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ONCOLOGY: RESEARCH ARTICLE

Comparative analysis of the clinical characteristics and outcomes of patients with Wilms tumor in the United Kingdom and Japan

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Abstract

Background: Wilms tumor (WT) demonstrates epidemiological differences by world region and ethnicity. To enhance understanding of these differences, we retrospectively analyzed clinical trial data sets from the UK and Japan over a 20-year period.

Procedure: We used data from three consecutive clinical trials in the UK and a single study in Japan that enrolled patients diagnosed during 1996-2015, to compare clinical characteristics and outcomes between countries.

Results: During 1996-2015, 1395 patients in the UK and 537 in Japan were included. Japanese patients have a significantly younger median age at diagnosis than those in the UK (28 months vs 39 months). The proportion of patients with stage IV, large tumors, and anaplastic histology appears to be higher in the UK than in Japan (18% vs 11%, 62% vs 49%, 8% vs 3%, respectively). During 2005-2015, 77 hospitals treated WT in Japan compared with only 20 hospitals in the UK. Five-year overall survival of patients with WT was over 90% in both countries, but five-year event-free survival of

Abbreviations: BWS, Beckwith-Wiedemann syndrome; CI, confidence interval; CT, computed tomography; EFS, event-free survival; GU, genitourinary; HH, hemihypertrophy; HR, hazard ratio; IMPORT, Improving Population Outcomes of Renal Tumours of childhood; JSPS, Japanese Society of Pediatric Surgeons; JWiTS, Japanese Wilms Tumour Study; LOI, loss of imprinting; NWTS, National Wilms Tumor Study; OS, overall survival; SIOP-RTSG, The Renal Tumour Study Group of the International Society of Paediatric Oncology; WAGR syndrome, syndrome characterized by Wilms tumor, aniridia, and genitourinary abnormalities as well as intellectual disability (formerly referred to as mental retardation); WT, Wilms tumor

patients with stage IV was significantly lower in Japan than in the UK (50.0% vs 76.2%, $P = 0.001$).

Conclusions: Differences in age of onset, tumor size at diagnosis, and histology may reflect differences in the genetic background of patients with WT between countries, but population-based phenotype-genotype data are lacking. The difference in survival probability for stage IV patients may be due to different diagnostic criteria or different treatment strategies. Prospective, international clinical studies including genomic analyses are needed to confirm these findings and improve clinical practice.

KEYWORDS
age at diagnosis, childhood renal tumor, Japan, survival, UK, Wilms tumor

1 | INTRODUCTION

Malignant renal tumors comprise 5% of all cancers occurring before the age of 15 years.[1] Wilms tumor (WT) is the most common renal tumor in children[2] and variation in incidence between regions or ethnicities has been reported.[3,4] According to a recent epidemiological report, the annual incidence rate of WT in East Asia is lower than in North America or Europe (4.3 vs 8-9 per million).[4] In the USA, Black ethnicity has the highest incidence (9.7 per million) and Asian and Pacific Islanders the lowest (3.7 per million).[4] East Asian children with WT have also been reported to be younger at diagnosis[4,5] and have fewer tumors with anaplasia histology than in other world regions.[6,7] Somatic tumor genetic analysis shows a lower frequency of tumors with IGF2 loss of imprinting (LOI) among Japanese patients with WT compared with Caucasian populations.[5] These findings indicate a difference in tumor etiology or biology between world regions; however, no direct comparison of the clinical features of patients with WT in Asia and those in European countries has been carried out.

The treatment strategy of the Japanese Wilms Tumor Study (JWiTS) is based on that of the National Wilms Tumor Study (NWTS) group in the USA, with immediate nephrectomy,[8,9] while European clinical studies, including the UK's most recent clinical trials (SIOP WT 2001 and the Improving Population Outcomes of Renal Tumours of childhood [IMPORT] study) use a preoperative chemotherapy approach.[10–12] In the UKW3 from 1991 to 2001, both approaches were used in a randomized trial.[13] Despite using different approaches, favorable outcomes for WT have already been reported in each country.[8–10,13]

Because outcomes of WT treatment have never been directly compared between countries, our aim was to compare clinical characteristics and outcomes of children with WT using clinical trial data sets from both countries in order to improve understanding and stimulate further research on the biology of this tumor and its clinical practice. The fact that the national clinical trials enrolled more than 60% of patients in each country over a 20-year period provided the opportunity for a collaboration between the leaders of the two national clinical trial groups from the UK and Japan, initiated in 2016.

2 | METHODS

2.1 | Study design and data sources

This study is a retrospective observational study using three consecutive clinical trial data sets (UKW3,[13] SIOP WT 2001,[11] and IMPORT study[12]) from the UK and a single data set from the registry of Japanese Society of Pediatric Surgeons (JSPS) in which approximately 75% of registered patients were enrolled in the JWiTS trial.[8,9] Compared with population-based cancer registry data, an estimated 89% of all patients in the UK and 64% in Japan were included.[14] From these data sets, information on patients with WT diagnosed between1996 and 2015 was extracted and included sex, age at diagnosis (months), associated congenital abnormalities, date of diagnosis, clinical stage of disease, tumor size, tumor histology, treatment hospital, vital status, and date of death or last follow-up for vital status. Regarding information on associated congenital abnormalities, the case report forms of each study except for UKW3 included a check box for each congenital abnormality. The UKW3 form had a field where the presence of a congenital abnormality and its type could be reported. Using this information, associated congenital abnormalities[15] were categorized into five groups: patients with aniridia or WAGR syndrome (characterized by WT, aniridia, and genitourinary abnormalities as well as intellectual disability [formerly referred to as mental retardation]), hemihypertrophy (HH) or Beckwith-Wiedemann syndrome (BWS), genitourinary (GU), or renal malformations including Denys-Drash syndrome, other abnormalities, and none. Clinical stage of disease was categorized into five groups (I, II, III, IV, or bilateral = V). Timing and staging criteria, except for stage IV, differed between the two countries and between studies. In the UK, clinical stage was assessed according to the criteria used in the NWTS-4 trial for patients registered in the UKW3,[13] and for patients registered in SIOP WT 2001 and IMPORT according to the criteria used in SIOP WT 2001 after preoperative chemotherapy.[16] In Japan, clinical stage for patients with stage I-III was assessed according to the classification of the JSPS[8] after immediate nephrectomy. Patients with metastasis were classified as stage IV in all studies in both countries, although detection methods such as computed tomography (CT) or X-ray were not clearly defined in JSPS. Tumor size was

defined as the maximum diameter of the resected tumor by immediate nephrectomy or that of tumor images at diagnosis before preoperative chemotherapy on magnetic resonance imaging, ultrasound, or CT. Using the information on treatment hospital, we calculated the number of patients registered per hospital from 2005 to 2015 in each country.

2.2 | Statistical analysis

We compared the distribution of patient sex, age at diagnosis, prevalence of associated congenital abnormalities, period of diagnosis, clinical stage, tumor size, tumor histology, and hospital volume for registered patients between the countries. The selection of variables and their subcategorizations were based on previous reports[7,17,18] or authors' discussion. We used the chi-square test to compare the distribution of categorical variables. Frequency distribution of age at diagnosis was estimated using nonparametric Gaussian kernel smoothing and median age at diagnosis was compared by the Mann-Whitney *U* test. The assessment of the number of patients registered per hospital only included patients diagnosed between 2005 and 2015 because the name of the treatment hospital only became available in 2005 in Japan. We calculated the probability of five-year event-free survival (EFS) and overall survival (OS) with 95% confidence intervals (CI) by each characteristic in each country using the Kaplan-Meier method and compared them between countries, using the log-rank test. EFS was defined as the time from the date of diagnosis to the first tumor recurrence or progression or death from any cause. OS was defined as the time from date of diagnosis to death from any cause. Patients without events were censored at their time of last follow-up. The assessment of EFS and OS only included patients diagnosed between 1996 and 2010, because in Japan, patient follow-up in JSPS was conducted at five-year intervals and follow-up information was available only for the patients diagnosed during this period. Focusing on the patients diagnosed between 2006 and 2010, we combined all the data from both countries and analyzed the predictors of EFS and OS using the Cox proportional hazards regression model. A two-sided *P* value less than 0.05 was considered statistically significant. All analyses were carried out using Stata version 14.2.

This study was approved by the Research Ethics Committee of the Hyogo Medical University (Reference number 2528).

3 | RESULTS

We identified 1395 (UK) and 537 (Japan) patients diagnosed with WT from 1996 to 2015. The characteristics of patients in each country are presented in Table 1. There was a female excess in both countries, less so in Japan, but the difference did not reach statistical significance. Japanese patients had a significantly younger median age at diagnosis than those in the UK (28 months vs 39 months). The peak age at diagnosis was 12-18 months in Japan compared with a much broader, bimodal peak spanning 12-42 months in the UK (Figure 1). Associated congenital abnormalities were found in 163 (11.7%) patients in the UK, and in 39 (7.3%) patients in Japan. HH/BWS was diagnosed in 35 (2.5%) patients in the UK, and only three patients (0.6%) in Japan. In the UK, proportions of patients with metastatic disease (stage IV), with larger tumor (largest diameter over 10 cm), or with anaplastic WT were all higher than in Japan (17.9% vs 11.0%, 61.5% vs 49.0%, 8.0% vs 3.2%, respectively). Among the patients with aniridia/WAGR syndrome, 2 of 9 (22.2%) in the UK and 4 of 11 (36.4%) in Japan had bilateral WTs (stage V) and none had stage IV. From 2005 to 2015, patients with WT were treated in 20 hospitals in the UK, and 77 hospitals in Japan. In Japan, 68 (22.2%) patients were treated at hospitals that registered 10 or more patients, 129 (42.0%) at hospitals that registered 5-9 patients, and 110 (35.8%) patients at hospitals that registered 1-4 patients. In the UK, almost all patients were treated at hospitals that registered 10 or more patients ($N = 746$, 95.9%) (Table 1). The number of patients per hospital in Japan was lower than in the UK for all patients, as well as patients with stage IV (Figure 2).

3.1 | Survival of patients with WT in the UK and Japan

The median follow-up time was 7.3 years (range, 0.01-13.4) in the UK and 5.3 years (0.008-11.5) in Japan. Of the total patients diagnosed from 1996 to 2010, five-year estimated EFS was 82.3% (95% CI = 79.9-84.5) in the UK and 80.1% (95% CI = 74.9-84.3) in Japan, five-year estimated OS was 91.4% (95% CI = 89.6-93.0) in the UK and 92.1% (95% CI = 88.2-94.7) in Japan (Table 2; Figure 3A and 3B). There were no significant differences in EFS and OS between the two countries ($P = 0.38$ for EFS and 0.52 for OS, respectively). We also analyzed the five-year EFS and five-year OS for each characteristic in each country and compared them across countries (Table 2). In both countries, most characteristics of patients had a five-year EFS and OS greater than 80%, but some had a survival lower than 70%—five-year EFS of patients with stage IV (50.0%, 95% CI = 32.4-65.3) or stage V (66.0%, 95% CI = 44.7-80.6) in Japan, and five-year EFS (58.7%, 95% CI = 47.1-68.6) or five-year OS (69.5%, 95% CI = 58.0-78.5) of patients with anaplastic WT in the UK. There were no significant differences in EFS and OS between the two countries for most characteristics. However, among patients with stage IV, five-year estimated EFS was significantly lower in Japan than in the UK (50.0% [95% CI = 32.4-65.3] vs 76.2% [95% CI = 69.6-81.5], $P = 0.001$) (Table 2 and Figure 3C).

3.2 | Predictors of survival for patients diagnosed with WT between 2006 and 2010

Among recently diagnosed (2006-2010) patients, based on combined data from both countries, female sex, stage IV, and anaplastic histology were significantly associated with a higher risk of death in multivariable analysis (hazard ratio, HR = 2.6, 2.7, 2.5, respectively) (Table 3). There was no difference in five-year estimated EFS or OS between the two countries. We applied a Cox proportional hazards regression model for all recently diagnosed patients by country. In the UK,

TABLE 1 Characteristics of patients with Wilms tumor between the UK and Japan during 1996-2015

	UK		Japan		*P* value[a]
Sex					
Male: *N* (%)	645	(46.2)	259	(48.2)	0.372
Female: *N* (%)	750	(53.8)	275	(51.2)	
Unknown/missing: *N* (%)	0	(0.0)	3	(0.6)	
Female:male ratio	1.16:1		1.06:1		
Age at diagnosis					
Median age, months (IQR)	39	(21-58)	28	(14-50)	<0.0001
Age at diagnosis (months): *N* (%)					
<6	39	(2.8)	27	(5.0)	0.000002
6-11	130	(9.3)	78	(14.5)	
12-23	240	(17.2)	119	(22.2)	
24-47	481	(34.5)	168	(31.3)	
≥48	505	(36.2)	145	(27.0)	
Congenital abnormalities: *N* (%)					
None	1232	(88.3)	498	(92.7)	0.00004
Aniridia/WAGR	9	(0.7)	11	(2.1)	
HH/BWS	35	(2.5)	3	(0.6)	
GU/renal abnormality	42	(3.0)	13	(2.4)	
Other abnormality	77	(5.5)	12	(2.2)	
Period of diagnosis: *N* (%)					
1996-2000	389	(27.9)	100	(18.6)	0.000008
2001-2005	304	(21.8)	150	(27.9)	
2006-2010	359	(25.7)	122	(22.7)	
2011-2015	343	(24.6)	165	(30.7)	
Stage: *N* (%)[b]					
I	472	(33.8)	190	(35.4)	0.00001
II	249	(17.9)	135	(25.1)	
III	300	(21.5)	98	(18.3)	
IV	249	(17.9)	59	(11.0)	
V	112	(8.0)	42	(7.8)	
Unknown/missing	13	(0.9)	13	(2.4)	
Size (largest diameter): *N* (%)					
≤5 cm	54	(3.9)	33	(6.2)	0.00000003
5-≤10 cm	393	(28.2)	170	(31.7)	
>10 cm	858	(61.5)	263	(49.0)	
Unknown/missing	90	(6.5)	71	(13.2)	
Histology: *N* (%)					
Non-anaplasia	1284	(92.0)	520	(96.8)	0.0001
Anaplasia	111	(8.0)	17	(3.2)	
Hospital volume[c] (2005-2015 only):					
No. hospitals registering ≥ 10 patients	17		4		
Total patients registered (% of all patients)	746	(95.9)	68	(22.2)	
No. hospitals registering 5-9 patients	3		18		
Total patients registered (% of all patients)	23	(3.0)	129	(42.0)	

(Continues)

TABLE 1 (Continued)

	UK		Japan		*P* value[a]
No. hospitals registering 1-4 patients	0		55		
Total patients registered (% of all patients)	0	(0.0)	110	(35.8)	
Patients with missing hospital name: (% of all patients)	9	(1.2)	0	(0.0)	

Abbreviations: BWS, Beckwith-Wiedemann syndrome; GU, genitourinary, HH, hemihypertrophy; IQR, interquartile range; WAGR, syndrome characterized by Wilms tumor, aniridia, and genitourinary abnormalities as well as intellectual disability (formerly referred to as mental retardation).

[a]Comparisons between the UK and Japan using Chi-square test, or Mann-Whitney *U* test.

[b]Staging criteria except for stage IV differed for each country and each study.

[c]Hospital volume was categorized according to the number of patients registered by each hospital from 2005 to 2015.

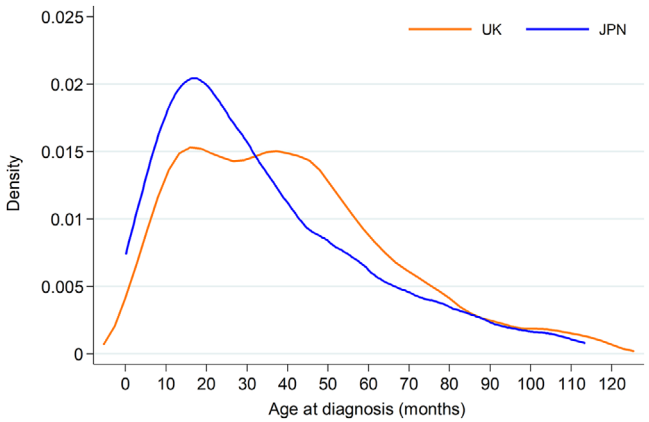

FIGURE 1 Frequency distributions of age at diagnosis in patients with Wilms tumor in the UK (yellow line) and Japan (blue line)

female sex was significantly associated with an increased risk of death in the multivariate analysis (HR = 3.0, *P* = 0.0137) but not in Japan (HR = 1.55, *P* = 0.671). We compared characteristics and outcomes of patients with WT between males and females by country (Supporting Information Table S1). The proportion of patients with stage V was higher in females in both countries but was not statistically significant.

4 | DISCUSSION

In this study, we assessed the clinical characteristics and outcomes of patients with WT in the UK and Japan, using clinical trial data sets that enrolled more than 60% of patients in each country over a 20-year period. We found several differences between the two countries in clinical characteristics. Japanese children were diagnosed at a younger age and had a unimodal early age-at-diagnosis distribution, while patients in the UK had a bimodal age-at-diagnosis distribution. Fukuzawa et al. reported differences in age-distribution patterns that were similar to our results, and they proposed differences in prevalence of epigenetic mutations between WT in white and East Asian children as an explanation.[5] They assessed IGF2 LOI of WT tumors, which was frequently present in WT in white children in New Zealand (13/41 tumors)

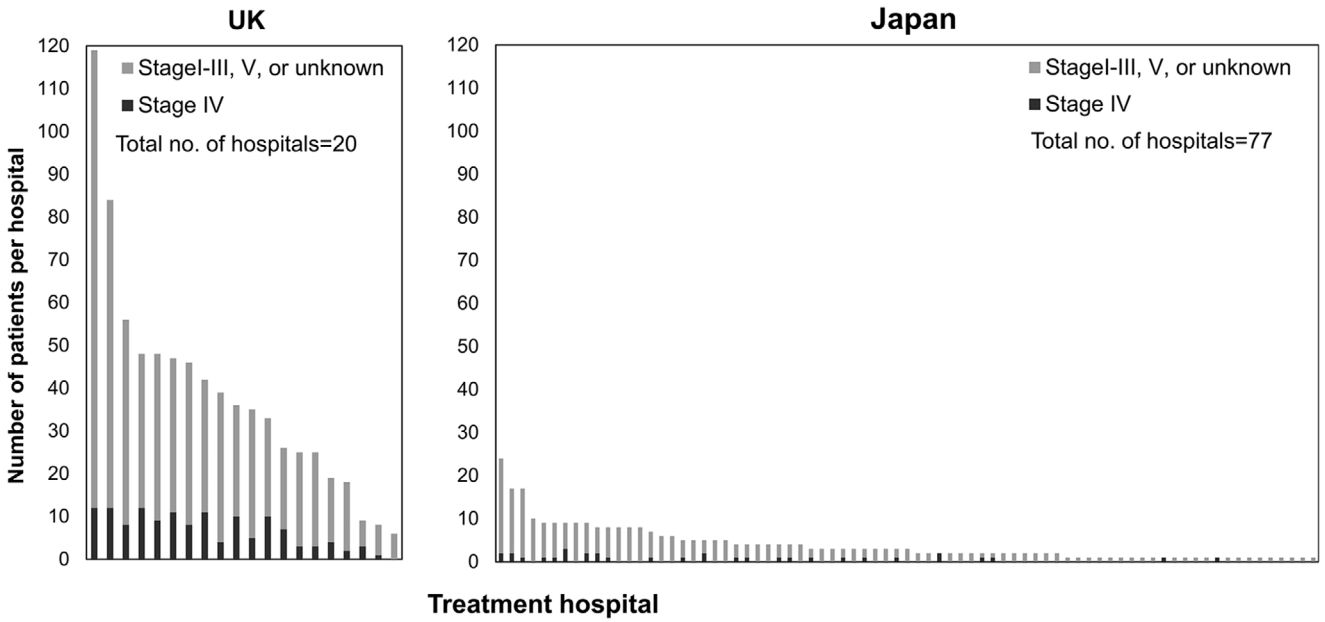

FIGURE 2 Total number of registered patients with Wilms tumor by hospital in the UK and Japan, 2005-2015

TABLE 2 Five-year EFS and OS in patients with Wilms tumor between UK and Japan during 1996-2010

	N at risk		EFS at five years							OS at five years						
	UK	Japan	UK			Japan				UK			Japan			
	N at risk	*N* at risk	%	95% CI		%	95% CI		*P* value[a]	%	95% CI		%	95% CI		*P* value[a]
Total	1049	303	82.3	79.9	84.5	80.1	74.9	84.3	*P* = 0.38	91.4	89.6	93.0	92.1	88.2	94.7	*P* = 0.52
Sex																
Male	485	151	84.9	81.3	87.8	80.4	72.9	86.0	*P* = 0.27	93.5	90.9	95.4	93.6	88.0	96.6	*P* = 0.81
Female	564	149	80.2	76.6	83.2	79.4	71.7	85.2	*P* = 0.72	89.7	86.8	91.9	90.4	84.0	94.3	*P* = 0.62
Age at diagnosis (months)																
<6	25	17	88.0	67.3	96.0	76.5	48.8	90.4	*P* = 0.35	92.0	71.6	97.9	94.1	65.0	99.1	*P* = 0.77
6-11	90	45	87.7	78.9	93.0	79.0	63.5	88.5	*P* = 0.27	95.3	88.0	98.2	92.8	79.2	97.6	*P* = 0.72
12-23	179	70	90.4	85.0	93.9	82.1	70.7	89.4	*P* = 0.07	97.2	93.3	98.8	96.8	88.0	99.2	*P* = 0.91
24-47	381	97	81.8	77.5	85.3	81.6	72.1	88.2	*P* = 0.98	91.8	88.5	94.1	89.0	80.5	93.9	*P* = 0.54
≥48	374	74	77.4	72.8	81.4	77.4	65.2	85.8	*P* = 0.87	87.4	83.6	90.4	90.9	80.9	95.8	*P* = 0.42
Congenital abnormalities																
None	928	286	81.9	79.2	84.2	80.0	74.7	84.3	*P* = 0.47	91.1	89.0	92.8	92.0	87.9	94.7	*P* = 0.48
Aniridia/WAGR, HH/BWS, GU/renal abnormality	68	11	83.8	72.6	90.7	80.0	40.9	94.6	*P* = 0.80	95.5	86.7	98.5	100.0	–	–	*P* = 0.42
Other abnormality	53	6	88.7	76.5	94.7	83.3	27.3	97.5	*P* = 0.64	92.5	81.1	97.1	83.3	27.3	97.5	*P* = 0.44
Period of diagnosis																
1996-2000	389	86	80.5	76.1	84.1	79.8	69.6	87.0	*P* = 0.67	91.5	88.2	93.9	90.4	81.7	95.1	*P* = 0.87
2001-2005	304	130	82.5	77.7	86.3	76.9	68.4	83.5	*P* = 0.27	91.7	88.0	94.3	92.3	85.6	95.9	*P* = 0.69
2006-2010	356	87	84.1	79.8	87.6	85.1	75.2	91.3	*P* = 0.76	91.1	87.5	93.7	93.6	85.2	97.3	*P* = 0.43
Stage																
I-III (all localized tumors)	759	235	85.0	82.3	87.4	87.4	82.2	91.1	*P* = 0.43	94.7	92.8	96.1	95.3	91.4	97.4	*P* = 0.54
IV (metastatic tumors)	198	34	**76.2**	**69.6**	**81.5**	**50.0**	**32.4**	**65.3**	***P* = 0.001**	81.2	75.0	86.0	76.4	58.2	87.4	*P* = 0.51
V (bilateral disease)	82	27	75.5	64.6	83.4	66.0	44.7	80.6	*P* = 0.36	87.7	78.3	93.2	91.7	70.6	97.8	*P* = 0.50

(Continues)

TABLE 2 (Continued)

	N at risk		EFS at five years							OS at five years						
	UK	Japan	UK			Japan				UK			Japan			
	N at risk	*N* at risk	%	95% CI		%	95% CI		*P* value[a]	%	95% CI		%	95% CI		*P* value[a]
Size (largest diameter)																
≤5 cm	43	21	92.9	79.6	97.7	80.4	55.6	92.2	*P* = 0.19	97.6	84.3	99.7	84.7	59.5	94.8	*P* = 0.06
5-≤10 cm	312	83	89.4	85.4	92.3	84.8	74.7	91.1	*P* = 0.24	96.7	94.0	98.2	94.9	87.0	98.1	*P* = 0.50
>10 cm	616	148	79.6	76.1	82.5	80.7	73.2	86.4	*P* = 0.78	89.4	86.6	91.6	92.7	86.8	96.0	*P* = 0.17
Unknown/missing	78	51	70.5	59.0	79.3	70.8	55.7	81.6	*P* = 0.83	83.3	73.0	90.0	89.0	75.5	95.3	*P* = 0.24
Histology																
Non-anaplasia	969	294	84.3	81.9	86.5	80.2	75.0	84.5	*P* = 0.11	93.2	91.4	94.7	92.6	88.8	95.2	*P* = 0.98
Anaplasia	80	9	58.7	47.1	68.6	76.2	33.2	93.5	*P* = 0.46	69.5	58.0	78.5	71.4	25.8	92.0	*P* = 0.82
Hospital volume (2005-2010 only)[b]																
Treated at hospitals registering ≥ 10 patients	413	26	82.4	78.4	85.8	84.6	64.0	93.9	*P* = 0.72	89.7	86.2	92.3	96.0	74.8	99.4	*P* = 0.29
Treated at hospitals registering 5-9 patients	14	48	85.1	52.3	96.1	86.4	72.1	93.7	*P* = 0.51	100.0	0.0	0.0	95.4	82.9	98.8	*P* = 0.43
Treated at hospitals registering 1-4 patients	0	32				85.9	66.5	94.5					88.1	67.6	96.0	

Note. Bold signifies statistical significance.

Abbreviations: BWS, Beckwith-Wiedemann syndrome; CI, confidence interval; EFS, event-free survival; GU, genitourinary, HH, hemihypertrophy; OS, overall survival; WAGR, syndrome characterized by Wilms tumor, aniridia, and genitourinary abnormalities as well as intellectual disability (formerly referred to as mental retardation).

[a]Comparisons of survival functions between the UK and Japan using the log-rank test.

[b]Survival analysis by hospital volume includes only cases diagnosed from 2005 to 2010.

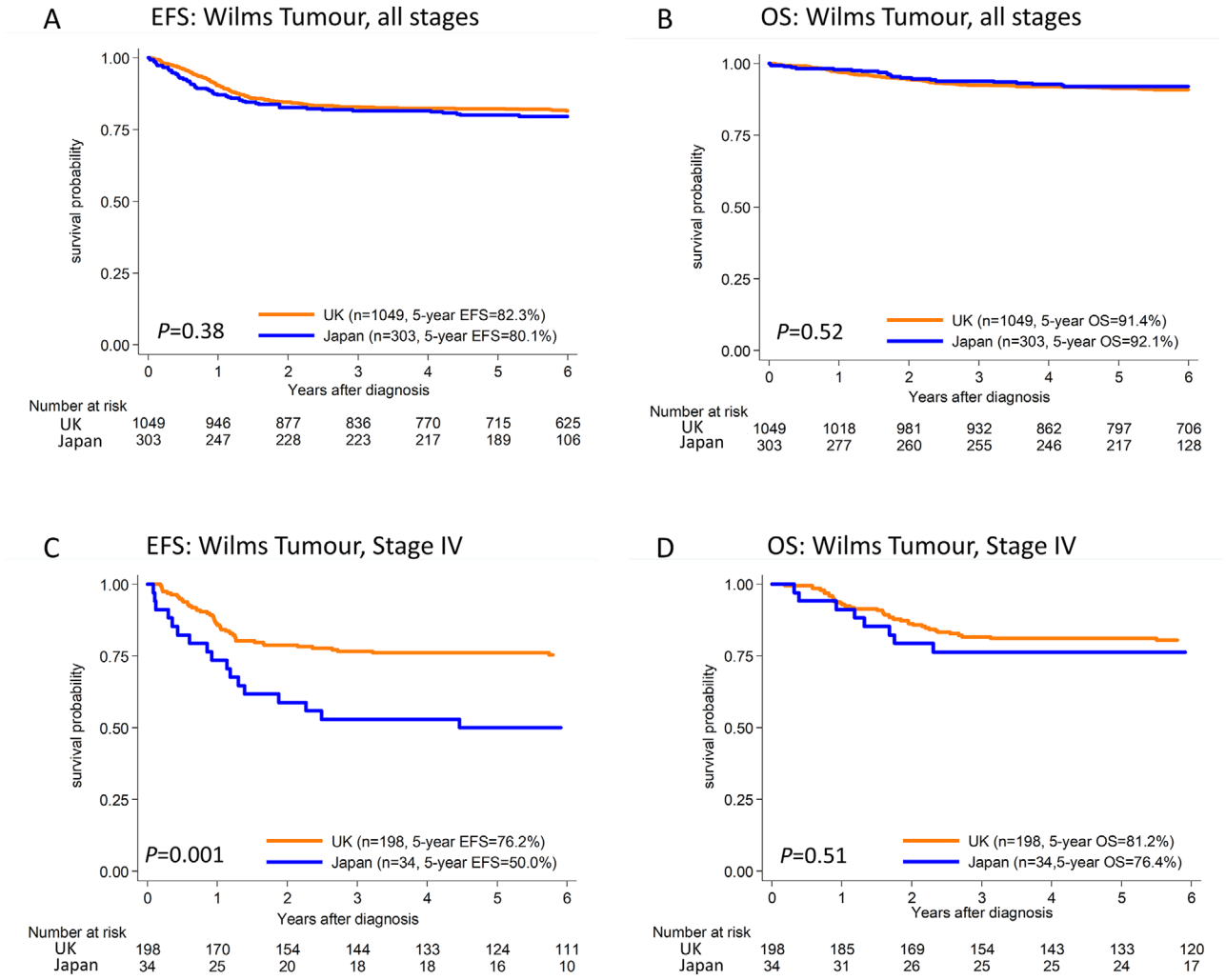

FIGURE 3 Kaplan-Meier survival curves for EFS and OS of patients with Wilms tumor in the UK and Japan, 1996-2010 EFS (A) and OS (B) of all registered patients with Wilms tumor. EFS (C) and OS (D) of patients with stage IV Wilms tumor. EFS, event-free survival; OS, overall survival

but absent in tumors in Japanese children (0/21 tumors). Patients who had WT with IGF2 LOI had previously been reported to have an older median age at diagnosis than patients with normal imprinting[19]; hence, they hypothesized that the lower incidence of IGF2 LOI contributes to the lower incidence and earlier age-at-diagnosis distribution of Japanese patients with WT. Another report also indicated lower incidence of IGF2 LOI in Japanese than in Caucasian children with WT.[20] Although tumor genomic information was not available in our study, these differences in genetic background are likely to explain our findings. In keeping with this interpretation, we also found that the proportion of patients with BWS/HH in Japan was over four-fold lower than that in the UK ($P = 0.00004$). Risk of WTs has been reported to be highest in the H19/IGF2 hypermethylation subgroup (24%) but lowest in the KCNQ1OT1 subgroup (0.2%).[21] A previous report revealed that Japanese patients with BWS had a significantly lower frequency of H19/IGF2 hypermethylation than North American and European patients with BWS.[22] Based on these reports and our findings, lower incidence of WT with BWS in Japan might be due to lower population prevalence of BWS with underlying H19/IGF2 hypermethylation. However, our data do not include information on genotype/phenotype and the information on the syndromes might be biased due to a lack of strictly defined syndrome criteria for the clinician completing the case report form. Therefore, careful monitoring with detailed data and international population-based registry for congenital abnormalities is needed to confirm this hypothesis. Regarding age at diagnosis, there are differences in routine physical examinations for children between countries. In the UK, a routine physical examination by a doctor is undertaken shortly after birth and again at six weeks. No further routine physical examinations are performed unless there are concerns about developmental milestones which are reviewed at age 1 year, 2-2.5 years, and 5 years. A child's primary medical care is provided by a general practitioner. In Japan, the Maternal and Child Health Law mandates infant health checks at 1.6 and 3 years of age. Many local governments also provide infant health checks at 3 to 4 months and 9 to 10 months of age. A child's primary medical care is usually provided by pediatricians. Bearing in mind that these differences in routine care may have affected age at diagnosis, interpretations should be made with caution.

TABLE 3 Univariate and multivariate predictors of EFS and OS using the Cox proportional hazards model for patients with Wilms tumor diagnosed during 2006-2010

	Univariate analysis				Multivariate analysis			
	HR	95% CI		*P* value	HR	95% CI		*P* value
EFS								
Country								
UK	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Japan	0.9	0.5	1.7	0.76	1.1	0.6	2.2	0.73
Sex								
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.5	0.9	2.5	0.10	1.5	0.9	2.4	0.11
Age at diagnosis (months)								
0-23	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥24	1.8	1.0	3.2	0.05	1.7	0.9	3.1	0.12
Stage								
I-III (all localized tumors)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
IV (metastatic tumors)	1.6	0.9	2.8	0.11	1.3	0.7	2.4	0.32
V (bilateral disease)	1.2	0.5	2.5	0.73	1.2	0.5	2.8	0.61
Size (largest diameter)								
≤10 cm	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
>10 cm	1.7	1.0	2.9	0.07	1.5	0.9	2.7	0.16
Histology								
Non-anaplasia	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Anaplasia	1.7	0.9	3.5	0.12	1.5	0.7	3.0	0.31
OS								
Country								
UK	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Japan	0.7	0.3	1.8	0.43	1.1	0.4	3.0	0.88
Sex								
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	**2.6**	**1.2**	**5.6**	**0.01**	**2.6**	**1.2**	**5.6**	**0.01**
Age at diagnosis (months)								
0-23	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥24	**3.6**	**1.3**	**10.2**	**0.02**	2.9	1.0	8.8	0.06
Stage								
I-III (all localized tumors)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
IV (metastatic tumors)	**3.5**	**1.7**	**6.9**	**0.0004**	**2.7**	**1.3**	**5.4**	**0.007**
V (bilateral disease)	1.6	0.6	4.8	0.37	2.0	0.6	5.9	0.24
Size (largest diameter)								
≤10 cm	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
>10 cm	**2.8**	**1.1**	**6.6**	**0.03**	2.0	0.8	4.9	0.15
Histology								
Non-anaplasia	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Anaplasia	**3.4**	**1.5**	**7.4**	**0.002**	**2.5**	**1.1**	**5.5**	**0.03**

Note. Bold signifies statistical significance.

Abbreviations: CI, confidence interval; HR, hazard ratio; Ref, reference.

The other striking difference was in the prevalence of anaplasia, which was more than twice as frequent (8.0% vs 3.2%, $P = 0.0001$) in the UK than in Japan. A previous study that included mutational analysis of the TP53 gene also reported a lower frequency of anaplasia in Japan than in the USA.[6] While this difference may be partially explained by the younger median age of Japanese patients with WT, differences in genetic background may also contribute, as well as variation in recognition of anaplasia. The recording of pathological subtypes in the Japanese data during the early period may have been less complete.[8]

In this study, prognosis of most patients was favorable in both countries. However, five-year EFS of children presenting with stage IV was significantly lower in Japan than in the UK. One possible reason might be in the imaging modalities used to detect lung metastases. In Japan and in the early years of the UK studies, only patients with lung metastasis detected by chest X-ray (or deemed large enough on CT scan to be visible on chest X-ray) were treated as stage IV disease. Therefore, patients with small lung metastasis that could not be detected by chest X-ray were not included in stage IV. This definition of stage IV disease may also have contributed to the lower proportion of patients with stage IV as well as lower EFS of patients with stage IV in Japan compared with the UK. Another possible reason might be differences in the treatment protocols. In the JWiTS protocol, according to which most Japanese patients were treated, patients with stage IV favorable histology WT were treated with DD-4A regimen, in which the total dose of doxorubicin was 150 mg/m^2, while in the UK, in the UKW3 and SIOP WT 2001 protocols, patients with stage IV received a total doxorubicin dose of 360 mg/m^2 falling to 300 mg/m^2 in the IMPORT study. However, the NWTS outcomes were better than those for patients in Japan with stage IV favorable histology WT using the same DD-4A regimen as the JWiTS protocol,[23] so that the difference in outcome between the UK and Japan might not be attributable to difference in doxorubicin dose. There was no difference between countries in OS at five years for stage IV patients, suggesting that Japanese patients more successfully salvaged. Further studies with clinical details, including first-line use of radiotherapy and salvage therapy, are needed to understand the reasons for this.

Among the recently diagnosed cases from both countries combined, female sex, stage IV, and anaplastic histology were significantly associated with higher risk of death in the multivariable analysis. Most of these factors have already been identified as indicators of poorer prognosis[18]; however, we found for the first time that female patients have significantly higher risk of death than male patients. Subgroup analysis showed the sex difference in risk of OS was only significant in the UK. There are no significant sex differences in characteristics between the countries. Thus, the reason for the higher risk of death in females remains unknown, and further studies such as genetic investigation or cause of death focusing on sex difference may be needed.

From the viewpoint of the cancer care system, we calculated the total number of patients treated by each hospital in each country throughout the period for which such data were collected. Between 2005 and 2015, 769 patients with WT were treated in 20 hospitals in the UK, while in Japan 307 patients were treated in 77 hospitals. We found that only four hospitals in Japan managed over 10 cases during an 11-year period and even patients with higher risk disease such as those with stage IV were not centralized. Gatta et al. reported that five-year survival was significantly better when primary treatment was given in high-volume hospitals compared with low-volume hospitals for childhood cancers.[24] In the UK, the national guidance for cancer services for children and young people was published in 2005 and recommends standards to be met by "principal treatment centers" for childhood cancer.[25] Prior to this, there was already an established network of only 22 specialized hospitals, now reduced to 20 centers to which nearly all childhood patients with cancer in the UK are referred.[14] In Japan, the second cancer control plan first raised the issue of care for children and young patients with cancer in 2012[14] and 15 hospitals have been designated as childhood cancer care hospitals that met the criteria including "experience in treating more than 30 children with cancer per year." Although survival probability did not differ by patient numbers per hospital in Japan in our study, a report from Germany showed that the rate of intraoperative rupture increased in less experienced hospitals.[26] Given that Japanese patients are actually treated in many hospitals and there is clearly less experience in each hospital than in the UK, the centralization of treatment of patients may have to be considered in Japan.

The strength of our study is that it provides direct comparisons of characteristics of WT between countries over a long-term period, using data with clinical information that is not collected in population-based cancer registries. We were able to calculate the proportion of congenital abnormalities, stage distribution, tumor size, tumor histology, and EFS in each country and compare them between countries. Despite this strength, our denominator data sets are not completely population-based. Hence, the population studied may be somewhat biased, particularly for the Japanese data. The criteria for stage, for diagnosis of congenital abnormalities, and treatment strategies were not identical across countries and have also evolved over the nearly 20-year time period. Although a central pathology review was performed for 93% of cases in the UKW3, 100% of cases in other studies in the UK,[27] and an estimated 72% of cases in Japan,[8,9] the quality of pathological review might not be the same between countries or studies and an international review is needed for more reliable comparisons. There is a lack of information on patients' ethnicities, the genetic characteristics of the tumor, site of recurrence, treatment information such as radiation doses, and long-term follow-up data for more than five years. Assessment of long-term survivors regarding renal function and quality of life is also essential for future studies. In addition, because WT is a very rare disease, prospective, international comparative studies should be introduced to compare the genetic variation of WT directly between countries or ethnicities.

The Renal Tumour Study Group of the International Society of Paediatric Oncology (SIOP-RTSG) has developed a new protocol for the diagnosis and treatment of renal tumors in children, the UMBRELLA SIOP-RTSG 2016 (the UMBRELLA study), to conduct international collaboration in the treatment of renal tumors in children.[28] Several Asian

countries, including Japan, plan to join this study. We expect to obtain more reliable and adequate results through such international joint research in the future.

5 | CONCLUSIONS

In this study, we assessed the clinical characteristics and outcomes of patients with WT in the UK and Japan over a 20-year period. Japanese patients had significantly younger median age at diagnosis. The proportion of patients with stage IV, large tumors, and anaplastic histology appears to be higher in the UK than in Japan. Survival prognosis of most patients was favorable in both countries; however, five-year EFS of patients with stage IV was significantly lower in Japan than in the UK. Female, stage IV, and anaplastic WT were still significantly associated with higher risk of death among recent cases in both countries. Prospective, international clinical studies including genomic analyses are needed to confirm these findings and identify their causes.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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