56 (62.5%); RT field: n/m; radiation dose: n/m
Outcomes	**Proteinuria** 5 participants, all other information unclear from the currently available information **Chronic renal failure** 1 participant, all other information unclear from the currently available information
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 46th congress of SIOP 2014, Toronto, Canada (abstract EP-557). From currently available data, it is unclear whether this study is eligible for inclusion in this review.

Oz 2015

Methods	Retrospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 46; N of participants study group of interest: 46; N of participants with renal function tests: n/m Tumour: unilateral WT 46/46 (100%). Time period diagnosis/treatment: 1995-2014. % M/F: n/m Age at diagnosis: 3.5 years (0.5-14); age at follow-up: n/m; follow-up duration: mean 7 years; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m ifosfamide cumulative dose: n/m N of participants cisplatin: n/m, cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 46/46 (100%); NP details: unilateral NP

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Oz 2015 *(Continued)*

	N of participants RT: n/m; RT field: n/m; radiation dose: n/m
Outcomes	**GFR calculated according to the Schwartz formula** Definition of renal adverse effect: GFR < 80 mL/min/1.73 m^2 Observed values of renal adverse effect: at presentation, mean GFR was 100 mL/min/1.73 m^2 At the last visit mean GFR was 103 mL/min/1.73 m^2 N of participants with renal adverse effect: at presentation 22% of participants; at last visit 18% of children **Risk factors** There was no correlation of CT type with decreased GFR. **BP** Definition of renal adverse effect: SBP > 95th percentile for age, sex, and height Observed values of renal adverse effect: n/m N of participants with renal adverse effect: at presentation 74% of participants had hypertension; at last visit 25% of participants had hypertension **Risk factors** There was no correlation of CT type with increased BP **Proteinuria measured by albuminuria** Definition of renal adverse effect: n/m Observed values of renal adverse effect: n/m N of participants with renal adverse effect: albuminuria was found in 22% **Risk factors** RT was a significant risk factor for protein secretion (P = 0.02) From currently available information, it is unclear if results on risk factors are based on univariable or multivariable analyses.
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th congress of the ESPN meeting 2015, Brussels, Belgium (abstract P-112). From currently available data, it is unclear whether this study is eligible for inclusion in this review.

Radvansky 2010

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: 151; N of participants study group of interest: n/m; N of participants with renal function tests: n/m Tumour: WT: 151/151 (100%). Time period diagnosis/treatment: 1980-2001. % M/F: 45%/55% Age at diagnosis: mean 3.7 years (SD 2.7 years); age at follow-up: mean 19.4 years (SD 5.8 years); follow-up duration: n/m; completion of follow-up: n/m Controls: n/m

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Radvansky 2010 *(Continued)*

Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: including anthracyclines: 25.9%; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: 34.2%; RT field: n/m; radiation dose: n/m
Outcomes	**GFR using creatinine clearance** Definition of renal adverse effect: unclear from the currently available information Observed values of renal adverse effect: mean (SD): 1.56 mL/sec/1.73 m^2 (SD 0.56) N of participants with renal adverse effect: unclear from the currently available information **Risk factors** Univariable analysis. Unclear from the currently available information **Proteinuria, method unclear from the currently available information** Definition of renal adverse effect: > 1 g/24 h Observed values of renal adverse effect: mean 0.18 g/24 h/m^2 (SD 0.30) N of participants with renal adverse effect: 3/151 (2.0%) with proteinuria and normal glomerular function and serum albumin Risk factors Univariable analyses. Unclear from the currently available information **BP** Definition of renal adverse effect: SBP > 135 mmHg, DBP > 90 mmHg or receiving treatment for hypertension Observed values of renal adverse effect: unclear from the currently available information N of participants with renal adverse effect: SBP: 8.3%; DBP: 10.2% Treatment for hypertension: 8.6% of participants (of which 6% treated by pharmacotherapy) **Risk factors** Univariable analyses. Unclear from the currently available information
Notes	The study is written in Czech. We are awaiting full text and the translation. based on currently available information, it is unclear whether this study meets all inclusion criteria

Sakellari 2010a

Methods	Retrospective cohort study
Participants	N of participants original cohort: 164; N of participants described study group: 164; N of participants study group of interest: unclear from the currently available information; N of participants with renal function tests: n/m

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Sakellari 2010a *(Continued)*

	Tumour: haematological disease, not further specified. Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: range 9-65 years; age at follow-up: n/m; follow-up duration: median 23.5 months; completion of follow-up: n/m Controls: unclear from the currently available information
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: thiotepa or fludarabine, numbers n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: unclear from currently available information; RT field: TBI; radiation dose: hypofractionated
Outcomes	**CKD/renal insufficiency and eGFR using the MDRD or the Schwartz formula** Definition of renal adverse effect: < 60 mL/min/1.73 m^2 Observed values of renal adverse effects: mean value of pre-HCT GFR was within normal limits (111.5 ± 26) for participants who did not develop CKD and 97.21 ± —19 for those who developed CKD, while the GFR at 12 months post-transplant was 108 ± 28 and 54.7 ± 5.4 (mL/min/1.73 m^2), respectively. The course of CKD was asymptomatic until end-stage disease, when 3 participants were on dialysis and 1 participant received a renal transplant from his mother N of participants with renal adverse effect: unclear from the currently available information **Risk factors** On univariable analyses, the probability of developing CKD was 25% at 18 months for participants with 0 or 1 event of kidney injury versus 60% for those with 2-5 preceding events (P = 0.006). On the other hand, the type of conditioning, hyperfractionated TBI, administration of thiotepa or fludarabine, acute or chronic GVHD and the toxicity of antiviral or antifungal treatment did not correlate with the CKD. Calcineurin inhibitors were not included as risk factors because of their universal administration as prophylaxis and because of their toxicity with long-term treatment. On multivariable analysis, the only predictive factors were older age (P = 0.01), the number of preceded events of acute kidney injury and the in vivo T cell depletion with antithymocyte globulin or alemtuzumab (0.013)
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 36th Annual Meeting of the European Group for Blood and Marrow Transplantation 2010, Vienna, Austria (abstract S107). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Schiavetti 2016

Methods	Unclear from the currently available information
Participants	N of participants original cohort: 42; N of participants described study group: 30; N of participants study group of interest: 30; N of participants with renal function tests: 30 Tumour: sarcoma (S): 30/30 (100%). Time period diagnosis/treatment: 1980-2010. % M/F: 66.7%/33.3% Age at diagnosis: n/m; age at follow-up: mean 27 years; follow-up duration: mean 17 years; completion of follow-up: n/m

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Schiavetti 2016 *(Continued)*

	Controls: 35 participants with unilateral non-syndromic renal tumour, % M/F: 30%/70%, age at follow-up: mean 25 years, follow-up duration: mean 20 years
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: n/m; RT field: n/m; radiation dose: n/m
Outcomes	**eGFR** Definition of renal adverse effect: eGFR < 90 mL/min/1.73 m^2 Observed values of renal adverse effects: mean eGFR was 110.6 mL/min/1.73 mEq (95% CI 103.6 to 118.0) in sarcoma group vs 99.7 mL/min/1.73 mEq (95% CI 94.5 to 104.9) in unilateral non-syndromic renal tumour group (P = 0.01) N of participants with renal adverse effect: 10% (sarcoma) vs 22.9% (unilateral non-syndromic renal tumour) (NS) **Risk factors** n/m **CKD** Definition of renal adverse effect: according to "Kidney Disease: Improving Global Outcomes (KDIGO)" guidelines Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 6.7% (sarcoma) vs 8.6% (unilateral non-syndromic renal tumour) (NS) **Risk factors** n/m **BP** Definition of renal adverse effect: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 13.3% (sarcoma) vs 2.9% (unilateral non-syndromic renal tumour) (NS) **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th Congress of SIOP 2016, Dublin, Ireland (abstract P0368). From currently available data, it is unclear whether this study is eligible for inclusion in this review

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Sierota 2005

Methods	Unclear from the currently available information
Participants	N of participants original cohort: n/m; N of participants described study group: 80; N of participants study group of interest: 80; N of participants with renal function tests: n/m Tumour: WT 38/38 (100%). Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: n/m; RT field: n/m; radiation dose: n/m
Outcomes	Unclear from the currently available information but includes renal insufficiency, proteinuria and hypertension
Notes	The study is written in Polish. We are awaiting full text and the translation. based on currently available information, it is unclear whether this study meets all inclusion criteria

Stronska 2003

Methods	Cross-sectional cohort study
Participants	N of participants original cohort: 40; N of participants described study group: 40; N of participants study group of interest: 40; N of participants with renal function tests: 40 Tumour: WT: 40/40 (100%). Time period diagnosis/treatment: n/m. % M/F: n/m Age at diagnosis: mean: 3.42 years (SD 2.5 years); age at follow-up: mean: 12.2 years (SD 5 years); follow-up duration: n/m; completion of follow-up: 40/40 (100%) Controls: 24 age-matched individuals further details unclear from the currently available information
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 40/40 (100%); NP details: unilateral NP: 40/40 (100%) N of participants RT including the kidney region: 24/40 (60%); RT field: n/m; radiation dose: n/m
Outcomes	Endogenous creatinine clearance and serum phosphate: details unclear from the currently available information
Notes	The study is written in Polish. We are awaiting the translation

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Terenziani 2010

Methods	Retrospective cohort study
Participants	N of participants original cohort: 27; N of participants described study group: 27; N of participants study group of interest: 27; N of participants with renal function tests: n/m Tumour: bilateral WT: 27/27 (100%). Time period diagnosis/treatment: n/m. % M/F: 33%/66% Age at diagnosis: median 30 months (range 11 to 86 months); age at follow-up: n/m; follow-up duration: median 31 months (range 3-76 months); completion of follow-up: n/m Controls: unclear from the currently available information
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: vincristine and dactinomycin: 27/27 (100%); other CT cumulative doses: n/m N of participants NP: 27/27 (100%); NP details: bilateral partial NP: 9/27 (33%). Combined partial and complete NP: 12/27 (44%). Data missing or too early for surgery: 6/27 (23%) N of participants RT including the kidney region: 24/40 (60%); RT field: n/m; radiation dose: n/m
Outcomes	Unclear from the currently available information
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 42nd Congress of SIOP 2010, Boston, MA, USA (abstract 883). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Vanrenterghem 2014

Methods	Retrospective cohort study
Participants	N of participants original cohort: n/m; N of participants described study group: n/m; N of participants study group of interest: n/m; N of participants with renal function tests: n/m Tumour: osteosarcoma and Ewing tumour. Time period diagnosis/treatment: 1998-2010. % M/F: n/m Age at diagnosis: mean 13.6 years (SD 2.6); age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: all participants; ifosfamide cumulative dose: mean cumulative dosage 51 +/- 18 g/m^2 N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: n/m N of participants RT including the kidney region: n/m; RT field: n/m; radiation dose: n/m
Outcomes	**GFR (Schwartz formula)**

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Vanrenterghem 2014 *(Continued)*

	Definition of renal adverse effect: n/m Observed values of renal adverse effects: at initiation, 6, 18 and 36 months' evolution mean GFR 145, 111, 107, 105 mL/min/1.73 m^2 N of participants with renal adverse effect: unclear from the currently available information **Risk factors** n/m **TPO4/GFR** Definition of renal adverse effect: n/m Observed values of renal adverse effects: at initiation, 6, 18 and 36 months' evolution 1.29, 0.95, 0.98, 0.8 mmol/L N of participants with renal adverse effect: unclear from the currently available information **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 47th ESPN Congress 2014, Porto, Portugal (abstract p341). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Wilde 2013

Methods	Cross-sectional study
Participants	N of participants original cohort: n/m; N of participants described study group: 186; N of participants study group of interest: 186; N of participants with renal function tests: n/m Tumour: unilateral WT 186/186 (100%). Time period diagnosis/treatment: 1966-?. % M/F: n/m Age at diagnosis: n/m; age at follow-up: n/m; follow-up duration: median follow-up was 15 years; completion of follow-up: n/m Controls: 544 CCS, treated for a non-WT malignancy and who received no nephrotoxic therapy
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: n/m; cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: n/m; other CT cumulative doses: n/m N of participants NP: 186/186 (100%); NP details: unilateral NP 186/186 (100%) N of participants RT including the kidney region: 70/186 (38%); RT field: n/m; radiation dose: n/m
Outcomes	**eGFR using the Schwartz and the CKD-EPI formulas whenever relevant** Definition of renal adverse effect: n/m Observed values of renal adverse effects: GFR was significantly lower N of participants with renal adverse effect: n/m **Risk factors**

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Wilde 2013 *(Continued)*

	n/m **Urine dipsticks for albuminuria** Definition of renal adverse effect: normal only if negative Observed values of renal adverse effects: n/m N of participants with renal adverse effect: n/m **Risk factors** n/m **BP** Definition of renal adverse effects: adults with a SBP > 140 mmHg and/or a DBP > 90 mmHg and children with a SBP and/or DBP 2 x the SD corrected for gender, age and height were considered hypertensive Observed values of renal adverse effects: n/m N of participants with renal adverse effect: n/m **Risk factors** n/m
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 45th Congress of SIOP 2013, Hong Kong, China (abstract O-0179). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Yanagisawa 2016

Methods	Unclear from the currently available information
Participants	N of participants original cohort: n/m; N of participants described study group: 31; N of participants study group of interest: 31; N of participants with renal function tests: 31 Tumour: advanced neuroblastoma 31/31 (100%). Time period diagnosis/treatment: n/m, % M/F: n/m Age at diagnosis: n/m, age at follow-up: n/m; follow-up duration: n/m; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: 31/31 (100%); cisplatin cumulative dose: n/m N of participants carboplatin: n/m; carboplatin cumulative dose: n/m Other types of CT: "multiple CT", not specified; other CT cumulative doses: n/m N of participants NP: n/m; NP details: unilateral NP n/m N of participants RT including the kidney region: n/m; RT field: n/m; radiation dose: n/m
Outcomes	**GFR** Definition of renal adverse effects: unclear from the currently available information

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Yanagisawa 2016 *(Continued)*

	Observed values of renal adverse effects: ratio of creatinine and eGFR in after/before the CT in each participant were each (0.63-2.17, median 1.05) and (0.47-1.60, median 0.92) N of participants with renal adverse effect: unclear from the currently available information **Risk factors** Unclear from the currently available information
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th Congress of SIOP, 2016, Dublin, Ireland (abstract P0552). From currently available data, it is unclear whether this study is eligible for inclusion in this review

Yazal Erdem 2016

Methods	Unclear from the currently available information
Participants	N of participants original cohort: n/m; N of participants described study group: 59; N of participants study group of interest: 59; N of participants with renal function tests: n/m Tumour: n/m. Time period diagnosis/treatment: n/m % M/F: n/m Age at diagnosis: median 6.5 years, age at follow-up: median 10.5 years; follow-up duration: 2 years; completion of follow-up: n/m Controls: n/m
Interventions	N of participants ifosfamide: yes, number n/m; ifosfamide cumulative dose: n/m N of participants cisplatin: yes, number n/m; cisplatin cumulative dose: n/m N of participants carboplatin: yes, number n/m; carboplatin cumulative dose: n/m Other types of CT: HD-MTX, number n/m; other CT cumulative doses: n/m N of participants NP: n/m; NP details: unilateral NP n/m N of participants RT including the kidney region: n/m; RT field: n/m; radiation dose: n/m
Outcomes	**GFR** Definition of renal adverse effects: GFR < 90 ml/min/1.73m^2 Observed values of renal adverse effects Median GFR was 129 mL/min/1.73 m^2 (range 48-414 mL/min/1.73 m^2) N of participants with renal adverse effect: 15/59 (25%) **Risk factors** Unclear from the currently available information **TPR** Definition of renal adverse effects: TPR < 85% Observed values of renal adverse effects: median TPR was 91.2% (range 42-98.9%) N of participants with renal adverse effect: 5/59 (8.5%) **Risk factors** Unclear from the currently available information

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Yazal Erdem 2016 *(Continued)*

	Serum Mg/hypomagnesaemia Definition of renal adverse effects: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 11/59 (18.6%) **Risk factors** Unclear from the currently available information **Serum phosphate/hypophosphataemia** Definition of renal adverse effects: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 16/59 (27.1%) **Risk factors** Unclear from the currently available information **Proteinuria (microalbuminuria)** Definition of renal adverse effects: n/m Observed values of renal adverse effects: n/m N of participants with renal adverse effect: 16% **Risk factors** Unclear from the currently available information
Notes	The full text of this study has not yet been published (as of 7 August 2017), but was presented at the 48th Congress of SIOP, 2016, Dublin, Ireland (abstract P0554). From currently available data, it is unclear whether this study is eligible for inclusion in this review

% M/F: percentage male/female; **ACEI:** angiotensin-converter-enzyme inhibitor; **APBM:** ambulant blood pressure monitoring; **AML:** acute myeloid leukaemia; **ASCO:** American Society of Clinical Oncology; **BMI:** body mass index; **BMT:** bone marrow transplantation; **CI:** confidence interval; **CKD:** chronic kidney disease; **CNS:** central nervous system; **CT:** chemotherapy; **eGFR:** estimated glomerular filtration rate; **ESPN:** European Society of Paediatric Nephrology; **ESPNIC:** European Society of Paediatric and Neonatal Intensive Care; **ESPN:** European Society of Pediatric Nephrology; **ESRD:** end-stage renal disease; **GFR:** glomerular filtration rate; **HD:** high-dose; **H(S)CT:** hematopoietic (stem) cell transplantation; **IPNA:** International Pediatric Nephrology Association; **n/m:** not mentioned; **Mg:** magnesium; **MTX:** methotrexate; **NP:** nephrectomy; **NS:** not significant; **RFR:** renal function reserve: **RN:** radical nephrectomy; **RT:** radiotherapy; **sBSA:** second body surface area; **SD:** standard deviation; **SIOP:** International Society of Paediatric Oncology; **TBI:** total body irradiation; **TPO4/GFR:** tubular phosphate reabsorption/glomerular filtration rate ratio; **TPR:** Tubular phosphate reabsorption; **WT:** Wilms' tumour

DATA AND ANALYSES

Comparison 1. Prevalence of renal dysfunction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Chronic kidney disease/renal insufficiency as defined by study authors	6		Prevalence (Random, 95% CI)	Totals not selected

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Ifosfamide, radiotherapy and/or nephrectomy	3		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Radiotherapy and/or nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
2 (Estimated) glomerular filtration rate < 90 mL/min/1.73m^2	12		Prevalence (Random, 95% CI)	Totals not selected
2.1 Cisplatin, carboplatin and/or ifos-famide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	5		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Carboplatin and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
2.4 Ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
2.5 Radiotherapy and/or nephrectomy	3		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
3 (Estimated) glomerular filtration rate < 80 mL/min/1.73m^2	7		Prevalence (Random, 95% CI)	Totals not selected
3.1 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Cisplatin, ifosfamide and/or nephrec-tomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Cisplatin	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
3.4 Radiotherapy and/or nephrectomy	4		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
4 (Estimated) glomerular filtration rate < 75 mL/min/1.73m^2	1		Prevalence (Random, 95% CI)	Totals not selected
4.1 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
5 (Estimated) glomerular filtration rate < 70 mL/min/1.73m^2	1		Prevalence (Random, 95% CI)	Totals not selected
5.1 Radiotherapy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
6 (Estimated) glomerular filtration rate < 60 mL/min/1.73m^2	7		Prevalence (Random, 95% CI)	Totals not selected

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 Cisplatin, carboplatin and/or ifos-famide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Cisplatin	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
6.4 Ifosfamide and/or radiotherapy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
6.5 Radiotherapy and/or nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
6.6 Nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
7 (Estimated) glomerular filtration rate: other definition or definition not men-tioned	5		Prevalence (Random, 95% CI)	Totals not selected
7.1 Cisplatin and/or ifosfamide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Radiotherapy and/or nephrectomy	4		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8 Proteinuria as defined by study authors	22		Prevalence (Random, 95% CI)	Totals not selected
8.1 Cisplatin, carboplatin, ifosfamide, ra-diotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Cisplatin, carboplatin and/or ifos-famide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Cisplatin, carboplatin, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.4 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.5 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	5		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.6 Carboplatin, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.7 Radiotherapy and/or nephrectomy	9		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
8.8 Nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
9 Serum phosphate/hypophoshataemia as defined by study authors	8		Prevalence (Random, 95% CI)	Totals not selected
9.1 Cisplatin, carboplatin, ifosfamide, ra-diotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Cisplatin, carboplatin and/or ifos-famide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Cisplatin, carboplatin, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
9.4 Carboplatin, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
9.5 Ifosfamide and/or radiotherapy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
9.6 Radiotherapy and/or nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
9.7 Radiotherapy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
10 Tubular phosphate regulation parameters as defined by the study authors	6		Prevalence (Random, 95% CI)	Totals not selected
10.1 Cisplatin, carboplatin and/or ifosfamide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Cisplatin, ifosfamide and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
10.4 Ifosfamide and/or radiotherapy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
10.5 Ifosfamide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
10.6 Radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
11 Serum magnesium/hypomagnesaemia as defined by study authors	4		Prevalence (Random, 95% CI)	Totals not selected
11.1 Cisplatin, carboplatin and/or ifosfamide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Cisplatin	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
11.3 Radiotherapy and/or nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
12 Blood pressure as defined by study authors	30		Prevalence (Random, 95% CI)	Totals not selected
12.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	6		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
12.4 Carboplatin, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]

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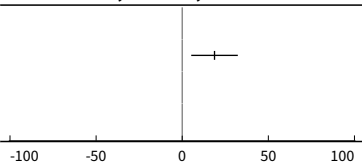
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.5 Ifosfamide, radiotherapy and/or nephrectomy	4		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
12.6 Radiotherapy and/or nephrectomy	14		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
12.7 Nephrectomy	2		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
13 Composite outcome as defined by Weirich 2004	1		Prevalence (Random, 95% CI)	Totals not selected
13.1 Carboplatin, ifosfamide, radiothera-py and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
14 Composite outcome as defined by Oue 2014	1		Prevalence (Random, 95% CI)	Totals not selected
14.1 Carboplatin, radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
15 Composite outcome as defined by Stohr 2007b	1		Prevalence (Random, 95% CI)	Totals not selected
15.1 Cisplatin, carboplatin, ifosfamide and/or radiotherapy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
16 Composite outcome as defined by von Schweinitz 1997	1		Prevalence (Random, 95% CI)	Totals not selected
16.1 Cisplatin and/or ifosfamide	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
17 Composite outcome as defined by Schiavetti 2015a	1		Prevalence (Random, 95% CI)	Totals not selected
17.1 Carboplatin, ifosfamide, radiothera-py and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]
18 Composite outcome as defined by Van Dijk 2010	1		Prevalence (Random, 95% CI)	Totals not selected
18.1 Radiotherapy and/or nephrectomy	1		Prevalence (Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Prevalence of renal dysfunction, Outcome 1 Chronic kidney disease/renal insufficiency as defined by study authors.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.1.1 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Stefanowicz 2011	32	0	18.8 (6.9)		18.75[5.23,32.27]
1.1.2 Ifosfamide, radiotherapy and/or nephrectomy					



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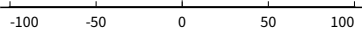
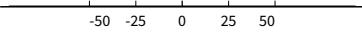
Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
Geenen 2010	62	0	4.8 (2.73)		4.84[-0.51,10.19]
Paulino 2000	42	0	2.4 (2.35)		2.38[-2.23,6.99]
Sasso 2010	34	0	2.9 (2.9)		2.94[-2.74,8.62]
1.1.3 Radiotherapy and/or nephrectomy					
Aronson 2011	25	0	32 (9.33)		32[13.71,50.29]
Sudour 2012	49	0	8.2 (3.91)		8.16[0.5,15.82]



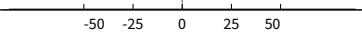
Analysis 1.2. Comparison 1 Prevalence of renal dysfunction, Outcome 2 (Estimated) glomerular filtration rate < 90 mL/min/1.73m².

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.2.1 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	73.7 (7.14)		73.68[59.69,87.67]
1.2.2 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Stefanowicz 2012	30	0	1.7 (2.33)		1.67[-2.9,6.24]
Davidoff 2015	36	0	36.1 (8.01)		36.11[20.41,51.81]
Schiavetti 2015a	35	0	40 (8.28)		40[23.77,56.23]
Stefanowicz 2011	32	0	43.8 (8.77)		43.75[26.56,60.94]
Interiano 2017	25	0	44 (9.93)		44[24.54,63.46]
1.2.3 Carboplatin and/or nephrectomy					
Cozzi 2012	25	0	36 (9.6)		36[17.18,54.82]
1.2.4 Ifosfamide, radiotherapy and/or nephrectomy					
Kubiak 2004	22	0	27.3 (9.5)		27.27[8.65,45.89]
1.2.5 Radiotherapy and/or nephrectomy					
Kostel Bal 2016	50	0	0 (0)		Not estimable
Stefanowicz 2010	26	0	3.9 (3.77)		3.85[-3.54,11.24]
Bailey 2002	40	0	22.5 (6.6)		22.5[9.56,35.44]
1.2.6 Nephrectomy					
Interiano 2015	73	0	21.9 (4.84)		21.92[12.43,31.41]



Analysis 1.3. Comparison 1 Prevalence of renal dysfunction, Outcome 3 (Estimated) glomerular filtration rate < 80 mL/min/1.73m².

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.3.1 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy					
Di Tullio 1996	34	0	2.9 (2.9)		2.94[-2.74,8.62]



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Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.3.2 Cisplatin, ifosfamide and/or nephrectomy					
Rossi 1994	69	0	8.7 (3.39)		8.7[2.06,15.34]
1.3.3 Cisplatin					
Brock 1991	40	0	42.5 (7.82)		42.5[27.17,57.83]
1.3.4 Radiotherapy and/or nephrectomy					
Bailey 2002	40	0	10 (4.74)		10[0.71,19.29]
Levitt 1992	53	0	18.9 (5.37)		18.87[8.34,29.4]
Mpofu 1992	55	0	5.5 (3.062)		5.45[-0.55,11.45]
Srinivas 1998	25	0	0 (0)		Not estimable

Analysis 1.4. Comparison 1 Prevalence of renal dysfunction, Outcome 4 (Estimated) glomerular filtration rate < 75 mL/min/1.73m^2.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.4.1 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Interiano 2017	17	0	47.1 (12.106)		47.06[23.33,70.79]

Analysis 1.5. Comparison 1 Prevalence of renal dysfunction, Outcome 5 (Estimated) glomerular filtration rate < 70 mL/min/1.73m^2.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.5.1 Radiotherapy					
Frisk 2002	26	0	26.9 (8.699)		26.92[9.87,43.97]

Analysis 1.6. Comparison 1 Prevalence of renal dysfunction, Outcome 6 (Estimated) glomerular filtration rate < 60 mL/min/1.73m^2.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.6.1 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	15.8 (5.92)		15.79[4.19,27.39]
1.6.2 Cisplatin					
Brock 1991	40	0	5 (3.45)		5[-1.76,11.76]
1.6.3 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Davidoff 2015	36	0	0 (0)		Not estimable

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Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.6.4 Ifosfamide and/or radiotherapy					
Skinner 2010b	24	0	12.5 (6.75)		12.5[-0.73,25.73]
1.6.5 Radiotherapy and/or nephrectomy					
Kern 2014	51	0	3.9 (2.72)		3.92[-1.41,9.25]
Mavinkurve-Groothuis 2016	24	0	4.2 (4.08)		4.17[-3.83,12.17]
1.6.6 Nephrectomy					
Interiano 2015	73	0	0 (0)		Not estimable

-100 -50 0 50 100

Analysis 1.7. Comparison 1 Prevalence of renal dysfunction, Outcome 7 (Estimated) glomerular filtration rate: other definition or definition not mentioned.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.7.1 Cisplatin and/or ifosfamide					
von Schweinitz 1997	41	0	0 (0)		Not estimable
1.7.2 Radiotherapy and/or nephrectomy					
Indolfi 2001	27	0	0 (0)		Not estimable
Kern 2014	51	0	15.7 (5.1)		15.69[5.69,25.69]
Kishore 2015	29	0	20.7 (7.52)		20.69[5.95,35.43]
Van Dijk 2010	181	0	6.6 (1.85)		6.63[3,10.26]

Survivors -100 -50 0 50 100 Control

Analysis 1.8. Comparison 1 Prevalence of renal dysfunction, Outcome 8 Proteinuria as defined by study authors.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.8.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schell 1995	21	0	4.8 (4.65)		4.76[-4.35,13.87]
1.8.2 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	13.2 (5.48)		13.16[2.42,23.9]
1.8.3 Cisplatin, carboplatin, radiotherapy and/or nephrectomy					
Mancini 1996	60	0	11.7 (4.14)		11.67[3.56,19.78]
1.8.4 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy					
Chevallier 1997	30	0	46.7 (9.11)		46.67[28.81,64.53]
Di Tullio 1996	34	0	32.4 (8.02)		32.35[16.63,48.07]
1.8.5 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Bardi 2004a	22	0	4.6 (4.44)		4.55[-4.15,13.25]
Interiano 2017	26	0	28.6 (8.54)		28.57[11.83,45.31]

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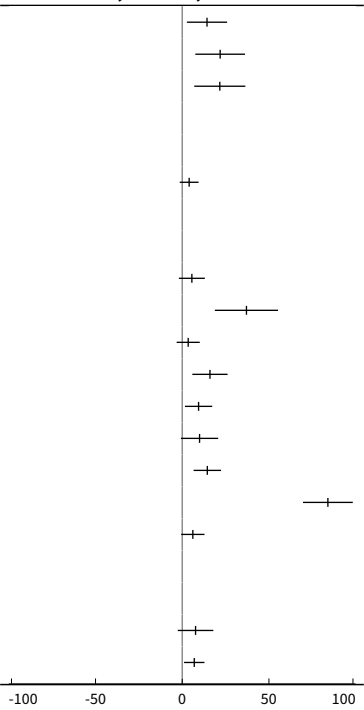
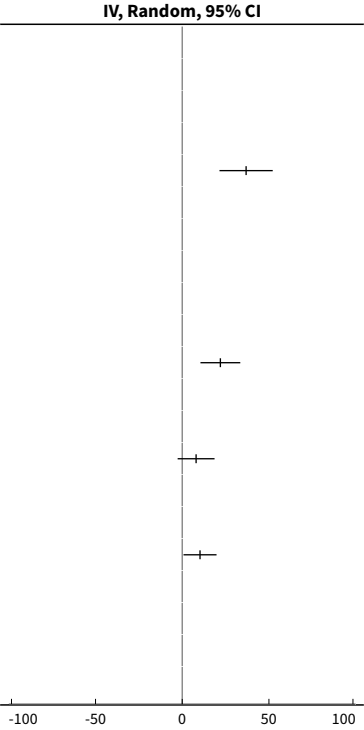
Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
Schiavetti 2015a	35	0	14.3 (5.92)		14.29[2.69,25.89]
Stefanowicz 2011	32	0	21.9 (7.31)		21.88[7.55,36.21]
Stefanowicz 2012	30	0	21.7 (7.52)		21.67[6.93,36.41]
1.8.6 Carboplatin, radiotherapy and/or nephrectomy					
Janeczko 2015	50	0	4 (2.77)		4[-1.43,9.43]
1.8.7 Radiotherapy and/or nephrectomy					
Bailey 2002	36	0	5.6 (3.82)		5.56[-1.93,13.05]
Indolfi 2001	27	0	37 (9.29)		37.04[18.83,55.25]
Kishore 2015	29	0	3.5 (3.39)		3.45[-3.19,10.09]
Kostel Bal 2016	50	0	16 (5.19)		16[5.83,26.17]
Levitt 1992	53	0	9.4 (4.01)		9.43[1.57,17.29]
Makipernaa 1991	30	0	10 (5.48)		10[-0.74,20.74]
Mpofu 1992	76	0	14.5 (4.04)		14.47[6.55,22.39]
Srinivas 1998	25	0	84 (7.33)		84[69.63,98.37]
Sudour 2012	49	0	6.1 (3.43)		6.12[-0.6,12.84]
1.8.8 Nephrectomy					
Cozzi 2005	26	0	7.7 (5.23)		7.69[-2.56,17.94]
Interiano 2015	72	0	6.9 (3)		6.94[1.06,12.82]



Analysis 1.9. Comparison 1 Prevalence of renal dysfunction, Outcome 9 Serum phosphate/hypophoshataemia as defined by study authors.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.9.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schell 1995	21	0	0 (0)		Not estimable
1.9.2 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	36.8 (7.83)		36.84[21.49,52.19]
1.9.3 Cisplatin, carboplatin, radiotherapy and/or nephrectomy					
Mancini 1996	60	0	0 (0)		Not estimable
1.9.4 Carboplatin, radiotherapy and/or nephrectomy					
Janeczko 2015	50	0	22 (5.86)		22[10.51,33.49]
1.9.5 Ifosfamide and/or radiotherapy					
Skinner 2010b	25	0	8 (5.43)		8[-2.64,18.64]
1.9.6 Radiotherapy and/or nephrectomy					
Bailey 2002	39	0	10.3 (4.86)		10.26[0.73,19.79]
Othman 2002	31	0	0 (0)		Not estimable
1.9.7 Radiotherapy					
Frisk 2007	23	0	0 (0)		Not estimable



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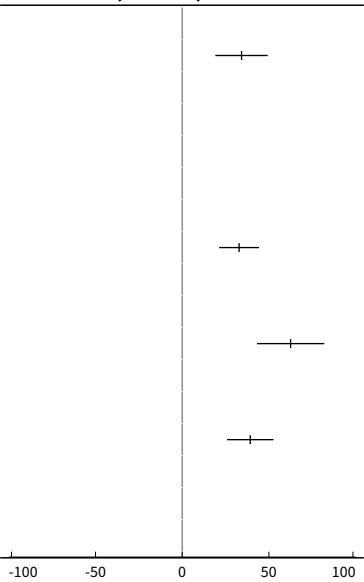
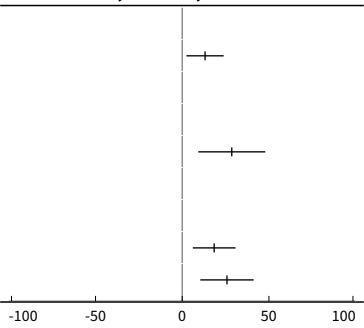
Analysis 1.10. Comparison 1 Prevalence of renal dysfunction, Outcome 10 Tubular phosphate regulation parameters as defined by the study authors.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.10.1 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	34.2 (7.7)		34.21[19.12,49.3]
1.10.2 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy					
Chevallier 1997	30	0	0 (0)		Not estimable
1.10.3 Cisplatin, ifosfamide and/or nephrectomy					
Rossi 1994	64	0	32.8 (5.87)		32.81[21.31,44.31]
1.10.4 Ifosfamide and/or radiotherapy					
Skinner 2010b	24	0	62.5 (9.88)		62.5[43.14,81.86]
1.10.5 Ifosfamide					
Rossi 1997	51	0	39.2 (6.84)		39.22[25.81,52.63]
1.10.6 Radiotherapy and/or nephrectomy					
Bailey 2002	39	0	0 (0)		Not estimable



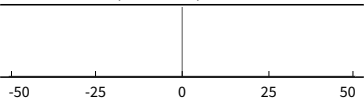
Analysis 1.11. Comparison 1 Prevalence of renal dysfunction, Outcome 11 Serum magnesium/hypomagnesaemia as defined by study authors.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.11.1 Cisplatin, carboplatin and/or ifosfamide					
Musiol 2016	38	0	13.2 (5.48)		13.16[2.42,23.9]
1.11.2 Cisplatin					
Brock 1991	21	0	28.6 (9.86)		28.57[9.24,47.9]
1.11.3 Radiotherapy and/or nephrectomy					
Bailey 2002	38	0	18.4 (6.29)		18.42[6.09,30.75]
Othman 2002	31	0	25.8 (7.86)		25.81[10.4,41.22]



Analysis 1.12. Comparison 1 Prevalence of renal dysfunction, Outcome 12 Blood pressure as defined by study authors.

Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.12.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schell 1995	21	0	0 (0)		Not estimable



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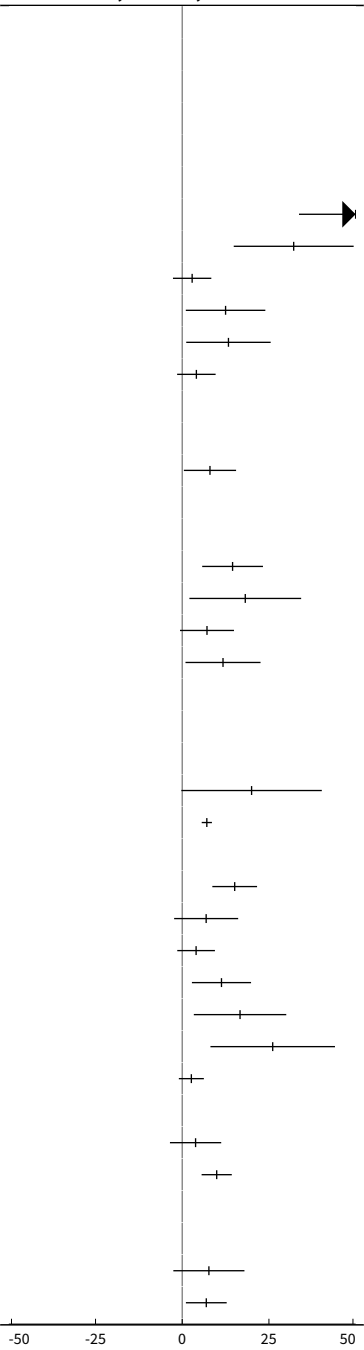
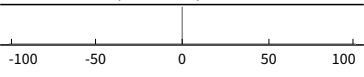
Study or subgroup	Survivors N	N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.12.2 Cisplatin, ifosfamide, radiotherapy and/or nephrectomy					
Chevallier 1997	30	0	0 (0)		Not estimable
Di Tullio 1996	34	0	0 (0)		Not estimable
1.12.3 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Davidoff 2015	36	0	50 (8.33)		50[33.67,66.33]
Interiano 2017	28	0	32.1 (8.82)		32.14[14.85,49.43]
Schiavetti 2015a	35	0	2.9 (2.82)		2.86[-2.67,8.39]
Stefanowicz 2011	32	0	12.5 (5.85)		12.5[1.03,23.97]
Stefanowicz 2012	30	0	13.3 (6.21)		13.33[1.16,25.5]
Trobs 2001	49	0	4.1 (2.83)		4.08[-1.47,9.63]
1.12.4 Carboplatin, radiotherapy and/or nephrectomy					
Janeczko 2015	50	0	8 (3.84)		8[0.47,15.53]
1.12.5 Ifosfamide, radiotherapy and/or nephrectomy					
Geenen 2010	62	0	14.5 (4.47)		14.52[5.76,23.28]
Kubiak 2004	22	0	18.2 (8.22)		18.18[2.07,34.29]
Paulino 2000	42	0	7.1 (3.97)		7.14[-0.64,14.92]
Sasso 2010	34	0	11.8 (5.52)		11.76[0.94,22.58]
1.12.6 Radiotherapy and/or nephrectomy					
Bailey 2002	36	0	0 (0)		Not estimable
Elli 2013	15	0	20 (10.33)		20[-0.25,40.25]
Finklestein 1993	1171	0	7.1 (0.75)		7.09[5.62,8.56]
Indolfi 2001	27	0	0 (0)		Not estimable
Kantor 1989	119	0	15.1 (3.29)		15.13[8.68,21.58]
Kishore 2015	29	0	6.9 (4.71)		6.9[-2.33,16.13]
Kostel Bal 2016	50	0	4 (2.77)		4[-1.43,9.43]
Levitt 1992	53	0	11.3 (4.35)		11.32[2.79,19.85]
Makipernaa 1991	30	0	16.7 (6.8)		16.67[3.34,30]
Mavinkurve-Groothuis 2016	23	0	26.1 (9.16)		26.09[8.14,44.04]
Mpofu 1992	76	0	2.6 (1.84)		2.63[-0.98,6.24]
Srinivas 1998	25	0	0 (0)		Not estimable
Stefanowicz 2010	26	0	3.9 (3.77)		3.85[-3.54,11.24]
Van Dijk 2010	181	0	9.9 (2.22)		9.94[5.59,14.29]
1.12.7 Nephrectomy					
Cozzi 2005	26	0	7.7 (5.23)		7.69[-2.56,17.94]
Interiano 2015	72	0	6.9 (3)		6.94[1.06,12.82]



Analysis 1.13. Comparison 1 Prevalence of renal dysfunction, Outcome 13 Composite outcome as defined by Weirich 2004.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.13.1 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					



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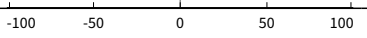
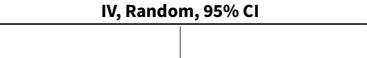
Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
Weirich 2004	385	0	7.3 (1.32)		7.27[4.68,9.86]



Analysis 1.14. Comparison 1 Prevalence of renal dysfunction, Outcome 14 Composite outcome as defined by Oue 2014.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.14.1 Carboplatin, radiotherapy and/or nephrectomy					
Oue 2014	25	0	40 (9.8)		40[20.79,59.21]



Analysis 1.15. Comparison 1 Prevalence of renal dysfunction, Outcome 15 Composite outcome as defined by Stohr 2007b.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.15.1 Cisplatin, carboplatin, ifosfamide and/or radiotherapy					
Stohr 2007b	593	0	3 (0.71)		3.04[1.65,4.43]

Analysis 1.16. Comparison 1 Prevalence of renal dysfunction, Outcome 16 Composite outcome as defined by von Schweinitz 1997.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.16.1 Cisplatin and/or ifosfamide					
von Schweinitz 1997	41	0	17.1 (5.88)		17.07[5.55,28.59]

Analysis 1.17. Comparison 1 Prevalence of renal dysfunction, Outcome 17 Composite outcome as defined by Schiavetti 2015a.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.17.1 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schiavetti 2015a	35	0	8.6 (4.73)		8.57[-0.7,17.84]

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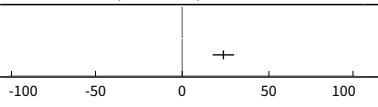
Analysis 1.18. Comparison 1 Prevalence of renal dysfunction, Outcome 18 Composite outcome as defined by Van Dijk 2010.

Study or subgroup	Survivors N	Control N	Prevalence (SE)	Prevalence IV, Random, 95% CI	Prevalence IV, Random, 95% CI
1.18.1 Radiotherapy and/or nephrectomy					
Van Dijk 2010	181	0	23.8 (3.16)		23.76[17.57,29.95]

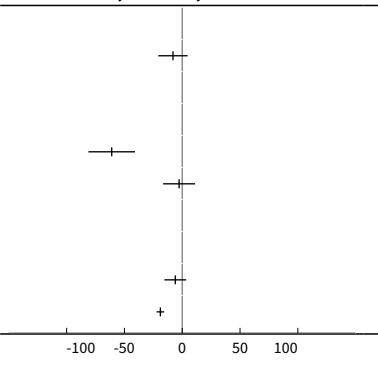


Comparison 2. Mean (estimated) glomerular filtration rate in mL/min/1.73m² at least 1 year after diagnosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean (estimated) glomerular filtration rate in studies that included internal or healthy controls	5		Mean Difference (Random, 95% CI)	Totals not selected
1.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy	1		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy	2		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Radiotherapy and/or nephrectomy	2		Mean Difference (Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Mean (estimated) glomerular filtration rate in mL/min/1.73m² at least 1 year after diagnosis, Outcome 1 Mean (estimated) glomerular filtration rate in studies that included internal or healthy controls.

Study or subgroup	Survivors N	Controls N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
2.1.1 Cisplatin, carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Schell 1995	21	6	-8 (6.46)		-8[-20.66,4.66]
2.1.2 Carboplatin, ifosfamide, radiotherapy and/or nephrectomy					
Bardi 2004a	22	86	-61 (10.28)		-61[-81.15,-40.85]
Stefanowicz 2012	30	17	-2.7 (7.04)		-2.7[-16.5,11.1]
2.1.3 Radiotherapy and/or nephrectomy					
Mavinkurve-Groothuis 2016	31	57	-6 (4.81)		-6[-15.43,3.43]
Wikstad 1986	22	6	-18.9 (1.64)		-18.9[-22.11,-15.69]



ADDITIONAL TABLES

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Table 1. Risk of bias assessment criteria for observational studies

Study group

Reporting bias (well-defined: yes/no):

- if the study specified the treatment regimen, including relevant cumulative chemotherapy and radiotherapy doses

Selection bias (representative: yes/no):

- if the described study group consisted of more than 90% of the original cohort of childhood cancer survivors
- *or* if the described study group was a random sample of the original cohort with respect to treatment

Follow-up

Reporting bias (well-defined: yes/no):

- if the duration of follow-up was mentioned

Attrition bias (adequate: yes/no)[a]:

- if the outcome was assessed for more than 90% of the study group of interest (++)
- *or* if the outcome was assessed for 60% to 90% of the study group of interest (+)

Outcome

Reporting bias (well-defined: yes/no):

- if the outcome definitions were objective and precise, that is, if the upper or lower limits of normal for renal function tests were described in the definition of renal late adverse effects for more than 50% of the included outcomes

Detection bias (blind: yes/no):

- if the outcome assessors were blinded to the investigated determinant

Risk estimation

Analysis (well-defined: yes/no):

- if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference, Chi^2 or any other relevant risk measure was calculated for more than 90% of the study group

Confounding (adjustment for other factors: yes/no):

- if important prognostic factors (i.e. age, sex, co-treatment, follow-up duration) were taken adequately into account

[a]if studies presented more than one follow-up measurement in time, we used the follow-up measurement with the highest percentage of follow-up to assess attrition bias.

Table 2. Glomerular filtration rate (GFR) equations

Name of equation	Reference	Age group	Components	Formula
Schwartz	Schwartz 1976	Paediatric	Height Creatinine[a]	eGFR (mL/min/1.73 m^2) = 0.55 x height (cm) / Scr (mg/dL)
Adapted Schwartz	Schwartz 1987	Paediatric	Height Creatinine[a] Age	eGFR (mL/min/1.73 m^2) = κ x height (cm) / Scr (mg/dL) The value of κ varies as a function of age and sex being 0.33 in preterm infants, 0.45 in full-term infants, 0.55 in children and adolescent girls, and 0.70 in adolescent boys

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Table 2. Glomerular filtration rate (GFR) equations *(Continued)*

			Sex	
Bedside Schwartz	Schwartz 2009	Paediatric	Height Creatinine[b]	eGFR (mL/min/1.73 m^2) = 0.413 x height (cm) / Scr (mg/dL)
New Schwartz	Schwartz 2009	Paediatric	Height Creatinine[b] Cystatin C BUN Sex	eGFR (mL/min/1.73 m^2) = 39.1 x [height (m)/Scr (mg/dL)]$^{0.516}$ x [1.8/Scys (mg/L)$^{0.294}$ [30/BUN (mg/dL)]$^{0.169}$[1.099]^{male}[height (m)/1.4]$^{0.188}$
CKiD Schwartz	Schwartz 2012	Paediatric	Height Creatinine[b] Cystatin C[c] BUN Sex	eGFR (mL/min/1.73 m^2) = 39.8 [height (m)/Scr (mg/dL)]$^{0.456}$ [1.8/Scys (mg/L)]$^{0.418}$[30/BUN (mg/dL)]$^{0.079}$1.076^{male}[height (m)/1.4]$^{0.179}$
Filler	Filler 2003	Paediatric	Cystatin C	log(GFR) = 1.962 + [1.123*log(1/CysC)]
Couna-han-Bar-ratt	Counahan 1976	Paediatric	Height Creatinine (enzymatic test)	eGFR (mL/min/1.73 m^2) = 38 x height (cm)/ Scr (µmol/L)
Cock-roft-Gault	Gault 1992	Adult	Creatinine[a] Body weight Sex	Creatinine clearance (mL/min) = [(140-age (years)) x body weight (kg)]/(Scr (mg/dL) x 72) (for women, x 0.85)
MDRD	Levey 2007	Adult	Creatinine[b] Age Sex Race	For Scr (mg/dL) is eGFR (mL/min/1.73 m^2) = 175 x standardized Scr $^{-1.154}$ x age $^{-0.203}$ x 1.212 (if black) x 0.742 (if female) for Scr (µmol/L) is eGFR (mL/min/1.73 m^2) = 30849 standardized Scr $^{-1.154}$ x age$^{-0.203}$ x 1.212 (if black) x 0.742 (if female)
CKD-EPI 2009	Levey 2009	Adult	Creatinine[b] Age Sex Race	eGFR (mL/min/1.73 m^2) = 141 × min (Scr/κ, 1)$^{\alpha}$ × max (Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} [× 1.018 if female] [× 1.159 if black] κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males min is the minimum of Scr/κ or 1 max is the maximum of Scr/κ or 1 Scr in mg/dL
CKD-EPI 2012	Inker 2012	Adult	Cystatin C[c]	eGFR (mL/min/1.73 m^2) = 133 × min (Scys/0.8, 1)$^{-0.499}$ × max (Scys/0.8, 1)$^{-1.328}$ × 0.996^{Age} [× 0.932 if female]

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Table 2. Glomerular filtration rate (GFR) equations *(Continued)*

Cystatin C			Age Sex	min indicates the minimum of Scr/κ or 1 max indicates the maximum of Scys/κ or 1 Scys in mg/L
CKD-EPI 2012 Creatinine + Cystatin C	Inker 2012	Adult	Creatinine[b] Cystatin C[c] Age Sex Race	eGFR (mL/min/1.73 m^2) = 135 × min (Scr/κ, 1)$^{\alpha}$ × max (Scr/κ, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ × max (Scys/0.8, 1)$^{-0.711}$ × 0.995^{Age} [× 0.969 if female] [× 1.08 if black] κ is 0.7 for females and 0.9 for males α is −0.248 for females and −0.207 for males min indicates the minimum of Scr/κ or 1 max indicates the maximum of Scr/κ or 1 Scr in mg/dL Scys in mg/L

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; **CKiD:** Chronic Kidney Disease in Children (study); **BUN:** blood urea nitrogen; **MDRD:** Modification of Diet in Renal Disease; **Scr:** serum creatinine; **Scys:** serum cystatin

[a,b]Note differences in calibration material used for the respective creatinine and/or cystatin C measurements: For creatinine the less specific Jaffé reaction[a] versus the modern, highly specific IDMS (isotope dilution mass spectrometry)-calibrated assays[b] (Myers 2006).
[c]For cystatin C, an international calibrator was introduced in 2010 by the International Federation of Clinical Chemistry (IFCC) allowing standardization across different assays (Grubb 2010).

Table 3. Treatment subgroups in studies included for the assessment of prevalence

Treatments included in study	Amount of studies	Included studies[a]
Cisplatin, carboplatin, ifosfamide, radiotherapy and nephrectomy	1	Schell 1995
Cisplatin, carboplatin, ifosfamide and radiotherapy	1	Stohr 2007b
Cisplatin, carboplatin and ifosfamide	1	Musiol 2016
Cisplatin, carboplatin, radiotherapy and nephrectomy	1	Mancini 1996
Cisplatin, ifosfamide, radiotherapy and nephrectomy	2	Chevallier 1997; Di Tullio 1996;
Cisplatin, ifosfamide and nephrectomy	1	Rossi 1994
Cisplatin and ifosfamide	1	von Schweinitz 1997
Cisplatin	1	Brock 1991
Carboplatin, ifosfamide, radiotherapy and nephrectomy	8	Bardi 2004a; Davidoff 2015; Interiano 2017; Schiavetti 2015a; Stefanowicz 2011; Stefanowicz 2012; Trobs 2001; Weirich 2004
Carboplatin, radiotherapy and nephrectomy	2	Janeczko 2015; Oue 2014
Carboplatin and nephrectomy	1	Cozzi 2012

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Table 3. Treatment subgroups in studies included for the assessment of prevalence *(Continued)*

Ifosfamide, radiotherapy and nephrectomy	4	Geenen 2010; Kubiak 2004 Paulino 2000; Sasso 2010
Ifosfamide and radiotherapy	1	Skinner 2010b
Ifosfamide	1	Rossi 1997
Radiotherapy and nephrectomy	22	Aronson 2011; Bailey 2002; Cost 2014; De Graaf 1996; Elli 2013; Finklestein 1993; Indolfi 2001; Kantor 1989; Kern 2014; Kishore 2015; Kostel Bal 2016; Lange 2011; Levitt 1992; Makipernaa 1991; Mavinkurve-Groothuis 2016; Mpofu 1992; Othman 2002; Srinivas 1998; Stefanowicz 2010; Sudour 2012; Van Dijk 2010; Wikstad 1986
Nephrectomy	2	Cozzi 2005; Interiano 2015
Radiotherapy	2	Frisk 2002; Frisk 2007

[a]Only the 52 studies included for the assessment of prevalence are shown in this table.

Table 4. Risk factors from multivariable analyses on chronic kidney disease/renal insufficiency: studies included for prevalence and risk factors

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Lange 2011[a]	Survivors of non-WT1 syndromic Wilms' tumour	End-stage renal disease	Age at diagnosis (< 24 months)	+	HR 2.8 (95% CI 1.4 to 5.6)
			Histologic type: stromal	+	HR 6.4 (95% CI 3.4 to 11.9)
			Histologic type: blastemal	-	HR 0.6 (95% CI 0.3 to 1.2)
			Histologic type: epithelial	-	HR 0.4 (95% CI 0.1 to 1.3)
			Nephrogenic rests: intralobar or both	+	HR 5.9 (95% CI (2 to 17.3)
			Nephrogenic rests: perilobar	-	HR 0.5 (95% CI 0.1 to 2.8)

CI: confidence interval; **HR:** hazard ratio

[a]Lange 2011 used multiple Cox regression analyses and adjusted for for histology and nephrogenic rests.

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Table 5. Risk factors from multivariable analyses on diminished (estimated) glomerular filtration rate: studies not fulfilling inclusion criteria

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Dekkers 2013[a]	Overall cohort of long-term CCS	GFR < 60 mL/min/1.73 m^2 (using MDRD formula)	Hypertension	-	Adjusted mean 104 (95% CI 88.00 to 120.00)
			Cisplatin < 450 mg/m^2	-	Adjusted mean 96 (95% CI 82.00 to 109.00)
			Cisplatin > 450 mg/m^2	+	Adjusted mean 83 (95% CI 66.00 to 100.00)
			Ifosfamide < 16000 mg/m^2	-	Adjusted mean 102 (95% CI 86.00 to 117.00)
			Ifosfamide > 16000 mg/m^2	+	Adjusted mean 88 (95% CI 73.00 to 103.00)
			Carboplatin	-	Adjusted mean 94 (95% CI 81.00 to 106.00)
			Cyclophosphamide < 3500 mg/m^2	-	Adjusted mean 96 (95% CI 83.00 to 110.00)
			Cyclophosphamide > 3500 mg/m^2	-	Adjusted mean 95 (95% CI 81.00 to 109.00)
			MTX	-	Adjusted mean 95 (95% CI 81.00 to 109.00)
			TBI	-	Adjusted mean 99 (95% CI 83.00 to 115.00)
			NP, no abdominal RT	+	Adjusted mean 91 (95% CI 76.00 to 106.00)
			Abdominal RT, no NP	-	Adjusted mean 96 (95% CI 78.00 to 113.00)
			NP and abdominal RT	+	Adjusted mean 90 (95% CI 74.00 to 106.00)

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Table 5. Risk factors from multivariable analyses on diminished (estimated) glomerular filtration rate: studies not fulfilling inclusion criteria *(Continued)*

Knijnenburg 2012[b]	Overall cohort of long-term CCS	GFR < 90 mL/min/1.73 m^2 (using Schwartz formula or CKD-EPI formula)	Cumulative ifosfamide dose (per 10 g/m^2)	+	OR 1.62 (95% CI 1.44 to 1.82)
			Cumulative cisplatin dose (per 100 mg/m^2)	+	OR 1.29 (95% CI 1.08 to 1.54)
			Cumulative carboplatin dose (per 100 mg/m^2)	-	OR 1.03 (95 % CI 1.00 to 1.07)
			HD-cyclophosphamide (no/yes) (≥ 1 g/m^2 per course)	+	OR 7.08 (95% CI 2.72 to 18.45)
			HD-MTX (no/yes) (≥ 1 g/m^2 per course)	-	OR 0.60 (95% CI 0.19 to 1.85)
			NP (no/yes)	+	OR 8.56 (95% CI 3.42 to 21.42)
			Total-body irradiation (no/yes)	-	OR 1.72 (95% CI 0.20 to 15.13)
			Abdominal irradiation (no/yes)	-	OR 1.50 (95% CI 0.62 to 3.63)
			Age at diagnosis (in years)	-	OR 1.05 (95% CI 0.97 to 1.13)
			Time since diagnosis (per 5 years)	+	OR 1.34 (95% CI 1.04 to 1.72)
			Male sex	-	OR 38.4 (95% CI 11.0 to 134.4)
	Mutually exclusive treatment group[c]	GFR < 90 mL/min/1.73 m^2 (using Schwartz formula or CKD-EPI formula)	Ifosfamide only	+	OR 38.4 (95% CI 11.0 to 134.4)
			Cisplatin only	+	OR 8.9 (95% CI 1.5 to 54.3)
			Carboplatin only	+	OR 15.2 (95% CI 1.5 to 155.5)
			Platinum agents + ifosfamide	+	OR 37.9 (95% CI 10.0 to 144.2)

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Table 5. Risk factors from multivariable analyses on diminished (estimated) glomerular filtration rate: studies not fulfilling inclusion criteria *(Continued)*

			HD-MTX only (≥ 1 g/m² per course)	-	OR 2.0 (95% CI 0.4 to 11.8)
			NP only	+	OR 19.3 (95% CI 5.1 to 72.9)
			RT only	+	OR 4.5 (95% CI 0.5 to 41.7)
			NP + NCTx	+	OR 108.6 (95% CI 18.1 to 651.1)
			NP + RT	+	OR 22.0 (95% CI 6.3 to 77.1)
			NP + NCTx + RT	+	OR 125.6 (95% CI 20.8 to 757.1)
			Other NCTx combinations	+	OR 17.7 (95% CI 4.5 to 70.3)
			RT + NCTx	+	OR 21.7 (95% CI 3.6 to 131.9)
Mudi 2016[d]	Overall cohort of long-term CCS	GFR < 90 mL/min/1.73 m² (using Schwartz formula)	Ifosfamide	+	OR 5.01 (95% CI 1.46 to 17.17)
			Carboplatinum	-	OR 3.25 (95% CI 0.83 to 12.59)
			NP	+	OR 6.35 (95% CI 1.84 to 21.89)
			RT	-	OR 3.31 (95% CI 0.55 to 19.98)
			Duration after treatment (years)	-	OR 1.20 (95% CI 1.00 to 1.44)
Mulder 2013[e]	Overall cohort of long-term CCS	GFR < 90 mL/min/1.73 m² (using CKD-EPI formula)	Ifosfamide	+	n/m
			Ifosfamide by time interaction	-	n/m
			Ifosfamide dose by time interaction	-	n/m
			Cisplatin	+	n/m
			Cisplatin by time interaction	+	n/m
			Cisplatin dose by time interaction	+	n/m

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Table 5. Risk factors from multivariable analyses on diminished (estimated) glomerular filtration rate: studies not fulfilling inclusion criteria *(Continued)*

			Carboplatin	+	n/m
			Carboplatin by time interaction	+	n/m
			Carboplatin dose by time interaction	+	n/m
			HD-cyclophosphamide (≥1 g/m²/course or a total cumulative dose of ≥ 10 g/m²)	+	n/m
			HD-cyclophosphamide by time interaction	+	n/m
			HD-MTX (≥ 1 g/m²/course)	-	n/m
			RT	-	n/m
			NP	+	n/m
			NP by time interaction	-	n/m
			NP age at diagnosis	+	n/m
Van Why 1991[f]	Bone marrow transplant survivors	Renal insufficiency defined as doubling of baseline serum creatinine concentration or creatinine clearance < 50 mL/min/1.73 m² (Schwartz formula)	Cyclosporin A use beyond day 60	+	n/m
			Amphotericin B use	+	n/m
			Conditioning with TBI	+	n/m
			Conditioning with chemotherapy	-	n/m
			Renal insufficiency in first 60 days post-BMT	-	n/m

BMT: bone marrow transplant; **CCS:** childhood cancer survivors; **CI:** confidence interval; **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration; **GFR:** glomerular filtration rate; **HD:** high-dose; **MDRD:** Modification of Diet in Renal Disease; **MTX:** methotrexate; **NCTx:** nephrotoxic chemotherapy; **n/m:** not mentioned; **NP:** nephrectomy; **OR:** odds ratio; **RR:** risk ratio; **RT:** radiotherapy; **TBI:** total body irradiation

[a]Dekkers 2013 used covariance analysis and adjusted for age, age at diagnosis, and body mass index.
[b]Knijnenburg 2012 used multivariable logistic regression analyses and adjusted for age at cancer diagnosis, and duration of follow-up since cancer diagnosis.
[c]Therapies were modelled as mutually exclusive treatment groups and entered into the models as a categorical variable.
[d]Mudi 2016 used multivariable logistic regression analyses and adjusted for co-treatment.
[e]Mulder 2013 used multivariable logistic regression analyses to assess predictors of glomerular function patterns over time and adjusted for follow-up time, gender, age at diagnosis, and co-treatment.

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[f]Van Why 1991 used stepwise logistical regression analyses and adjusted for co-treatment.

Table 6. Risk factors from multivariable analyses on diminished (estimated) glomerular filtration rate: studies included for prevalence and risk factors

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Frisk 2002[a]	CCS treated with TBI	GFR < 70 mL/min/1.73 m^2 by 51-Cr clearance	Concomitant treatment with aminoglycosides and vancomycin	+	Beta: —32 mL/min/1.73 m^2 (95% CI: —54 to —10)
			Age	-	n/m
	CCS treated without TBI	GFR < 70 mL/min/1.73 m^2 by 51-Cr clearance	Concomitant treatment with aminoglycosides and vancomycin	-	n/m

51-Cr: 51-chromium; **CCS:** childhood cancer survivors; **CI:** confidence interval; **GFR:** glomerular filtration rate; **n/m:** not mentioned; **TBI:** total body irradiation

[a]Frisk 2002 used multivariable regression analyses and adjusted for age and pre-transplant glomerular filtration rate.

Table 7. Risk factors from multivariable analyses on proteinuria: studies not fulfilling inclusion criteria

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Dekkers 2013[a]	Overall cohort of long-term CCS	Microalbuminuria U-ACR > 3.5 mg/mmol Cr (women) and > 2.5 mg/mmol Cr (men) Macroalbuminuria U-ACR > 35 mg/mmol Cr (women) and > 25 mg/mmol Cr (men)	Hypertension	-	OR 1.71 (95% CI 0.86 to 3.40)
			Cisplatin < 450 mg/m^2	-	OR 1.73 (95% CI 0.44 to 6.85)
			Cisplatin > 450 mg/m^2	+	OR 5.19 (95% CI 1.21 to 22.21)
			Ifosfamide < 16000 mg/m^2	-	OR 1.35 (95% CI 0.34 to 5.33)
			Ifosfamide >16000 mg/m^2	-	OR 1.49 (95% CI 0.49 to 4.54)
			Carboplatin	-	OR 2.18 (95% CI 0.45 to 10.54)
			Cyclophosphamide < 3500 mg/m^2	-	OR 0.54 (95% CI 0.21 to 1.39)

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Table 7. Risk factors from multivariable analyses on proteinuria: studies not fulfilling inclusion criteria *(Continued)*

			Cyclophosphamide > 3500 mg/m²	-	OR 0.84 (95% CI 0.35 to 2.00)
			MTX	-	OR 0.94 (95% CI 0.49 to 2.16)
			TBI	-	OR 3.28 (95% CI 0.88 to 12.22)
			NP, no abdominal RT	-	OR 2.12 (95% CI 0.21 to 21.21)
			Abdominal RT, no NP	-	OR 3.29 (95% CI 0.69 to 15.67)
			NP and abdominal RT	+	OR 3.14 (95% CI 1.02 to 9.69)
Knijnenburg 2012[b]	Overall cohort of long-term CCS	Albuminuria dipstick Normal: negative Abnormal: high 150 mg/dL, moderate: 75 mg/dL equivocal: 25 mg/dL	Cumulative ifosfamide dose (per 10 g/m²)	+	OR 1.34 (95% CI 1.23 to 1.46)
			Cumulative cisplatin dose (per 100 mg/m²)	-	OR 0.95 (95% CI 0.81 to 1.12)
			Cumulative carboplatin dose (per 100 mg/m²)	-	OR 1.02 (95% CI 1.00 to 1.04)
			HD-cyclophosphamide (no/yes) (≥ 1 g/m² per course)	-	OR 0.82 (95% CI 0.43 to 1.57)
			HD-MTX (no/yes) (≥ 1 g/m² per course)	-	OR 1.37 (95% CI 0.87 to 2.14)
			NP (no/yes)	-	OR 1.70 (95% CI 0.97 to 2.96)
			TBI (no/yes)	-	OR 2.73 (95% CI 0.95 to 7.90)
			Abdominal RT (no/yes)	-	OR 1.10 (95% CI 0.57 to 2.16)
			Age at diagnosis (in years)	-	OR 1.02 (95% CI 0.98 to 1.06)
			Time since diagnosis (per 5 years)	-	OR 1.13 (95% CI 0.98 to 1.31)

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Table 7. Risk factors from multivariable analyses on proteinuria: studies not fulfilling inclusion criteria *(Continued)*

			Male sex	-	OR 0.80 (95% CI 0.58 to 1.11)
	Mutually exclusive treatment group[c]	Albuminuria dipstick Normal: negative Abnormal: high 150 mg/dL, moderate: 75 mg/dL equivocal: 25 mg/dL	Ifosfamide only	+	OR 4.50 (95% CI 2.44 to 8.31)
			Cisplatin only	-	OR 2.20 (95% CI 0.94 to 5.14)
			Carboplatin only	+	OR 6.01 (95% CI 2.21 to 16.35)
			Platinum agents + ifosfamide	+	OR 2.12 (95% CI 1.03 to 4.63)
			HD-MTX only (≥ 1 g/m^2 per course)	-	OR 1.59 (95% CI 0.94 to 2.66)
			HD-cyclophosphamide only (≥ 1 g/m^2 per course)	-	OR 0.58 (95% CI 0.07 to 4.47)
			NP only	-	OR 1.55 (95% CI 0.77 to 3.09)
			RT only	-	OR 2.06 (95% CI 0.74 to 5.73)
			NP + NCTx	+	OR 6.67 (95% CI 2.01 to 22.14)
			NP + RT	-	OR 2.01 (95% CI 0.98 to 4.11)
			NP + NCTx + RT	+	OR 5.35 (95% CI 1.27 to 22.63)
			Other NCTx combinations	-	OR 1.79 (95% CI 0.91 to 3.54)
			RT + NCTx	-	OR 1.76 (95% CI 0.49 to 6.29)
Ramirez 2016[d]	Overall cohort of long-term CCS	> 1+ protein via urine dipstick or automated analysis	HD (≥ 30 g/m^2) ifosfamide	+	OR 6.8 (95% CI 2.9 to 16.0)

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Table 7. Risk factors from multivariable analyses on proteinuria: studies not fulfilling inclusion criteria *(Continued)*

	TBI	+	OR 3.0 (95% CI 1.0 to 8.4)
	Age 10-14 years at diagnosis	-	OR 0.7 (95% CI 0.3 to 1.4)

CCS: childhood cancer survivors; **CI:** confidence interval; **HD:** high-dose; **MTX:** methotrexate; **NCTx:** nephrotoxic chemotherapy; **NP:** nephrectomy; **OR:** odds ratio; **RT:** radiotherapy; **TBI:** total body irradiation; **U-ACR:** urinary albumin-to-creatinine ratio

[a]Dekkers 2013 used logistic regression analyses and adjusted for age, gender, age at diagnosis, and BMI.
[b]Knijnenburg 2012 used multivariable logistic regression analyses and adjusted for age at cancer diagnosis, and duration of follow-up since cancer diagnosis.
[c]therapies were modelled as mutually exclusive treatment groups and entered into the models as a categorical variable.
[d]Ramirez 2016 used multivariable logistic regression analyses and adjusted for age at diagnosis.

Table 8. Risk factors from multivariable analyses on serum phosphate/hypophosphataemia: studies not fulfilling inclusion criteria

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Knijnenburg 2012[a]	Overall cohort of long-term CCS	Serum phosphate adults, < 0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement	Cumulative ifosfamide dose (per 10 g/m^2)	-	OR 1.02 (95% CI 0.82 to 1.27)
			Cumulative cisplatin dose (per 100 mg/m^2)	-	OR 1.00 (95% CI 0.77 to 1.30)
			Cumulative carboplatin dose (per 100 mg/m^2)	-	OR 1.00 (95% CI 0.92 to 1.07)
			HD-cyclophosphamide (no/yes) (≥ 1 g/m^2 per course)	-	OR 0.63 (95% CI 0.08 to 5.22)
			HD-MTX (no/yes) (≥ 1 g/m^2 per course)	-	OR 0.34 (95% CI 0.07 to 1.76)
			NP (no/yes)	-	OR 0.70 (95% CI 0.06 to 8.26)
			Abdominal RT (no/yes)	-	OR 1.16 (95% CI 0.11 to 12.47)
			Age at diagnosis (in years)	-	OR 1.10 (95% CI 0.98 to 1.24)
			Time since diagnosis (per 5 years)	-	OR 0.97 (95% CI 0.61 to 1.55)
			Male sex	-	OR 0.36 (95% CI 0.12 to 1.05)

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Table 8. Risk factors from multivariable analyses on serum phosphate/hypophosphataemia: studies not fulfilling inclusion criteria *(Continued)*

	Mutually exclusive treatment group[b]	Serum phosphate adults, < 0.81 mmol/L; children, age-dependent. Additionally, CCS receiving a phosphate supplement	Ifosfamide only	-	OR 1.32 (95% CI 0.22 to 7.89)
			Cisplatin only	-	OR 1.21 (95% CI 0.19 to 7.69)
			Platinum agents + ifosfamide	-	OR 1.71 (95% CI 0.34 to 8.76)
			HD-MTX only (≥ 1 g/m² per course)	-	OR 0.58 (95% CI 0.10 to 3.46)
			NP only	-	OR 2.12 (95% CI 0.20 to 22.39)
			RT only	-	OR 3.77 (95% CI 0.36 to 39.40)
			Other NCTx combinations	-	OR 0.46 (95% CI 0.05 to 4.60)

CCS: childhood cancer survivors; **CI:** confidence interval; **HD:** high-dose; **MTX:** methotrexate; **NCTx:** nephrotoxic chemotherapy; **NP:** nephrectomy; **OR:** odds ratio; **RT:** radiotherapy

[a]Knijnenburg 2012 used multivariable logistic regression analyses and adjusted for age at cancer diagnosis, and duration of follow-up since cancer diagnosis.
[b]Therapies were modelled as mutually exclusive treatment groups and entered into the models as a categorical variable.

Table 9. Risk factors from multivariable analyses on serum magnesium/hypomagnesaemia: studies not fulfilling inclusion criteria

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Knijnenburg 2012[a]	Overall cohort of long-term CCS	Serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement	Cumulative ifosfamide dose (per 10 g/m²)	-	OR 1.08 (95% CI 0.87 to 1.34)
			Cumulative cisplatin dose (per 100 mg/m²)	+	OR 1.66 (95% CI 1.34 to 2.05)
			Cumulative carboplatin dose (per 100 mg/m²)	-	OR 0.97 (95% CI 0.87 to 1.07)

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Table 9. Risk factors from multivariable analyses on serum magnesium/hypomagnesaemia: studies not fulfilling inclusion criteria *(Continued)*

			HD-cyclophosphamide (no/yes) (≥ 1 g/m² per course)	-	OR 2.98 (95% CI 0.92 to 9.63)
			HD-MTX (no/yes) (≥ 1 g/m² per course)	-	OR 1.32 (95% CI 0.43 to 4.05)
			NP (no/yes)	+	OR 17.46 (95% CI 4.63 to 65.79)
			Abdominal RT (no/yes)	-	OR 0.30 (95% CI 0.06 to 1.47)
			Age at diagnosis (in years)	-	OR 1.05 (95% CI 0.96 to 1.16)
			Time since diagnosis (per 5 years)	+	OR 1.55 (95% CI 1.09 to 2.20)
			Male sex	-	OR 0.97 (95% CI 0.46 to 2.05)
	Mutually exclusive treatment group[b]	Serum Mg: males, < 0.75 mmol/L; females, < 0.71 mmol/L; < 15 years of age, < 0.68 mmol/L, or CCS receiving a Mg supplement	Ifosfamide only	-	OR 5.53 (95% CI 0.42 to 72.94)
			Cisplatin only	+	OR 96.31 (95% CI 12.68 to 731.36)
			Platinum agents + ifosfamide	+	OR 75.53 (95% CI 9.75 to 584.89)
			HD-MTX only (≥ 1 g/m² per course)	-	OR 2.17 (95% CI 0.17 to 27.61)
			NP only	+	OR 121.85 (95% CI 15.97 to 929.97)
			NP + RT	+	OR 14.80 (95% CI 2.25 to 97.12)
			Other NCTx combinations	+	OR 64.29 (95% CI 8.49 to 486.65)
Stohr 2007a[c]	Sarcoma survivors	Serum Mg < 0.7 mmol/L or receiving Mg supplementation	Cisplatin treatment	+	Mean serum Mg: 0.86 vs 0.82 mmol/L
			Carboplatin treatment	+	Mean serum Mg: 0.86 vs 0.82 mmol/L
			Abdominal irradiation	—	Mean serum Mg: 0.84 vs 0.84 mmol/L

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Table 9. Risk factors from multivariable analyses on serum magnesium/hypomagnesaemia: studies not fulfilling inclusion criteria *(Continued)*

			Longer follow-up duration	—	n/m
			Ifosfamide treatment	—	n/m

CCS: childhood cancer survivors; **CI:** confidence interval; **HD:** high-dose; **Mg:** magnesium; **MTX:** methotrexate; **NCTx:** nephrotoxic chemotherapy; **NP:** nephrectomy; **OR:** odds ratio; **RT:** radiotherapy

[a]Knijnenburg 2012 used multivariable logistic regression analyses and adjusted for age at cancer diagnosis, and duration of follow-up since cancer diagnosis.
[b]Therapies were modelled as mutually exclusive treatment groups and entered into the models as a categorical variable.
[c]Stohr 2007a performed multivariable longitudinal analyses by analysis of variance with repeated measurement and adjusted for the remaining factors, and age and sex.

Table 10. Risk factors from multivariable analyses on blood pressure: studies included for prevalence and risk factors

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Kantor 1989[a]	Long-term CCS of a renal tumour	SBP > 160 mmHg or > DBP > 95 mmHg or receiving treatment for hypertension	Radiation dose	—	n/m
			Dactinomycin use	—	n/m
			Combination of radiation dose and dactinomycin	—	n/m
Geenen 2010[b]	Long-term survivors of WT and ALL	SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg	Older age at screening (per year)	+	OR 1.30 (95% CI 1.09 to 1.54)
			Abdominal RT	+	OR 30.14 (95% CI 3.98 to 228.44)
			Sex	—	OR 0.26 (95% CI 0.06 to 1.16)
			Family history of premature cardiovascular disease	-	OR 2.01 (95% CI 0.36 to 11.27)
			Cranial radiotherapy	-	OR 5.59 (95% CI 0.47 to 65.85)
			Alkylating agents	-	OR 1.17 (95% CI 0.08 to 16.70)
			Anthracyclines	-	OR 1.47 (95% CI 0.19 to 14.44)

ALL: acute lymphoblastic leukaemia; **CCS:** childhood cancer survivors; **CI:** confidence interval; **DBP:** diastolic blood pressure; **mmHg:** millimetre mercury; **n/m:** not mentioned; **OR:** odds ratio; **RT:** radiotherapy; **SBP:** systolic blood pressure; **WT:** Wilms' tumour

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[a]Kantor 1989 used a case comparison study and analyses were adjusted for age at survey, stage at diagnosis of Wilms' tumour, cigarette smoking, family history of hypertension, and Quetelet index.
[b]Geenen 2010 used multivariable logistic regression analyses and adjusted for age at screening, gender, and positive family history of premature cardiovascular disease.

Table 11. Risk factors from multivariable analyses on blood pressure: studies not fulfilling inclusion criteria

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Cardous-Ubbink 2010[a]	Overall cohort of long-term CCS	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg on at least 3 consecutive visits	BMI ≥ 25	+	OR 3.95 (95% CI 1.71 to 9.09)
			Cisplatin	-	OR 4.32 (95% CI 0.64 to 29.01)
			Cyclophosphamide	-	OR 2.06 (95% CI 0.73 to 5.78)
			Ifosfamide	-	OR 1.33 (95% CI 0.22 to 8.03)
			Other CT (inclusive anthracyclines)	-	OR 0.88 (95% CI 0.28 to 2.82)
			Abdominal RT	-	OR 1.79 (95% CI 0.60 to 5.34)
			Cranial RT	-	OR 0.88 (95% CI 0.36 to 2.14)
Hoffmeister 2010[b]	Long-term HCT survivors	SBP/DBP ≥ 140/90 mmHg for adults or > 95th percentile for age, sex and height in children	Acute kidney injury	+	HR 2.53 (95% CI: 1.7 to 3.7)
			TBI	+	HR 2.06 (95% CI 1.3 to 3.3)
			Hepatitis C virus infection	+	HR 0.52 (95% CI: 0.3 to 0.9)
			Stem cell donor type	+	Related: HR 1.00 Unrelated: HR 1.79 (95% CI 1.0 to 3.2) Autologous: HR 2.39 (95% CI 1.3 to 4.4)
			Obesity (BMI ≥ 30 kg/m^2 for adults and ≥ 95th percentile of normal for children)	+	HR 3.98 (95% CI 2.3 to 6.8)
			Growth hormone therapy	+	HR 1.58 (95% 1.0 to 2.5)
			Sex	—	N/m
			Race/ethnicity	—	N/m

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Table 11. Risk factors from multivariable analyses on blood pressure: studies not fulfilling inclusion criteria *(Continued)*

			Family history of hypertension	—	N/m
			Single kidney	—	N/m
			Cranial irradiation	—	N/m
			Abdominal RT	—	N/m
			Pretransplant NCTx agents	—	N/m
			Age at transplantation	—	N/m
			Diagnosis at transplantation	—	N/m
			Degree of HLA mismatching between donor and recipient	—	N/m
			SOS	—	N/m
			Cyclosporine (CsA)/tacrolimus for acute GVHD prophylaxis	—	N/m
			Acute GVHD grade (0-I vs II-IV)	—	N/m
			Chronic GVHD	—	N/m
			Chronic GVHD therapy	—	N/m
			Duration of chronic GVHD therapy	—	N/m
			Smoking history	—	N/m
			Diabetes	—	N/m
			Growth hormone deficiency	—	N/m
Knijnenburg 2012[c]	Overall cohort of long-term CCS	Adults SBP >140 and/or DBP > 90 mmHg. Children SBP and/or DBP ≥ 95th percentile for sex, age, and height, using height z-scores for Dutch children. Or use of antihypertensive medication	Cumulative ifosfamide dose (per 10 g/m^2)	-	OR 1.05 (95% CI 0.94 to 1.18)
			Cumulative cisplatin dose (per 100 mg/m^2)	-	OR 1.13 (95% CI 0.98 to 1.28)
			Cumulative carboplatin dose (per 100 mg/m^2)	-	OR 0.98 (95% CI 0.95 to 1.02)

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Table 11. Risk factors from multivariable analyses on blood pressure: studies not fulfilling inclusion criteria *(Continued)*

			HD-cyclophosphamide (no/yes) (≥ 1 g/m² per course)	-	OR 1.16 (95% CI 0.56 to 2.43)
			HD-MTX (no/yes) (≥ 1 g/m² per course)	-	OR 0.66 (95% CI 0.39 to 1.11)
			NP (no/yes)	-	OR 1.55 (95% CI 0.88 to 2.71)
			TBI (no/yes)	-	OR 1.91 (95% CI 0.52 to 6.94)
			Abdominal RT (no/yes)	+	OR 2.48 (95% CI 1.36 to 4.54)
			Age at diagnosis (in years)	+	OR 1.07 (95% CI 1.02 to 1.11)
			Time since diagnosis (per 5 years)	+	OR 1.47 (95% CI 1.28 to 1.69)
			BMI > 25-30 kg/m²	+	OR 1.94 (95% CI 1.27 to 2.96)
			BMI > 30 kg/m²	+	OR 5.93 (95% CI 3.18 to 11.07)
			Male sex	+	OR 2.09 (95% CI 1.47 to 2.98)
	Mutually exclusive treatment group[d]	Adults SBP > 140 and/or DBP > 90 mmHg. Children SBP and/or DBP ≥ 95th percentile for sex, age, and height, using height z-scores for Dutch children. Or use of antihypertensive medication	Ifosfamide only	-	OR 0.80 (95% CI 0.35 to 1.81)
			Cisplatin only	-	OR 0.83 (95% CI 0.30 to 2.29)
			Carboplatin only	-	OR 0.46 (95% CI 0.06 to 3.63)
			Platinum agents + ifosfamide	-	OR 1.09 (95% CI 0.48 to 2.48)
			HD-MTX only (≥ 1 g/m² per course)	-	OR 0.57 (95% CI 0.31 to 1.02)
			HD-cyclophosphamide only (≥ 1 g/m² per course)	-	OR 0.40 (95% CI 0.05 to 3.11)
			NP only	-	OR 1.00 (95% CI 0.49 to 2.02)
			RT only	-	OR 1.02 (95% CI 0.36 to 2.89)
			NP + NCTx	-	OR 2.87 (95% CI 0.58 to 14.22)
			NP + XRT	+	OR 4.92 (95% CI 2.63 to 9.19)
			NP + NCTx + RT	-	OR 1.21 (95% CI 0.15 to 9.96)

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Table 11. Risk factors from multivariable analyses on blood pressure: studies not fulfilling inclusion criteria *(Continued)*

	Other NCTx combinations	-	OR 0.73 (95% CI 0.34 to 1.59)
	RT + NCTx	-	OR 1.36 (95% CI 0.37 to 5.00)

ALL: acute lymphoblastic leukaemia; **BMI:** body mass index; **CCS:** childhood cancer survivors; **CI:** confidence interval; **CT:** chemotherapy; **DBP:** diastolic blood pressure; **GVHD:** graft versus host disease; **HCT:** hematopoietic stem cell transplant; **HLA:** human leukocyte antigen; **HR:** hazard ratio; **mmHg:** millimetre mercury; **MTX:** methotrexate; **NCTx:** nephrotoxic chemotherapy; **n/m:** not mentioned; **NP:** nephrectomy; **OR:** odds ratio; **RT:** radiotherapy; **SBP:** systolic blood pressure; **SOS:** sinusoidal obstruction syndrome; **TBI:** total body irradiation; **WT:** Wilms' tumour

[a]Cardous-Ubbink 2010 used multivariable logistic regression analyses and adjusted for all other treatment factors included in analyses.
[b]Hoffmeister 2010 used multivariable Cox regression analysis, but did not explicitly mention adjustments.
[c]Knijnenburg 2012 used multivariable logistic regression analyses and adjusted for BMI, age at cancer diagnosis, and duration of follow-up since cancer diagnosis.
[d]Therapies were modelled as mutually exclusive treatment groups and entered into the models as a categorical variable.

Table 12. Risk factors from multivariable analyses on composite outcome measures: studies included for prevalence and risk factors

Study	Study population	Outcome definition	Risk factor	P < 0.05	Extent of the effect
Stohr 2007b[a]	Survivors of Ewing's sarcoma, osteosarcoma and soft tissue sarcoma	Composite outcome: tubulopathy, including hypophosphataemia, glucosuria, proteinuria	Cumulative ifosfamide dose (> 60 g/m^2)	+	HR 18.6 (95% CI 2.4 to 143.2)
			Age at diagnosis (< 4 year)	+	HR 8.7 (95% CI 3.5 to 21.8)
Van Dijk 2010[b]	WT survivors	Composite outcome: nephrological adverse events (including hypertension, glomerular dysfunction not further specified and tubular dysfunction not further specified)	Sex (female vs male)	-	OR 0.69 (95% CI 0.30 to 1.58)
			Age at diagnosis	-	OR 0.86 (95% CI 0.69 to 1.06)
			RT flank/abdomen	-	OR 1.02 (95% CI 0.89 to 1.06)
			RT chest	-	OR 0.94 (95% CI 0.85 to 1.03)
			CT anthra and/or alky +/- other CT vs other CT only	-	OR 3.01 (95% CI 0.96 to 9.43)

alkyl: alkylating agents; **anthra:** anthracyclines; **CI:** confidence interval; **CT:** chemotherapy; **HR:** hazard ratio; **OR:** odds ratio; **RT:** radiotherapy; **WT:** Wilms' tumour

[a]Stohr 2007b used multivariable Cox's proportional hazards model and adjusted for gender, concomitant treatment with carboplatin and abdominal irradiation.
[b]Van Dijk 2010 used multivariable logistic regression analyses and adjusted for gender, age at diagnosis, and follow-up time.

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APPENDICES

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

1. For**ifosfamide** we used the following text words:

ifosfamide OR iphosphamide OR iso-endoxan OR iso endoxan OR isophosphamide OR isofosfamide OR holoxan OR asta z 4942 OR NSC-109,724 OR NSC 109,724 OR NSC109,724 OR NSC 109724 OR NSC-109724 OR NSC109724 OR cyclic p-oxides OR ethylamines OR oxazines OR ifosfa* OR iphospha* OR isofosfa* OR isophospha* OR “br cl fosfamide” OR cyfos OR ifex OR “ifo-cell” OR ifolem OR ifomide OR ifosfamidum OR ifosforamide mustard OR ifoxan OR ipambr OR iphosphamid OR isophosphoramide bromide mustard OR isophosphoramide mustard OR mitoxana OR mjf 9325 OR naxamide OR seromida OR tronoxal OR z 4942

2. For**carboplatin and cisplatin** we used the following text words:

Platinum OR Platinum Compounds OR cis-diamminedichloroplatinum* OR cis-platinum OR cis platinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875 or NSC 119875 or NSC119875 OR platidiam OR platino OR platinol OR platinum* OR CDDP OR CACP OR cisplatin OR carboplatin OR abiplatin OR paraplatin OR CBDCA OR cis-DDP OR neoplatin OR platidiam OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR platinum diamminodichloride OR Platinum Diamminodichloride OR 15663-27-1 OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR Carbosin OR Pharmachemie Brand of Carboplatin OR Carbotec OR Columbia Brand of Carboplatin OR Ercar OR Almirall Brand of Carboplatin OR JM-8 OR JM 8 OR JM8 OR Neocarbo OR Neocorp Brand of Carboplatin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Bristol-Myers Squibb Brand of Carboplatin OR Carboplat OR Paraplatine OR Platinwas OR Chiesi Brand of Carboplatin OR Ribocarbo OR ribosepharm Brand of Carboplatin OR Blastocarb OR Lemery Brand of Carboplatin OR Nealorin OR Prasfarma Brand of Carboplatin OR 41575-94-4

3. For**radiotherapy** we used the following text words:

Radiotherapy OR radiotherapies OR Targeted Radiotherapies OR Targeted Radiotherapy OR radiother* OR (radiation AND therapy) OR "radiation therapy" OR "x ray therapy" OR ("x-ray" AND therapy) OR total body irradiation OR TBI OR whole-body irradiation OR Whole Body Irradiation OR Whole-Body Radiation OR Whole Body Radiation OR Whole-Body Radiations OR Total Body Irradiations OR Whole-Body Irradiations

4. For**nephrectomy** we used the following text words:

Nephrectomy OR nephrectomies OR nephrect* OR nephron-sparing surgery

5. For**children** we used the following text words:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

6. For c**hildhood cancer** we used the following text words:

leukemia OR leukemi* OR leukaemi* OR childhood ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR primitive neuroectodermal tumors OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR acute lymphocytic leukemia

7. For**cancer** we used the following text words:

cancer OR oncology OR oncolog* OR neoplasms OR neoplas* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR cancer* OR malignan* OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo* OR bone marrow transplantation OR bone marrow transplant* OR leukemia OR leukaemia OR lymphoma

8. For**nephrotoxicity** we used the following text words:

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glomerular filtration rate OR GFR OR Glomerular Filtration Rates OR glomerular OR glomerul* OR tubular OR tubula* OR renal tubular acidosis OR RTA OR Distal Renal Tubular Acidosis OR Classic Distal Renal Tubular Acidosis OR Proximal Renal Tubular Acidosis OR Type II Renal Tubular Acidosis OR renal acidosis OR renal insufficiency OR Renal Insufficiencies OR Kidney Insufficiency OR Kidney Insufficiencies OR microalbuminuria OR microalbumin*OR hypophosphatemia OR hypophosphataemia OR hypophospha* OR hypomagnes* OR hypomagnesemia OR hypomagnesaemia OR magnesium OR 7439-95-4 OR phosphate OR phosphates OR Inorganic Phosphates OR Phosphates, Inorganic OR Orthophosphate OR phosphorus OR Hyponatremia OR Hyponatremias OR hyponatraemia OR hyponatraemias OT hyponatrem* OR hyponatraem* OR Hypocitraturia OR Hypocitraturias OR Hypocitraturi* OR Potassium OR Potassium Ion Level OR Ion Level, Potassium OR Level, Potassium Ion OR 7440-09-7 OR Hypokalemia OR Hypokalemias OR Hypopotassemia OR Hypopotassemias OR hypokalemic OR hypokalem* OR hypokalaemic OR hypokalaem* OR Hypocalcemia OR hypocalcemias OR hypocalciuria OR hypocalciuri* OR hypocalcem* OR hypocalc* OR “hypocarbia” OR Proteinuria OR proteinurias OR proteinuri* OR albuminuria OR albuminurias OR albuminuri* OR Aminoaciduria OR Renal Aminoaciduria OR Renal Aminoacidurias OR Aminoacidurias, Renal OR Aminoaciduria, Renal OR aminoacidur* OR Glucosuria OR glucosurias OR glucosur* OR glycosuria OR glycosurias OR glycosuria, renal OR Fanconi syndrome OR Syndrome, Fanconi OR Renal Fanconi Syndrome OR Proximal Renal Tubular Dysfunction OR Fanconi Renotubular Syndrome OR Syndrome, Fanconi Renotubular OR De Toni-Debre-Fanconi Syndrome OR De Toni Debre Fanconi Syndrome OR Syndrome, De Toni-Debre-Fanconi OR Lignac-Fanconi Syndrome OR Lignac Fanconi Syndrome OR Syndrome, Lignac-Fanconi OR low molecular weight OR LMW OR alpha 1 microglobulin OR a1 microglobulin OR beta 2 microglobulin OR b2 microglobulin OR 2-Microglobulin, beta OR Thymotaxin OR retinol binding protein OR RBP OR Retinol Binding Proteins OR Binding Proteins, Retinol OR Retinoid Binding Proteins OR Binding Proteins, Retinoid OR Retinoid Binding Protein, F-Type OR Retinoid Binding Protein, F Type OR creatinine OR Krebiozen OR Creatinine Sulfate Salt OR Salt, Creatinine Sulfate OR Sulfate Salt, Creatinine OR 60-27-5 OR inulin OR 9005-80-5 OR "(51) Cr EDTA" OR 51chromium edetic acid OR “(99) Tc DTPA” OR Tc DTPA OR 65454-61-7[rn] OR Technetium Tc 99m Pentetate OR (99m)Tc-DMSA OR 99mTc(V)DMSA OR DMSA OR dimercaptosuccinic acid OR Technetium Tc 99m Dimercaptosuccinic Acid OR 65438-08-6 OR 99Tc-Succimer OR 99Tc Succimer OR 99mTc-Dimercaptosuccinate OR 99mTc Dimercaptosuccinate OR renal scan OR “kidney size” OR cystatin c OR gamma-Trace OR gamma Trace OR Post-gamma-Globulin OR Post gamma Globulin OR Cystatin 3 OR Neuroendocrine Basic Polypeptide OR Basic Polypeptide, Neuroendocrine OR CST3 gene OR cystatins OR cystatin* OR renal failure OR kidney failure OR Failure, Kidney OR Failures, Kidney OR Kidney Failures OR Failure, Renal OR Failures, Renal OR Renal Failures OR renal plasma flow OR Plasma Flow, Renal OR Flow, Renal Plasma OR RPF OR ERPF OR Renal clearance OR reabsorption OR re-absorption OR nephrotoxicity OR nephrotox* OR rickets OR rickets* OR Hypertension OR hypertens* OR hypertension, renal OR Hypertensions, Renal OR Renal Hypertension OR Renal Hypertensions OR Blood Pressure, High OR Blood Pressures, High OR High Blood Pressure OR High Blood Pressures OR blood pressure OR blood pressures OR blood pressur* OR diastolic pressure OR systolic pressure

9. Final search (1 or 2 or 3 or 4) and 5 and (6 or 7) and 8

The search was performed in title, abstract or keywords

[* = 1 or more characters]

Appendix 2. Search strategy for MEDLINE/PubMed

1. For**ifosfamide** we used the following MeSH headings and text words:

ifosfamide OR iphosphamide OR iso-endoxan OR iso endoxan OR isophosphamide OR isofosfamide OR holoxan OR asta z 4942 OR NSC-109,724 OR NSC 109,724 OR NSC109,724 OR NSC 109724 OR NSC-109724 OR NSC109724 OR cyclic p-oxides OR ethylamines OR oxazines OR ifosfa* OR iphospha* OR isofosfa* OR isophospha* OR “br cl fosfamide” OR cyfos OR ifex OR “ifo-cell” OR ifolem OR ifomide OR ifosfamidum OR ifosforamide mustard OR ifoxan OR ipambr OR iphosphamid OR isophosphoramide bromide mustard OR isophosphoramide mustard OR mitoxana OR mjf 9325 OR naxamide OR seromida OR tronoxal OR z 4942

2. For c**arboplatin and cisplatin** we used the following MeSH headings and text words:

Platinum OR Platinum Compounds OR cis-diamminedichloroplatinum* OR cis-platinum OR cis platinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875 or NSC 119875 or NSC119875 OR platidiam OR platino OR platinol OR platinum* OR CDDP OR CACP OR cisplatin OR carboplatin OR abiplatin OR paraplatin OR CBDCA OR cis-DDP OR neoplatin OR platidiam OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR platinum diamminodichloride OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR 15663-27-1 OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR Carbosin OR Pharmachemie Brand of Carboplatin OR Carbotec OR Columbia Brand of Carboplatin OR Ercar OR Almirall Brand of Carboplatin OR JM-8 OR JM 8 OR JM8 OR Neocarbo OR Neocorp Brand of Carboplatin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Bristol-Myers Squibb Brand of Carboplatin OR Carboplat OR Paraplatine OR Platinwas OR Chiesi Brand of Carboplatin OR Ribocarbo OR ribosepharm Brand of Carboplatin OR Blastocarb OR Lemery Brand of Carboplatin OR Nealorin OR Prasfarma Brand of Carboplatin OR 41575-94-4

3. For**radiotherapy** we used the following MeSH headings and text words:

Radiotherapy OR radiotherapy[sh] OR radiotherapies OR Radiotherapy, Targeted OR Radiotherapies, Targeted OR Targeted Radiotherapies OR Targeted Radiotherapy OR radiother* OR ("radiation"[All Fields] AND "therapy"[All Fields]) OR "radiation therapy"[All Fields] OR "x ray therapy"[All Fields] OR "x-ray therapy"[MeSH Terms] OR ("x-ray"[All Fields] AND "therapy"[All Fields]) OR "x-ray therapy"[All Fields] OR

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total body irradiation OR TBI OR whole-body irradiation OR Whole Body Irradiation OR Radiation, Whole-Body OR Radiation, Whole Body OR Whole-Body Radiation OR Radiations, Whole-Body OR Whole Body Radiation OR Whole-Body Radiations OR Irradiation, Total Body OR Irradiations, Total Body OR Total Body Irradiations OR Irradiation, Whole-Body OR Irradiation, Whole Body OR Irradiations, Whole-Body OR Whole-Body Irradiations

4. For**nephrectomy** we used the following MeSH headings and text words:

Nephrectomy OR nephrectomies OR nephrect* OR nephron-sparing surgery

5. For **children** we used the following MeSH headings and text words:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR perinat* OR postnat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

6. For **childhood cancer** we used the following MeSH headings and text words:

leukemia OR leukemi* OR leukaemi* OR ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR leukemia lymphocytic acute OR leukemia, lymphocytic, acute[mh]

7. For **cancer** we used the following MeSH headings and text words:

cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant OR hematooncological OR hemato oncological OR hemato-oncological OR hematologic neoplasms OR hematolo*

8. For **nephrotoxicity** we used the following MeSH headings and text words:

glomerular filtration rate OR GFR OR Filtration Rate, Glomerular OR Filtration Rates, Glomerular OR Glomerular Filtration Rates OR Rate, Glomerular Filtration OR Rates, Glomerular Filtration OR glomerular OR glomerul* OR tubular OR tubula* OR renal tubular acidosis OR RTA OR Acidosis, Renal Tubular OR Renal Tubular Acidosis, Type I OR Type I Renal Tubular Acidosis OR Distal Renal Tubular Acidosis OR Acidosis, Renal Tubular, Type I OR Classic Distal Renal Tubular Acidosis OR Renal Tubular Acidosis, Distal, Autosomal Dominant OR Renal Tubular Acidosis, Type II Acidosis, Renal Tubular, Type II OR Renal Tubular Acidosis, Proximal, with Ocular Abnormalities OR Proximal Renal Tubular Acidosis OR Type II Renal Tubular Acidosis OR renal acidosis OR renal insufficiency OR Renal Insufficiencies OR Kidney Insufficiency OR Insufficiency, Kidney OR Kidney Insufficiencies OR microalbuminuria OR microalbumin* OR hypophosphatemia OR hypophosphataemia OR hypophospha* OR hypomagnes* OR hypomagnesemia OR hypomagnesaemia OR magnesium OR 7439-95-4[rn] OR phosphate OR phosphates OR Inorganic Phosphates OR Phosphates, Inorganic OR Orthophosphate OR phosphorus OR Hyponatremia OR Hyponatremias OR hyponatraemia OR hyponatraemias OR hyponatrem* OR hyponatraem* OR Hypocitraturia OR Hypocitraturias OR Hypocitraturi* OR Potassium OR Potassium Ion Level OR Ion Level, Potassium OR Level, Potassium Ion OR 7440-09-7[rn] OR Hypokalemia OR Hypokalemias OR Hypopotassemia OR Hypopotassemias OR hypokalemic OR hypokalem* OR hypokalaemic OR hypokalaem* OR Hypocalcemia OR hypocalcemias OR hypocalciuria OR hypocalciuri* OR hypocalcem* OR hypocalc* OR “hypocarbia” OR Proteinuria OR proteinurias OR proteinuri* OR albuminuria OR albuminurias OR albuminuri* OR Aminoaciduria OR Renal Aminoaciduria OR Renal Aminoacidurias OR Aminoacidurias, Renal OR Aminoaciduria, Renal OR aminoacidur* OR Glucosuria OR glucosurias OR glucosur* OR glycosuria OR glycosurias OR glycosuria, renal OR Fanconi syndrome OR Syndrome, Fanconi OR Renal Fanconi Syndrome OR Proximal Renal Tubular Dysfunction OR Fanconi Renotubular Syndrome OR Syndrome, Fanconi Renotubular OR De Toni-Debre-Fanconi Syndrome OR De Toni Debre Fanconi Syndrome OR Syndrome, De Toni-Debre-Fanconi OR Lignac-Fanconi Syndrome OR Lignac Fanconi Syndrome OR Syndrome, Lignac-Fanconi OR low molecular weight OR LMW OR alpha 1 microglobulin OR a1 microglobulin OR beta 2 microglobulin OR b2 microglobulin OR 2-Microglobulin, beta OR Thymotaxin OR retinol binding protein OR RBP OR Retinol Binding Proteins OR Binding Proteins, Retinol OR Retinoid Binding Proteins OR Binding Proteins, Retinoid OR Retinoid Binding Protein, F-Type OR Retinoid Binding Protein, F Type OR creatinine OR Krebiozen OR Creatinine Sulfate Salt OR Salt, Creatinine Sulfate OR Sulfate Salt, Creatinine OR 60-27-5[rn] OR inulin OR 9005-80-5[rn] OR "(51) Cr EDTA" OR 51chromium edetic acid OR “(99) Tc DTPA” OR Tc DTPA OR 65454-61-7[rn] OR Technetium Tc 99m Pentetate OR (99m)Tc-DMSA OR 99mTc(V)DMSA OR DMSA OR dimercaptosuccinic acid OR Technetium Tc 99m Dimercaptosuccinic Acid OR 65438-08-6[rn] OR 99Tc-Succimer OR 99Tc Succimer OR 99mTc-Dimercaptosuccinate OR 99mTc Dimercaptosuccinate OR renal scan OR “kidney size” OR cystatin c OR gamma-Trace OR gamma Trace OR Post-gamma-Globulin OR Post gamma Globulin OR Cystatin 3 OR

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Neuroendocrine Basic Polypeptide OR Basic Polypeptide, Neuroendocrine OR CST3 gene OR cystatins OR cystatin* OR renal failure OR kidney failure OR Failure, Kidney OR Failures, Kidney OR Kidney Failures OR Failure, Renal OR Failures, Renal OR Renal Failures OR renal plasma flow OR Plasma Flow, Renal OR Flow, Renal Plasma OR RPF OR ERPF OR Renal clearance OR reabsorption OR re-absorption OR nephrotoxicity OR nephrotox* OR rickets OR rickets* OR Hypertension OR hypertens* OR hypertension, renal OR Hypertensions, Renal OR Renal Hypertension OR Renal Hypertensions OR Blood Pressure, High OR Blood Pressures, High OR High Blood Pressure OR High Blood Pressures OR blood pressure OR blood pressures OR blood pressur* OR diastolic pressure OR systolic pressure

9. Final search (1 OR 2 OR 3 OR 4) AND 5 AND (6 OR 7) AND 8

[* = 1 or more characters; mh = MeSH heading; rn = registry number]

Appendix 3. Search strategy for Embase (OVID)

1. For**ifosfamide** we used the following Emtree terms and text words:

1. exp ifosfamide/
2. (ifosfamide or iphosphamide or iso-endoxan or iso endoxan or isophosphamide or isofosfamide or holoxan or asta z 4942 or NSC-109,724 or NSC 109,724 or NSC109,724 or NSC 109724 or NSC-109724 or NSC109724 or cyclic p-oxides or ethylamines or oxazines or ifosfa$ or iphospha$ or isofosfa$ or isophospha$).mp.
3. (br cl fosfamide or cyfos or ifex or ifo-cell or ifolem or ifomide or ifosfamidum or ifosforamide mustard or ifoxan or ipambr or iphosphamid or isophosphoramide bromide mustard or isophosphoramide mustard or mitoxana or mjf 9325 or naxamide or seromida or tronoxal or z 4942).mp.
4. 3778-73-2.rn.
5. or/1-4

2. For**carboplatin and cisplatin** we used the following Emtree terms and text words:

1. exp platinum/ or platinum.mp.
2. Platinum Compounds.mp. or exp platinum derivative/
3. (cis-diamminedichloroplatinum or cis diamminedichloroplatinum or cis-diamminedichloroplatinum$).mp.
4. cis-diamminedichloroplatinum II.mp. or exp cisplatin/
5. (cis-platinum or cis platinum or biocisplatinum).mp.
6. (dichlorodiammineplatinum or NSC-119875 or NSC 119875 or NSC119875).mp.
7. (platidiam or platino or platinol or platinum$).mp.
8. (CDDP or CACP or CBDCA or cis-DDP).mp.
9. (cisplatin or carboplatin or abiplatin or paraplatin or neoplatin or platidiam).mp.
10. (platinum diamminodichloride or Platinum Diamminodichloride).mp.
11. 15663-27-1.rn.
12. (cis-Diammine cyclobutanedicarboxylato platinum II or Carbosin).mp.
13. (carbotec or ercar or JM-8 or JM 8 or JM8 or neocarbo or NSC-241240 or NSC 241240 or NSC241240 or carboplat or paraplatine or platinwas or blastocarb or nealorin).mp.
14. 41575-94-4.rn.
15. or/1-14

3. For**radiotherapy** we used the following Emtree terms and text words:

1. exp radiotherapy/ or exp cancer radiotherapy/ or radiotherapy.mp.
2. radiotherapy.sh.
3. (radiotherapies or targeted radiotherapies or targeted radiotherapy or radiother$).mp.
4. ((radiation and therapy) or (radiation and x ray therapy)).mp.
5. (x ray therapy or (x ray and therapy)).mp
6. (total body irradiation or TBI).mp.
7. whole-body irradiation.mp. or exp whole body radiation/
8. (whole body irradiation or whole body radiation).mp.
9. (whole-body radiation or whole-body radiations or whole body radiations).mp.
10. (whole-body irradiations or Total Body Irradiation or Total Body Irradiations).mp.
11. or/1-10

4. For**nephrectomy** we used the following Emtree terms and text words:

1. exp partial nephrectomy/ or exp nephrectomy/ or nephrectomy.mp.
2. (nephrectomies or nephrect$).mp.
3. nephron sparing surgery.mp. or exp nephron sparing surgery/
4. or/1-3

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5. For**children** we used the following Emtree terms and text words:

1. infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
2. adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
3. primary school/ or high school/ or kindergarten/ or nursery school/ or school/
4. or/1-3
5. (infant$ or newborn$ or (new adj born$) or baby or baby$ or babies or neonate$ or perinat$ or postnat$).mp.
6. (child$ or (school adj child$) or schoolchild$ or (school adj age$) or schoolage$ or (pre adj school$) or preschool$).mp.
7. (kid or kids or toddler$ or adoles$ or teen$ or boy$ or girl$).mp.
8. (minors$ or (under adj ag$) or underage$ or juvenil$ or youth$).mp.
9. (puber$ or pubescen$ or prepubescen$ or prepubert$).mp.
10. (pediatric$ or paediatric$ or peadiatric$).mp.
11. (school or schools or (high adj school$) or highschool$ or (primary adj school$) or (nursery adj school$) or (elementary adj school) or (secondary adj school$) or kindergar$).mp.
12. or/5-11
13. 4 or 12

6. For**childhood cancer** we used the following Emtree terms and text words:

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.
10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.
11. intracranial neoplasm$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

7. For**cancer** we used the following Emtree terms and text words:

1. (cancer or cancers or cancer$).mp.
2. (oncology or oncolog$).mp. or exp oncology/
3. (neoplasm or neoplasms or neoplasm$).mp. or exp neoplasm/
4. (carcinoma or carcinom$).mp. or exp carcinoma/
5. (tumor or tumour or tumor$ or tumour$ or tumors or tumours).mp. or exp tumor/
6. (malignan$ or malignant).mp.
7. (hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo$).mp. or exp hematologic malignancy/
8. or/1-7

8. For **nephrotoxicity** we used the following Emtree terms and text words:

1. glomerular filtration rate.mp. or exp glomerulus filtration rate/
2. (GFR or glomerular filtration rates).mp.
3. (glomerular or glomerul$).mp.
4. (tubular or tubula$).mp.
5. exp tubular dysfunction/ or tubular.mp.
6. renal tubular acidosis.mp. or exp kidney tubule acidosis/
7. (RTA or renal tubular acidosis or type I renal tubular acidosis or distal renal tubular acidosis or classic distal renal tubular acidosis).mp.
8. (type II renal tubular acidosis or proximal renal tubular acidosis or renal acidosis).mp.
9. renal insufficiency.mp.
10. (renal insufficiencies or kidney insufficiency or kidney insufficiencies).mp.

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11. (microalbuminuria or microalbumin$).mp.
12. exp microalbuminuria/
13. hypophosphatemia.mp. or exp hypophosphatemia/
14. (hypophosphataemia or hypophospha$).mp.
15. hypomagnesemia.mp. or exp hypomagnesemia/
16. (hypomagnes$ or hypomagnesaemia or magnesium).mp. or 7439-95-4.rn.
17. phosphate.mp. or exp phosphate/
18. (phosphates or inorganic phosphates or orthophosphate or phosphorus).mp.
19. Hyponatremia.mp. or exp hyponatremia/
20. (hyponatremias or hyponatraemia or hyponatraemias or hyponatrem$ or hyponatraem$).mp.
21. exp hypocitraturia/ or hypocitraturia.mp.
22. (hypocitraturias or hypocitraturi$).mp.
23. exp potassium/ or Potassium.mp.
24. Potassium Ion Level.mp. or 7440-09-7.rn.
25. Hypokalemia.mp. or exp hypokalemia/
26. (hypokalemias or hypopotassemia or hypopotassemias or hypokalemic or hypokalem$ or hypokalaemic or hypokalaem$).mp.
27. Hypocalcemia.mp. or exp hypocalcemia/
28. (hypocalcemias or hypocalciuria or hypocalciuri$ or hypocalcem$ or hypocalc$ or hypocarbia).mp.
29. Proteinuria.mp. or exp proteinuria/
30. (proteinurias or proteinuri$).mp.
31. albuminuria.mp. or exp albuminuria/
32. (albuminurias or albuminuri$).mp.
33. aminoaciduria.mp. or exp aminoaciduria/
34. (Renal Aminoaciduria or Renal Aminoacidurias or aminoacidur$).mp.
35. glucosuria.mp. or exp glucosuria/
36. (glucosurias or glucosur$ or glycosuria or glycosurias).mp.
37. Fanconi syndrome.mp. or exp Fanconi renotubular syndrome/
38. (renal Fanconi syndrome or proximal renal tubular dysfunction or Fanconi renotubular syndrome).mp.
39. (De Toni-Debre-Fanconi Syndrome or De Toni Debre Fanconi Syndrome or Lignac-Fanconi Syndrome or Lignac Fanconi Syndrome).mp.
40. (low molecular weight or LMW or alpha 1 microglobulin or a1 microglobulin or beta 2 microglobulin or b2 microglobulin or thymotaxin).mp.
41. retinol binding protein.mp. or exp retinol binding protein/
42. (RBP or retinol binding proteins or retinoid binding proteins or F type retinoid binding protein).mp.
43. creatinine.mp. or exp creatinine/
44. (krebiozen or creatinine sulfate salt).mp. or 60-27-5.rn.
45. exp inulin clearance/ or exp inulin/ or inulin.mp. or 9005-80-5.rn.
46. (51 Cr EDTA or 51chromium edetic acid or 99 Tc DTPA or Tc DTPA).mp. or 65454-61-7.rn.
47. Technetium Tc 99m Pentetate.mp. or exp pentetate technetium tc 99m/
48. exp succimer tc 99m/ or exp succimer/ or (99m Tc-DMSA or 99mTc V DMSA or DMSA).mp.
49. (dimercaptosuccinic acid or Technetium Tc 99m Dimercaptosuccinic Acid).mp. or 65438-08-6.rn.
50. (99Tc-Succimer or 99Tc Succimer or 99mTc-Dimercaptosuccinate or 99mTc Dimercaptosuccinate).mp.
51. (renal scan or kidney size).mp.
52. cystatin.mp. or exp cystatin/
53. (gamma-Trace or gamma Trace or Post-gamma-Globulin or Post gamma Globulin or Cystatin 3 or Neuroendocrine Basic Polypeptide).mp.
54. (CST3 gene or cystatins or cystatin$).mp.
55. renal failure.mp. or exp kidney failure/
56. (kidney failure or kidney failures or renal failures).mp.
57. renal plasma flow.mp. or exp kidney plasma flow/
58. (RPF or ERPF or Renal clearance or reabsorption or re-absorption or nephrotoxicity or nephrotox$ or rickets or rickets$).mp.
59. exp hypertension/ or (Hypertension or hypertens$).mp.
60. (Renal Hypertension or Renal Hypertensions or Renal Hypertension$).mp. or exp renovascular hypertension/
61. (High Blood Pressure or High Blood Pressures or High Blood Pressure$).mp.
62. (blood pressure or blood pressures or blood pressure$).mp. or exp blood pressure/
63. (diastolic pressure or systolic pressure).mp.
64. or/1-63

9. Final search (1 or 2 or 3 or 4) and 5 and (6 or 7) and 8

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; rn = registry number; $ = 1 or more characters; / = Emtree term]

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Appendix 4. Search strategy for conference proceedings

We used the following terms independently when searching in the PDFs of conference proceedings: renal, kidney, nephrotoxicity, late effect, survivor and childhood cancer survivor.

WHAT'S NEW

Date	Event	Description
30 April 2018	New citation required but conclusions have not changed	With adapted selection criteria, we included 24 new studies in the review, and excluded 20 studies from the initial review. In total, we have included 61 studies; 46 on the prevalence of renal dysfunction, 6 for both prevalence and risk factors, and 9 studies that did not fulfil the inclusion criteria, but performed risk factor analysis. The 52 studies included for prevalence included 13,327 participants of interest and 4499 participants with a renal function test. Overall, prevalence range of adverse renal effects has not changed. Only studies that were not eligible for this review, but performed multivariable analyses identified new risk factors for adverse renal effects after potentially nephrotoxic treatment for childhood cancer. New reported risk factors for impaired glomerular filtration rate were nephrectomy +/- abdominal radiotherapy, (high-dose (HD)) ifosfamide, (HD) cisplatin, and follow-up time. For proteinuria studies identified the following risk factors; (HD) ifosfamide, HD cisplatin, total body irradiation, and nephrectomy combined with abdominal radiotherapy. For hypomagnesaemia, new reported risk factors were nephrectomy and follow-up time. However, studies were often contradictory and incomparable. The update did not change the conclusion of the initial review.
31 March 2017	New search has been performed	The search for eligible studies was updated to 31 March 2017

CONTRIBUTIONS OF AUTHORS

Originial review 2012

Sebastiaan Knijnenburg designed the study and wrote the protocol. He identified studies meeting the inclusion criteria (both by initial screening of the titles and abstract and by screening of the full-text articles). He performed data extraction and the risk of bias assessment of included studies, analysed the data and interpreted the results. He wrote and revised the manuscript.

Renée L Mulder designed the study and critically reviewed the protocol. She identified studies meeting the inclusion criteria (part of the initial screening and all full-text articles). She performed data extraction and the risk of bias assessment of included studies. She critically revised the manuscript.

Antoinette Schouten-Van Meeteren critically reviewed the protocol. She identified parts of studies that met the inclusion criteria. She critically reviewed the manuscript.

Arend Bökenkamp critically reviewed the protocol. He identified parts of studies that met the inclusion criteria. He critically reviewed the manuscript.

Hester Blufpand identified parts of studies that met the inclusion criteria. She critically reviewed the manuscript.

Eline van Dulmen-den Broeder identified parts of studies that met the inclusion criteria. She critically reviewed the manuscript.

Margreet A Veening identified parts of studies that met the inclusion criteria. She critically reviewed the manuscript.

Leontien CM Kremer designed the study and critically reviewed the protocol. She identified parts of studies that met the inclusion criteria and contributed to the interpretation of results. She critically reviewed the manuscript.

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Monique WM Jaspers critically reviewed the protocol. She identified parts of studies that met the inclusion criteria. She critically reviewed the manuscript.

All authors approved the final version of the manuscript.

Review update 2017

Esmee CM Kooijmans identified studies meeting the inclusion criteria. She performed data extraction and the 'Risk of bias' assessment of included studies, analysed the data and interpreted the results. She wrote and revised the manuscript.

Arend Bökenkamp identified parts of studies that met the inclusion criteria. He critically reviewed the manuscript.

Nic S Tjahjadi identified parts of studies that met the inclusion criteria. He critically reviewed the manuscript.

Jesse M Tettero identified parts of studies that met the inclusion criteria. He critically reviewed the manuscript.

Eline van Dulmen-den Broeder critically reviewed the manuscript.

Helena JH van der Pal identified parts of studies that met the inclusion criteria. She critically reviewed the manuscript.

Margreet A Veening identified parts of studies that met the inclusion criteria. She performed data extraction and the 'Risk of bias' assessment of included studies. She critically reviewed the manuscript.

All authors approved the final version of the manuscript.

DECLARATIONS OF INTEREST

Esmee CM Kooijmans: none known

Arend Bökenkamp: none known

Nic S Tjahjadi: none known

Jesse M Tettero: none known

Eline van Dulmen-den Broeder: none known

Heleen van der Pal is author of several studies included in this review (i.e. Mulder 2013 and Knijnenburg 2012).

Margreet A Veening: none known

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- KWF Kankerbestrijding, Netherlands.

  Financial support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol (Knijnenburg 2011), stated that we would include all renal outcome measures as reported by the study authors. During the data synthesis of this Cochrane Review, it became clear that the heterogeneity in reported outcomes of all included studies was very high. After careful deliberation about whether it would be useful to report all these outcomes, we decided that this would add too little information. Instead, we focused on the outcomes that were reported most often and that had the highest clinical relevance. We added a sentence to state that we included studies reporting composite outcome measures covering one of the included outcomes. Additionally, we included only studies investigating hypertension when they had a clear focus on renal function, to prevent the inclusion of studies focusing on metabolic abnormalities. During the update, we changed the name of the outcome 'fractional phosphate excretion' to 'fractional phosphate reabsorption' as this better reflects the definition.

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For the update in 2017, we further attempted to minimise clinical heterogeneity limiting study eligibility by sharpening the selection criteria. In the initial review, if a study had not stated whether they had given a particular treatment to participants, we considered that the study had excluded participants with that treatment. In this update, when an article had not stated all the potential nephrotoxic treatment modalities as stated in this review, and we could not assume that a treatment had been given, based on information about tumour type or treatment protocol, or both, we excluded a study from the evaluation of prevalence. When the study group of interest was unclear or the study authors had not described the study group of interest separately, we excluded studies from the evaluation of prevalence. Even if we excluded studies for prevalence, we could still include them for the assessment of risk factors, but only when they had performed multivariable analysis. We did not use results of univariable analyses in this update, because these results are less reliable.

In the original review, we included studies with participants up to 21 years, even though we had not stated this in the methods. In this update, we adjusted the methods to show the changed upper age limit, from 18 to 21 years, because many health institutions include young adults up to this age in their definition of childhood cancer and treat them following the same protocol.

In the Data Extraction section, we removed two points in comparison with the protocol: the number of participants treated with a specific combination of potentially nephrotoxic treatment (point 3.f. in the protocol), and the number of participants treated with potentially nephrotoxic antibiotics (point 3.g. in the protocol), were both reported so sporadically that systematic extraction was not relevant. In the initial review, no specific approach was described when a study used multiple methods to investigate (e)GFR. For the update in 2017, we used the following approach. We preferred the result of the estimation using an exogenous marker (i.e. inulin clearance, 51Cr-EDTA clearance, Tc-99m DTPA clearance, and 125-I-iothalamate clearance), as this is more accurate than equations using endogenous markers to estimate GFR. When GFR was estimated using an endogenous marker of GFR (eGFR), we only included this in the review if the estimating equation had been applied correctly. In case eGFR was estimated using different tests in a given paper, we used the arithmetic mean for analysis in this review. Although this is not yet a generally accepted measure of the renal function, we chose this approach because one of the main limitations of the currently available GFR estimation equations is the lack of universality across the multiple clinical settings in which it is applied. Our approach is in part supported by several recent studies that have demonstrated that the average of a cystatin C and a creatinine-based eGFR has higher diagnostic accuracy when compared to estimations based on a single marker (Den Bakker 2018; Leion 2017). However, we also combined more/other eGFR outcomes then used in these studies and our overall combined measure has not been validated. In addition, no approach was described in the previous review when an outcome was measured several times during follow-up. For this update, we decided to use the result at last follow-up for data synthesis.

We made some changes regarding the 'Risk of bias' assessment. We added the word 'relevant' to the definition of a well-defined study group in Table 1, "if the study specified the treatment regimen, including relevant cumulative chemotherapy and radiotherapy doses." We assessed chemotherapy and radiotherapy dosages as relevant when a study explicitly stated that potentially nephrotoxic therapy was part of the study's treatment protocol. For the definition of a well-defined outcome, we added, "for more than 50% of the included outcomes."

We adapted the 'Risk of bias' assessment criteria for an adequate follow-up and for a well-defined outcome. The original definition of low risk of follow-up bias according to the protocol was as follows: if the outcome was assessed at the end date of the study for 60% to 90% of the study group, or if the outcome was assessed for more than 90% of the study group but with an unknown end date. Because no straightforward definition is available for the end-date of the study, we decided to change this risk of bias item. The new definition of low risk of follow-up bias is as follows: if the outcome was assessed for more than 90% of the study group of interest (++), or if the outcome was assessed for 60% to 90% of the study group of interest (+). In this update, we assessed attrition bias for each outcome separately but we had not defined a 'well-defined outcome' in the protocol. The definition is as follows: if the outcome definition was objective and precise, that is, if the upper or lower limits of normal for renal function tests were described in the definition of adverse renal effects.

In the protocol we stated that we would (hand)search for conference proceedings and ongoing trials mentioned below. In the initial review this was not performed at all, because no resources were available due to the sheer volume of references retrieved from the online databases. In this update, we partially performed this, as we (hand)searched the conference proceedings of the International Society for Paediatric Oncology (SIOP) from 2010 to 2016 and the and The American Society of Pediatric Hematology/Oncology (ASPHO) from 2010 to 2017. We also searched for information about trials not in CENTRAL, MEDLINE or Embase, published or unpublished, by searching the reference lists of relevant articles and review articles. The protocol stated that we would also search the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer and the European Symposium on Late Complications After Childhood Cancer 2009. In addition, it stated that we would scan the International Standard Randomised Controlled Trials Number (ISRCTN) register and the National Institutes of Health (NIH) register for ongoing trials, for information about ongoing trials. However, we did not do this as it is no longer CCG policy for adverse effects reviews to search these sources.

Regarding data analysis, we clarified in this update that we would only pool data when studies were clinically homogeneous.

INDEX TERMS

Medical Subject Headings (MeSH)

*Survivors; Antineoplastic Agents [*adverse effects]; Carboplatin [adverse effects]; Cisplatin [adverse effects]; Glomerular Filtration Rate [drug effects] [physiology] [radiation effects]; Hypertension [epidemiology] [etiology]; Hypophosphatemia [epidemiology] [etiology]; Ifosfamide [adverse effects]; Magnesium Deficiency [epidemiology] [etiology]; Nephrectomy [*adverse effects];

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Proteinuria [epidemiology] [etiology]; Radiotherapy [*adverse effects]; Renal Insufficiency, Chronic [epidemiology] [*etiology]; Risk Factors

MeSH check words

Adult; Child; Humans

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