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Clinical Factors in Relapses of Wilms' Tumor – Results for the Polish Pediatric Solid Tumors Study Group

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Abstract

Background. The risk factors responsible for recurrences of Wilms' tumor (nephroblastoma) are still under discussion. The aim of the study was to analyze the relationship between relapses of Wilms' tumor and the patients' clinical history.

Material and Methods. Clinical data from children registered in the Polish Pediatric Solid Tumors Study Group were analyzed. The clinical stages (CS), pathology variants (high risk: HR, intermediate risk: INT, and low risk: LOW) and chemotherapy regimens were correlated with the outcomes.

Results. Recurrences developed in 34 out of 288 (11.8%) patients with Wilms' tumor treated in accordance with International Society for Pediatric Oncology 2001 (SIOP 2001) protocols. Of these 34 patients, 11 initially had CS I, seven were at CS II, four were at CS III, 11 were at CS IV and one had CS V. There were eight patients with second recurrences; of these, seven were in the INT risk group and one in the high histological risk group. There was no correlation between age ($p = 0.256$) or gender ($p = 0.538$) and the risk of tumor recurrence. In the study group, seven out of 10 patients with local recurrences are alive; as are 13 out of 22 patients with distant recurrences

($p = 0.703$). Those who died due to disease progression comprised six out of 26 patients with a first recurrence (four HR, two INT), and seven out of eight with a second recurrence (one HR, six INT).

Conclusions. The prognosis after relapse in initially metastatic patients did not differ from that in patients who had primarily localized disease. The pathology variants probably had more significance (*Adv Clin Exp Med* 2014, 23, 6, 925–931).

Key words: nephroblastoma, risk factors, Wilms' tumor, relapse.

Wilms' tumor (nephroblastoma) is a typical primary kidney tumor in childhood; the most common age of onset is between the second and fifth year of life. In Poland nephroblastoma represents approximately 6–8% of all cancers in this age group. With current therapeutic programs based on a combination of surgery, chemotherapy and radiotherapy, it is possible to cure 85% of patients with Wilms' tumor [1].

Current methods of stratification into risk groups based on tumor histopathology, clinical stage and the initial response to chemotherapy seem to require additional factors that would allow patients at risk of recurrence to be identified even more precisely. Since the onset of advanced genetic and molecular studies, new prognostic markers responsible for the course and outcome of relapse treatment are also being looked into [2].

Material and Methods

Data from patients with nephroblastoma treated in the Polish Pediatric Solid Tumors Study Group in accordance with the International Society for Pediatric Oncology 2001 (SIOP 2001) protocol were analyzed. The following factors were assessed: age, gender, clinical stage (localized vs. diffuse lesions) and histopathology, and these data

were compared to assess the risk of recurrence and the effects of relapse treatment. The study included 288 patients (154 females and 134 males) treated for Wilms' tumor in the years 2003–2010. The age of the children at diagnosis ranged from 15 days to 17.5 years, with a median of 3.3 years. Initially, the tumor occurred locally in 233 patients; in 43 patients distant lung metastases were observed (for 12 of the patients there was no data on initial localization). Clinical stage I was diagnosed in 117 children, stage II in 43 patients, stage III in 55 patients, stage IV in 42 patients; and bilateral nephroblastoma (stage V) was diagnosed in 19 patients. Low-risk histopathology (LOW) was found in 36 patients, 169 had intermediate-risk histopathology (INT) and 62 had high-risk histopathology (HR); there was no data for 21 of the patients. The characteristics of the study group are presented in Table 1. The evaluation of clinical stage is shown in Table 2 and the pathological stage according to SIOP 2001 protocol [3] is shown in Table 3.

Statistical Methods

The results obtained were subjected to statistical analysis. For each group the number of cases (N), mean (X), median (M), range (min-max), lower and upper quartile (25Q–75Q) and standard deviation (SD) of the constant parameters studied

Table 1. The distribution of the study group according to their clinical stage and histopathology

	CSI (42%)	CSII (15%)	CSIII (20%)	CSIV (16%)	CSV (7%)
LOW (13.5%)	29	1	2	3	1
INT (63%)	68	38	29	22	12
HR (23.5%)	20	4	21	13	4

LOW – low-risk tumors, INT – intermediate-risk tumors, HR – high-risk tumors, CS – clinical stage, CR – complete remission.

Table 2. Histopathological classification of Wilms' tumors

LOW	INT	HR
Completely necrotic Mesoblastic nephroma Cystic partially differentiated	focal anaplasia epithelial type stromal type mixed type regressive type	diffuse anaplasia blastemal type clear cell sarcoma of the kidney rhabdoid tumor of the kidney

LOW – low-risk tumors, INT – intermediate-risk tumors, HR – high-risk tumors.

Table 3. Criteria for staging according to the SIOP 2001 protocol

CS I	The tumor is limited to the kidney and is completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. No evidence of tumor is present at or beyond the margins of resection.
CS II	The tumor is completely resected. No evidence of tumor at or beyond the margins of resection is noted. The tumor extends beyond the kidney (penetration of the renal capsule, involvement of the renal sinus).
CS III	Incomplete excision of the tumor, which extends beyond the resection margins (gross or microscopic tumor remains post-operatively). Abdominal lymph nodes are involved. Tumor rupture pre- or intra-operatively (irrespective of other criteria for staging). The tumor has penetrated through the peritoneal surface. Tumor implants are found on the peritoneal surface. Tumor thrombi present at resection margins of vessels or ureter, transected or removed piecemeal by surgeon. The tumor has been surgically biopsied (wedge biopsy) prior to pre-operative chemotherapy or surgery.
CS IV	Hematogeneous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region.
CS V	Bilateral renal involvement by the tumor is present at diagnosis.

CS – clinical stage.

were calculated. Verification of the hypothesis of equal average of individual samples was performed with the ANOVA variance analysis method or, for groups with heterogeneous variance or a small number of cases, with the Kruskal-Wallis non-parametric rank sum test (the homogeneity of variance was checked with the Bartlett test). For discrete parameters, the frequency of characteristics in the groups was analyzed using the χ^2 test with the Yates correction, or, when the expected value in a cell was less than 5, F was identified using the Fisher test. $P \leq 0.05$ was considered statistically significant. The statistical analysis was performed using the Epi Info statistical software package (version 3.5.2, dated 17-12-2010).

Results

Tumor recurrence was diagnosed in 34 children (16 females and 18 males), which accounted for 11.8% of the studied patients. Of this group, eight children were subsequently diagnosed with a second relapse. The first recurrence occurred in the lungs in 17 patients; in 10 the first recurrence was local; in two the first recurrence was observed in the liver; in one in the central nervous system (CNS); there were 2 cases of multi-organ metastatic relapse; in 2 cases, there was no data. The second recurrence was diagnosed in the lungs in 2 patients; in the CNS in 3 children; and multi-organ metastases were diagnosed in another 3 patients.

There was no correlation between the patients' age and the risk of tumor recurrence (3.98 years $\pm$ $\pm$ 3.29 in patients without recurrence vs. 4.81 years $\pm$ $\pm$ 3.96 in patients with relapse, $p = 0.256$); nor was there any correlation between gender and the risk of recurrence (138 females/116 males without relapse vs. 16 females/8 males with relapse, $p = 0.538$).

Recurrences were observed from 3 months to 5 years (median 10 months) after diagnosis. There was no evidence that the time to relapse had an impact on the prognosis ($p = 0.110$).

Histopathological type was not correlated to a higher risk of first recurrence ($p = 0.158$). A first recurrence was diagnosed in 11 patients who initially had stage I disease; of these, 1 had LOW histopathology, 8 had INT and 2 had HR. Seven patients initially had stage II disease; in all of them the pathology variants of the tumors were INT. Four relapsing patients initially had stage III disease; of these, three were HR and one was INT. Initial stage IV was observed in 11 patients; of these, four were HR and seven were INT. In one case, the recurrence occurred following bilateral nephroblastoma of intermediate-risk histopathology. Second recurrences occurred in 7 patients with intermediate risk histopathology and in one patient with HR. The characteristics of the group with relapses are presented in Table 4.

The results of the treatment of Wilms' tumor recurrences did not differ ($p = 1.00$ F) in patients with the disseminated nephroblastoma (4 out of 11 patients with stage IV tumors died) compared

Table 4. The distribution of the study group (relapse of disease) according to their clinical stage and histopathology

	CS I (11 patients)	CS II (7 patients)	CS III (4 patients)	CS IV (11 patients)	CS V (1 patient)
LOW	1	0	0	0	0
INT	8	7	1	7	1
HR	2	0	3	4	0

LOW – low-risk tumors, INT – intermediate-risk tumors, HR – high-risk tumors, CS – clinical stage, CR – complete remission.

Table 5. Recurrences of the disease (clinical stage, histopathology) and the results of treatment

	CS I: 11 patients	CS II: 7 patients	CS III: 4 patients	CS IV: 11 patients	CS V: 1 patient
LOW	1 in CR	–		–	–
INT	3 in CR	5 in CR	1 in CR	4 in CR	1 in CR
	4 died	2 died	–	2 died	–
	1 in PR	–	–	1 in PR	–
HR	1 in PR	–	1 in PR	2 in CR	–
	1 died		2 died	2 died	

LOW – low-risk tumors, INT – intermediate-risk tumors, HR – high-risk tumors, CS – clinical stage, CR – complete remission, PR – partial remission.

Table 6. Clinical stage and histopathology compared to Wilms' tumor recurrence

	CS I	CS II	CS III	CS IV	CS V	LOW	INT	HR
Remission	106	36	51	31	18	35	145	55
Recurrence	11	7	4	11	1	1	24	9

LOW – low-risk tumors, INT – intermediate-risk tumors, HR – high-risk tumors, CS – clinical stage.

to the group with localized disease (9 of the 22 children in stages I to III died).

The pathology variant influenced prognosis after relapse, with a higher mortality in the high-risk group (5 out of nine HR died, vs. 8 out of 24 INT).

There was no relationship between the location of the recurrence (local vs. distant) and treatment results; 7 out of 10 patients with local recurrences are alive, as are 13 out of 22 with distant recurrences ($p = 0.703$). The data are presented in Tables 5 and 6.

In patients with recurrences, radiotherapy was used as the first-line treatment of the primary disease in 14 cases, and in 12 in treating the relapse. In 34 patients with recurrent Wilms' tumor, the following treatments were applied:

- “high-risk protocol” (Doxorubicin combined with Cyclophosphamide, alternated with Etoposide and Carboplatin) in 15 children, 3 of whom died, while 12 are in remission;

- ICE (Ifosfamide, Carboplatin, Etoposide) protocol in 11 children; in this group there have been 4 deaths, while 7 patients are in remission;

- megachemotherapy (Melfalan, Etoposide, Carboplatin) with autologous hematopoietic stem cell transplantation (auto-HSCT) in 7 patients, of whom 6 died and 1 is in remission. The auto-HSCT was carried out in 3 females and 4 males. All the patients had intermediate-risk histopathology; in terms of clinical stage, three were at stage I, 2 were at stage II and 2 were at stage IV. Two of them had multi-organ metastases, the rest had local recurrences. Time to death ranged from 6.5 to 26 months after auto-HSCT. A second recurrence was diagnosed in 4 patients; in these cases death occurred due to disease progression. Treatment complications were the cause of death in 2 patients.

Discussion

Prognostic factors in children with nephroblastoma have undergone many years of investigation. Various parameters that increase the risk of relapse have been subjected to analysis. The National Wilms' Tumor Study (NWTS 1-4) has evaluated prognostic factors for children with recurrent Wilms' tumor several times. The most important predictors of relapse in a study in 1978 were "anaplastic or sarcomatous histology, specimen weight over 250 grams, positive regional lymph nodes, treatment with only a single drug and age over two years" [4]. The report from the second National Wilms' Tumor Study (NWTS-2) determined that the 2 most important predictors for relapse were anaplastic or sarcomatous histology and microscopically confirmed disease in the regional lymph nodes [5]. The NWTS-3 also revealed that lymph node involvement, age at diagnosis and tumor size were highly correlated with relapse [4]. The risk of local relapse and lung metastases in patients with favorable histopathology and localized stage was analyzed. In 1999, Shamberger's study (NWTS-4) highlighted the importance of local surgical control [7]. The 2-year relapse-free survival of children exceeded 91%. Local recurrence was diagnosed in 100 of the 2482 patients who were included in the study. The highest relative risks for local recurrence were observed in patients at clinical stage III, those with diffuse anaplasia and those with tumor spillage during surgery. Surgical spill correlated strongly with local relapse, even after accounting for other prognostic factors.

The list of factors that increase the risk of recurrence has become longer and more detailed as more experience is gained and the issue is more widely explored. Weirich et al. demonstrated that Wilms' tumor therapy should be individualized and based on the patient's age, the presence of anaplasia and the response to initial chemotherapy [8]. That analysis included 440 patients treated in accordance with the SIOP-9 protocol. The 5-year survival rate was 92.3% for patients without anaplasia vs. 48.5% for those with anaplasia. Factors increasing mortality therefore include anaplasia, poor response to preoperative chemotherapy and clinical stage IV.

On the other hand, a favorable prognosis in patients without anaplasia was associated with age less than 2 years at diagnosis ($p = 0.026$). Also, in a study by Pritchard-Jones, it was shown that older children (> 4 years) are at increased risk of recurrence ($p = 0.001$) [9]. In that study, 242 patients with stage I tumors and favorable histopathology were studied. Relapses were confirmed in

33 cases. Event-free survival (EFS) was 93.2% in children < 2 years, 87.2% between ages 2 and 4 years and 71.3% in children > 4 years. The current study did not confirm these results; sex and age seem to have no relation to the risk of recurrence or the prognosis in case of relapse.

In a study by Reinhard et al., early recurrence (< 6 months), stage III, high-risk histology and "combination" recurrence (local recurrence + distant metastases) were listed as factors contributing to a poor prognosis after nephroblastoma relapse [10]. The study included 1392 patients from Germany and Switzerland (SIOP/GPOH) with a total of 170 relapses. Factors influencing relapse such as the patient's age at diagnosis, gender, the initial stage of the disease, the presence of metastases, histology, time to recurrence and tumor volume were taken into account. Relapsing patients were significantly older (median 4.5 years) compared to the group of patients who remained in remission (median 3.1 years, $p = 0.001$). In addition, clinical stages I and II had a significantly better prognosis than CS III ($p = 0.008$). On the other hand, high-risk histopathology ($p = 0.003$), relapse less than 6 months from the end of therapy ($p = 0.0001$), as well as combined local and metastatic relapse ($p = 0.001$) were associated with a poor prognosis. The current study has not shown that the risk of relapse depends on the pathology variant, although this finding may be influenced by the relatively small number of patients analyzed. The pathology variant, however, influences treatment failure after relapse, with a higher mortality in the high-risk group. The current study failed to confirm that the time to recurrence ($p = 0.110$) and its locations ($p = 0.703$) is correlated with outcome.

A retrospective analysis by Kaste et al. drew attention once again to known risk factors for nephroblastoma recurrence [11]. The prognosis was worsened by unfavorable histopathology with diffuse anaplasia, which were associated with lower sensitivity to chemotherapy. Stages III and IV and complications during surgery also increased the risk of relapse. Reports concerning biological agents which could possibly indicate a higher risk of relapse were summarized. Among these, a loss of heterozygosity (LOH) in chromosomes 1p and 16q was emphasized. In addition, a poorer prognosis was observed in cases of chromosome 1q ploidy.

New combinations of drugs, including the use of megachemotherapy, which potentially improve the outcomes in relapses, are being explored [12]. Great importance is being placed on the role of etoposide, but its use has also been associated with a higher risk of hematologic complications. Among other things, Abu-Ghosh et al. reported a good response

in children treated with ICE (ifosfamide, carboplatin, etoposide) [13]. In a study by Cambell et al., after applying megachemotherapy and autologous stem cell transplant, a 4-year survival free of relapse was achieved in about 60% of the cases, and a total 4-year survival rate of 73% [14]. There was no evidence that the transplant itself was associated with increased mortality. A retrospective study by Dalorso et al. showed that in the years 1985–2005 a total of 343 transplants were carried out in patients with nephroblastoma [15]. Most patients received melphalan, etoposide and carboplatin (MEC). Overall survival in the second complete remission group was 40%, while in the first complete remission group it was 71%. The current study does not confirm the above reported data, but a more thorough analysis can take place only after the study group has increased in size. Consolidation with auto-HSCT; however, used in patients with the highest risk, had limited impact on outcome. It seems that megachemotherapy offered only a slight chance for cure in high-risk relapses, but a more detailed study on a larger group of patients could identify new factors influencing these results.

A 2013 literature review by Ha et al. (2013) covered 19 studies that included a total of 1226 patients [16]. The researchers compared treatment results in patients who received high dose therapy (HDT – $n = 234$) with those who did not (NoHDT – $n = 992$). The results should be interpreted with caution, because they come from non-randomized studies. Pooling all the studies suggested the superiority of HDT, with a hazard ratio (HR) for event-free survival (EFS) of 0.87 and 0.94 for overall survival (OS). The researchers proposed that a randomized trial comparing the role of HDT in patients with relapses of Wilms' tumor for each risk group could lead to an improvement in treatment outcomes in patients in the high and very high risk groups.

A 2011 study by Furtwängler et al. showed that subsequent therapeutic protocols improve the outcome of relapses for localized stages I–III, but not for the initially metastatic stages [17]. The study included 251 patients with first-line treatment failure, treated according to the following protocols:

SIOP9/GPO ($n = 77$), SIOP93-1/GPOH ($n = 93$) and SIOP2001/GPOH ($n = 81$). The 3-year overall survival of patients with stages I–III was respectively 43% for the SIOP9/GPO protocol, 65% for the SIOP93-1/GPOH protocol and 68% for the SIOP2001/GPOH; for stage IV the overall survival rate for the same protocols was 43%, 53% and 44% respectively. In the current study, the outcomes following relapse did not differ between localized stages and stage IV cases. It should be noted; however, that disease recurrence was confirmed in only 11 patients in stage IV, and also – surprisingly – in 11 children with stage I and seven with stage II. A thorough analysis of these events will be possible only by increasing the size of the study group.

In addition to the known factors contributing to a poor prognosis after relapse in nephroblastoma, biological markers of disease recurrence, investigated through advanced genetic, molecular and immunological testing, are also being evaluated. Some of the previously mentioned chromosomal aberrations, such as loss of heterozygosity (LOH) of chromosomes 1p, 11q and 16q, are indicators of a poor prognosis [18–20]. Li et al. have attempted to isolate the genes most commonly involved in Wilms' tumor development, and also to identify the genes associated with a poor prognosis, from the group of over 4900 genes influencing carcinogenesis [21]. Four genes associated with a higher risk of relapse (92% probability of recurrence) have been identified: C/EBPB, cDNA CF542255, p21 and H4FG. Of the new biological markers, the B7-H1 protein may have prognostic significance for patients with Wilms' tumor. Routh et al. found that in tumors with anaplasia, the expression of the B7-H1 protein was observed more frequently than in tumors with favorable histopathology, and its presence increased the risk of recurrence 2.7-fold [22].

The authors concluded that age, gender, clinical stage and histopathology have no influence on recurrence. There is no correlation between outcomes and the time of the first recurrence. The prognosis after relapse in initially metastatic patients was not different from that in patients who had initially localized disease. Pathology variants probably had more significance on the outcomes.

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