

## Wilms' tumour in Malaysian children: a histopathological study of cases encountered at the University Hospital, Kuala Lumpur over a 22-year period

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### Abstract

Formerly thought to have a constant incidence rate throughout the world, Wilms' tumour (nephroblastoma) has been shown to be less common among Asian children. A retrospective demographic and morphological study of Wilms' tumour histologically diagnosed over a 22-year period at the Department of Pathology, University Hospital, Kuala Lumpur was conducted to assess for inherent demographic and morphological differences between tumours in Malaysian children and those of Western populations.

Thirty-seven cases of histologically proven Wilms' tumour qualified for inclusion in this study. 19 patients were Chinese, 13 Malay, 4 Indian and 1 Anglo-asian. 21 were male and 16 were female (M:F ratio = 1.3:1). Their ages ranged from 1 month to 4 years. 70.3% of the patients were below 2 years of age. 36 cases had unilateral and 1 bilateral tumours. Of unilateral tumours, 19 involved the left kidney and 17 the right. Histological assessment, based on criteria of the National Wilms' Tumor Study Group, revealed 20 (52.6%) tumours with a mixed pattern while 8 (21.1%) showed epithelial, 7 (18.4%) blastemal and 3 (7.8%) stromal-predominant patterns. Anaplasia was observed in only 2 tumours (5.3%).

There was no obvious difference in age range and sex distribution, laterality of tumours and incidence of anaplasia between this and Western studies. No ethnic predilection was observed. A notably larger percentage of cases were below 2 years of age. Also, a larger proportion of epithelial-predominant and a lower proportion of blastemal-predominant tumours was observed compared with patterns reported from Western populations.

*Key words:* Wilms' tumour, nephroblastoma, childhood tumour.

### INTRODUCTION

Wilms' tumour or nephroblastoma, is generally ranked among the five most common solid malignancies of childhood.<sup>1</sup> On the basis of cancer data from five continents, Innis in 1972<sup>2</sup> proposed that Wilms' tumour be regarded as an "index tumour," its relatively constant worldwide incidence rate allowing its usage as a common denominator in ratio studies of tumours from various countries. However, recent studies have shown a lower incidence among Asians. Breslow and Langholz reported that Wilms' tumour incidence rates among the Japanese, Singapore Chinese and Indians were approximately 60% of those among North Americans and the British.<sup>3</sup> Stiller and Parkin observed a similar trend in a worldwide study of childhood cancer incidence involving 50 countries.<sup>4</sup> In view of the lower incidence of Wilms' tumour among Asian children, including those living in the West,

workers have postulated that genetic constitution plays a predominant role in its aetiology.<sup>4,5</sup> Taking this into account, we were interested to know whether Wilms' tumour encountered in Malaysia, a country with a multiethnic background, expressed any inherent demographic or morphological difference from those occurring in children elsewhere. To this end, we conducted a retrospective study of all cases of Wilms' tumour diagnosed histologically in the Department of Pathology, University Hospital, Kuala Lumpur over the 22-year period from January 1968 to December 1989. Whenever applicable, the published observations of large western series, primarily those of the National Wilms' Tumour Study (NWTS) Group, were used for comparison. We believe that this is the first study of its kind in a Malaysian population.

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## MATERIALS AND METHODS

Records of all Wilms' tumour cases filed at the Department of Pathology, University Hospital, Kuala Lumpur over the 22-year period from January 1968 to December 1989 were retrieved. Information pertaining to the age, sex, race, macroscopical features, laterality, and the number of blocks sampled for each tumour were obtained from the anatomical pathology reports of the cases. Macroscopical variables noted were (1) number of tumour nodules, (2) maximum tumour dimension, (3) haemorrhage, (4) necrosis, (5) cystic change, and (6) tumour capsule rupture or penetration.

Using an Olympus BHS binocular microscope, all available histological sections were reviewed. Whenever necessary, re-cuts from the paraffin blocks were made. For a case to be admissible at least 1 cm<sup>2</sup> of viable tumour tissue had to be seen in the microscopical sections. Haematoxylin and eosin stained sections were primarily used in the histological assessment. Occasionally, phosphotungstic acid haematoxylin (PTAH) staining was used to confirm the presence of cross striations (Fig.1). The tumours were histologically assessed for the

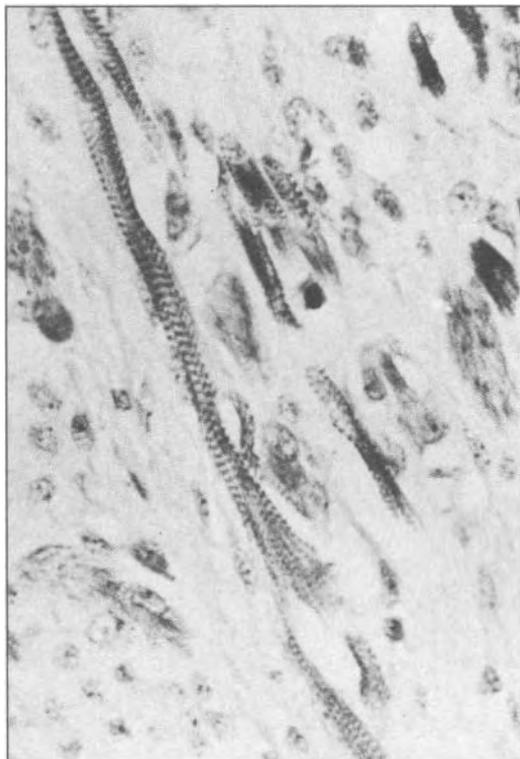


FIG.1: Rhabdomyomatous differentiation of the stromal cells. Cross striations are easily seen in this case. PTAH X 500

presence of (1) epithelial elements i.e. tubular, glomeruloid and papillary structures, (2) stromal elements, whether undifferentiated i.e. resembling fibroblasts or differentiated along a particular mesenchymal cell line, (3) blastema, (4) anaplasia, whether focal or diffuse, and (5) predominant tumour pattern. In the histological assessment, particularly in areas of histological controversy, the NWTS criteria<sup>6</sup> were adhered to. In differentiating a blastemal cell from an undifferentiated stromal cell, the ratio of its nuclear length to diameter was considered. If the ratio exceeded 3 : 1, the cell was classified as "stromal" and vice versa. Anaplasia was considered to be present when all three of the following were seen i.e (1) cells with a nuclear diameter at least 3 times that of adjacent nuclei of the same cell type, (2) hyperchromatism of the enlarged nuclei and (3) abnormal, usually multipolar, mitotic figures. The scoring of anaplasia as "diffuse" or "focal" depended on whether more or less than 10% of microscopical fields respectively, examined at high dry magnification, were involved by the anaplastic change. The proportion of epithelial, stromal or blastemal tissue within the viable tumour determined the predominant tumour pattern. If one component was identified in 65% or more of the tumour, it was categorised as being predominant for that component. Tumours which showed no predominant component were classified as "mixed." Demographic data was obtained from case records. Cases of clear cell sarcoma of the kidney, malignant rhabdoid tumour, and extra-renal Wilms' tumour were excluded from this study.

## RESULTS

Thirty seven cases of Wilms' tumour were entered into this study. A 7-year-old boy, diagnosed on core needle biopsy, was excluded because of inadequate material for histological assessment.

### Demographic data

Table 1 summarises the demographic profile of the cases. 19 patients were Chinese, 13 Malay, 4 Indian and 1 Anglo-asian. 21 patients were male while 16 were female (male:female ratio = 1.3:1). The patients' ages ranged from 1 month to 4 years, with 26 (70.3%) patients under 2 years of age.

**TABLE 1: Demographic profile of Wilms' tumour (n = 37)**

<b>Race:</b>	Chinese	19
	Malay	13
	Indian	4
	Others	1
<b>Sex:</b>	Male	21
	Female	16
	M:F	1.3: 1
<b>Age range:</b> 1 month - 4 years		

**Laterality of tumours**

19 children had tumours arising solely from the left kidney and 17 the right. One patient, a 3-year-old girl, had bilateral Wilms' tumours. Of the 38 Wilms' tumours studied, 32 manifested as single nodules while 2 were multicentric. Information on the number of tumour nodules was not available for the remaining 4. One of the 2 multicentric tumours occurred in a kidney of the patient with bilateral Wilms' tumour while the other occurred in a 1-year-old boy.

**Macroscopical features**

No documentation of maximum tumour diameters was available in 16 tumours. For the remaining 22, the largest diameter was 25 cm while the smallest was 4.5 cm. Table 2 shows the distribution of haemorrhage, necrosis, cystic change and tumour capsular breach or rupture observed macroscopically.

**Microscopical features**

A minimum of 2 and a maximum of 17 blocks were sampled from the tumours. The main

**TABLE 2: Macroscopical features of Wilms' tumour (n = 38)**

	Present	?
Haemorrhage	20 (53)	18 (47)
Necrosis	19 (50)	19 (50)
Cystic change	6 (16)	32 (84)
Tumour capsule rupture/penetration	6 (16)	24 (63)

? = The presence of haemorrhage, necrosis and cystic change was not definitely determined in the numbers represented in this column.

histological components of the tumours are shown in Table 3. Except for one, all the tumours were triphasic (Fig. 2). Diffuse anaplasia of the stromal component was observed in a unilateral tumour arising in a 4-year-old girl while focal anaplasia was seen in the right sided lesion of the case of bilateral Wilms' tumour (Fig. 3). 8 tumours showed epithelial predominance, 7 were predominantly blastemal and 3 stromal. 20 had a "mixed" pattern.

**TABLE 3: Main histological components of Wilms' tumour (n=38)**

	No. present (%)
<b>Epithelial</b>	
tubules	36 (95)
glomeruloid structures	14 (37)
papillary structures	3 (8)
<b>Stromal</b>	
undifferentiated	37 (97)
skeletal muscle	8 (21)
chondroid	1 (3)
osteoid	0 (0)
<b>Blastema</b>	37(97)

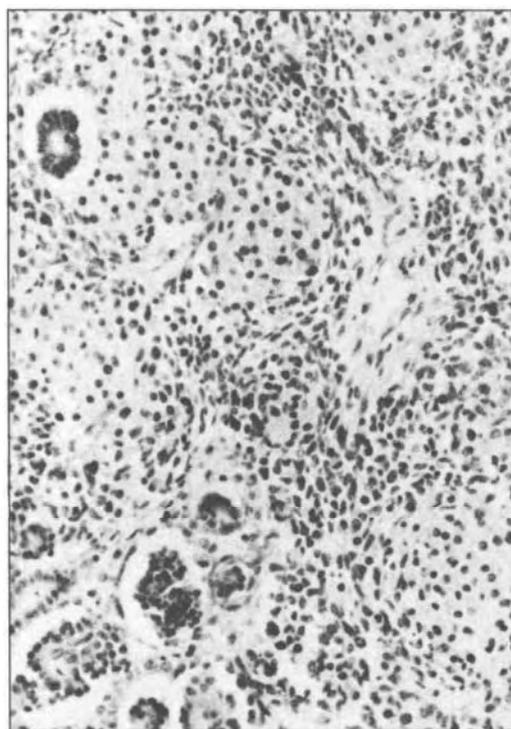


FIG.2. Wilms' tumour exhibiting a classical triphasic pattern. Immature tubules, abortive glomeruloid structures, stroma and blastema are seen in the same field. H+E X 300

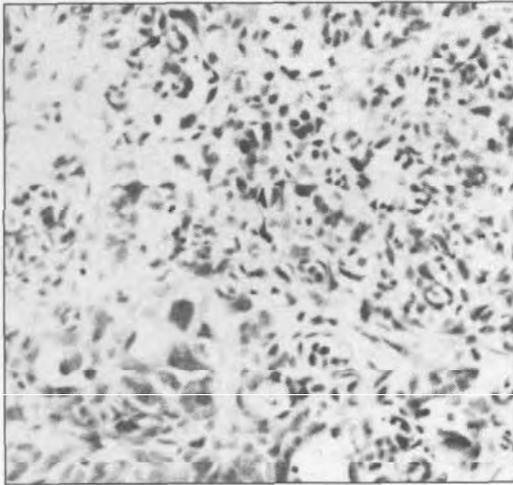


FIG.3. A focus of anaplasia is seen on the lower left corner, with enlargement of the cellular nuclei. The enlargement is easily appreciated by comparing with the nuclei of cells in the upper right corner. H+E X 300

## DISCUSSION

51% of Wilms' tumour occurred among the Chinese, 35% Malay, 11% Indian and 2% other minority ethnic groups. Over the same period, the ethnic distribution of paediatric admissions to the University Hospital was 45% Chinese, 29% Malay, 25% Indian and 2% other minority ethnic groups. Although ethnic predisposition cannot be confidently analysed due to the limited number of cases, the racial distribution observed in this study does not appear to show any significant ethnic predilection of Wilms' tumour.

The slight male preponderance (M:F ratio of 1.3:1) observed in this study is similar to that (M:F ratio of 1.4:1) observed by Stiller and Parkin among East Asians but is also not grossly dissimilar to M:F ratios ranging from 0.8:1 to 1.3:1 in most other large series from different parts of the world.<sup>4</sup> The significance of this marginal male preponderance is not clear.

The age range of our patients (1 month to 4 years) parallels the peak age range usually observed for Wilms' tumour.<sup>1</sup> The oldest Wilms' tumour case in our records, a 7-year-old boy, was however excluded from this study. Mean age could not be calculated due to inconsistencies in age charting, some being recorded to the nearest year while others were in exact months.

About 5 to 6% of Wilms' tumour are said to be bilateral at the time of original diagnosis.<sup>7,8</sup> In contrast, only one case of synchronous bilat-

eral tumours was observed in this study giving a ratio of 2.7%. In view of the small number of cases in this study, the lower frequency of bilateral tumours cannot be inferred to represent a true rate. It is not unexpected that multicentricity was observed in one of the two involved kidneys of this case with bilateral tumour involvement, as multicentricity is often associated with bilaterality.

Of unilateral tumours in this study, 51.3% involved the left while 45.9% the right kidney. These figures correspond with Schmidt's which showed that 50% of unilateral Wilms' tumour involved the left while 45% involved the right.<sup>8</sup> Breslow *et al.* also noted a predominance of left sided tumours (51.4%) in 632 cases entered into the Second National Wilms' Tumor Study.<sup>9</sup> These findings suggest that the left kidney carries a higher risk for development of Wilms' tumour. The role of tumour laterality in the pathogenesis of Wilms' tumour needs further clarification although it is believed to be unimportant in prognosis.<sup>9</sup>

The macroscopical features of the tumours were poorly documented. The large number of cases in which no mention was made in the original histopathology report regarding the maximum tumour diameters (42%) and presence of haemorrhage (47%), necrosis (50%), cystic change (84%) and tumour capsular penetration or rupture (63%) precludes any reliable interpretation of the results.

Data derived from Beckwith and Palmer's paper,<sup>6</sup> indicates that 11.5% of the Wilms' tumours in the First National Wilms' Tumor Study (NWTS-I) were epithelial-predominant, 23.2% blastemal-predominant and 6.1% stromal-predominant. A mixed pattern was seen in the majority (59.2%). In our study, 52.6% of the tumours exhibited a mixed pattern, while 21.1% were epithelial-predominant, 18.4% blastemal-predominant and 7.8% stromal-predominant in pattern. Epithelial and stromal-predominant tumours occurred more frequently while blastemal-predominant and mixed tumours were less commonly found in our study compared with the NWTS-1. It should be pointed out that in 1978 when Beckwith and Palmer published their study, the definition of a "stromal" pattern was still unsettled. Undoubtedly, some cases classified then as stromal predominant Wilms' tumour would now be categorised, in the light of current histological criteria, into entities such as clear cell sarcoma of the kidney, malignant rhabdoid tumour or cellular mesoblastic nephroma, making the prevalence of stromal-predominant

tumours lower than the original figure of 6.1%. In our study, cases with the above lesions were automatically excluded during retrieval of cases or at review of the histopathology. Hence the prevalence figure of 7.8% for stromal-predominant tumours observed in our study probably exceeds that of the NWTS-1 by a wider margin than is present in reality. On analysing the files of the Paediatric Tumor Registry in Kiel, Schmidt also noted more stromal-predominant and less mixed tumours than the NWTS group.<sup>8</sup> However both the NWTS and Kiel Paediatric Tumor Registry had a lower proportion of epithelial-predominant and more blastemal-predominant tumours than our study. It is of note that epithelial-predominant tumours were observed by Beckwith and Palmer to occur more frequently among children under 2 years of age in the NWTS-1.<sup>6</sup> It is therefore interesting that 70.3% of our patients were below 2 years of age. In comparison, the majority of cases in the NWTS-1 were above 2 years of age and only 31.2% below. This difference in age composition has to be considered in the interpretation of the larger proportion of epithelial-predominant tumours seen in this study. Nonetheless, it remains uncertain whether any significance should be attached to the differences in histological patterns. Studies correlating these patterns with clinical outcome, treatment response and survival rates may cast some light on this question.

Anaplasia, as defined by the NWTS criteria, was observed in 5.3% of tumours in this study. This is intermediate between the figure of 4% reported in the NWTS-3<sup>7</sup> and 6.1% by Harms *et al.*<sup>10</sup> Anaplasia, whether focal or diffuse, is now known to be one of the most important ominous prognostic factors in Wilms' tumour, except when found in Stage I tumours. It usually occurs in older children, beyond the age of 2 years and is more commonly seen in girls." Interestingly, in our study, both cases of Wilms' tumour exhibiting anaplasia occurred in girls, one 3 years of age and the other 4 years of age. In view of the importance of anaplasia in the histological evaluation of Wilms' tumour, we re-emphasise the need for adequate sampling of the tumour. This is particularly important because anaplasia can occur in localized foci in the tumour.

In summary, this study shows that there was no major noticeable difference in the age range and sex distribution of patients, tumour laterality and incidence of anaplasia from that of Western

populations. The most notable differences observed in comparison with Western studies was the higher percentage of cases under 2 years of age and the larger proportion of epithelial-predominant and lower proportion of blastemal-predominant tumour patterns.

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