Analysis of prognostic factors of nephroblastoma in a Tunisian cohort

Analyse des facteurs pronostiques du néphroblastome dans une cohorte Tunisienne.

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RÉSUMÉ

Introduction: Le Néphroblastome est la tumeur abdominale la plus fréquente chez l'enfant. Plusieurs études ont analysé les facteurs pronostiques permettant ainsi d'adapter le traitement selon des groupes de risques.
Objectif: Analyser les facteurs qui influencent de façon significative la survie des patients diagnostiqués avec le néphroblastome.
Méthodes: Nous avons mené une étude rétrospective de 42 enfants porteurs de néphropblastome sur une période de 10 ans (2001-2010) à l'institut Salah Azaiz. Les tumeurs étaient divisées selon le type histologique et le groupe de risque histologique selon la classification du SIOP 2001. Les analyses statistiques étaient réalisées en utilisant le Kaplan-Meir et Cox regression.
Résultats: L'âge médian était de 38 mois. Le type histologique mixte était le prédominant (40%). Les tumeurs étaient réparties en groupe de risque histologique intermédiaire (81%) et haut (14%). Les tumeurs étaient classées en stade I (38%), II (24%), III (9%), IV (17%) et V (12%). La survie à 4 ans était de 83% et la survie sans événement était de 85%. L'âge, la latéralité, le groupe de risque histologique, le volume tumoral, le volume blastémateux, le stade, la rupture capsulaire et la résection incomplète présentaient un impact significatif sur la survie. Les facteurs prédictifs de rechute étaient la latéralité, le volume tumoral, le volume blastémateux, le groupe de risque histologique, la rupture capsulaire et la résection incomplète.
Conclusion: Le type histologique et le stade sont les principaux facteurs pronostiques du néphroblastome. De nouvelles et larges études sont nécessaires pour établir l'impact du volume blastémateux absolu.

Mots-clés
Néphroblastome, facteurs histopronostiques, histologie, chirurgie, chimiothérapie, radiothérapie, composant blastémateux

SUMMARY

Background: Nephroblastoma is the most common childhood abdominal malignancy. Many studies allowed a better understanding of prognostic factors and they permitted to adapt treatment according to a risk stratification approach.
Aim: To assess the most significant factors influencing the survival of patients presenting nephroblastoma.
Methods: We conducted a retrospective study over a 10-year period between 2001 and 2010 including 42 nephrectomy specimens, assessed in the pathology department of Salah Azaiz Institute, from all children diagnosed with nephroblastoma.
The tumors were subdivided into histological subtypes and histological risk groups according to the SIOP-2001 classification. Statistical analyses were performed using the Kaplan-Meir and the Cox regression methods.
Results: The median age was 38 months. The mixed type was the most common (40% of cases). The tumors were subdivided into intermediate histological risk group (81%) and high risk group (14%). The tumors were classified as stage I (38%), stage II (24%), stage III (9%), stage IV (17%) and stage V (12%). The four-year survival rate was 83% and the event free survival rate was 85%. Age, laterality, histological risk group, tumor volume, blastema volume, stage, capsular rupture and incomplete resection had a significant impact on survival. Predictive factors of relapse were: laterality, tumor volume, blastema volume, histological risk group, stage, capsular rupture and incomplete resection.
Conclusion: Histological type and stage were identified as the most important prognostic factors in nephroblastoma. Further large studies are needed to establish the impact of absolute blastemal volume.

Key-words
Nephroblastoma, Histopronostic factors, Histology, surgery, chemotherapy, radiotherapy, blastemal component

Nephroblastoma or wilms tumor (WT) is the most frequent renal malignancy in childhood. Its treatment has been integrated into large clinical studies since the 70's such as the National Wilms Tumor Study (NWTS) of the USA and the European International society of Paediatric Oncology (SIOP) trials. These studies allowed a better understanding of prognostic factors and thus they permitted to adapt treatment according to a risk stratification approach. Treatment is actually multidisciplinary and stratification is based essentially on histology and stage. Although survival rates had been largely improved, current research focuses mainly on more specific issues, such as reduction of toxicity and increasing therapy for patients with high risk tumor. Currently, the histological report contains the main prognostic factors in nephroblastoma defining the therapeutic approach. The purpose of our study was to investigate histoclinical features of WT in relation to SIOP 2001 Classification of Renal Tumors of Childhood and their prognostic value.

METHODS

Records of 42 consecutive cases of nephroblastoma, diagnosed in the Pathology Department of Salah Azaiz Institute during a period of 10 years from January 2001 to December 2010, were retrospectively reviewed.

All patients had multimodal therapy according to the SIOP protocols. Treatment for patients aged more than 6 months, was initiated with preoperative chemotherapy after the diagnosis of nephroblastoma based on clinical, biological and radiological presentation without histological verification. Patients under 6 months of age had primary surgical nephrectomy without preoperative chemotherapy.

After nephrectomy, histological diagnosis of nephroblastoma was established and restaging was performed. Post-operative treatments were decided following the Franco-Africain Group of Pediatric Oncology recommendation (GFAOP). The assessment of the clinical course of the disease included: distant or local recurrence, progression of the disease confirmed by imaging studies and death.

Clinical data including sex, age, congenital abnormalities, laterality, tumor radiologic measures before and after primary chemotherapy, therapies and course of the disease were extracted from clinical records and analyzed. When sonographic tumor measurements were available, tumor volume were measured using the ellipsoid formula: lenght×depth×large×0,523.

The absolute volume of remaining blastemal component (Vb) was calculated using the formula: V(b)= V (radiologic tumor volume after pre-operative chemotherapy) × (1- % of necrotic fraction) ×% of blastema cell fraction.

According to V(b), two groups were distinguished : (1) V(b) < 20 ml and (2) V(b) ≥ 20 ml.

Results were obtained using SPSS 21 for windows. The differences in the four-year overall survival (OS) and event-free-survival (EFS) were calculated by the Kaplan Meier method. Comparisons of the prognostic impact of each factor were performed using the Log Rank test.

P value was considered statistically significant if it was inferior to 0,05. Multivariate analysis was analyzed using the Cox model.

RESULTS

Clinical data

The mean age at diagnosis was 38 months (range 2-156 months). There were 17 male (40%) and 25 female (60%). Sex ratio was of 1,4. Tumors ultrasonography measurements at diagnosis were available in 29 cases. The median initial tumor volume (IV) was 620 ml (range23-2987). Tumor volume after primary chemotherapy (SV) was available in 21 cases; the median volume was 225 ml (range 5-740).

Histological Data

The distribution of cases by histological subtype, histological risk group and stage is shown in table 1. Stage distribution by histological subtypes is shown in table 2.

Table1: Distribution of cases by histologic subtype,histologicalrisk group and stage

Parameters	N (%)
Histologic subtype	
Mixed	17 (40.5)
Stromal	6 (14)
Regressive	6 (14)
Blastemal	5 (12)
Epithelial	4 (9.5)
Completely necrotic	2 (5)
Diffuse anaplasia	2 (5)
Histological risk group	
Low	2 (5)
Intermediate	34 (81)
High	6 (14)
Stage	
I	16 (38)
II	10 (24)
III	4 (9)
IV	7 (17)
V	5 (12)

Table 2: Stage distribution by histological subtypes

histological subtype	Stage I-II	Stage III-IV	bilateral	Total
completely necrotic	1	1	0	2
epithelial	3	0	1	4
Stromal	3	2	1	6
Mixed	14	1	2	17
Regressive	3	3	0	6
Blastemal	2	2	1	5
Diffuse anaplasia	0	2	0	2

Lymph node sampling was performed in 78% of cases (33 patients). Lymph nodes were involved in 12% of cases (5 patients).
Renal sinus involvement was observed in 38% of cases. Inferior vena cava involvement was found in 1 case and renal vena involvement in 2 cases. Capsular rupture was found in 3 cases. Surgical margins were involved in 3 cases. Nephrogenic rests were observed in 9 cases.

Treatments

Thirty-eight patients (90%) received primary chemotherapy. Only 4 patients didn't receive chemotherapy, 3 of them were aged less than 6 months and one patient had a metastatic nephroblastoma with uncertain diagnosis. Thirty patients received AV regimen (vincristine+actinomycin D) and 8 patients received AVD regimen (vincristine+actinomycinD+Doxorubicin). Total nephrectomy was realized for 41 patients. One patient with bilateral tumor had partial nephrectomy.
We observed only three capsular rupture. All patients had post-operative chemotherapy: 37 patients had only chemotherapy and 5 patients had radiotherapy and chemotherapy. One patient was treated according to SIOP93-01 recommendations and he received AV regimen for 17 weeks (stage I, intermediate risk).
For the rest of the patients, chemotherapy followed the recommendation of the GFAOP. Seventeen patients received AV regimen,17 patients had AVD regimen and 7 patients received CDCV regimen (cyclophosphamide-Doxorubicin-Carboplatin-etoposide).
Radiotherapy was proposed in 9 cases but received only in 5 cases (1 parental refusal and 3 cases of Age-related constraints).

Evolution course

The time of follow up ranged from 13 to138 months (median 54 months). During this period we observed 4 local recurrences and 7 distant metastases. 8patients died of their cancer.
Four-year event-free survival rate in the entire examined group was 85% and four-year survival rate was 83%.

Prognostic factors

Patients younger than 2 years had significantly better 4-year overall survival rate (p=0,04). Tumors smaller than 500 ml at diagnosis had significantly better 4-year overall survival and event-free survival rates. The OS and EFS rates according to age, sex, laterality and radiologic volume are summarized in table 3. The OS and EFS by histological subtypes are summarized in table 4.

Table 3: Overall survival and event-free-survival according to clinical parameters

Parameters		OS	p	EFS	p
sex	Male	88%	0.23	88	0.09
	Female	70%		63	
age	<2 year	94%	0.04	87%	0.08
	≥ 2 year	66%		63%	
laterality	Unilateral	82%	0.01	77%	0.03
	Bilateral	40%		40%	
Initial radiologic volume			0.017		0.006
	< 500 ml	94%		94%	
	≥ 500 ml	56%		47%	
Radiologic volume after primary chemotherapy			0.6		0.5
	< 500 ml	75%		83%	
	≥ 500 ml	55%		67%	

Table 4: Overall survival and event-free-survival by histological subtypes

Histological types	OS	p	EFS	p
Completely necrotic type	50%		50%	
mixed type	88%		88%	
regressive type	100%		67%	
stromal type	62%		67%	
Epithelial type	100%	0.05	100%	0.2
blastemal predominant type	40%		40%	
diffuse anaplasia	50%		50%	

Blastemal predominant subtype had worse outcomes than other histological subtypes (p=0,028).
Regarding the absolute blastemal tumor volume, 4-year OS rate in group (1) (Vb< 20 ml) was 100% while it was 53% in group 2 (Vb≥20 ml) (p=0,02). 4-year EFS rate was 84% in group 1 while it was 40% in group (2) (p=0,03).
Other factors demonstrating significantly inferior 4-year OS rate by the log-rank test were advanced stage disease: stage III and IV (p=0. 03), high risk group (p= 0,01), capsular rupture (p=0,001) and incomplete resection (p=0,003).
Factors significantly correlated with relapse wereadvanced stage disease (p=0. 02), high risk group (p= 0,004), capsular rupture (p=0,0001) and incomplete resection (p=0,003).

In multivariate studies, only relapse was identified as an independent risk factor for survival.

DISCUSSION

Nephroblastoma is the most frequent solid tumor in children, representing 8-10% of pediatric malignances (1). It frequently occurs at the age of 2 to 5 years. It represents almost 95% of malignant renal tumor in childhood (2).

Treatment regimens for nephroblastoma, in both (SIOP) and NWTS trials, are based essentially on clinical and histological prognostic factors.

Primary chemotherapy allows downstaging and increasing lower stage which permit a complete tumor resection and avoid per-operative capsular rupture (3). In our study, only 4 patients didn't receive primary chemotherapy, 3 of them were aged less than 6 months. Nephroblastoma were of stage 1 and 2 in 62% of cases. We observed only 3 capsular rupture.

The SIOP 2001 protocol proposed a preoperative chemotherapy with actinomycin D and vincristine in patients with unilateral localized disease (stage I–III) for 4 weeks and 6 weeks with additional adriamycine for patients with distant metastases. The duration and intensity of preoperative therapy in bilateral WT (stage V) was individualized depending on the response and the operability of tumors (4).

One of the inconvenient of primary chemotherapy is that it significantly alters the histological features of WT (5).

In the SIOP 9/GPOH study(6), the most common subtype of tumors immediately operated was mixed histology (45. 1%), followed by blastemal (39. 4%) and epithelial dominant (15. 5%), whereas in tumors that received preoperative chemotherapy, the most common histology was regressive (37. 6%), followed by mixed (29. 4%), stromal(14%), blastemal (9. 3%) and epithelial predominant (3. 1%); 6. 6% of tumors were completely necrotic.

In the SIOP trials, tumor volume after primary chemotherapy had prognostic significance but this was not the case for initial tumor volume. In SIOP 93-01, the median tumor volume did shrink from 353 to 126 ml (7). A cut point volume of 500 ml inpatients with intermediate-risk tumors, excluding those with epithelial and stromal subtypes, showed a significant difference in outcome. These two subtypes often present as large tumors, do not shrink during preoperative chemotherapy. Five-year OS were 95% for smaller tumors, compared to 90% with larger tumors (p=0. 0002). Five-year EFS were 88% for smaller tumors, compared to 5-year EFS of 76% with larger tumors (p=0. 0001). In our study, initial tumor volume had a prognostic impact but this is not the case for tumor volume after chemotherapy. This discordance could be explained by the limited number of cases reviewed in our study.

Completely necrotic tumors are reported to have excellent prognostic (8), however in our study one of the two patients having completely necrotic nephroblastoma died. Our study showed that epithelial and regressive subtype had better prognosis than other subtypes within intermediate risk (4-year overall survival rate of 100%). Some authors suggested that tumor differentiation could have also a prognostic impact. Niedzielski et al demonstrated that poorly differentiated epithelial subtype and regressive subtype were features with decreased OS (94. 1%) in the group of intermediate-risk tumors (9,10).

Results of SIOP/GPOH trials showed that the relapse rate of the blastemal predominant type was 21. 1%, whereas that of the epithelial type was 3. 5% and that of the stromal type was 2. 3% (11). Similarly, our study demonstrated that blastemal predominant tumors had a significantly worse prognosis.

Analysis based on the absolute volume of blastemal component after preoperative chemotherapy, rather than remaining blastemal percentage, showed that there is a sharp threshold of blastemal volume discriminating between good and poor outcome. For unilateral localized intermediate risk tumors, this volume is about 20 mL. Five-year EFS was 91% in patients with less than 20 mL blastema compared to only 75% in patients with more than 20 mL blastema ($p<0.01$) (12). In patients with stage IV disease the effect of absolute blastemal component was even more striking. As these patients receive AVD over six weeks instead of AV therapy over 4 weeks, the remaining blastema might be more resistant to chemotherapy. In this group of patients, a blastemal volume less than 10 mL is associated with EFS of 87% compared to EFS of only 23% for those with higher volumes of blastema . The differences in OS are not significant (13). Our study showed similar results.

A prospective evaluation of the absolute blastemal volume will be carried out in the upcoming SIOP Renal Tumor Study Group trials to define an optimal threshold of V[b] for a better risk stratification.

Stage is also an important factor in risk stratification in nephroblastoma. Prognosis is inversely proportional to stage. The determination of tumor stage is based on intraoperative and pathological findings. Surgical procedures for Wilms tumor must include complete inspection of abdominal cavity with biopsy of suspicious sites, lymph node sampling and tumor resection.

Although our study failed to demonstrate the importance of lymph node dissection, most studies demonstrated that failure to sample the lymph nodes was an adverse prognostic factor, even if compared with lymph nodes involvement as this could lead to under treatment of a subset of those patients (14,15).

Capsular rupture and the quality of resection were identified as prognostic factors in our study. These factors are dependent partially on surgeon's skill. Stage is still particularly important to adapt treatment protocols. It's

important to distinguish stage I and II as post-operative treatment could be avoided in patients with stage I with low risk histology, or Stages II and III as radiotherapy could be avoided in stage 2 with low or intermediate risk (16).

Our patients received postoperative treatment according to the GFAOP recommendations. Treatment was based on the SIOP 9 and SIOP 2001 protocols, with a few adjustments for fear of underestimating the disease stage. The low-risk group was treated like the intermediate-risk group. Patients with stage I disease received vincristine and actinomycin D chemotherapy over nine weeks. In case of stage II, III, or IV disease, patients received postoperative chemotherapy in respect of the schedule of the SIOP 2001 protocols. Patients with stage III tumors received abdominal radiotherapy (17).

CONCLUSION

Despite its limited number of cases and its retrospective aspect, our study allowed focusing on the heterogeneity of the intermediate risk group nephroblastoma and the prognostic value of the absolute blastemal remaining volume. On the other hand, the high risk group tumors still have bad prognosis despite the aggressiveness of its therapy.

Nowadays, the cornerstones of prognosis in nephroblastoma are histology and tumor stage. Other molecular indicators have recently been investigated as possible prognostic factors, such as chromosome 1q gain and LOH at 11p15 (18,19).

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