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Original Research

Wilms tumour event-free and overall survival in Southern and Eastern Europe: Pooled analyses of clinical data from four childhood cancer registries (1999–2017)☆

Dimitrios Doganis [a,b], Anna Zborovskaya [c], Maciej Trojanowski [d], Tina Zagar [e], Panagiota Bouka [a], Margaret Baka [b], Maria Moschovi [f], Sofia Polychronopoulou [g], Eugenia Papakonstantinou [h], Athanasios Tragiannidis [i], Eftichia Stiakaki [j], Helen Dana [k], Kalliopi Stefanaki [l], Katerina Strantzia [m], Dmitry Kochubinsky [n], Patrycja Marciniak [o], Simona Avcin [p], Kondilia Antoniadi [g], Nick Dessypris [a], Eleni Th. Petridou [a,q,*]

[a] *Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Greece*
[b] *Oncology Department, "P & A Kyriakou" Children's Hospital, Athens, Greece*
[c] *Belarusian Research Center for Paediatric Oncology, Haematology and Immunology, Childhood Cancer Subregistry of Belarus, Minsk, Belarus*
[d] *Greater Poland Cancer Registry, Greater Poland Cancer Center, Poznan, Poland*
[e] *Cancer Registry of Slovenia, Institute of Oncology Ljubljana, Ljubljana, Slovenia*
[f] *Pediatric Hematology-Oncology Unit, First Department of Pediatrics, National and Kapodistrian University of Athens, "Agia Sofia" Children's Hospital, Athens, Greece*
[g] *Department of Pediatric Hematology-Oncology, "Agia Sofia" Children's Hospital, Athens, Greece*
[h] *Department of Pediatric Hematology and Oncology, Hippokration Hospital, Thessaloniki, Greece*
[i] *Hematology-Oncology Unit, 2nd Pediatric Department, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece*
[j] *Department of Pediatric Hematology-Oncology, University of Crete, Heraklion, Greece*
[k] *Pediatric Hematology-Oncology Department, "Mitera" Children's Hospital, Athens, Greece*
[l] *Pathology Laboratory, "Agia Sofia" Children's Hospital, Athens, Greece*
[m] *Pathology Laboratory, "P & A. Kyriakou" Children's Hospital, Athens, Greece*
[n] *Belarusian Research Center for Paediatric Oncology, Hematology and Immunology, Head of Oncology Department No1, Minsk, Belarus*
[o] *Patrycja Marciniak, University of Medical Sciences, Department of Pediatric Oncology Hematology and Transplantology, Poznan, Poland*
[p] *University Medical Center, Clinic of Pediatrics, University Children's Hospital, Ljubljana, Slovenia*
[q] *Clinical Epidemiology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden*

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* *Corresponding author*: Department of Hygiene, Epidemiology and Medical Statistics Medical School, National and Kapodistrian University of Athens 75 Mikras Asias Str, Athens, 11527, Greece. Fax: +30 210 7462105.
E-mail address: epetrid@med.uoa.gr (E.Th. Petridou).

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Abstract ***Background:*** Wilms tumour (WT) management represents a success story in pediatric oncology. We aimed to assess, for the first time, the event-free survival (EFS) vs. overall survival (OS) in Southern and Eastern Europe (SEE) using harmonised clinical data collected by childhood cancer registries and to identify respective prognostic factors.
Methods: From 1999 to 2017, data for incident WT cases aged 0–14 years from 3 nationwide (Greece, Belarus and Slovenia) and one regional (Greater Poland) SEE registries were collected following common coding. Kaplan–Meier curves were constructed, and EFS vs. OS values were derived from Cox proportional hazard models by study variables.
Results: A total of 338 WT cases (45.6% males; median age, 3.19 years; age<5 years, 75%) were included in the analyses. Bilateral were 21 tumours (6.2%). Among the 317 unilateral cases, the majority (93.7%) received International Society of Pediatric Oncology–based protocols; $EFS_{5\text{-year}}$ was 85.1%, and $OS_{5\text{-year}}$ 91.1%; both outcomes were significantly worse in stage IV patients or in those with high-risk/unfavourable histology. Relapse rate among high-risk/unfavourable histology cases was 2.3 times higher than among low-intermediate risk/favourable histology cases, with respective death rate 5.6 times higher. Both relapse and death rates increased significantly in patients with advanced anatomical stage and high-risk/unfavourable histology. Finally, significantly worse was the outcome in bilateral tumours ($OS_{5\text{-year}}$: 76.3%) vs. unilateral non-metastatic tumours ($OS_{5\text{-year}}$: 94.7%).
Conclusions: Our results delineate the potential of high-quality childhood cancer registration entailing clinical data to assess predictors of WT outcome over and beyond those derived from enrolment into clinical trials. Specifically, outcomes among children with WT residing in the four participating SEE countries were comparable with those reported by major cooperative international groups, albeit somehow inferior. Despite the excellent overall prognosis, however, subgroups of patients with advanced or bilateral disease and/or high-risk histology still suffer poor outcomes.

1. Introduction

Wilms tumour (WT) or nephroblastoma is a rare embryonal type of cancer affecting approximately 1 in 10.000 children. The disease accounts for around 6% of all childhood cancer cases and for approximately 93% of all renal tumours, ranking second most common intra-abdominal solid tumour of childhood. The majority of patients (77%) are diagnosed before the age of 5 years; of note is a slight female preponderance [1,2].

The 8.2/million overall age-standardised incidence rate varies across Europe [1] and has been estimated to 9.2/million in Southern and Eastern European (SEE) countries in a recent study from our group. A plausible interplay of genetics with societal factors in disease aetiology was suggested in this study on account of the change in sex ratio with age, from a slight male (1.1) to a female (0.7) preponderance with advancement of age and the positive associations of the incidence of the disease with Human Development Index (HDI) [3].

Diagnostic and therapeutic achievements including imaging evaluation, central pathology review, optimal risk stratification, higher rates of enrolment into clinical trials and modern multidisciplinary therapies have led to dramatically improved survival rates for patients with WT reaching an impressive overall 5-year survival of 93% in the SIOP-2001 trial [4]. Despite these striking advances, outcomes are inferior by disease characteristics, namely, unfavourable histology and/or advanced disease [4,5]. Age group at diagnosis and pre-operative chemotherapy versus upfront surgery have also been evaluated as predictors of outcomes [6,7], whereas variations in survival rates across European countries have been observed [8,9]. Similarly, in some parts of Europe, survival is lower among those residing in rural areas and in lower HDI countries areas, leading to a 78% 5-year overall survival (OS) in a recent study comprising several SEE countries. Albeit the combined OS was heavily weighted by the low rates in Ukraine, this figure indicates strong socioeconomic differentials in healthcare delivery for the young patients suffering WT [9].

In the present study, we aimed to assess, for the first time, the event-free survival (EFS), as contrasted to the OS, in SEE using a common platform for registration of clinical data developed by the Nationwide Registry for Childhood Hematological Malignancies and Solid Tumours (NARECHEM-ST) in Greece. Subsequently, harmonised data registered by three national SEE registries (Belarus, Greece and Slovenia) and a regional (Greater Poland) registry were used to estimate clinical end-points and predictors of outcome, namely demographic, pathology and clinical characteristics of the disease.

2. Methods

2.1. Data collection and codification issues

All patients registered in the four participating registries (Belarus: nationwide 2009–2016, Greece: nationwide 2009–2017, Greater Poland: regional 1999–2014, Slovenia: nationwide 2000–2014) with a histologically confirmed WT (ICD-O-3 code 8960, behaviour code 3) were included [10]. Age at diagnosis, gender, associated birth defects, nephroblastomatosis, pre-operative treatment, stage, histology report and outcomes were abstracted, after a thorough evaluation of treatment centres' reports, on the basis of a common mask developed by NARECHEM-ST; staging and histology classification was according to standard protocols conducted by the National Wilms Tumor Study Group (NWTSG), which was supplanted by the Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP) [5,11]. Specifically, for staging, patients were classified according to the protocol they were enrolled in: an upfront, surgery-based system developed by the NWTSG and an upfront chemotherapy-based system developed by the SIOP. Histologic classification also defined either according to NWTSG or SIOP studies [12]. In SIOP studies, three groups have been defined: low, intermediate and high risk based on cell differentiation observed after the pre-operative chemotherapy [13]. On the other hand, anaplasia is the basis of histologic classification in National Wilms Tumor Study (NWTS), where only two risk groups, favourable (lack of findings of anaplasia) and unfavourable, are included [5,11,12]. For harmonisation purposes in our analysis, patients treated according to SIOP protocols had to be also classified into two groups: favourable (low and intermediate risk in SIOP classification) and unfavourable (high risk in SIOP classification).

SIOP-treated patients followed overall the recommended initial chemotherapy aiming at reducing the risks of immediate nephrectomy, whereas NWTSG-treated patients followed overall the upfront surgery under the assumption that it is vital to identify accurate tumour staging. For both groups, post-operative treatment (chemotherapy and radiotherapy) was stratified according to the tumour staging and histological subtype information obtained at the time of surgery [5,14]. Finally, an upfront surgery was overall followed for a subgroup of SIOP-treated patients, whereas pre-operative chemotherapy was administered in some patients enrolled in the NWTS [11].

2.2. Data analyses

Demographics, medical history and disease characteristics of WT cases in terms of relapse or death were considered. Kaplan–Meier curves, for the event-free survival (time from diagnosis until tumour recurrence or death from any cause, EFS) and OS (time from diagnosis to death from any cause or last follow-up) were developed combined for the 4 registries. The censored date was 31/12/2016 for Greater Poland and 31/12/2017 for the other 3 registries. Log-rank test was used to compare patient subgroups and assess the most important prognostic factors affecting OS and EFS. Finally, to explore the role of age, gender, stage, histology, pre-operative chemotherapy and registry, Cox proportional hazard model–derived hazard ratios (HRs) and 95% confidence intervals (CIs) for EFS/OS were used. Statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc).

3. Results

During the periods for which the four registries could participate in the present study, a total of 357 WT cases were recorded [3], of whom clinical data were made available for 338 (154 males and 184 females; Belarus: 113, Greater Poland: 74, Greece: 115, Slovenia: 36). Twenty-one tumours were bilateral.

The median age at diagnosis for unilateral cases was 3.2 years, significantly higher for females than for males (3.63 vs. 2.86 years, respectively, $p = 0.0078$). The majority of patients with unilateral tumours (n = 297/317, 93.7%) were reported as being treated according to SIOP guidelines, albeit only a small minority of patients were actually registered in the SIOP trials. Of note, 272 of 317 patients (85.8%) received pre-operative chemotherapy.

Table 1 presents the characteristics of unilateral cases and their distribution by stage and histology risk group. Older patients were diagnosed with a higher stage, and patients of higher stage were associated more frequently with high-risk histology.

A total of 41 relapses and 27 deaths were observed as shown in Table 2, presenting the distribution of characteristics of patients with unilateral tumour as well as the corresponding relapse and death rates. Among relapsed patients, 20 were still alive (49%) at the

Table 1
Distribution of unilateral Wilms tumour cases by study variables.

		Stage					Histology		
	Total n (%)	I n (%)	II n (%)	III n (%)	IV n (%)	*p*-value	Low-intermediate/ favourable n (%)	High n (%)	*p*-value
Total	317 (100.0)	66 (20.8)	113 (35.7)	85 (26.8)	53 (16.7)		243 (76.7)	74 (23.3)	
Gender									
Male	143 (45.1)	32 (22.4)	51 (35.6)	38 (26.6)	22 (15.4)	0.47	113 (79.0)	30 (21.0)	0.37
Female	174 (54.9)	34 (19.6)	62 (35.6)	47 (27.0)	31 (17.8)		130 (74.7)	44 (25.3)	
Age (years)									
<2	94 (29.7)	36 (38.3)	34 (36.2)	19 (20.2)	5 (5.3)	**0.0001**	80 (85.1)	14 (14.9)	0.07
2–4	143 (45.1)	19 (13.3)	51 (35.7)	41 (28.7)	32 (22.3)		104 (72.7)	39 (27.3)	
5–14	80 (25.2)	11 (13.8)	28 (35.0)	25 (31.2)	16 (20.0)		59 (73.8)	21 (26.2)	
Histology risk group									
Low–intermediate/favourable	243 (76.7)	60 (24.7)	92 (37.9)	58 (23.9)	33 (13.5)	**0.0001**			
High/unfavourable	74 (23.3)	6 (8.1)	21 (28.4)	27 (36.5)	20 (27.0)				
Pre-operative chemotherapy									
No	45 (14.2)	10 (22.2)	21 (46.7)	12 (26.7)	2 (4.4)	0.06	35 (77.8)	10 (22.2)	0.85
Yes	272 (85.8)	56 (20.6)	92 (33.8)	73 (26.8)	51 (18.8)		208 (76.5)	64 (23.5)	

In bold: statistically significant (*p*-value <0.05) results.

censored date, whereas 21 succumbed, because of disease progression (n = 20) and during second surgery (n = 1). Of note, one more patient succumbed because of parental refusal to receive treatment (n = 1). Another 5 patients succumbed because of refractory disease (n = 3), surgical complications during primary nephrectomy (n = 1) and bilateral pneumonia (n = 1). Factors significantly correlated with relapse and death included higher stage and high-risk histology. The relapse rates among patients with high-risk/unfavourable histology were 2.3 times higher than those of low-intermediate risk/favourable histology, whereas the death rate was 5.6 times higher.

The 5-year EFS and OS for patients with unilateral tumours were 85.1% and 91.1%, respectively (Table 3). Fig. 1 shows EFS and OS rates by stage I–V (1a, 1c) and histology risk groups (1b, 1d) among all patients (n = 338, $EFS_{5\text{-year}}$: 84.2%, $OS5_{\text{-year}}$: 90.3%).

As expected, factors correlated with a lower EFS or OS were stage and high-risk histology. Specifically, the Cox-derived hazard ratios (Table 4) for stage III WT were 2.47 for EFS and 3.41 for OS, increasing to HR_{EFS} of 5.21 and HR_{OS} of 7.51 for stage IV patients; for high-risk histology, HR_{EFS} of 2.25 and HR_{OS} of 4.93 were observed. The results remained unchanged when the registry was introduced in the model as a covariate.

Table 2
Outcomes of unilateral Wilms tumour cases: relapse, death rates and distribution by study variables.

	n (%)	Relapse n (%)	*p*-value	Death n (%)	*p*-value
Total	317 (100.0)	41 (12.9)		27 (8.5)	
Gender					
Male	143 (45.1)	22 (15.4)	0.24	12 (8.4)	0.94
Female	174 (54.9)	19 (10.9)		15 (8.6)	
Age (years)					
<2	94 (29.7)	7 (7.5)	0.28	2 (2.1)	0.09
2–4	143 (45.1)	24 (16.8)		18 (12.6)	
5–14	80 (25.2)	10 (12.5)		7 (8.8)	
Birth defects					
Yes	12 (3.8)	1 (8.3)	0.99[a]	0 (0.0)	0.61[a]
No	305 (96.2)	40 (13.1)		27 (8.9)	
Stage					
I	66 (20.8)	3 (4.6)	**0.0001**	0 (0.0)	**0.0001**
II	113 (35.7)	9 (8.0)		4 (3.5)	
III	85 (26.8)	13 (15.3)		9 (10.6)	
IV	53 (16.7)	16 (30.2)		14 (26.4)	
Histology risk group					
Low–intermediate/favourable	243 (76.7)	24 (9.9)	**0.003**	10 (4.1)	**0.0001**
High/unfavourable	74 (23.3)	17 (23.0)		17 (23.0)	
Pre-operative chemotherapy					
No	45 (14.2)	6 (13.3)	0.93	4 (8.9)	0.99[a]
Yes	272 (85.8)	35 (12.9)		23 (8.5)	

In bold: statistically significant (*p*-value <0.05) results.
[a] Fisher's exact test.

Table 3
Outcomes of unilateral Wilms tumour cases: event-free survival (EFS), overall survival (OS) and distribution by study variables.

	Events up to 5 years/no events after completed 5 years (n/n)	EFS-5 year % (95% CIs)	*p*-value	Deaths up to 5 years/Alive after completed 5 years (n/n)	OS-5 year % (95% CI)	*p*-value
Total	44/135	85.1 (80.5–88.8)		25/144	91.1 (87.1–94.0)	
Gender						
Male	21/65	84.7 (77.4–89.8)	0.56	11/72	91.5 (85.1–95.3)	0.95
Female	23/70	85.5 (78.9–90.2)		14/72	90.9 (85.0–94.6)	
Age						
<2	7/43	91.6 (83.1–95.9)	0.06	2/45	97.4 (89.7–99.3)	**0.02**
2-4	27/60	80.1 (72.2–86.0)		17/66	86.9 (79.6–91.7)	
5-14	10/32	87.0 (77.2–92.8)		6/33	91.7 (82.5–96.2)	
Stage						
I	3/29	95.4 (86.4–98.5)	**0.0001**	0/32	100.0	**0.0001**
II	8/55	92.5 (85.4–96.2)		3/57	97.2 (91.4–99.1)	
III	14/32	81.8 (71.0–88.9)		9/32	86.9 (75.8–93.1)	
IV	19/19	61.8 (46.6–73.9)		13/23	73.6 (58.6–83.9)	
Histology						
Low-intermediate/favourable	23/112	89.7 (84.8–93.1)	**0.0001**	8/120	96.3 (92.7–98.1)	**0.0001**
High-risk/unfavourable	21/23	70.0 (57.6–79.4)		17/24	73.8 (60.7–83.1)	
Pre-operative chemotherapy						
No	7/16	82.9 (67.1–91.6)	0.84	4/17	89.8 (74.6–96.1)	0.85
Yes	37/119	85.5 (80.6–89.3)		21/127	91.4 (87.0–94.3)	

In bold: statistically significant (*p*-value <0.05) results.

Table 5 presents the characteristics and outcome of patients with bilateral WT (stage V) in comparison with those with unilateral localised (stage I–III) tumours. Bilateral tumours were correlated more frequently with high-risk histology. No metastatic disease was found in bilateral tumours. Among the 21 bilateral tumours, 3 relapses were observed (alive 1/3) and 4 deaths (2 after relapse, 1 due to refractory disease and 1 due to sepsis). OS for bilateral tumours was found to be worse than that for unilateral localised tumours.

4. Discussion

For the first time, disease outcomes by demographic, clinical and pathology features, as well as pre-operative treatment, for 338 children with WT diagnosed and registered from 1999 to 2017 using harmonised clinical data embedded in 4 SEE registries were estimated. High $EFS_{5\text{-year}}$ (84.2%) and $OS_{5\text{-year}}$ (90.3%) were noticed. For unilateral tumours, in particular, we found an 85.1% 5-year EFS and 91.1% OS, which are comparable with the 87% $EFS_{2\text{-year}}$ and 93% $OS_{5\text{year}}$ reported in SIOP-2001 [4]. Despite this remarkable overall outcome, however, the $EFS_{5\text{-year}}$ rates for certain patient subgroups, including those with stage III (81.8%) or metastatic (stage IV) disease (61.8%) and high-risk/unfavourable histology (70.0%) at diagnosis as well as bilateral disease (68.6%) were still not optimal; these findings are also in line with the $EFS_{2\text{-year}}$ of 84%, 76% and 74% reported, respectively, for stage III, IV and high-risk histology groups by major collaborative studies (SIOP-2001) [4].

Our 4-SEE registries study showed that patients with unilateral tumours and high-risk/unfavourable histology were at 2.3 times higher risk for relapse than those of low- or intermediate-risk/favourable histology, whereas the death rate was 5.6 times higher in line with findings previously described [15,16]. The impact of stage and/or histology on outcomes have been widely evaluated, albeit not found statistically significant for both EFS and OS in all investigations [17–22]. The conflicting results may be attributed to differences in the proportion of advanced-stage and/or high-risk histology among patients participating in the different studies. In the present study, we found almost identical rates of stage IV patients with those treated with NWTS-5 and SIOP-2001. Regarding stage III patients, the calculated ratio was in between those reported by the NWTS-5 and SIOP-2001 studies (Table 6), albeit the majority of our patients had received pre-operative chemotherapy and were expected to present a significant shift to lower stages due to pre-operative chemotherapy. It is not easy to explore whether this is an indication of delayed presentation of the patients or mis-staging [23]; in any case, lack of central pathology review and evaluation of staging, at least in Greece, is a limitation.

The incidence of bilateral tumours in the present study (6.2%) was in the same range of that reported by the NWTS-5 (6.3) and SIOP (6.4%) studies [24,25]. Bilateral tumours are generally diagnosed in younger age groups [1], a finding not confirmed by our study, probably because of the small figures. By contrast, the worse outcome for stage V patients than for those with unilateral localised tumours was evident [1]. The 4-year EFS and OS in NWTS-5 for bilateral tumours was 61%

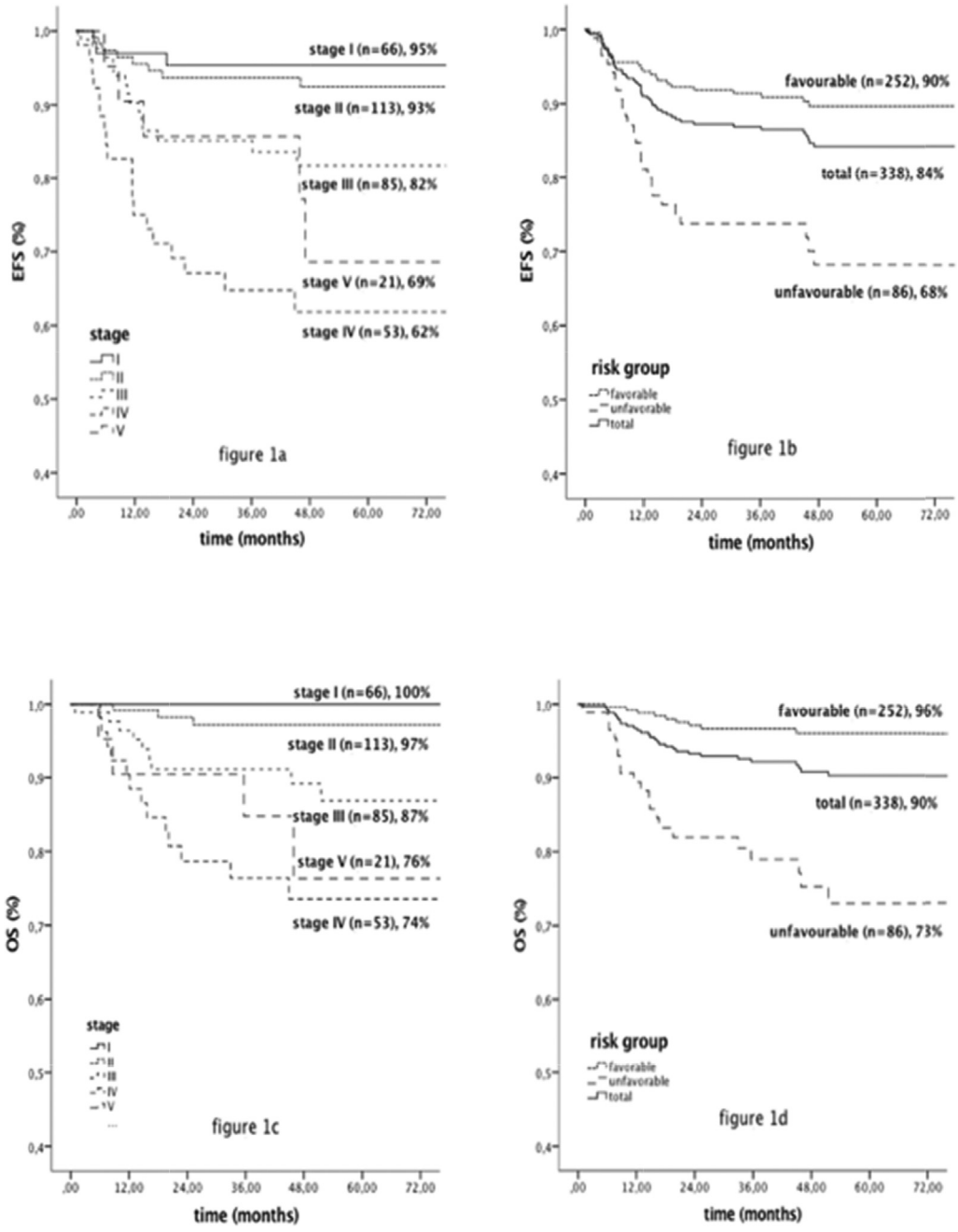

Fig. 1. Outcomes (event-free survival$_{5\text{-year}}$ and overall survival$_{5\text{-year}}$) by stage and histology risk group for all Wilms tumour cases (n = 338). EFS, event-free survival; OS, overall survival.

and 80%, respectively [26], whereas in SIOP studies, the relapse-free survival and OS were 80.5% and 85.1%, respectively [24].

The expected correlation of unfavourable histology features with advanced disease, previously reported in the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) protocol (TW2003) [27], the SIOP-2001 and the NWTS-5 studies [4,25], was more enhanced in our study, possibly on account of the higher proportion of stage III patients. Under the assumption that the clinical data were harmonised to the extent possible regarding risk classification, the higher rate of unfavourable histology in comparison to NWTS/SIOP studies may indicate possible geographic/ethnic disparities which partly explain the higher rate of advanced disease in the study base or inclusion of blastemal subtype in the high-risk histology group. Given the minimal outcome differences with the SIOP/NWTS results, however, the higher proportion of unfavourable histology in our study did not seem to remarkably impact on OS. Of note, the Japanese Wilms' Tumor Study Group reported that anaplastic histology WTs are less aggressive than

Table 4
Unilateral Wilms tumour cases: Cox proportional model–derived hazard ratios (HR) for event-free survival (EFS) and overall survival (OS) along with 95% confidence intervals (CIs) by study variables.

	EFS				OS			
Variable	HR	95% CIs		*p*-value	HR	95% CIs		*p*-value
Age (years)								
<2	Reference				Reference			
2–4	1.66	0.74	3.73	0.21	3.77	0.86	16.61	0.08
5–14	1.10	0.42	2.87	0.83	2.32	0.45	11.88	0.31
Gender								
Male	Reference				Reference			
Female	0.83	0.46	1.50	0.55	0.99	0.45	2.19	0.98
Stage								
I–II	Reference				Reference			
III	2.47	1.13	5.38	**0.02**	3.41	1.02	11.38	**0.04**
IV	5.21	2.42	11.23	**0.0001**	7.51	2.38	23.77	**0.0006**
Histology								
Low–intermediate/favourable	Reference				Reference			
High-risk/unfavourable	2.25	1.23	4.08	**0.008**	4.93	2.16	11.22	**0.0001**
Pre-operative chemotherapy								
No	Reference				Reference			
Yes	0.65	0.28	1.48	0.30	0.60	0.20	1.79	0.36

In bold: statistically significant (*p*-value <0.05) results.

Table 5
Comparison of bilateral vs. unilateral localised Wilms tumour cases by study variables.

	Bilateral (Stage V) n (%)	Unilateral localised (stage I-II-III) n (%)	
Total	21 (100.0)	264 (100.0)	*p*-value
Demographics			
Gender			
Male	11 (52.4)	121 (45.8)	0.56
Female	10 (47.6)	143 (54.2)	
Age (years)			
median (standard error)	3.1 (0.40)	3.0 (0.16)	0.91
<2	7 (33.3)	89 (33.7)	0.84
2–4	10 (47.6)	111 (42.1)	
5–14	4 (19.1)	64 (24.2)	
Birth defects			
Yes	2 (9.5)	10 (3.8)	0.22[a]
No	19 (90.5)	254 (96.2)	
Disease characteristics			
Nephroblastomatosis[b]			
Yes	4 (19.0)	28 (11.3)	0.29[a]
No	17 (81.0)	220 (88.7)	
Histology[c]			
Low-intermediate/favourable	9 (42.9)	210 (79.6)	**0.0005**[a]
High-risk/unfavourable	12 (57.1)	54 (20.4)	
Pre-operative chemotherapy			
No	0 (0.0)	43 (16.3)	0.05[a]
Yes	21 (100.0)	221 (83.7)	
Outcomes			
Relapse			
No	18 (85.7)	239 (90.5)	0.45[a]
Yes	3 (14.3)	25 (9.5)	
Death			
No	17 (81.0)	251 (95.1)	**0.03**[a]
Yes	4 (19.0)	13 (4.9)	
$EFS_{5\text{-year}}$	68.6 (38.0–86.3)	89.7 (85.2–93.0)	0.06
$OS_{5\text{-year}}$	76.3 (46.8–90.8)	94.7 (90.8–97.0)	**0.006**

In bold: statistically significant (*p*-value <0.05) results.
[a] *p-value* derived from Fisher's exact test.
[b] Missing values: 16.
[c] For bilateral cases the histology risk group was classified according to the higher risk histology between the two kidneys.

Table 6
Stage and histology risk group distribution in NWTS-5, SIOP-2001 and present study.

Total	Stage				Stage I–IV low or intermediate/favourable
	I	II	III	IV	
NWTS-5, Dome *et al.*, 2006 [25]	22.8%	29.6%	32.8%	14.8%	89.9%
SIOP-2001, Brok *et al.* [4]	45.2%	21.0%	19.0%	14.8%	86.1%
Present study	20.8%	35.7%	26.8%	16.7%	76.7%
High-risk/unfavourable histology risk group	I	II	III	IV	Stage I-IV high-risk/unfavourable
NWTS-5, Dome *et al.*, 2006 [25]	7.9%	5.7%	13.0%	15.8%	10.1%
SIOP-2001, Brok *et al.* [4]	10.1%	15.4%	20.8%	14.3%	13.9%
Present study	8.1%	28.4%	36.5%	27.0%	23.3%

that in the NWTS-5 study, indicating a possible biological heterogeneity of anaplastic WT [28].

We did not observe any significant differences in survival between the group of patients who overall received pre-operative chemotherapy (85.8%) and the minority group who underwent upfront surgery (Tables 2–4). In any case, our two groups were not comparable, with more metastatic cases in the pre-operatively treated group, and our population-based study is not powered to test such a difference. Of note, in the past, the United Kingdom Children's Cancer Study Group Wilms tumor trial 3 (UKW3) study showed a significant improvement in the stage distribution for patients receiving delayed surgery [7].

Female gender [15] at diagnosis used to be considered a tentative predictor for worse outcome; this notion was not confirmed either in our study or in the SIOP investigations [20]. Similarly, recent SEER data showed no difference regarding OS by gender, whereas our previous study regarding 12 SEE registries showed a better OS for girls [9].

Our study, confined to children aged 0–14 years, showed that diagnosis at an older age was associated with advanced stage, albeit not unfavourable histology, whereas children aged <2 years had a higher OS rate. An association of older age at diagnosis with advanced disease and/or unfavourable histology has been reported in some studies [18,24,27] that may partly explain the adverse outcome also among adolescents [29]. Nevertheless, advanced disease at diagnosis is generally associated with high-risk histology. Several studies report no association of outcome with age [18,30,31], whereas others show better EFS and/or OS rates for younger children [6,20,24,32–34]. In our previous study comprising numerous SEE countries, OS was found to be less favorable among children aged 10–14 years [9]. The diverse results may be due to heterogeneity of population characteristics, differential inclusion of disease stage and histology subtypes or age groups as well as evolution of protocols, minimising the prognostic significance of age. Alternative stipulations may be a delay of diagnosis in older patients, adverse prognostic biologic features and higher vulnerability for life-threatening treatment–related toxicity in this age group [32,35].

Socioeconomic disparities and healthcare delivery differentials may also adversely impact, at least on OS, as shown in our previous study comprising children residing in rural areas and SEE countries with inferior HDI [9]. In other developed countries (Germany vs. Britain), factors related to the primary care system and the subsequent possible delays in diagnosis have been used to explain minimal differences in EFS/OS rates [36], whereas completion of treatment has been reported as crucial determinant of outcome, especially, in developing countries [37]. It was not feasible to undertake analyses on individual-level socioeconomic and healthcare delivery factors or enrolment in clinical trials status in the present study; the gross control by registry, however, did not significantly change the results.

Use of national or regional cancer registration data under common disease coding, enriched with detailed high-quality medical record variables abstracted voluntarily by the treating physicians in the four participating SEE countries on the basis of a harmonised form developed and checked for accuracy by the coordination center, is among the strengths of the study. Despite lack of electronic linkage, outcome data on EFS compared to OS from this part of the European Union comprising all children diagnosed and treated for WT with different treatment modalities during the last decades have been made available for international comparisons. Harmonisation issues have been identified as areas for improvement as well as high-risk target groups, but overall, the outcome results are encouraging. Hence, the experience gained by this collaboration highlighting the unique role of high-quality and clinically linked childhood cancer registration for purposes of public health is of importance for both clinicians and policy makers.

Expansion to data on diagnosis delays, clinical findings at presentation, tumour volume, lymph node involvement, detailed surgical report, histology subclassification and histology review by a coordinating center, as well as molecular markers for optimal stratification already incorporated in the current cooperative protocols [4] and extra-treatment details or late effects

would be future targets should human resources be available to continue the study prospectively with concurrent completion of the harmonised variables and monitoring of the clinical registration. Owing to the—by necessity—retrospective data abstraction of data and current advances in medical care, we opted for comparability reasons to limit the study period to the more recent years during which international treatment collaboration and enrolment of patients in clinical protocols have been enhanced. As early relapses have been observed in our study and there is no established mean time of relapse, we also decided to include in the analyses all children diagnosed until the end of 2017. This may have led to a degree of overestimation of EFS/OS. Moreover, patients have been treated according to different protocols and by different multidisciplinary teams working in different healthcare delivery systems. Despite the relatively large study size for a rare type of cancer, results on subgroups of patients should be interpreted with caution. Finally, because only 4 SEE registries made it to contribute clinical data, generalisability of the results to the wider SEE area is hampered.

In conclusion, outcome of WT patients in the four participating SEE countries approached that reported by major collaborative trials, albeit somehow inferior. Despite the outstanding prognosis, subgroups of patients were still at higher risk for poor outcomes, indicating a need for novel strategies including optimal risk stratification with central pathology units and treatment intensification for these subgroups. In improving outcomes, clinical childhood cancer registration may play a crucial and inexpensive role along with higher enrolment rates into clinical trials.

Conflicts of interest statement

None declared.

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