CLINICAL STUDY

Final height and IGF1 in adult survivors of Wilms tumour

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Abstract

Objective: One-sided nephrectomy is followed by increased levels of IGF1, associated with linear growth during childhood. The aim was to evaluate final height and IGF1 levels in nephrectomized Wilms tumour survivors when compared with healthy Dutch references and survivors of other cancer types. **Design:** Cross-sectional retrospective study.

Methods: Data of 575 adult childhood cancer survivors were analysed. Median follow-up time was 17.8 (range 5.0–48.8) years. Analysis of (co)variance was performed to evaluate differences between subgroups: nephrectomized Wilms survivors treated with or without abdominal irradiation ($n=41$ and $n=36$) and survivors of other cancer types treated with or without irradiation involving the cranium, abdomen or total body ($n=149$ and $n=349$). Main outcome measures were IGF1 and height, expressed as SDS.

Results: After adjustment for age at diagnosis, former corticosteroid treatment and renal impairment, height SDS in non-irradiated nephrectomized Wilms survivors was significantly higher than that in non-irradiated survivors of other cancer types (estimated mean SDS -0.09 vs -0.49 , $P=0.044$), abdominal irradiated survivors (SDS -0.70 , $P=0.015$) and other irradiated survivors (SDS -1.47 , $P<0.001$). Non-irradiated nephrectomized Wilms tumour survivors had significantly higher IGF1 SDS than other irradiated survivors (estimated mean SDS -0.05 vs -1.36 , $P<0.001$ and 0.11 vs 1.37 , $P<0.001$), while there was no significant difference with the other two subgroups.

Conclusions: Adult survivors of Wilms tumour showed better attainment of final height and relatively higher IGF1 levels than those of other cancer types who had significantly shorter stature and lower IGF1 levels than Dutch references.

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Introduction

Wilms tumour or nephroblastoma is the most common solid tumour during childhood (1). The survival of Wilms tumour patients has increased over the past decades due to improved treatment regimens and better stratification. In Europe, treatment exists of tumour nephrectomy after pre-operative chemotherapy and, depending on histology and stage, chemotherapy (e.g. vincristine, dactinomycin and doxorubicin). Additionally, abdominal irradiation is given in stage III and in some stage IV patients (2, 3).

In general, nephrectomy is followed by compensatory renal growth of the contralateral kidney, possibly as a result of hypervascularization and increased glomerular pressures (4, 5). Simultaneously, serum insulin-like growth factor 1 (IGF1) increases after surgery and is associated with recovery of renal function and regeneration of kidney tissue (5, 6, 7). As IGF1 is responsible for linear growth during childhood, we hypothesize that

temporary high IGF1 levels after nephrectomy during childhood contribute to accelerated growth in survivors of Wilms tumour. This may result in a taller stature than survivors of other childhood cancer types.

We have to take into account that Wilms tumour is associated with predisposing syndromes, including WT1-associated syndromes and overgrowth syndromes, which are present in 9–19% of Wilms tumour patients (8). Previous studies have shown that the pathophysiology of both Wilms tumour and overgrowth syndromes might be associated with growth factor excess (9, 10, 11, 12, 13, 14). The fact that Wilms tumour patients often have a significantly higher birth weight than healthy newborns supports this hypothesis (15). The effect of this suggested mechanism on final height in adulthood is however not elucidated. The aim of the current study was to compare final height and IGF1 levels of nephrectomized Wilms tumour survivors with healthy Dutch references and survivors of other cancer types.

Subjects and methods

Subjects

We performed a cross-sectional, single-centre study in all adult long-term survivors of childhood cancer, including Wilms tumour, diagnosed between 1952 and 2005. Data on height and IGF1 described in this study were retrieved between 1997 and 2012 during regular follow-up at the late effects outpatient clinic for long-term childhood cancer survivors, which starts 5 years after cessation of treatment and is individualized based on cancer diagnosis, treatment protocol and clinical condition. Exclusion criteria for our evaluation were no availability of height or IGF1 during follow-up, growth hormone (GH) treatment during follow-up, former diagnosis of Wilms tumour without one-sided nephrectomy and treatment with nephrectomy for other diagnoses than Wilms tumour. An official written informed consent from every patient that visited the outpatient clinic was obtained according to the standards of the institutional review board.

Data collection

Data concerning disease and treatment protocol were retrieved from our local paediatric oncology database and missing data were retrieved from the medical records. Follow-up time was defined as time since cessation of treatment. Follow-up data of the most recent visit at the late effects clinic for all survivors were retrieved and included height, oral contraceptive (OC) use, GH replacement, IGF1 and renal function, as defined by estimated glomerular filtration rate (eGFR), calculated with the abbreviated Modification of Diet in Renal Disease equation using serum creatinine (16, 17, 18). Final height SDS were calculated using reference values for Dutch adults: a mean (s.d.) of 184.0 (7.1) cm for males and 170.6 (6.5) cm for females (19). In Wilms tumour survivors, the diameter of the remaining kidney was retrieved from abdominal ultrasounds and compared with a normal value of 10.8 cm (20). In all cases, IGF1 was assessed by Immulite 2000 (DPC Biermann GmbH/Siemens, Fernwald, Germany), a solid-phase, enzyme-labelled chemiluminescent immunometric assay, with an intra-assay variability of 2–5% and an inter assay variability of 3–7% (21). IGF1 levels were compared with reference values using age- and sex-adjusted SDS (21). Serum creatinine, assessed using the Roche enzymatic assay, was analysed in a fully automated computerized laboratory system with a Hitachi 917 chemistry analyzer (Roche Diagnostics).

Genetic analysis

All Wilms tumour survivors were offered clinical genetic assessment, genetic counselling and molecular analysis of the *WT1* gene and the methylation status of the

imprinted gene clusters on locus 11p15 after informed consent from the included patients as described previously by Segers *et al.* (8).

Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS 19.0). Results are reported as medians (range) for baseline characteristics and non-normative outcome variables and as means (95% CI) for SDS. Included survivors were divided into four subgroups: Wilms survivors treated with nephrectomy without abdominal irradiation and without stem cell transplantation (SCT) ($n=36$); other survivors treated without SCT and without irradiation of the cranium, abdomen, spine or total body (TBI) as these treatments affect height and/or IGF1 ($n=349$); Wilms survivors treated with nephrectomy and abdominal irradiation ($n=41$) and other survivors treated with SCT or one of the above-mentioned types of irradiation ($n=149$). To compare IGF1 and height of these four subgroups of survivors with healthy references, SDS were calculated and analysed with the one-sample *t*-test. ANOVA was used for univariate comparisons between subgroups and analysis of covariance (ANCOVA) for multivariate comparisons to adjust for potential confounders. Models for height SDS and IGF1 SDS were adjusted for age at diagnosis and renal impairment, defined as eGFR <60 ml/min per 1.73 m^2 . Because of its negative effect on IGF1 levels, OC use was added to the model with IGF1 SDS as outcome measure. Furthermore, BMI was added as covariate to this model. Former corticosteroid treatment has been described to negatively influence final height attainment and therefore was added to the model for height SDS. ANCOVA, adjusted for sex, age at follow-up and age at diagnosis, was used to compare kidney length between Wilms survivors treated with or without abdominal irradiation. *P* values of <0.05 (two-tailed) were considered statistically significant.

Results

Survivors

Of 885 adult survivors of childhood cancer diagnosed between 1964 and 2005, 600 survivors had visited the outpatient clinic at least once, of which 79 adults survived a Wilms tumour more than 5 years since cessation of treatment. Baseline and treatment characteristics are presented in Tables 1 and 2. Median age at diagnosis was 3.3 (range 0.2–12.7) years for Wilms tumour survivors and 7.1 (0–18.0) years for survivors of other cancer types. Median follow-up time was 24.5 (range 5.1–48.8) years for Wilms tumour survivors and 17.3 (range 5.0–48.8) years for other survivors. A second tumour was diagnosed in one Wilms tumour

Table 1 Baseline characteristics of adult Wilms tumour survivors and other survivors.

	Wilms survivors (n=79)	Other survivors (n=521)
Male sex (n)	41 (52)	293 (56)
Age at diagnosis (years)	3.3 (0.2–12.7)	7.1 (0–18.0)
Age at follow-up (years)	28.4 (18.1–50.8)	25.8 (18.0–57.4)
Follow-up time (years)	24.5 (5.1–48.8)	17.3 (5.0–48.8)
Diagnosis		
Wilms tumour	79 (100)	–
Non-Wilms renal tumours	–	5 (1)
ALL and T-NHL	–	182 (35)
ANLL	–	20 (4)
B-NHL	–	50 (10)
Hodgkin	–	46 (9)
Bone tumour	–	29 (6)
Neuroblastoma	–	39 (8)
LCH	–	13 (3)
Extracranial GCT	–	12 (2)
MMT	–	51 (10)
Brain tumour	–	55 (11)
Hepatoblastoma	–	3 (0.5)
Other cancers	–	16 (3)
Second tumour	1 (1)	8 (2)
Recurrence	12 in nine patients	83 in 70 patients

ALL, acute lymphoblastic leukaemia; T-NHL, T-cell non-Hodgkin lymphoma; ANLL, acute non-lymphoblastic leukaemia; B-NHL, B-cell non-Hodgkin lymphoma; MMT, malignant mesenchymal tumour.

^aExcluded from the analyses.

survivor (1.2%) and eight other survivors (1.5%). Forty-two Wilms tumour survivors had been additionally treated with abdominal radiotherapy.

Clinical genetic assessment was performed in 42 Wilms tumour survivors and a genetic mutation was found in four cases. In one survivor, a *WT1* mutation

was found and in one survivor hypomethylation of *LIT1*. None of these survivors had been clinically diagnosed with overgrowth. Two Wilms tumour survivors had been clinically diagnosed with Stickler syndrome; in one survivor, this syndrome was confirmed by mutation of *COL2A1*.

Excluded from the analysis were two Wilms survivors not treated with nephrectomy, ten non-Wilms survivors treated with nephrectomy and 13 survivors treated with GH replacement during follow-up.

Final height

Rough data on height and IGF1 as well as SDS and kidney length per sex category are outlined in Table 3. IGF1 SDS was significantly correlated with height SDS ($\rho=0.24$, $P<0.001$). Figure 1 shows height SDS in the four different subgroups. Except for non-irradiated Wilms survivors treated with nephrectomy (SDS -0.24 , $P=0.155$), height SDS was significantly lower than Dutch references in all other three groups (others treated without irradiation: SDS -0.47 , $P<0.001$; Wilms treated with abdominal irradiation: SDS -0.87 , $P<0.001$; others treated with irradiation: SDS -1.45 , $P<0.001$). After adjustment for age at diagnosis, former treatment with corticosteroids and renal impairment, height SDS in non-irradiated nephrectomized Wilms survivors was significantly higher than height SDS in non-irradiated survivors of other cancer types (estimated mean SDS -0.09 vs -0.49 , $P=0.044$), survivors treated with abdominal irradiation (SDS -0.70 , $P=0.015$) and other irradiated survivors treated with irradiation (SDS -1.47 , $P<0.001$).

Table 2 Treatment details and follow-up data of adult Wilms tumour survivors and other survivors.

	Wilms survivors (n=79)		Other survivors (n=521)	
	n (%)	Cumulative RT dose (Gy)	n (%)	Cumulative RT dose (Gy)
Abdominal RT	42 (53)	25 (15–40)	12 (2)	20 (10–50)
CRT	–	NA	59 (11)	25 (15–30)
BRT	–	NA	61 (12)	45 (10–66)
TBI	–	NA	25 (5)	8 (6–12)
SCT autologous/allogeneous	1/0		8/17	
Spinal irradiation	–	NA	23 (5)	33.6 (12–50.4)
Corticosteroids	–	NA	287 (55)	Unknown
Follow-up data				
GH treatment	–		13 (3) ^a	
eGFR <60 ml/min per 1.73 m ²	2 (3)		6 (1)	
Therapy				
Nephrectomy	77 (98)		10 (2) ^a	
Left kidney	42 (55)		6 (1)	
Right kidney	35 (46)		4 (1)	
No nephrectomy	2 (3) ^a		511 (98)	

RT, radiotherapy; CRT, cranial RT; BRT, brain tumour RT; TBI, total body irradiation; GH, growth hormone.

^aExcluded from the analyses.

Table 3 Height, insulin-like growth factor-1 and kidney length in male and female survivors of different subgroups. Data of height, IGF-I and kidney length are expressed as mean (range); SDS data are expressed as mean (95% CI).

	Male survivors				Female survivors			
	Group 1 n=21	Group 2 n=188	Group 3 n=18	Group 4 n=93	Group 1 n=15	Group 2 n=161	Group 3 n=23	Group 4 n=56
Height	183 (175–191)	180 (155–197)	176 (165–191)	174 (145–191)	168 (149–182)	168 (141–184)	166 (151–184)	161 (141–184)
Height SDS	–0.18 (–0.47; 0.11)	–0.54 (–0.69; –0.39)	–1.09 (–1.53; –0.64)	–1.44 (–1.69; –1.19)	–0.33 (–1.08; 0.43)	–0.38 (–0.55; –0.21)	–0.69 (–1.11; –0.27)	–1.45 (–1.81; –1.09)
IGF1	31.8 (11.9–74.5)	27.3 (11.6–69.9)	23.4 (11.7–50.4)	20.1 (4.4–43.0)	28.0 (10.2–52.9)	27.7 (8.3–60.6)	21.4 (7.6–46.3)	17.4 (4.2–46.4)
IGF1 SDS	0.10 (–0.31; 0.51)	–0.34 (–0.48; –0.21)	–0.46 (–1.03; 0.11)	–1.17 (–1.48; –0.86)	–0.25 (–1.08; 0.58)	–0.20 (–0.36; –0.04)	–0.55 (–0.12; 0.01)	–1.68 (–2.17; –1.19)
Kidney length	13 (12–19)	NA	13 (11–15)	NA	13 (11–15)	NA	12 (11–15)	NA

Group 1: Wilms tumour survivors treated with nephrectomy not with RT or SCT; group 2: survivors of other cancer types treated without SCT or RT; group 3: Wilms tumour survivors treated with nephrectomy and RT; group 4: survivors of other cancer types treated with RT and/or SCT. SCT, stem cell transplantation; RT, radiotherapy (Wilms: abdominal RT; other: RT involving the cranium, abdomen, spine and total body).

IGF1 levels

IGF1 SDS per subgroup are outlined in Fig. 2. Except for non-irradiated Wilms survivors treated with nephrectomy (SDS -0.05 , $P=0.817$), IGF1 SDS was significantly lower than Dutch references in all other three groups (others treated without irradiation: SDS -0.28 , $P<0.001$; Wilms treated with abdominal irradiation: SDS -0.51 , $P=0.011$; others treated with irradiation: SDS -1.36 , $P<0.001$). In univariate and multivariate analysis, non-irradiated Wilms tumour survivors treated with nephrectomy had significantly higher IGF1 than others treated with irradiation (estimated mean SDS -0.05 vs -1.36 , $P<0.001$ and 0.11 vs 1.37 , $P<0.001$), while there was no significant difference with the other two subgroups (Fig. 2).

Kidney size

Kidney size of the contralateral kidney in survivors treated with nephrectomy was significantly larger than Dutch references (12.8 vs 10.8 cm, $P<0.001$, Fig. 3). Survivors treated with nephrectomy without abdominal irradiation had larger kidney size than abdominal irradiated Wilms survivors (13.1 vs 12.5, $P=0.049$), but this difference was not significant after adjustment for sex, age at follow-up and age at diagnosis (Fig. 3).

Figure 1 Univariate and multivariate analysis of height SDS in the four subgroups. Data are expressed as mean (95% CI) and represent the estimated mean in univariate analysis (first whisker) and multivariate analysis (second whisker). P values represent the differences between groups after adjusting for age at diagnosis, renal impairment and corticosteroid treatment. Group 1: Wilms tumour survivors treated with nephrectomy not with RT or SCT; group 2: survivors of other cancer types treated without SCT or RT; group 3: Wilms tumour survivors treated with nephrectomy and RT; group 4: survivors of other cancer types treated with RT and/or SCT. SCT, stem cell transplantation; RT, radiotherapy (Wilms: abdominal RT; other: RT involving the cranium, abdomen, spine and total body).

Figure 2 Univariate and multivariate analysis of IGF1 SDS in the four subgroups. Data are expressed as mean (95% CI) and represent the estimated mean in univariate analysis (first whisker) and multivariate analysis (second whisker). *P* value represents the difference between groups after adjusting for age at diagnosis, renal impairment, oral contraceptive use and BMI. Group 1: Wilms tumour survivors treated with nephrectomy, not with RT or SCT; group 2: survivors of other cancer types treated without SCT or RT; group 3: Wilms tumour survivors treated with nephrectomy and RT; group 4: survivors of other cancer types treated with RT and/or SCT. SCT, stem cell transplantation; RT, radiotherapy (Wilms: abdominal RT; other: RT involving the cranium, abdomen, spine and total body).

Discussion

At very long-term follow-up, we found that adult survivors of Wilms tumour treated with nephrectomy showed better attainment of final height than survivors of other cancer types, in whom final height was significantly lower than Dutch references. We hypothesize that temporary high IGF1 levels after nephrectomy in paediatric Wilms tumour patients contribute to accelerated and prolonged growth post-therapy than in survivors of other cancer types, leading to a better attainment of final height. The mechanism of increasing serum IGF1 levels after nephrectomy has been described in both adults (6) and children (22). In adults, IGF1 levels showed a significant increment post-surgery, with a peak at 6 months and thereafter normalized to baseline within 1 year. In nephrectomized children, higher IGF1 levels than in controls were found more than 3 years after surgery. IGF1 is associated with hypervascularization, compensatory growth of the contralateral kidney and recovery of renal function (6, 7, 23, 24). The fact that we found larger kidney size than references in all our Wilms tumour survivors supports this mechanism. The effect of high IGF1 levels on growth in paediatric patients undergoing nephrectomy has not been elucidated yet, but a positive relationship is plausible as IGF1 is an important determinant of linear growth during childhood. Although data on IGF1 levels pre- and post-surgery

were not available, our cross-sectional data support this hypothesis as nephrectomized Wilms tumour survivors had significantly higher final height than a comparable group of non-irradiated survivors of other cancer types. Another explanation for the attainment of a normal height in Wilms tumour survivors is the relatively short duration of chemotherapy (even though this is 6 months in a large subset of Wilms tumour patients) and low risk for under-nutrition when compared with acute lymphoblastic leukaemia survivors.

The only way to confirm this hypothesis would be to longitudinally evaluate and compare IGF1 levels in relation to growth data shortly after treatment in both Wilms survivors and survivors of other cancer types. As IGF1 levels are temporarily high after nephrectomy, we do not expect IGF1 SDS to be higher in adult long-term nephrectomized Wilms survivors, which indeed was not the case. However, comparable to height SDS data, we found lower IGF1 levels than Dutch references in all childhood cancer survivors, except for non-irradiated survivors of Wilms tumour. Reduced IGF1 levels and shorter stature in childhood cancer survivors might partly be explained by treatment factors, as it is well known that irradiation at young age involving the whole brain, or any part of it, and TBI affects growth and IGF1 levels (25, 26, 27). However, even in the group of non-irradiated survivors, IGF1 levels were significantly lower than in the normal population in contrast to non-irradiated survivors of Wilms tumour, who had IGF1 levels comparable to the normal population and showed a trend to be higher

Figure 3 Kidney size as expressed by maximal diameter of the contralateral kidney in survivors of Wilms tumour treated with nephrectomy with and without abdominal irradiation. Data are expressed as mean (95% CI) and represent the estimated mean in univariate analysis (first whisker) and multivariate analysis (second whisker). Group 1: Wilms tumour survivors treated with nephrectomy, not with RT or SCT; group 3: Wilms tumour survivors treated with nephrectomy and RT; RT, abdominal radiotherapy.

than other non-irradiated survivors, which is a remarkable finding.

Although in one survivor a hypomethylation of LIT1 was found, no clinically diagnosed overgrowth syndrome was present in this patient. However, several studies suggested that growth factor excess may not be limited to patients diagnosed with known germ line mutations, which could be illustrated by the fact that Wilms tumour patients without associated anomalies had higher birth weights than controls (15, 28). However, there is inconsistency about this association, as several studies could not confirm the finding that those with high birth weights are at increased risk for Wilms tumour (29, 30). IGF2 binds to the IGF1 receptor (IGFIR) and is over-expressed in Wilms tumour patients. *In vitro* studies showed that inhibition of IGFIR suppressed growth of Wilms tumour cells (31), suggesting that indeed growth factor excess may be an important determinant of clinical overgrowth in survivors of Wilms tumour. It is important to realize that IGF2 is a potent fetal growth factor and plays a significant role in particularly overgrowth syndromes but is not responsible for linear growth, like IGF1.

Limitations It would have been appropriate to include data on target height, as it indicates individual height attainment. Unfortunately, due to the retrospective character of this study, these data were not available. Furthermore, due to the retrospective design of the study, data on sitting height, to evaluate spinal growth, was not available. It is well known that abdominal irradiation negatively affects spinal growth, especially in young patients, resulting in a shorter and more disproportionate stature (32). Furthermore, abdominal irradiation is a risk factor for gonadal dysfunction and may affect pubertal development, thereby affecting final height attainment (33). Therefore, in this study, we compared height of non abdominal irradiated Wilms tumour survivors with that of non-irradiated survivors of other childhood cancers, and our main conclusions were based on this comparison. Furthermore, the effect of gonadal dysfunction was evaluated, as in the case of primary gonadal dysfunction in combination with intact pituitary axes, one could expect a longer stature. Linear regression showed no significant association of gonadal dysfunction (defined as testosterone supplementation and/or testosterone level ≤ 8 nmol/l in men and oestrogen supplementation and/or AMH levels < 0.1 in women) with height SDS. Furthermore, when adding gonadal dysfunction as covariate to the model of height SDS, results did not change. Furthermore, data on clinical genetic analysis and related clinical overgrowth were lacking in half of the Wilms tumour patients. However, final height and birth weight did not significantly differ between survivors with and without available genetic data.

In conclusion, non-irradiated nephrectomized adult survivors of Wilms tumour showed better attainment

of final height and relatively higher IGF1 levels than survivors of other cancer types who had significantly shorter stature and lower IGF1 levels than Dutch references.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- Grovas A, Fremgen A, Rauck A, Ruymann FB, Hutchinson CL, Winchester DP & Menck HR. The National Cancer Data Base report on patterns of childhood cancers in the United States. *Cancer* 1997 **80** 2321–2332. (doi:10.1002/(SICI)1097-0142(19971215)80:12<2321::AID-CNCR14>3.0.CO;2-W)
- Metzger ML & Dome JS. Current therapy for Wilms' tumor. *Oncologist* 2005 **10** 815–826. (doi:10.1634/theoncologist.10-10-815)
- de Kraker J, Graf N, van Tinteren H, Pein F, Sandstedt B, Godzinski J & Tournade MF. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. *Lancet* 2004 **364** 1229–1235. (doi:10.1016/S0140-6736(04)17139-0)
- Cozzi F, Zani A, Schiavetti A, Morini F, Degaetano V, Matrunola M & Cozzi DA. Compensatory renal growth in children with unilateral renal tumor treated by nephron-sparing surgery or nephrectomy. *European Journal of Pediatric Surgery* 2007 **17** 382–386. (doi:10.1055/s-2007-989219)
- Chang SG, Kim JH, Lee SJ, Choi JM & Huh JS. Factors influencing contralateral renal hypertrophy after living donor nephrectomy. *Transplantation Proceedings* 2002 **34** 1139–1142. (doi:10.1016/S0041-1345(02)02762-8)
- Nam UC, Lee CH & Chang SG. Clinical study of insulin-like growth factor-I and compensatory renal growth in patients with donor nephrectomy. *Transplantation Proceedings* 1999 **31** 2114–2117. (doi:10.1016/S0041-1345(99)00279-1)
- Hammerman MR & Miller SB. Effects of growth hormone and insulin-like growth factor I on renal growth and function. *Journal of Pediatrics* 1997 **131** S17–S19. (doi:10.1016/S0022-3476(97)70004-0)
- Segers H, Kersseboom R, Alders M, Pieters R, Wagner A & van den Heuvel-Eibrink MM. Frequency of WT1 and 11p15 constitutional aberrations and phenotypic correlation in childhood Wilms tumour patients. *European Journal of Cancer* 2012 **48** 3249–3256. (doi:10.1016/j.ejca.2012.06.008)
- Brown KW & Malik KT. The molecular biology of Wilms tumour. *Expert Reviews in Molecular Medicine* 2001 **2001** 1–16.
- Huff V. Genotype/phenotype correlations in Wilms' tumor. *Medical and Pediatric Oncology* 1996 **27** 408–414. (doi:10.1002/(SICI)1096-911X(199611)27:5<408::AID-MPO4>3.0.CO;2-Q)
- Huff V. Wilms tumor genetics. *American Journal of Medical Genetics* 1998 **79** 260–267. (doi:10.1002/(SICI)1096-8628(19981002)79:4<260::AID-AJMG6>3.0.CO;2-Q)

- 12 Md Zin R, Murch A & Charles A. Pathology, genetics and cytogenetics of Wilms' tumour. *Pathology* 2011 **43** 302–312. (doi:10.1097/PAT.0b013e3283463575)
- 13 Scott RH, Stiller CA, Walker L & Rahman N. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. *Journal of Medical Genetics* 2006 **43** 705–715. (doi:10.1136/jmg.2006.041723)
- 14 Miller RW, Fraumeni JF Jr & Manning MD. Association of Wilms's tumor with aniridia, hemihypertrophy and other congenital malformations. *New England Journal of Medicine* 1964 **270** 922–927. (doi:10.1056/NEJM196404302701802)
- 15 Leisenring WM, Breslow NE, Evans IE, Beckwith JB, Coppes MJ & Grundy P. Increased birth weights of National Wilms' Tumor Study patients suggest a growth factor excess. *Cancer Research* 1994 **54** 4680–4683.
- 16 Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW & Van Lente F. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clinical Chemistry* 2007 **53** 766–772. (doi:10.1373/clinchem.2006.077180)
- 17 Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J & Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Annals of Internal Medicine* 2003 **139** 137–147. (doi:10.7326/0003-4819-139-2-200307150-00013)
- 18 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N & Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine* 1999 **130** 461–470. (doi:10.7326/0003-4819-130-6-199903160-00002)
- 19 Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP & Wit JM. Continuing positive secular growth change in The Netherlands 1955–1997. *Pediatric Research* 2000 **47** 316–323. (doi:10.1203/00006450-200003000-00006)
- 20 Robben SGF. Normaalwaarden kinderechografie. <http://www.mbber.nl/index.php/forum/15> Accessed on 8-8-2013.
- 21 Elmlinger MW, Kuhnle W, Weber MM & Ranke MB. Reference ranges for two automated chemiluminescent assays for serum insulin-like growth factor I (IGF-I) and IGF-binding protein 3 (IGFBP-3). *Clinical Chemistry and Laboratory Medicine* 2004 **42** 654–664. (doi:10.1515/CCLM.2004.112)
- 22 Yildiz B, Kural N, Colak O, Ak I & Akcar N. IGF-1, IGFBP-3, VEGF and MMP-9 levels and their potential relationship with renal functions in patients with compensatory renal growth. *Clinical Physiology and Functional Imaging* 2008 **28** 107–112. (doi:10.1111/j.1475-097X.2007.00783.x)
- 23 Rabkin R, Fervenza FC, Maidment H, Ike J, Hintz R, Liu F, Bloedow DC, Hoffman AR & Gesundheit N. Pharmacokinetics of insulin-like growth factor-1 in advanced chronic renal failure. *Kidney International* 1996 **49** 1134–1140. (doi:10.1038/ki.1996.164)
- 24 el Nahas AM, Le Carpentier JE & Bassett AH. Compensatory renal growth: role of growth hormone and insulin-like growth factor-I. *Nephrology, Dialysis, Transplantation* 1990 **5** 123–129. (doi:10.1093/ndt/5.2.123)
- 25 Blijdorp K, van den Heuvel-Eibrink M, Pieters R, Boot A, Sluimer J, van der Lelij AJ & Neggers S. The limited screening value of insulin-like growth factor-I as a marker for alterations in body composition in very long-term adult survivors of childhood cancer. *Pediatric Blood & Cancer* 2012 **59** 711–716. (doi:10.1002/pbc.24015)
- 26 Achermann JC, Hindmarsh PC & Brook CG. The relationship between the growth hormone and insulin-like growth factor axis in long-term survivors of childhood brain tumours. *Clinical Endocrinology* 1998 **49** 639–645. (doi:10.1046/j.1365-2265.1998.00585.x)
- 27 Steffens M, Beauloye V, Brichard B, Robert A, Alexopoulou O, Vermyn C & Maiter D. Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). *Clinical Endocrinology* 2008 **69** 819–827. (doi:10.1111/j.1365-2265.2008.03283.x)
- 28 Daling JR, Starzyk P, Olshan AF & Weiss NS. Birth weight and the incidence of childhood cancer. *Journal of the National Cancer Institute* 1984 **72** 1039–1041.
- 29 Olshan AF, Breslow NE, Falletta JM, Grufferman S, Pendergrass T, Robison LL, Waskerwitz M, Woods WG, Vietti TJ & Hammond GD. Risk factors for Wilms tumor, Report from the National Wilms Tumor Study. *Cancer* 1993 **72** 938–944. (doi:10.1002/1097-0142(19930801)72:3<938::AID-CNCR2820720345>3.0.CO;2-C)
- 30 Lindblad P, Zack M, Adami HO & Ericson A. Maternal and perinatal risk factors for Wilms' tumor: a nationwide nested case-control study in Sweden. *International Journal of Cancer* 1992 **51** 38–41. (doi:10.1002/ijc.2910510108)
- 31 Bielen A, Box G, Perryman L, Bjerke L, Popov S, Jamin Y, Jury A, Valenti M, Brandon Ade H, Martins V *et al.* Dependence of Wilms tumor cells on signaling through insulin-like growth factor 1 in an orthotopic xenograft model targetable by specific receptor inhibition. *PNAS* 2012 **109** E1267–E1276. (doi:10.1073/pnas.1105034109)
- 32 Wallace WH, Shalet SM, Morris-Jones PH, Swindell R & Gattamaneni HR. Effect of abdominal irradiation on growth in boys treated for a Wilms' tumor. *Medical and Pediatric Oncology* 1990 **18** 441–446. (doi:10.1002/mpo.2950180602)
- 33 Scott JE. Pubertal development in children treated for nephroblastoma. *Journal of Pediatric Surgery* 1981 **16** 122–125. (doi:10.1016/S0022-3468(81)80336-3)

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