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ORIGINAL ARTICLE

Botryoid Wilms tumor: a non-existent "entity" causing diagnostic and staging difficulties

Gordan M. Vujanić[1] · Marco Schiavo Lena[2] · Neil J. Sebire[3]

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Abstract

Wilms tumors growing in a botryoid fashion into the renal pelvis have been reported since the 1960s as a rare tumor type usually associated with stromal histology and a good prognosis. However, the true frequency, association with Wilms tumor subtypes, and stage have never been comprehensively studied. We analyzed all Wilms tumors enrolled into the International Society of Paediatric Oncology (SIOP) United Kingdom 2001 Trial (2001–2011), which showed botryoid growth. In addition, we reviewed published series reporting papers on botryoid Wilms tumors. 77/739 patients (10.4%) showed at least one Wilms tumor with a botryoid pattern, and they were sub-classified according to the SIOP criteria as follows: 28 stromal, 21 mixed, 7 regressive, 3 completely necrotic, 4 blastemal, 2 epithelial, 3 diffuse anaplasia, 1 focal anaplasia, and 10 non-anaplastic type (treated with primary surgery). Stage was as follows: 25 stage I, 21 stage II, 12 stage III, 11 stage IV, and 8 stage V. In six cases, local pathologists incorrectly upstaged the tumor from stage I to stage II based on botryoid growth. The event-free and overall survivals were 90 and 96%, respectively. We concluded that botryoid growth pattern is a common finding in Wilms tumor and that all histological types and stages can share this feature. The botryoid growth itself is not a criterion for stage II. Botryoid Wilms tumor is not an entity but merely represents a pattern of tumor growth; such tumors should be sub-classified according to their overall histological features, which will determine treatment and prognosis.

Keywords Wilms tumor · Botryoid growth · Non-existent subtype

Introduction

Wilms tumor is the most common renal tumor of childhood, representing ~90% of all renal tumors up to 15 years of age. Patients are treated according to one of two major protocols, the Children's Oncology Group (COG, which incorporated the National Wilms Tumor Study Group), in which primary surgery is followed by postoperative chemotherapy and, in indicated cases, radiotherapy, or the International Society of Paediatric Oncology (SIOP), in which treatment includes preoperative chemotherapy followed by chemotherapy and radiotherapy, if necessary [1]. The prognosis for patients with Wilms tumor is generally excellent and depends on histological type and stage [1].

"Botryoid" is a descriptive term used for tumors with a lobular "grape-like" appearance gross pattern growing in a polypoid fashion into the lumen. Botryoid rhabdomyosarcoma, which refers to such tumors protruding into mucosa-lined hollow organs (such as bladder, uterus/vagina, biliary tree), is a typical example; and for a long time, it was regarded as a tumor type with superior prognosis, but in the latest World Health Organization classification, it was classified with other embryonal rhabdomyosarcomas as a tumor of an intermediate risk [2].

In 1981, the term "botryoid Wilms tumor" was introduced to describe a specific growth pattern of Wilms tumor [3], and since then, numerous cases have been reported claiming it to be a separate subtype of Wilms tumor with better prognosis. However, botryoid Wilms tumor is not recognized as a separate type of Wilms tumor in the two major renal tumor study groups, COG and SIOP [1].

The aim of this study was to establish the frequency of "botryoid" Wilms tumor, which histological types of Wilms

✉ Gordan M. Vujanić
gvujanic@sidra.org

[1] Department of Pathology, Sidra Medicine, H2M Pathology Room 2MF 140, Al Luqta Street, Doha, Qatar

[2] Department of Pathology, Ospitale San Raffaele, Milan, Italy

[3] Department of Histopathology, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London, UK

tumor are associated with a botryoid growth pattern, and whether or not botryoid Wilms tumor has a better prognosis. Literature was also reviewed to ascertain the clinico-pathologic features of published cases of botryoid Wilms tumor.

Materials and method

Patients

The SIOP UK WT 2001 trial was a United Kingdom (UK) multicenter study that was a part of the SIOP WT 2001 trial, which registered patients with renal tumors from all pediatric primary cancer treatment centers in the UK and Ireland (841 cases) (and in addition included a few patients from centers in New Zealand (six cases) and Australia (two cases)). Informed consent was provided for all participants. Patients were initially treated with primary surgery or preoperative chemotherapy (4 weeks with two drugs for localized tumors and 6 weeks with three drugs for metastatic tumors at presentation), followed by surgery and further chemo- and radiotherapy, if necessary, as per SIOP WT 2001 protocol [1].

Inclusion criteria

The study included the patients who fulfilled the following criteria: (a) diagnosed pre- or postoperatively as having intrarenal Wilms tumor; (b) had total and/or partial nephrectomy; and (c) tumors reviewed by the UK Renal Tumor Pathology Panel.

Histological review

A retrospective analysis of institutional and central pathology reviewer's reports was performed to identify cases in which the term botryoid was mentioned on either gross or histological examination and slides of such cases re-reviewed. All registered cases were sampled according to the SIOP 2001 Trial Pathology protocol [4] and submitted for central pathology review for diagnosis, classification, and staging [4], performed by the Children's Cancer and Leukaemia Group (CCLG) Renal Tumor Pathology Panel (chaired by one of the authors, GMV). Each case included a full set of histological slides. Cases were also reviewed by the SIOP Renal Tumor Pathology Panel. The number of slides submitted varied from 6 to 78 (median 28), with only 3% of cases having fewer than 10 slides. In these cases, it was clearly stated that tumors were small and virtually completely sampled. Wilms tumors treated with preoperative chemotherapy were classified as low risk (completely necrotic tumors), intermediate risk (epithelial, stromal, mixed, regressive, focal anaplasia types), or high risk (blastemal or diffuse anaplasia type) as per the SIOP WT 2001 Classification [5]. Primarily operated tumors were classified as non-anaplastic and anaplastic Wilms tumors [5]. Where nephrogenic rests were present, they were classified as perilobar nephrogenic rests, intralobar nephrogenic rests, both/combined (perilobar and intralobar nephrogenic rests), and multiple nephrogenic rests—nephroblastomatosis.

The significance of differences in proportions of histological subtypes and outcomes between tumor subtypes was evaluated using comparison of proportions test (modified Chi-squared test) using StatsDirect software (Manchester, UK). In addition, a literature search was carried out using descriptive terms of botryoid Wilms tumor, fetal rhabdomyomatous nephroblastoma, and teratoid Wilms tumor.

Results

There were 739 patients with Wilms tumor registered in the study, of whom 77 patients (10.4%) had Wilms tumors showing botryoid growth pattern. The male-to-female distribution was not significantly different from the whole UKW3 Study group (Table 1). The median age at presentation for all Wilms tumor patients and those with botryoid Wilms tumor was

Table 1 Characteristics of patients with botryoid Wilms tumor in our series and the literatureCharacteristics

	Botryoid WTs		Overall WTs		Literature	
	($n = 77$)		($n = 739$)		($n = 35$)	
	No	%	No	%	No	%
Sex						
Male	41	53	345	47	24	71
Female	36	47	394	53*	10	29
Unknown					1	
Age at diagnosis (months)						
Median	39		39		24	
Range	4–172		1–189		4–108	
Side						
Right	29				17	
Left	40				14	
Bilateral	8				2	
Extra-renal	–				1	
Not stated	–				1	
Stage						
I	25	32	–		4	25
II	21	27	–		7	44
III	12	16	–		3	19
IV	11	14	–		–	
V	8	10	–		2	12

*$Z = 1.22$, $P = 0.22$

39 months. One patient with botryoid Wilms tumor had Denys-Drash syndrome.

Of the 77 patients, 69 had unilateral disease only, and eight had bilateral disease (including six with bilateral Wilms tumor and two with Wilms tumor in one kidney and nephrogenic rests in the contralateral kidney). Two out of six patients with bilateral Wilms tumor showed botryoid features in both kidney tumors, giving a total of 79 tumors with botryoid features in the current study.

Wilms tumors showing botryoid growth (Fig. 1a–c) were histologically sub-classified as stromal—28 (including 17 cases of fetal rhabdomyomatous nephroblastoma), mixed—21; regressive—7; blastemal—4; completely necrotic—3; epithelial—2; diffuse anaplasia—3; focal anaplasia—1, and non-anaplastic (no preoperative-chemoterapy)—10 cases. In 26/79 (33%) patients, tumor extended down the ureter's lumen, but without infiltration of its wall (Fig. 1d–e). In one patient, tumor reached the urinary bladder but, again, without infiltration of its wall. There was a significantly greater proportion of stromal type ($Z = 6.64$, $P < 0.0001$) and lower proportion of regressive type ($Z = -5.2$, $P < 0.0001$) tumors in the Wilms tumors showing botryoid growth compared to the overall Wilms tumor population.

The stage distribution is shown in Table 1. In six patients, the institutional pathologists assigned tumors as stage 2 because of the botryoid growth alone—they were down-staged to stage 1 on central pathology review.

Nephrogenic rests were found in 38/79 (48%) tumors, including intralobar nephrogenic rests in 22 (in eight cases the intralobar nephrogenic rests accounted for the botryoid growth itself) (Fig. 1f), perilobar nephrogenic rests in 12, and both intra- and perilobar nephrogenic rests in four tumors.

Ten patients underwent primary nephrectomy due to young age, cystic nature of the lesion on imaging studies, sudden bleeding, and unknown indication. All other patients (67 in total) underwent tumor biopsy, followed by preoperative chemotherapy and surgery. Postoperative treatment was given according to tumor's type and stage, as per SIOP Wilms Tumour 2001 protocol. Surgery was total nephrectomy in 74 patients; in one patient, it was partial nephrectomy; in one, double partial nephrectomy; and in one, a resection of the isthmus in a horseshoe kidney was done.

Out of 77 patients, 69 (90%) were alive and with no evidence of disease on a long follow-up (from 6 to 15 years, median 10 years) (Table 2). There were five (7%) patients who relapsed, but after the relapse treatment, they were alive and

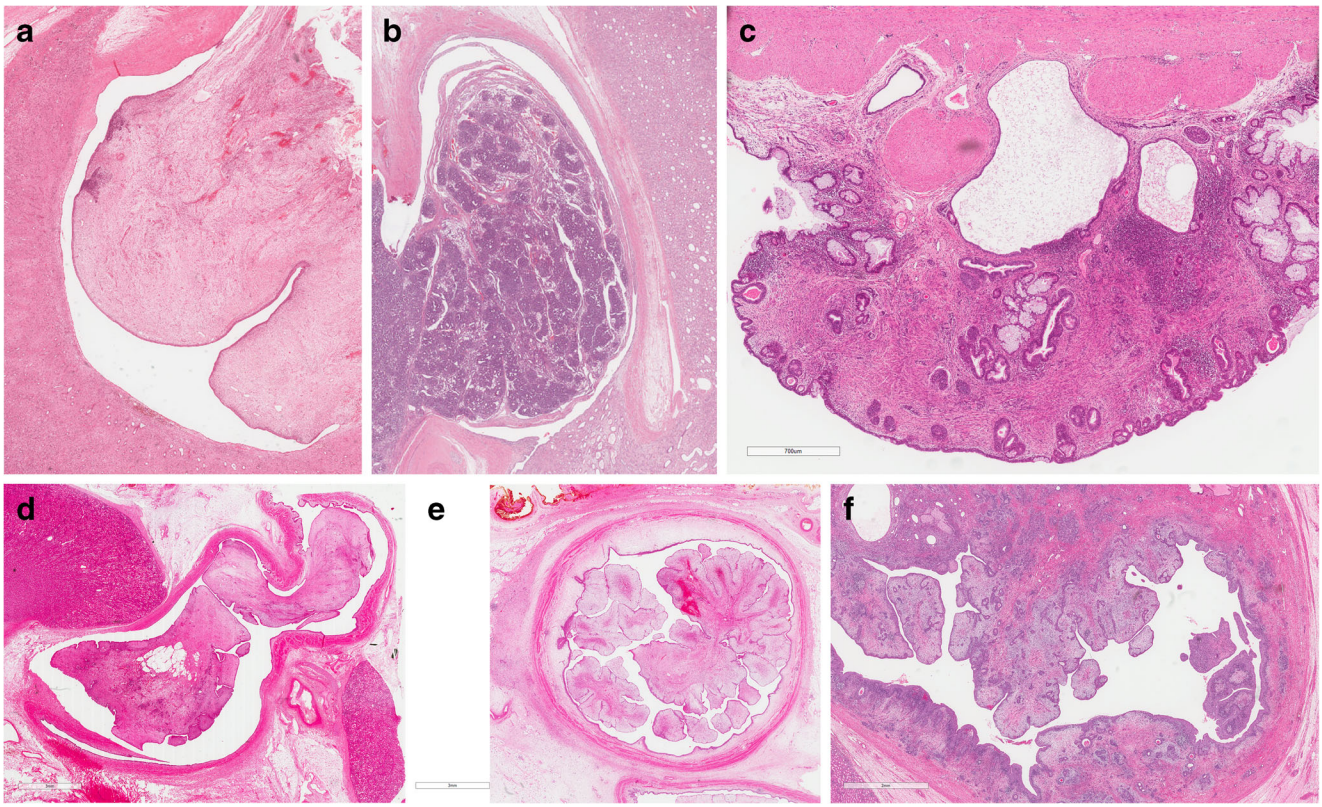

Fig. 1 Botryoid growth of Wilms tumor stromal type (**a**), blastemal type (**b**), and mixed type showing "teratoid" features (**c**). Tumor is occupying the renal pelvis and extending into the distal ureter (**d**) or further down the ureter (**e**). Intralobar nephrogenic rest shows intrapelvic, botryoid growth pattern (**f**)

Table 2 Outcome of patients in the current series and in the published cases

Outcome	Present series		Published series	
	No	%	No	%
Lost to follow-up	–	–	8	23
Alive and without evidence of disease	69	90	23	85
Relapse and alive	5	7	1	4
Relapse + metastases, lost to follow-up	–	–	1	4
Relapsed and died	3	4	–	–
Died	–	–	2	7
Total	77	100	35	100

with no evidence of disease and 3 (4%) who relapsed and died (Table 3). There was no difference in overall outcome between the botryoid and non-botryoid cases ($Z = 1.44$, $P = 0.15$).

Literature review

Literature review revealed a heterogeneous collection of publications over a 50-year timeframe (1968–2017), from different clinical specialties (radiologists, surgeons, pathologists), approaches, and scopes. Botryoid Wilms tumor growth was mentioned within series of fetal rhabdomyomatous nephroblastoma, but often, the definition of botryoid tumors was not clearly defined, so their features could not be included in the review.

To our knowledge, the term botryoid was used for the first time referring to kidney tumors by Harbaugh in 1968 [6], for a neoplasm growing into the renal pelvis. It showed prominent rhabdomyomatous differentiation, and at that time, it was considered to be a sarcoma.

In total, 35 patients were reported from different countries/regions (Table 4), with Asia (17) and the USA (9 patients) being the most common ones [7–36]. The main characteristics are summarized in Tables 1 and 4. Two Japanese children had Wilms tumor-Aniridia-Growth Restriction (WAGR) syndrome [17, 24].

Histological type of Wilms tumor was not mentioned in all cases, or they were classified as classic, triphasic Wilms tumors not further specified, but in 9/28 (32%) tumors, the presence of rhabdomyoblasts was mentioned and six tumors were labeled as fetal rhabdomyomatous nephroblastoma. In one case, anaplastic Wilms tumor was diagnosed [31]. In 17/35 (49%) cases, tumor extended into the ureter, and in five cases, it reached the bladder. Even in cases with stated stage, it was not always possible to understand the reason for staging, and in six cases, it appeared that botryoid growth alone was the reason for stage 2 or even stage 3 [12, 25, 27, 28, 33, 35]. Nephrogenic rests were reported in eight cases, all intralobar nephrogenic rests, but in three cases, the authors were not absolutely certain whether or not they were genuinely present. For example, figures in Mahoney et al. case [3] suggest intralobar nephrogenic rests showing botryoid growth, rather than botryoid sarcoma as it was called in the paper, although the authors considered a possibility of these structures being Wilms "tumorlets"—the term which in the past was used to describe some types of nephrogenic rests.

The patients were treated differently, depending on the protocols followed in their countries (Table 4). Primary surgery was carried out in 25 patients followed by no further treatment in one patient [20], chemotherapy in 17 patients, and chemotherapy and radiotherapy in six patients (unknown postoperative treatment in one patient). Only two patients were treated with preoperative chemotherapy followed by chemotherapy (one patient) and chemotherapy and radiotherapy (one patient).

Follow-up was available in 28/35 patients. One patient died postoperative due to pneumonia [13] and the other one due to renal failure following bilateral nephrectomy [33]. Two patients had ureteral and ureteral and bladder recurrences, respectively [7, 9], and one developed abdominal metastases 1 year after that and was lost to follow up afterwards [9]. The other one was doing well 2 years after further treatment. Twenty-four patients were disease free on the follow-up

Table 3 Relapsed "botryoid" Wilms tumors in the current series

Type	Age (mo)	Stage	Reason for staging	Outcome
Epithelial	16	1		Relapse, NED after treatment
Mixed	44	2	Sinus invasion	Relapse, NED after treatment
Mixed	48	3	IVC thrombus*	Relapse, NED after treatment
Regressive	44	4 (3)	LN metastases, viable	Relapse, NED after treatment
Stromal	17	5 (1)		Relapse, NED after treatment
Mixed	44	1		Relapse, died
Stromal	45	4 (3)	D.A. in lung metastasis**	Relapse, died
Blastemal	75	3	LN metastases, viable	Relapse, died

*IVC = inferior vena cava, piecemeal removal

**Progressed on treatment, lung metastasis removed, showed diffuse anaplasia

LN = lymph node; NED = no evidence of disease; D.A. = diffuse anaplasia

Table 4 Botryoid Wilms tumors reported in the literature

Author (first)/year	Country	Age	Sex	Side	NRs	Stage	Histology	Follow-up	Treatment
Harbaugh/1968 [6]	USA	84	F	L		NS	Original diagnosis: E-RMS	NED, 10 months	NS
Reziciner/1970 [7]	France	72	M	R		NS	Triphasic (rhabdomyomatous)	Ureteral relapse after 3 months, NED, 2 years	S + Cx
Taykurt/1972 [8]	Turkey	60	NS	L		NS	Triphasic	No FU	NS
Pagano/1974 [9]	Italy	72	M	L		NS	Triphasic	Ureteral and bladder recurrence, then met 1 year later	S + Cx + Rx
Engel/1976 [10]	USA	56	F	R		NS	Triphasic	No FU	NS
Wicklund/1980 [11]	USA	15	M	L		NS	/	NED, 2 years	S + Cx + Rx
Chiba/1980 [12]	Japan	18	F	L		NS	/	No FU	S + Cx + Rx
Mahoney/1981 [3]	USA	12	M	L	ILNR	NS	> 90% rhabdomyomatous	NED, 29 months	S + Cx
Eble/1983 [13]	USA	40	F	R	ILNR?	NS	> 90% rhabdomyomatous	Postoperative death (pneumonia)	NS
Weinberg/1984 [14]	USA	9	F	R		NS	Triphasic (rhabdomyoblasts+)	NED, 4 years	NS
Tunali/1987 [15]	Turkey	48	M	L		I	Triphasic + scattered foci of rhabdomyoblasts	No FU	S + ?
Johnson/1987 [16]	USA	96	M	R		II	/	No FU	NS
Kabayashi/1990 [17]	Japan	19	M	NS	ILNR	I	Triphasic	No FU	NS
Fu/1992 [18]	China	24	F	L		NS	Mixed	NED, 2 years	S + Cx
Losty/1993 [19]	Ireland	12	M	R		NS	/	NED, 3 months	S + Cx
Niu/1993 [20]	China	4	M	L		II	Blastema + epithelial	NED, 2 years	S
“ ”	China	108	M	R		NS	Blastema + epithelial	NED, 10 months	S + Cx
Groeneveld/1995 [21]	The Netherlands	24	M	R		NS	/	NED, 2 years	S + Cx
Mitchell/1997 [22]	USA	23	F	R	ILNR	II	> Blastema	NED, 9 months	S + Cx
Pawell/1998 [23]	USA	84	M	ER		I	Teratoid	NED, 18 months	S + Cx
Natsume/1999 [24]	Japan	31	F	R	ILNR?	NS	Triphasic	NED, 18 months	S + Cx
Honda/2000 [25]	Japan	12	M	R	ILNR?	NS	Triphasic	NED, 5 years	S + Cx
Gupta/2003 [26]	India	24	M	R		III	Triphasic	NED, 5 months	NS
Yanai/2005 [27]	Japan	36	M	R		III	Triphasic (rhabdomyoblasts+)	NED, 4 years	S + Cx + Rx
“ ”	Japan	24	M	R		II	Triphasic	NED, 9 months	S + Cx
Nagahara/2006 [28]	Japan	36	M	R		II	Triphasic (rhabdomyoblats+)	NED, 10 months	S + Cx
Wang/2006 [29]	Taiwan	22	M	L		NS	Triphasic	No FU	S + Cx
Lamalmi/2009 [30]	Morocco	14	M	R		III	Triphasic (rhabdomyomatous)	NED, 2 years	Cx + S + Cx + Rx
Basaran/2009 [31]	Turkey	48	F	L		I	Anaplastic	NED, 6 months	S + Cx
Mizuno/2010 [32]	Japan	36	M	L	ILNR	II	Hyperplastic ILNR	NED, 14 months	S + Cx
Tu/2011 [33]	China	24	M	BL		V	Triphasic	Died—renal failure after 6 months	S + Cx + Rx
“‘“	China	19	M	L		NS	Triphasic	No FU	S + Cx + Rx
Conlon/2012 [34]	Ireland	16	F	BL	ILNRs	V	Triphasic (rhabdomyoblasts+)	NED, 18 months	Cx + S + Cx

Table 4 (continued)

Author (first)/year	Country	Age	Sex	Side	NRs	Stage	Histology	Follow-up	Treatment
Xu/2013 [35]	China	48	M	R		II	Triphasic	NED, 24 months	S + Cx
Gao/2017 [36]	China	48	M	L		NS	/	NED, 6 months	S + Cx

NS = not stated; M = male; R = right; L = left; E-RMS = embryonal rhabdomyosarcoma; NED = no evidence of disease; FU = follow up; ILNR = intralobar nephrogenic rest; S = surgery; Cx = chemotherapy; Rx = radiotherapy

varying from 2 months to 6.5 years (in nine patients follow-up was less than 1 year).

Discussion

Although the term botryoid Wilms tumor was first used by Mahoney et al. in 1981 [3], an intrapelvic growth of Wilms tumor was reported preciously [6–12], especially in Wilms tumors labeled as fetal rhabdomyomatous nephroblastoma [37]. However, no publication clearly defined this alleged type by providing criteria, such as how much of the botryoid growth is required to make the diagnosis—any polypoid growth, exclusively polypoid tumor, or a combination of polypoid and parenchymal tumor. In the COG and SIOP classifications and terminology, the term botryoid Wilms tumor has never been used.

The present study demonstrated that botryoid growth in Wilms tumor is common, occurring in about 10% of cases. Epidemiological features, such as male to female ratio and age at presentation, were not significantly different between typical Wilms tumors and botryoid Wilms tumor. We found only one case of botryoid Wilms tumor associated with a syndrome (Denys-Drash syndrome), and there have been two further cases in the literature associated with WAGR syndrome [17, 25].

Unlike fetal rhabdomyomatous nephroblastoma which, allegedly, is bilateral in ~ 30% of cases, and not infrequently shows a botryoid growth (~ 20% of our and published cases were fetal rhabdomyomatous nephroblastoma), bilateral presentation of botryoid Wilms tumor was not a striking feature in our series or in the literature—10 and 6%, respectively.

The majority of botryoid Wilms tumors treated with preoperative chemotherapy in the current series were of stromal type (37% in total and 72% of them were fetal rhabdomyomatous nephroblastoma), but other subtypes were also represented, including mixed (28%) and regressive (9%) types as the most frequent ones. Interestingly, in high-risk tumors in SIOP classification, blastemal (5%) and diffuse anaplasia types (4%) were also associated with a botryoid growth—only one anaplastic botryoid Wilms tumor has been reported before, and it was not specified whether it was diffuse or focal anaplasia [31]. In our group of Wilms tumors treated with primary surgery, 10/25 (40%) of tumors showed botryoid growth and were histologically classified as non-anaplastic Wilms tumors.

Nephrogenic rests were found in a nearly half of botryoid Wilms tumors, similar to the frequency in the whole SIOP UK WT 2001 Study series [38]. Since intralobar nephrogenic rests are frequently found in the renal pelvis, it is not surprising that they were found more frequently than perilobar nephrogenic rests in botryoid Wilms tumors, and in 10% of cases, they were the only structure showing intrapelvic, botryoid growth. In the published papers, nephrogenic rests were found in 22% of cases

(some of which were not very convincing, judging by the figures in the papers), and in rare cases [32], they were responsible for a botryoid appearance. Yanai et al. suggested that botryoid Wilms tumors originate from these intralobar nephrogenic rests [27].

Since postoperative treatment depends on Wilms tumor's histological type and stage, it is critical to diagnose and stage tumors accurately. The staging issue in botryoid Wilms tumor has never been specifically addressed, and not all published papers mentioned which stage had been assessed and for what reason. In 17% of the reported cases, it seemed that the stage 2 or even stage 3 assignment was based upon the botryoid growth only [12, 25, 27, 28, 33, 35], as it was in 8% of tumors in the present series. In the earlier publications, the botryoid growth has been referred as "rupture into the collecting system" [11, 20]. This is misleading because a Wilms tumor growing in a botryoid fashion is usually not infiltrating the pelvic wall, so intrapelvic botryoid growth should not be regarded as renal sinus/pelvic invasion and a reason for upstaging a tumor. Even when tumor extends into the ureter and reaches the bladder without infiltrating the wall, as it was in one third of our cases and in over 50% of reported cases, it should still be regarded as stage 1 if completely excised. Genuine infiltration of the ureter wall is a rare event and has not been recorded in the NWTS study (0/45 cases) [39]. It is important to be aware of this growth when planning surgery. Distal ureteral and vesical relapses were reported in the past [7], but they are prevented by early ligation of the distal ureter before the tumor is manipulated [10, 26, 40].

The differential diagnosis between nephrogenic rests and Wilms tumor is particularly difficult in pure botryoid lesions without any parenchymal involvement. Intralobar nephrogenic rests were regarded as the only component of a botryoid growth in ~ 10% of our cases. There is clearly a continuum between nephrogenic rests and Wilms tumors, and it must be said that stringent, widely accepted, and reproducible criteria have not been provided yet and this distinction still relies upon subjective, more experience-based than evidence-based criteria.

While children in our study were treated according to the SIOP WT 2001 Trial and Study Protocol for pre-treated or primarily operated tumors, treatment given in the published cases varied significantly. Still, the outcomes were very good: the event-free survival in our series was ~ 90% and the overall survival as high as 96%, whereas in the published cases, the event-free and overall survival was lower (85 and 89%, respectively). However, two deaths in the published series were not due to tumor but due to postoperative pneumonia and renal failure secondary to bilateral nephrectomies [13, 33].

Conclusions

Botryoid Wilms tumor does not represent a distinct "entity" and has no distinguishing clinico-pathological features. Wilms tumors showing this growth pattern should be classified on the basis of their overall histological features. The term botryoid Wilms tumor is a descriptive term that should not be used in the final diagnosis, since it has no clinical or prognostic significance. It is a relatively common finding (found in ~ 10% of Wilms tumors in the present large series) and with the spectrum of Wilms tumor sub-types (from completely necrotic to diffuse anaplasia), but more commonly associated with stromal type Wilms tumors. Staging assignment may be difficult as some misinterpret intrapelvic, botryoid growth as evidence of tumor's invasion in the renal pelvis. The prognosis of these tumors depends on tumor's histological subtype and stage, rather than on the presence of botryoid growth.

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Author contributions G.M. Vujanic and N.J. Sebire reviewed all renal tumor cases originally, as part of their Panel's work. G.M. Vujanic then re-reviewed the cases included in the study together with M. Shiavo Lena, who identified the cases from the whole archive.

M. Schiavo Lena did the search of the literature, found and read the papers, and extracted the data we needed for the review.

G.M. Vujanic and M. Schiavo Lena prepared a first draft of the manuscript. It was then further discussed and improved in collaboration with N.J. Sebire. The final draft was approved by all three authors.

Compliance with ethical standards

All cases included in the present study were identified from the SIOP UK 2001 Trial and Study, which recruited patients in the UK, and for whose inclusion a full, informed consent has been obtained.

Conflict of interest The authors declare that there is no conflict of interest.

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