Mapping relapse of Wilms tumour and detection methods:
A report from the SIOP Renal Tumour Study Group

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Summary

Background Wilms tumour (WT) is the most common renal cancer in childhood and about 15% of patients will relapse. The optimum surveillance schedules and methods for detecting tumour relapse post therapy lack firm evidence.

Methods Retrospective cohort study of the multicentre renal tumour study group International Society of Paediatric Oncology (RTSG-SIOP) WT-2001 database. We aimed to map the site, timing and modality of detection of relapse, and the number of surveillance scans needed to detect one relapse. Our further aim was to provide stronger evidence for refinement of the RTSG-SIOP relapse surveillance recommendations.

Findings Of 4271 eligible patients, 538 (13%) relapsed. Relapse site involved lung (63%), abdomen (49%), liver (11%), bone (1%) and brain (1%). Overall, 80% of relapses occurred within two years of nephrectomy. Planned surveillance imaging captured 70% of the relapses, which were predominantly asymptomatic, and the remaining relapses mainly presented with clinical symptoms in the interim between scheduled surveillance. Relapse was identified by abdominal ultrasound (32%), chest X-ray (31%), chest/abdomen computed tomography scan (25%/8%), and abdominal magnetic resonance imaging (4%). Most (68%) relapses were undetectable by physical examination. The estimated number of scans needed to detect one subclinical relapse in the interval 0-2 years and 2-5 years post-nephrectomy was, respectively, 112 (95% CI 106-119) and 500 (95% CI 416-588). Post-relapse 5-year overall survival rate was 56% (95% CI 51%-61%). Children presenting with clinical symptoms between scheduled surveillance had inferior post-relapse survival [Hazard ratio 1.85 (95% CI 1.24-2.77); p=0·01].

Interpretation WT relapses predominantly occur within two years of nephrectomy, are usually asymptomatic and frequently involve the lung. Surveillance imaging captured more than two thirds of relapses, and these patients had better prognosis. Beyond two years post-nephrectomy a considerable number of surveillance scans are needed to capture one relapse, which places a disputable burden on families and health care systems.

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Evidence before this study

We searched PubMed for all manuscripts published up to November 2017, using the search terms "Wilms' tumour" or "nephroblastoma" AND "surveillance" or "follow-up". We excluded studies on screening for primary Wilms tumour (WT) in children with pre-disposition syndromes. The lung and abdomen are the predominant sites of relapse, whereas liver, brain, and bone involvement is rare. The majority of relapses occur within the first years after end of treatment. The International Society of Paediatric Oncology (SIOP) approach is to monitor for relapse post treatment with chest X-rays and abdominal ultrasound whereas alternating chest X-rays/abdominal ultrasound and chest/abdominal computed tomography (CT) is advocated by the Children Oncology Group (COG). Both groups adhere to five years of surveillance. Few relatively small retrospectives reports have indicated that CT could be omitted whilst highlighting the need for larger prospective studies to assess the benefit and harms of surveillance strategies for WT.

Added value of this study

This study provides new knowledge on how relapse of WT is detected. Adoption of the SIOP-WT-2001 study surveillance recommendation, acknowledging that regional and individual hospitals may make possible minor adjustments, enables centres to capture more than two thirds of predominantly asymptomatic WT relapses. We also found that a considerable number of scans are needed to capture one asymptomatic relapse. However, asymptomatic relapses, captured by surveillance scans, have a superior prognosis compared with relapses presenting with clinical symptoms between routine follow-up.

Implications of all available evidence

Current SIOP recommendations, with abdominal ultrasound and chest X-ray, seem to capture a high proportion of asymptomatic relapses. Surveillance recommendations may benefit from some refinement and a focus on the two years post treatment using three months intervals, considering shorter intervals for subgroups at higher risk of early relapse. Surveillance beyond two years post treatment could be considered (mandatory for bilateral tumours with increased risk of metachronous relapse and patients with WT pre-disposition syndromes), but the overall number of abdominal ultrasounds and chest X-rays needed to capture one asymptomatic relapse would likely be about 500. To further guide this individual decision, we have constructed a 'surveillance map' that takes into account stage, histology and time-point. Randomised trials are needed to assess different surveillance regimens but are less likely to be prioritised.

Introduction

Wilms tumour (WT) is the most common renal cancer in childhood with about 1000 new patients diagnosed in Europe each year[1]. With optimised use of current treatment strategies, ie, chemotherapy, nephrectomy and sometime radiotherapy, an overall survival rate of 90% can be achieved[2-4]. Relapse of WT is still observed in about 15% of treated patients, with the vast majority occurring within two years post nephrectomy and only occasionally later than five years[5]. The lung is the predominant site of relapse for WT, local or regional abdominal relapses occur slightly less frequently, whereas liver and especially brain and bone involvement is very rare.[6,7] Overall survival rate following relapse is approximately 50% but the outcome varies depending on several factors. Key prognostic factors used to stratify relapse treatment in contemporary guidelines are histological risk group, tumour stage and previous treatment intensity.[6-10]

As the number of children with WT or other childhood cancers achieving first complete remission increases, scrutiny to detect recurrent tumours places a burden on the family and the healthcare system. The well-intentioned aim of such surveillance is to detect relapse at an earlier stage, when prognosis may be better or require less intensive treatment. However, fundamental knowledge about costs, benefits and potential risks of different surveillance strategies for WT and other childhood cancers is very limited.[11] Intensive imaging may add unnecessary radiation exposure, and frequent hospital visits post treatment may cause psychological distress in the child and families.[12,13]

Efficacy of surveillance strategies and schedules for WT has never been prospectively assessed, and are unlikely to be prioritised. The few randomised clinical trials conducted in adults with cancers have demonstrated conflicting results as to whether intensive monitoring for relapse improves outcome.[14]

In this vein, the methods, duration and frequency of surveillance for WT patients post treatment is debated. Accordingly, follow-up strategies may vary geographically in the context of available resources and national or regional habitual practices. To date nearly 6000 children and adolescents with renal tumours have been registered on the International Society of Paediatric Oncology (SIOP) 2001 trial and study by the SIOP Renal Tumour Study Group (RTSG). This protocol recommended regular chest X-rays and abdominal ultrasound scans for a number of years depending on initial tumour stage and histology (table 1).[15] Data from this large cohort may capture additional useful evidence about the efficacy of routine surveillance imaging in detecting relapse.

In this analysis, we describe the timing, anatomical site and mode of detection of all first relapse in WT reported in the SIOP-WT-2001 trial and study. Furthermore, we estimate the number of scans needed to identify one relapse and explore prognostic factors for post-relapse survival. We use the results to evaluate current surveillance guidelines.

Methods

Protocol and study population

The SIOP-WT-2001 trial and study is an international, multi-centre registration and biological study with an embedded randomised clinical trial for children with renal tumours between six months and 18 years old. The study comprises 27 countries from 243 different centres. It was launched in November 2001, and is still open for registration in some countries. The randomisation closed on January 1, 2010 and the reduced therapy ‘experimental’ arm has become the new standard of care.[15,16] Regulatory and ethical approvals were obtained according to the national/local regulations and all participants or legal guardians authorised consent. The protocol (Eudra-CT 2007-004591-39) is available online (www.siop-rtsg.eu).

The SIOP-WT-2001 protocol recommended standardised pre-operative chemotherapy regimens for localised and metastatic tumours. Bilateral tumours likewise received pre-operative chemotherapy but were managed case-by-case to optimise conditions for bilateral nephron-sparing surgery. Following nephrectomy, tumour histopathology and stage dictated the intensity and duration of post-operative chemotherapy, occasionally combined with radiotherapy[15-19] (appendix 1). The SIOP histologic classification of pre-treated WT considers three risk groups, which accounts for the relative proportion of viable tumour cells and necrotic/regressive changes; low- (100% necrotic or cystic tumour), intermediate- (epithelial, stromal type, mixed type, focal anaplasia and regressive type), and high-risk (diffuse anaplasia and blastemal predominance). Biomarkers were not used to stratify risk groups.

The current protocol SIOP surveillance for WT recommends 3-monthly abdominal ultrasound and chest X-ray for the first two years post treatment, 4-6 monthly in the 3rd and 4th year. Cessation of follow up five years post end of treatment is recommended. All participating centres accepted the surveillance scheme but with few regional and individual variation (table 1).

Data extraction

All participating institutions provided data through paper case record forms designed for initial diagnosis, follow-up, relapse, and end of relapse treatment. We collected the following data: gender, age, country of origin, tumour histology, tumour stage, tumour volume at nephrectomy (based on radiological dimensions and calculated in cm^3 as: length x width x height x 0.523), date of nephrectomy, relapse status, scan modality that captured relapse, site and date and clinical symptoms at relapse, interval between nephrectomy and relapse, interval between relapse and latest normal scan, and survival. If no information ('empty box' in the case record) was provided, this was considered missing data.

For the purpose of the present analysis, we have classified any subsequent tumour-related event in patients with initial bilateral WT or WT pre-disposition syndromes as 'relapse', but are aware that a certain proportion may be a new metachronous tumour.

Outcomes

The primary outcomes were how relapse of WT was detected, and to estimate the number of scans needed to capture one subclinical relapse. Secondary outcomes were timing and site of relapse, as well as prognostic factors for relapse and overall survival after relapse.

Statistical methods

For all patients, relapse-free interval (RFI) was calculated from the time of nephrectomy until the time of first relapse. Among relapsing patients, overall survival (OS) was calculated from the time of relapse until death from any cause. Patients without an event at the end of follow-up were censored at that time. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. From the computed survival probabilities, incidence of relapse within a time period was calculated, as well as accounting for competing risk events (mortality) in a separate analysis. Nonparametric estimation of the incidence of relapse in the presence of competing risks events was performed in a two-step process[20,21]: i) calculate the KM estimate of the overall survival from any event (ie, including both relapse and death to be events in this model); ii) calculate the conditional probabilities of experiencing the event of interest (standard error of the cumulative incidence function estimator based).[22] Uni- and multivariable Cox proportional hazards regression analysis, stratified by country, was performed for both OS and RFI. For continuous variables, appropriate categorisation was done, and linear trend tests were based on the slope for the variable.

Some case record forms were incomplete. Hence, a missing date of nephrectomy was imputed as being four (localised WT) or six weeks (metastatic WT) after start of treatment. Bilateral WT with missing day of surgery were excluded because duration of pre-operative chemotherapy was not standardized. Multiple imputations with the fully conditional method were performed on missing patient clinical characteristics, assuming data were missing at random. This was considered a plausible assumption, given that there are indications that missingness of data is related to centre (not all information from all centres could be incorporated to the database in time for the current analyses) but not due to unobserved characteristics or the missing data themselves (appendix 4). Multiple imputation analyses were performed on 100 generated datasets, and resulting model estimates were combined using SAS PROC MIANALYZE.

RFI was compared by gender, age, tumour stage, tumour volume, period of diagnosis, and histopathology. OS among relapsed patients was compared by same variables including interval from nephrectomy to relapse, site of relapse, relapse detected at follow-up with or without symptoms, and interval from last 'normal' scan. The used cut-off points for grouped continuous variables are in alignment with previous SIOP studies. Median follow-up was calculated from time of randomisation and determined using the reverse Kaplan Meier method. Analyses were performed with R version 3.4.1 and SAS version 9.4.

Role of funding
The funders had no role in the study design, collection and analysis of the data, interpretation, or writing the manuscript. JB, MYL, and HVT had full access to all the data in the study and JB had the final responsibility for submitting the manuscript.

Results

A total of 5769 children with renal tumours were registered in the SIOP-WT-2001 study database between November 2001 and June 2015. We excluded 694 cases of non-Wilms renal tumours, 121 with insufficient data, 646 not treated with pre-operative chemotherapy according to the protocol or outside the age range (6 months-18 years) and 37 patients with progressive disease during pre-operative chemotherapy. Accordingly, 4271 patients with WT were included. At diagnosis 3409 (80%) WT were localised, 580 (14%) metastatic and 279 were bilateral (6%) (table 2). Median follow-up from surgery was 62 months (range 3-156).

Site of relapse
Relapse was reported in 538 (12·6%) patients. Of the relapses, 17% had combined local and distant relapse and 83% had a localised disease. The site of relapse was registered for 461 (86%) of 538 patients. Relapse involved the lung in 63% of the patients (including cases with extra-pulmonar sites), whereas abdominal/pelvic involvement with or without extra-abdominal sites was seen in 49% of cases. Abdominal relapse included cases with loco-regional relapse, liver relapse and metachronous tumours in the contralateral kidney. Isolated liver relapse was rare (4%). Bone or central nervous system relapse was very rare (2%) (appendix 2).

Method of relapse detection
The method of relapse detection was registered or partly registered for 410 (76%) of 538 relapses (table 3). Of these, 289 (70%) were captured during scheduled follow-up visits (48 also had clinical symptoms), and the proportion of relapses captured by routine scans before or after two years from nephrectomy was very similar (71% *vs* 67%). A total of 89 (22%) relapses were diagnosed due to patients presenting with clinical symptoms between scheduled follow-up imaging. Relapse was only detectable by physical examination in 129 cases (31%). The primary imaging modality used for identification of relapse was registered for 251 patients as: abdominal ultrasound, 80 (32%);

computed tomography (CT), 84 (chest, 33% and abdomen; 8%); chest X-ray, 78 (31%); and magnetic resonance imagining, 9 (4%).

Timing of relapse
Timing of relapse was registered for 511 patients. Of these, 80% occurred within 24 months post-nephrectomy, 13% within 24-60 months and very late relapse (> 60 months) was registered for 7% of the patients. Very late relapses occurred more frequently in the abdomen compared to the lung (37 *vs* 5 cases). Subgroup analyses indicated that patients with high-risk histology and advanced tumour stage (III-V) had a higher incidence of relapses occurring shortly after nephrectomy. For stage V patients with low/intermediate-risk histology relatively more relapses occurred later than 24 months (table 4). The absolute risk of relapse after two years across any subgroup of stage/histology was very similar (3-8%).

Number of scans (ultrasound, x-ray or CT scan) needed to detect one subclinical relapse
If centres adhered to the surveillance protocol (table 1) and, knowing the number of relapses captured in the SIOP-WT-2001 cohort by imaging alone (306 and 47 patients in the interval 0-2 and 2-5 years post-nephrectomy, respectively), we estimated the number of scans needed to detect one relapse; about 112 (95% CI 106-119) scans in the interval 0-2 years and 500 (95% CI 416-588) scans in the interval 2-5 years post-nephrectomy would be necessary**.**

Prognostic factors for relapse and overall survival after relapse
In both uni- and multivariable Cox regression analyses, higher histological risk and stage, larger tumour volume and older age at diagnosis were all statistically significantly associated with a shorter relapse-free interval (figure 2 and appendix 3).

5-year OS post-relapse rate was 56% (95% CI 51%-61%). In the univariable Cox regression analyses of OS after relapse, presenting with clinical symptoms between scheduled follow-up, older age, larger tumour volume at initial nephrectomy, interval <6 months from nephrectomy to relapse, advanced stage (II, III and IV), and high-risk histology were all significantly associated with lower OS rate ($p< 0{\cdot}05$). In a multivariable analysis the following variables remained statistically significant: presenting with clinical symptoms at relapse, interval <6 months from nephrectomy to relapse, larger tumour volume, stage (II, III and IV), and high-risk histology (table 5).

Discussion
The assumption that earlier recognition of relapse, rather than data from controlled studies, will lead to a better prognosis frequently guides the physician's attitude towards recommending surveillance imaging. There is limited knowledge about how relapse of WT is detected, and the evidence supporting current surveillance strategies is weak. As surveillance can be a burden for the families and the healthcare system, we aimed to strengthen this evidence base by analysing the very large cohort of patients with WT (n=4271) treated according to a standardised protocol with pre-operative chemotherapy in the international SIOP-WT-2001 study.

We observed that 13% of children with WT relapsed. About four of five relapses occurred within two years post-nephrectomy and predominantly involved the lung. Our analyses indicated that relapses among patient with high-risk histology and advanced-stage (III-V) occurred relatively early, whilst stage V without high-risk histology tend to relapse later (although it is difficult to distinguish between new metachronous and recurrent tumours for stage V). However, for all tumour stage and histological subgroups the absolute risk of relapse at two years post-nephrectomy was very comparable (3-8%) (table 4). Guided by the current protocol surveillance recommendation we found that routine follow-up scans captured at least 70% of the relapses, whereas physical

examination, usually done by a paediatrician, was unable to identify recurrence in about two thirds of children. Furthermore, early relapse, presentation with symptoms in the interval between two scheduled follow-up visits, advanced stage (excluding stage V), and high-risk histology were all variables associated with reduced OS amongst relapsed patients.

The principal strengths of this study are the substantial number of patients, the prospective data collection, and the assessment of long-term outcome. For the past 15 years, patients have been treated according to the same protocol without significant changes in management and with homogeneous case record forms. As for all registration studies, incompleteness of certain items, which led to exclusion of a small proportion of patients from our analyses, mitigated by use of statistical imputation methods, may represent some limitations. In particular, we are aware that precise details of site of relapse, scan modality used for relapse detection, and presence of clinical symptoms could be difficult to classify in a number of cases. Finally, individual and centre surveillance strategies were not recorded in this study. Hence, calculating the number of scans needed to detect one relapse was based on the assumption that all patients adhered to the recommended SIOP surveillance. We therefore recognise that possible minor unrecorded deviations in the real-life practice of imaging surveillance might introduce a limitation when interpreting our data.

We observed that up to two years after surgery, the vast majority had an interval of less than three months from last normal imaging to relapse. This vaguely indicates that most centres adhered to the protocol regarding timing of surveillance imaging. However, in contrast to the protocol recommendations to perform X-rays, one third of relapses were reported to be detected by chest CT scan. Unfortunately, in some cases it was not possible to conclude whether CT scan was used up-front or only to confirm equivocal chest X-ray findings, which is more likely, so this issue could not be further explored. Regarding the radiation exposure, we estimate that through five years of standard surveillance, at least 14 X-rays per patient would be carried out with an average dose of 0.1 mSv. Low dose CT chest (1-2 mSV/scan) or abdomen might be able to detect smaller nodules but will increase the radiation burden and the value of routine CT surveillance is debated.[12, 23-26]

Mortality rate was nearly twofold for patients presenting with clinical symptoms between planned surveillance compared to patients with asymptomatic relapse captured by planned surveillance visits. Despite this remarkable difference, the benefits of surveillance are less certain as the mortality difference may be due to other factors such as location of the tumour and tumour-specific growth rate ie, ‘biological aggressiveness' as a confounding variable. The benefits of surveillance imaging would have been further supported if inferior outcome was associated with parameters such as prolonged interval between last normal surveillance scan and relapse, or larger tumour size at relapse. However, we found no significant association regarding interval between normal scan and relapse, and tumour size at relapse was not registered. Interestingly, the SIOP surveillance capture and survival rates are very similar to North American data from the Children’s Oncology Group and we are not aware of any other relevant sized studies on WT or other extra-cranial solid tumours for further comparison.[26,27]

One key decision when planning WT surveillance is the cut-off relapse risk for entering and continuing surveillance. To guide this decision we have constructed a ‘surveillance map’ that estimated the risk of relapse for subgroups of WT at a given time-point after nephrectomy (table 4). For example: a high-risk stage I WT, will have a future relapse risk at 24 months post-nephrectomy of about 3%, and a risk of relapse within the 24-30 months interval of about 1%. As one in four relapses are detected due to clinical symptoms, we estimated that the number of relapses detected solely by biannual surveillance imaging at two years post-nephrectomy would be about one in 130 patients. Similar calculations can be made for other time-points and other WT subgroups, but these

numbers illustrate that a significant proportion of 'healthy' children undergo scans (ultrasound, x-ray, or even CT) with potential harmful effects.[12] Worthy to mention, a pragmatic cut-off risk of 5% to develop a tumour is used for children with WT pre-disposition syndromes to enter a screening programme of 3-monthly abdominal ultrasounds. This interval takes into account the doubling rate of WT and the sensitivity of abdominal ultrasound.[28,29] Our results confirm that the risk of very late relapse is very low, which supports that prolonging surveillance imaging beyond 5 years seems unjustified.[5]

The cost-effectiveness of relapse surveillance is very complex to evaluate including weighing the balance between induction of stress in families after treatment and a relief of continuous complete remission. To our knowledge, no prospective trials have assessed the efficacy of surveillance imaging in childhood cancer. Pragmatically, it seems less likely that such a randomised trial (eg, comparing frequent versus less frequent monitoring, or CT scan versus ultrasound/chest X-ray for the high-risk group) will be prioritised despite being relatively cheap to execute. We also recognise that additional challenges might be parent engagement, and the epidemiology of WT relapse itself. Even if adequately explained to families, it would be difficult to obtain consent for an experimental arm prescribing 'less intensive' surveillance. Secondly, the relapse rate for WT is relatively low. Hence, it would require a substantial sample size to identify a clinical meaningful difference. Finally, this area is not regarded as a priority and will likely not receive sufficient financing because there is much more focus on eg, novel agents in relapse settings. Despite the evidence gap, patients should not be precluded from monitoring and surveillance is standard practice amongst children post-cancer treatment. Additionally, the purpose of follow-up is multifactorial, including social and emotional aspects, rehabilitation, physical examination and both monitoring and management of treatment-related adverse late effects.

In conclusion, guided by the SIOP-WT-2001 surveillance recommendation enabled centres to capture more than two thirds of the WT relapses. We found that asymptomatic relapses, captured by routine scans, have a superior prognosis compared with relapses presenting with clinical symptoms between follow-up. We recommend abdominal ultrasound and chest X-rays for WT surveillance and that focus is on the two years post treatment using three months intervals, considering shorter intervals for subgroups with high risk of early relapse (ie, high-risk histology and/or stage IV tumours). Surveillance beyond two years post treatment could be considered but the overall number of abdominal ultrasounds and chest X-rays needed to capture one asymptomatic relapse is substantial.

Contributors

All authors contributed to the conception and design.
JB, MLY, HVT, KPJ and FS contributed to data analysis and interpretation.
JB, TT, KPJ and FS prepared the first draft and all authors provided substantial additional input and approved the final version of the manuscript.

Declaration of interests

We have no competing interest to declare.

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Patient group	Chest X-ray	Abdominal ultrasound
Localised and metastatic Wilms tumour*	1st & 2nd year: every 3 months 3rd year: every 4 months 4th year: every 6 months 5th year: annually	1st & 2nd year: every 3 months 3rd year: every 4 months 4th year: every 6 months 5th year: annually
Bilateral tumours and nephrogenic rests	1st & 2nd year: every 2 months 3rd & 4th year: every 3 months 5th - 10th year: annually	1st & 2nd year: every 2 months 3rd & 4th year: every 3 months 5th - 10th year: annually

*Centres usually conduct 3-monthly abdominal ultrasound/chest X-rays throughout the first 2 years after nephrectomy or end of treatment, with few individual and institutional variation in the total duration and frequency of surveillance imaging up to 5 years. (personal communication with national CI's of the SIOP WT 2001 trial and study)

***Table 1:* SIOP-2001 imaging surveillance after stopping treatment**

	All patients (N = 4271)	Relapse subgroup (N = 538)
Gender		
Female	2284	281
Male	1969	256
Not specified	18	1
Age at diagnosis (Median, IQR)	39.4 (22.1-59.7)	50.7 m (33.7-71.5)
Grouped		
6 months – 2 years	1189 (28%)	85 (16%)
2-4 years	1449 (34%)	162 (30%)
4-17.5 years	1629 (38%)	291 (54%)
Not specified	4 (0%)	
Tumour stage		
I	1677 (39%)	153 (28%)
II	776 (18%)	100 (19%)
III	696 (16%)	104 (19%)
IV (metastatic)	582 (14%)	122 (23%)
V (bilateral)*	280 (7%)	44 (8%)
Localised, stage unknown	260 (6%)	15 (3%)
Histological risk group		
High-risk	556 (13%)	139 (26%)
Intermediate-risk	3177 (74%)	368 (68%)
Low-risk	203 (5%)	10 (2%)
Not specified	335 (8%)	21 (4%)
Tumour volume at surgery (Median, IQR)	1.4 (0.5-3.3)	2.1 (1.0-4.5)
<500 ml	2909 (68%)	348 (64%)
≥500 ml	507 (12%)	101 (19%)
Not specified	855 (20%)	89 (17%)

IQR=interquartile range

*stage V includes local stage 1-3 and a few metachronous relapses

***Table 2:* Characteristics of patients with Wilms tumour from the SIOP-WT-2001 database**

Presentation	Identification of relapse				
	Physical examination	Imaging	Physical examination and imaging	Not specified	Total
Symptomatic between scheduled surveillance	1 (0.2)	34 (6.3)	54 (10.0)	0 (0)	89 (16.5)
Asymptomatic at scheduled surveillance	3 (0.6)	203 (37.7)	33 (6.1)	2 (0.4)	241 (44.8)
Symptomatic at scheduled surveillance	1 (0.2)	26 (4.8)	21 (3.9)	0 (0)	48 (8.9)
Aymptomatic between scheduled surveillance	1 (0.2)	13 (2.42)	6 (1.1)	0 (0)	20 (3.7)
Not specified	2 (0.4)	3 (0.6)	7 (1.3)	128 (23.8)	140 (26.0)
Total	8 (1.5)	279 (51.9)	121 (22.5)	130 (24.2)	538

Number of cases and overall proportion (%) are listed in each box

***Table 3*: Detection methods of 538 Wilms tumour relapse in the SIOP-WT-2001 database**

Surveillance map		Stage									
		I		II		III		IV		V	
Histology	n/N	131/1395		76/647		64/525		70/398		26/196	
		Relapse incidence according to time period of surveillance post nephrectomy*									
	Months after nephrectomy	Within period	Beyond period	Within period	Beyond period	Within period	Beyond period	Within period	Beyond period	Within period	Beyond period
Low/inter-mediate-risk	0-6	2%	9%	2%	12%	2%	11%	3%	17%	2%	13%
	6-12	3%	6%	4%	8%	4%	7%	6%	11%	3%	10%
	12-18	1%	5%	3%	5%	2%	5%	4%	7%	1%	9%
	18-24	0%	4%	1%	4%	2%	3%	1%	6%	1%	8%
	24-30	0%	4%	0%	3%	0%	3%	0%	5%	2%	6%
	30-36	0%	4%	0%	3%	1%	2%	0%	5%	1%	5%
	36-42	0%	4%	0%	3%	0%	2%	0%	5%	2%	3%
	42-48	0%	3%	0%	3%	0%	2%	1%	4%	1%	2%
	48-54	0%	3%	0%	3%	0%	2%	0%	4%	0%	2%
	54-60	0%	3%	0%	2%	0%	1%	0%	4%	0%	2%
High-risk	n/N	17/169		24/119		40/142		34/75		16/59	
	0-6	2%	9%	2%	20%	9%	20%	32%	26%	12%	22%
	6-12	4%	6%	6%	14%	11%	9%	11%	15%	10%	12%
	12-18	2%	4%	8%	6%	4%	5%	10%	5%	7%	5%
	18-24	1%	3%	1%	5%	3%	2%	0%	5%	0%	5%
	24-30	1%	2%	2%	4%	1%	1%	2%	3%	0%	5%
	30-36	2%	1%	1%	3%	0%	1%	0%	3%	0%	5%
	36-42	0%	1%	0%	3%	0%	1%	0%	3%	0%	5%
	42-48	0%	1%	0%	3%	0%	1%	0%	3%	0%	5%
	48-54	0%	1%	0%	3%	0%	1%	0%	3%	2%	3%
	54-60	0%	1%	1%	2%	0%	1%	0%	3%	3%	0%

n/N=observed number of relapses/total number of patients.

HR=Hazard ratio

* Incidence within (eg, 0-6 months post nephrectomy) or beyond (eg, after 6 months post nephrectomy) period calculated by adding up incidences corresponding to relapse times observed in or after period.

**Time to end of study (June 2015) taken for those patients not experiencing a relapse, in order to minimize the impact of very late relapses on the estimates. Based on data from the SIOP-WT-2001 database.

Table 4: **Approximated incidence of relapse (%) according to initial tumour stage, histology and time from nephrectomy****

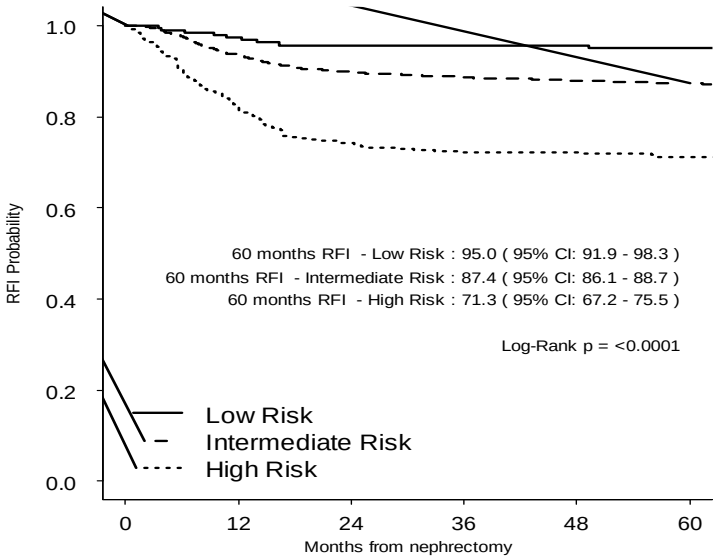
Variables	Univariable		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender				
Female	1 (reference)		1 (reference)	
Male	0.71 (0.52-0.95)	.02	0.74 (0.54-1.02)	.06
Age grouped**				
6 months-2 years	0.57 (0.31-1.03)	.06	0.72 (0.37-1.40)	.33
2-4 years	1		1	
4-17.5 years	1.54 (1.10-2.15)	.01	1.32 (0.92-1.90)	.13
Time from nephrectomy to relapse***				
< 6 months	1.88 (1.38-2.55)	<.0001	1.64 (1.15-2.33)	.01
≥ 6 months	1		1	
Site of relapse				
Local	1		1	
Local + distant	2.00 (1.30-3.10)	.002	1.18 (0.74-1.87)	.49
Lung only	1.26 (0.89-1.80)	.19	1.08 (0.73-1.60)	.70
Detection of relapse				
Follow-up without symptoms	1		1	
Follow-up with symptoms	1.34 (0.83-2.17)	.23	1.24 (0.71-2.17)	.45
Symptoms only	1.86 (1.29-2.68)	.0008	1.85 (1.24-2.77)	.01
Other	1.49 (0.72-3.09)	.29	1.28 (0.63-2.60)	.50
Stage of Wilms tumour****				
I	1		1	
II	2.35 (1.36-4.07)	.0023	2.31 (1.30-4.12)	.01
III	4.10 (2.45-6.84)	<.0001	3.08 (1.78-5.33)	<.0001
IV	5.71 (3.54-9.22)	<.0001	4.33 (2.56-7.34)	<.0001
V	2.23 (1.10-4.51)	.03	1.70 (0.76-3.77)	.19
Histological risk group				
High-risk	5.44 (3.95-7.48)	<.0001	4.61 (3.22-6.61)	<.0001
Intermediate-risk	1		1	
Low-risk	2.58 (1.04-6.42)	.04	1.97 (0.75-5.18)	.17
Volume at nephrectomy				
100 ml/unit	1.05 (1.01-1.08)	.01	1.01 (0.97-1.05)	.52

*Multiple imputation of missing values shown for 471 patients, of the 538 relapses, with follow-up information after relapse. Volume and detection of relapse were missing for 17% and 26%. Other variables had less than 10% missing values.
** Linear trend test p=.0008 (univariable), p=.39 (multivariable); *** Linear trend test p=.0003 (univariable), p=.01 (multivariable); **** Linear trend test p<.0001 (both)

Table 5: **Cox regression analysis* of risk factors for survival after relapse in Wilms tumour.**

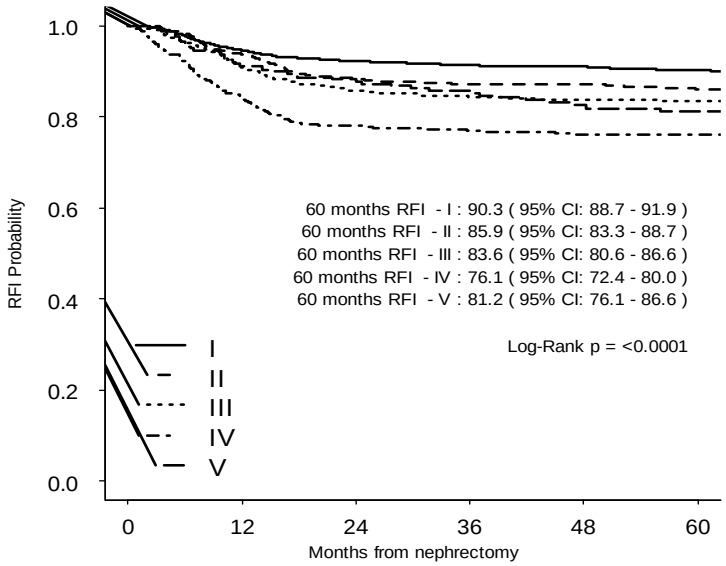
Figure 1: **Five-year Relapse-free interval – from time of nephrectomy according to histology (A), tumour stage (B), patient age (C), and tumour volume (D)**

A



Low Risk	196	179	168	149	132	111
Intermediate Risk	3011	2569	2239	1960	1686	1411
High Risk	512	380	316	274	239	187

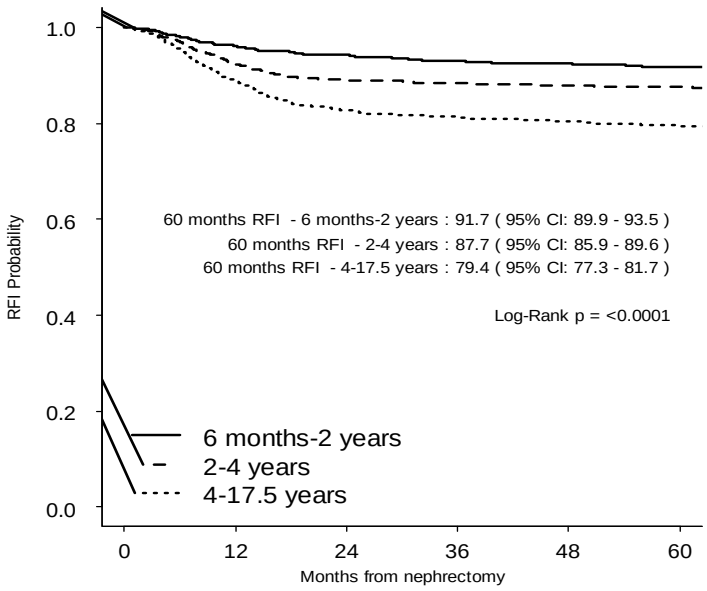
B



I	1585	1338	1182	1044	916	767
II	732	641	554	487	416	348
III	656	557	477	420	360	294
IV	535	411	344	287	241	202
V	261	215	195	165	138	108

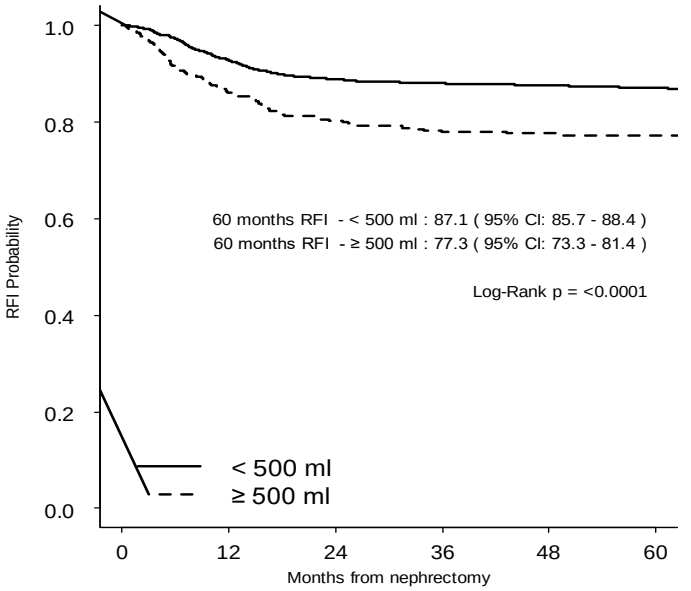
- * **stage V includes local stage 1-3.**

C:



6 months-2 years	1089	922	815	721	618	514
2-4 years	1336	1127	983	850	733	609
4-17.5 years	1502	1219	1031	888	765	625

D:



< 500 ml	2747	2325	2029	1783	1538	1279
≥ 500 ml	479	369	304	251	220	189

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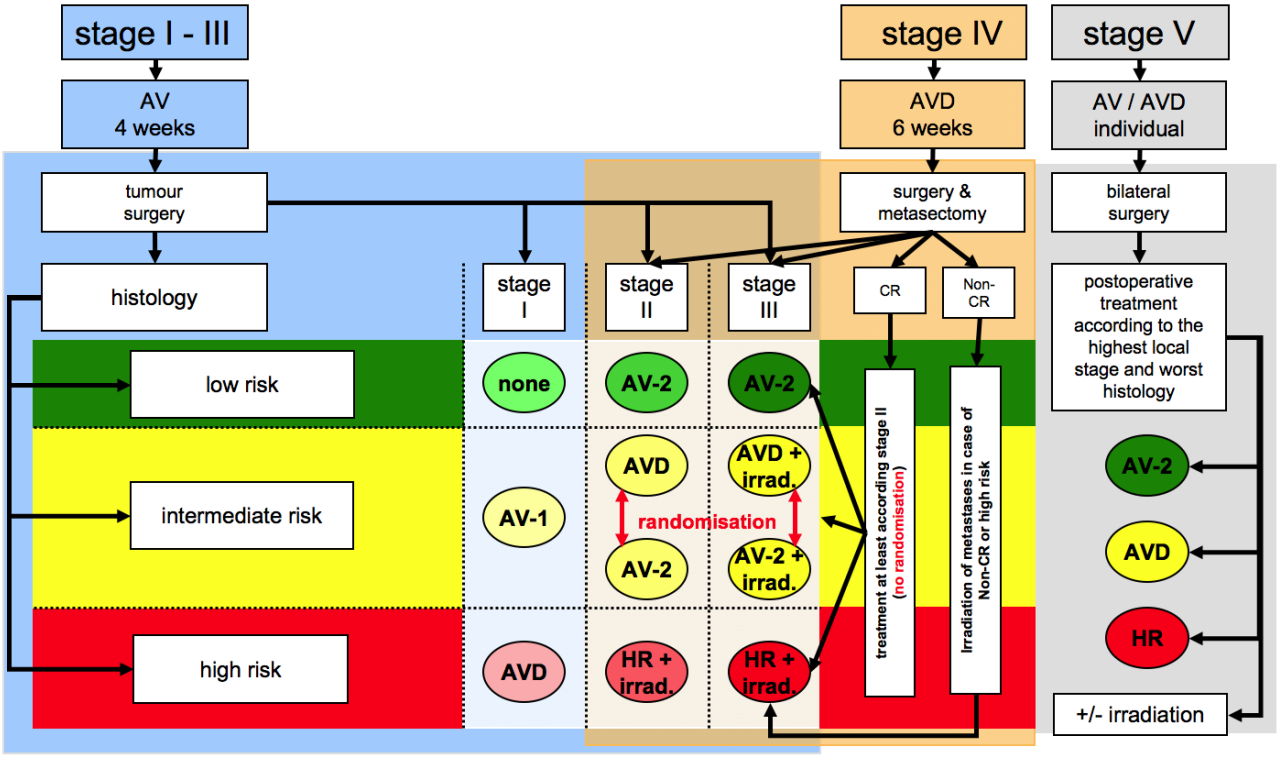

Appendix 1: **Treatment overview for WT in the SIOP-2001 protocol[16]. NB: Stage II, high-risk blastemal subtype does not receive irradiation.**

Lungs only: 228 (49%)
Lung and other (abdominal): 63 (14%) - Liver involvement: 15
Abdomen or pelvis: 162 (35%) - Liver involvement: 35 (Only liver: 19) - Contralateral kidney: 10
Central nerve system/Spine: 4 (1%)
Bone: 4 (1%)
Not recorded: 77
Appendix 2: **Site of relapse for Wilms tumour in the SIOP-2001 trial and study**

Variables	HR (95% CI)	*P*-value
Gender		
Female	1 (reference)	
Male	1.10 (0.93-1.31)	.28
Age grouped**		
6 months-2 years	0.65 (0.50-0.85)	.002
2-4 years	1	
4-17.5 years	1.48 (1.22-1.80)	<.0001
Stage of Wilms tumour**		
I	1	
II	1.14 (0.88-1.47)	.32
III	1.25 (0.97-1.62)	.09
IV	2.33 (1.82-2.98)	<.0001
V	1.87 (1.32-2.64)	.0004
Histological risk group		
High-risk	2.16 (1.76-2.65)	<.0001
Intermediate-risk	1	
Low-risk	0.32 (0.17-0.59)	.0003
Volume at nephrectomy		
100 ml/unit	1.08 (1.06-1.11)	<.0001

*Multiple imputation of missing values shown for 3928 patients, of the 4271 considered, with follow-up information after relapse

** Linear trend test p<0.0001

***Appendix 3:* Multivariable Cox regression analysis* of relapse-free interval after nephrectomy**

Group	Sex	Age	Risk	Stage	Tumour volume	Months between surgery and relapse	Detection of relapse	Relapse site	Months between last "normal" imaging and relapse	Freq.	Percent
1	X	X	X	X	X	X	X	X	X	272	50.56
2	X	X	X	X	X	X	X	X	.	36	6.69
3	X	X	X	X	X	X	X	.	X	6	1.12
4	X	X	X	X	X	X	.	X	X	1	0.19
5	X	X	X	X	X	X	.	X	.	56	10.41
6	X	X	X	X	X	X	.	.	.	58	10.78
7	X	X	X	X	.	X	X	X	X	59	10.97
8	X	X	X	X	.	X	X	X	.	10	1.86
9	X	X	X	X	.	X	X	.	X	1	0.19
10	X	X	X	X	.	X	.	X	X	1	0.19
11	X	X	X	X	.	X	.	X	.	6	1.12
12	X	X	X	X	.	X	.	.	.	8	1.49
13	X	X	X	.	X	X	X	X	X	2	0.37
14	X	X	.	X	X	X	X	X	X	5	0.93
15	X	X	.	X	X	X	.	X	.	3	0.56
16	X	X	.	.	X	X	X	X	X	3	0.56
17	X	X	.	.	X	X	X	.	X	2	0.37
18	X	X	.	.	X	X	.	X	.	3	0.56
19	X	X	.	.	X	X	.	.	.	1	0.19
20	X	X	.	.	.	X	X	X	X	2	0.37
21	X	X	.	.	.	X	.	X	.	1	0.19
22	X	X	.	.	.	X	.	.	.	1	0.19
23	.	X	X	X	X	X	.	X	.	1	0.19

X = not missing
. = missing

Appendix 4: **Table 4. Missing data patterns for the relapse subgroup (N=538)**