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REVIEW ARTICLE

Wilms' tumour – an update

John Lazarus and Lisa Kaestner

Abstract:

Wilms' Tumour accounts for 6% of all paediatric cancers. With modern multimodal therapy outcomes for patients is generally good (with an overall survival of >90%) and a reduction in treatment related morbidity. This review highlights recent developments risk stratification using histological grade and tumour stage. A rational approach to workup of these children is presented focusing on imaging interpretation. Management is discussed with emphasis on surgical technique and an update of chemotherapeutic strategies.

Keywords: Wilms tumor, children, diagnosis, therapy

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Introduction

Wilms' tumour (WT) or nephroblastoma is the commonest primary renal malignancy of childhood. WT survival rates of >90% can be expected today (compared with 30% in 1930) and are a testament to the success of collaborative trials and their use of multimodal therapy [1-3].

Unlike adult renal carcinomas, childhood renal tumours are largely of embryonic origin, have rapid growth and a better response to therapy. Emphasis now lies in reducing the morbidity of treatment in low-risk patients while reserving intensive treatment for high-risk patients where survival is still poor [4]. This paper aims to review recent advances in the understanding of WT's etiology, presentation, diagnosis and changing management strategies.

Epidemiology

The average age of presentation is 3.5 years. WT represents 6% of all childhood malignant tumours [5]. A family history is found in 1-2%. Black children have a 2,5 times increased incidence over their white counterparts. The sex ratio is close to 1 [1].

WT genetics

Genetics can be expected to assume an expanding role in risk stratification and resultant management of WT. NWTS – 5 has reported that loss of heterozygosity at the 16q and 1p loci is associated with a poorer prognosis, regardless of tumour stage and histology [2]. The identification of this cohort allows intensification of

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therapy [3]. The p53 tumour suppressor gene has been found in 75% of patients with anaplastic histology [1].

Genetic abnormalities in WT include the WT1 and WT2 gene deletions. WT is associated with a number of recognised syndromes including: WAGR, Beckwith-Wiedemann and Denys-Drash syndromes. These can be divided into overgrowth and non-overgrowth syndromes. Biannual ultrasound screening for WT is recommended for these children until 5 years [4].

Histopathology

In 1899 Max Wilms, while not the first to identify nephroblastoma, correctly identified it as being made up of

3 tissue types [1]. This “triphasic” histology reflects its embryonic origin and describes the coexistence of blastemal, epithelial and stromal cells. This histology characterises the “classic” WT [4].

Histology is the most important prognostic indicator for WT [3]. The majority of WT patients have favourable histology. Here epithelial differentiation predominates, the diagnosis is usually made early and they have a low risk of recurrence. This contrast with blastemal predominance that is more aggressive. Anaplasia (5%) portends a poor prognosis, with chemoresistance and these tumours tend to occur in an older subset of children. Anaplasia is characterised as focal or diffuse. These histological features are used to stratify WT patients into risk groups [3]. See Table 1.

Table 1. Simplified SIOP working classification of renal tumours in children [2]

| |
|--|
| (1) Low risk: completely necrotic nephroblastoma or cystic partially differentiated nephroblastoma, |
| (2) Intermediate risk: regressive, epithelial, stroma, mixed, or focal anaplastic nephroblastoma, and |
| (3) High risk: blastemal or diffuse anaplastic nephroblastoma. |

WT must be distinguished from clear cell sarcoma and malignant rhabdoid tumours of the kidney, both of which have a poor prognosis and were once thought to be subtypes of WT, but are now considered separate entities.

Macroscopically WT are soft, friable tumours which compress adjacent tissue to form a pseudocapsule. Necrosis and haemorrhage is typically present [4].

WT develops from precursor lesions known as nephrogenic rests (NR). NR are embryonic remnants of the developing kidney and are seen in 25-40% of kidneys with WT [3]. While NR are precursors to WT and are usually seen bilaterally if present, most in fact involute. Contralateral NR require surveillance to diagnose metachronous tumours. Differentiating large NR from WT is difficult. Histology can distinguish between the two, NR lack a pseudocapsule, a feature of WT [2].

NR are characterised as perilobar (peripheral) or intralobar (deep in the lobe) and these have differing pathological and clinical presentation. Perilobar NR in young infants are at greater risk of metachronous lesions [4]. Multiple NR are termed nephroblastomatosis.

Presentation

The incidental palpation of a smooth abdominal mass by parents is the commonest presentation. Haematuria is seen in a third and renin mediated hypertension in a quarter of patients [1]. Gross haematuria may indicate extension into the collecting system [3]. Constitutional symptoms are common.

Rupture, haemorrhage and resultant acute abdominal pain is a rare presentation, as is venous extension (4%) with possibly resultant varicocele, hepatomegaly, ascites and heart failure. Clinical feature of the associated genetic syndromes should be sought as mentioned above. 6% of WT are bilateral [3].

Imaging studies

Ultrasound and CT/MRI are the most effective diagnostic, staging and follow-up imaging techniques [1]. Information regarding tumour size, local invasion, function of contralateral kidney, nodal or venous involvement is sought. Doppler ultrasound plays a role in the latter to exclude intracaval extension. Since children have many benign causes for retroperitoneal lymphadenopathy, caution needs to be exercised if nodes are seen. Apparent extracapsular extension likely represents compression rather than local invasion, thus inoperability is a decision at surgery and not from imaging [4].

Lung and liver metastasis should be excluded on CT/MRI prior to surgery. While the significance to management of the finding of lung nodules is controversial, it is still recommended [4].

Improved imaging has obviated the traditional requirement to explore and biopsy the contralateral kidney prior to nephrectomy [4]. The “as low as reasonably achievable” (ALARA) principle guides the choice of MRI over CT. MRI is additionally the investigation of choice where Doppler ultrasound is unable to define caval extension [2]. MRI is able to define nephroblastomatosis, monitor their response to chemotherapy and confirm contralateral function. Thin slice multidetector CT scanning can also achieve these goals [4].

It should be noted that imaging while suggestive is not diagnostic. In a study from the United Kingdom 12% of renal tumours clinically and radiologically consistent with WT were found to have some other diagnosis on biopsy [4]. This is particularly relevant in SIOP protocols where pre-operative chemotherapy is required. Neuroblastoma,

inflammatory/infective pseudotumour and congenital mesoblastic nephroma can be confused with WT.

Collaborative trials

In 1969, with the establishment of the National Wilms tumour Study Group (NWTSG) in North America and thereafter in Europe with the Societe' Internationale d'Oncologie Pediatrique (SIOP), the management of WT was greatly enhanced by the collaborative pooling of data. NWTSG has recently changed its name to the Children's Oncology Group (COG).

Staging

The staging of WT is shown in Table 2. The most important determinants of outcome are stage and histopathology. Two important staging systems exist. COG/NWTSG staging is based on preoperative imaging, surgical findings and pathology. SIOP staging is done after preoperative chemotherapy. Although the staging systems seem similar, significant differences in resultant management protocols should be noted.

Treatment options

Modern multimodality treatment can expect an overall survival of >90% [5]. Treatment aims to identify patients who require aggressive therapy to optimize survival rates and to reduce morbidity and late effects, especially in patients with low risk disease. In broad terms COG protocols use initial surgery followed by adjuvant chemotherapy and radiotherapy as indicated, while SIOP use neo-adjuvant chemotherapy followed by surgery.

Proponents of neo-adjuvant chemotherapy quote down-staging and decreased spillage rates and assessment of chemotherapy response as beneficial. However, with this approach a few children may receive chemotherapy unnecessarily even if pre-chemotherapy biopsies are done [9].

Surgery

Percutaneous needle biopsy (2 to 3 cores with an 18-gauge needle) is used to obtain tissue before treatment in patients with non-metastatic disease [6].

A transperitoneal approach through a transverse abdominal or thoraco-abdominal incision is recommended. Midline laparotomy has higher rates of tumour rupture and complications than the transverse abdominal or thoraco-abdominal approach [10]. The surgeon determines tumour extent, local extension, liver metastases, nodal metastases and peritoneal seeding intra-operatively. Formal RPLND is not recommended. Sampling of para-hilar and ipsilateral para-aortic or para-caval nodes is mandatory.

Meticulous technique and gentle handling of the tumour with complete removal of the tumour without spillage is essential. Spillage increases abdominal relapse rate six-

fold [12]. The adrenal need only be removed if infiltration suspected. The ureter should be resected close to the bladder. Palpation of the renal vein and vena cava before clamping is helpful to exclude involvement by tumour. Exploration of the contra-lateral kidney is not required if preoperative cross-sectional imaging is normal [13].

Table 2. Staging system for Wilms' tumour

| | NWTS | SIOP |
|-----|---|---|
| I | Tumour is limited to kidney Totally excised There is no tumoural involvement in surgical margin The vessels of renal sinus are not involved There is no tumoural rupture before or during removal | Tumour is limited to kidney No tumour cells at the surgical margin The vessels of the renal sinus are not involved Intrarenal vessels may be involved |
| II | Tumour is outside the kidney Totally removed Local spillage and intrarenal vessels could be involved | Tumour extends outside of the kidney Totally resected but capsule, adjacent tissues, renal sinus and renal vessels can be involved |
| III | Intra-abdominal tumour Renal hilus, abdominal lymph nodes are involved Diffuse spillage Peritoneal involvement Thrombus in vena cava | Incomplete resection Intra-abdominal lymph node involvement but renal hilus lymph node positivity makes it stage II Ureteral, peritoneal, and caval involvement Preoperative or perioperative biopsy or rupture Peritoneal metastases |
| IV | Haematogeneous or distant lymph node metastases | Hematogeneous and extra-abdominal lymph node metastases |
| V | Bilateral renal tumours | Bilateral renal tumours |

Although small series and case reports have shown that laparoscopic nephrectomy is possible in WT, there is presently insufficient evidence to confirm equivalent oncological outcome to standard surgical management [14]. Increased risk of rupture due to lack of tactile

feedback and inadequate abdominal exploration, especially lymph node sampling, have been cited as concerns with the laparoscopic approach.

Partial nephrectomy, although generally accepted for bilateral WT, is controversial in the setting of unilateral WT. The incidence of renal failure after unilateral WT is below 1% [15]. Most of the reported cases of renal failure had Denys-Drash syndrome or intrinsic renal disease. Less than 5% of tumours are suitable for partial nephrectomy at presentation [26]. Tumours detected by screening of BWS and aniridia patients are often small and amenable to partial nephrectomy. Criteria for partial nephrectomy include stage I disease with a clear margin, with no vascular or collecting system invasion and at least 50% of the kidney salvageable [25]. Although partial nephrectomy may increase risk of local recurrence, it may be considered in solitary kidneys, bilateral tumours, renal insufficiency and in patients with aniridia and genitourinary abnormalities, as they have increased risk of late renal failure [15]. During partial nephrectomy frozen sections to ensure negative margins are essential.

Bleeding is the most common intra-operative complication (2.3%) and small bowel obstruction is the most common post operative complication (4.5%) [16]. Chylous ascites has also been reported.

Chemotherapy

Summaries of the current COG and SIOP protocols are represented in tables 3, 4 and 5. The addition of

Vincristine and Dactinomycin to the previous standard of care (surgery and radiotherapy) has significantly improved survival. Numerous trials by COG and SIOP have endeavoured to identify the most effective treatment regimens. Stratification of treatment based on tumour stage, histology and biologic features aims to optimise overall survival while minimising late effects of treatment. SIOP protocols include preoperative chemotherapy. COG applies adjuvant chemotherapy, except in bilateral tumours and intravascular extension above the hepatic vessels where neo-adjuvant chemotherapy is recommended.

NWTSG/COG

The Children's Oncology Group protocols based on the National Wilms' Tumour Study Group findings recommends initial surgery in operable tumours followed by adjuvant chemotherapy (Table 3). Neoadjuvant chemotherapy is recommended for bilateral tumours, horseshoe kidneys, solitary kidneys, for tumour within the vena cava extending above the hepatic veins and if the tumour is extremely large and causes respiratory distress [2,11].

Current studies stratify patients into very low, low, standard and high risk groups. In very low risk patients (age<2 years, tumour<550 grams, stage I with favourable histology) the possibility of omitting adjuvant chemotherapy was investigated by NWTS-5 [18]. This study was terminated due to a reduction in relapse free rate although overall survival was 98%.

Table 3. Treatment regimens used in COG/NWTS-5 [7]

| Stage | Histology | Radiotherapy | Chemotherapy regimen | Duration (weeks) |
|--------|-----------------|--------------|----------------------|------------------|
| I-II | Favourable | No | EE4A | 18 |
| I | Anaplastic | No | EE4A | 18 |
| III-IV | Favourable | Yes | DD4A | 24 |
| II-IV | Focal anaplasia | Yes | DD4A | 24 |
| II-IV | Anaplastic | Yes | I | 24 |
| I-IV | CCSK | Yes | I | 24 |
| I-IV | RTK | Yes | RTK | 24 |

CCSK=clear-cell sarcoma of the kidney; RTK=rhabdoid tumour of the kidney. EE4A=vincristine plus pulse-intensive dactinomycin; DD4A=vincristine plus pulse-intensive dactinomycin and doxorubicin; I=vincristine, doxorubicin, cyclophosphamide, and etoposide; RTK=carboplatin, etoposide, and cyclophosphamide

International Society of Paediatric Oncology (SIOP)

SIOP protocols recommend neo-adjuvant chemotherapy followed by nephrectomy (see Table 4) and adjuvant therapy dictated by pathologic stage (see Table 5). If no

metastases are present Vincristine and Dactinomycin are given for 4 weeks prior to surgery. If metastases are present Vincristine, Dactinomycin and Doxorubicin are given for 6 weeks before surgery [21]. SIOP protocols do not biopsy before chemotherapy. However, in the UK a

Table 4. Management of WT pre-op as per SIOP protocol [8]

| Clinical staging | | |
|---|------------------------|--------------------------|
| Localized | 4 weeks of DAM/VCR | Surgical staging |
| Metastatic | 6 weeks of DAM/VCR/EPI | (Histological diagnosis) |
| DAM-Dactinomycin; VCR-Vincristine; EPI-Epirubicin | | |

Table 5. Regimen of post-operative therapy as per SIOP protocol [8]

| | Stage | Treatment |
|--|---|--|
| Localized | Stage I, Low grade | None |
| | Stage I, Intermediate grade + anaplasia | 18 weeks DAM/VCR |
| | Stage II – (no lymph nodes) | 28 weeks DAM/VCR/EPI |
| | Stage II + and III | 28 weeks DAM/VCR/EPI + RT tumour bed |
| | High grade | 34 weeks EPI/IF/VP16/CARBO + RT |
| Metastatic | IV | As per the local stage for tumour + treatment of metastases – RT and/or excision |
| DAM-Dactinomycin; VCR-Vincristine; EPI-Epirubicin; IF-Ifosfamide; VP-16, Etoposide; CARBO-Carboplatin; RT-Radiotherapy | | |

trucut biopsy is done to confirm histological diagnosis [32,33]. Further treatment is based on post-operative staging and risk group.

Late effects

Survival for early stage disease approaches 90% with modern multimodal therapy. Studies have shown chronic health problems in 60% of survivors of childhood malignancies [23]. Treatment may affect cardiac and endocrine function, musculoskeletal development, fertility and may cause secondary malignancies.

Doxorubicin induced cardiotoxicity causes congestive cardiac failure in 4.4% of patients [24]. They may present early or years after treatment. Although toxicity is usually proportionate to cumulative dose, a degree of myocyte damage occurs with any exposure.

Radiation has detrimental effect on growth and development of tissue [25]. Musculoskeletal deformities including scoliosis and short stature with severity proportional to total radiation dose. Significant dose reduction and limiting the application of radiotherapy has made these complications less common. Radiation may affect cardiac and pulmonary function. Irradiation of ovaries may cause ovarian failure and infertility. Irradiated women may also have adverse pregnancy outcomes including miscarriage and intrauterine growth retardation [26]. Irradiation of testes may cause hypogonadism and infertility [28]. WT survivors also have an increased risk

of secondary malignancies. These usually occur in irradiated patients within the radiation field. There is a 1% cumulative incidence of secondary malignancies at 10 years, which increases thereafter [27]. Secondary malignancies include sarcomas, breast cancer, hepatocellular carcinoma, lymphomas, gastrointestinal tumours, leukaemia and melanoma.

Renal dysfunction may occur after bilateral WT, but concern also exists about renal dysfunction after treatment of unilateral WT. However, the incidence of the latter is low, at roughly 0.25% [15].

Bilateral Wilms'

Synchronous tumours occur in 5% of patients [20]. Due to the significant risk of renal insufficiency in bilateral WT preoperative chemotherapy and renal preserving surgery is recommended by COG protocol [15]. Chemotherapy and reimaging at 6 weeks is recommended. If there is a poor clinical response, biopsy should be considered. Further reduction of tumour volume beyond 12 weeks of chemotherapy is unlikely therefore delay of surgery beyond this period is not recommended [3]

Intravascular tumour extension

Tumour extension into the vena cava occurs in approximately 5% of patients [9,22]. Ultrasonography and MRI can be used to image the extent of the thrombus.

Surgical excision of the tumour and thrombus is recommended. Infra-hepatic thrombus can be removed through a trans-abdominal approach. Atrial lesions by contrast require cardiopulmonary bypass. Preoperative chemotherapy should be considered to decrease the extent of the thrombus and to facilitate removal.

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