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Full Length Article

Wilms tumor in childhood: Single centre retrospective study from the National Institute of Oncology of Rabat and literature review

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ABSTRACT

Background: Wilms tumor is a very common renal malignancy in children. Prognosis has been improved dramatically during the last few decades because of multimodal treatment and successful sequential studies. Through a retrospective study conducted in the National Institute of Oncology of Rabat, concerning children with Wilms tumor treated following the International Society of Pediatric Oncology protocol (93-01) between 2005 and 2010, we report the experience of our institute in treatment of this malignancy. We analyze also the clinicopathologic and therapeutic aspects impacting the outcome results and compared to literature data.

Results: Fifty-two patients with Wilms tumor treated in the department of radiotherapy after receiving chemotherapy and surgery at the department of hemato-oncology in children hospital of Rabat were enrolled. The main characteristic was the high prevalence of locally advanced and metastatic stages (32.6% of stage IV). With a median follow up of 54.8 months [20–79], we observed a complete response in 32 cases (61.5%), local recurrence in only one case (1.9%), metastatic relapse in 3 cases (5.8%), both local and metastatic recurrence in 3 cases (5.8%) and disease progression in 8 cases (15.4%). The mean duration of overall survival was 91.2 months. The estimated 2-year and 5-year overall survival were 78.7% and 70.1% and for metastatic patients 68.8% and 62.5% respectively. At univariate analysis several parameters were tested for survival, but only age, anaplasia, lymph node involvement, type of metastasis and response to treatment were found to significantly impact the overall survival. Outcome was better for localized tumors (stage I, II and III) compared with disseminated tumors (stage IV and V) combined. Also a better survival rate was found in the low and intermediate risk group compared to high risk, but not statistically significant.

Conclusion: The relatively low outcome found in this series compared to literature can be mainly explained by the higher prevalence of metastatic disease compared to other series, but also by diagnosis and therapeutic delay, more likely because of bad socioeconomic conditions and lack of coordination between different operators. However, our results are nevertheless comparable to maghrebian series. Our department has established many procedures for improving the outcome and further studies are necessary to evaluate their efficiency.

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1. Background

Wilms tumor or nephroblastoma is the most common renal malignancy in children and the sixth pediatric cancer. It represents 5–10% of solid tumors and 1/3 of embryonic neoplasia [1–3]. The last few decades have seen a dramatic change in the prognosis of this disease. Indeed, survival rates have improved to a current five-year overall survival rate of 90%, whereas it was only 30% with surgery alone and only 47% with the combination radiotherapy-surgery [4–6]. This improvement in outcome is due mainly to multimodal treatment regimens (chemotherapy, surgery, and radiation) based on sequential clinical trials.

The target of this survey is to report the epidemiological, clinical and therapeutic features of patients treated for nephroblastoma in the department of radiotherapy in the National Institute of Oncology (NIO) of Rabat, Morocco with a summary review of literature data.

2. Methods

2.1. Data collection

This is a retrospective study of 52 cases of Wilms tumor (WT) treated in the department of radiotherapy during a period of 6 years (2005–2010), after receiving chemotherapy and surgery at the department of hemato-oncology in children hospital of Rabat.

Analysis of clinical features, pathological findings, imaging studies, different therapeutic modalities and outcome was achieved based on data from both hospitals' cancer registry of the NIO and the children hospital of Rabat.

We got permission to access and use data from the department head of cancer registry of Rabat. We also obtained verbal consent from all parents or legal guardians of the patients included in this study.

Patients were treated according to SIOP protocol 93-01 [5]. This regimen included upfront chemotherapy followed by surgery and then postoperative histopathological confirmation of diagnosis. A risk-based therapy (including adjuvant chemotherapy and radiotherapy) is assigned based on results of the initial staging and histological group disease.

Histological subtype determining histoprognosis group and staging (I, II, III, IV or bilateral) were assessed according to the revised SIOP Working Classification of Renal Tumours of Childhood (2001) [7,8].

2.2. Statistical analysis

Several factors were tested for outcome: age, gender, stage at presentation, histological sub-type, risk group, lymph node status, metastasis and response to treatment.

Median follow-up time was defined from the date of diagnosis to date of death or date last follow-up.

Overall survival (OS) is defined as time from diagnosis to mortality (for all-cause death) and patients still alive were censored at the date of last follow-up.

Survival rates were evaluated for all patients using the Kaplan Meier curve (SPSS 13.0) and compared by log-rank test with a statistical significance of 5%.

3. Results

Our series enrolled 52 patients, with a median age of 4 [3–5] years (range from 17 months to 14 years), sex ratio (F/M) was 0.9 (Table 1). A single case of hemihypertrophy was found. However, no other associated congenital syndrome has been noted.

Table 1
Clinico-pathological and evolutionary features.

Clinico-pathological and evolutionary features		Number of cases (%)
Age	<5 years	29 (55.8)
	>5 years	23 (44.2)
Gender	Male	27 (51.9)
	Female	25 (48.1)
Stage at presentation	I	1 (1.9)
	II	4 (7.7)
	III	28 (53.9)
	IV	17 (32.7)
	V	2 (3.8)
Histology	Low risk	2 (3.8)
	Intermediate risk	35 (67.3)
	High risk	15 (28.8)
Anaplasia	Absent	47 (90.4)
	Diffuse	4 (7.7)
	Focale	1 (1.9)
Metastasis at presentation	Lung only	12
	Liver only	2
	Lung + Liver	4
Response to treatment	Complete response	32 (61.5)
	Local relapse	1 (1.9)
	Metastatic relapse	3 (5.8)
	Progression	8 (15.4)
	Local and metastatic relapse	3 (5.8)
	Total	47 (100)

The median time to medical visit was 30 days [15–60], and 84% of children consulted within three months from the beginning of their symptoms. Clinical features were dominated by abdominal mass in 96.2% of cases associated with pain in 30.8% of cases, hematuria in only 19.2% (10 cases) and fever in 13 cases (25%). However no case of hypertension or acute abdomen symptoms was noted.

Diagnosis was based mainly on the clinical and imaging data. Indeed, abdominal ultrasound made in all patients and coupled to CT scan in 82.6% of cases have shown the tumor usually as a large renal mass, greater than 10 cm of diameter in 80.8% of cases and well limited. They have found thrombosis of inferior vena cava (IVC) in 10 cases (19.3%), combined to an intra-cardiac thrombosis in 5 cases which was shown by a chest CT scan.

The two imaging modalities have allowed evoking diagnosis of WT in 88.4% of cases. However, in 6 atypical cases (11.5%), diagnosis has been assessed histologically by fine needle aspiration and/or percutaneous cutting needle biopsy for the strong suspicion of neuroblastoma in 5 cases and of a retroperitoneal abscess in the sixth one. Both CT scan and chest radiography have been used for screening lung metastases. The approach used in our institution is the routine use of chest radiography (performed in 96% of children), supplemented by chest CT scan (performed in 36.5% of cases), only in cases of abnormal chest radiography. This assessment revealed 18 metastatic cases (34.6%) at diagnosis (67% in the lung only, 11% in the liver only and 22% in both lung and liver).

Fifty children (96%) received preoperative chemotherapy according to SIOP protocol 93-01 [5], which allowed the regression of 50% or more of the tumor mass in 43 cases (82.7%).

Surgery was performed in 96% after neoadjuvant chemotherapy, except for 2 patients who have undergone initial surgery (because the diagnosis of WT was missed). The surgical treatment consisted on radical nephrectomy in all cases associated with partial contralateral nephrectomy in one case of bilateral nephroblastoma, and a metastasectomy was achieved in two cases (liver in one case and lung in the other one). Lymph node dissection has been performed in 15 cases (28.8%) and revealed metastatic nodes in 9 of them (17.3%).

Histological sub-type and tumor stage were defined according to pathological assessment, which revealed 3.8% of low risk tumors, 67.3% of intermediate risk and 28.8% of high risk tumors, according to the SIOP WT 2001 staging criteria for renal tumors of childhood [8]. We must note that rhabdoid and clear cell subtype have not been registered in our series. Complete necrosis was seen in 2 cases, whereas a rate of necrosis/chemotherapy inducted changes up to 66% (witch define regressive histology) was noted in 40.4% of cases, this feature indicates low and intermediate risk respectively [2]. Nephrogenic rests have been noted on 13 surgical specimens (25%). Diffuse anaplasia mentioned in one case and focal in four cases. One tumor was classified stage I, 4 tumors stage II, 28 tumors stage III, 17 tumors stage IV and two tumors stage V (Table 1).

Post-operative chemotherapy was administered in all patients according to SIOP protocol 93-01 [5]. Radiotherapy was delivered with cobalt 60 or high energy photons X in 47 cases (96.8%). The indications retained for post-operative loco-regional radiation therapy were stage II/III high risk group and stage III with intermediate risk. Radiotherapy was delivered within an average time of treatment of 16.6 ± 6.4 days, with a daily fraction of 1.5 Gy (for whole abdomen irradiation) and 1.8 Gy (for flank irradiation). The median time between surgery and radiation therapy was 43 days [33–60.5]. The fields involved were flank in 32 cases (61.5%) (Doses varied between 10.8 and 25.2 Gy), whole abdomen in 12 cases (23%) (Doses varied between 14.4 and 16.2 Gy), with a boost to residual nodes in 7 cases (13.5%) and to thrombosis in 6 cases (11.5%) (Doses varied from 10.8 to 14 Gy). Also 4 lung metastatic cases (7%) received chest radiotherapy to the lung at a dose ranging between 10.5 and 12.6 Gray (chest radiotherapy only (N = 2), one case of combined flank and chest and the last of combined whole abdomen and chest). Chest irradiation was indicated only in cases of residual tumors after chemotherapy and/or surgery of metastases.

With a median follow up of 54.8 months [20–79], we observed a complete response in 32 cases (61.5%), local recurrence in only one case (1.9%), metastatic relapse in 3 cases (5.8%), both of local and metastatic recurrence in 3 cases (5.8%) and disease progression in 8 cases (15.4%). Five patients (9.6%) were lost of sight either before or just after the end of radiation therapy (these patients have been excluded from outcome results).

The mean duration of overall survival was 91.2 months. The estimated two-year and five-year survival rates were 78.7% and 70.1% respectively (Fig. 1).

At univariate analysis several parameters were tested for survival, but only age, anaplasia, lymph node involvement, type of metastasis and response to the treatment were found to significantly influence the overall survival (Fig. 2).

Outcome was better for localized tumors (stage I, II and III) compared with disseminated tumors (stage IV and V) combined, although this difference did not reach statistical significance. Also for histological sub-groups where was better survival in the low-risk group compared to the intermediate one and this was better than the high-risk group, but not statistically significant.

At multivariate analysis, after adjustment for age, anaplasia, lymph node involvement and delay before first consultation none of the studied variables was statistically associated to survival duration.

4. Discussion

To the best of our knowledge, this study is the largest series from Moroccan radiotherapy-oncology centers about the outcome of WT using SIOP protocols. The age and gender distribution were similar to other large series, with majority (55.8%) of patients less than 5 years old [6,9,10]. An age less than 5 years was associated with better overall survival in our series. This joined in part the data from the literature where better survival rate was found for

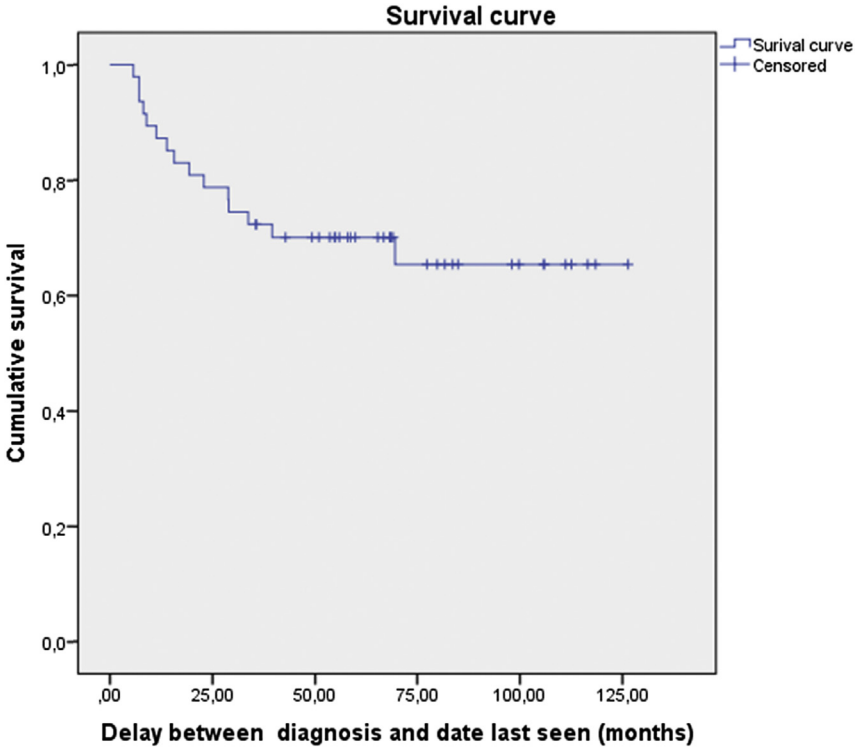

Fig. 1. Overall survival.

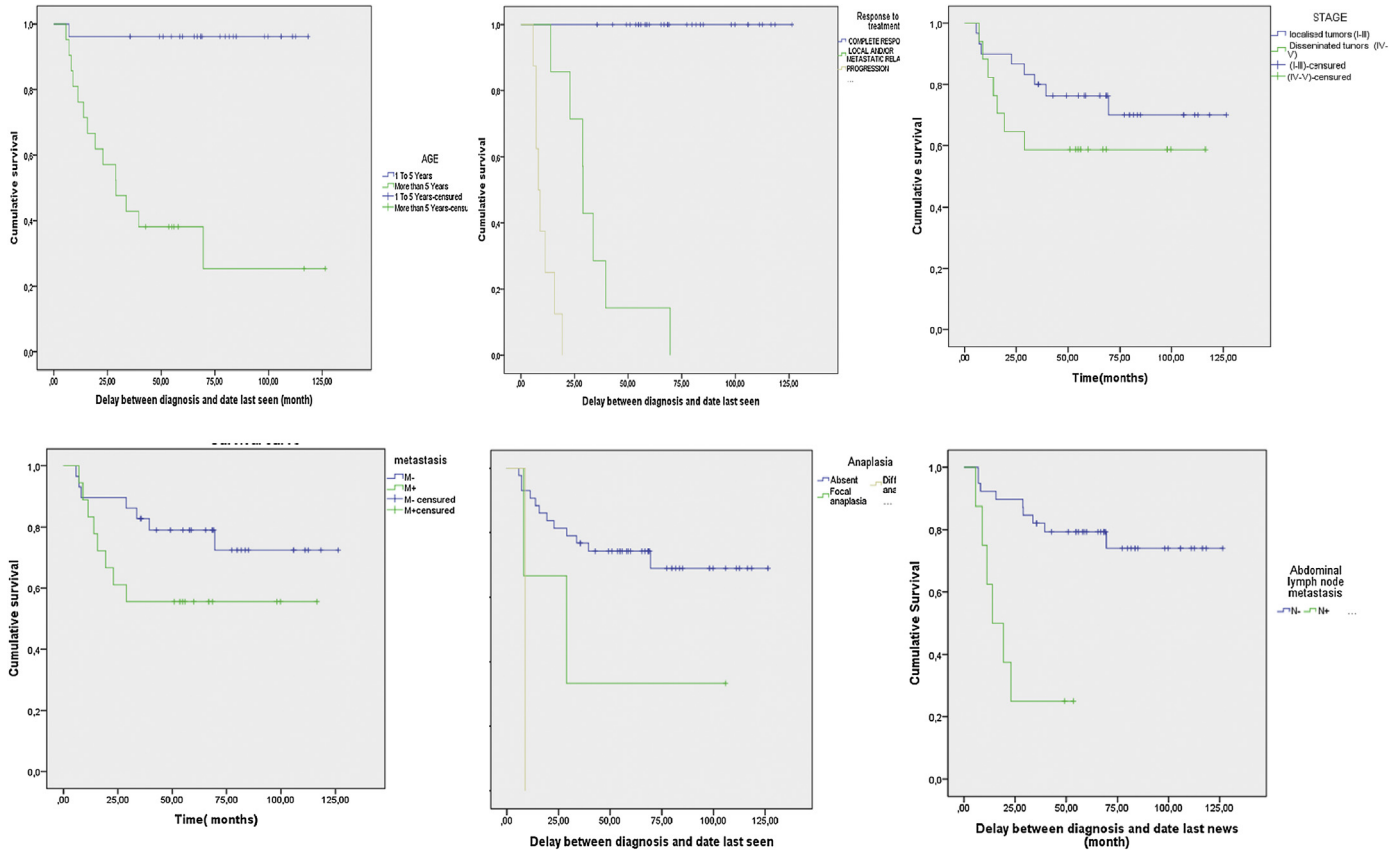

Fig. 2. Survival curves.

an age less than 2 years, with a lower relapse rates for this group age (Fig). However, the impact of age as a prognostic factor has been reduced currently, with the improvement of therapeutic approaches [11].

There was a lower incidence of associated anomalies in our study compared to the NWTS group (1.9% in our study Vs 7.3% in NWTS group) [12]. Hemi-hypertrophy is seen in 3% of nephroblastomas and it is often ipsilateral to the tumor [13].

The most frequent clinical feature in our study was abdominal mass (96,2%) compared to only 74% in United Kingdom Children's Cancer Study Group [14]. The disparity may be due to longer time to medical visit and then a higher number of patients presenting with advanced disease. Therefore, in contrast to other larger studies which have most of their patients presenting with early stage disease [12], only one patient presented with stage I and 4 patients with stage II in our study. Other symptoms included abdominal pain (30–40%), hematuria (12–25%) and hypertension (25%). Our results were similar to the literature reports [15,16].

5. Diagnostic evaluation

As in literature, diagnosis was based in our series on clinical and radiological findings [15]. But in rare cases histological evidence (fine needle aspiration and/or biopsy fine needle) was required to rule out differential diagnosis.

The first aim of imaging is to establish the presence of a renal tumor and to differentiate WT from other causes of abdominal masses [15]. Abdominal US is the initial imaging study, and should be associated with Doppler-US to detect tumor infiltration of the renal vein and the presence of eventual thrombosis which was found in 10 cases (19.3%) in our study. Contrast-enhanced CT scan is recommended to further evaluate the nature and extent of the mass.

Imaging of the chest (X-rays and CT scan) is needed to determine whether there are lung metastases and CT appears to be more sensitive than chest radiography [17,18]. There is controversy regarding the best screening modality to use for lung metastases. In fact, it is unclear whether diagnosing these lesions improves outcome as illustrated by the two studies of SIOP and COG with contradictory results (no benefit of routine chest CT at diagnosis for patients with unilateral WT in SIOP study, whereas the COG found that it improved the 5-year EFS for patients with lung metastases detected only by CT scan and have received more intensive therapy) [19,20]. The approach adopted in our series was the routine use of chest radiography. A patient with normal chest radiography is interpreted as being free of metastatic lung disease. Thus almost all of our children benefited from a chest radiograph, whereas CT scan was performed only in 36% of cases.

5.1. Treatment

5.1.1. Preoperative chemotherapy

Pre-operative chemotherapy is recommended to prevent intra-operative tumor rupture, to decrease the risk of intra-operative hemorrhage and to induce down-staging [8,21]. The SIOP reported that the risk of tumor rupture decreased in sequential studies from 33.3% to 8.0% when pre-operative chemotherapy was done [21,22]. In our series, 96% of cases received preoperative chemotherapy allowing regression of 50% or more of the tumor

mass in 82.7% of cases, this rate is higher than that reported in a Tunisian WT series (only 56.2%) [1].

The third United Kingdom Children's Cancer Study Group trial (UKW3), tested the optimal initial treatment approach for this malignancy. Patients were randomized to immediate nephrectomy or preoperative chemotherapy with a planned delayed nephrectomy at week 6. The study showed more favorable staging and significant reduction in the overall burden of therapy in preoperative therapy arm with the same outcomes [23]. The NWTS group reported that extensive hemorrhage occurred less frequently among patients with tumor thrombosis in the IVC when preoperative chemotherapy was administered (17.8%) [24] compared to immediate nephrectomy (32.5%) [25]. In our study, IVC thrombosis occurred in 10 cases (19.3%), associated with intra-cardiac thrombosis in 5 cases, they all received preoperative chemotherapy without any intra-operative extensive hemorrhage case noted.

However, the potential disadvantages of pre-operative chemotherapy include loss of staging information. In fact, preoperative chemotherapy alters the tumor's histological features, distribution of subtypes, and makes staging more difficult [8].

5.2. Surgery and histological findings

Total surgical excision is the standard treatment of unilateral WT [26]. In our series, all patients underwent radical nephrectomy, associated to a partial contro-lateral nephrectomy in only one case of bilateral WT. Surgery of residual metastases (excision), always recommended whenever possible, was done in 2 cases, for liver and pulmonary metastases. A review of both NWTS-4 and 5 databases and a SIOP study suggest that sampling lymph nodes (LN) from the hilar region is probably adequate to ensure accurate staging and extensive LN dissection is not necessary as it appears to confer no clinical benefit [27,28]. However, the surgeon should carefully examine all the hilar and periaortic nodes and excise any that are suspicious [29]. Lymph node resection was achieved in 15 cases in our series and has objectified lymph node involvement in 9 of them.

The presence of anaplasia, has been shown as the most important predictor of adverse outcome in children with WT in both NWTS group and SIOP studies [30–33]. In fact, 5-year survival of anaplastic cases in SIOP-9 does not exceed 48%. These results are comparable to those from the NWTS study group where patients with diffuse anaplasia accounted for more than 60% of deaths [33]. In our study, we noted only one case of diffuse anaplasia which was resistant to first line chemotherapy, he died during treatment with a follow up of 8.9 months. Focal anaplasia, has been registered in 4 cases, one of them experienced complete response and still in life with follow up of 105 months, whereas two others patients died by progression of their disease and one was lost of sight (Fig. 2).

5.3. Postoperative treatment

Postoperative treatment includes chemotherapy and sometimes RT in a risk-adapted approach based on histological subclassification and staging [8].

5.4. Radiotherapy (RT)

5.4.1. Localized disease

WT is one of the most radiosensitive malignancies, but the sequelaes caused by irradiation led to limit its use in advanced stages (irradiation is currently indicated for approximately 20% of patients in SIOP studies). Its main objective is to control retroperitoneal disease (tumor site and first lymph nodes relay) in children with a significant risk of locoregional relapse.

RT should be given with a delay inferior to 10 days after surgery. In fact the NWTS studies have shown that a delay upon or equal to 10 days after surgery was associated with a significantly higher abdominal relapse rate, particularly among patients with unfavorable histology tumors [34–36]. In the COG protocols, RT should be given preferably by day 9 but not later than 14 after surgery [37]. The median RT delay in our series was 43 [33–60.5] days, and all patients have received RT after 15 days from surgery. This delay, relatively long compared to what is recommended in literature, is most likely related to lower OS rates in our series. For this reason our department has adopted a new program of priority of starting RT treatment according to the degree of tumor emergency and WT is among the priority number II (with the others childhood malignancies) which should be treated by a delay less than 14 days. Postoperative RT was administered to our patients according to SIOP 93-01 protocol. The recommended dose of RT is 15 Gy in low- and intermediate-risk group with stage III disease and 30 Gy in high-risk patients [38]. In NWTS studies (1–4), no RT dose response has been shown. Therefore it was decided to treat all abdominal disease with 10 Gy [35,36,39]. Similar dose is used in the COG protocols for most indications (except for stage III diffuse anaplasia and stages I to III Rhabdoid tumor of the kidney, where a higher dose of 19.8 Gy is recommended) [40,41].

5.4.2. Metastatic disease

Negative impact on survival of omitting RT in metastatic sites, has been shown in an analysis of the effect of whole-lung RT on EFS and OS from UKW3 [42,43]. However, the morbidity associated with RT, and the risk of secondary malignancies have again been confirmed in an analysis of more than 8000 WT pooled from European and North American studies [42,44].

The metastatic response-adapted approach by omission of RT in the SIOP WT 2001 trial aimed to address this balance of risk. The results showed that survival correlates with completeness of lung node response. Comparable results have been found by the recently completed COG AREN0533 study [42,45]. Results from the complete response group (favorable histology) who did not receive whole-lung RT, have just been presented in the 2015 ASCO Annual Meeting. They have shown a slight decrease of EFS non statistically significant, whereas OS remained excellent (95%). These findings suggest that omission of lung RT may provide an acceptable treatment approach for this patient subgroup [46]. So clinicians should balance the benefit of avoidance of lung RT against the possibility of a modest increase in relapse risk [46].

In our series we noted 4 lung metastatic cases (7%) which received RT to the whole-lung at a dose ranging between 10.5 and 12.6 Gray, two of them are still alive with complete response (follow up of 56 and 60 months respectively), while the two remaining cases died by progression of their disease.

5.5. Adjuvant chemotherapy

In our series, all patients have received adjuvant chemotherapy according to SIOP protocol 93-01 [5]. Currently, the most important question regarding adjuvant chemotherapy in WT is the possibility of omission of doxorubicin from stage II–III intermediate-risk WT. That has been studied in SIOP 2001 trial and concluded that doxorubicin could be safely removed when histological response to preoperative chemotherapy is incorporated into the risk stratification. This approach will spare many patients the potential adverse effects of doxorubicin exposure [45,47].

5.6. Outcome

The overall survival rate relatively low in this series compared to literature data can be explained by the higher prevalence of metastatic disease compared to that reported in large series (10–15% Vs 32.6% in our series). This high rate is probably related to a referral bias, in fact patients who are referred to our department are more advanced stages and/or at high-risk of recurrence than standard series and they are potential candidates to receive adjuvant RT. OS of these metastatic patients does not exceed 68.8% at 2 years and 62.5% at 5 years (Fig. 2).

Our results are nevertheless comparable to maghrebian series. Indeed in a Tunisian retrospective study enrolling 35 WTs over a period of 8 years (with a minority of patients from stage IV), the 5-years OS was only 80% [1].

6. Conclusion

Patients with childhood WT are still treated with diagnosis and therapeutic delay in our setting, more likely because of bad socio-economic conditions and lack of coordination between different operators. These factors negatively impacted the prognosis in our series. Our department has established many procedures for improving the outcome and further studies are necessary to evaluate their efficiency. Better coordination between the various operators including onco-pediatricians, surgeons, pathologists and radiotherapists remains essential for better management of this tumor. The focus of ongoing studies is still continuing the improvement of outcome, particularly for high-risk group patient and minimization of long-term treatment burden in this malignancy.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RF, EH, RG, BN, LH, KF, MA, BK, SC, MM, AJ participated to the acquisition of data and drafting the Manuscript. BN, KT, ES have revised the manuscript. All authors read and approved the final manuscript.

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Abbreviations

WT	Wilms' tumor
US	ultra-sonography
RT	Radiation therapy
EFS	event free survival
OS	overall survival
SIOP	International Society of Pediatric Oncology
NWTSG	National Wilms' Tumor Study Group
COG	Children's Oncology Group
UKCCSG	United Kingdom Children's Cancer Study Group

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