

Adult Wilms' tumor – diagnosis and current therapy

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Introduction. Wilms' tumour is one of the commonest malignant tumours of childhood. It appears mainly in the first 5 years of life. Incidental examples of nephroblastoma in adults have been described in literature (about 3% of all described cases). There are diagnostic and therapeutic difficulties in that older age group. The preoperative diagnosis of nephroblastoma in adults is difficult because there are no specific radiographic findings that allow to distinguished it from the more common adult renal tumors. Histopathologically, there is no difference between adult and childhood Wilms' tumor.

Materials and methods. The PubMed database and current literature search was conducted for reports on clinical and histopathological features of nephroblastoma in adults. We also reviewed the literature in terms of treatment strategy, toxicity and prognostic factors.

Results. Up till now, several biological factors have been identified that may be in future new prognostic factors. Modern treatment regiments improved OS in this group of patients (OS rates of 90%). The prognosis remain still worse for about 25% of patients with anaplastic, bilateral and recurrent disease.

Conclusions. Due to the fact that nephroblastoma is a very rare type of cancer, adult patients should be treated in an individual way based on the available schemes used in children. Toxicity in adults is higher than in children.

Key Words: nephroblastoma ◊ adults ◊ diagnosis ◊ treatment ◊ toxicity ◊ prognosis

INTRODUCTION

Wilm's tumour (nephroblastoma, WT) is one of the commonest malignant tumours of childhood. It appears mainly in the first 5 years of life. Single cases of nephroblastoma in adults were described in literature [1], larger groups of adult patients are rare [2]. First symptoms in adults include pain and haematuria, while children experience palpation detectable, painless, rapidly increasing in size, abdominal mass. Distant metastasis of nephroblastoma usually occurs in lungs, liver and less frequently in bones, skin, bladder, large intestine, central nervous system, and the opposite kidney.

Treatment protocols in children were developed by multicenter American and European expert groups named The National Wilms' Tumor Study Group (NWTSG) in North America and the International Society of Pediatric Oncology (SIOP) and the Polish group called the Wilms' Tumor Team of the Polish Pediatric Solid Tumor Treatment Group (PPGGL) in Europe. The aim of this study was to make a re-

view of the literature for diagnosis and treatment of nephroblastoma in adults.

Staging of Wilms' tumor

Staging criteria of Wilms' tumor are based on the anatomic extent of the tumor. There are distinguished two main staging systems as a prechemotherapy, surgery-based system developed by the National Wilms' Tumor Study Group (NWTSG) and a post-chemotherapy-based system developed by the International Society of Pediatric Oncology (SIOP) (Table 1 and Table 2). The NWTSG and COG (Future Children's Oncology Group) recommend resection of the primary tumor before chemotherapy is given. In contrast, SIOP recommends the administration of chemotherapy for 4 weeks before surgery.

Histology

Histopathologically there is no difference between Wilms' tumor occurred in adult and child. The genetic

basis of Wilms' tumor is complicated. The WT1 gene (11p13) is mutated in 10% of tumors. Changes in 11p, at 7p, 16q, and 1p are also recognized. Classical histopathological pattern is triphasic: blastemal, epithelial, and stromal. Blastemal-predominant Wilms' tumors are more aggressive than others types and has a poor outcome. Epithelial and stromal kinds represent intermediate risk tumors. Pathological diagnosis of adult nephroblastoma is based on criteria developed by Kilton et. al. that is: the presence of the tumor primarily originating from the kidney; the presence of primitive blastemic spindle or round cell component; the formation of abortive or embryonal tubules or glomerular structures or no area of renal cell carcinoma histopathology; confirmation of the diagnosis in the histopathological tests; and the age above 15 years old [3]. Additional diagnostics such as immunohistochemical staining for the presence of cytokeratin, vimentin, desmin, actin, and WT1 allows to distinguish between other rare cancer types such as: renal sarcoma, mesoblastic nephroma, clear cell sarcoma, or rhabdoid tumor. The WT1 expression is diagnosed in the blastemic area and proliferating epithelial tissue, but not in mature stroma and mature epithelial tissue [4]. The classification to one of the three risk groups depends

of the histopathologic features of the tumor. It is necessary for choice of adequate treatment schemes. The SIOP histologic classification reflects chemotherapy-induced changes including "regressive" changes. The NWTSG classifies nephroblastoma based on the presence of anaplasia [5, 6]. The revised SIOP classify Wims' tumor into three risk groups such as low, intermediate, and high risk (Table 3).

TREATMENT

The classification of the tumor to one of the three risk groups allows to use of adequate treatment schemes (Table 3). Radical nephrectomy (the removal of the tumor along with the kidney with the adrenal gland and lymph nodes of the same side) is treatment of choice of one-sided nephroblastoma. According to SIOP, a partial kidney resection (nephron sparing treatment) is only allowed in precisely designated cases such as in the presence of developmental disadvantages in the other kidney, genetically predisposed diseases in which the risk of nephroblastoma development is high, and in patients who only have one kidney [7]. The SIOP strategy does not recommend the nephron sparing surgery in patients with one-sided nephroblastoma without the presence of the above-mentioned criteria [8]. In the NWTSG and COG studies treatment starts by surgical resection of the tumor. Surgical complica-

Table 1. Staging system for renal tumors according SIOP 2001 protocols (after chemotherapy)

Stage I	Tumor is limited to the kidney or surrounded with fibrous pseudocapsule. The renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface. Tumor is completely resected (resection margins „clear“). – tumor may be protruding into the pelvic system and “dipping” into the ureter but not infiltrates its wall. – the vessels of the renal sinus are not involved – intrarenal vessel involvement may be present
Stage II	The tumor extends beyond kidney or penetrates through the renal capsule and/ or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins „clear“). – the tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but is completely resected. – the tumor infiltrates adjacent organs or vena cava but is completely resected.
Stage III	Incomplete excision of the tumor which extends beyond resection margins – any abdominal lymph nodes are involved – tumor rupture before or intraoperatively – the tumor has penetrated through the peritoneal surface – tumor thrombi present at resection margins of vessels or ureter – the tumor has been surgically biopsied prior to preoperative chemotherapy or surgery.
Stage IV	Hematogenous metastases (Lung, liver, bone, brain etc.) or lymph node metastases outside the abdomino-pelvic region.
Stage V	Bilateral renal tumors at diagnosis.

Table 2. Staging system for renal tumors according NWTSG protocols (before chemotherapy)

Stage I	Tumor is limited to the kidney and completely resected (resection margins „clear“). – tumor was not ruptured before or during removal – the vessels of the renal sinus are not involved beyond 2 mm –there is no residual tumor apparent beyond the margins of excision.
Stage II	– Tumor extends beyond the kidney but is completely excised. – No residual tumor is apparent at or beyond the margins of excision – tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en block with the tumor.
Stage III	Residual tumor confined to the abdomen. – lymph nodes in the renal hilum or the periaortic chains – diffuse peritoneal contamination by the tumor. – implants are found on the peritoneal surfaces – tumor extends beyond the surgical margins either microscopically or glossy – tumor is not completely respectable because of local infiltration into vital structures.
Stage IV	Presence of hematogenous metastases or metastases to distal lymph nodes.
Stage V	Bilateral renal involvement at the time of initial diagnosis.

tions such as bowel obstruction (5,1%), extensive hemorrhage, wound infection (1.9% each), extensive vascular injuries (1.4%) and injuries to other visceral organs (1%) were observed in NWTSG – 4 study. The risk factor of surgical complications were intravascular extension into the inferior vena cava, the atrium, or both, a tumor diameter greater than 10 cm [9].

Systemic treatment

The most effective chemotherapeutics in treatment of nephroblastoma are: actinomycin D (ACT), vincristine (VCR), doxorubicin (ADM), cyclophosphamide (ctx), ifosfamide (IFO), etoposide and carboplatin (as in monotherapy as in drug combination). The treatment schemes of nephroblastoma according to NWTSG and SIOP were presented in Table IV. According SIOP strategy preoperative chemotherapy reduces the risk of tumor rupture during surgery and thereby reduce the probability of local and distant recurrence (recurrence and its treatment strategy will be shown later) [5, 6]. NWTSG recommends polchemotherapy (ACT, VCR, ADM) for a period of 15 weeks in adjuvant treatment in tumor stage III. Less aggressive treatment using two medications (VCR and ACT) can be used in cancer stages I and II [10, 11]. No advantage was shown of the three-medication therapy including ACT, VCR and ADM comparing over the two-medication scheme ACT with VCR in stage II [12]. Adult patients can be treated according to pediatric protocols. The toxicity of such treatment is higher in adults than in children [13].

Radiotherapy

Nephroblastoma is a radiotherapy sensitive cancer. Currently, radiation therapy is usually part of treatment only for more advanced Wilms tumors (stages III, IV, and V) and for some earlier stages tumors with unfavorable histology. The recommended dose according to NWTSG, SIOP, and PPGGL is 10, 15, and 20 Gy, respectively. The benefits from pre-operative radiotherapy in prevention of tumor rupture and

in improving the stage distribution were confirmed in several SIOP trials such as: SIOP1, SIOP2 and SIOP5. Initially irradiation and later chemotherapy cause the shrinkage of the tumor [14]. Treatment regimens for Wilms' tumor from NWTSG and SIOP studies shows Table 4.

Bilateral Wilms' tumor

There are distinguished synchronous and metachronous bilateral Wilms' tumor. Synchronous WT occurred in about 6–7% of the tumors and metachronous WT in approximately 2% of all nephroblastoma [15, 16]. Treatment strategy rely on kidney – preserving resection (NSS, nephron sparing surgery) after preoperative chemotherapy which often results in significant reduction of tumor size. NWTSG–2 and NWTSG–3 trials showed no differences in survival between initial surgical resection and initial biopsy with preoperative chemotherapy [15]. The NWTSG–5 trial recommend initial biopsy, chemotherapy and second – look surgery at week 5 [16]. The surgery is recommended within 12 weeks of diagnosis to limit the risk of chemoresistant clonal expansion.

Recurrent Wilms' tumor

The prognosis and treatment for patients with recurrent Wilms tumor depends on their prior treat-

Table 4. Treatment regimens for Wilms' tumor from NWTSG and SIOP studies

Stage	NWTSG–5		SIOP –01		
	Chemotherapy	Radiotherapy	Chemotherapy		Radiotherapy
			Preoperative	Postoperative	
I	VA x 18 weeks	–	VA x 4 weeks	VA x 4 weeks	No
II	VA x 18 weeks	–	VA x 4 weeks	VDA x 27 weeks	Node negative: none Node positive: 15 Gy
III	VDA x 24 weeks	10.8 Gy	VA x 4 weeks	VDA x 27 weeks	15 Gy
IV	VDA x 24 weeks	12 Gy lung (if the lung metastasis) 10.8 Gy flank (if local stage III)	VDA x 6 weeks	No CR after 9 weeks ICED x 34 weeks	None if lung lesions disappear by week 9 otherwise 12 Gy

Table 3. Histological classification of Wilms' tumor according to the risks groups – SIOP 2001 protocols

Low risk tumor (LR)	Intermediate risk tumor (IR)	High risk tumor (HR)
– mesoblastic nephroma	– epithelial type	– blastema type
– completely necrotic nephroblastoma	– stromal type	– diffuse anaplasia
– cystic partially differentiated nephroblastoma	– regressive type	– clear cell sarcoma of kidney
	– mixed type	– rhabdoid tumor of kidney
	– focal anaplasia	

ment, the histology (favorable or unfavorable), localization of recurrence. The outcome for recurrent disease is better if following features are present: favorable histology (low-risk tumors), initial stage of I or II, initial chemotherapy with vincristine and actinomycin D, recurrence at least 12 months after initial diagnosis and lack of previous radiotherapy [17, 18]. The use of etoposide, carboplatin and ifosfamide as single agents have shown anti-tumor activity in children with relapsed Wilms' tumor [19]. The combination of either etoposide/carboplatin or ifosfamide/etoposide is also examined in many phase II clinical trials in children with recurrence of solid tumors. ICE (ifosfamide/carboplatin/ etoposide) treatment was found to be associated with a response in over 80% of the patients, including those with CR (complete remission) in 27% and those with PR (partial remission) in 55% [20]. The response rate and most common toxic effects are shown in Table 5.

Toxicity

In three drug regiment with vincristine, dactinomycin and adriamycin the main acute toxicity was neuropathy due to vincristine. Grade 4 hemathological toxicity occurred in patients with higher stages. Hepatotoxicity was rare. Another side effect was mucositis [21]. During chemotherapy conducted according to ICE (ifosfamide/carboplatin/ etoposide) scheme all patients had hematological toxicity such as neutropenia and thrombocytopenia in stage IV toxicity. The described nonhematological toxicity include septic shock, complications of the digestive tract, hepatotoxicity, proteinuria, hypophosphatemia, low concentration of potassium and chronic renal insufficiency [22]. The type, timing and dosage of chemotherapy have been major risk factors in the combined treatment.

The clinically significant late side effects are predominantly cardiotoxicity, reproductive problems, renal dysfunction and the development of benign and malignant second tumours [23]. Clinical heart failure is the commonest presentation and can occur acutely or many years following treatment. Posttherapy left ventricular fractional shortening was reduced in 2.5% patients. An additive effect might occur with radiation involving the heart, as in patients requiring lung radiotherapy or left flank radiotherapy for upper pole WT. Regular monitoring with echocardiograms is recommended [24, 25].

Gonads are particularly sensitive to radiation. In some cases fertility and a successful pregnancy outcome may be impaired, especially in girls who have abdominal radiation in which both ovaries or the uterus are within the field [26].

Development of renal disease can be observed in patients with progression of bilateral nephroblastoma or receiving irradiation in the opposite kidney in unilateral disease [27]. Chronic renal insufficiency has been reported in 19–73% of WT patients. The most important risk factors are: nephrectomy, abdominal radiotherapy and less compensatory renal hypertrophy [28]. The risk of nephrotoxicity may be reduced by avoiding nephrotoxic chemotherapy, optimizing radiation therapy and nephron-sparing surgery for bilateral disease [29].

The types of second cancers include bone and soft-tissue sarcomas, breast cancer, lymphoma, tumours of the digestive tract, melanoma and acute leukemias [30, 31]. In some studies secondary tumors increase with the increase in radiation dose and the use of doxorubicin intensified the effect of radiotherapy [32].

Prognosis

Wilms' tumor metastasis occurs in children and adults in 10% and 29% of the cases, respectively [33, 34]. Nephroblastoma in adults is considered worse than

Table 5. The treatment of recurrent solid tumors in children – response and toxicity

Chemotherapy	Dose of medication	Treatment response	The most common toxic effect
Etoposide monotherapy	200 mg/m ² /day for 5 days	CR in 7% PR in 35%	Neutropenia Thrombocytopenia
Carboplatin monotherapy	550 mg/m ² every three weeks	CR in 26% PR in 26%	Neutropenia Thrombocytopenia
Ifosfamide monotherapy	3 mg/m ² for 2 days, every two weeks	CR in 28% PR in 24%	Leukopenia
Etoposide with carboplatin	100 mg/m ² for 5 days of etoposide and 160 mg/m ² for 5 days of carboplatin with a 21-day interval between the two courses.	CR in 30% PR in 43%	Thrombocytopenia Anemia Neutropenia
Ifosfamide with etoposide	2 g/m ² of ifosfamide and 100 mg/m ² of etoposide with 500 mg/m ² of mesna every 3 hours x 3 intravenously for 3 days with a 21-day interval between the two courses	CR in 31% PR in 20%	Neutropenia Vomiting Thrombocytopenia
ICE (ifosfamide, carboplatin, and etoposide)	1800 mg/m ² for 5 days of ifosfamide; 400 mg/m ² for 2 days of carboplatin; and 100 mg/m ² for 5 days of etoposide	CR in 27% PR in 55%	Neutropenia Thrombocytopenia Non-hematological

in children. Stages III and IV are present in 50% of adults and 30% of children. A higher advancement stage and common metastatic events are the reasons for worse treatment outcomes in adults compared to children. The prognosis depends on the primary advancement stage, the histopathology, time since the first remission, type of therapy, and the recurrence location. In patients with recurrence three-year survival is about 30%, especially in the presence of poor prognostic factors such as advanced stage greater than I, abdominal relapse at the site of previous radiotherapy, early recurrence (<12 months), and after previous three-medication therapy [8]. The use of etoposide, carboplatin and ifosfamide as single agents have shown anti-tumor activity in children with relapsed Wilms' tumor [9]. The combination of either etoposide/carboplatin or ifosfamide/etoposide were also examined in many phase II clinical trials in children with disease recurrence. ICE treatment (ifosfamide/carboplatin/ etoposide) was found to be associated with a overall response in 80% of the patients, including those with CR in 27% and those with PR in 55% [10].

Biologic prognostic factors

Up till now some potential molecular factors have been identified. One is loss of heterozygosity (LOH) at chromosomes 1p and 16q. Children with LOH at 16q had greater risk of relapse and mortality than did children without these changes [35]. A similar results applied to LOH at chromosome 1p [36]. LOH for both chromosomes 1p and 16q was identified in approximately 5% of Wilms tumors. Other promising prognostic factors are; an increase in gene copy number or expression at chromosome 1q [37], and telomerase expression level [38].

CONCLUSIONS

Wilms' tumor in adulthood is extreme rare. The cure rates for adult Wilms' tumor are improving. Therapy schemes based on pediatric protocols leads to similar results as observed in children. Treatment toxicity in adults is higher than in children. Up till now, several molecular prognostic factors have been identified. The novel treatment approaches development are necessary.

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