Journal of Pediatric Surgery 53 (2018) 1611–1614

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Oncology

# Evaluation of effect of preoperative chemotherapy on Wilms' tumor histopathology☆

Seppo Taskinen [a,*], Jouko Lohi [b], Minna Koskenvuo [c], Mervi Taskinen [c]

[a] Department of Pediatric Surgery, Children's Hospital, Helsinki University Hospital, Helsinki, Finland
[b] Department of Pathology, Helsinki University Hospital, Helsinki, Finland
[c] Division of Pediatric Hematology/Oncology and Stem Cell Transplantation, Children's Hospital, Helsinki University Hospital, Helsinki, Finland

ARTICLE INFO

*Article history:*
Received 12 June 2017
Received in revised form 26 September 2017
Accepted 1 October 2017

*Key words:*
Wilms tumor
Pathology
Kidney
Children
Chemotherapy

ABSTRACT

*Purpose:* To evaluate usefulness of cutting needle biopsy (CNB) to recognize pediatric renal tumors and to predict the evolution of histology during preoperative chemotherapy of Wilms tumors.
*Methods:* Ninety pediatric patients were operated for renal tumors at our institution in 1988–2015. We included all 64 patients who had undergone CNB at diagnosis and whose CNB and nephrectomy samples were available for re-evaluation.
*Results:* The CNB was diagnostic in all 59 Wilms tumors but only in two out of five non-Wilms tumors. Anaplasia was missed by CNB in one of three with diffuse anaplasia in nephrectomy specimens. In Wilms tumors the proportions of the blastemal, stromal and epithelial components were 55% (IQR 25–85), 28% (IQR 10–58) and 2% (IQR 0–10) in CNB samples and 5% (IQR 0–64), 15% (IQR 0–50) and 15% (IQR 0–44) in the nephrectomy specimens (p-values 0.002, 0.599 and 0.005 respectively). The degree of tumor necrosis was in median 80% (IQR 21–97), after preoperative chemotherapy. The degree of tumor necrosis after chemotherapy had a positive correlation with the proportion of blastemal component ($p = 0.008$) and a negative correlation with proportion of epithelial component in pre-chemotherapy CNB samples ($p < 0.001$).
*Conclusions:* Wilms tumors are usually recognizable unlike non-Wilms tumors in CNB at diagnosis. In Wilms tumors, high blastemal cell content is associated with significant tumor necrosis during pre-operative chemotherapy. Our results do not support routine use of CNB in diagnosis of renal tumors.
*Type of study:* Retrospective review.
*Level of evidence:* Level III.



Wilms' tumor is treated primarily using strategies created by the Wilms' tumor study (NWTSG), and its successor Children's Oncology Group (COG) Renal Tumor Committee or by International Society of Pediatric Oncology (SIOP) Renal Tumor Committee [1]. North-American NWTS/COG protocols are based on primary surgery followed by chemotherapy. This approach allows an accurate and comprehensive evaluation of tumor histology. The SIOP protocol is used mainly in Europe and an essential part of it has been preoperative chemotherapy. During preoperative chemotherapy the tumor size shrinks and the operation becomes easier with a decreased risk for tumor rupture [2,3]. However, the preoperative chemotherapy may be directed to the wrong type of tumor, if histological verification is lacking, and accurate histological classification may occasionally be impossible from the nephrectomy specimen because of tumor necrosis. The use of cutting needle biopsy (CNB) was presented previously in 1991 in studies from Helsinki, London and Toronto, followed later by Sweden [4–7]. In general, positive experience has been reported from UK from the use of cutting needle biopsies: 12% of the patients who turned out to have non-Wilms' tumor avoided inappropriate chemotherapy [8]. The drawback of this approach is that the primary CNB represents small foci of the tumor. In addition, the diagnosis of anaplasia has been particularly challenging by CNB in prior reports [8].

Diagnostic biopsy and preoperative chemotherapy have been part of our protocol in children with a renal tumor since the initial report in

☆ An abstract has been presented in the annual congress of European Society for Pediatric Urology 2017.

* Corresponding author at: Children's Hospital, Helsinki University Hospital, Stenbäckinkatu 11, 00290 Helsinki, Finland. Tel.: +358 504272542; fax: +358 9 47175314.
*E-mail address:* seppo.taskinen@hus.fi (S. Taskinen).

https://doi.org/10.1016/j.jpedsurg.2017.10.002
0022-3468/

**Table 1**
The chemotherapy administered pre-operative for all the children. The chemotherapy protocols used were mainly based on SIOP and NWTS protocols.

| Preoperative chemotherapy (n = 59) | Median, range | % of Children |
|---|---|---|
| Dactinomycin mg/kg | 0.17, 0.06–0.29 | 100% |
| Vincristine mg/m$^2$ | 8.3, 1.8–25.9 | 100% |
| Doxorubicin mg/m$^2$ | 53, 20–99 | 15% |
| Cyclophosphamide mg/m$^2$ | 1338, 556–3375 | 25% |
| Etoposide mg/m$^2$ | 368, 218–542 | 8% |
| Ifosfamide mg/m$^2$ | 6824, 3034–10,784 | 7% |
| Cisplatin mg/m$^2$ | 111, 111 | 1.7% |

1991 [4]. This gives us an opportunity to compare the histological findings of the primary biopsy to the nephrectomy sample in order to characterize the effect of the initial chemotherapy.

## 1. Methods

The study cohort was identified by a retrospective review of surgical database for patients operated on for renal tumors in 1988 through 2015 at our hospital. The institutional Ethics Committee had approved the study. Altogether 90 patients were found of whom 70 had had preoperative CNB. We included to the final analysis all the 64 renal tumor patients who had both original preoperative CNB and nephrectomy histology samples available. We excluded the 20 patients who had not undergone preoperative CNB and six patients whose pathology slides could not be found for re-evaluation.

The general policy of our hospital has been in favor of diagnostic renal biopsy excluding intrarenal stage 1 tumors, cystic tumors and tumors with active bleeding. CNB has been taken by using ultrasound guidance from a posterior or flank approach avoiding the peritoneal cavity. In the early series manually used Tru-Cut™ cutting needles were used but have been replaced by automatic cutting needles (nowadays: BioPince® 18ga; Argon Medical Devices, TX, USA) during the last 20 years. CNB has been repeated each time until at least two acceptable-quality cylinders were collected.

The pathology slides were re-evaluated by an experienced pediatric pathologist (JL) together with senior pediatric oncologist (MT) to confirm the diagnosis and to classify the response to preoperative chemotherapy according to current guidelines [9]. In case of Wilms' tumor the structured histological evaluation included the estimation of the degree of necrosis (necrotic = 100% necrosis, regressive = 66–99% necrosis, poor response = necrosis <66%), proportions of cellular components of Wilms' tumor (epithelial, blastemal, stromal) expressed as a percent of the total surface area of the viable tissue of the tumor, and presence of anaplasia (focal or diffuse) [9].

The complications of the tumor biopsy or nephrectomy as well as the cumulative doses of preoperative chemotherapy agents were collected from the patient charts. Preoperative chemotherapy was based on vincristine and actinomycin D. According to the institutional policy during the early years of the evaluation period, either cyclophosphamide or doxorubicin was used in preoperative chemotherapy of metastatic, anaplastic or blastemal predominance Wilms' tumors (Table 1). We evaluated the response to preoperative chemotherapy by analyzing the proportion of tumor necrosis at the time of nephrectomy.

**Table 2**
Occurrence of different Wilms's tumor cellular elements from cutting needle biopsy (CNB) at diagnosis and from nephrectomy after preoperative chemotherapy. The figures in parenthesis indicate the frequency of the component in the CNB or nephrectomy sample only.

| Cellular components | CNB sample | Nephrectomy specimen | p-value |
|---|---|---|---|
| Wilms tumor | 59 | 59 | |
| Blastemal cells (n) | 55 (17) | 40 (2) | <0.001 |
| Epithelial cells (n) | 36 (5) | 44 (13) | 0.168 |
| Stromal cells (n) | 45 (13) | 37 (5) | >0.99 |
| Anaplasia | 3 (1) | 6* (4) | |

* Three patients had diffuse anaplasia and three had focal anaplasia.

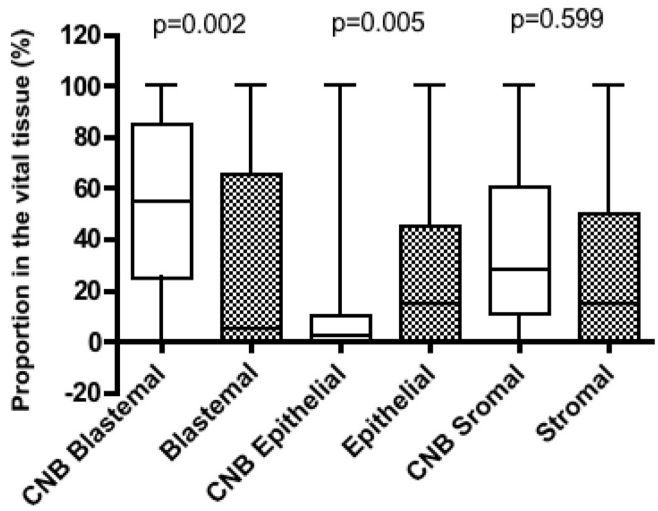


**Fig. 1.** Proportion of different cellular elements in 59 Wilms tumor patients. The white and dark boxes indicate the proportion of individual component in the primary cutting needle biopsy and the nephrectomy sample respectively.

### 1.1. Statistical analysis

Existence of different cellular components in the CNB and in nephrectomy samples were compared by using Fisher's exact test and the change in the proportions of the cellular components with Wilcoxon signed rank test. The association between different cellular components on CNB and the degree of necrosis was evaluated with linear regression. Continuous variables are expressed as medians and interquartile ranges (IQR) or ranges. For the analyses Statview® 5.0.1, SAS Institute Inc. was used. $p < 0.05$ was considered significant.

## 2. Results

### 2.1. Patient characteristics

Twenty-nine of the 64 patients were male. The median age at diagnosis was 3.1 years (IQR 1.8–4.5, range 0.1–17.1). The tumor was located on the right or left side, or bilaterally in 33 (52%), 27 (42%) and four (6%) patients, respectively. Fifteen patients (23%) presented with lung metastases at diagnosis and five (8%) had tumor thrombus extending to the vena cava (3 with lung metastases) and one patient had a tumor extending to the ureter.

### 2.2. Complications of CNB and nephrectomy

CNB was safe: one patient required a blood transfusion because of bleeding and three patients had hematuria caused by CNB. No other severe side effects were noted. We did not have a tumor rupture during nephrectomy and previous CNB did not complicate nephrectomy and tumor growth was not observed in the CNB tract.

### 2.3. Histology in CNB and nephrectomy samples

Originally 61 tumors got Wilms' tumor diagnosis by CNB. However, after nephrectomy one of them turned out to be clear cell carcinoma and another was primitive neuroectodermal tumor. In the re-evaluation, both of these false positive CNBs were found to be insufficient for diagnosis. CNB was considered non-diagnostic both in initial and in re-evaluation in one additional clear cell sarcoma case. The sensitivity of CNB samples both in the original and in this study evaluation